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(54) 발명의 명칭 **ＨＣＶ 프로테아제 저해제**

(57) 요 약

본 발명은 명세서 내에 나타낸 마크로시클릭 화합물에 관한 것이다. 이러한 화합물들은 C 형 간염 바이러스 치료에 사용될 수 있다.

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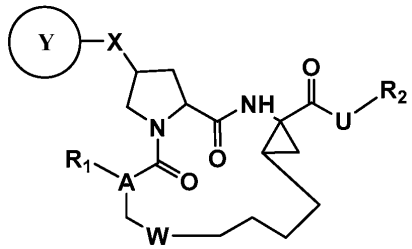
명 세 서

청구범위

청구항 1

하기 화학식의 화합물:



여기서, R_1은 -H, -OH, C_{1-6} 알킬, C_{1-6} 알콕실, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 헤테로아릴, 또는 -NH-Z-R 이고; 여기서 R은 H, 또는 C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며; 및 Z은 -C(O)-, -C(O)O-, -C(O)C(O)O-, -C(O)C(O)NH-, -C(O)NR'-, -OC(S)-, -C(S)NR'-, 또는 -C(NH)O- 이고, R'는 H, C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴이고;

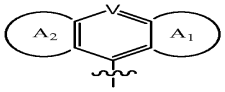
R_2는 H, 또는 C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며;

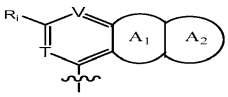
A는 N 또는 CH 이고;

U는 -O-, -NH-, -NH(CO)-, -NHS(O)-, 또는 $-NHSO_2-$ 이고;

W는 $-(CH_2)_m-$, $-NH(CH_2)_n-$, $-(CH_2)_nNH-$, $-O(CH_2)_n-$, $-(CH_2)_nO-$, $-S(CH_2)_n-$, $-(CH_2)_nS-$, -S(O)-, $-SO(CH_2)_n-$, $-(CH_2)_nS(O)-$, $-SO_2(CH_2)_n-$, 또는 $-(CH_2)_nSO_2-$ 이고, m은 1, 2, 또는 3 이고 n은 0, 1, 또는 2 이고;

X는 -O-, -S-, -NH-, 또는 $-OCH_2-$ 이고;

Y는 

또는 

이고, 여기서 각각의 V 및 T는 독립적으로 -CH- 또는 -N- 이고; 각각의 A_1 및 A_2는 독립적으로 C_{4-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합되고; 및 R_i은 H, 할로, 니트로, 시아노, 또는 아미노이고, 또는 C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로부터 선택된 부분(moiety)이며, 각각의 C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, 및 C_{2-6} 알키닐은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 및 각각의 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 모노-, 디- 또는

트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합된다.

청구항 2

제 1항에 있어서, X는 O인 화합물.

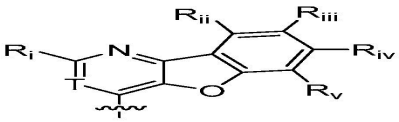
청구항 3

제 1항에 있어서, A는 CH 이고 W는 $-CH_2CH_2-$, $-OCH_2-$, $-SCH_2-$, 또는 $-SOCH_2-$ 인 화합물.

청구항 4

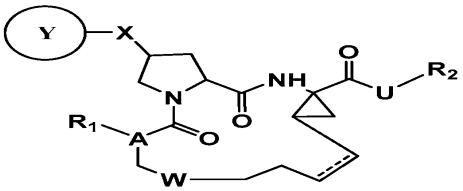
제 1항에 있어서, U는 $-NHSO_2-$ 인 화합물.

청구항 5

제 1항에 있어서, Y는  이고, 여기서 T는 CH 또는 N 이고 각 R_i, R_{ii}, R_{iii}, R_{iv}, 및 R_v는 독립적으로 H, 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, 또는 C_{2-6} 알키닐이고, 또는 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로부터 선택된 부분이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합된 것을 특징으로 하는 화합물.

청구항 6

하기 화학식의 화합물:



여기서, R_1은 -H, -OH, C_{1-6} 알킬, C_{1-6} 알콕실, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 헤테로아릴, 또는 -Z-R 이고; 여기서 R은 H, 또는 C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며; 및 Z은 -C(O)-, -C(O)O-, -C(O)C(O)O-, -C(O)C(O)NH-, -C(O)NR'-, -OC(S)-, -C(S)NR'-, 또는 -C(NH)O- 이고, R'는 H, C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴이고;

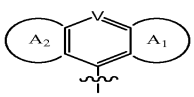
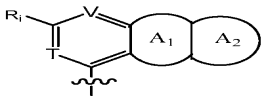
R_2는 H, 또는 C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며;

A는 CH 또는 N 이고;

U는 -O-, -NH-, -NH(CO)-, -NHS(O)-, 또는 $-NHSO_2-$ 이고;

W는 $-(CH_2)_m-$, $-NH(CH_2)_n-$, $-(CH_2)_nNH-$, $-O(CH_2)_n-$, $-(CH_2)_nO-$, $-S(CH_2)_n-$, $-(CH_2)_nS-$, -S(O)-, $-SO(CH_2)_n-$, $-(CH_2)_nS(O)-$, $-SO_2(CH_2)_n-$, 또는 $-(CH_2)_nSO_2-$ 이고, m은 1, 2, 또는 3 이고 n은 0, 1, 또는 2 이고;

X는 -O-, -S-, -NH-, 또는 $-OCH_2-$ 이고;

Y는  또는  이고, 여기서 각각의 V 및 T는 독립적으로 -CH- 또는 -N- 이고; 각각의 A_1 및 A_2는 독립적으로 C_{4-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합되고; 및 R_i은 H, 할로, 니트로, 시아노, 또는 아미노이고, 또는 C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로부터 선택된 부분(moiety)이며, 각각의 C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, 및 C_{2-6} 알키닐은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 및 각각의 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합되고; 및

---는 단일 결합 또는 이중 결합이다.

청구항 7

제 6항에 있어서, X는 O인 화합물.

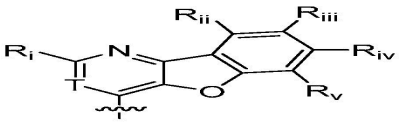
청구항 8

제 6항에 있어서, W는 $-CH_2CH_2-$, $-OCH_2-$, $-SCH_2-$, 또는 $-SOCH_2-$ 이고; 및 ---는 이중 결합인 화합물.

청구항 9

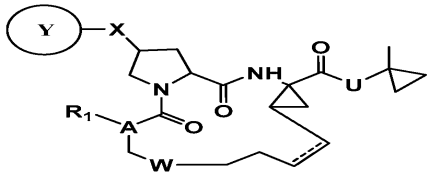
제 6항에 있어서, U는 $-NHSO_2-$ 인 화합물.

청구항 10

제 6항에 있어서, Y는  이고, 여기서 T는 CH 또는 N 이고 각 R_i, R_{ii}, R_{iii}, R_{iv}, 및 R_v는 독립적으로 H, 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, 또는 C_{2-6} 알키닐이고, 또는 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로부터 선택된 부분이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합된 것을 특징으로 하는 화합물.

청구항 11

하기 화학식의 화합물:



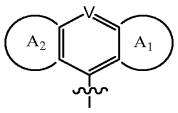
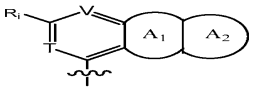
여기서, R_1은 -H, -OH, C_{1-6} 알킬, C_{1-6} 알콕실, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 헤테로아릴, -Z-R, 또는 -NH-Z-R 이고; 여기서 R은 H, 또는 C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며; 및 Z은 -C(O)-, -C(O)O-, -C(O)C(O)O-, -C(O)C(O)NH-, -C(O)NR'-, -OC(S)-, - C(S)NR'-, 또는 -C(NH)O- 이고, R'는 H, C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴이고;

A는 N 또는 CH 이고;

U는 -O-, -NH-, -NH(CO)-, -NHS(O)-, 또는 $-NHSO_2-$ 이고;

W는 $-(CH_2)_m-$, $-NH(CH_2)_n-$, $-(CH_2)_nNH-$, $-O(CH_2)_n-$, $-(CH_2)_nO-$, $-S(CH_2)_n-$, $-(CH_2)_nS-$, -S(O)-, $-SO(CH_2)_n-$, $-(CH_2)_nS(O)-$, $-SO_2(CH_2)_n-$, 또는 $-(CH_2)_nSO_2-$ 이고, m은 1, 2, 또는 3 이고 n은 0, 1, 또는 2 이고;

X는 -O-, -S-, -NH-, 또는 $-OCH_2-$ 이고;

Y는  또는  이고, 여기서 각각의 V 및 T는 독립적으로 -CH- 또는 -N- 이고; 각각의 A_1 및 A_2는 독립적으로 C_{4-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합되고; 및 R_i은 H, 할로, 니트로, 시아노, 또는 아미노이고, 또는 C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로부터 선택된 부분(moiety)이며, 각각의 C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, 및 C_{2-6} 알키닐은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 및 각각의 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합되고; 및

---는 단일 결합 또는 이중 결합이다.

청구항 12

제 11항에 있어서, X는 O인 화합물.

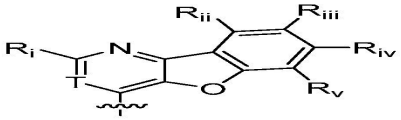
청구항 13

제 11항에 있어서, A는 CH 이고; W는 $-CH_2CH_2-$, $-OCH_2-$, $-SCH_2-$, 또는 $-SOCH_2-$ 이고; 및 ===는 이중 결합인 화합물.

청구항 14

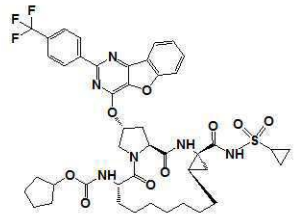
제 11항에 있어서, U는 $-NHSO_2-$ 인 화합물.

청구항 15

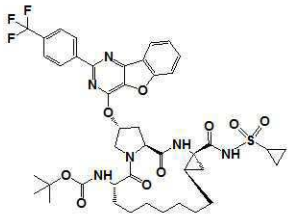
제 11항에 있어서, Y는  이고, 여기서 T는 CH 또는 N 이고 각 R_i, R_{ii}, R_{iii}, R_{iv}, 및 R_v는 독립적으로 H, 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, 또는 C_{2-6} 알키닐이고, 또는 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로부터 선택된 부분이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합된 것을 특징으로 하는 화합물.

청구항 16

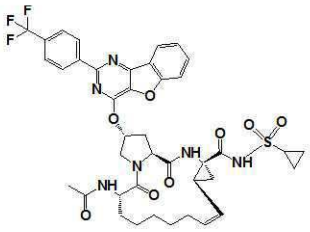
하기 화합물(compound) 1~281 중 하나인 화합물:



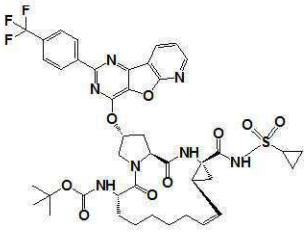
화합물 1



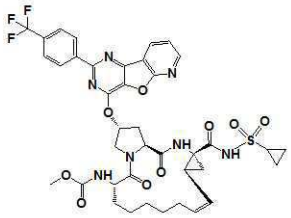
화합물 2



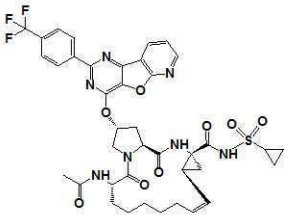
화합물 3



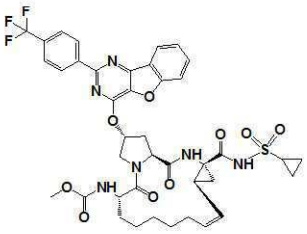
화합물 4



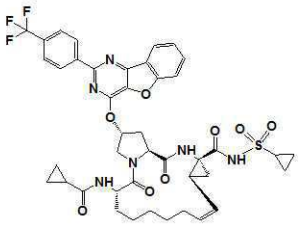
화합물 5



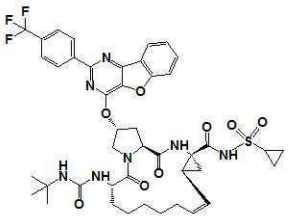
화합물 6



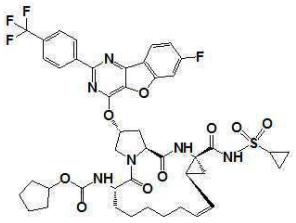
화합물 7



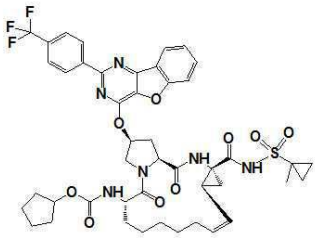
화합물 8



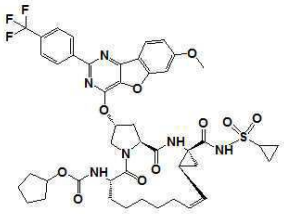
화합물 9



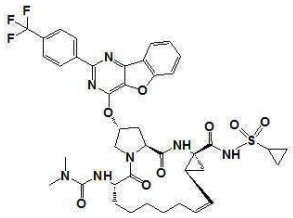
화합물 10



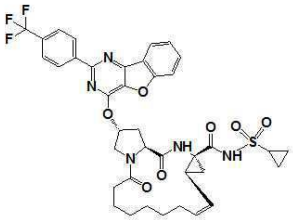
화합물 11



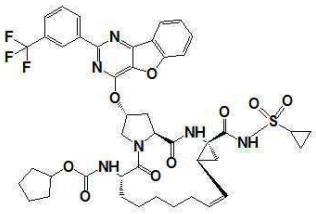
화합물 12



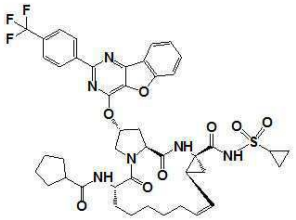
화합물 13



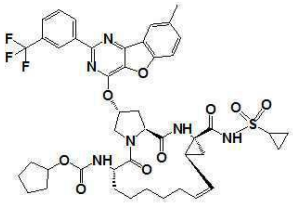
화합물 14



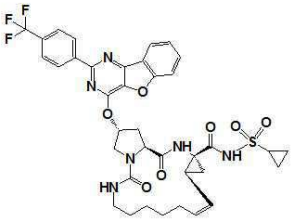
화합물 15



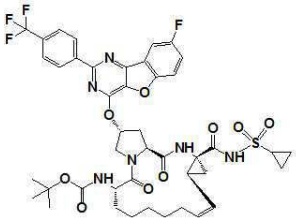
화합물 16



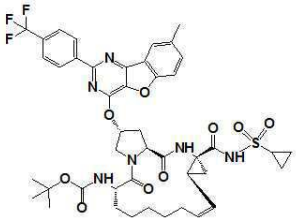
화합물 17



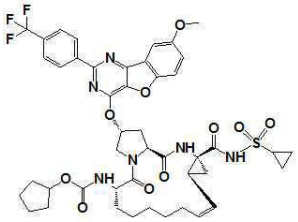
화합물 18



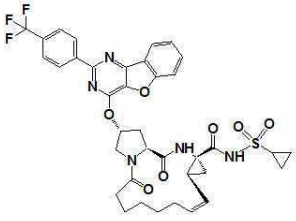
화합물 19



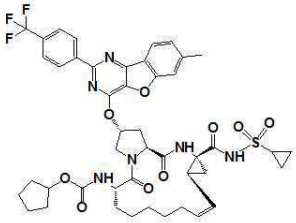
화합물 20



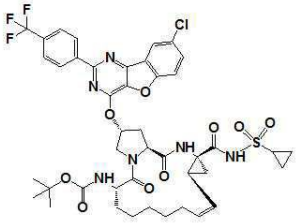
화합물 21



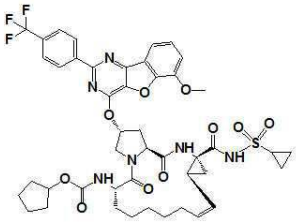
화합물 22



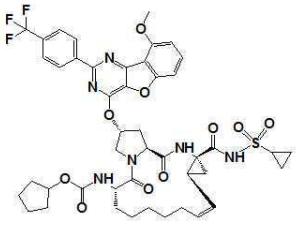
화합물 23



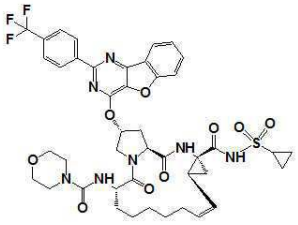
화합물 24



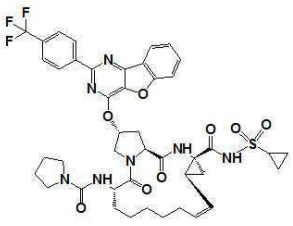
화합물 25



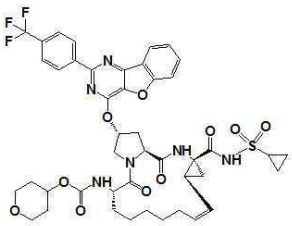
화합물 26



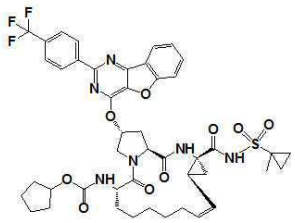
화합물 27



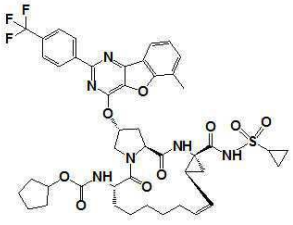
화합물 28



화합물 29



화합물 30



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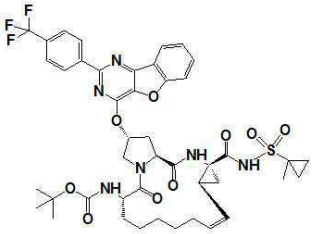

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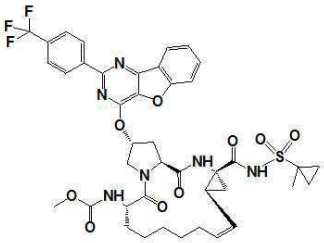

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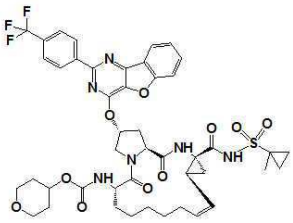

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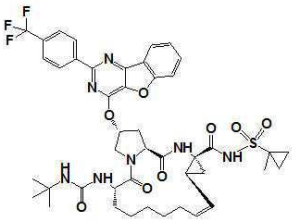

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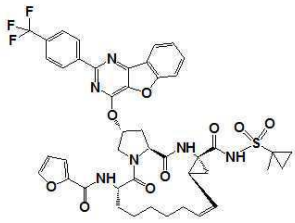

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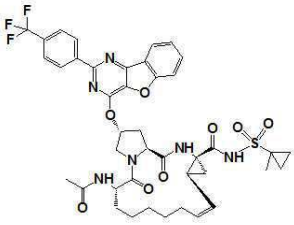

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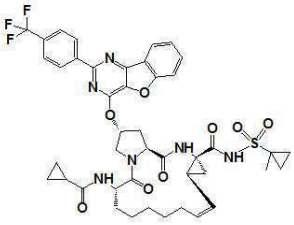

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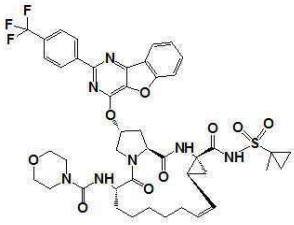

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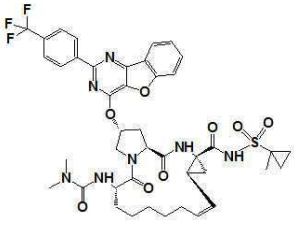

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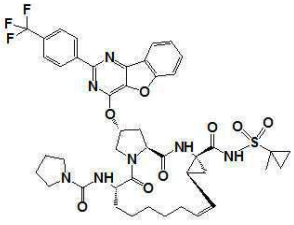

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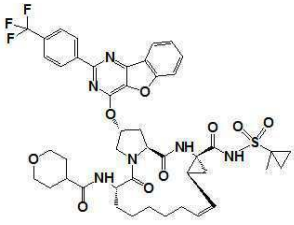

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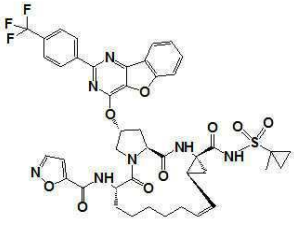

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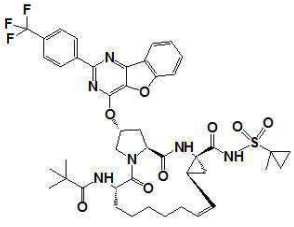

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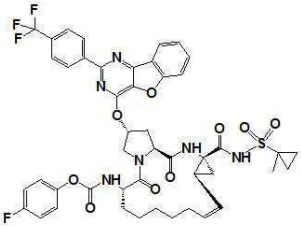

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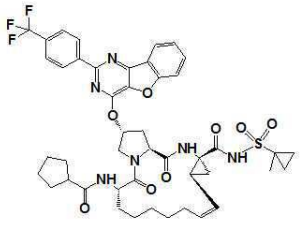

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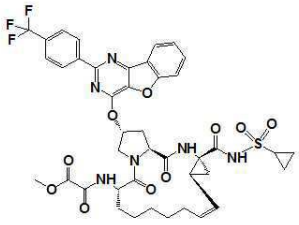

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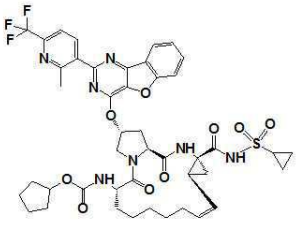

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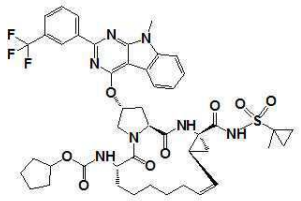

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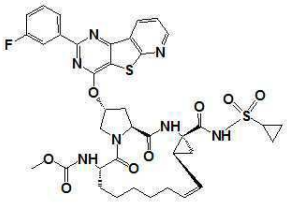

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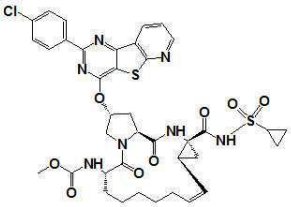

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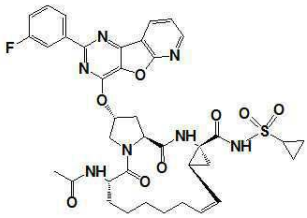

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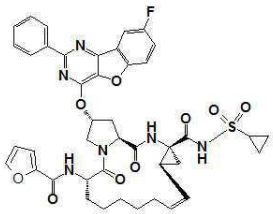

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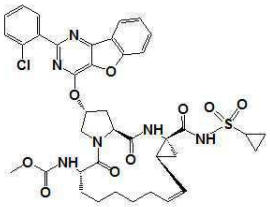

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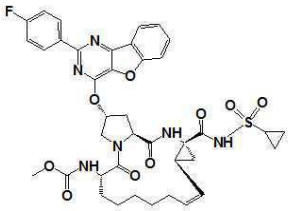

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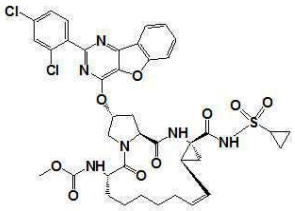

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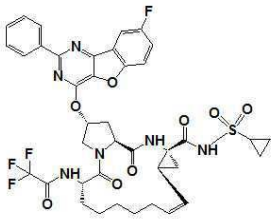

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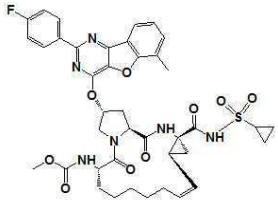

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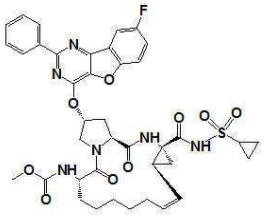

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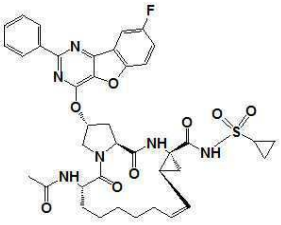

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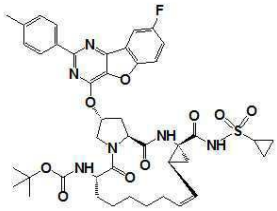

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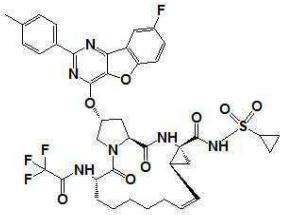
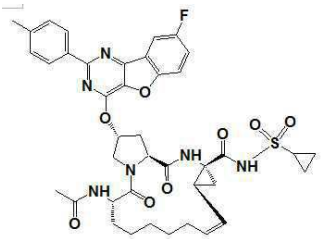


화합물 62

화합물 63



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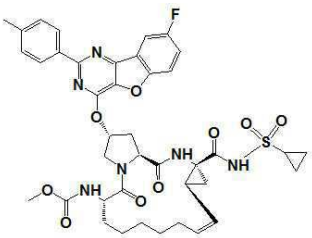

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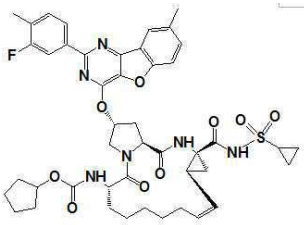

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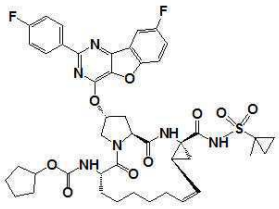

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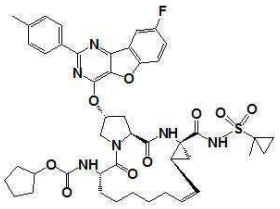

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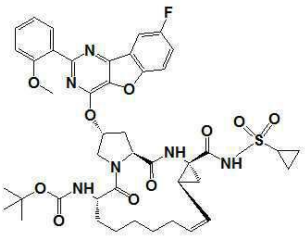

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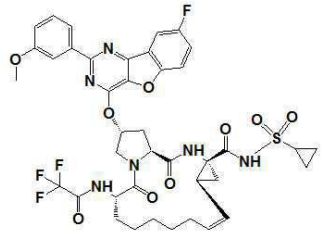

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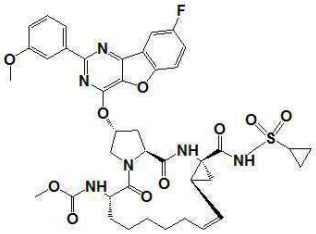

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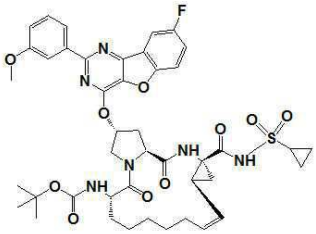

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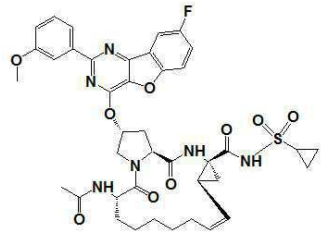

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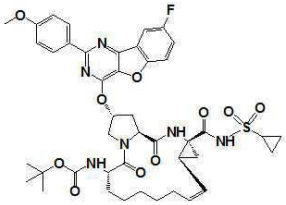

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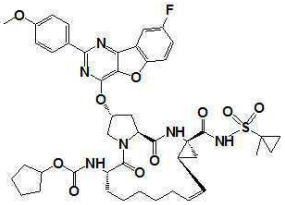

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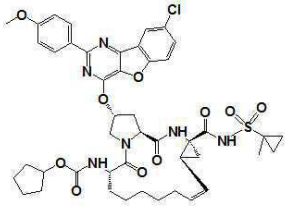

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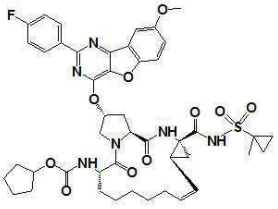

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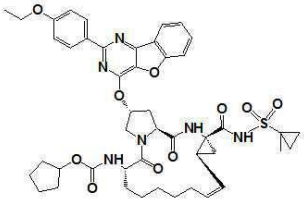

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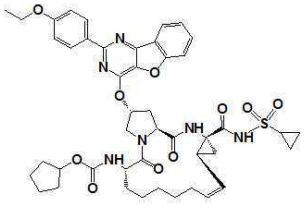

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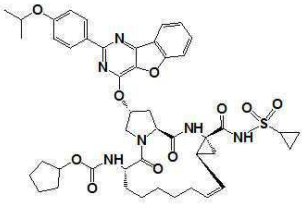

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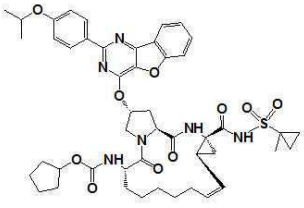

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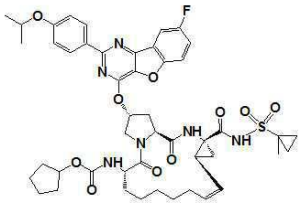

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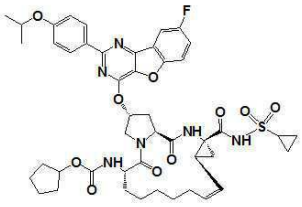

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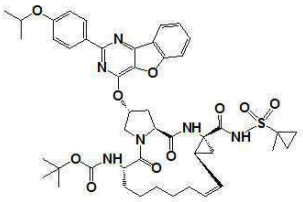

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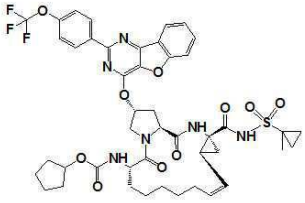

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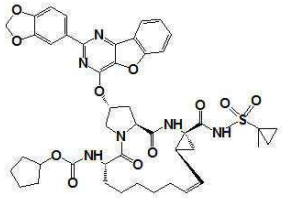

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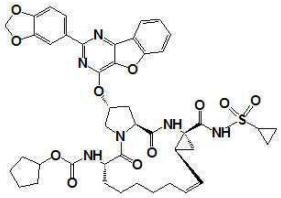

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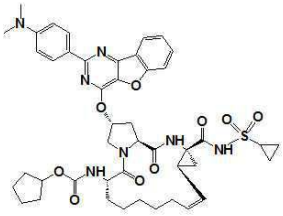

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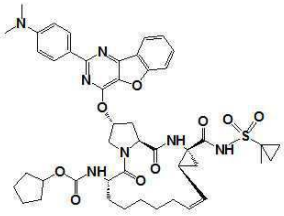
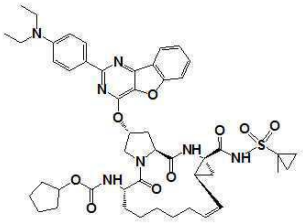


화합물 89



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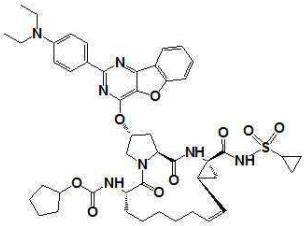

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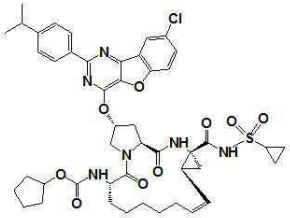

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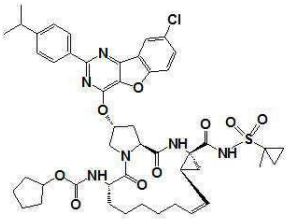

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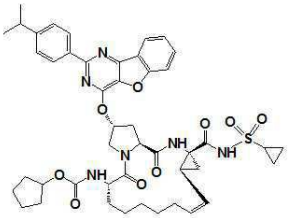

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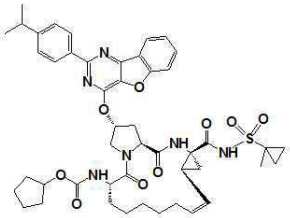

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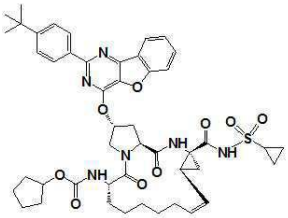

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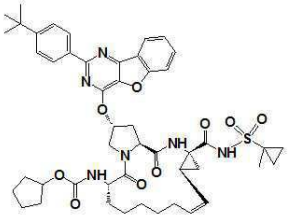

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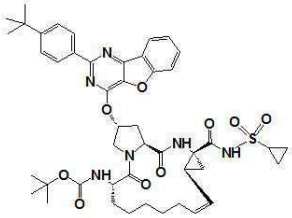

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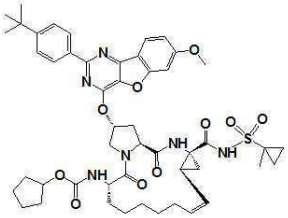

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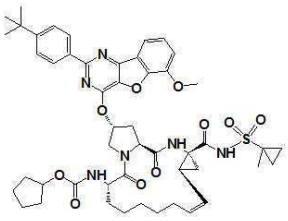

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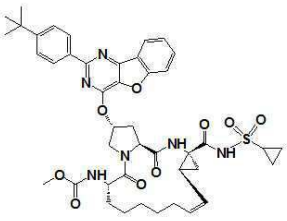

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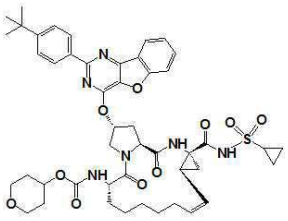

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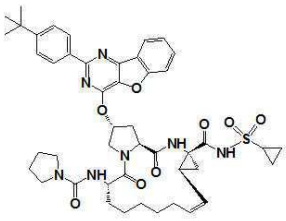

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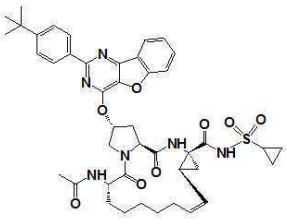

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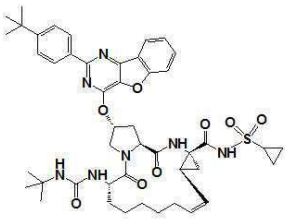

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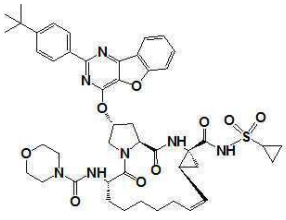

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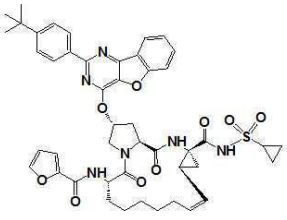

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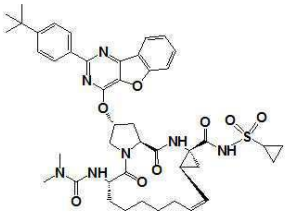

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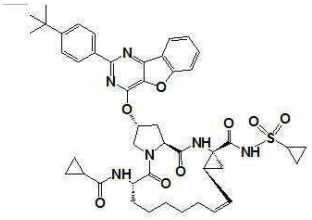

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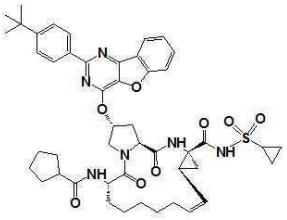

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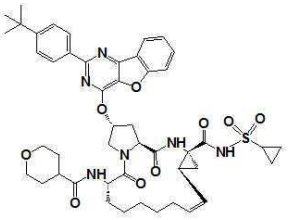

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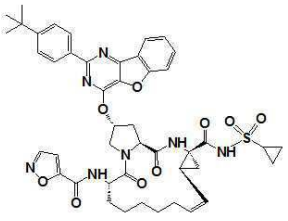

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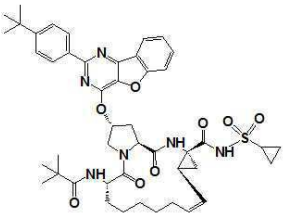

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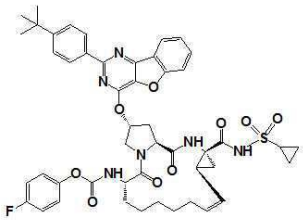

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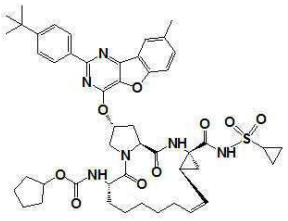

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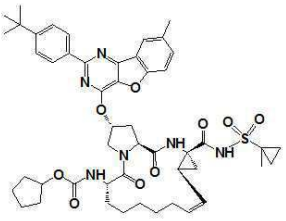

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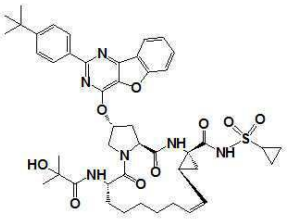

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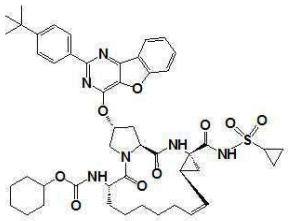

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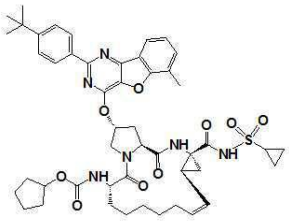

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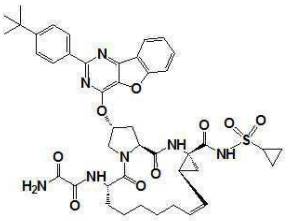

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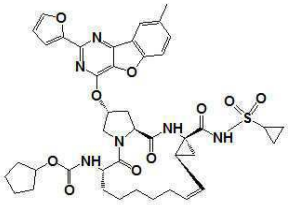

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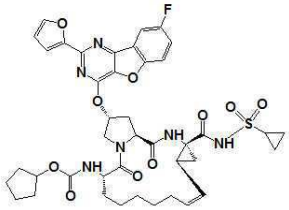

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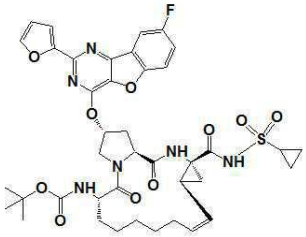

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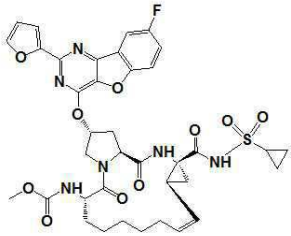

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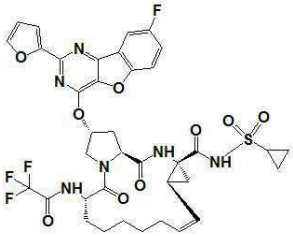

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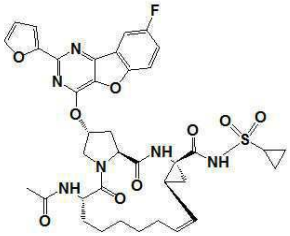

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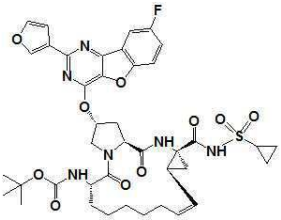

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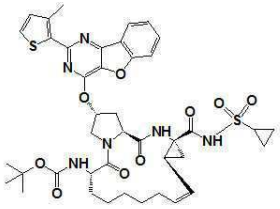

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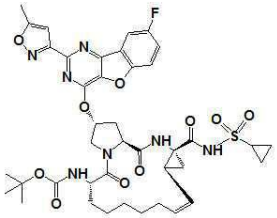

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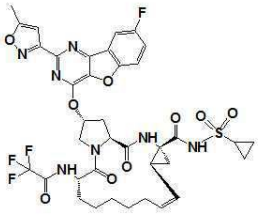

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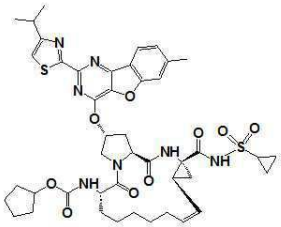

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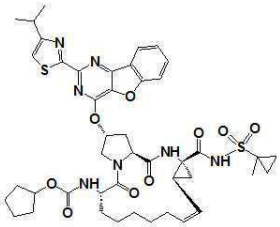

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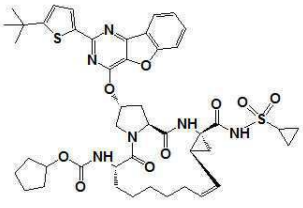

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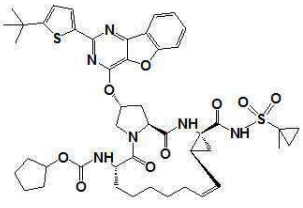

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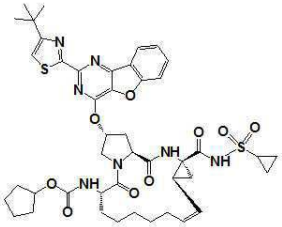

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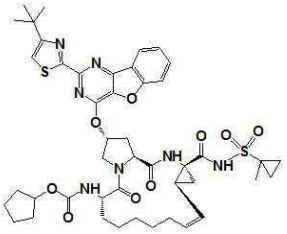

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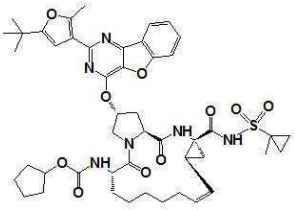

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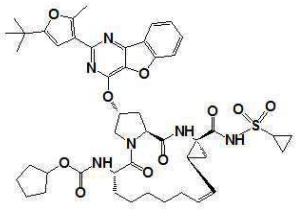

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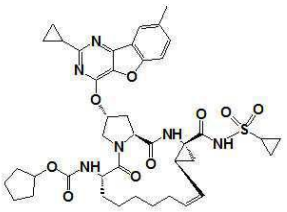

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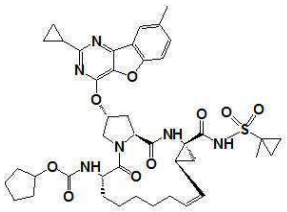

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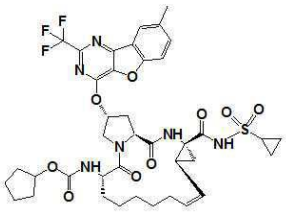

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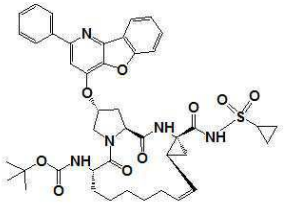

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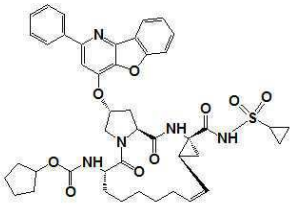

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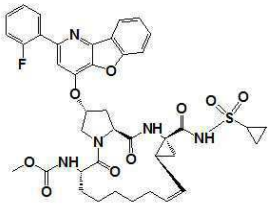

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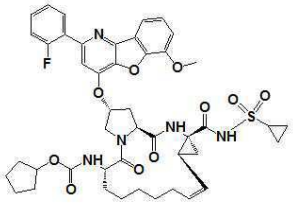

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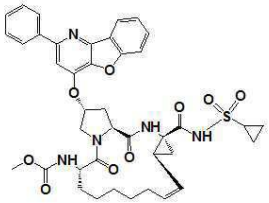

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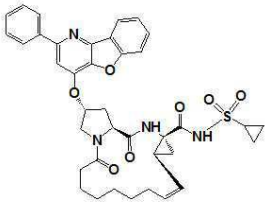
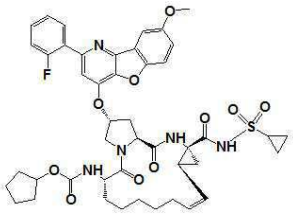
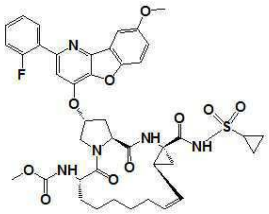


화합물 147



화합물 148



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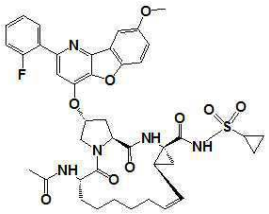

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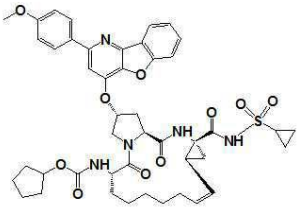

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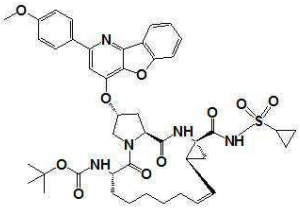

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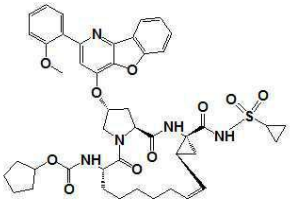

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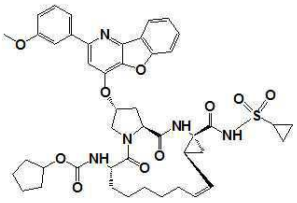

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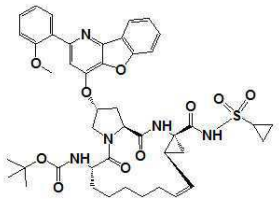

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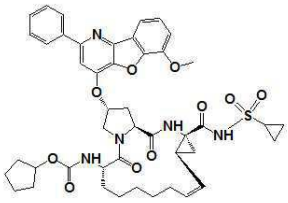

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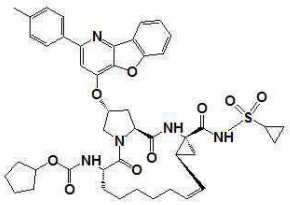

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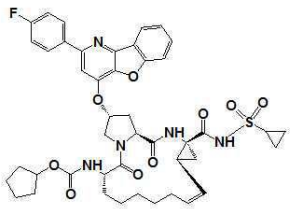

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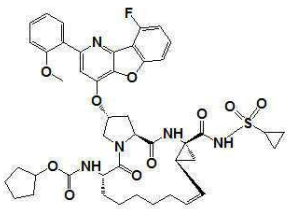

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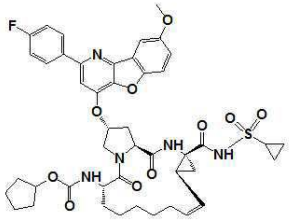

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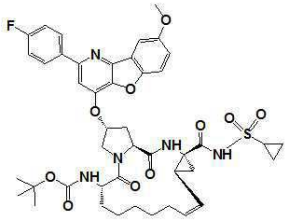

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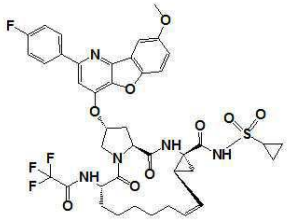

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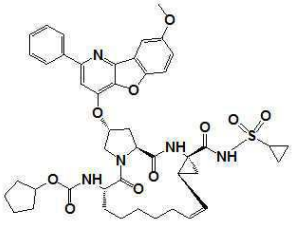

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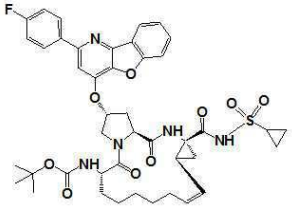

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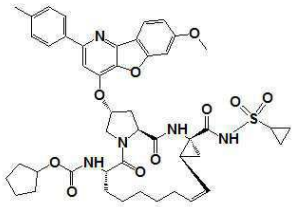

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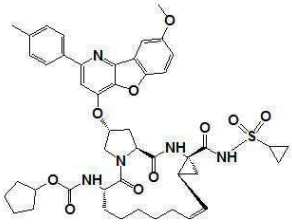

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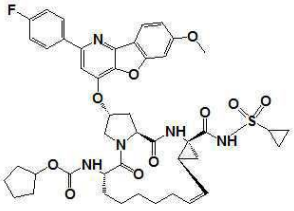

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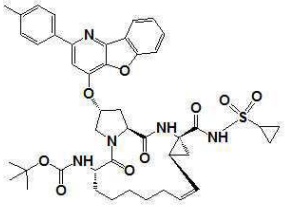

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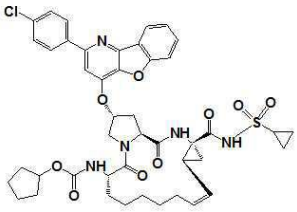

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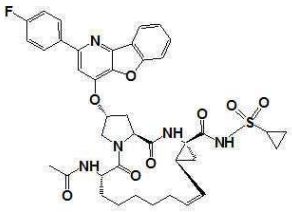

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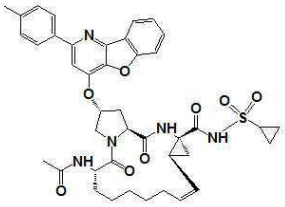

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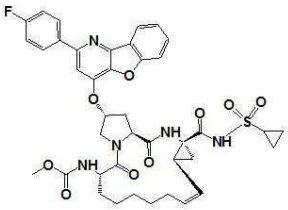

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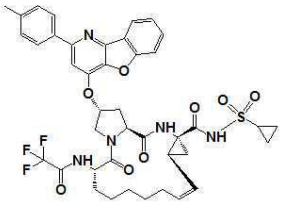

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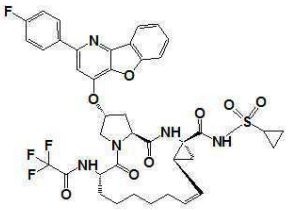

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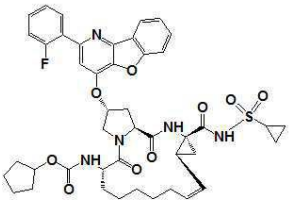

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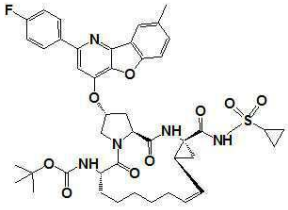

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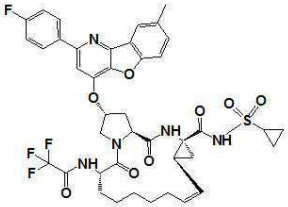

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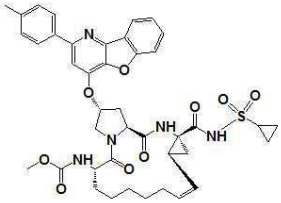

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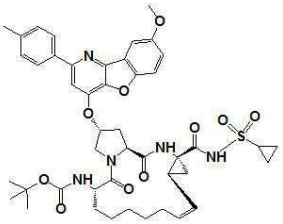

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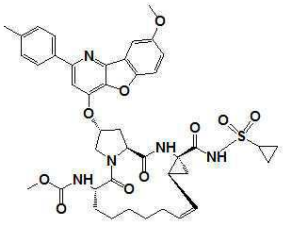

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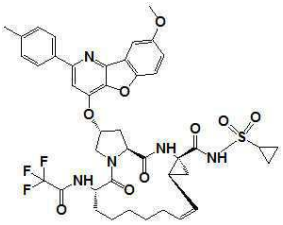

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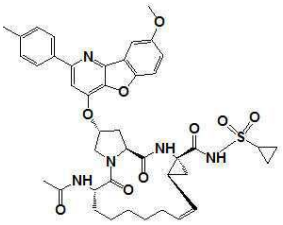

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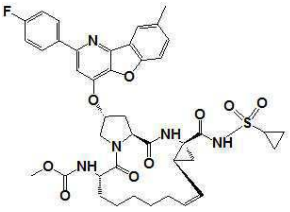

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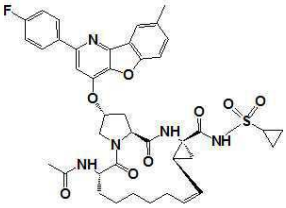

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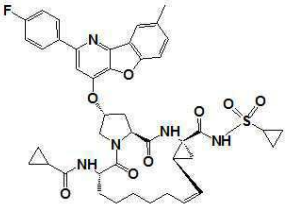

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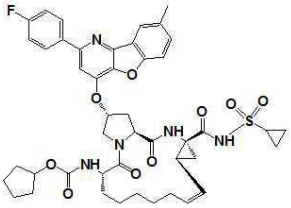

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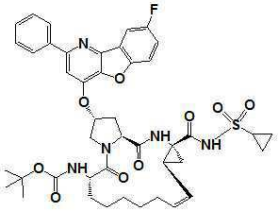

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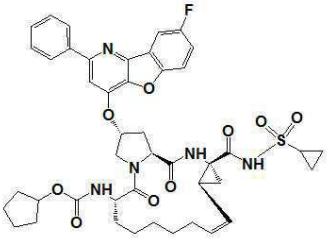

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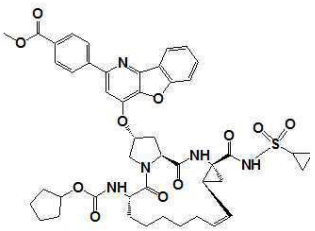

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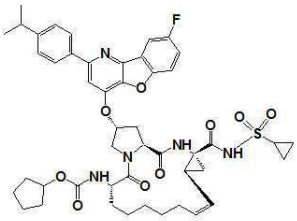
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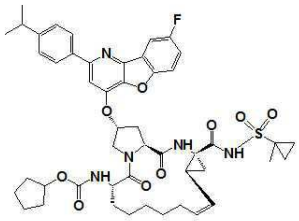
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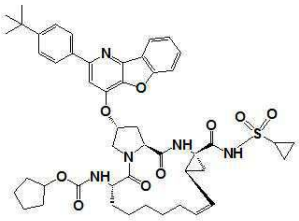
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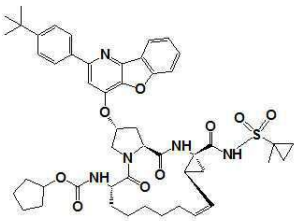
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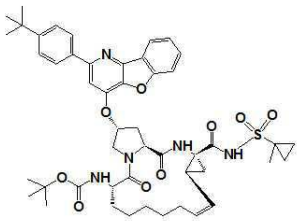
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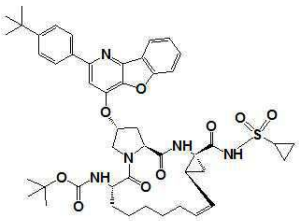
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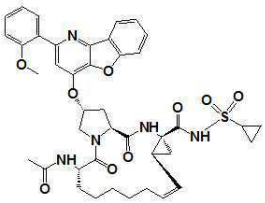
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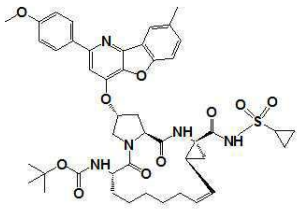
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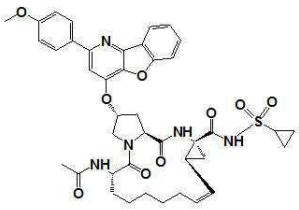
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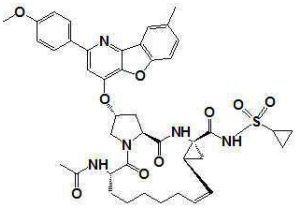
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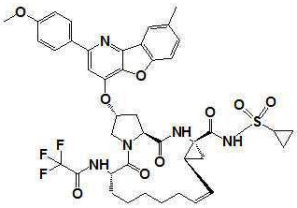
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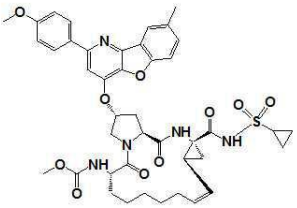
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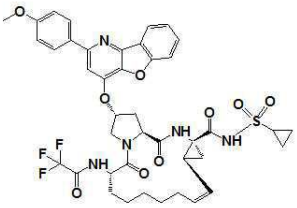
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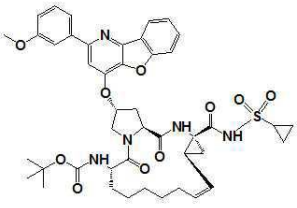
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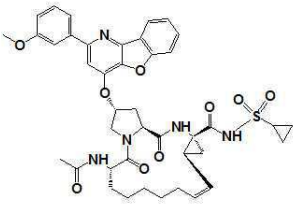
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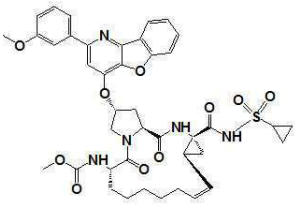
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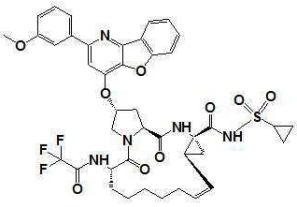
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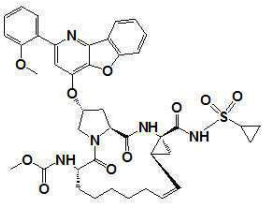
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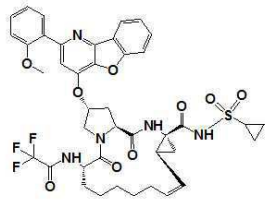

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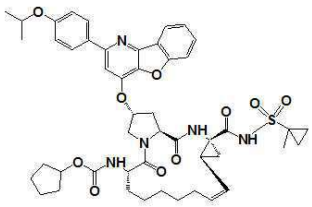
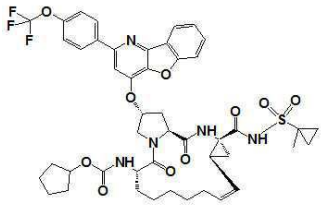


화합물 209

화합물 210



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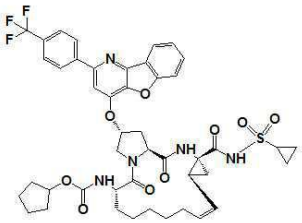

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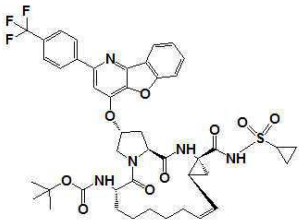

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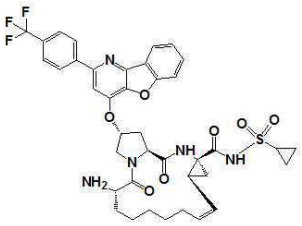

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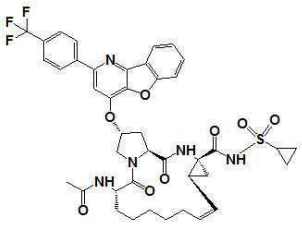

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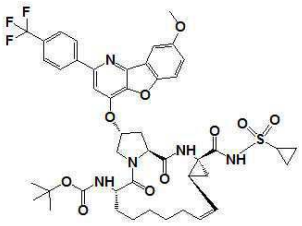

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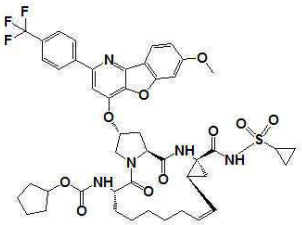

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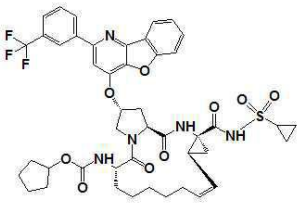

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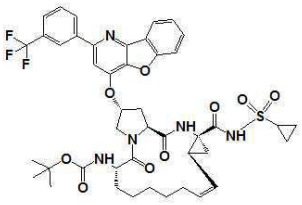

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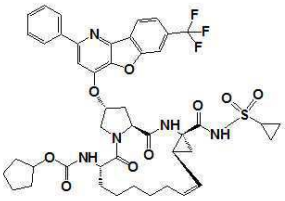

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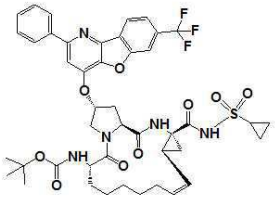

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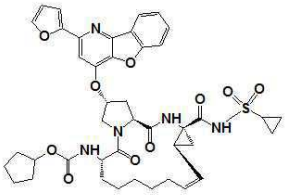

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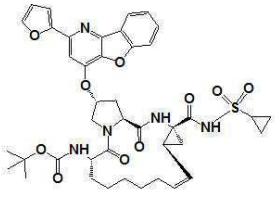

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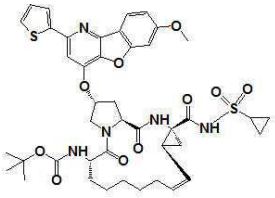

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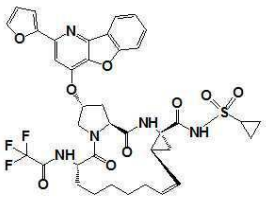
화합물 225



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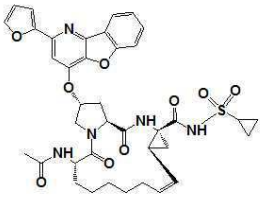

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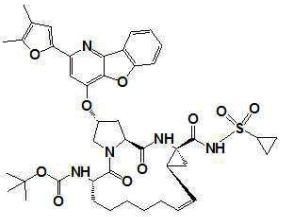

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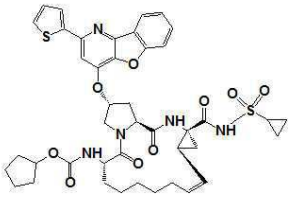

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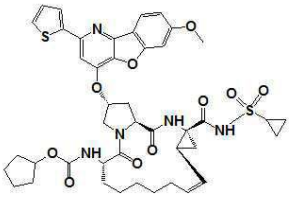

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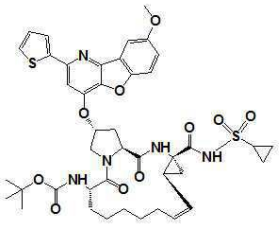

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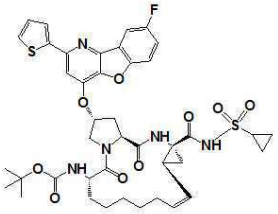

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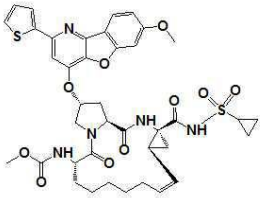

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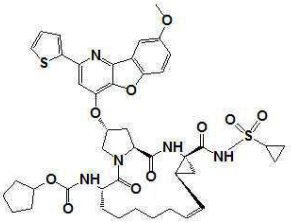

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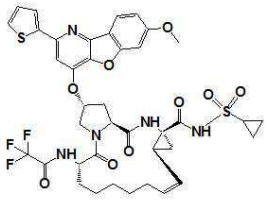

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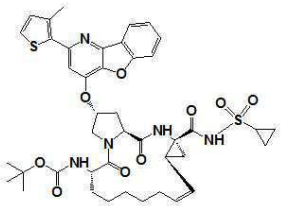

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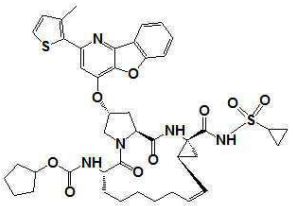

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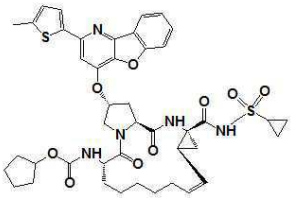

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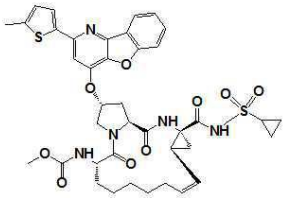

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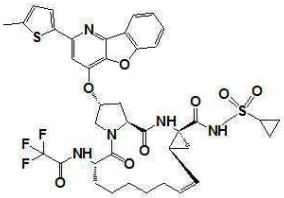

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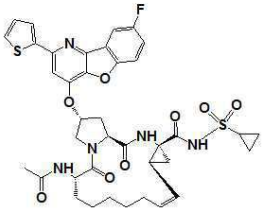

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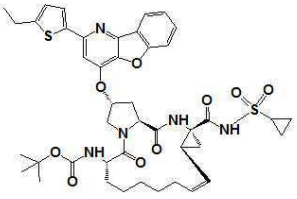

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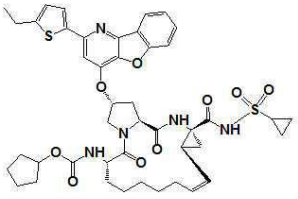

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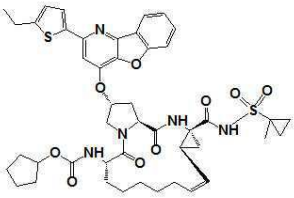

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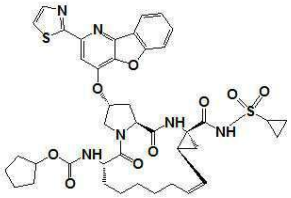

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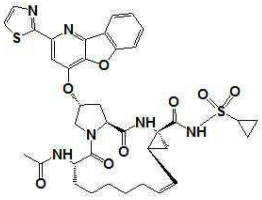

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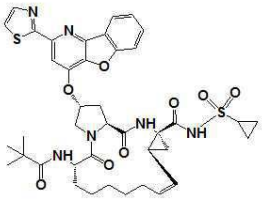

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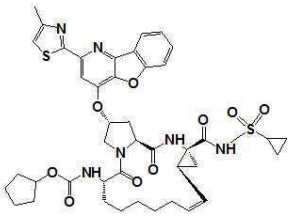

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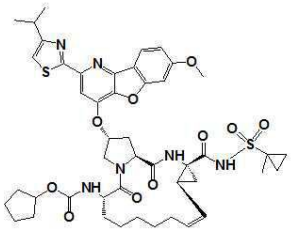

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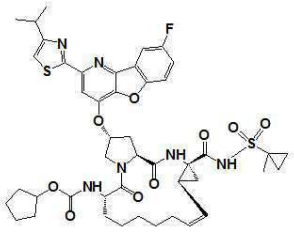

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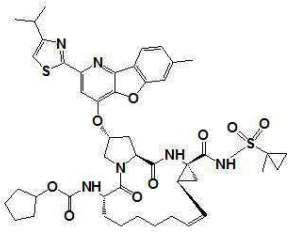

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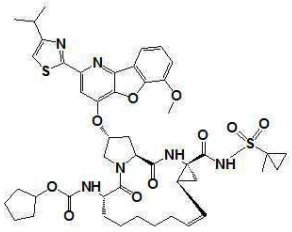

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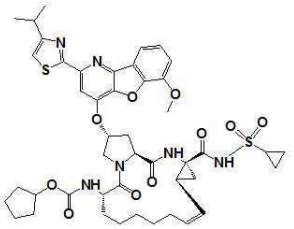

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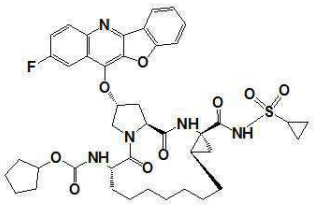

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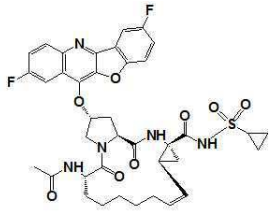

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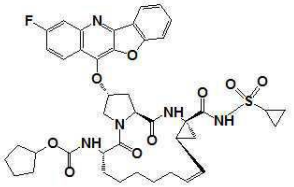

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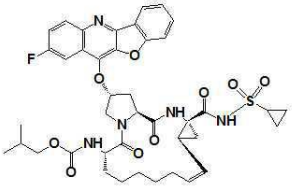

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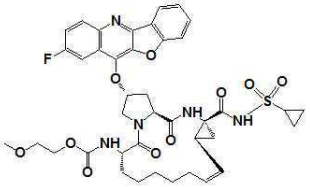

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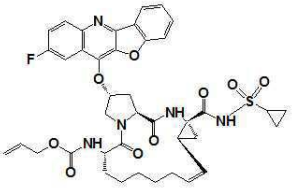

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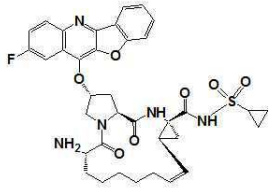
화합물 260



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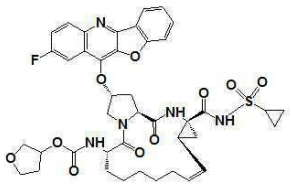

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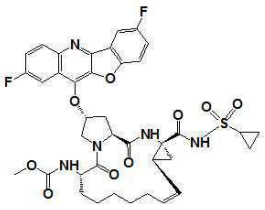

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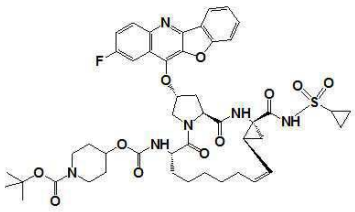

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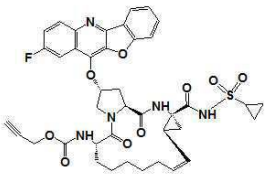

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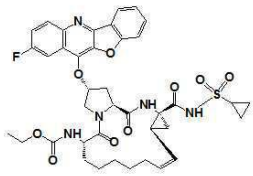
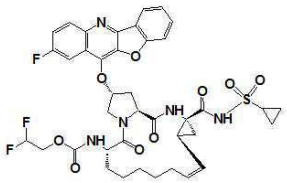
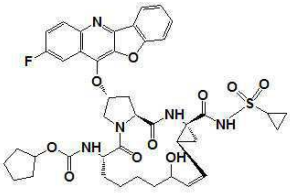


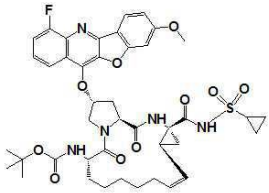
화합물 266



화합물 267



화합물 268



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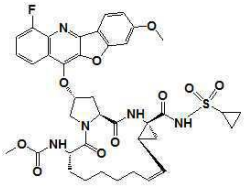

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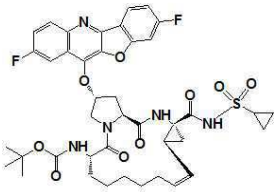

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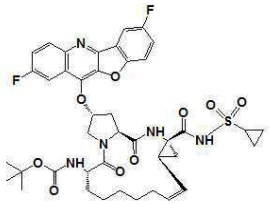
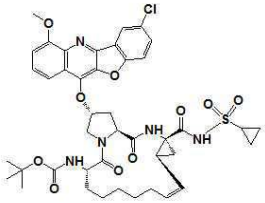


화합물 272



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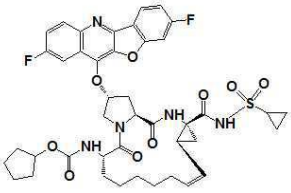

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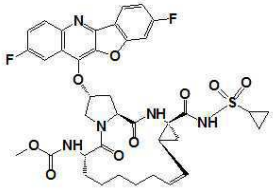
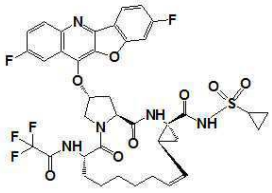
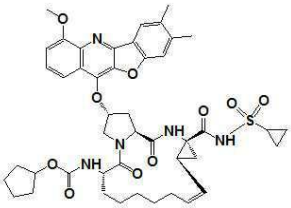


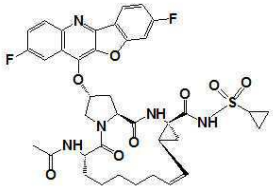
화합물 275



화합물 276



화합물 277



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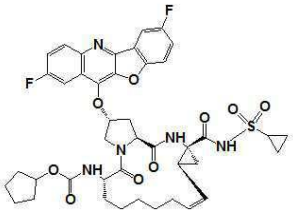
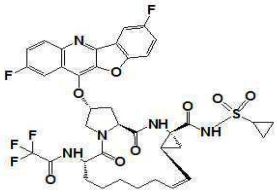
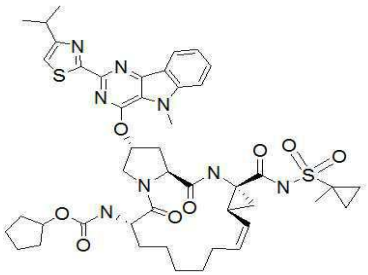


화합물 279



화합물 280



화합물 281.

청구항 17

삭제

청구항 18

제1항 내지 제16항 중 어느 한 항에 있어서, 상기 화합물은 C형 간염 바이러스 치료를 위한 것을 특징으로 하는, 화합물.

청구항 19

제 18항에 있어서, 화합물은 치료를 필요로 하는 피험자에게 경구 투여되는 것을 특징으로 하는 화합물.

청구항 20

제 18항에 있어서, 화합물은 하루에 한번 투여되는 것을 특징으로 하는 화합물.

청구항 21

제1항 내지 제16항 중 어느 한 항에 있어서, 상기 화합물은 C형 간염 바이러스 치료를 위한 약제의 제조에 사용하기 위한 것을 특징으로 하는, 화합물.

발명의 설명

기 술 분 야

[0001] 본 발명은 ＨＣＶ 프로테아제 저해제에 관한 것이다.

배 경 기 술

[0002] (+)-센스 단일-가닥 RNA 바이러스인 C 형 간염 바이러스(hepatitis C virus, HCV)는 비-A 형 간염, 비-B 형 간염의 대부분 주요 원인이 되는 물질이다. HCV에 의한 감염은 강력한 인간 건강 문제이다 (참조, WO 05/007681; WO 89/04669; EP 381216; Alberti et al., *J. Hepatology*, 31 (Suppl. 1), 17-24 (1999); Alter, *J. Hepatology*, 31 (Suppl. 1), 88-91 (1999); and Lavanchy, *J. Viral Hepatitis*, 6, 35-47 (1999)).

[0003] HCV 감염에 의한 간염은 바이러스가 자연 면역 반응을 빠르게 변형하고 피할 수 있기 때문에 치료하기가 어렵다. 현재 사용가능한 유일한 항-HCV 치료는 인터페론-α, 인터페론-α/리바비린 조합, 및 페그(pegylated) 인터페론-α 이다. 그러나, 인터페론-α 또는 인터페론-α/리바비린 조합에 대한 지속적인 반응 속도는 <50%로 발견되었는데, 환자는 이러한 치료제의 부작용으로부터 크게 고통받는다 (참조, Walker, *DDT*, 4, 518-529 (1999); Weiland, *FEMS Microbial. Rev.*, 14, 279-288 (1994); 및 WO 02/18369). 따라서, 더 효과적이고 잘 견디는 치료 약물을 개발하기 위한 필요성이 남아 있다.

[0004] 바이러스 복제에 필요한 HCV 프로테아제는 약 3000개의 아미노산을 함유한다. 이것은 뉴클레오캡시드 단백질 (C), 표면 단백질 (envelope proteins) (E1 및 E2), 및 여러 비-구조적 단백질 (NS2, NS3, NS4a, NS5a 및 NS5b)을 포함한다.

[0005] NS3 단백질은 세린 프로테아제 활성을 지니고, 바이러스성 복제 및 감염성에 필수적인 것으로 간주된다. NS3 프로테아제의 본성은 황열병 바이러스 NS3 프로테아제의 돌연변이가 바이러스 감염성을 감소시켰다는 사실에서 추론되었다(참조, Chamber et al., *Proc. Natl. Acad. Sci.* USA 87, 8898-8902 (1990)). 또한, HCV NS3 프로테아

제의 활성 사이트에서 돌연변이가 침팬지 모델에서 HCV 감염을 완전히 저해하였다는 것을 설명하였다 (참조, Rice et al., *J. Virol.* 74 (4) 2046-51 (2000)). 또한, HCV NS3 프로테아제가 NS3/NS4a, NS4a/NS4b, NS4b/NS5a, NS5a/NS5b 접합에서 단백질가수분해(proteolysis)를 용이하게 하는 것을 발견하였으며, 따라서 바이러스 복제 동안 4개의 바이러스 단백질을 생성하는데 책임이 있다(참조, US 2003/0207861). 그 결과, HCV NS3 프로테아제 효소는 HCV 감염 치료에 매력적인 표적이다. 잠재적인 NS3 HCV 프로테아제 저해제는 WO 02/18369, WO 00/09558, WO 00/09543, WO 99/64442, WO 99/07733, WO 99/07734, WO 99/50230, WO 98/46630, WO 98/17679, WO 97/43310, US 5,990,276, Dunsdon et al., *Biorg. Med. Chem. Lett.* 10, 1571-1579 (2000); Llinas-Brunet et al., *Biorg. Med. Chem. Lett.* 10, 2267-2270 (2000); and S. LaPlante et al., Biorg. Med. Chem. Lett. 10, 2271-2274 (2000)에서 얻을 수 있다.

발명의 내용

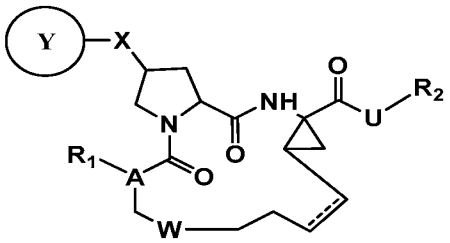
해결하려는 과제

[0006] **개요**

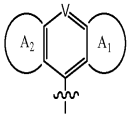
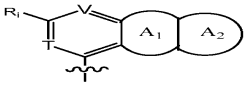
[0007] 본 발명은 특정 마크로사이클릭 화합물이 NS3-4A 프로테아제의 활성을 차단하고, HCV RNA 수준을 감소시키며, 기타 저해제에 저항하는 HCV 프로테아제 돌연변이체를 저해하고, 혈관계에서 지속성 반감기를 나타내는 예상치 못한 발견을 토대로 하고 있다.

[0008] 하나의 양상에서, 본 발명은 화학식 (I)의 화합물에 관한 것이다:

[0009] [화학식 I]

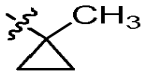
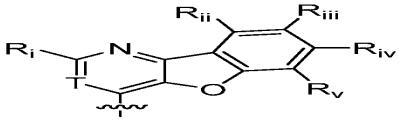


[0010]

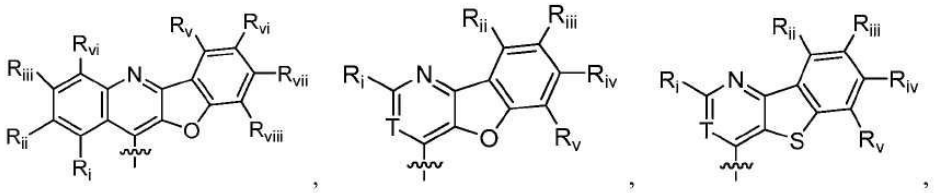
[0011] 여기서, R_1은 -H, -OH, C_{1-6} 알킬, C_{1-6} 알콕실, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 헤테로아릴, -Z-R, 또는 -NH-Z-R 이고; 여기서 R은 H, 또는 C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며; 및 Z은 -C(O)-, -C(O)O-, -C(O)C(O)O-, -C(O)C(O)NH-, -C(O)NR'-, -OC(S)-, - C(S)NR'-, 또는 -C(NH)O- 이고, R'는 H, C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴이고; R_2는 H, 또는 C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며; A는 N 또는 CH 이고; U는 -O-, -NH-, -NH(CO)-, -NHS(O)-, 또는 $-NHSO_2-$ 이고; W는 $-(CH_2)_m-$, $-NH(CH_2)_n-$, $-(CH_2)_nNH-$, $-O(CH_2)_n-$, $-(CH_2)_nO-$, $-S(CH_2)_n-$, $-(CH_2)_nS-$, -S(O)-, $-SO(CH_2)_n-$, $-(CH_2)_nS(O)-$, $-SO_2(CH_2)_n-$, 또는 $-(CH_2)_nSO_2-$ 이고, m은 1, 2, 또는 3 이고 n은 0, 1, 또는 2 이고; X는 -O-, -S-, -NH-, 또는 $-OCH_2-$ 이고; Y는  또는  이고, 여기서 각각의 V 및 T는 독립적으로 -CH- 또는 -N- 이고; 각각의 A_1 및 A_2는 독립적으로 C_{4-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로 이루어진 군으로부터 선택된 부분(moiety)이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴

로 융합되고; 및 R_i은 H, 할로, 니트로, 시아노, 또는 아미노이고, 또는 C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로부터 선택된 부분(moiety)이며, 각각의 C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, 및 C_{2-6} 알키닐은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 및 각각의 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합되고; 및 ---는 단일 결합 또는 이중 결합이다.

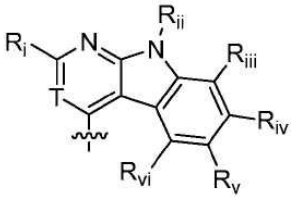
[0012] 변수 U, W, X, 및 Z에 할당된 기는 이가(bi-valent) 이다. 각각의 기는 변수가 화학식에 표시된 것과 같이 동일한 방향으로 위에 표시된다. 예를 들어, 화학식에 나타낸 대로, 변수 U에 할당된 기 -NHSO-는 C=O 및 R_2 사이에 둔다. 이 -NHS(O)- 기 내 N 원자는 C=O에 결합되고, S 원자는 R_2에 결합된다. 다른 예로서, 변수 Z에 할당된 기 -C(O)O-는 NH 및 R 사이에 둔다 (즉, -NH-Z-R). -C(O)O- 내 C 원자는 NH에 결합되고 O 원자는 R에 결합된다.

[0013] 화학식 (I)과 관련하여, 화합물의 부분집합(subset)은 R_1이 -NH-Z-R 이고, 여기서 Z은 -C(O)-, -C(O)O-, -C(O)C(O)O-, 또는 -C(O)C(O)NH- 이고; R_2는  또는  이고; X는 O 이고; A는 CH 이고; W는 $-CH_2CH_2-$, $-OCH_2-$, $-SCH_2-$, 또는 $-SOCH_2-$ 이고; U는 $-NHSO_2-$ 이고; ---는 이중 결합이고; 또는 Y는  이고, 여기서 T는 CH 또는 N 이고; R_i은 임의로 할로, 아미노, C_{1-6} 알킬, 또는 C_{1-6} 알콕실로 치환된 페닐 또는 티아졸릴이고; 및 각 R_i, R_{ii}, R_{iii}, R_{iv}, 및 R_v는 독립적으로 H, 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, 또는 C_{2-6} 알키닐이며, 또는 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로부터 선택된 부분이며, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며, 또는 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합된다. R_1의 예는 -NH-C(O)O-t-Bu, -NH-C(O)O-시클로펜틸, 및 -NH-C(O)-푸릴인 것을 특징으로 한다.

[0014] 화합물의 다른 부분집합(subset)은 Y가



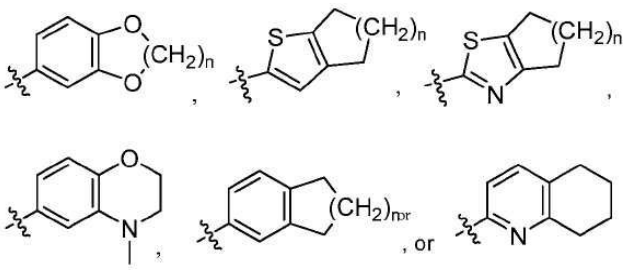
[0015]



[0016] 또는 이고,

[0017] 여기서, 각 R_i, R_{ii}, R_{iii}, R_{iv}, R_v, 및 R_{vi}은 독립적으로 H, 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴이며, 각 시클로알킬, 헤테로시클로알킬, 아릴, 및 헤테로아릴은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며; 및 임의로 C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴로 융합된 것을 특징으로 한다.

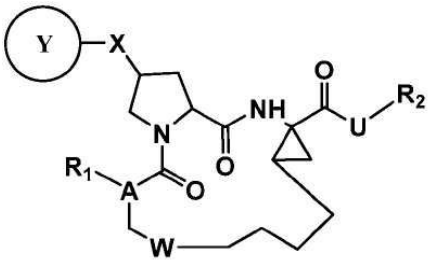
[0018] 상기 화합물에서, R_i는



[0019] 일 수 있으며,

[0020] 여기서 n은 1 또는 2 이다.

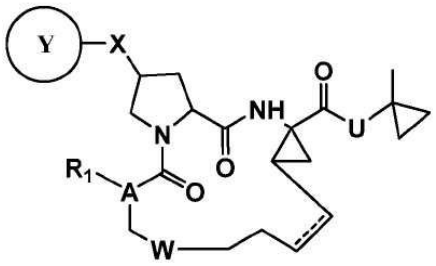
[0021] 하나의 실시예에서, 본 발명의 화합물은 하기 화학식을 갖는다:



[0022]

[0023] 여기서, R_1, R_2, A, U, W, X, 및 Y는 상기 정의된 바와 같다.

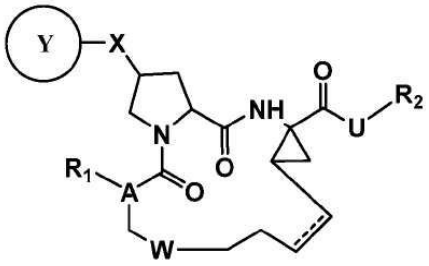
[0024] 다른 실시예에서, 본 발명의 화합물은 하기 화학식을 갖는다:



[0025]

[0026] 여기서, R_1, A, U, W, X, 및 Y는 상기 정의된 바와 같다.

[0027] 다른 실시예에서, 본 발명의 화합물은 하기 화학식을 갖는다:



[0028]

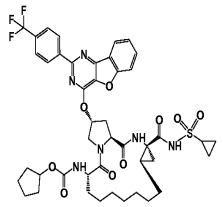
[0029] 여기서, R_1은 -H, -OH, C_{1-6} 알킬, C_{1-6} 알콕실, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 헤테로아릴, 또는 -Z-R 이고; 여기서 R은 H, 또는 C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 및 헤테로아릴로부터 선택된 부분이고, 이들 각각은 임의로 할로, 니트로, 시아노, 아미노, C_{1-6} 알킬, C_{1-6} 알콕실, C_{2-6} 알케닐, C_{2-6} 알키닐, 아릴, 또는 헤테로아릴로 모노-, 디- 또는 트리-치환되며; 및 Z는 -C(O)-, -C(O)O-, -C(O)C(O)O-, -C(O)C(O)NH-, -C(O)NR'-, -OC(S)-, - C(S)NR'-, 또는 -C(NH)O- 이며, R'는 H, C_{1-6} 알킬, C_{3-10} 시클로알킬, C_{1-10} 헤테로시클로알킬, 아릴, 또는 헤테로아릴이고; 및 R_2, A, U, W, X, 및 Y는 상기 정의된 바와 같다.

[0030] 용어 "알킬(alkyl)"은 $-CH_3$ 또는 $-CH(CH_3)_2$와 같은 포화, 선형 또는 분지 탄화수소 부분이다. 용어 "알콕시(alkoxy)"는 -O-(C_{1-6} 알킬) 라디칼을 나타낸다. 용어 "알케닐(alkenyl)"은 $-CH=CH-CH_3$와 같은 적어도 하나의 이중 결합을 함유하는 선형 또는 분지 탄화수소 부분을 나타낸다. 용어 "알키닐(alkynyl)"은 $-C\equiv C-CH_3$와 같은 적어도 하나의 삼중 결합을 함유하는 선형 또는 분지 탄화수소 부분을 나타낸다. 용어 "시클로알킬(cycloalkyl)"은 시클로헥실과 같은 포화, 고리형 탄화수소(cyclic harocarbon) 부분을 나타낸다. 용어 "시클로알케닐(cycloalkenyl)"은 시클로헥세닐과 같은 적어도 하나의 이중 결합을 함유하는 비방향족, 고리형 탄화수소 부분을 나타낸다. 용어 "헤테로시클로알킬(heterocycloalkyl)"은 4-테트라히드로피라닐과 같은 적어도 하나의 고리 헤테로원자(예를 들어, N, O, 또는 S)를 갖는 포화, 고리형 부분을 나타낸다. 용어 "헤테로시클로알케닐(heterocycloalkenyl)"은 피라닐과 같은 적어도 하나의 고리 헤테로원자(예를 들어, N, O, 또는 S) 및 적어도 하나의 고리 이중 결합을 갖는 비-방향족, 고리형 부분을 나타낸다. 용어 "아릴(aryl)"은 하나 이상의 방향족

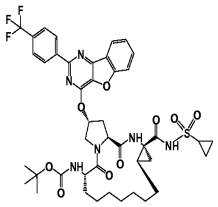
고리를 갖는 탄화수소 부분을 나타낸다. 아릴 부분의 예는 페닐 (Ph), 페닐렌, 나프틸, 나프틸렌, 피레닐, 안트릴, 및 페난트릴을 포함한다. 용어 "헤테로아릴(heteroaryl)"은 적어도 하나의 헤테로원자(예를 들어, N, O, 또는 S)를 함유하는 하나 이상의 방향족 고리를 갖는 탄화수소 부분을 나타낸다. 헤테로아릴 부분의 예는 푸릴, 푸릴렌(furylene), 플루오레닐(fluorenyl), 피롤릴, 티에닐, 옥사졸릴, 이미다졸릴, 티아졸릴, 피리딜, 피리미디닐, 퀴나졸리닐, 퀴놀릴, 이소퀴놀릴 및 인돌릴을 포함한다. 용어 "아미노(amino)"는 $-NH_2$, $-NH-(C_{1-6}$ 알킬), 또는 $-N(C_{1-6}$ 알킬$)_2$의 라디칼을 나타낸다.

[0031] 본 명세서에 언급된 알킬, 알케닐, 알키닐, 시클로알킬, 시클로알케닐, 헤테로시클로알킬, 헤테로시클로알케닐, 아릴, 및 헤테로아릴은 달리 명시되지 않는 한 치환 및 비치환 부분을 모두 포함한다. 시클로알킬, 시클로알케닐, 헤테로시클로알킬, 헤테로시클로알케닐, 아릴, 및 헤테로아릴에 있는 가능한 치환체는 C_1-C_{10} 알킬, C_2-C_{10} 알케닐, C_2-C_{10} 알키닐, C_3-C_{20} 시클로알킬, C_3-C_{20} 시클로알케닐, C_1-C_{20} 헤테로시클로알킬, C_1-C_{20} 헤테로시클로알케닐, C_1-C_{10} 알콕시, 아릴, 아릴옥시, 헤테로아릴, 헤테로아릴옥시, 아미노, C_1-C_{10} 알킬아미노, C_1-C_{20} 디알킬아미노, 아릴아미노, 디아릴아미노, C_1-C_{10} 알킬설폰아미노, 아릴설폰아미노, C_1-C_{10} 알킬이미노, 아릴이미노, C_1-C_{10} 알킬설폰이미노, 아릴설폰이미노, 히드록실, 할로, 티오, C_1-C_{10} 알킬티오, 아릴티오, C_1-C_{10} 알킬설포닐, 아릴설포닐, 아실아미노, 아미노아실, 아미노티오아실, 아미디노, 구아니딘, 우레이도(ureido), 시아노, 니트로, 니트로소, 아지도, 아실, 티오아실, 아실옥시, 카복실, 및 카복실릭 에스터를 포함하나 이에 한정되지 않는다. 반면, 알킬, 알케닐, 또는 아키닐에 있는 가능한 치환체는 C_1-C_{10} 알킬을 제외한 상기 열거된 치환체를 모두 포함한다. 또한, 시클로알킬, 시클로알케닐, 헤테로시클로알킬, 헤테로시클로알케닐, 아릴, 및 헤테로아릴은 서로 융합될 수 있다.

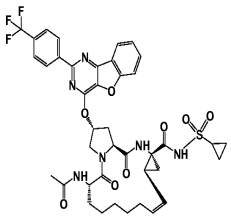
[0032] 본 발명의 281개의 대표적인 화합물을 하기에 나타낸다.



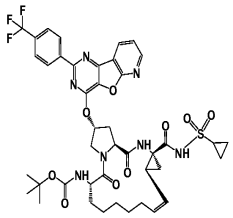
Compound 1



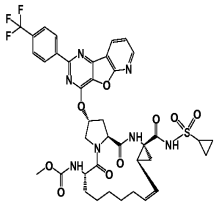
Compound 2



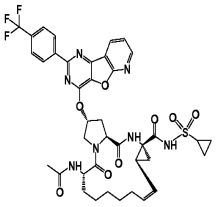
Compound 3



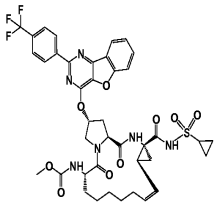
Compound 4



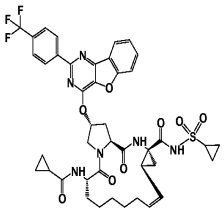
Compound 5



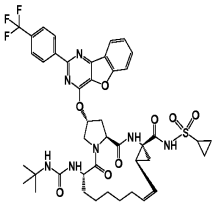
Compound 6



Compound 7



Compound 8



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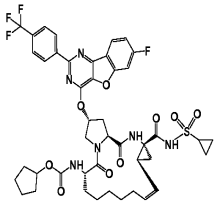

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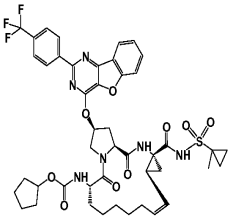

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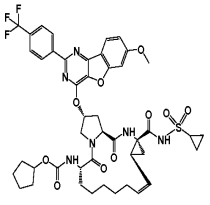

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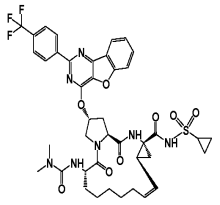

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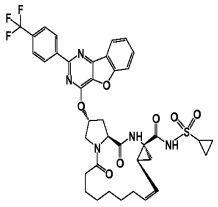

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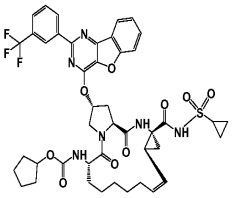

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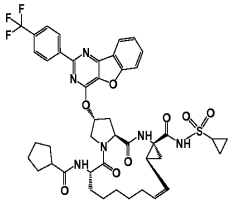
[0033]

[0034]



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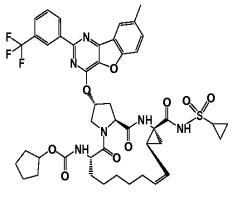

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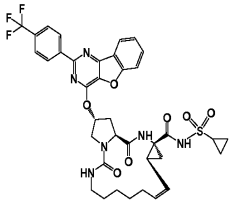

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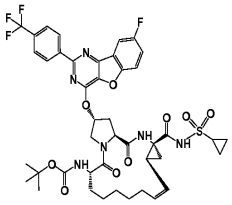

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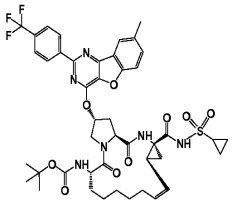

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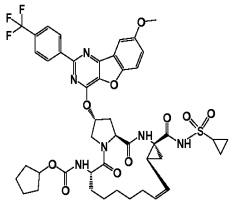

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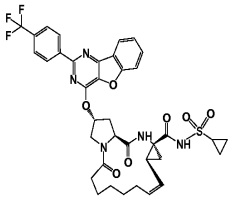

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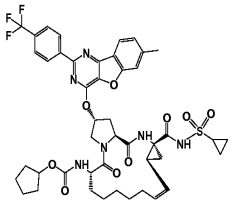

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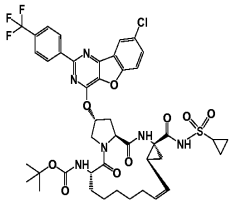

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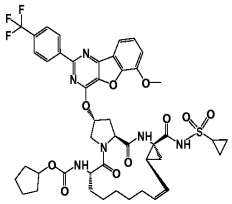

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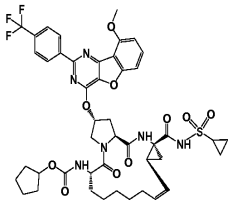

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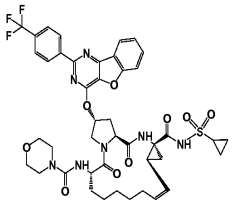

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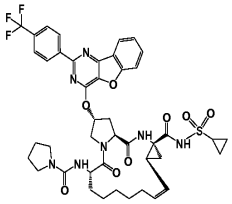

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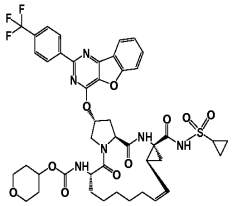

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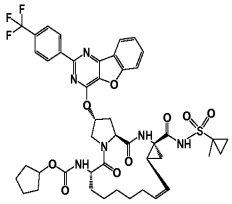

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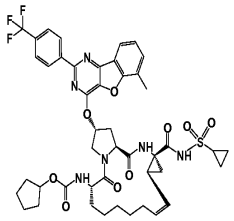

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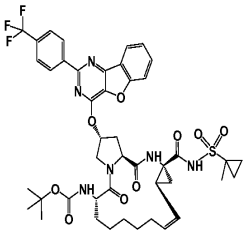

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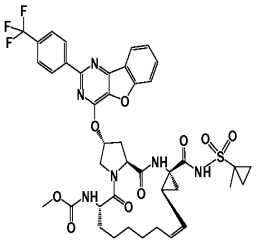

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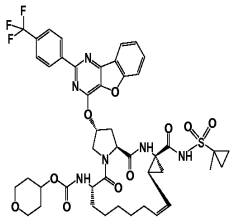

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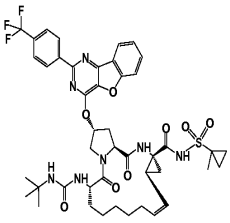

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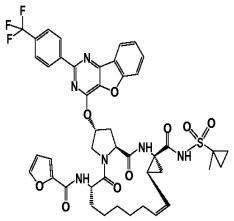

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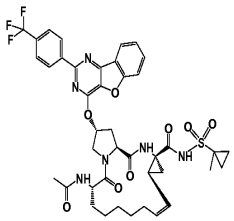

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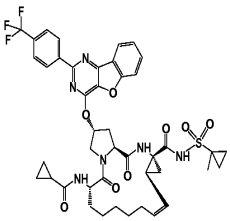

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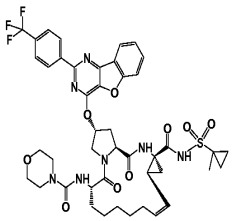

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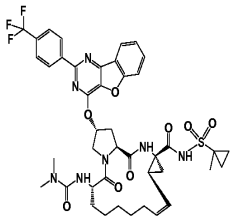

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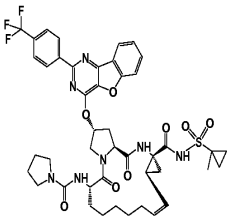

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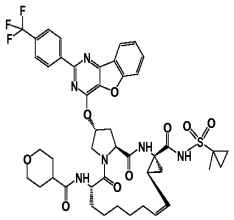

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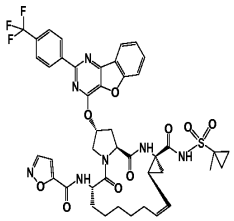

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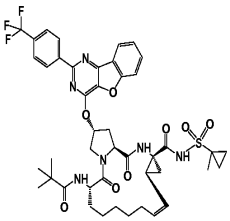

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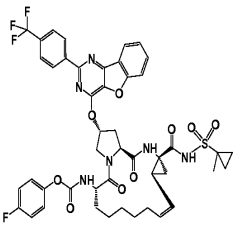

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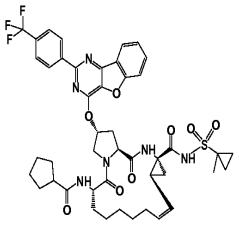

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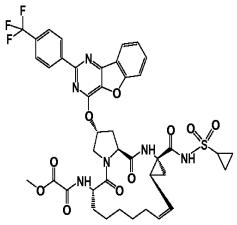

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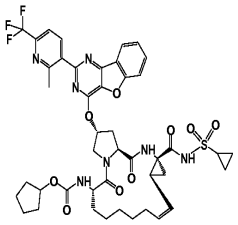

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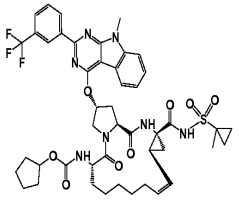

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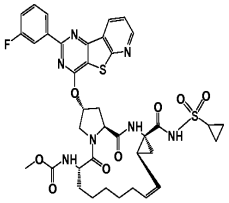

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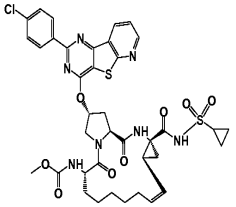

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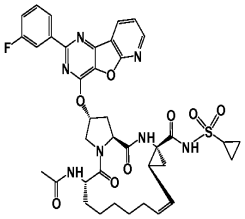

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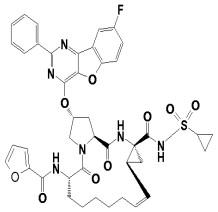

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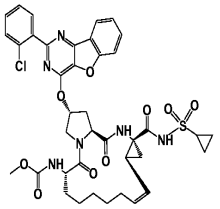

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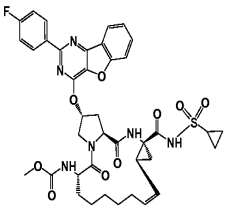

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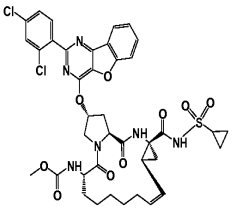

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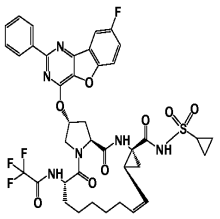

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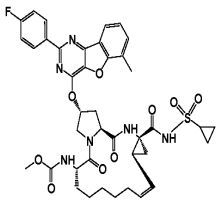

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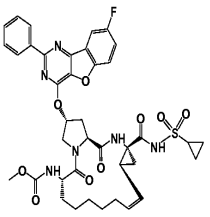

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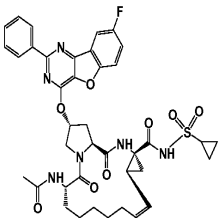

Compound 60

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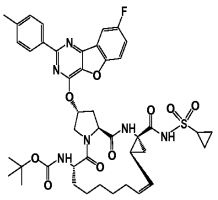
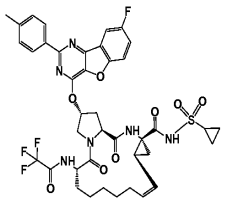


Compound 61



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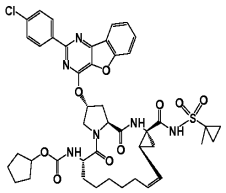

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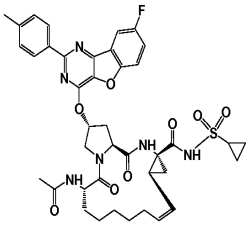

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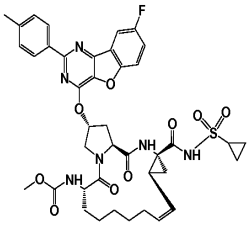

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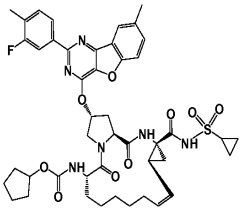

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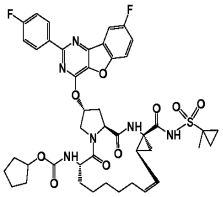

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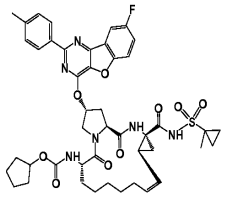

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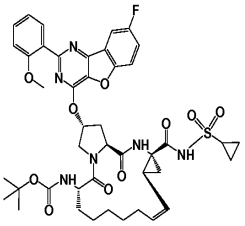
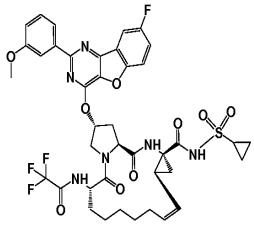


Compound 69



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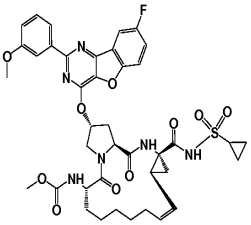

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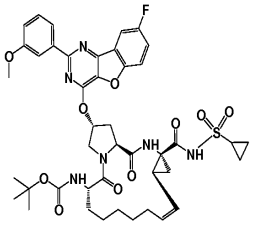

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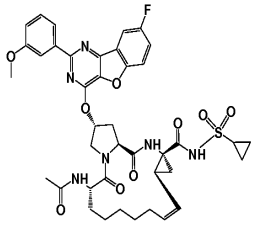

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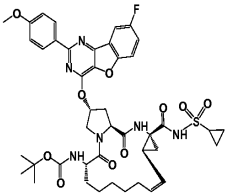

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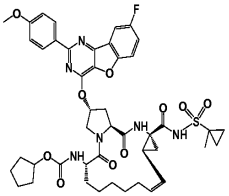

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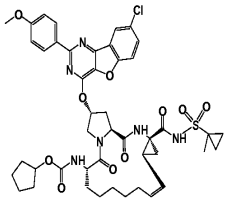
[0037]



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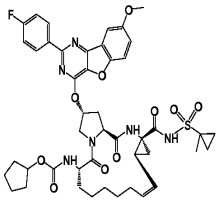

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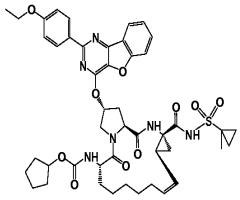

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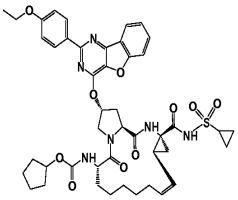

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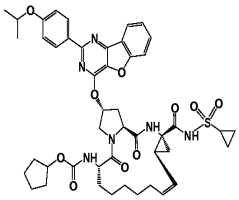

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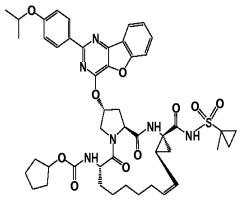

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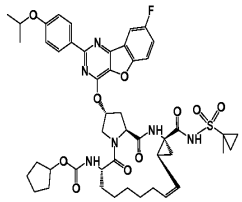

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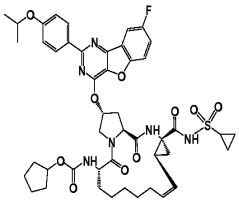

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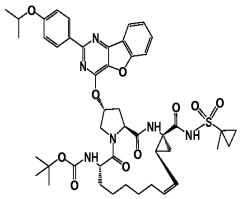

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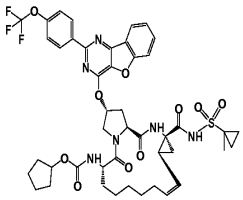

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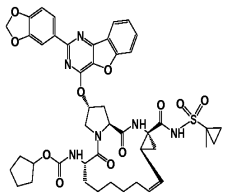

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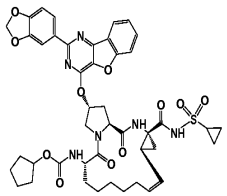

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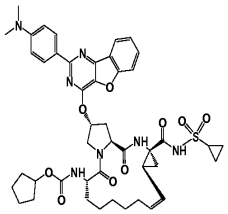

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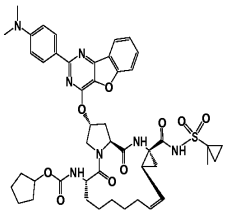

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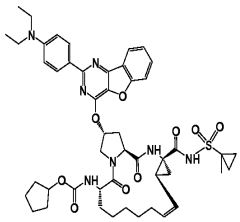
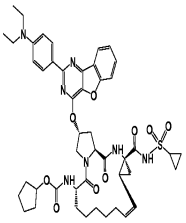


Compound 90

[0038]

[0039]



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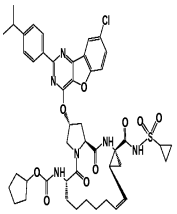

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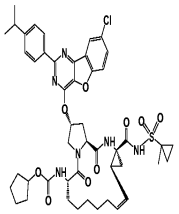

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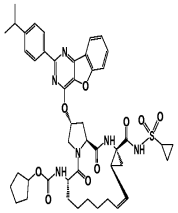

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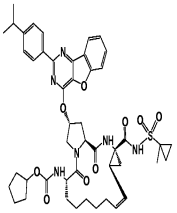

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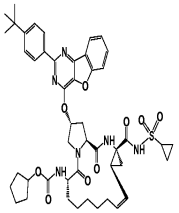

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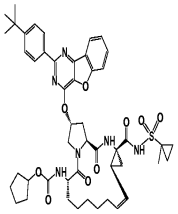

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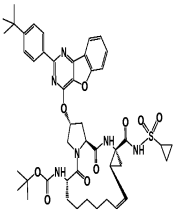

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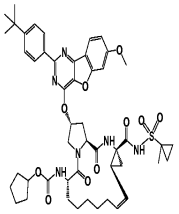

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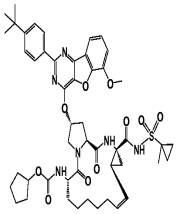

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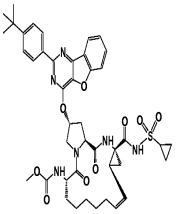

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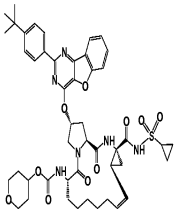

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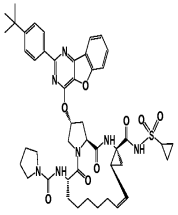

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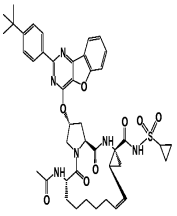

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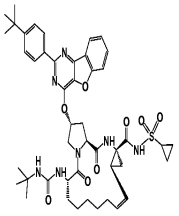

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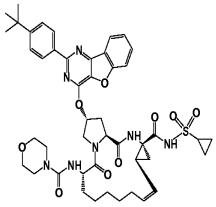

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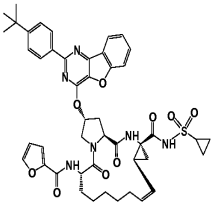

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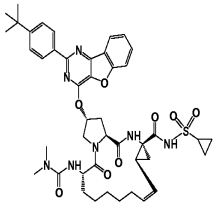

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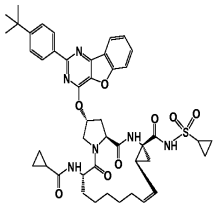

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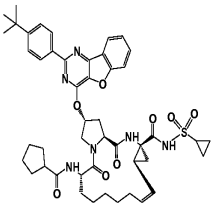

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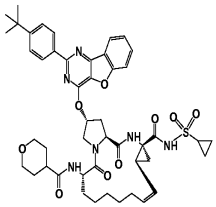

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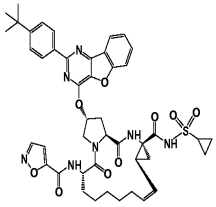

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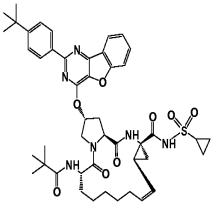

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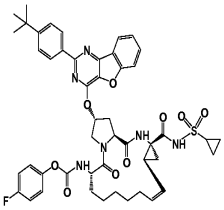

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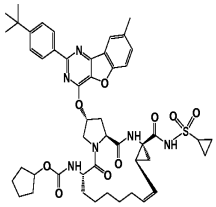

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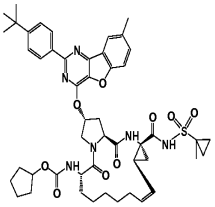

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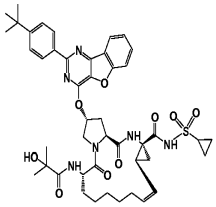

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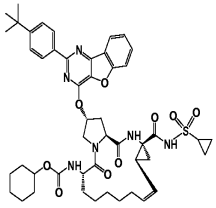

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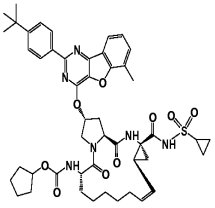

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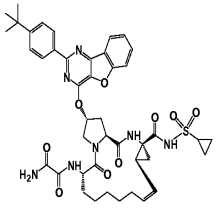

Compound 120

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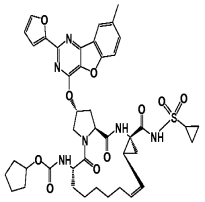

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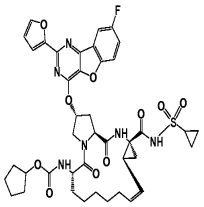
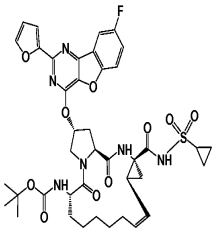


Compound 122



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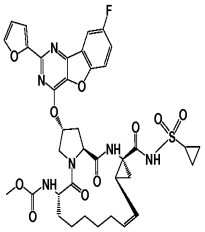

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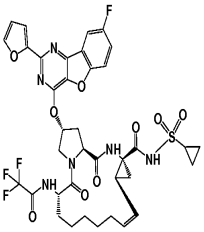

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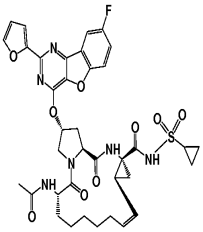

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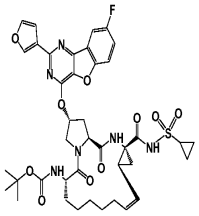

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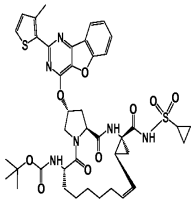

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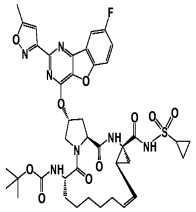
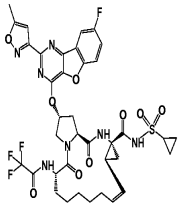


Compound 129



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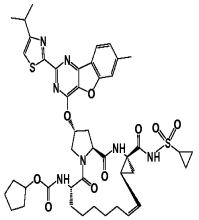

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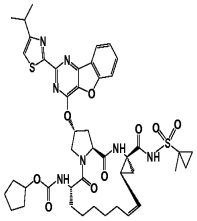

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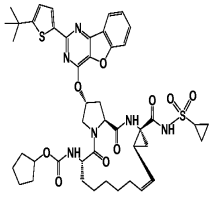
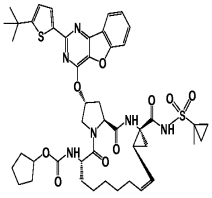


Compound 133



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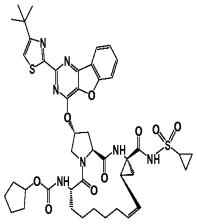
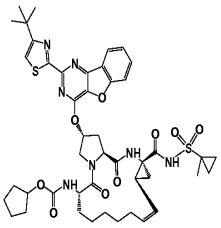


Compound 135

[0041]



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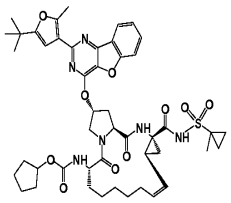

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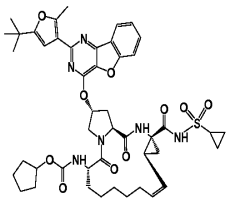

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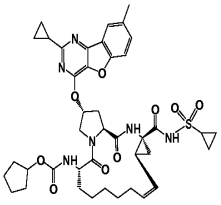

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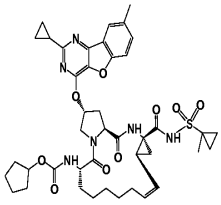

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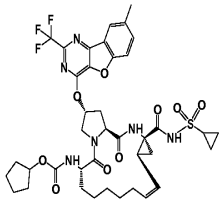
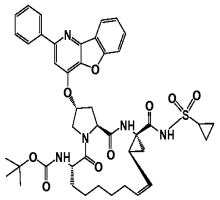


Compound 141



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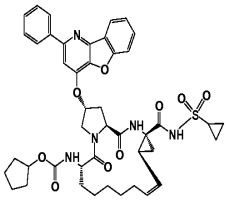

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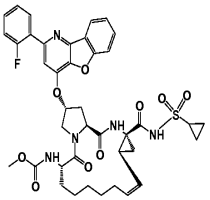

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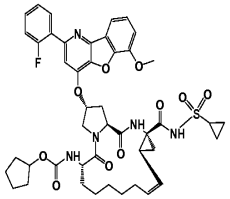

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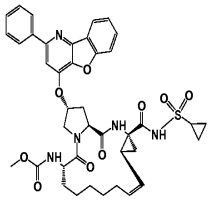

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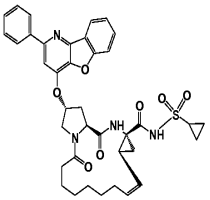

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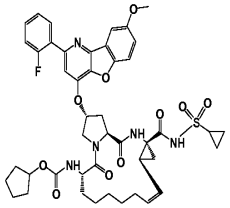

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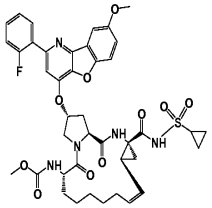

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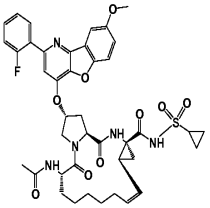
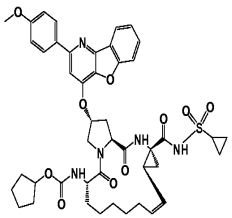
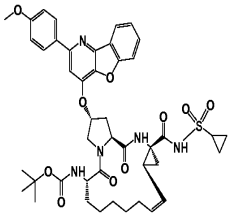


Compound 150

[0042]



Compound 151



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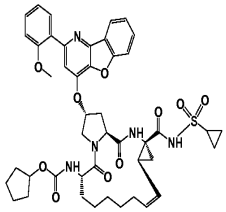

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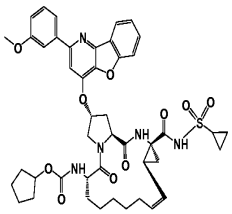

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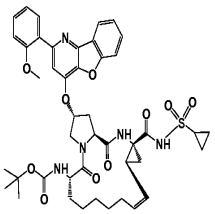

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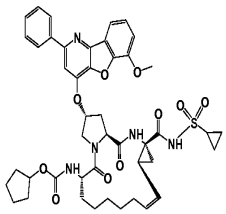

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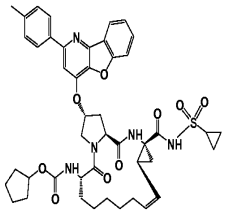

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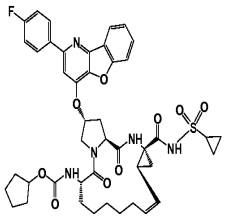

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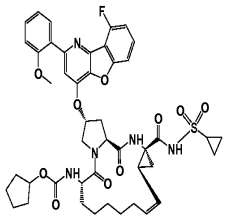

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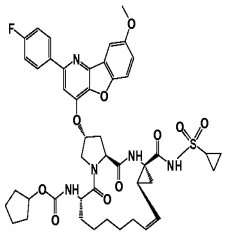

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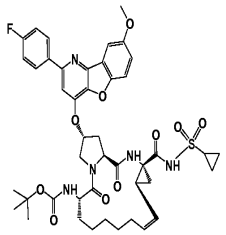

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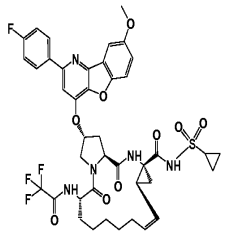

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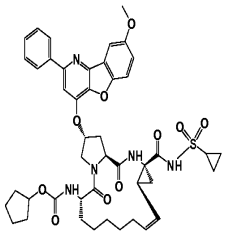

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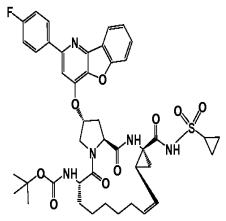
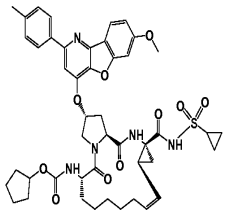
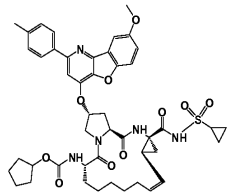


Compound 164

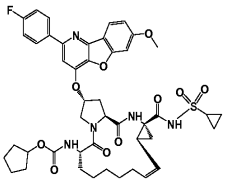


Compound 165

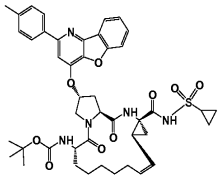
[0043]



Compound 166



Compound 167



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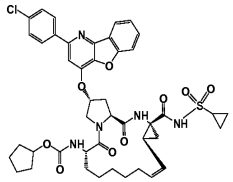

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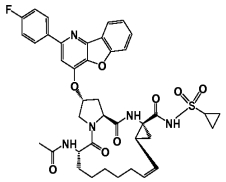

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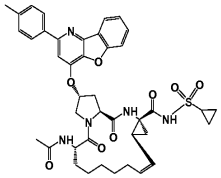

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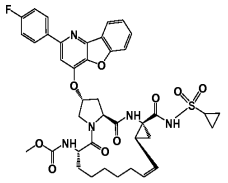
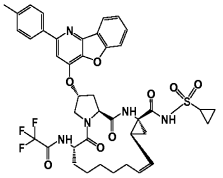
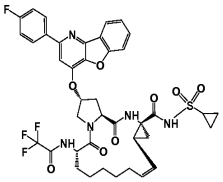


Compound 172



Compound 173



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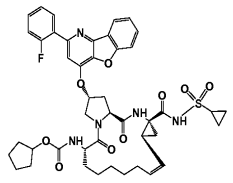
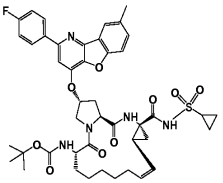


Compound 175



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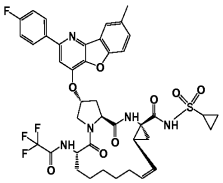

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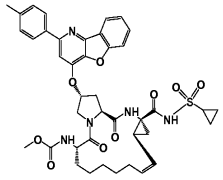

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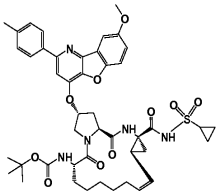
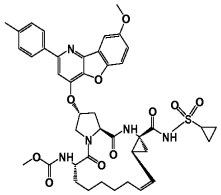
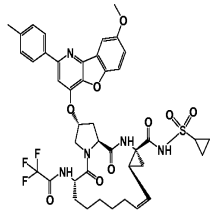


Compound 179

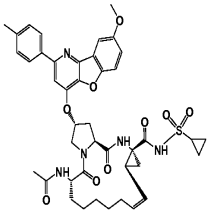


Compound 180

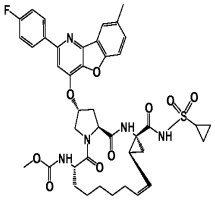
[0044]



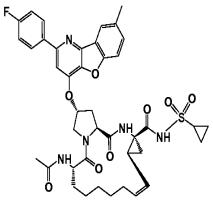
Compound 181



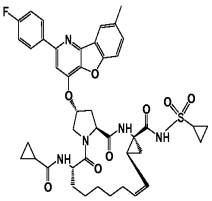
Compound 182



Compound 183



Compound 184



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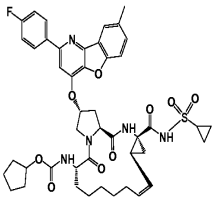

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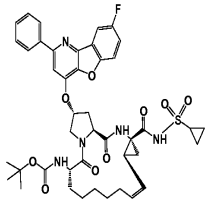
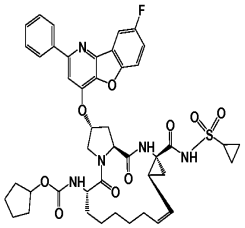
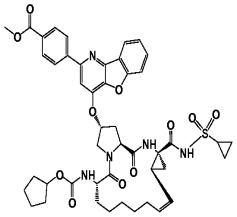


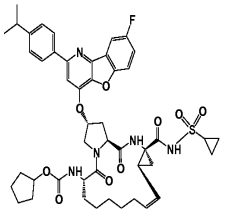
Compound 187



Compound 188



Compound 189



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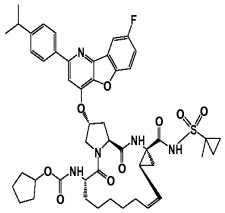

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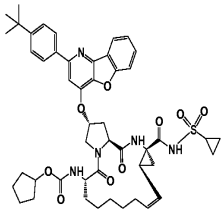

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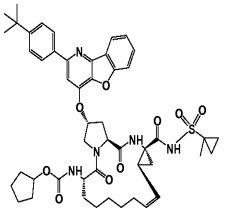

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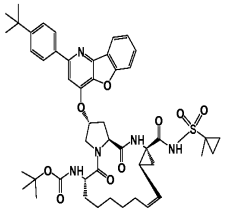

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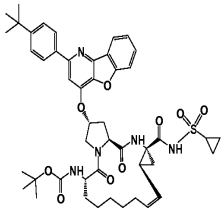
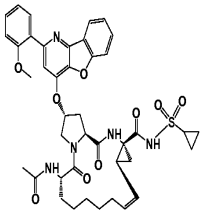


Compound 195

[0045]



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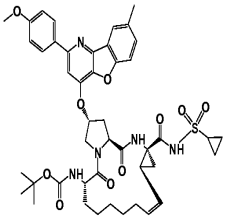

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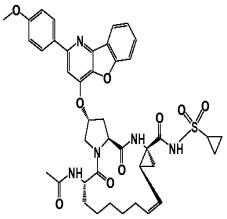

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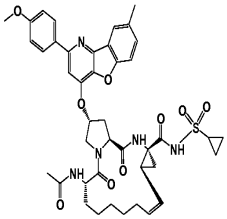

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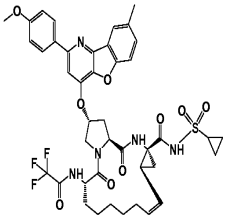

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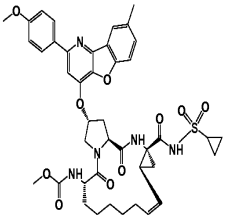

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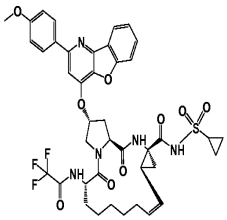

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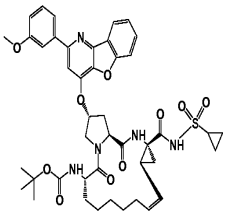

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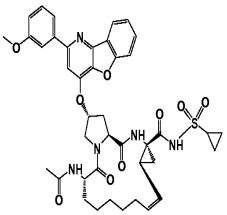

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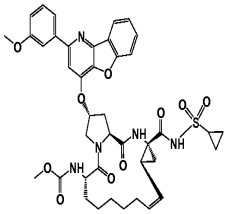

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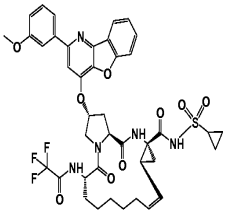

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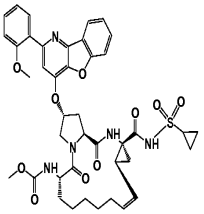

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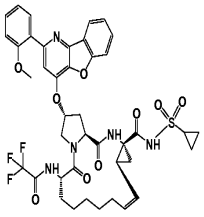

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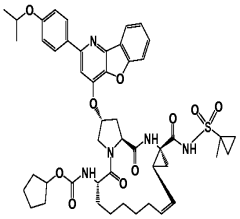

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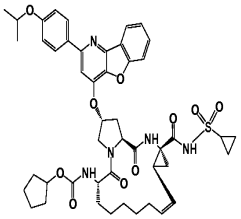
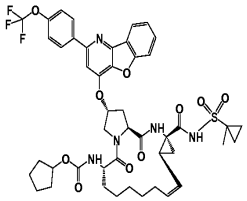


Compound 210

[0046]



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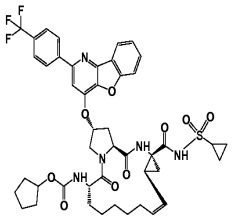

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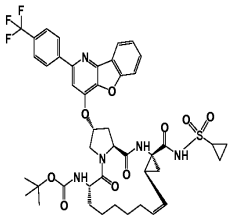

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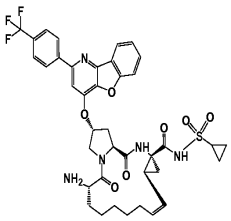

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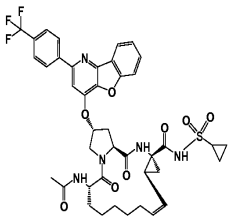

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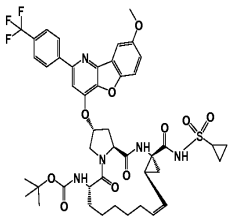

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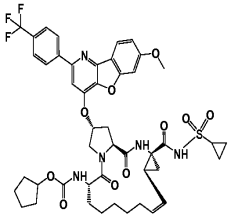

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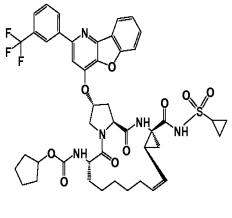

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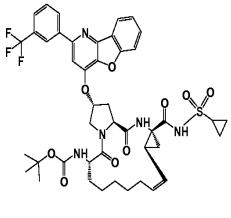

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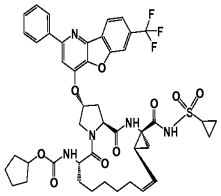

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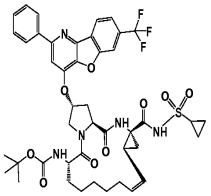

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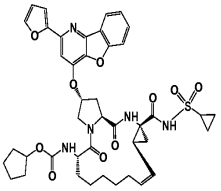

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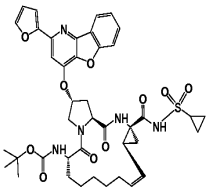

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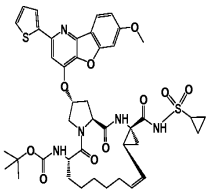

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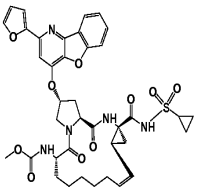

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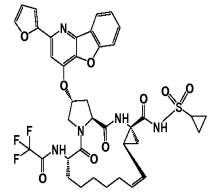
[0047]



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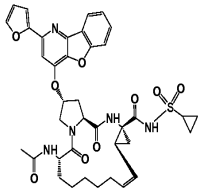

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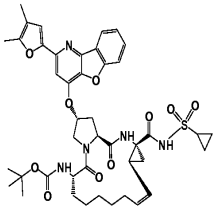

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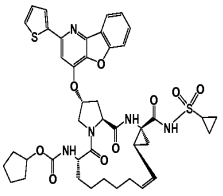

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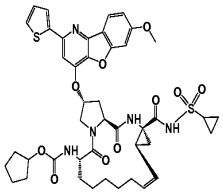

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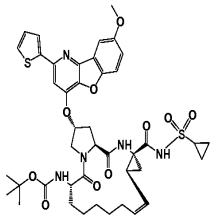

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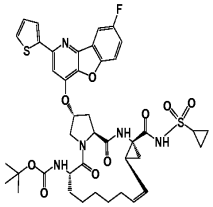

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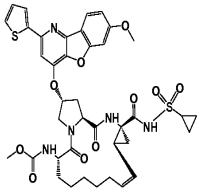

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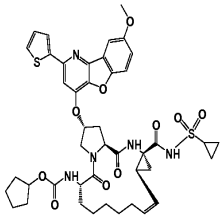

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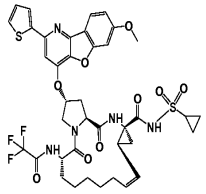
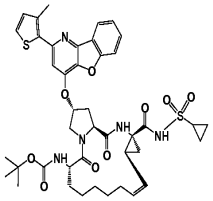


Compound 235



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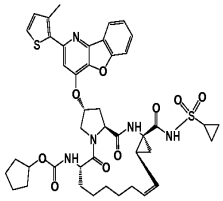
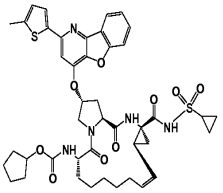
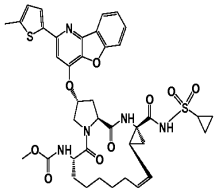


Compound 237



Compound 238



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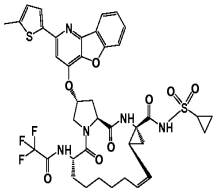
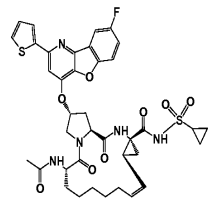
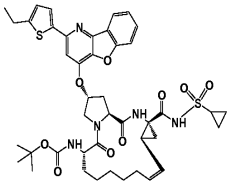


Compound 240

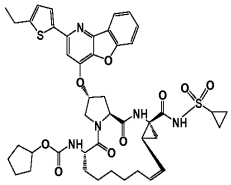
[0048]



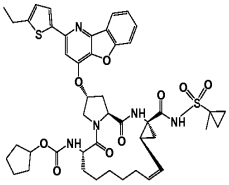
Compound 241



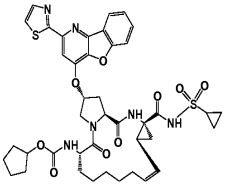
Compound 242



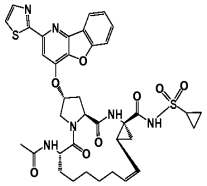
Compound 243



Compound 244



Compound 245



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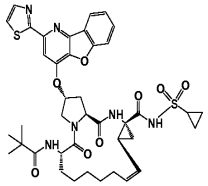
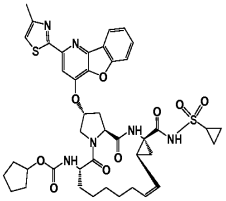
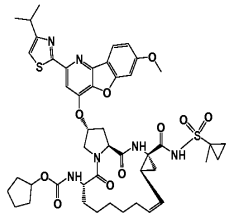


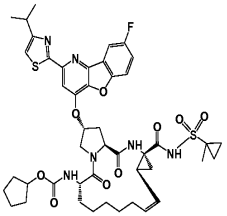
Compound 247



Compound 248



Compound 249



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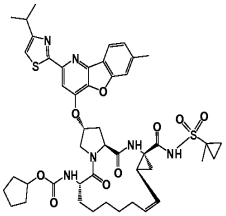

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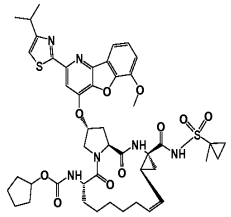

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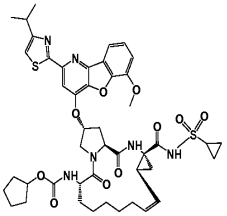
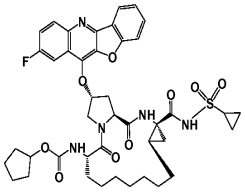


Compound 253



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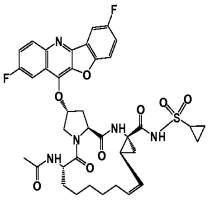
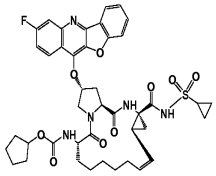


Compound 255

[0049]



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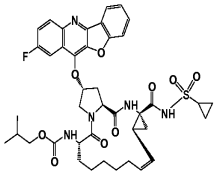

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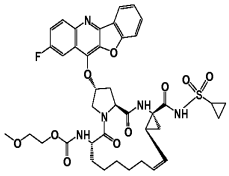

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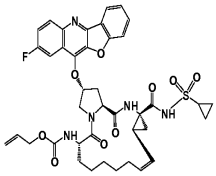

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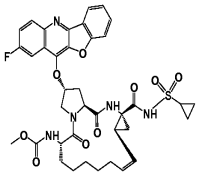

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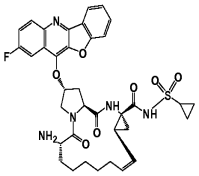

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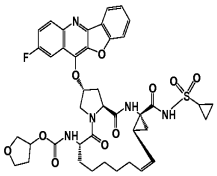

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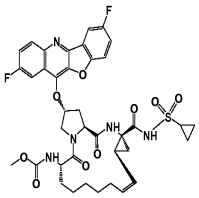

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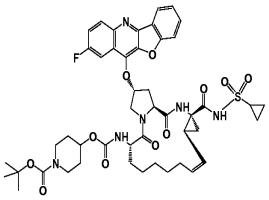
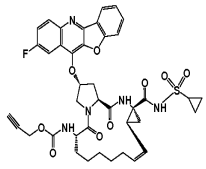


Compound 264



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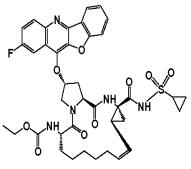
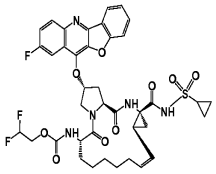


Compound 266



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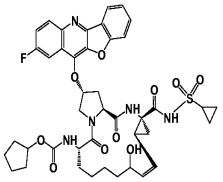

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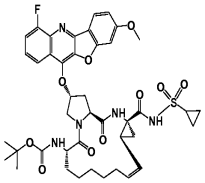

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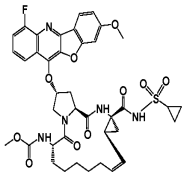

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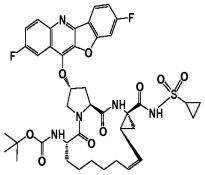
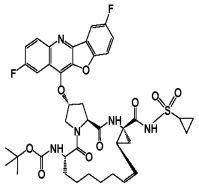
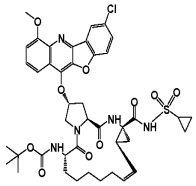


Compound 271

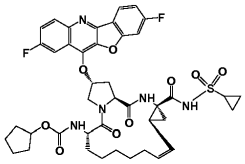


Compound 272



Compound 273

[0050]



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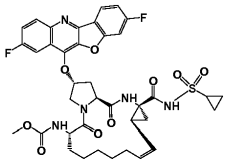
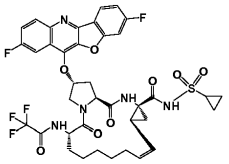
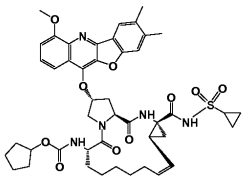


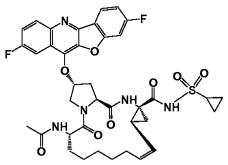
Compound 275



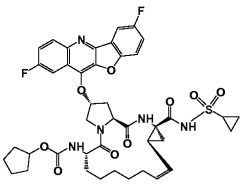
Compound 276



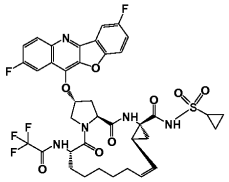
Compound 277



Compound 278



Compound 279



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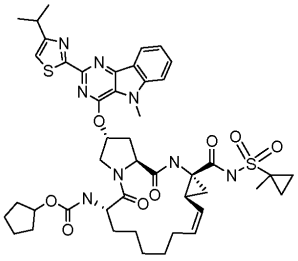


Compound 281

[0051]

[0052] 다른 양상에서, 본 발명은 C 형 간염 바이러스의 치료방법에 관한 것이다. 방법은 상기 나타낸 화학식 (Ⅰ)의 화합물의 유효량을 이를 필요로 하는 피험자에게 투여하는 단계를 포함한다.

[0053] 여전히 다른 양상에서, 본 발명은 HCV 감염 치료에 사용하기 위한 약학적 조성물에 관한 것이다. 조성물은 유효량의 적어도 하나의 화학식 (Ⅰ)의 화합물 및 약학적으로 허용가능한 담체를 함유한다. HCV 수명 주기(life cycle)에서 HCV NS3 프로테아제 외에 다른 표적의 저해제, 예를 들어 NS5B 폴리머라제, NS5A, NS4B, 또는 p7을 포함할 수 있다.

[0054] 이러한 물질의 예는 N-[3-(1-시클로부틸메틸-4-히드록시-2-옥소-1,2-디히드로-퀴놀린-3-일)-1,1-디옥소-1,4-디히드로-1l6-벤조[1,2,4]티아디아진-7-일]-메탄설폰아미드 (WO04041818), 트랜스-1,2-디-4-[(페닐아세틸-피롤리딘-2-(S)-카보닐) 아미노]-페닐에틸렌 (WO0401413), 및 1-아미노아다만탄 (Amentadine, Griffin, 2004, J. Gen. Virol. 85: p451)을 포함하나, 이에 한정되지 않는다. 또한, 약학적 조성물은 면역조절제 또는 제 2 항바이러스제를 함유할 수 있다. 면역조절제는 면역 반응을 조정하는 활성제를 나타낸다. 면역조절제의 예로는 Nov-205 (Novelos Therapeutics Inc., WO02076490) 및 IMO-2125 (Idera Pharmaceuticals Inc., WO05001055)를 포함하나, 이에 한정되지 않는다. 항바이러스제는 바이러스를 죽이거나 또는 이의 복제를 억제하는 활성제를 나타낸다. 항바이러스제의 예로는 리바비린, 리바미딘, 인터페론-α, 페그 인터페론(pegylated interferon), 및 2-(2-{2-시클로헥실-2-[(피라진-2-카보닐)-아미노]-아세틸아미노}-3,3-디메틸-부티릴)-옥타히드로-시클로펜타[c]피롤-1-카복실산 (1-시클로프로필아미노옥살릴-부틸)-아미드 (Telaprevir, Vertex Pharmaceuticals Inc., WO02018369), 3-[2-(3-tert-부틸-우레이도)-3,3-디메틸-부티릴]-6,6-디메틸-3-아자-비시클로[3.1.0]헥산-2-카복실산 (2-카바모일-1-시클로부틸메틸-2-옥소-에틸)-아미드 (Boceprevir, Schering-Plough Research Institute, WO03062265), 및 4-플루오로-1,3-디히드로-이소인돌-2-카복실산 14-tert-부톡시카보닐아미노-4-시클로프로판설포닐아미노카보닐-2,15-디옥소-3,16-디아자-트리시클로[14.3.0.04,6]노나덱-7-엔-18-일 에스터 (ITMN-191, InterMune Inc., US2005/0267018)와 같은 HCV 프로테아제 저해제를 포함하나, 이에 한정되지 않는다.

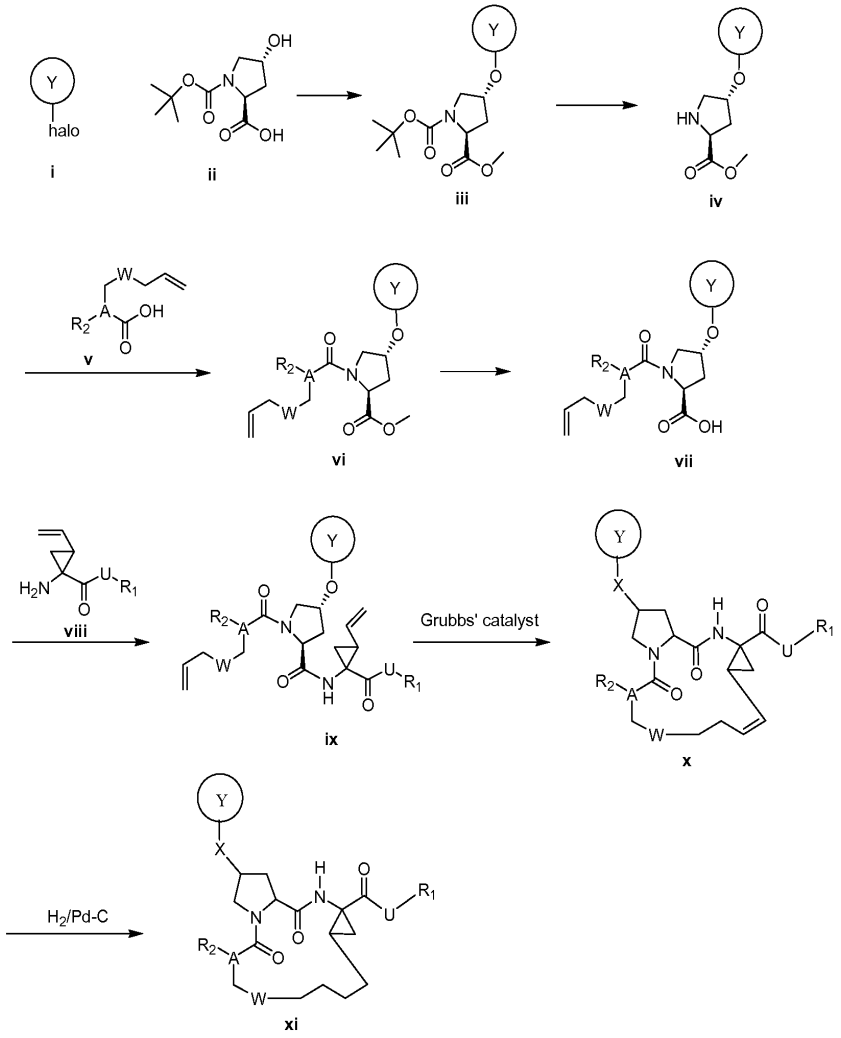
[0055] HCV 감염 치료 또는 치료용 약제의 제조를 위한 이러한 조성물의 용도도 본 발명의 범위 내이다.

[0056] 본 발명의 하나 이상의 실시예의 세부 사항은 하기의 설명에 명시되어 있다. 발명의 기타 특징, 목적, 및 장점은 설명과 청구항으로부터 명백할 것이다.

과제의 해결 수단

[0057] 본 발명의 화합물은 기술 분야에서 잘 알려진 방법에 의해 시판되는 출발물질로부터 합성될 수 있다. 예를 들어, 하나는 하기 반응식 1에 나타난 과정을 통해 본 발명의 화합물을 제조할 수 있다:

[0058] [반응식 1]

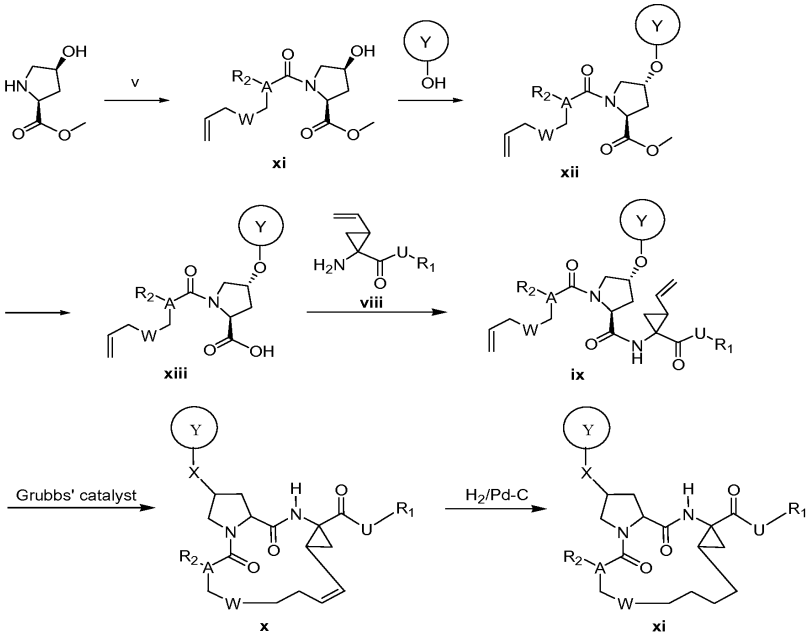


[0059]

[0060] 반응식 1에 도시된 바와 같이, 먼저 다중고리 화합물 (**i**)은 N-(t-부톡시카보닐)-L-프롤린 (**ii**)과 결합하고 메틸화하여 중간체 (**iii**)을 형성한다. 중간체 (**iii**)을 탈보호화하여 N-부톡시카보닐기를 제거하고 N-유리 화합물 (**iv**)을 생성하고, 이를 카복실산 (**v**)과 결합시켜 중간체 (**vi**)를 제공한다. 중간체 (**vi**)를 가수분해하여 산 (**vii**)을 얻고, 이를 아민 화합물 (**viii**)과 결합시켜 2개의 말단 알케닐기를 갖는 피롤리딘 화합물 (**ix**)을 제공한다. 중간체 (**ix**)는 Grubbs' 촉매 존재 하에 올레핀 복분해(metathesis)를 수행하여 원하는 마크로시클릭 화합물 (**x**)을 제공한다. 마크로시클릭 유사체 (xi)의 이중 결합은 Pd-C 존재 하에 더 수소화하여 포화-마크로시클릭 화합물 (**xi**)을 얻을 수 있다.

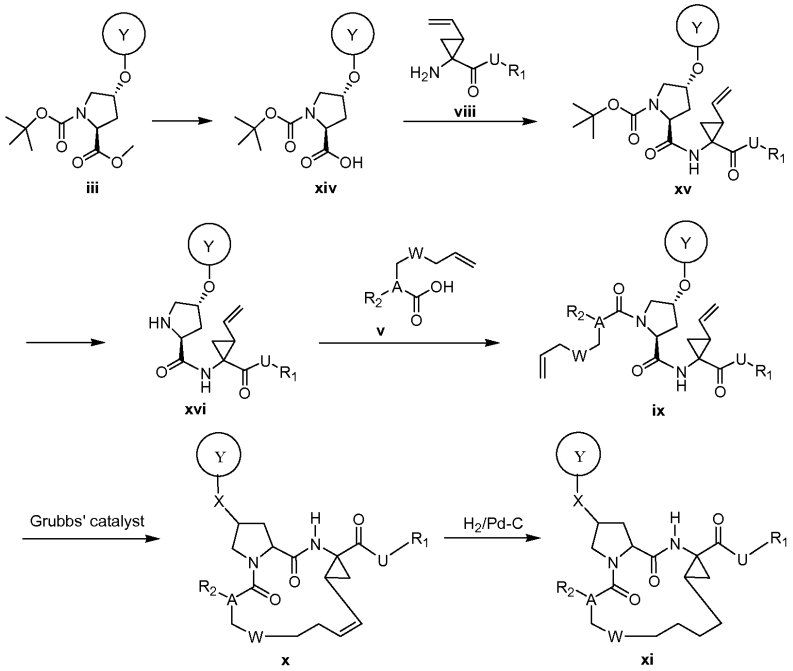
[0061] 본 발명의 화합물의 2개의 대체 합성 과정을 하기 반응식 2 및 3에 도시한다.

[0062] [반응식 2]



[0063]

[0064] [반응식 3]

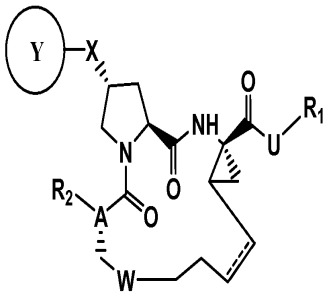


[0065]

[0066] 상기 기재된 방법 또한 궁극적으로 원하는 화합물의 합성을 위하여 반응식 1~3에 상세히 기재된 단계 전 또는 후에 적당한 보호기를 가하거나 또는 제거하는 단계를 추가적으로 포함할 수 있다. 또한, 다양한 합성 단계는 원하는 화합물을 얻기 위해 대체 순서 또는 순서로 수행될 수 있다. 화학식 (Ⅰ)의 적용가능한 화합물의 합성에 유용한 합성화학 변형 및 보호기 방법론(보호 및 탈보호)은 선행기술에 알려져 있으며, 예를 들어 R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 2nd Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) 및 이의 후 판(subsequent editions)에 기재된 것을 포함한다.

[0067] 하기 실시예 1~281은 대표적인 화합물 1~281이 실제로 제조되는 방법의 상세한 설명을 제공한다.

[0068] 본 명세서에 언급된 화합물은 비-방향족 이중 결합 및 비대칭 중심을 함유한다. 따라서, 이들은 라세미체 및 라세믹 혼합물, 단일 에난티오머, 각각의 부분입체이성질체, 부분입체이성질체 혼합물, 호변이성질체(tautomers) 및 시스- 또는 트랜스-이성질체 형태로 발생할 수 있다. 모든 이러한 이성질체 형태가 예상된다. 예를 들어, 상기 나타낸 화학식 (Ⅰ)의 화합물은 하기 입체화학 배열 (Ⅱ)을 가질 수 있다.



(Ⅱ)

[0069]

[0070] 해당되는 경우, 상기 기재된 화합물은 화합물 자체뿐 아니라 이의 염, 프로드럭, 및 용매화물을 포함한다. 예를 들어, 염은 화학식 (Ⅰ)의 화합물에 대해 음이온과 양전하 기(예를 들어, 아미노) 사이에 형성될 수 있다. 적당한 음이온은 클로라이드, 브로마이드, 요오드, 설페이트, 니트레이트, 포스페이트, 시트레이트, 메탄설포네이트, 트리플루오로아세테이트, 아세테이트, 말레이트, 토실레이트, 타르트레이트, 푸마레이트, 글루타메이트, 글루쿠로네이트, 락테이트, 글루타레이트, 및 말레이트를 포함한다. 유사하게, 염 또한 화학식 (Ⅰ)의 화합물에 대해 양이온과 음전하 기(예를 들어, 카복실레이트) 사이에 형성될 수 있다. 적당한 양이온은 나트륨 이온, 칼륨 이온, 마그네슘 이온, 칼슘 이온, 및 테트라메틸암모늄 이온과 같은 암모늄 양이온을 포함한다. 또한, 화학식 (Ⅰ)의 화합물은 4차 질소 원자를 함유한 이러한 염을 포함한다. 프로드럭의 예는 피험자에게 투여하는 화학식 (Ⅰ)의 활성 화합물을 제공할 수 있는 에스터 및 기타 약학적으로 허용가능한 유도체를 포함한다. 용매화물은 화학식 (Ⅰ)의 활성 화합물 및 약학적으로 허용가능한 용매 사이에 형성된 복합체를 나타낸다. 약학적으로 허용가능한 용매의 예는 물, 에탄올, 이소프로판올, 에틸아세테이트, 아세트산 및 에탄올아민을 포함한다.

[0071] 환자에게 유효량의 하나 이상의 화학식 (Ⅰ)의 화합물을 투여함으로써 HCV 감염의 치료방법도 본 발명의 범위 내이다. 용어 "치료하는(treating)" 또는 "치료 (treatment)"는 HCV 감염, 이의 증상, 또는 이에 대한 소인(predisposition)의 치료적 효과, 예를 들어 치료, 경감, 변경, 침범(affect), 개선, 또는 예방을 부여하기 위한 목적과 함께 HCV 감염, 이의 증상, 또는 이에 대한 소인을 갖는 피험자에게 화합물을 투여하는 단계를 나타낸다. 용어 "유효량(an effective amount)"은 치료받는 피험자에게 치료 효과를 부여하기 위해 필요한 본 발명의 활성 화합물의 양을 나타낸다. 효과적인 복용은 당업자에게 인식되는 것 처럼, 치료받는 질환, 투여 경로, 부형제 사용량, 및 다른 치료법과 공동-사용의 가능성에 따라 달라질 것이다.

[0072] 본 발명의 화합물은 오랜기간 동안 효과적인 수준에서 혈관계에 남아있을 수 있다. 따라서, 이러한 화합물은 치료 효과를 부여하기 위해 하루에 한번 유효량으로 투여될 수 있다.

[0073] 본 발명의 방법을 실행하기 위해, 본 발명의 하나 이상의 화합물을 갖는 조성물은 비경구, 경구, 비강, 직장, 국소, 또는 구강 투여될 수 있다. 본 명세서에 기재된 대로, 용어 "비경구(parenteral)"는 피하, 피내(intracutaneous), 정맥내, 근육내, 관절내(intraarticular), 동맥내, 활액내(intrasynovial), 흉골내(intrasternal), 수막강내(intrathecal), 병변내(intralesional), 또는 두개강내 (intracranial) 주사, 및 어느 적당한 주입기술(infusion technique)을 나타낸다.

[0074] 멸균 주사용 조성물은 1,3-부탄디올의 용액과 같은 비-독성 비경구적으로 허용가능한 희석액 또는 용매의 용액 또는 현탁액일 수 있다. 허용가능한 비히클 및 용매 중에서 만니톨, 물, 링거 용액, 및 등장성 염화나트륨 용액이 사용될 수 있다. 또한, 고정된 오일은 용매 또는 현탁 배지로서 전통적으로 사용된다(예를 들어, 합성 모노- 또는 디글리세라이드). 올레산 및 이의 글리세라이드 유도체와 같은 지방산은 올리브 오일 또는 피마자유와 같은 천연 약학적으로 허용가능한 오일로서 주사가능한 제제, 특히 이의 폴리옥시에틸화 형태로 유용하게 사용된다. 이러한 오일 용액 또는 현탁액 또한 긴 사슬 알콜 희석액 또는 분산제, 카복시메틸 셀룰로오스, 또는 유사한 분산제를 함유한다. 트윈 또는 스판과 같은 다른 통상적으로 사용된 계면활성제 또는 기타 유사한 에멀젼화제 또는 약학적으로 허용가능한 고체, 액체, 또는 기타 복용 형태의 제조에서 통상적으로 사용된 생체이용률 인

핸서 또한 제형의 목적을 위해 사용될 수 있다.

[0075] 경구 투여용 조성물은 캡슐, 정제, 에멀젼 및 수성 현탁액, 분산액, 및 용액을 포함한 경구적으로 허용가능한 복용 형태일 수 있다. 정제의 경우, 통상적으로 사용된 담체는 락토오스 및 옥수수 전분을 포함한다. 마그네슘 스테아레이트와 같은 윤활제 또한 일반적으로 추가된다. 캡슐 형태의 경구 투여에 유용한 희석제는 락토오스 및 건조 옥수수 전분을 포함한다. 수성 현탁액 또는 에멀젼이 경구로 투여된 경우, 활성 성분은 에멀젼화제 또는 현탁제와 함께 결합된 오일 상에 현탁될 수 있거나 또는 용해될 수 있다. 원하는 경우 특정 감미료, 향료, 또는 착색제를 추가할 수 있다.

[0076] 비강 에어로졸 또는 흡입 조성물은 약학적 제형의 기술분야에서 잘 알려진 기술에 따라 제조될 수 있다. 예를 들어, 이러한 조성물은 기술분야에서 알려진 벤질 알콜 또는 기타 적합한 방부제, 생체이용률을 향상시키기 위한 흡수 프로모터, 플루오로탄소, 및/또는 기타 용해제 또는 분산제를 사용하여 식염수로서 제조될 수 있다.

[0077] 또한, 본 발명의 하나 이상의 활성 화합물을 갖는 조성물은 직장 투여를 위해 좌제의 형태로 투여될 수 있다.

[0078] 약학적 조성물에서 담체는 조성물의 활성 성분과 호환될 수 있으며 (바람직하게는, 활성 성분을 안정화시킬 수 있는) 치료받는 피험자에게 해롭지 않다는 의미에서 "허용가능한(acceptable)"임에 틀림없다. 하나 이상의 용해제는 본 발명의 활성 화합물의 전달을 위해 약학적 부형제로서 이용될 수 있다. 기타 담체의 예는 콜로이드성 실리콘 옥사이드, 마그네슘 스테아레이트, 셀룰로오스, 소듐 라우릴 설페이트, 및 D&C Yellow # 10을 포함한다.

[0079] 본 발명의 화합물은 HCV 수명 주기에서 HCV NS3 프로테아제 외의 표적의 저해제와 같은 제 2 항-HCV 물질, 면역조절제, 및 다른 항바이러스제와 함께 HCV를 치료하기 위해 사용될 수 있다. 본 발명의 화합물 및 제 2 항-HCV 물질은 동시에 또는 다른 시간에 투여될 수 있다. 동시 투여를 위해서, 이들은 혼합되어 단일 환약을 형성할 수 있거나, 또는 별개의 환약으로 제조될 수 있다. 이러한 두 개의 물질은 모두 HCV 치료에 효과적인 것으로 당업자에게 인식될 정도의 양으로 각각 사용될 수 있다.

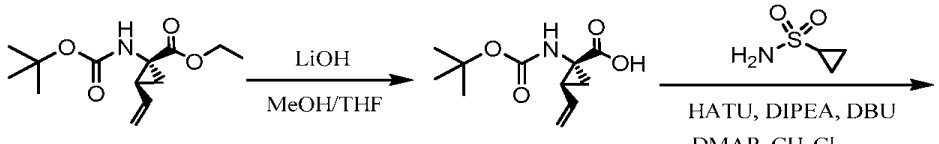
[0080] 상기 기재된 본 발명의 화합물은 in vitro 어세이에 의해 HCV 감염 치료에 있어서 이의 효능에 대해 미리 스크리닝될 수 있으며(실시예 282 및 283 참조), 그 다음 동물 실험 및 임상 시험에 의해 확인될 수 있다. 다른 방법도 당업자에게 명백할 것이다.

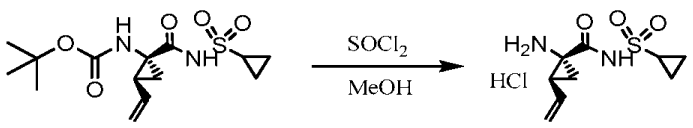
발명을 실시하기 위한 구체적인 내용

[0081] 하기의 특정 실시예는 단지 예시적인 것일 뿐, 어떠한 방법으로 공개의 나머지를 한정적이지 않은 것으로 해석되어야 한다. 더 이상 상술하지 않고, 본 명세서의 설명을 기초로 하여 당업자는 본 발명을 충분히 이용할 수 있다고 믿는다. 본 명세서에 인용된 모든 공개본은 이들의 전체 참조로 통합된다.

[0082] 실시예 1: {4-시클로프로판설포닐아미노카보닐-2,15-디옥소-18-[2-(4-트리플루오로메틸-페닐)-벤조[4,5]푸로[3,2-d]피리미딘-4-일옥시]-3,16-디아자-트리시클로[14.3.0.04,6]노나덱-14-일}-카바민산 시클로펜틸 에스터 (화합물 1)의 합성

[0083] 먼저, 화합물 I-3은 하기에 나타낸 경로를 통해 시판되는 1-*t*-부톡시카보닐아미노-2-비닐-시클로프로판카복실산 에틸 에스터로부터 제조되었다:





I-2 I-3

[0084]

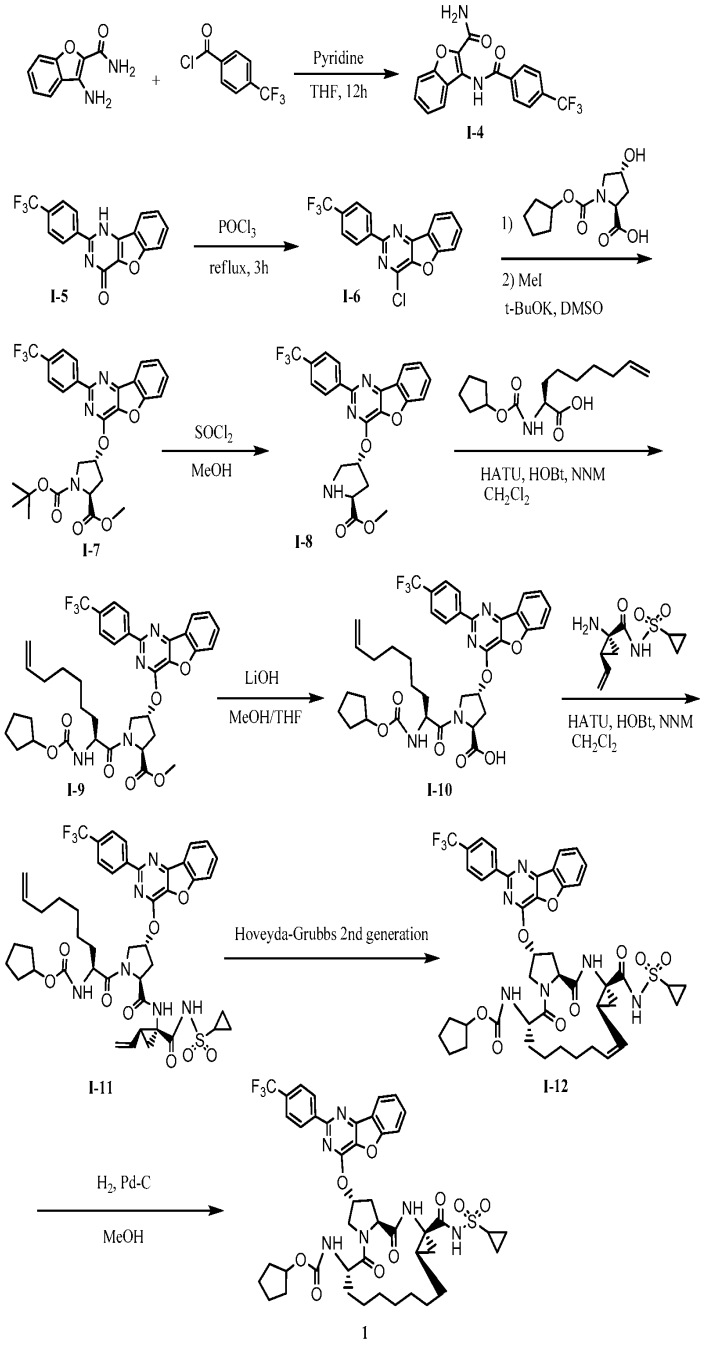
[0085] THF (5 mL) 및 메탄올 (5 mL) 내 1-*t*-부톡시카보닐아미노-2-비닐-시클로프로판카복실산 에틸 에스터 (0.34 g, 1.3 mmol)의 용액에 물 (1.4 mL) 내 LiOH (0.13 g, 5.3 mmol)의 현탁액을 가하였다. 실온에서 밤새도록 교반한 후, 반응을 10% HCl (2 mL)로 종결시키고 진공 하에서 용매를 제거하였다. 결과로 생긴 고체 분말을 물 (10 m

L)로 세척하여 화합물 I-1 (0.27 g, 90%)을 얻었다. MS m/z 249.9 (M^++23); ^{1}H NMR ($CDCl_3$) δ 10.35 (brs, 1H), 5.84-5.71 (m, 1H), 5.29 (d, J = 17.4 Hz, 1H), 5.12 (d, J = 10.2 Hz, 1H), 2.23-2.14 (m, 1H), 1.87-1.65 (m, 1H), 1.58-1.41 (m, 1H), 1.43 (s, 9H).

[0086] CH_2Cl_2 (40 mL) 내 화합물 I-1 (0.52 g, 2.3 mmol), 2-(1H-7-아자벤조트리아졸-1-일)-1,1,3,3-테트라메틸 우로늄 헥사플루오로-포스페이트 메탄아미늄 (HATU, 1.74 g, 4.6 mmol), 및 4-디메틸아미노피리딘 (1.39 g, 11.6 mmol)의 용액을 1시간 동안 실온에서 교반한 후, 시클로프로판설폰아미드 (0.57 g, 4.7 mmol), 디이소프로필에틸아민 (1.81 mL, 14.0 mmol), 및 1,8-디아자비시클로[5,4,0]운덱-7-엔 (1.80 g, 11.7 mmol)을 15분에 걸쳐 천천히 가하였다. 반응 혼합물을 실온에서 밤새도록 교반한 후, 용매를 진공 하에 제거하였다. 잔류물을 실리카겔 컬럼 크로마토그래피로 정제하여 화합물 I-2 (0.51 g, 66%)을 얻었다. MS m/z 353.1 (M^++23); ^{1}H NMR ($CDCl_3$) δ 9.75 (brs, 1H), 5.64-5.51 (m, 1H), 5.30 (d, J = 17.4 H), 5.16 (d, J = 10.2 Hz, 1H), 2.95-2.89 (m, 1H), 2.19-2.10 (m, 1H), 1.93-1.88 (m, 1H), 1.47 (s, 9H), 1.46-1.38 (m, 1H), 1.32-1.23 (m, 2H), 1.15-1.00 (m, 2H).

[0087] MeOH (8 mL) 내 화합물 I-2 (0.50 g, 1.5 mmol)의 용액에 $SOCl_2$ (0.26 g, 2.2 mmol)를 실온에서 가하였다. 반응 혼합물을 1시간 동안 환류시키고, MeOH 및 $SOCl_2$를 진공 하에 제거하였다. 잔류물을 펜탄으로부터 가루로 만들고 여과하여 회색을 띤 백색 고체로서 중간체 I-3 (0.32 g, 91%)을 얻었다. MS m/z (M^++1); ^{1}H NMR (CD_3COD) δ 5.77-5.65 (m, 1H), 5.43 (d, J = 17.4 Hz, 1H), 5.32 (d, J = 10.2 Hz, 1H), 3.06-2.97 (m, 1H), 2.45 (dd, J = 17.4 Hz, J = 7.8, 1H), 2.16 (dd, J = 8.0 Hz, J = 7.8 Hz, 1H), 1.75 (dd, J = 10.1 Hz, J = 7.8 Hz, 1H), 1.32-0.86 (m, 4H).

[0088] 화합물 I 은 하기 나타낸 경로를 통해 제조되었다.



[0089]

[0090] THF (25 mL) 내 3-아미노-벤조푸란-2-카복실산 아미드 (1.00 g, 5.7 mmol) 및 피리딘(1 mL, 12.26 mmol)의 용액을 0℃에서 10분 동안 교반하였다. 결과 용액에 4-트리플루오로메틸-벤조일 클로라이드 (1.48 g, 7.1 mmol)를 천천히 가하였다. 그 다음 온도를 실온으로 올리고 혼합물을 12시간 동안 교반하였다. 감압 하에서 용매를 제거한 후, 결과로 생긴 고체를 모으고, 물로 세척하고, 공기 건조시켜 화합물 I-4 (1.92 g, 96.0 %)를 얻었다. MS: m/z 349.0 (M^++1).

[0091] EtOH (25 mL) 내 화합물 I-4 (1.92 g, 5.5 mmol) 및 2N NaOH (13 mL)의 현탁액을 85℃에서 12시간 동안 가열하였다. 냉각시킨 후, 혼합물을 산성화한 다음 EtOH를 제거하였다. 결과로 생긴 고체를 모으고, 여과하고, 물로 세척하고, 건조하여 화합물 I-5 (1.71 g, 95.0%)를 얻었다. MS m/z 331 (M^++1).

[0092] 화합물 I-5 (1.71 g, 5.2 mmol) 및 과량의 포스포러스 옥시클로라이드 ($POCl_3$)의 용액을 2시간 동안 환류하였다. 냉각시키고 완전히 농축한 후, 혼합물을 메틸렌클로라이드와 10% 소듐 히드록사이드로 추출하였다. 유기층을 $MgSO_4$로 건조시키고, 농축시킨 다음 CH_2Cl_2 및 *n*-헥산으로 결정화하여 화합물 I-6 (1.49 g, 82%)을 얻었다. MS m/z 348.8, 350.9 (M^++1); ^1H NMR ($CDCl_3$) δ 8.70 (d, 2H), 8.34 (d, 1H), 7.82-7.75 (m, 4H), 7.57 (ddd, 1H).

[0093] DMSO (25 mL) 내 boc-trans-4-히드록시-L-프롤린 (0.53 g, 2.3 mmol)의 현탁액에 *t*-BuOK (0.82 g, 5.1 mmol)을 0℃에서 가하였다. 혼합물을 실온으로 따뜻하게 하고 1시간 동안 교반한 후, 화합물 I-6 (0.81 g, 2.3 mmol)을 10℃에서 천천히 가하였다. 밤새도록 교반을 계속하였다. 아이오도메탄 (1.02 g, 6.9 mmol)을 가하고 반응 혼합물을 실온에서 30분 더 교반하였다. 반응 혼합물을 10% HCl 수용액으로 pH 6~7로 중화하고 메틸렌클로라이드로 추출하였다. 유기층을 $MgSO_4$로 건조시키고, 진공하에 증발시키고 실리카겔 컬럼 크로마토그래피로 정제하여 화합물 I-7 (1.12 g, 86%)을 얻었다. MS m/z 557.8 (M^++1); ^1H NMR ($CDCl_3$) δ 8.63 (d, 2H), 8.28 (d, 1H), 7.80-7.74 (m, 2H), 7.70 (d, 2H), 7.51 (ddd, 1H).

[0094] MeOH (20 mL) 내 화합물 I-7 (1.13 g, 2.0 mmol)의 용액에 $SOCl_2$ (1.21 g, 9.8 mmol)를 실온에서 가하였다. 반응 혼합물을 1시간 동안 환류시키고, MeOH 및 $SOCl_2$를 제거하였다. 잔류물을 펜탄에서 가루로 만들었다. 현탁액을 여과하여 회색을 띤 백색 고체로서 화합물 I-8 (0.87 g, 95%)을 얻었다. MS m/z 458.1 (M^++1).

[0095] CH_2Cl_2 (40 mL) 내 HATU (1.12 g, 3.0 mmol), 1-히드록시벤조트리아졸 (HOBT, 0.41 g, 3.0 mmol), 화합물 I-8 (0.86 g, 1.9 mmol) 및 2-*t*-부톡시카보닐아미노-논-8-에노산 (1.21 g, 1.9 mmol)의 용액에 실온에서 N-메틸모폴린 (NMM, 1.02 g, 9.9 mmol)을 가하였다. 밤새도록 교반한 후, 혼합물을 진공 하에서 농축하였다. 잔류물을 실리카겔 컬럼 크로마토그래피로 정제하여 화합물 I-9 (1.03 g, 73%)를 얻었다. MS m/z 711.3 (M^++1).

[0096] THF (20 mL) 내 화합물 I-9 (1.01 g, 1.4 mmol)의 용액에 0.5 M LiOH (5.7 mL, 2.9 mmol)를 실온에서 가하였다. 밤새도록 교반한 후, 반응 혼합물을 10% HCl로 pH < 7로 중화하고 진공 하에서 농축하였다. 결과로 생긴 잔류물을 여과하고 물로 세척하여 화합물 I-10 (0.91 g, 92%)을 얻었다. MS: m/z 697.3 (M^++1).

[0097] CH_2Cl_2 (10 mL) 내 화합물 I-3 (0.28 g, 0.4 mmol), HATU(0.31 g, 0.8 mmol), HOBT (0.08 g, 0.6 mmol) 및 화합물 I-10 (0.09 g, 0.4 mmol)의 용액에 NMM (0.12 g, 1.2 mmol)을 실온에서 가하였다. 밤새도록 교반한 후, 반응 혼합물을 진공 하에서 농축하였다. 잔류물을 실리카겔 컬럼 크로마토그래피로 정제하여 화합물 I-11 (0.10 g, 85%)을 얻었다. MS m/z 921.3 (M^++1); ^1H NMR ($CDCl_3$) δ 10.24 (s, 1H), 8.61 (d, 2H), 8.26 (d, 1H), 7.77 (d, 2H), 7.73-7.64 (m, 2H), 7.54-7.47 (m, 1H), 7.11 (s, 1H), 6.19 (d, 1H), 5.88-5.70 (m, 2H), 5.38-5.25 (m, 2H), 5.16 (d, 1H), 5.00-4.90 (m, 2H), 4.60 (dd, 1H), 4.88-4.34 (m, 2H), 4.18-4.10 (m, 1H), 2.98-2.89 (m, 1H), 2.68 (dd, 2H), 2.18-1.96 (m, 6H), 1.50-1.32 (m, 7H), 1.28 (s, 9H), 1.09-1.25 (m, 2H).

[0098] CH_2Cl_2 (10 mL) 내 화합물 I-11 (0.10 g, 0.11 mmol)의 용액에 Hoveyda-Grubbs 2nd (35 mg, 0.056 mmol)을 N_2 하에서 실온에서 가하였다. 그 다음, 반응 혼합물을 40℃에서 24시간 동안 교반하고 복분해 고리화를 수행하였다. 반응을 종결시키고 반응 혼합물을 실리카겔 컬럼 크로마토그래피로 정제하여 화합물 I-12 (30 mg, 31%)를

얻었다. MS: m/z 893.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.39 (s, 1H), 8.59 (d, 2H), 8.21 (d, 1H), 7.77 (d, 2H), 7.69-7.57 (m, 2H), 7.46 (dd, 1H), 7.20 (s, 1H), 6.12 (s, 1H), 5.69 (q, 1H), 5.12 (d, 1H), 4.97 (dd, 1H), 4.81-4.68 (m, 2H), 4.28-4.07 (m, 2H), 2.96-2.49 (m, 3H), 2.30 (q, 1H), 1.96-1.12 (m, 14H), 1.08 (s, 9H), 0.96-0.82 (m, 2H).

[0099] MeOH (10 mL) 내 화합물 I-12 (30 mg, 0.034 mmol)의 용액에 5% Pd-C (5 mg)를 N_2 하에서 실온에서 가하였다. 그 다음, 반응 혼합물을 실온에서 수소 하에서 60 psi의 압력에서 4시간 동안 교반하였다. 반응 혼합물을 여과하고 실리카겔 컬럼 크로마토그래피로 정제하여 화합물 1 (16.5 mg, 55%)을 얻었다. MS: m/z 895.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.79 (s, 1H), 8.57 (d, 2H), 8.21 (d, 1H), 7.75 (d, 2H), 7.64 (m, 2H), 7.46 (d, 1H), 7.11 (s, 1H), 6.11 (s, 1H), 5.29 (d, 1H), 4.72 (m, 2H), 4.38 (m, 2H), 4.12 (m, 1H), 3.02-2.58 (m, 3H), 1.98-0.86 (m, 29H).

[0100] 실시예 2~141 : 화합물 2~141의 합성

[0101] 각각의 화합물 2~141를 실시예 1에 기재된 방법과 유사한 방법으로 제조하였다.

[0102] 화합물 2: MS: m/z 883.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.51 (s, 1H), 8.53 (d, 2H), 8.16 (d, 1H), 7.73 (d, 2H), 7.62 (m, 2H), 7.22 (m, 2H), 6.07 (s, 1H), 5.23 (d, 1H), 4.77 (dd, 1H), 4.49 (d, 1H), 4.35 (m, 1H), 4.13 (m, 1H), 3.02-2.57 (m, 3H), 1.99-0.91 (m, 30H).

[0103] 화합물 3: MS: m/z 823.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 8.53 (d, 2H), 8.16 (d, 1H), 7.73 (d, 2H), 7.61(m, 2H), 7.41 (m, 2H), 6.13 (m, 2H), 5.69 (q, 1H), 4.98 (dd, 1H), 4.78 (m, 1H), 4.55 (m, 1H), 4.42 (m, 1H), 4.19 (m, 1H), 2.89 (m, 1H), 2.78 (m, 2H), 2.52 (m, 1H), 2.23 (q, 1H), 1.96-0.84 (m, 15H), 1.90 (s, 3H).

[0104] 화합물 4: MS: m/z 882.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.47 (s, 1H), 8.64 (d, 1H), 8.52 (m, 3H), 7.70 (d, 2H), 7.44 (dd, 1H), 6.07 (s, 1H), 5.63 (q, 1H), 5.01-4.73 (m, 3H), 4.07-4.01 (m, 2H), 2.90-2.22 (m, 4H), 1.97-1.09 (m, 17H), 0.94 (s, 9H), 0.90-0.88 (m, 1H).

[0105] 화합물 5: MS: m/z 840.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.64-8.47 (m, 4H), 7.80 (d, 2H), 7.50-7.27 (m, 2H), 6.15 (s, 1H), 5.69 (q, 1H), 5.23 (d, 1H), 5.02 (dd, 1H), 4.84 (dd, 1H), 4.53 (d, 1H), 4.25-4.11 (m, 2H), 3.32 (s, 3H), 2.93-2.15 (m, 4H), 1.92-0.83 (m, 16H).

[0106] 화합물 6: MS: m/z 824.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.48 (s, 1H), 8.63 (d, 1H), 8.62-8.48 (m, 3H), 7.78 (d, 2H), 7.44-7.40 (m, 1H), 6.16-6.14 (m, 2H), 5.73 (q, 1H), 5.04 (dd, 1H), 4.85 (dd, 1H), 4.55 (s, 1H), 4.51 (s, 1H), 4.15 (d, 1H), 2.93-2.89 (m, 2H), 2.77-2.22 (m, 3H), 1.95-1.85 (m, 1H), 1.79 (s, 3H), 1.76-0.83 (m,15H).

[0107] 화합물 7: MS: m/z 839.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.39 (s, 1H), 8.46 (d, 2H), 8.15 (d, 1H), 7.71 (d, 2H), 7.62-7.37 (m, 3H), 7.16 (s, 1H), 6.08 (s, 1H), 5.71 (q, 1H), 5.25 (d, 1H), 4.96 (dd, 1H), 4.75 (dd, 1H), 4.44 (d, 1H), 4.35-4.09 (m, 2H), 3.34 (s, 3H), 2.96-2.71 (m, 2H), 2.57 (brs, 1H), 2.28 (q, 1H), 2.08-0.87 (m, 16H).

[0108] 화합물 8: MS: m/z 849.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.54 (s, 1H), 8.45 (d, 2H), 8.06 (d, 1H), 7.71 (d, 2H), 7.57 (m, 3H), 7.35 (s, 1H), 6.28 (d, 1H), 6.04 (s, 1H), 5.71 (q, 1H), 4.96 (dd, 1H), 4.67 (dd, 1H), 4.47 (d, 1H), 4.45 (brs, 1H), 4.11 (m, 1H), 2.92-2.45 (m, 4H), 2.32 (q, 1H), 1.96-0.84 (m, 20H).

[0109] 화합물 9: MS: m/z 880.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.40 (d, 2H), 8.14 (s, 1H), 7.97 (d,

1H), 7.64 (d, 2H), 7.48-7.41 (m, 2H), 7.25-7.20 (m, 1H), 5.96 (s, 1H), 5.63 (q, 1H), 4.92-4.86 (m, 2H), 4.77 (d, 1H), 4.44 (s, 1H), 4.20 (dd, 1H), 4.03 (dd, 1H), 2.90-2.84 (m, 2H), 2.80-2.63 (m, 1H), 2.38-2.32 (m, 1H), 1.98-1.02 (m, 15H), 0.91 (s, 9H), 0.90-0.86 (m, 1H).

[0110] 화합물 10: MS: m/z 911.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.23 (s, 1H), 8.54 (d, 2H), 7.87-7.80 (m, 1H), 7.71 (d, 2H), 7.56 (dd, 1H), 7.33-7.20 (m, 1H), 6.88 (s, 1H), 6.13 (s, 1H), 5.65 (q, 1H), 5.07-4.94 (m, 2H), 4.69 (dd, 1H), 4.57 (d, 1H), 4.43-4.38 (m, 1H), 4.24-4.01 (m, 2H), 2.91-2.80 (m, 2H), 2.74 (s, 3H), 2.65-2.63 (m, 1H), 2.60-2.41 (m, 1H), 2.22 (q, 1H), 1.98-0.86 (m, 20H).

[0111] 화합물 11: MS: m/z 907.3 (M^++1).

[0112] 화합물 12: MS: m/z 923.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.57 (d, 2H), 8.06 (d, 1H), 7.76 (d, 2H), 7.51 (s, 1H), 7.14-6.93 (m, 2H), 6.13 (s, 1H), 5.80-5.60 (m, 1H), 5.31 (d, 1H), 4.97-4.83 (m, 2H), 4.79 (dd, 1H), 4.64-4.04 (m, 3H), 3.88 (s, 3H), 2.94-2.43 (m, 3H), 2.36-0.86 (m, 25H).

[0113] 화합물 13: MS: m/z 852.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.68 (s, 1H), 8.38 (d, 2H), 7.95 (d, 1H), 7.72-7.58 (m, 3H), 7.47 (d, 2H), 7.24-7.19 (m, 1H), 6.01 (s, 1H), 5.69 (q, 1H), 4.94 (dd, 1H), 4.78 (dd, 1H), 4.70 (d, 1H), 4.46 (d, 1H), 4.22-3.98 (m, 2H), 2.97-2.80 (m, 2H), 2.57 (s, 6H), 2.67-2.41 (m, 1H), 2.23 (q, 1H), 1.85-0.84 (m, 16H).

[0114] 화합물 14: MS: m/z 766.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.62 (m, 2H), 8.24 (m, 1H), 7.77 (d, 2H), 7.67 (m, 2H), 7.48 (m, 1H), 6.90 (s, 1H), 6.18 (s, 1H), 5.72 (q, 1H), 4.98 (dd, 1H), 4.65 (dd, 1H), 4.24 (m, 1H), 4.05 (m, 1H), 2.92 (m, 1H), 2.76 (m, 2H), 2.58-2.28 (m, 4H), 1.94-1.05 (m, 13H), 0.97-0.86 (m, 2H).

[0115] 화합물 15: MS: m/z 893.3(M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.88 (s, 1H), 8.68 (d, 1H), 8.26 (d, 1H), 7.80-7.65 (m, 4H), 7.35-7.26 (m, 1H), 6.98 (d, 1H), 6.20 (d, 1H), 5.71 (q, 1H), 5.18 (d, 1H), 5.00 (dd, 1H), 4.77 (dd, 1H), 4.64 (d, 1H), 4.46 (s, 1H), 4.25 (dd, 1H), 4.15 (dd, 1H), 2.92-2.28 (m, 4H), 2.17-0.82 (m, 24H).

[0116] 화합물 16: MS: m/z 877.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.40 (s, 1H), 8.45 (d, 2H), 8.04 (d, 1H), 7.62 (d, 2H), 7.58-7.50 (m, 2H), 7.44 (s, 1H), 7.35 (dd, 1H), 6.02 (s, 1H), 5.95 (d, 1H), 5.63 (q, 1H), 4.81 (dd, 1H), 4.70 (dd, 1H), 4.49 (d, 1H), 4.42-4.38 (m, 1H), 4.04 (dd, 1H), 2.90-2.20 (m, 6H), 1.96-0.83 (m, 23H).

[0117] 화합물 17: MS: m/z 907.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.73 (s, 1H), 8.62 (d, 1H), 7.96 (s, 1H), 7.71 (d, 1H), 7.64 (dd, 1H), 7.59-7.25 (m, 3H), 6.11 (s, 1H), 5.62 (q, 1H), 5.21 (d, 1H), 4.99 (dd, 1H), 4.79 (dd, 1H), 4.61 (d, 1H), 4.52 (s, 1H), 4.25-4.10 (m, 2H), 2.95-2.51 (m, 3H), 2.47 (s ,3H), 2.31 (q, 1H), 2.03-0.91 (m, 24H).

[0118] 화합물 18: MS: m/z 767.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 8.49 (d, 2H), 8.15 (d, 1H), 7.77 (d, 2H), 7.64-7.58 (m, 2H), 7.41-7.32 (m, 1H), 7.29 (s, 1H), 6.08 (s, 1H), 5.78 (q, 1H), 5.08 (dd, 1H), 4.66 (dd, 1H), 4.42 (d, 1H), 4.09-4.06 (m, 1H), 3.85-3.62 (m, 4H), 2.93-2.45 (m, 4H), 2.04-0.87 (m, 13H).

[0119] 화합물 19: MS: m/z 899.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 8.51 (d, 2H), 7.80 (dd, 1H), 7.70 (d, 2H), 7.51-7.42 (m, 1H), 7.37-7.23 (m, 1H), 6.97 (s, 1H), 6.06 (s, 1H), 5.63 (q, 1H), 4.96-4.85 (m, 2H), 4.75-4.63 (m, 2H), 4.09-4.02 (m, 2H), 2.93-2.43 (m, 4H), 2.21 (q, 1H), 1.96-0.76 (m, 24H).

[0120] 화합물 20: MS: m/z 895.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.43 (d, 2H), 7.81 (s, 1H), 7.67 (d,

2H), 7.51 (s, 1H), 7.35-7.28 (m, 2H), 5.92 (s, 1H), 5.57 (q, 1H), 5.19 (d, 1H), 4.88-4.61 (m, 3H), 4.14-4.00 (m, 2H), 2.83-2.41 (m, 4H), 2.38 (s, 3H), 2.24 (q, 1H), 1.96-1.16 (m, 15H),1.05 (s, 9H), 0.97-0.78 (m, 1H).

[0121] 화합물 21: MS: m/z 923.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.50 (d, 2H), 7.67 (d, 2H), 7.59 (s, 1H), 7.41 (d, 1H), 7.34 (s, 1H), 7.16 (d, 1H), 6.06 (s, 1H), 5.64 (q, 1H), 5.23 (d, 1H), 4.94 (dd, 1H), 4.87 (dd, 1H), 4.58-4.42 (m, 2H), 4.30-4.02 (m, 2H), 3.84 (s, 3H), 2.88-2.44 (m, 4H), 2.21 (q, 1H), 1.84-0.78 (m, 23H).

[0122] 화합물 22: MS: m/z 752.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.76 (s, 1H), 8.61 (d, 2H), 8.25 (m, 1H), 7.79 (d, 2H), 7.67 (d, 2H), 7.52 (m, 1H), 6.70 (s, 1H), 6.19 (s, 1H), 5.69 (q, 1H), 5.08 (m, 1H), 4.65 (dd, 1H), 4.23 (dd, 1H), 4.02 (m, 1H), 3.05-1.98 (m, 7H), 1.96-0.82 (m, 13H).

[0123] 화합물 23: MS: m/z 907.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.40 (s, 1H), 8.56 (d, 2H), 8.08 (d, 1H), 7.73 (d, 2H), 7.29 (s, 1H), 7.26-7.20 (m, 2H), 6.13 (s, 1H), 5.71 (q, 1H), 5.22 (d, 1H), 4.95 (dd, 1H), 4.82-4.73 (m, 1H), 4.63-4.51 (m, 1H), 4.33-4.06 (m, 2H), 2.96-2.51 (m, 4H), 2.53 (s, 3H), 2.24 (q, 1H), 1.96-0.94 (m, 24H).

[0124] 화합물 24: MS: m/z 916.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 8.48 (d, 2H), 8.08 (s, 1H), 7.68 (d, 2H), 7.50-7.37 (m, 3H), 6.01 (s, 1H), 5.59 (q, 1H), 5.13 (d, 1H), 4.83 (dd, 1H), 4.74-4.63 (m, 2H), 4.15 (dd, 1H), 4.05 (d, 1H), 2.94-2.41 (m, 4H), 2.21 (q, 1H), 1.89-1.14 (m, 14H), 1.03 (s, 9H), 0.96-0.85 (m, 1H).

[0125] 화합물 25: MS: m/z 923.3 (M^++1).

[0126] 화합물 26: MS: m/z 923.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 1035 (s, 1H), 8.50 (d, 2H), 7.69 (d, 2H), 7.52 (dd, 1H), 7.40 (s, 1H), 7.12 (d, 1H), 6.75 (d, 1H), 6.05 (s, 1H), 5.63 (q, 1H), 5.27 (d, 1H), 4.97-4.83 (m, 1H), 4.75 (dd, 1H), 4.42 (brs, 1H), 4.28-4.08 (m, 2H), 4.08 (s, 3H), 2.91-2.38 (m, 4H), 2.23 (q, 1H), 1.96-0.82 (m, 24H).

[0127] 화합물 27: MS: m/z 894.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 8.47 (d, 2H), 8.08 (d, 1H), 7.62 (d, 2H), 7.58-7.54 (m, 2H), 7.40-7.33 (m, 1H), 7.31 (s, 1H), 6.07 (s, 1H), 5.63 (q, 1H), 4.95 (dd, 1H), 4.83 (d, 1H), 4.87 (dd, 1H), 4.58 (d, 1H), 4.31-4.19 (m, 1H), 4.09 (dd, 1H), 3.40-3.32 (m, 4H), 3.01-2.41 (m, 8H), 2.19 (q, 1H), 1.92-0.83 (m, 15H).

[0128] 화합물 28: MS: m/z 878.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.56 (s, 1H), 8.41 (d, 2H), 8.02 (d, 1H), 7.74 (s, 1H), 7.68 (d, 2H), 7.53-7.47 (m, 2H), 7.35-7.32 (m, 1H), 6.01 (s, 1H), 5.62 (q, 1H), 4.90 (dd, 1H), 4.78 (dd, 1H), 4.59-4.43 (m, 2H), 4.35-4.25 (m, 1H), 4.05 (dd, 1H), 3.61-3.49 (m, 1H), 3.01-2.45 (m, 8H), 2.21 (q, 1H), 1.85-0.83 (m, 18H).

[0129] 화합물 29: MS: m/z 909.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.27 (s, 1H), 8.53 (d, 2H), 8.16 (d, 1H), 7.67 (d, 2H), 7.64-7.43 (m, 4H), 6.03 (s, 1H), 5.61 (q, 1H), 5.22-5.19 (m, 1H), 4.87 (dd, 1H), 4.66 (dd, 1H), 4.57 (d, 1H), 4.19-4.01 (m, 3H), 3.71-3.42 (m, 4H), 3.19-2.97 (m, 2H), 2.91-2.43 (m, 4H), 2.20 (q, 1H), 1.95-0.81 (m, 17H).

[0130] 화합물 30: MS: m/z 906.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.18 (s, 1H), 8.62 (d, 2H), 8.25 (d, 1H), 7.78 (d, 2H), 7.70-7.61 (m, 2H), 7.55-7.46 (m, 1H), 7.01 (1H), 6.18 (1H), 5.71 (q, 1H), 5.12 (d, 1H), 5.02 (dd, 1H), 4.77 (dd, 1H), 4.64 (d, 1H), 4.53-4.43 (1H), 4.31-4.18 (m, 2H), 2.83-2.44 (m, 3H), 2.28 (q, 1H), 1.95-1.22 (m, 23H), 0.83 (s, 3H).

[0131] 화합물 31: MS: m/z 907.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.39 (s, 1H), 8.57 (d, 2H), 8.05 (d, 1H), 7.77 (d, 2H), 7.42-7.26 (m, 3H), 6.15 (s, 1H), 5.69 (q, 1H), 5.29 (d, 1H), 4.96 (dd, 1H), 4.78 (dd, 1H), 4.63-4.56 (m, 1H), 4.40-4.13 (m, 3H), 2.91-2.64 (m, 3H), 2.62 (s, 3H), 2.56-2.22 (m, 2H), 1.89-0.96 (m, 23H).

[0132] 화합물 32: MS: m/z 895.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.60 (d, 2H), 8.22 (d, 1H), 7.55 (d, 2H), 7.67-7.60 (m, 2H), 7.45 (dd, 1H), 7.20 (s, 1H), 6.12 (s, 1H), 5.65 (q, 1H), 5.13 (d, 1H), 4.97 (dd, 1H), 4.81-4.71 (m, 2H), 4.14-4.10 (m, 2H), 2.82-2.45 (m, 3H), 2.27 (q, 1H), 1.97-1.21 (m, 14H), 1.08 (s, 9H), 0.89-0.80 (m, 4H).

[0133] 화합물 33: MS: m/z 853.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.22 (s, 1H), 8.58 (s, 1H), 8.48 (d, 2H), 8.08 (d, 1H), 7.57 (d, 2H), 7.53-7.44 (m, 2H), 7.39-7.26 (m, 1H), 6.05 (s, 1H), 5.65 (q, 1H), 5.21 (d, 1H), 4.95 (dd, 1H), 4.82 (dd, 1H), 4.40 (d, 1H), 4.21-4.03 (m, 2H), 3.27 (s, 3H), 2.81-2.40 (m, 3H), 2.22 (q, 1H), 1.95-1.20 (m,15H), 0.81 (s, 3H).

[0134] 화합물 34: MS: m/z 923.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.17 (s, 1H), 8.61 (d, 2H), 8.25 (d, 1H), 7.80 (d, 2H), 7.65-7.50 (m, 2H), 7.41 (dd, 1H), 6.97 (s, 1H), 6.18 (s, 1H), 5.72 (q, 1H), 5.15 (d, 1H), 5.05 (dd, 1H), 4.77 (dd, 1H), 4.65 (d, 1H), 4.29-4.10 (m, 2H), 3.78-3.52 (m, 2H), 3.23-3.03 (m, 2H), 2.79-2.85 (m, 2H), 2.56 (brs, 1H), 2.27 (q, 1H), 1.98-1.19 (m, 20H), 0.88 (s, 3H).

[0135] 화합물 35: MS: m/z 894.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.47 (d, 2H), 8.12 (s, 1H), 8.05 (d, 1H), 7.70 (d, 2H), 7.53-7.46 (m, 2H), 7.31-7.22 (m, 1H), 6.03 (s, 1H), 5.70 (q, 1H), 5.03-4.84 (m, 4H), 4.24 (d, 1H), 2.95-2.47 (m, 3H), 2.38 (q, 1H), 1.94-1.11 (m, 25H), 0.85 (s, 3H).

[0136] 화합물 36: MS: m/z 889.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 8.47 (d, 2H), 8.07 (d, 1H), 7.65 (d, 2H), 7.57 (s, 1H), 7.55-7.42 (m, 2H), 7.38-7.27 (m, 2H), 6.82 (d, 1H), 6.62 (d, 1H), 5.63 (dd, 1H), 6.15 (s, 1H), 5.63 (q, 1H), 4.92 (dd, 1H), 4.74-4.59 (m, 2H), 4.42 (d, 1H), 4.17 (dd, 1H), 2.79-2.42 (m, 3H), 2.23 (q, 1H), 1.95-1.05 (m, 15H), 0.76 (s, 3H).

[0137] 화합물 37: MS: m/z 837.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.16 (s, 1H), 8.48 (d, 2H), 8.11 (d, 1H), 7.69 (d, 2H), 7.58 (d, 2H), 7.36 (dd, 1H), 7.17 (s, 1H), 6.15 (s, 1H), 6.04 (d, 1H), 5.64 (q, 1H), 4.94 (dd, 1H), 4.67 (dd, 1H), 4.47 (dd, 1H), 4.41 (d, 1H), 4.12 (dd, 1H), 2.78-2.68 (m, 1H), 2.43 (brs, 1H), 2.22 (q, 1H), 1.98-1.64 (m, 7H), 1.53-1.11 (m, 12H), 0.78 (s, 3H).

[0138] 화합물 38: MS: m/z 863.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.52 (s, 1H), 8.38 (d, 2H), 7.92 (d, 1H), 7.88 (s, 1H), 7.65 (d, 2H), 7.58-7.52 (m, 2H), 7.35-7.21 (m, 1H), 6.19 (d, 1H), 5.92 (s, 1H), 5.71 (q, 1H), 5.01 (dd, 1H), 4.81 (dd, 1H), 4.62 (d, 1H), 4.37 (brs, 1H), 4.11-4.01 (m, 1H), 2.98-2.87 (m, 1H), 2.74-2.52 (m, 2H), 2.33 (q, 1H), 1.98-1.19 (m, 16H), 0.88 (s, 3H), 0.68-0.41 (m, 4H).

[0139] 화합물 39: MS: m/z 908.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 8.48 (d, 2H), 8.15 (d, 1H), 7.67 (d, 2H), 7.57-7.46 (m, 2H), 7.39-7.35 (m, 2H), 6.07 (s, 1H), 5.62 (q, 1H), 4.98-4.86 (m, 2H), 4.77 (dd, 1H), 4.58 (d, 1H), 4.02 (dd, 1H), 3.38-3.24 (m, 4H), 2.99-2.81 (m, 4H), 2.82-2.42 (m, 3H), 2.19 (q, 1H), 1.88-1.04 (m, 15H), 0.92-0.72 (m, 4H).

[0140] 화합물 40: MS: m/z 866.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.51 (s, 1H), 8.37 (d, 2H), 7.91 (d, 1H), 7.69 (s, 1H), 7.61 (d, 2H), 7.53-7.42 (m, 2H), 7.23-7.14 (m, 1H), 6.01 (s, 1H), 5.67 (q, 1H), 4.94 (dd, 1H), 4.72 (dd, 1H), 4.61 (d, 1H), 4.43 (d, 1H), 4.30-4.02 (m, 2H), 2.94-2.60 (m, 3H), 2.57 (s, 6H), 2.20 (q, 1H), 1.80-1.15 (m, 15H), 0.77 (s, 3H).

[0141] 화합물 41: MS: m/z 892.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.40 (s, 1H), 8.51 (d, 2H), 8.16 (d, 1H), 7.85 (d, 2H), 7.65 (s, 1H), 7.58 (d, 1H), 7.41-7.37 (m, 1H), 6.14 (s, 1H), 5.59 (q, 1H), 4.99 (dd, 1H), 4.80 (dd, 1H), 4.62 (d, 1H), 4.57 (d, 1H), 4.45-4.37 (m, 1H), 4.17 (dd, 1H), 3.75-3.65 (m, 2H), 3.60-3.48 (m, 2H), 2.80-2.45 (m, 3H), 2.24 (q, 1H), 1.89-1.41 (m,20H), 0.8 (s, 3H).

[0142] 화합물 42: MS: m/z 907.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H), 8.43 (d, 2H), 8.10 (d, 1H), 7.65 (d, 2H), 7.60-7.55 (m, 2H), 7.39-7.35 (m, 1H), 7.25 (s, 1H), 6.05 (s, 1H), 5.98 (d, 1H), 5.66 (q, 1H), 4.93 (dd, 1H), 4.72 (dd, 1H), 4.52-4.42 (m, 2H), 4.08 (dd, 1H), 3.78-3.60 (m, 2H), 3.21-3.11 (m, 2H), 3.81-2.43 (br, 3H), 2.19-2.05 (m, 2H), 1.85-1.09 (m, 19H), 0.77 (s, 3H).

[0143] 화합물 43: MS: m/z 890.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.16 (s, 1H), 8.55 (d, 2H), 8.21 (d, 1H), 8.14 (s, 1H), 7.68 (d, 2H), 7.58-7.41 (m, 4H), 7.21 (s, 1H), 6.40 (s, 1H), 6.18 (s, 1H), 5.63 (q, 1H), 4.95 (dd, 1H), 4.78-4.62 (m, 2H), 4.44 (d, 1H), 4.16 (dd, 1H), 2.69-2.44 (m, 3H), 2.24 (q, 1H), 1.98-1.15 (m, 15H), 0.79 (s, 3H).

[0144] 화합물 44: MS: m/z 879.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.22 (s, 1H), 8.59 (d, 2H), 8.22 (d, 1H), 7.76 (d, 2H), 7.75-7.60 (m, 2H), 7.48-7.42 (m, 1H), 7.17 (s, 1H), 6.20 (s, 1H), 6.16 (d, 1H), 5.71 (q, 1H), 5.02 (dd, 1H), 4.77 (dd, 1H), 4.60-4.52 (m, 2H), 4.20 (dd, 1H), 2.79-2.45 (m, 3H), 2.21 (q, 1H), 1.96-1.07 (m, 15H), 1.03 (s, 9H), 0.82 (s, 3H).

[0145] 화합물 45: MS: m/z 933.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.22 (s, 1H), 8.56 (d, 2H), 8.19 (d, 1H), 7.88 (d, 2H), 7.69-7.42 (m, 3H), 7.19 (s, 1H), 6.81-6.62 (m, 4H), 6.11 (s, 1H), 5.68 (q, 1H), 5.00 (dd, 1H), 4.77 (dd, 1H), 4.55 (d, 2H), 4.41-4.12 (m, 2H), 2.82-2.42 (m, 3H), 2.28 (q, 1H), 2.01-1.11 (m, 15H), 0.83 (s, 1H).

[0146] 화합물 46: MS: m/z 891.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.34 (s, 1H), 8.35 (d, 2H), 7.94 (d, 1H), 7.66 (s, 1H), 7.62 (d, 2H), 7.54-7.46 (m, 2H), 7.22 (dd, 1H), 5.93-5.84 (m, 2H), 5.61 (q, 1H), 4.92 (dd, 1H), 4.87 (dd, 1H), 4.58 (d, 1H), 4.41-4.36 (m, 1H), 4.04 (dd, 1H), 2.82-2.75 (m, 1H), 2.65-2.50 (m, 2H), 2.24 (q, 1H), 1.80-1.00 (m, 24H), 0.81 (s, 3H).

[0147] 화합물 47: MS: m/z 867.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 8.54 (d, 2H), 8.18 (d, 1H), 7.86 (d, 1H), 7.66 (d, 2H), 7.61 (m, 2H), 7.46 (m, 2H), 6.13 (s, 1H), 5.67 (q, 1H), 4.94 (dd, 1H), 4.77 (m, 1H), 4.61 (m, 1H), 4.40 (d, 1H), 4.20 (m, 1H), 3.72 (s, 3H), 2.91 (m, 1H), 2.72-2.39 (m, 3H), 2.25 (q, 1H), 1.96-0.82 (m, 15H).

[0148] 화합물 48: MS: m/z 908.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 8.44 (d, 1H), 8.23 (d, 1H), 7.67 (m, 3H), 7.52 (m, 1H), 7.07 (s, 1H), 6.04 (s, 1H), 5.68 (q, 1H), 5.12 (d, 1H), 4.98 (dd, 1H), 4.79-4.68 (m, 2H), 4.34 (s, 1H), 4.20 (dd, 1H), 4.00 (m, 1H), 2.95 (s, 3H), 2.93 (m, 1H), 2.72 (m, 2H), 2.52 (m, 1H), 2.26 (q, 1H), 1.94-0.82 (23H).

[0149] 화합물 49: MS: m/z 920.2 (M^++1).

[0150] 화합물 50: MS: m/z 806.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.47 (s, 1H), 8.77-8.53 (m, 2H), 8.19 (d, 1H), 8.13 (d, 1H), 7.73 (s, 1H), 7.53-7.30 (m, 2H), 7.26-7.18 (m, 1H), 6.07 (s, 1H), 5.70-5.40 (m, 2H), 4.98-4.61 (m, 2H), 4.40-4.03 (m, 3H), 3.47 (s, 3H), 2.95-2.90 (m, 1H), 2.87-2.50 (m, 3H), 2.20 (dd, 1H), 2.10-1.86 (m, 3H), 1.61-1.08 (m, 11H), 0.96 (m, 1H).

[0151] 화합물 51: MS: m/z 822.3, 824.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.69-8.44 (m, 3H), 8.34 (d, 2H), 7.65 (s, 1H), 7.42-7.30 (m, 3H), 6.04 (s, 1H), 5.70-5.45 (m, 2H), 4.91-4.63 (m, 2H), 4.35-4.03 (m, 3H), 3.42 (s, 3H), 2.84 (s, 1H), 2.72-2.50 (m, 3H), 2.22 (dd, 1H), 2.19 (m, 3H), 1.54-0.78 (m,

11H).

[0152] 화합물 52: MS: m/z 774.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.65-8.58 (m, 1H), 8.46 (d, 1H), 8.18 (d, 1H), 8.06 (d, 1H), 7.46-7.38 (m,3H), 7.19-7.11 (m, 1H), 6.13 (s, 1H), 6.04 (d, 1H), 5.66 (dd, 1H), 5.27-5.08 (m, 1H), 5.07-4.67 (m, 2H), 4.52-4.39 (m, 2H), 4.13-4.09 (m, 1H), 3.62-3.60 (m, 1H), 2.95-2.10 (m, 4H), 1.98 (s, 3H), 1.90-0.81 (m, 14H).

[0153] 화합물 53: MS: m/z 825.3 (M^++1).

[0154] 화합물 54: MS: m/z 805.3, 807.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.46 (s, 1H), 8.28-8.19 (m, 1H), 7.98 (s, 1H), 7.88-7.85 (m, 1H), 7.63-7.39 (m, 6H), 6.07 (s, 1H), 5.67-5.46 (m, 2H), 4.96-4.79 (m, 2H), 4.41-4.09 (m, 3H), 3.37 (s, 3H), 2.97-0.88 (m, 20H).

[0155] 화합물 55: MS: m/z 789.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.61 (s, 1H), 8.49 (s, 1H), 8.39-8.24 (m, 2H), 8.05-7.94 (m, 2H), 7.56-7.04 (m, 5H), 5.90 (s, 1H), 5.47 (br, 1H), 4.93-4.69 (br, 2H), 4.40-4.07 (m, 3H), 3.46 (s, 1H), 3.23 (s, 3H), 2.91-2.07 (m, 11H), 1.99-1.54 (m, 4H), 1.32-0.81 (m, 5H).

[0156] 화합물 56: MS: m/z 839.3, 843.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.27 (s, 1H), 8.24 (d, 1H), 7.89 (d, 1H), 7.63 (d, 1H), 7.56 (s, 1H), 7.52-7.40 (m, 2H), 7.14 (brs, 1H), 6.08 (s, 1H), 5.69 (q, 1H), 5.30 (brs, 1H), 4.97 (dd, 1H), 4.74 (dd, 1H), 4.46 (d, 1H), 4.40-4.22 (m, 1H), 4.13-4.08 (m, 1H), 3.36 (s, 3H), 2.99-2.05 (m, 5H), 1.90-1.10 (m, 15H), 0.99-0.88 (m, 1H).

[0157] 화합물 57: MS: m/z 827.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.17 (s, 1H), 8.42 (d, 2H), 7.84 (d, 1H), 7.49-7.41 (m, 4H), 7.28 (m, 1H), 7.13 (brs, 1H), 6.16 (s, 1H), 5.63 (q, 1H), 4.95 (m, 1H), 4.70 (dd, 1H), 4.63 (m, 1H), 4.31-4.11 (m, 2H), 2.97-2.70 (m, 3H), 2.50-1.06 (m,17H), 0.91 (m,1H).

[0158] 화합물 58: MS: m/z 803.3 (M^++1).

[0159] 화합물 59: MS: m/z 789.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.39 (s, 1H), 8.53-8.41 (m, 3H), 7.81 (d, 1H), 7.59-7.42 (m, 4H), 7.26 (m, 1H), 7.18 (s, 1H), 6.17 (s, 1H), 5.17 (q, 1H), 5.28 (dd, 1H), 4.95 (dd, 1H), 4.75 (m, 1H), 4.43 (d, 1H), 4.38-4.04 (m, 2H), 3.40 (s, 3H), 2.96-2.67 (m, 3H), 2.60-2.41 (m, 1H), 2.37-2.22 (m, 1H), 1.99-0.85 (m, 14H).

[0160] 화합물 60: MS: m/z 773.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.46 (d, 2H), 7.88-7.84 (m, 1H), 7.60-7.50 (m, 4H), 7.35-7.17 (m, 1H), 6.20 (s, 1H), 6.08 (d, 1H), 5.72 (q, 1H), 4.98 (dd, 1H), 4.72 (dd, 1H), 4.56 (m, 1H), 4.41 (d, 1H), 4.21 (m, 1H), 2.94-2.90 (m, 1H), 2.80-2.77 (m, 1H), 2.55-2.52 (m, 1H), 2.23 (q, 1H), 1.98-1.90 (m, 1H), 1.84 (s, 3H), 1.80-0.80 (m, 16H).

[0161] 화합물 61: MS: m/z 845.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.41 (s, 1H), 8.34 (d, 2H), 7.84 (d, 1H), 7.53-7.44 (m, 1H), 7.40-7.33 (m, 3H), 7.19 (s, 1H), 6.14 (s, 1H), 5.71 (q, 1H), 5.15 (d, 1H), 4.98 (dd, 1H), 4.89-4.80 (m, 2H), 4.25-4.19 (m, 2H), 2.95-2.90 (m, 1H), 2.88-2.42 (m, 3H), 2.44 (s, 3H), 2.29 (m, 1H), 1.98-1.20 (m, 14H), 1.11 (s, 9H), 1.00-0.87 (1H).

[0162] 화합물 62: MS: m/z 841.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1H), 8.35 (d, 2H), 7.89 (d, 1H), 7.60-7.57 (m, 1H), 7.33 (d, 2H), 7.17 (d, 1H), 7.05 (s, 1H), 6.22 (s, 1H), 5.68 (q, 1H), 4.97 (dd, 1H), 4.77-4.64 (m, 2H), 4.33-4.17 (m, 2H), 2.93-2.74 (m, 3H), 2.44 (s, 3H), 2.21 (m, 1H), 1.95-0.91 (m, 17H).

[0163] 화합물 63: MS: m/z 903.3; 905.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.18 (s, 1H), 8.45 (d, 2H), 8.23 (d, 1H), 7.64 (m, 2H), 7.49 (d, 3H), 7.01 (s, 1H), 6.17 (s, 1H), 5.72 (q, 1H), 5.13 (d, 1H), 4.99 (dd, 1H), 4.77 (dd, 1H), 4.58 (d, 1H), 4.53 (brs, 1H), 4.27 (m, 1H), 4.14 (m, 1H), 2.83-2.44 (m, 3H), 2.27 (q,

1H), 1.95-1.22 (m, 23H), 0.83 (s, 3H).

[0164] 화합물 64: MS: m/z 787.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.25 (d, 2H), 7.75 (d, 1H), 7.67 (s, 1H), 7.53-7.52 (m, 1H), 7.26 (d, 2H), 6.29 (d, 1H), 6.19 (s, 1H), 5.67 (q, 1H), 4.94 (dd, 1H), 4.75 (dd, 1H), 4.52 (brs, 1H), 4.42 (d, 1H), 4.10-4.18 (m, 1H), 2.89-2.50 (m, 3H), 2.43 (s, 3H), 2.35-2.20 (m, 1H), 1.98-1.85 (m, 1H), 1.82 (s, 3H), 1.62-0.81 (m, 16H).

[0165] 화합물 65: MS: m/z 803.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.46 (s, 1H), 8.30 (d, 1H), 8.17 (d, 2H), 7.63 (d, 1H), 7.55 (s, 1H), 7.45-7.41 (m, 1H), 7.25-7.20 (m, 2H), 5.97 (s, 1H), 5.65-5.59 (m, 1H), 5.36 (d, 1H), 4.91-4.87 (m, 1H), 4.73 (dd, 1H), 4.37-4.05 (m, 3H), 3.30 (s, 3H), 2.84-2.47 (m, 3H), 2.38 (s, 3H), 2.40-2.16 (m, 1H), 1.90-0.87 (m, 16H).

[0166] 화합물 66: MS: m/z 871.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.19-8.02 (m, 2H), 7.93 (s, 1H), 7.67 (s, 1H), 7.47-7.26 (m, 3H), 6.05 (s, 1H), 5.62 (q, 1H), 5.34 (d, 1H), 4.96-4.42 (m, 4H), 4.36-4.10 (m, 2H), 2.95-2.90 (m, 1H), 2.77 (s, 3H), 2.76-2.48 (m, 3H), 2.35 (s, 3H), 2.30-0.87 (m, 24H).

[0167] 화합물 67: MS: m/z 875.3 (M^++1).

[0168] 화합물 68: TG-2379: MS: m/z 871.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.34 (d, 2H), 7.85 (d, 1H), 7.73 (s, 1H), 7.54-7.46 (m, 1H), 7.38-7.22 (m, 3H), 6.12 (s, 1H), 5.65 (q, 1H), 5.35 (d, 1H), 4.93 (dd, 1H), 4.78 (dd, 1H), 4.62-4.50 (m, 2H), 4.32-4.08 (m, 2H), 2.81-2.42 (m, 3H), 2.40 (s, 3H), 2.26 (q, 1H), 1.93-1.11 (m, 23H), 0.80 (s, 3H).

[0169] 화합물 69: MS: m/z 861.3 (M^++1).

[0170] 화합물 70: MS: m/z 857.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.23 (s, 1H), 8.09 (s, H), 8.05 (s, 1H), 7.96 (dd, 1H), 7.58 (dd, 1H), 7.47-7.19 (m, 3H), 7.06 (d, 1H), 6.21 (s, 1H), 5.69 (q, 1H), 4.95 (dd, 1H), 4.81-4.60 (m, 2H), 4.35-4.17 (m, 2H), 3.94 (s, 3H), 2.92-2.41 (m, 3H), 2.23 (q, 1H), 1.92-0.82 (m, 17H).

[0171] 화합물 71: MS: m/z 819.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.01-7.81 (m, 3H), 7.71 (d, 1H), 7.34-7.22 (m, 3H), 6.96 (d, 1H), 6.01 (s, 1H), 5.61 (q, 1H), 5.27 (dd, 1H), 4.90 (dd, 1H), 4.69 (dd, 1H), 4.38 (d, 1H), 4.22-4.03 (m, 2H), 3.87 (s, 3H), 3.28 (s, 3H), 2.86-2.42 (m, 3H), 2.20 (q, 1H), 1.97-0.88 (m, 16H).

[0172] 화합물 72: MS: m/z 861.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 8.10-7.98 (m, 2H), 7.86 (d, 1H), 7.54-7.22 (m, 3H), 7.20 (s, 1H), 7.06 (d, 1H), 6.10 (s, 1H), 5.70 (q, 1H), 5.29 (d, 1H), 4.97 (dd, 1H), 4.79-4.67 (m, 2H), 4.18-4.04 (m, 2H), 3.94 (s, 3H), 2.95-2.57 (m, 3H), 2.28 (q, 1H), 1.91-0.87 (m, 25H).

[0173] 화합물 73: MS: m/z 803.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 8.12-8.96 (m, 2H), 7.85 (d, 1H), 7.56-7.26 (m, 4H), 7.05 (d, 1H), 6.19-6.15 (m, 2H), 5.71 (q, 1H), 4.96 (dd, 1H), 4.74 (s, 1H), 4.53-4.42 (m, 2H), 4.19 (d, 1H), 3.93 (s, 3H), 2.91-2.20 (m, 4H), 2.10-0.82 (m, 19H).

[0174] 화합물 74: MS: m/z 861.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.39 (d, 2H), 7.81 (d, 1H), 7.50-7.26 (m, 3H), 7.00 (d, 2H), 6.05 (s, 1H), 5.65 (q, 1H), 5.21 (d, 1H), 4.95 (dd, 1H), 4.84 (dd, 1H), 4.68 (d, 1H), 4.21-4.07 (m, 2H), 3.90 (s, 3H), 2.90-2.45 (m, 4H), 2.22 (q, 1H), 1.98-1.20 (m, 14H), 1.13 (s, 9H), 0.99-0.84 (m, 1H).

[0175] 화합물 75: MS: m/z 887.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.38 (d, 2H), 7.82 (d, 1H), 7.61 (s, 1H), 7.59-7.43 (m, 1H), 7.35-7.20 (m, 1H), 7.01 (d, 2H), 6.07 (s, 1H), 5.68 (q, 1H), 5.42 (d, 1H), 4.98 (dd, 1H), 4.75 (dd, 1H), 4.58 (s, 1H), 4.38-4.13 (m, 3H), 3.88 (s, 3H), 2.86 (br, 2H), 2.59-2.11

(m, 2H), 1.96-1.20 (m, 22H), 0.92-0.78 (m, 4H).

[0176] 화합물 76: MS: m/z 903.3, 905.3 (M^++1).

[0177] 화합물 77: MS: m/z 887.3 (M^++1).

[0178] 화합물 78: MS: m/z 883.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 1H), 8.46 (d, 2H), 8.25 (d, 1H), 7.62 (m, 2H), 7.46 (m, 1H), 7.04 (d, 2H), 6.96 (s, 1H), 6.19 (s, 1H), 5.73 (q, 1H), 5.15 (d, 1H), 5.02 (dd, 1H), 4.77 (m, 1H), 4.58 (m, 2H), 4.30 (m, 1H), 4.15 (m, 3H), 2.79 (m, 2H), 2.54 (m, 1H), 2.26 (q, 1H), 1.92-0.83 (m, 26H), 0.83 (s, 3H).

[0179] 화합물 79: MS: m/z 869.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.44 (d, 2H), 8.24 (d, 1H), 7.60 (m, 2H), 7.44 (m, 1H), 7.04 (s, 1H), 7.00 (d, 2H), 6.16 (s, 1H), 5.71 (q, 1H), 5.21 (d, 1H), 4.97 (dd, 1H), 4.74 (m, 1H), 4.57 (m, 2H), 4.30 (m, 1H), 4.15 (m, 3H), 2.91 (m, 1H), 2.75 (m, 2H), 2.56 (m, 1H), 2.26 (q, 1H), 1.92-0.83 (m, 26H).

[0180] 화합물 80: MS: m/z 883.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.43 (d, 2H), 8.23 (d, 1H), 7.61-7.39 (m, 4H), 7.03 (d, 2H), 6.18 (s, 1H), 5.71 (q, 1H), 5.30 (d, 1H), 4.96 (dd, 1H), 4.79-4.57 (m, 4H), 4.41-4.22 (m, 1H), 4.15-4.08 (m, 1H), 2.96-2.67 (m, 3H), 2.57-2.42 (m, 1H), 2.25 (q, 1H), 1.98-0.87 (m, 29H).

[0181] 화합물 81: MS: m/z 897.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 8.42 (d, 2H), 8.21 (d, 1H), 7.57-7.25 (m, 4H), 7.02 (d, 2H), 6.14 (s, 1H), 5.67-5.64 (m, 1H), 5.40 (d, 1H), 5.03-4.93 (m, 1H), 4.79-4.54 (m, 4H), 4.39-4.12 (m, 2H), 2.77-2.72 (m, 2H), 2.54 (br, 1H), 2.26 (q, 1H), 2.03-1.24 (m, 29H), 0.80 (s, 3H).

[0182] 화합물 82: MS: m/z 915.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.38 (d, 2H), 7.74 (d, 1H), 7.57-7.24 (m, 3H), 7.27 (d, 2H), 6.14 (s, 1H), 5.66 (q, 1H), 5.32 (d, 1H), 4.98 (dd, 1H), 4.76 (dd, 1H), 4.71-4.48 (m, 3H), 4.39-4.08 (m, 2H), 2.85-2.42 (m, 3H), 2.31 (q, 1H), 2.03-1.24 (m, 29H), 0.80 (s, 3H).

[0183] 화합물 83: MS: m/z 901.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.46 (d, 2H), 7.82 (d, 1H), 7.54 (dd, 1H), 7.42 (s, 1H), 7.32 (m, 1H), 6.98 (d, 2H), 6.14 (s, 1H), 5.65 (q, 1H), 5.33 (d, 1H), 4.97 (dd, 1H), 4.76 (dd, 1H), 4.71-4.50 (m, 3H), 4.41-4.08 (m, 2H), 2.93-2.42 (m, 4H), 2.31 (q, 1H), 2.03-0.80 (m, 29H).

[0184] 화합물 84: MS: m/z 885.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 8.42 (d, 2H), 8.23 (d, 1H), 7.58 (m, 2H), 7.44 (dd, 1H), 7.22 (s, 1H), 7.01 (d, 2H), 6.17 (s, 1H), 5.67 (q, 1H), 5.16 (d, 1H), 4.98 (dd, 1H), 4.75 (dd, 1H), 4.62 (m, 2H), 4.38-4.08 (m, 2H), 2.80-2.42 (m, 3H), 2.32 (q, 1H), 1.96-1.20 (m, 21H), 1.13 (s, 9H), 0.81 (m, 3H).

[0185] 화합물 85: MS: m/z 923.2 (M^++1).

[0186] 화합물 86: MS: m/z 883.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.41 (s, 1H), 8.19 (d, 1H), 8.06 (d, 1H), 7.95 (s, 1H), 7.61-7.41 (m, 4H), 6.92 (d, 1H), 6.12 (s, 1H), 6.04 (s, 2H), 5.67 (q, 1H), 5.35 (d, 1H), 4.97 (dd, 1H), 4.77 (dd, 1H), 4.58 (d, 1H), 4.36-4.11 (m, 2H), 2.85-2.43 (m, 3H), 2.27 (q, 1H), 1.98-1.21 (m, 24H), 0.81 (s, 3H).

[0187] 화합물 87: MS: m/z 869.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.17 (d, 1H), 7.97 (d, 1H), 7.88 (s, 1H), 7.58-7.32 (m, 4H), 6.85 (d, 1H), 6.02 (s, 1H), 5.98 (s, 2H), 5.59 (q, 1H), 5.37 (d, 1H), 4.87 (d, 1H), 4.68 (dd, 1H), 4.52-4.02 (m, 3H), 2.90-2.38 (m, 4H), 2.23 (q, 1H), 1.91-0.88 (m, 24H).

[0188] 화합물 88: MS: m/z 868.5 (M^++1).

[0189] 화합물 89: MS: m/z 882.5 (M^++1).

[0190] 화합물 90: MS: m/z 910.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.32 (s, 1H), 8.34 (d, 2H), 8.22 (d, 1H), 7.61-7.43 (m, 3H), 7.44 (dd, 1H), 6.76 (d, 2H), 6.14 (s, 1H), 5.62 (q, 1H), 5.39 (d, 1H), 4.96 (dd, 1H), 4.72 (dd, 1H), 4.63 (brs, 1H), 4.55 (d, 1H), 4.41-4.04 (m, 2H), 3.42 (q, 4H), 2.80-2.42 (m, 3H), 2.32 (q, 1H), 1.98-1.17 (m, 29H), 0.83 (s, 3H).

[0191] 화합물 91: MS: m/z 896.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.46 (s, 1H), 8.33 (d, 2H), 8.21 (d, 1H), 7.62-7.43 (m, 3H), 7.43 (dd, 1H), 6.77 (d, 2H), 6.13 (s, 1H), 5.65 (q, 1H), 5.39 (d, 1H), 4.93 (dd, 1H), 4.73 (dd, 1H), 4.64 (brs, 1H), 4.53 (d, 1H), 4.43-4.05 (m, 2H), 3.43 (q, 4H), 2.94-2.42 (m, 4H), 2.29 (q, 1H), 2.14-0.83 (m, 29H).

[0192] 화합물 92: MS: m/z 901.4, 903.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.40 (s, 1H), 8.36 (d, 2H), 8.23 (s, 1H), 7.58-7.26 (m, 5H), 6.15 (s, 1H), 5.65 (q, 1H), 5.19 (d, 1H), 4.96 (dd, 1H), 4.77 (dd, 1H), 4.62-4.52 (m, 2H), 4.33-4.08 (m, 2H), 3.01-2.42 (m, 5H), 2.25 (q, 1H), 1.96-0.89 (m, 29H).

[0193] 화합물 93: MS: m/z 915.4, 917.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.27 (s, 1H), 8.38 (d, 2H), 8.22 (s, 1H), 7.59-7.34 (m, 5H), 6.13 (s, 1H), 5.70 (q, 1H), 5.29 (d, 1H), 4.98 (dd, 1H), 4.78 (dd, 1H), 4.62-4.55 (m, 2H), 4.35-4.08 (m, 2H), 3.04-2.96 (m, 1H), 2.80-2.43 (m, 3H), 2.25 (q, 1H), 1.97-1.20 (m, 29H), 0.81 (s, 3H).

[0194] 화합물 94: MS: m/z 867.4 (M^++1).

[0195] 화합물 95: MS: m/z 881.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 8.41 (d, 2H), 8.22 (d, 1H), 7.63-7.21 (m, 4H), 7.20 (d, 2H), 6.16 (s, 1H), 5.65 (q, 1H), 5.38 (d, 1H), 4.94 (dd, 1H), 4.80 (dd, 1H), 4.65-4.56 (m, 2H), 4.38-4.12 (m, 2H), 3.08-2.92 (m, 1H), 2.83-2.67 (m, 2H), 2.59-2.41 (m, 1H), 2.25 (q, 1H), 1.98-1.08 (,m, 28H), 0.95-0.86 (m, 4H).

[0196] 화합물 96: MS: m/z 881.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.47 (s, 1H), 8.40 (d, 2H), 8.23 (d, 1H), 7.76 (s, 1H), 7.62-7.41 (m, 5H), 6.13 (s, 1H), 5.65 (q, 1H), 5.33 (d, 1H), 5.03-4.87 (m, 2H), 4.78 (dd, 1H), 4.57 (d, 1H), 4.38-4.04 (m, 2H), 2.95-2.43 (m, 4H), 2.21 (q, 1H), 2.01-1.37 (m, 20H), 1.33 (s, 9H), 1.21-0.86 (m, 3H).

[0197] 화합물 97: MS: m/z 895.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.40 (d, 2H), 8.23 (d, 1H), 7.59-7.43 (m, 5H), 6.98 (d, 1H), 6.16 (s, 1H), 5.65 (q, 1H), 5.41 (d, 1H), 4.98 (dd, 1H), 4.79 (q, 1H), 4.62-4.52 (m, 1H), 4.36-4.09 (m, 3H), 2.75 (brs, 2H), 2.59-2.56 (m, 1H), 2.28 (q, 1H), 1.91-1.18 (m, 31H), 0.89-0.78 (m, 4H).

[0198] 화합물 98: MS: m/z 869.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.41 (s, 1H), 8.42 (d, 2H), 8.23 (d, 1H), 7.62-7.43 (m, 5H), 7.44 (dd, 1H), 6.17 (s, 1H), 5.64 (q, 1H), 5.17 (d, 1H), 4.97 (dd, 1H), 4.77-4.63 (m, 2H), 4.21-4.10 (m, 2H), 2.94-2.55 (m, 4H), 2.27 (q, 1H), 1.891.15 (m, 23H), 1.10 (s, 9H), 0.98-0.87 (m, 1H).

[0199] 화합물 99: MS: m/z 925.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 8.37 (d, 2H), 8.03 (d, 1H), 7.50 (d, 2H), 7.48 (s, 1H), 7.01-6.92 (m, 2H), 6.13 (s, 1H), 5.65 (q, 1H), 5.39 (d, 1H), 4.98 (dd, 1H), 4.88 (dd, 1H), 4.64 (s, 1H), 4.53 (d, 1H), 4.41-4.23 (m, 1H), 4.19-4.11 (m, 1H), 3.88 (s, 3H), 2.78-2.42 (m, 3H), 2.26 (q, 1H), 2.04-1.18 (m, 31H), 0.89-0.78 (m, 4H).

[0200] 화합물 100: MS: m/z 925.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.23 (s, 1H), 8.35 (d, 2H), 7.77 (d, 1H), 7.48 (d, 2H), 7.38-7.22 (m, 1H), 7.04-6.81 (m, 2H), 6.16 (s, 1H), 5.68 (q, 1H), 5.21 (d, 1H), 4.99 (dd, 1H), 4.78 (dd, 1H), 4.57 (d, 1H), 4.22-4.03 (m, 3H), 4.00 (s, 3H), 2.80-2.43 (m, 3H), 2.31 (q, 1H), 1.96-1.20 (m, 31H), 0.95-0.78 (m, 4H).

[0201] 화합물 101: MS: m/z 827.3 (M^++1).

[0202] 화합물 102: MS: m/z 897.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.39 (d, 2H), 8.20 (d, 1H), 7.59-7.37 (m, 5H), 7.14 (s, 1H), 6.04 (s, 1H), 5.61 (q, 1H), 5.21 (d, 1H), 4.87 (dd, 1H), 4.77 (dd, 1H), 4.57 (d, 1H), 4.19-4.07 (m, 4H), 3.67-3.42 (m, 2H), 3.17-2.40 (m, 6H), 2.20 (q, 1H), 1.93-0.78 (m, 27H).

[0203] 화합물 103: MS: m/z 866.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.31 (d, 2H), 8.12 (d, 1H), 7.51-7.42 (m, 5H), 7.32-7.25 (m, 1H), 6.09 (s, 1H), 5.61 (q, 1H), 4.90 (dd, 1H), 4.81 (dd, 1H), 4.59 (d, 1H), 4.50-4.36 (m, 2H), 4.13 (dd, 1H), 3.69-3.27 (m, 3H), 3.10 (brs, 4H), 2.90-2.41 (m, 4H), 2.19 (q, 1H), 1.98-0.78 (m, 25H).

[0204] 화합물 104: MS: m/z 811.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 8.38 (d, 2H), 8.19 (d, 1H), 7.60-7.31 (m, 5H), 7.32-7.25 (m, 1H), 6.15 (s, 1H), 5.65 (q, 1H), 4.88 (dd, 1H), 4.70 (dd, 1H), 4.57 (dd, 1H), 4.40 (d, 1H), 4.21-4.05 (m, 2H), 2.95-2.41 (m, 4H), 2.22 (q, 1H), 2.01 (s, 3H), 1.98-0.79 (m, 24H).

[0205] 화합물 105: MS: m/z 868.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.57 (s, 1H), 8.37 (d, 2H), 8.15 (d, 1H), 8.09 (s, 1H), 7.58-7.51 (m, 4H), 7.27 (dd, 1H), 6.09 (s, 1H), 5.61 (q, 1H), 4.98-4.79 (m, 4H), 4.44 (s, 1H), 4.10 (dd, 1H), 3.79-3.68 (m, 2H), 2.92-2.45 (m, 4H), 2.24 (q, 1H), 1.98-0.88 (m, 32H).

[0206] 화합물 106: MS: m/z 882.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 8.35 (d, 2H), 8.16 (d, 1H), 7.56-7.48 (m, 2H), 7.42 (d, 2H), 7.36-7.33 (m, 1H), 7.30 (s, 1H), 6.09 (s, 1H), 5.63 (q, 1H), 4.97-4.86 (m, 2H), 4.76 (dd, 1H), 4.58 (d, 1H), 4.28-4.11 (m, 2H), 3.39-3.25 (m, 4H), 3.01-2.82 (m, 5H), 2.75-2.44 (m, 2H), 2.16 (q, 1H), 1.95-0.76 (m, 25H).

[0207] 화합물 107: MS: m/z 863.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.34 (s, 1H), 8.33 (d, 2H), 8.32 (d, 1H), 7.59-7.40 (m, 6H), 7.37 (s, 1H), 6.81 (d, 1H), 6.65 (d, 1H), 6.25 (s, 1H), 6.13 (s, 1H), 5.62 (q, 1H), 4.87 (dd, 1H), 4.69-4.52 (m, 2H), 4.42 (d, 1H), 4.18 (dd, 1H), 2.95-2.40 (m, 4H), 2.24-0.78 (m, 25H).

[0208] 화합물 108: MS: m/z 840.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.67 (s, 1H), 8.32 (d, 2H), 8.19 (d, 1H), 7.77 (s, 1H), 7.58-7.44 (m, 4H), 7.34-7.25 (m, 1H), 6.14 (s, 1H), 5.77 (q, 1H), 4.98 (dd, 1H), 4.78-4.71 (m, 2H), 4.44 (d, 1H), 4.29 (brs, 1H), 4.11-4.05 (m, 1H), 2.96-2.72 (m, 2H), 2.64 (s, 6H), 2.41 (br, 1H), 2.20 (q, 1H), 1.96-0.78 (m, 25H).

[0209] 화합물 109: MS: m/z 837.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.49 (s, 1H), 8.35-8.25 (m, 3H), 7.71 (s, 1H), 7.55-7.41 (m, 4H), 7.26 (s, 1H), 6.19 (d, 1H), 6.01 (s, 1H), 5.63 (q, 1H), 4.88 (dd, 1H), 4.71 (brs, 1H), 4.56 (d, 1H), 4.39 (brs, 1H), 4.06 (d, 1H), 2.81-2.45 (m, 4H), 2.23 (q, 1H), 1.99-1.64 (m, 4H), 1.58-0.77 (m, 21H), 0.51 (brs, 4H).

[0210] 화합물 110: MS: m/z 865.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.39 (s, 1H), 8.29 (d, 2H), 8.15 (d, 1H), 7.56-7.42 (m, 5H), 7.36-7.24 (m, 1H), 6.05 (s, 1H), 5.98 (d, 1H), 5.64 (q, 1H), 4.87 (dd, 1H), 4.69 (dd, 1H), 4.55 (d, 1H), 4.42 (dd, 1H), 4.04 (dd, 1H), 2.81-2.05 (m, 5H), 1.95-1.71 (m, 4H), 1.57-0.76 (m, 29H).

[0211] 화합물 111: MS: m/z 881.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.33 (d, 2H), 8.30 (s, 1H), 7.58-7.41 (m, 4H), 7.39 (dd, 1H), 7.22 (s, 1H), 6.10 (s, 1H), 5.98 (d, 1H), 5.62 (q, 1H), 4.91 (dd, 1H), 4.68 (dd, 1H), 4.46-4.40 (m, 2H), 4.05 (dd, 1H), 3.79-3.62 (m, 2H), 3.21-3.09 (m, 2H), 2.88-2.40 (m, 3H), 2.22-1.72 (m, 6H), 1.47-0.78 (m, 25H).

[0212] 화합물 112: MS: m/z 864.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.38 (d, 2H), 8.23 (d, 1H), 8.09 (s, 1H), 7.57-7.45 (m, 5H), 7.41 (dd, 1H), 7.28 (s, 1H), 6.42 (s, 1H), 6.15 (s, 1H), 5.62 (q, 1H), 4.86 (dd, 1H), 4.75-4.66 (m, 2H), 4.49 (d, 1H), 4.17 (dd, 1H), 2.83-2.43 (m, 3H), 2.25 (q, 1H), 1.99-0.78 (m, 25H).

[0213] 화합물 113: MS: m/z 853.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.34 (s, 1H), 8.36 (d, 2H), 8.30 (d, 1H), 7.62-7.46 (m, 4H), 7.41-7.36 (m, 1H), 7.17 (s, 1H), 6.19 (s, 1H), 6.17 (d, 1H), 5.68 (q, 1H), 4.92 (dd, 1H), 4.73 (dd, 1H), 4.58-4.43 (m, 2H), 4.19 (dd, 1H), 2.89-2.43 (m, 3H), 2.22 (q, 1H), 1.99-1.82 (m, 6H), 1.59-0.83 (m, 28H).

[0214] 화합물 114: MS: m/z 907.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.39 (d, 2H), 8.21 (d, 1H), 7.56 (dd, 1H), 7.48 (d, 2H), 7.40 (dd, 1H), 7.24 (s, 1H), 7.18 (d, 2H), 7.03 (d, 2H), 6.92 (s, 1H), 6.06 (s, 1H), 5.74 (d, 1H), 5.61 (q, 1H), 4.87 (dd, 1H), 4.70 (dd, 1H), 4.42 (d, 1H), 4.31 (dd, 1H), 4.08 (dd, 1H), 2.84-2.79 (m, 1H), 2.65-2.43 (m, 2H), 2.23 (q, 1H), 1.88-1.62 (m, 6H), 1.49-0.78 (m, 19H).

[0215] 화합물 115: MS: m/z 895.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.40 (d, 2H), 8.01 (s, 1H), 7.55 (d, 2H), 7.46-7.32 (m, 3H), 6.13 (s, 1H), 5.61 (q, 1H), 5.32 (brs, 1H), 5.01-4.87 (m, 1H), 4.89 (dd, 1H), 4.62-4.55 (m, 2H), 4.34-4.08 (m, 2H), 2.94-2.55 (m, 4H), 2.50 (s, 3H), 2.23 (q, 1H), 1.95-1.10 (m, 32H).

[0216] 화합물 116: MS: m/z 909.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.40 (d, 2H), 8.01 (s, 1H), 7.55 (d, 2H), 7.47-7.26 (m, 3H), 6.14 (s, 1H), 5.69 (q, 1H), 5.37 (d, 1H), 4.99 (dd, 1H), 4.78 (dd, 1H), 4.60 (d, 1H), 4.40-4.05 (m, 3H), 2.80-2.51 (m, 3H), 2.50 (s, 3H), 2.29 (q, 1H), 1.98-1.12 (m, 32H), 0.82 (s, 3H).

[0217] 화합물 117: MS: m/z 855.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.08 (s, 1H), 8.22 (d, 2H), 8.03 (d, 2H), 7.44-7.18 (m, 3H), 7.26-7.17 (m, 1H), 7.13 (d, 1H), 6.12 (s, 1H), 5.65 (q, 1H), 4.89 (dd, 1H), 4.77 (dd, 1H), 4.49 (d, 1H), 4.42-4.36 (m, 1H), 4.13 (dd, 1H), 3.16 (s, 1H), 2.84-2.46 (m, 4H), 2.16 (q, 1H), 1.95-0.77 (m, 31H).

[0218] 화합물 118: MS: m/z 895.4 (M^++1).

[0219] 화합물 119: MS: m/z 895.4 (M^++1).

[0220] 화합물 120: MS: m/z 840.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 8.38 (d, 2H), 8.20 (d, 1H), 8.00 (d, 1H), 7.61-7.54 (m, 2H), 7.50 (d, 2H), 7.41-7.35 (m, 1H), 7.15 (s, 1H), 6.72 (d, 1H), 6.10 (d, 1H), 5.63 (q, 1H), 5.27 (d, 1H), 4.89 (dd, 1H), 4.68 (dd, 1H), 4.51-4.42 (m, 2H), 4.12 (dd, 1H), 2.84-2.43 (m, 4H), 2.22 (q, 1H), 1.98-0.84 (m, 24H).

[0221] 화합물 121: MS: m/z 829.3 (M^++1).

[0222] 화합물 122: MS: m/z 833.3 (M^++1).

[0223] 화합물 123: MS: m/z 821.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.27 (s, 1H), 7.90 (dd, 1H), 7.60 (s, 1H), 7.27 (dd, 1H), 7.32-7.20 (m, 2H), 6.91 (s, 1H), 6.53 (dd, 1H), 6.03 (s, 1H), 5.64 (q, 1H), 4.98-4.89 (m,

2H), 4.71-4.58 (m, 2H), 4.14-4.03 (m, 2H), 2.86-2.80 (m, 1H), 2.67-2.40 (m, 2H), 2.22 (q, 1H), 1.98-1.10 (m, 15H), 1.05 (s, 9H), 0.98-0.82 (m, 1H).

[0224] 화합물 124: MS: m/z 779.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 7.93 (dd, 1H), 7.70 (s, 1H), 7.65-7.55 (dd, 1H), 7.41-7.26 (m, 2H), 7.04 (s, 1H), 6.61 (s, 1H), 6.15 (s, 1H), 5.72 (q, 1H), 5.37 (d, 1H), 5.01-4.91 (m, 1H), 4.77 (dd, 1H), 4.46 (d, 1H), 4.37-4.09 (m, 2H), 3.36 (s, 3H), 2.92-2.53 (m, 3H), 2.23 (q, 1H), 1.99-0.86 (m, 16H).

[0225] 화합물 125: MS: m/z 817.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 7.98 (d, 1H), 7.66 (s, 1H), 7.60 (dd, 1H), 7.40-7.09 (m, 3H), 6.11 (s, 1H), 6.60 (s, 1H), 6.17 (s, 1H), 5.72 (q, 1H), 4.99 (dd, 1H), 4.76-4.67 (m, 2H), 4.31-4.18 (m, 2H), 2.91-2.75 (m, 2H), 2.45 (br, 1H), 2.22-0.84 (m, 17H).

[0226] 화합물 126: MS: m/z 763.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 7.81 (dd, 1H), 7.60 (s, 1H), 7.52 (dd, 1H), 7.35-7.18 (m, 3H), 6.52 (d, 1H), 6.13-6.01(m, 2H), 5.61 (q, 1H), 4.83 (dd, 1H), 4.62 (dd, 1H), 4.45 (dd, 1H), 4.38 (d, 1H), 4.17 (dd, 1H), 2.85-2.79 (m, 1H), 2.67 (d, 1H), 2.41 (m, 1H), 2.21-0.84 (m, 20H).

[0227] 화합물 127: MS: m/z 821.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 8.15 (s, 1H), 7.79 (d, 1H), 7.45-7.42 (m, 3H), 7.35-7.25 (m, 1H), 7.01 (s, 1H), 5.89 (s, 1H), 5.54 (q, 1H), 5.19 (d, 1H), 4.85 (dd, 1H), 4.67 (dd, 1H), 4.54 (d, 1H), 4.20 (dd, 1H), 4.04 (d, 1H), 2.91-2.44 (m, 3H), 2.24 (q, 1H), 2.01-1.11 (m, 15H), 1.06 (s, 9H), 0.83-0.78 (m, 1H).

[0228] 화합물 128: MS: m/z 833.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 8.07 (d, 1H), 7.56-7.22 (m, 5H), 6.89 (d, 1H), 5.96 (s, 1H), 5.57-5.49 (m, 1H), 5.21-5.17 (m, 1H), 4.96-4.83 (m, 1H), 4.72 (dd, 1H), 4.67 (d, 1H), 4.18-4.03 (m, 2H), 2.90-2.79 (m, 1H), 2.69 (s, 3H), 2.64-2.46 (m, 2H), 2.22 (q, 1H), 1.97-1.04 (m, 15H), 1.04 (s, 9H), 0.96-0.87 (m, 1H).

[0229] 화합물 129: MS: m/z 836.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 7.88 (d, 1H), 7.53-7.50 (m, 1H), 7.49 (dd, 1H), 7.19 (s, 1H), 6.65 (s, 1H), 6.04 (s, 1H), 5.70-5.50 (m, 1H), 5.12-4.48 (m, 4H), 4.19-3.98 (m, 2H), 2.95-2.58 (m, 3H), 2.48 (s, 3H), 2.32-2.12 (m, 1H), 1.97-1.18 (m, 15H), 1.00 (s, 9H), 0.98-0.86 (m, 1H).

[0230] 화합물 130: MS: m/z 832.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H), 7.84 (dd, 1H), 7.52 (dd, 1H), 7.39 (, 1H), 7.38-7.26 (m, 2H), 6.62 (s, 1H), 6.05 (s, 1H), 5.60 (q, 1H), 4.83 (dd, 1H), 4.67 (dd, 1H), 4.55 (dd, 1H), 4.36 (d, 1H), 4.08 (dd, 1H), 2.81-2.50 (m, 3H), 2.48 (s, 3H), 2.45-2.37 (m, 1H), 2.18 (q, 1H), 1.99-0.87 (m, 15H).

[0231] 화합물 131: MS: m/z 888.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.23 (d, 1H), 7.41 (s, 1H), 7.30 (m, 2H), 7.11 (s, 1H), 6.16 (s, 1H), 5.68 (q, 1H), 5.23 (d, 1H), 4.98 (dd, 1H), 4.75 (brs, 1H), 4.54 (d, 1H), 4.36-4.11 (m, 3H), 3.39-3.27 (m, 1H), 2.96-2.63 (m, 3H), 2.54 (s, 3H), 2.25 (q, 1H), 1.89-0.93 (m, 30H).

[0232] 화합물 132: MS: m/z 888.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.24 (s, 1H), 8.37 (d, 1H), 7.74-7.51 (m, 2H), 7.48-7.42 (m, 1H), 7.22 (s, 1H), 7.12 (s, 1H), 6.17 (s, 1H), 5.70 (q, 1H), 5.28 (d, 1H), 4.99 (dd, 1H), 4.76 (dd, 1H), 4.58 (d, 1H), 4.52 (brs, 1H), 4.35-4.16 (m, 2H), 3.40-3.35 (m, 1H), 2.79-2.43 (m, 3H), 2.25 (q, 1H), 1.95-1.23 (m, 29H),0.87-0.76 (m, 3H).

[0233] 화합물 133: MS: m/z 887.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 8.59 (s, 1H), 8.22 (d, 1H), 7.81 (d, 1H), 7.58-7.42 (m, 3H), 6.95-6.89 (m, 2H), 6.09 (s, 1H), 5.68 (q, 1H), 5.32 (d, 1H), 4.99 (m, 1H), 4.74 (m, 1H), 4.54 (d, 1H), 4.39-4.22 (m, 1H), 4.14-4.11 (m, 1H), 2.90 (m, 1H), 2.78 (m, 2H), 2.55 (m,

1H), 2.27 (q, 1H), 1.90-1.10 (m, 21H), 1.45 (s, 9H), 0.94-0.83 (m, 2H).

[0234] 화합물 134: MS: m/z 901.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1H), 8.8.51 (s, 1H), 8.23 (d, 1H), 7.81 (d, 1H), 7.59-7.43 (m, 3H), 7.13 (s, 1H), 6.90 (d, 1H), 6.09 (s, 1H), 5.68 (q, 1H), 5.22 (d, 1H), 4.99 (dd, 1H), 4.76 (m, 1H), 4.55 (d, 1H), 4.39-4.22 (m, 1H), 4.14-4.11 (m, 1H), 2.78 (m, 2H), 2.55 (m, 1H), 2.27 (q, 1H), 1.90-0.83 (m, 23H), 1.46 (s, 9H).

[0235] 화합물 135: MS: m/z 888.3 (M^++1).

[0236] 화합물 136: MS: m/z 902.3 (M^++1).

[0237] 화합물 137: MS: m/z 899.4 (M^++1).

[0238] 화합물 138: MS: m/z 885.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.17 (d, 1H), 7.58 (m, 2H), 7.42-7.33 (m, 2H), 6.63 (m, 1H), 6.07 (s, 1H), 5.67 (q, 1H), 5.29 (d, 1H), 4.97 (dd, 1H), 4.77 (m, 1H), 4.57 (m, 1H), 4.42-4.03 (m, 3H), 2.89 (m, 1H), 2.75 (m, 5H), 2.52 (m, 1H), 2.27 (q, 1H), 1.91-0.82 (m, 32H).

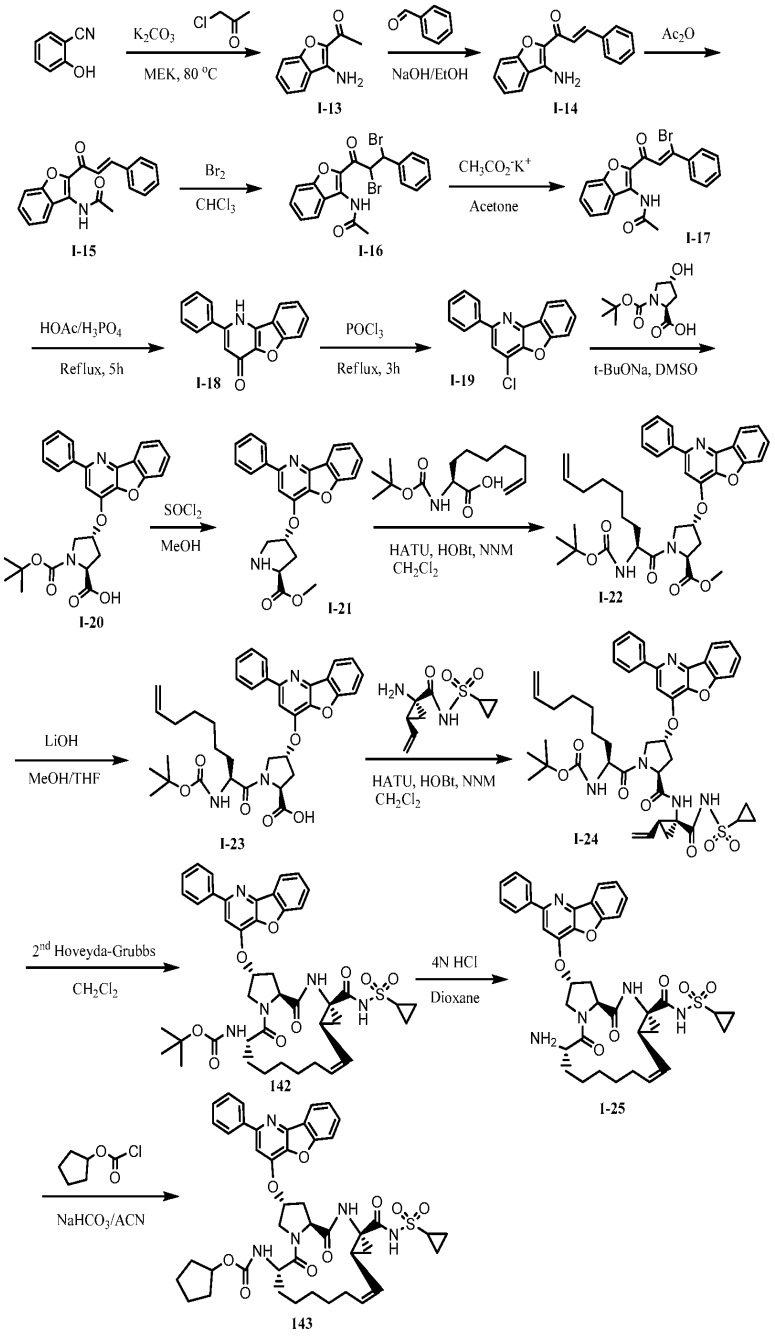
[0239] 화합물 139: MS: m/z 803.3 (M^++1).

[0240] 화합물 140: MS: m/z 817.3 (M^++1).

[0241] 화합물 141: MS: m/z 831.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.05 (s, 1H), 7.56-7.48 (m, 3H), 6.06 (s, 1H), 5.62 (q, 1H), 5.15 (dd, 1H), 4.91 (dd, 1H), 4.75 (dd, 1H), 4.59 (d, 1H), 4.35-4.02 (m, 3H), 2.96-2.88 (m, 1H), 2.74-2.65 (m, 2H), 2.53 (s, 3H), 2.24 (q, 1H), 1.96-0.89 (m, 24H).

[0242] 실시예 142 및 143 : [4-시클로프로판설포닐아미노카보닐-2,15-디옥소-18-(2-페닐-벤조[4,5]푸로[3,2-b]피리딘-4-일옥시)-3,16-디아자-트리시클로[14.3.0.04,6]노나덱-7-엔-14-일]-카바민산 tert-부틸 에스터 (화합물 142) 및 [4-시클로프로판설포닐아미노카보닐-2,15-디옥소-18-(2-페닐-벤조[4,5]푸로[3,2-b]피리딘-4-일옥시)-3,16-디아자-트리시클로[14.3.0.04,6]노나덱-7-엔-14-일]-카바민산 시클로펜틸 에스터 (화합물 143)의 합성

[0243] 화합물 142 및 143은 하기 나타낸 경로를 통해 제조되었다:



[0244]

[0245] 에틸 메틸 케톤 (320 mL) 내 2-히드록시벤조니트릴 (30 g, 251.6 mmol)의 용액에 포타슘 카보네이트 (69.6 g, 755.5 mmol)를 가하였다. 실온에서 30분 동안 교반한 후, 결과 혼합물에 클로로아세톤 (34.95 g, 377.8 mmol)을 가한 다음 용액을 100℃에서 밤새도록 가열하였다. 최종적으로, 반응 용매를 감압 하에 제거하고 결과로 생긴 고체를 물과 에틸 에테르로 세척하여 화합물 I-13 (31 g, 70.3% 수율)을 얻었다. MS: m/z 176.0 (M^+ +1); ^{1}H NMR ($CDCl_3$) δ 7.59 (d, 1H), 7.46 (dd, 1H), 7.41 (d, 1H), 7.24 (dd, 1H), 2.50 (s, 3H).

[0246] 5~10℃에서 에탄올 (30 mL) 내 2-아세틸-3-아미노벤조푸란 I-13 (2.17 g, 12.38 mmol) 및 벤즈알데히드 (1.31 g, 12.38 mmol)의 용액에 소듐 히드록사이드 수용액 (70%, 5 mL)을 일정한 교반 하에 방울방울 가하였다. 밤새도록 교반한 후, 밝은 노란색 고체의 미정제 생성물을 반응 용액에 현탁시켰다. 고체를 여과하여 모으고, 에탄올로 재결정화하여 실키 바늘 모양의 화합물 I-14 (2.7 g, 90%)를 얻었다. MS: m/z 264.0 (M^++1); ^{1}H NMR ($CDCl_3$) δ 7.83 (d, 1H), 7.71 (dd, 2H), 7.64 (d, 1H), 7.62 (d, 1H), 7.58-7.39 (m, 5H), 7.29-7.24 (m,

1H), 5.83 (broad, 2H).

[0247] 중간체 I-14 (1.32 g, 5.0 mmol)를 무수 아세트산 (10 mL)에 현탁시키고 따뜻한 수욕조에서 교반하였다. 밤새도록 교반한 후, 반응 혼합물을 얼음물에 쏟아 부었다. 현탁된 미정제 생성물을 분리하여 모은 다음 에탄올로 재결정화하여 화합물 I-15 (1.52g, 90%)를 얻었다. MS: m/z 306.0 (M^++1); ^{1}H NMR ($CDCl_3$) δ 8.58 (d, 1H), 7.91 (d, 1H), 7.72 (m, 3H), 7.54-7.44 (m, 5H), 7.34-7.7.28 (m, 1H), 2.35 (s, 3H).

[0248] $CHCl_3$ (20 mL) 내 중간체 I-15 (1.22 g, 4.0 mmol)의 용액을 $CHCl_3$ (15mL) 내 브롬 (0.72 g 4.5 mmol) 용액에 방울방울 천천히 가하였다. 밤새도록 교반한 후, 반응 혼합물을 얼음물로 종결하였다. 현탁된 고체를 분리하여 모으고, 에탄올/H_2O로 재결정화하여 화합물 I-16 (1.12 g, 60%)을 얻었다. MS: m/z 465.9 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.22 (brs, 1H), 8.63 (d, 1H), 7.61-7.25 (m, 8H), 5.92 (d, 1H), 5.62 (d, 1H), 2.37 (s, 3H).

[0249] 아세톤 (25 mL) 내 화합물 I-16 (0.93 g, 2.0 mmol)의 용액에 무수 포타슘 아세테이트 (0.2 g, 2.0 mmol)를 가하였다. 밤새도록 교반한 후, 반응 혼합물을 얼음물에 쏟아 부었다. 현탁된 고체를 분리하여 모으고, 에탄올로 재결정화하여 모노브로마이드-화합물 I-17 (0.46 g, 60%)을 얻었다. MS: m/z 385.9 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.50 (brs, 1H), 8.54 (d, 1H), 8.48 (s, 1H), 7.93 (m, 2H), 7.56-7.46 (m, 5H), 7.36-7.31 (m,1H), 2.35 (s, 3H).

[0250] 아세트산 (5 mL) 및 오르토-인산 (5 mL) 내 화합물 I-17 (0.35 g, 1.0 mmol)을 5시간 동안 환류시켰다. 반응 혼합물을 실온으로 냉각시키고, 얼음물에 쏟아붓고 30분 더 교반하였다. 현탁된 고체를 분리하여 모으고, DMF로 재결정화하여 화합물 I-18 (0.2 g, 80%)을 얻었다. MS: m/z 262.0 (M^++1).

[0251] 화합물 I-18 (1.0 g, 3.8 mmol) 및 포스포러스 옥시클로라이드 ($POCl_3$) (10 mL)의 용액을 2시간 동안 환류시켰다. 용액을 냉각시키고 완전히 농축한 후, 결과로 생긴 잔류물을 10% 소듐 히드록사이드로 종결시키고 메틸렌클로라이드 (20 mL x 3)로 추출하였다. 유기층을 모으고 소듐 설페이트로 건조시키고, 농축하였다. 미정제 생성물을 CH_2Cl_2 및 *n*-헥산으로 재결정화하여 화합물 I-19 (0.7 g, 75%)를 얻었다. MS: m/z 279.9 (M^++1); ^{1}H NMR ($CDCl_3$) δ 8.45 (d, 1H), 8.09 (d, 2H), 7.84 (s, 1H), 7.71-7.64 (m, 2H), 7.56-7.47 (m, 4H).

[0252] DMSO (10 mL) 내 Boc-trans-4-히드록시-L-프롤린 (0.53 g, 2.3 mmol)의 현탁액에 *t*-BuONa (0.49 g, 5.08 mmol)을 0℃에서 가하였다. 실온으로 따뜻하게 하고 1시간 동안 교반한 후, 중간체 I-19 (0.64 g, 2.3 mmol)를 10℃에서 천천히 가하였다. 반응 혼합물을 4시간 동안 교반한 다음 10% HCl 수용액으로 pH 6~7로 하여 반응을 종결하였다. 미정제 고체를 여과하고 물로 세척한 후 진공 하에 건조하여 화합물 I-20 (0.94g, 86.3%)을 얻었다. MS: m/z 475.1 (M^++1); ^{1}H NMR ($CDCl_3$) δ 8.27 (d, 1H), 7.97 (m, 2H), 7.86-7.76 (m,3H), 7.66-7.44 (m, 4H), 5.81 (s, 1H), 4.47 (m, 1H), 4.03-3.89 (m, 2H), 2.81 (m,1H), 2.50 (q, 1H).

[0253] MeOH (20 mL) 내 화합물 I-20 (1.1 g, 2.3 mmol)의 용액에 $SOCl_2$ (1.17 g, 9.9 mmol)를 실온에서 가하였다. 1시간 동안 환류시킨 후, 반응 용매를 진공 하에 제거하여 미정제 화합물 I-21를 얻었다. 이 화합물은 더 이상 정제 없이 다음 단계에서 사용하였다. MS: m/z 389.1 (M^++1).

[0254] CH_2Cl_2 (20 mL) 내 화합물 I-21 (0.78g, 2.0 mmol), 2-(1H-7-아자벤조트리아졸-1-일)-1,1,3,3-테트라메틸 우로늄 헥사플루오로-포스페이트 메탄아미늄 (HATU, 1.12 g, 3.0 mmol), N-히드록시벤조트리아졸 (HOBT, 0.4 g, 3.0 mmol), 및 2-tert-부톡시카보닐아미노-논-8-에노산 (1.19 g, 5.2 mmol)의 용액에 NMM (1.0 g, 9.9 mmol)을 실온에서 가하였다. 반응 혼합물을 밤새도록 교반한 후, 진공 하에서 농축하였다. 잔류물을 실리카겔 컬럼 크로마토그래피로 정제하여 화합물 I-22 (1.02 g, 80.7%)을 얻었다. MS: m/z 642.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 8.24 (d, 1H), 8.05 (d, 2H), 7.58 (m, 2H), 7.56-7.41 (m, 4H), 7.28 (d, 1H), 5.83-5.76 (q, 1H), 5.71 (s, 1H), 5.24 (d, 1H), 5.01-4.82 (m, 2H), 4.76 (dd, 1H), 4.75-4.34 (m, 2H), 4.03 (m, 1H), 3.77 (s, 3H), 2.78 (m, 1H), 2.36 (q, 1H), 2.01 (m, 2H), 1.75 (m, 1H), 1.54 (m, 1H), 1.42 (m, 6H), 1.31 (s, 9H).

[0255] THF (20 mL) 내 화합물 I-22 (1.0 g, 1.6 mmol)의 용액에 0.5 M LiOH (5.7 mL, 2.9 mmol)을 실온에서 가하였다. 반응 혼합물을 밤새도록 교반한 후, 10% HCl로 pH < 7로 산성화하고 진공 하에서 농축하여 고체 생성물을 얻었다. 이 화합물을 여과하고 물로 세척하여 화합물 I-23을 얻었다. MS: m/z 628.1 (M^++1); ^{1}H NMR ($CDCl_3$) δ 8.34 (brs, 1H), 8.04 (d, 2H), 7.62 (m, 2H), 7.60-7.41 (m, 4H), 7.28 (m, 2H), 5.81-5.72 (q, 1H), 5.70 (s, 1H), 5.29 (d, 1H), 5.00-4.87 (m, 3H), 4.48 (m, 2H), 4.01 (m, 1H), 2.77 (m, 2H), 1.98 (m, 2H), 1.72 (m, 1H), 1.61 (m, 1H), 1.44 (m, 6H), 1.33 (s, 9H).

[0256] CH_2Cl_2 (10 mL) 내 화합물 I-23 (0.26 g, 0.41 mmol), HATU (0.31 g, 0.81 mmol), HOBT (0.084 g, 0.61 mmol), 및 시클로프로판설폰산 (1-아미노-2-비닐-시클로프로판카보닐)-아미드 (0.094 g, 0.41 mmol)의 용액에 NMM (0.12 g, 1.2 mmol)을 실온에서 가하였다. 반응 혼합물을 밤새도록 교반한 후, 진공 하에서 농축하였다. 잔류물을 실리카겔 컬럼 크로마토그래피로 정제하여 화합물 I-24 (0.15g, 45%)를 얻었다. MS: m/z 804.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.22 (s, 1H), 8.35 (d, 1H), 8.01 (d, 2H), 7.59 (d, 2H), 7.48-7.30 (m, 5H), 7.04 (s, 1H), 5.78 (m, 3H), 5.35 (d, 1H), 5.23 (d, 1H), 5.15 (d, 1H), 4.93 (m, 2H), 4.53 (dd, 1H), 4.41-4.30 (m, 2H), 4.05 (m, 1H), 2.91 (m, 1H), 2.61 (m, 2H), 2.14 (dd, 1H), 2.04 (m, 3H), 1.91-1.52 (m,3H), 1.45-1.22 (18H), 1.21 (m, 2H).

[0257] CH_2Cl_2 내 화합물 I-24 (100 mg, 0.12 mmol)의 용액에 Hoveyda-Grubbs 2nd generation catalyst (35mg, 0.056 mmol)을 N_2 하에서 실온에서 가한 다음, 반응 혼합물을 40℃로 가열하고 24시간 동안 교반하였다. 반응 혼합물을 농축하고 컬럼으로 정제하여 화합물 142 (30 mg, 31%)을 얻었다. MS: m/z 812.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.28 (d,1H), 8.04 (d, 2H), 7.61-7.41 (m, 7H), 7.00 (s, 1H), 5.69 (m, 2H), 5.19 (d, 1H), 4.97 (dd, 1H), 4.67 (m, 2H), 4.31 (m, 1H), 4.05 (m, 1H), 2.89 (m, 1H), 2.70 (m, 2H), 2.55 (m, 1H), 2.29 (q, 1H), 1.89-1.11 (m, 13H), 1.19 (s, 9H), 0.97-0.86 (m, 2H).

[0258] CH_2Cl_2 (5 mL) 내 화합물 142 (0.1 g, 0.14 mmol)의 용액에 디옥산 (2 mL) 내 과량의 4 N HCl 용액을 실온에서 가하였다. 4시간 동안 교반한 후, HCl, 디옥산 및 CH_2Cl_2를 증발시켜 제거하여 미정제 화합물 I-25을 얻었다. 이 화합물은 더 이상 정제 없이 다음 단계에서 사용하였다. MS: m/z 712.3 (M^++1).

[0259] 화합물 I-25를 아세토니트릴 (2 mL)에 용해시킨 다음 포화 $NaHCO_3$ (1 mL)를 가하였다. 반응 혼합물을 10분 동안 교반하였다. 반응 혼합물에 시클로펜틸 클로로포르메이트 (0.02 g, 0.15 mmol)를 실온에서 가하였다. 2시간 더 교반한 후, 반응 혼합물을 포화 $NaHCO_3$로 종결시키고 CH_2Cl_2로 추출하였다. 잔류물을 실리카겔 컬럼 크로마토그래피로 정제하여 화합물 143 (0.1 g, 87%)을 얻었다. MS: m/z 824.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H),

8.29 (d,1H), 8.07 (d, 2H), 7.62-7.32 (m, 7H), 7.00 (s, 1H), 5.75 (s, 1H), 5.70 (q, 1H), 5.22 (d, 1H), 4.99 (dd, 1H), 4.75 (m, 2H), 4.56 (d, 1H), 4.32 (m, 1H), 4.05 (m, 1H), 2.89 (m, 1H), 2.70 (m, 2H), 2.52 (m, 1H), 2.29 (q, 1H), 1.91-0.85 (m, 23H).

[0260] 실시예 144~253 : 화합물 144~253의 합성

[0261] 각각의 화합물 144~253을 실시예 142 및 143에 기재된 방법과 유사한 방법으로 제조하였다.

[0262] 화합물 144: MS: m/z 7887.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.40 (s, 1H), 8.21 (d,1H), 8.08 (dd, 1H), 7.56-7.11 (m, 7H), 6.80 (s, 1H), 5.63 (m, 2H), 4.93 (m, 1H), 4.79 (m, 1H), 4.31 (m, 2H), 4.05 (m, 1H), 3.45 (s, 3H), 2.87 (m, 1H), 2.70 (m, 2H), 2.52 (m, 1H), 2.25 (q, 1H), 1.91-0.84 (m, 15H).

[0263] 화합물 145: MS: m/z 872.3 (M^++1).

[0264] 화합물 146: MS: m/z 770.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 8.25 (d,1H), 8.00 (d, 2H), 7.56-7.25 (m, 7H), 6.66 (s, 1H), 5.69 (m, 2H), 5.45 (d, 1H), 4.95 (dd, 1H), 4.70 (m, 1H), 4.40-4.28 (m, 2H), 4.05 (m, 1H), 3.52 (s, 3H), 2.88 (m, 1H), 2.70 (m, 2H), 2.51 (m, 1H), 2.30 (q, 1H), 1.87-1.09 (m, 13H), 0.97-0.84 (m, 2H).

[0265] 화합물 147: MS: m/z 697.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 8.24 (d, 1H), 8.04 (d, 2H), 7.56-7.31 (m, 8H), 5.63 (m, 2H), 4.97 (dd, 1H), 4.63 (m, 1H), 4.09 (m, 1H), 3.96 (m, 1H), 2.84 (m,1H), 2.62 (m, 2H), 2.6-2.03 (m, 4H), 1.95-0.84 (m, 15H).

[0266] 화합물 148: MS: m/z 872.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.09 (dd, 1H), 7.69 (d, 1H), 7.48-7.14 (m, 7H), 5.71 (m, 2H), 5.31 (d,1H), 4.98 (dd, 1H), 4.74 (m, 1H), 4.55 (d, 1H), 4.36 (m, 1H), 4.05 (m, 2H), 3.96 (s, 3H), 2.89 (m, 1H), 2.68 (m, 2H), 2.52 (m, 1H), 2.28 (q, 1H), 2.00-0.88 (m, 23H).

[0267] 화합물 149: MS: m/z 818.2 (M^++1).

[0268] 화합물 150: MS: m/z 802.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.23 (s, 1H), 8.08 (dd, 1H), 7.68 (d, 1H), 7.49 (d, 1H), 7.39-7.13 (m, 6H), 6.10 (d, 1H), 5.72 (m, 2H), 4.95 (dd, 1H), 4.63 (m, 2H), 4.17 (d, 1H), 4.06 (m, 1H), 3.92 (s, 3H), 2.89 (m, 1H), 2.69 (m, 2H), 2.46 (m, 1H), 2.26 (q, 1H), 1.94-0.86 (m, 15H), 1.91 (s, 3H).

[0269] 화합물 151: MS: m/z 854.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 8.27 (d, 1H), 8.03 (d, 2H), 7.59 (m, 3H), 7.45 (dd, 1H), 7.01 (d, 2H), 6.88 (m, 1H), 5.74 (m, 2H), 5.19 (d, 1H), 4.96 (m, 2H), 4.75 (s, 1H), 4.53 (d, 1H), 4.32 (m, 1H), 4.04 (m, 1H), 3.87 (s, 3H), 2.89 (m, 1H), 2.69 (m, 2H), 2.46 (m, 1H), 2.27 (q, 1H), 1.90-1.12 (m,21H), 0.92-0.87(m,2H).

[0270] 화합물 152: MS: m/z 842.3 (M^++1).

[0271] 화합물 153: MS: m/z 854.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 8.58 (s, 1H), 8.43 (m,1H), 7.85 (d, 1H), 7.59 (m, 2H), 7.37 (m, 3H), 7.12 (dd, 1H), 7.01 (d, 1H), 5.65 (m, 2H), 5.31 (d, 1H), 4.94 (dd, 1H), 4.72 (m, 2H), 4.53 (d, 1H), 4.37 (m, 1H), 4.07 (m, 1H), 3.87 (s, 3H), 2.88 (m,1H), 2.66 (m, 2H), 2.50 (m, 1H), 2.28 (q, 1H), 1.88-0.82 (m, 23H).

[0272] 화합물 154: MS: m/z 854.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.50 (s, 1H), 8.29 (d, 1H), 7.63 (s, 1H), 7.56 (m, 3H), 7.43 (m, 2H), 7.28 (m, 1H), 7.11 (s, 1H), 6.98 (dd,1H), 5.74 (s, 1H), 5.69 (q, 1H), 5.29 (d, 1H), 4.94 (dd, 1H), 4.73 (m, 1H), 4.57 (d, 1H), 4.34 (m, 1H), 4.04 (m, 1H), 3.92 (s, 3H),

2.88 (m, 1H), 2.68 (m,2H), 2.51 (m, 1H), 2.29 (q, 1H), 1.87-0.84 (m, 23H).

[0273] 화합물 155: MS: m/z 842.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 8.28 (d,1H), 7.85 (d, 1H), 7.57 (m, 2H), 7.40 (m, 3H), 7.14 (dd, 1H), 7.01 (d, 2H), 5.68 (q, 1H), 5.58 (s, 1H), 5.19 (d, 1H), 4.92 (dd, 1H), 4.67 (m, 2H), 4.33 (m, 1H), 4.03 (m, 1H), 3.87 (s, 3H), 2.89 (m,1H), 2.68 (m, 2H), 2.54 (m, 1H), 2.28 (q, 1H), 1.90-1.11 (m, 13H), 1.21 (s, 9H), 0.97-0.87 (m, 2H).

[0274] 화합물 156: MS: m/z 854.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.24 (s, 1H), 8.59 (s, 1H), 8.04 (m, 2H), 7.84 (d, 1H), 7.49-7.28 (m, 4H), 7.08 (d, 1H), 6.91 (s, 1H), 5.72 (s, 1H), 5.68 (q, 1H), 5.21 (d, 1H), 4.97 (dd, 1H), 4.71-4.67 (m, 2H), 4.56 (d, 1H), 4.36 (m, 1H), 4.05 (s, 3H), 4.04 (m, 1H), 2.90 (m, 1H), 2.69 (m, 2H), 2.54 (m, 1H), 2.31 (q, 1H), 1.96-1.06 (m, 21H), 0.95-0.83 (m, 2H).

[0275] 화합물 157: MS: m/z 838.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.59 (s, 1H), 8.27 (d, 1H), 7.92 (d, 2H), 7.57 (m, 2H), 7.44 (m, 1H), 7.26-7.17 (m, 3H), 5.68 (s, 1H), 5.64 (q, 1H), 5.37 (d, 1H), 4.96 (m, 1H), 4.76 (m, 1H), 4.67 (m, 1H), 4.56 (d, 1H), 4.36 (m, 1H), 4.04 (m, 1H), 2.89 (m, 1H), 2.69 (m, 2H), 2.53 (m, 1H), 2.40 (s, 3H), 2.31 (q, 1H), 1.94-1.07 (m, 21H), 0.95-0.83 (m, 2H).

[0276] 화합물 158: MS: m/z 842.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 8.26 (d, 1H), 8.05 (m, 2H), 7.58 (m, 2H), 7.43 (m, 1H), 7.25-7.19 (m, 4H), 5.72 (s, 1H), 5.68 (q, 1H), 5.35 (d, 1H), 4.96 (dd, 1H), 4.75-4.69 (m, 2H), 4.56 (d, 1H), 4.36 (m, 1H), 4.04 (m, 1H), 2.87 (m, 1H), 2.67 (m, 2H), 2.50 (m, 1H), 2.28 (q, 1H), 1.91-1.07 (m, 21H), 0.97-0.84 (m, 2H).

[0277] 화합물 159: MS: m/z 872.3 (M^++1).

[0278] 화합물 160: MS: m/z 872.1 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.48 (s, 1H), 8.02 (m, 2H), 7.68 (d, 1H), 7.47 (d, 1H), 7.23-7.17 (m, 4H), 5.74 (m, 2H), 5.68 (q, 1H), 5.23 (d, 1H), 4.97 (dd, 1H), 4.76 (s, 1H), 4.67 (m, 1H), 4.54 (d, 1H), 4.33 (m, 1H), 4.04 (m, 1H), 3.93 (s, 3H), 2.89 (m, 1H), 2.67 (m, 2H), 2.52 (m, 1H), 2.27 (q, 1H), 1.92-1.06 (m, 21H), 0.97-0.84 (m, 2H).

[0279] 화합물 161: MS: m/z 860.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.34 (s, 1H), 8.01 (m, 2H), 7.67 (d, 1H), 7.47 (d, 1H), 7.29-7.16 (m, 5H), 5.68 (m, 2H), 5.23 (d, 1H), 4.95 (dd, 1H), 4.69-4.63 (m, 2H), 4.31 (m, 1H), 4.04 (m, 1H), 3.92 (s, 3H), 2.88 (m, 1H), 2.67 (m, 2H), 2.54 (m, 1H), 2.27 (q, 1H), 1.92-0.83 (m, 15H), 1.20 (s, 9H).

[0280] 화합물 162: MS: m/z 856.1 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.23 (s, 1H), 8.03 (m, 2H), 7.66 (d, 1H), 7.48 (d, 1H), 7.32 (s, 1H), 7.29-7.15 (m, 5H), 5.73 (m, 2H), 4.92 (dd, 1H), 4.69 (m, 2H), 4.31 (d, 1H), 4.06 (m, 1H), 3.91 (s, 3H), 2.85 (m, 1H), 2.68 (m, 2H), 2.44 (m, 1H), 2.20 (q, 1H), 1.93-0.83 (m, 15H).

[0281] 화합물 163: MS: m/z 854.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.60 (s, 1H), 8.01 (m, 2H), 7.68 (d, 1H), 7.46 (m, 4H), 7.15 (m, 2H), 5.71 (s, 1H), 5.68 (q, 1H), 5.37 (d, 1H), 4.96 (dd, 1H), 4.67 (s, 1H), 4.64 (m, 1H), 4.55 (d, 1H), 4.36 (m, 1H), 4.03 (m, 1H), 3.93 (s, 3H), 2.88 (m, 1H), 2.68 (m, 2H), 2.52 (m, 1H), 2.28 (q, 1H), 1.94-1.07 (m, 21H), 0.97-0.84 (m, 2H).

[0282] 화합물 164: MS: m/z 830.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.25 (d, 1H), 8.04 (m, 2H), 7.57 (m, 2H), 7.42 (m, 1H), 7.25-7.14 (m, 4H), 5.68 (m, 2H), 5.25 (d, 1H), 4.92 (dd, 1H), 4.66 (m, 2H), 4.32 (m, 1H), 4.05 (m, 1H), 2.87 (m, 1H), 2.68 (m, 2H), 2.55 (m, 1H), 2.28 (q, 1H), 1.91-1.06 (m, 13H), 1.20 (s,9H), 0.97-0.84 (m, 2H).

[0283] 화합물 165: MS: m/z 868.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.53 (s, 1H), 8.13 (d, 1H), 7.91 (m, 2H), 7.58 (m, 1H), 7.19 (m, 1H), 7.00 (m, 3H), 5.72 (s, 1H), 5.68 (q, 1H), 5.28 (d, 1H), 4.95 (dd,

1H), 4.79 (s, 1H), 4.68 (m, 1H), 4.53 (d, 1H), 4.37 (m, 1H), 4.05 (m, 1H), 3.91 (s, 3H), 2.88 (m, 1H), 2.66 (m, 2H), 2.50 (m, 1H), 2.40 (s, 3H), 2.25 (q, 1H), 1.90-1.06 (m, 21H), 0.97-0.83 (m, 2H).

[0284] 화합물 166: MS: m/z 868.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.59 (s, 1H), 7.98 (m, 2H), 7.71 (s, 1H), 7.46 (d, 1H), 7.27 (m, 2H), 7.15 (m, 2H), 5.71 (s, 1H), 5.68 (q, 1H), 5.29 (d, 1H), 4.94 (dd, 1H), 4.78 (s, 1H), 4.67 (m, 1H), 4.54 (d, 1H), 4.36 (m, 1H), 4.04 (m, 1H), 3.93 (s, 3H), 2.88 (m, 1H), 2.68 (m, 2H), 2.53 (m, 1H), 2.40 (s, 3H), 2.28 (q, 1H), 1.92-1.08 (m, 21H), 0.97-0.83 (m, 2H).

[0285] 화합물 167: MS: m/z 872.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.51 (s, 1H), 8.08 (d, 1H), 8.01 (m, 2H), 7.15 (d, 2H), 7.04 (m, 3H), 5.73 (s, 1H), 5.69 (q, 1H), 5.30 (d, 1H), 4.95 (dd, 1H), 4.79 (s, 1H), 4.65 (m, 1H), 4.53 (d, 1H), 4.37 (m, 1H), 4.04 (m, 1H), 3.91 (s, 3H), 2.88 (m, 1H), 2.66 (m, 2H), 2.50 (m, 1H), 2.28 (q, 1H), 1.90-1.05 (m, 21H), 0.97-0.83 (m, 2H).

[0286] 화합물 168: MS: m/z 826.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.23 (s, 1H), 8.28 (d, 1H), 7.94 (d, 2H), 7.56 (m, 2H), 7.42 (m, 1H), 7.28 (m, 3H), 7.03 (s, 1H), 5.68 (m, 2H), 5.21 (d, 1H), 4.94 (dd, 1H), 4.67 (m, 2H), 4.32 (m, 1H), 4.05 (m, 1H), 2.89 (m, 1H), 2.68 (m, 2H), 2.55 (m, 1H), 2.55 (s, 3H), 2.35 (q, 1H), 1.94-1.07 (m, 13H), 1.20 (s, 9H), 0.97-0.84 (m, 2H).

[0287] 화합물 169: MS: m/z 858.3, 859.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 8.58 (s, 1H), 8.24 (d, 1H), 8.00 (d, 2H), 7.57 (m, 2H), 7.45 (m, 3H), 7.25 (s, 1H), 5.71 (s, 1H), 5.66 (q, 1H), 5.41 (d, 1H), 4.96 (dd, 1H), 4.75 (m, 2H), 4.55 (d, 1H), 4.35 (m, 1H), 4.04 (m, 1H), 2.87 (m, 1H), 2.69 (m, 2H), 2.57 (m, 1H), 2.28 (q, 1H), 1.92-0.83 (m, 23H).

[0288] 화합물 170: MS: m/z 772.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 8.22 (d, 1H), 8.00 (m, 2H), 7.59 (m, 2H), 7.41 (m, 1H), 7.20-7.10 (m, 4H), 6.12 (d, 1H), 5.72 (m, 2H), 4.96 (dd, 1H), 4.64 (m, 1H), 4.55 (m, 1H), 4.40 (d, 1H), 4.01 (m, 1H), 2.88 (m, 1H), 2.66 (m, 2H), 2.50 (m, 1H), 2.26 (q, 1H), 1.92-1.05 (m, 13H), 1.91 (s,3H), 0.97-0.85 (m, 2H).

[0289] 화합물 171: MS: m/z 768.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.26 (d, 1H), 7.93 (d, 2H), 7.57 (m, 2H), 7.42 (m, 1H), 7.27 (m, 4H), 6.16 (d, 1H), 5.69 (m, 2H), 4.94 (dd, 1H), 4.67 (m, 1H), 4.57 (m, 1H), 4.40 (d, 1H), 4.05 (m, 1H), 2.89 (m, 1H), 2.68 (m, 2H), 2.51 (m, 1H), 2.39 (s, 3H),2.30 (q, 1H), 1.94-1.05 (m, 13H), 1.92 (s, 3H), 0.97-0.84 (m, 2H).

[0290] 화합물 172: MS: m/z 788.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.32 (s, 1H), 8.22 (d, 1H), 8.01 (m, 2H), 7.57 (m, 2H), 7.42 (m, 1H), 7.22-7.11 (m, 4H), 5.72 (m, 2H), 5.39 (d, 1H), 4.96 (dd, 1H), 4.71 (m, 1H), 4.39 (m, 2H), 4.04 (m, 1H), 3.54 (s, 3H), 2.89 (m, 1H), 2.71 (m, 2H), 2.54 (m, 1H), 2.25 (q, 1H), 1.91-1.06 (m, 13H), 0.93-0.83 (m, 2H).

[0291] 화합물 173: MS: m/z 822.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.15 (s, 1H), 8.27 (d, 1H), 7.91 (d, 2H), 7.59 (m, 2H), 7.44 (m, 1H), 7.27 (m, 3H), 7.15 (d, 1H), 7.07 (s, 1H), 5.75 (s, 1H), 5.69 (q, 1H), 4.91 (dd, 1H), 4.68 (m, 2H), 4.32 (d, 1H), 4.06 (m, 1H), 2.89 (m, 1H), 2.68 (m, 2H), 2.41 (m, 1H), 2.39 (s, 3H), 2.21 (q, 1H), 1.96-1.08 (m, 13H), 0.96-0.83 (m, 2H).

[0292] 화합물 174: MS: m/z 826.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1H), 8.22 (d, 1H), 8.02 (m, 2H), 7.59 (m, 2H), 7.41 (m, 1H), 7.24-7.13 (m, 5H), 5.73 (s, 1H), 5.67 (q, 1H), 4.89 (dd, 1H), 4.72 (m, 2H), 4.31 (d, 1H), 4.05 (m, 1H), 2.87 (m, 1H), 2.69 (m, 2H), 2.47 (m, 1H), 2.24 (q, 1H), 1.93-1.04 (m, 13H), 0.93-0.82 (m, 2H).

[0293] 화합물 175: MS: m/z 842.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.58 (s, 1H), 8.26 (d,1H), 8.10 (dd, 1H), 7.61-7.14 (m, 7H), 6.91 (s, 1H), 5.67 (m, 2H), 5.38 (d, 1H), 4.96 (dd, 1H), 4.70 (m, 1H), 4.56

(d, 1H), 4.36 (m, 1H), 4.06 (m, 1H), 2.88 (m, 1H), 2.69 (m, 2H), 2.51 (m, 1H), 2.28 (q, 1H), 1.87-0.88 (m, 23H).

[0294] 화합물 176: MS: m/z 844.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 8.00 (m, 3H), 7.42 (d, 1H), 7.37 (d, 1H), 7.19 (m, 3H), 6.98 (s, 1H), 5.68 (m, 2H), 5.19 (d, 1H), 4.96 (dd, 1H), 4.66 (m, 2H), 4.30 (m, 1H), 4.04 (m, 1H), 2.89 (m, 1H), 2.67 (m, 2H), 2.52 (s, 3H), 2.51 (m, 1H), 2.26 (q, 1H), 1.94-1.05 (m, 13H), 1.20 (s, 9H), 0.98-0.83 (m, 2H).

[0295] 화합물 177: MS: m/z 840.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H), 8.00 (m, 3H), 7.42 (d, 1H), 7.35-7.11 (m, 6H), 5.73 (s, 1H), 5.69 (q, 1H), 4.93 (dd, 1H), 4.66 (m, 2H), 4.32 (d, 1H), 4.04 (m, 1H), 2.89 (m, 1H), 2.70 (m, 2H), 2.51 (s, 3H), 2.48 (m, 1H), 2.23 (q, 1H), 1.95-1.04 (m, 13H), 0.96-0.82 (m, 2H).

[0296] 화합물 178: MS: m/z 784.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.27 (d, 1H), 7.92 (d, 2H), 7.55 (m, 2H), 7.41 (m, 1H), 7.27 (m, 4H), 5.70 (m, 2H), 5.45 (d, 1H), 4.95 (dd, 1H), 4.67 (m, 1H), 4.36 (m, 2H), 4.06 (m, 1H), 3.49 (s, 3H), 2.89 (m, 1H), 2.69 (m, 2H), 2.51 (m, 1H), 2.39 (s, 3H),2.26 (q, 1H), 1.96-1.06 (m, 13H), 0.97-0.83 (m, 2H).

[0297] 화합물 179: MS: m/z 856.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 7.92 (d, 2H), 7.69 (d, 1H), 7.44 (d, 1H), 7.29 (d, 2H), 7.15 (s, 1H), 7.05 (dd, 1H), 6.97 (s, 1H), 5.68 (m, 2H), 5.22 (d, 1H), 4.95 (dd, 1H), 4.62 (m, 2H), 4.30 (m, 1H), 4.03 (m, 1H), 3.93 (s, 3H), 2.87 (m, 1H), 2.66 (m, 2H), 2.54 (m, 1H), 2.41 (s, 3H), , 2.29 (q, 1H), 1.94-0.82 (m, 15H), 1.21 (s, 9H).

[0298] 화합물 180: MS: m/z 814.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 7.92 (d, 2H), 7.63 (d, 1H), 7.42 (d, 1H), 7.33-7.21 (m, 4H), 7.10 (dd, 1H), 5.66 (m, 2H), 5.41 (d, 1H), 4.94 (dd, 1H), 4.65 (m, 1H), 4.37 (m, 2H), 4.03 (m, 1H), 3.91 (s, 3H), 3.50 (s, 3H), 2.87 (m, 1H), 2.66 (m, 2H), 2.51 (m, 1H), 2.41 (s, 3H), 2.25 (q, 1H), 1.94-1.07 (m, 13H), 0.93-0.83 (m, 2H).

[0299] 화합물 181: MS: m/z 852.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 1H), 7.91 (d, 2H), 7.71 (d, 1H), 7.48 (d, 1H), 7.30-7.15 (m, 5H), 7.13 (dd, 1H), 5.66 (s, 1H), 5.64 (q, 1H), 4.94 (dd, 1H), 4.65 (m, 2H), 4.30 (d, 1H), 4.03 (m, 1H), 3.93 (s, 3H), 2.84 (m, 1H), 2.67 (m, 2H), 2.46 (m, 1H), 2.40 (s, 3H), 2.22 (q, 1H), 1.95-0.84 (m, 15H).

[0300] 화합물 182: MS: m/z 798.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 7.92 (d, 2H), 7.72 (d, 1H), 7.43 (d, 1H), 7.39 (s, 1H), 7.21 (m, 3H), 7.11 (dd, 1H), 6.18 (d, 1H), 5.70 (q, 1H), 5.64 (s, 1H), 4.94 (dd, 1H), 4.66 (dd, 1H), 4.56 (m, 1H), 4.39 (d, 1H), 4.02 (m, 1H), 3.93 (s, 3H), 2.84 (m, 1H), 2.68 (m, 2H), 2.47 (m, 1H), 2.39 (s, 3H), 2.25 (q, 1H), 1.95-0.83 (m, 15H), 1.91 (s, 3H).

[0301] 화합물 183: MS: m/z 802.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.39 (s, 1H), 7.96 (m, 3H), 7.44 (m, 2H), 7.35 (m, 1H), 7.14 (m, 3H), 5.66 (m, 2H), 5.41 (d, 1H), 4.92 (dd, 1H), 4.61 (m, 1H), 4.30 (m, 2H), 4.00 (m, 1H), 3.50 (s, 3H), 2.89 (m, 1H), 2.72 (m, 2H), 2.51 (s, 3H), 2.50 (m, 1H), 2.26 (q, 1H), 1.93-1.06 (m, 13H), 0.97-0.83 (m, 2H).

[0302] 화합물 184: MS: m/z 786.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 7.96 (m, 3H), 7.42 (m, 2H), 7.32 (m, 1H), 7.15 (m, 3H), 6.12 (d, 1H), 5.69 (q, 1H), 5.65 (s, 1H), 4.94 (dd, 1H), 4.64 (m, 1H), 4.54 (m, 1H), 4.38 (d, 1H), 3.98 (m, 1H), 2.88 (m, 1H), 2.71 (m, 2H), 2.50 (m, 1H), 2.49 (s, 3H), 2.27 (q, 1H), 1.92-0.82 (m, 15H), 1.91 (s, 3H).

[0303] 화합물 185: MS: m/z 812.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 7.96 (m, 3H), 7.41 (d, 1H), 7.36 (d, 1H), 7.25 (m, 1H), 7.10 (m, 3H), 6.19 (d, 1H), 5.71 (q, 1H), 5.64 (s, 1H), 4.95 (dd, 1H), 4.66 (m,

1H), 4.48 (m, 2H), 3.99 (m, 1H), 2.89 (m, 1H), 2.70 (m, 2H), 2.51 (m, 1H), 2.50 (s, 3H), 2.27 (q, 1H), 1.91-1.10 (m, 14H), 0.97-0.80 (m, 2H), 0.80-0.68 (m, 4H).

[0304] 화합물 186: MS: m/z 856.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 8.00 (m, 3H), 7.42 (d, 1H), 7.37 (d, 1H), 7.25-7.13 (m, 3H), 7.04 (s, 1H), 5.72 (s, 1H), 5.69 (q, 1H), 5.23 (d, 1H), 4.97 (dd, 1H), 4.77 (s, 1H), 4.67 (m, 1H), 4.55 (d, 1H), 4.35 (m, 1H), 4.04 (m, 1H), 2.89(m, 1H), 2.68 (m, 2H), 2.52 (s, 3H), 2.51 (m, 1H), 2.25 (q, 1H), 1.93-1.06 (m, 21H), 0.97-0.83 (m, 2H).

[0305] 화합물 187: MS: m/z 830.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.01 (d, 2H), 7.93 (d, 1H), 7.50 (m, 4H), 7.29 (m, 2H), 7.07 (s, 1H), 5.67 (m, 2H), 5.19 (d, 1H), 4.94 (dd, 1H), 4.67 (m, 2H), 4.30 (m, 1H), 4.04 (m, 1H), 2.89 (m, 1H), 2.69 (m, 2H), 2.52 (m, 1H), 2.28 (q, 1H), 1.94-1.05 (m, 13H), 1.19 (s, 9H), 0.97-0.84 (m, 2H).

[0306] 화합물 188: MS: m/z 842.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.27 (s, 1H), 8.02 (d, 2H), 7.93 (d, 1H), 7.52 (m, 4H), 7.32 (s, 1H), 7.26 (m, 1H), 7.08 (s, 1H), 5.68 (s, 1H), 5.66 (q, 1H), 5.22 (d, 1H), 4.92 (dd, 1H), 4.71 (m, 2H), 4.57 (d, 1H), 4.33 (m, 1H), 4.05 (m, 1H), 2.89(m, 1H), 2.68 (m, 2H), 2.53 (m, 1H), 2.28 (q, 1H), 1.95-0.83 (m, 23H).

[0307] 화합물 189: MS: m/z 882.4 (M^++1).

[0308] 화합물 190: MS: m/z 884.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 7.96 (m, 3H), 7.54 (m, 1H), 7.36-7.26 (m, 5H), 5.70 (m, 2H), 5.27 (d, 1H), 4.95 (dd, 1H), 4.74 (m, 1H), 4.53 (d, 1H), 4.32 (m, 1H), 4.05 (m, 2H), 2.95 (m, 2H), 2.69 (m, 2H), 2.52 (m, 1H), 2.28 (q, 1H), 1.94-0.83 (m, 23H), 1.29 (d, 6H).

[0309] 화합물 191: MS: m/z 898.2 (M^++1).

[0310] 화합물 192: MS: m/z 880.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 8.28 (d, 1H), 7.95 (d, 2H), 7.50 (m, 4H), 7.42 (dd, 1H), 7.27 (s, 1H), 7.21 (s, 1H), 5.68 (s, 1H), 5.65 (q, 1H), 5.35 (d, 1H), 4.94 (dd, 1H), 4.72 (m, 2H), 4.57 (d, 1H), 4.35 (m, 1H), 4.04 (m, 1H), 2.88 (m, 1H), 2.68 (m, 2H), 2.53 (m, 1H), 2.28 (q, 1H), 1.93-1.05 (m, 21H), 1.36 (s, 9H), 0.97-0.82 (m, 2H).

[0311] 화합물 193: MS: m/z 894.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1H), 8.28 (d, 1H), 7.95 (d, 2H), 7.52 (m, 4H), 7.41 (dd, 1H), 7.34 (s, 1H), 7.26 (s, 1H), 5.70 (s, 1H), 5.65 (q, 1H), 5.41 (d, 1H), 4.95 (dd, 1H), 4.75 (m, 2H), 4.57 (d, 1H), 4.36 (m, 1H), 4.05 (m, 1H), 2.70 (m, 2H), 2.50 (m, 1H), 2.29 (q, 1H), 1.93-0.82 (m, 23H), 1.46 (s, 3H), 1.36 (s, 9H).

[0312] 화합물 194: MS: m/z 857.3 (M^++1).

[0313] 화합물 195: MS: m/z 857.3 (M^++1).

[0314] 화합물 196: MS: m/z 784.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H), 8.27 (d,1H), 7.88 (d, 1H), 7.57 (m, 2H), 7.39 (m, 3H), 7.13 (dd, 1H), 7.01 (d, 2H), 6.14 (d, 1H), 5.68 (q, 1H), 5.62 (s, 1H), 4.97 (dd, 1H), 4.64 (m, 2H), 4.41 (d, 1H), 4.07 (m, 1H), 3.87 (s, 3H), 2.87 (m,1H), 2.67 (m, 2H), 2.45 (m, 1H), 2.25 (q, 1H), 1.93-0.85 (m, 15H), 1.92 (s, 3H).

[0315] 화합물 197: MS: m/z 856.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.34 (s, 1H), 8.03 (s, 1H), 8.00 (d, 2H), 7.45 (d, 1H), 7.35 (d, 1H), 7.16 (m, 2H), 7.00 (d, 2H), 5.71 (s, 1H), 5.69 (q, 1H), 5.23 (d, 1H), 4.95 (dd, 1H), 4.62 (m, 2H), 4.30 (m, 1H), 4.03 (m, 1H), 3.86 (s, 3H), 2.88 (m, 1H), 2.66 (m, 2H), 2.51 (s, 3H), 2.50 (m, 1H), 2.31 (q, 1H), 1.91-0.82 (m, 15H), 1.22 (s, 9H).

[0316] 화합물 198: MS: m/z 784.2 (M^++1).

[0317] 화합물 199: MS: m/z 798.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 7.96 (m, 3H), 7.58 (s, 1H), 7.43 (d, 1H), 7.32 (d, 1H), 7.16 (s, 1H), 6.97 (d, 2H), 6.24 (d, 1H), 5.69 (q, 1H), 5.64 (s, 1H), 4.96 (dd, 1H), 4.66 (m, 1H), 4.55 (m, 1H), 4.40 (d, 1H), 4.02 (m, 1H), 3.84 (s, 3H), 2.87 (m, 1H), 2.68 (m, 2H), 2.49 (s, 3H), 2.50 (m, 1H), 2.28 (q, 1H), 1.91-0.83 (m, 15H), 1.91 (s, 3H).

[0318] 화합물 200: MS: m/z 852.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 8.03 (s, 1H), 7.96 (d, 2H), 7.52 (s, 1H), 7.45 (d, 1H), 7.34 (d, 1H), 7.23 (s, 1H), 6.98 (d, 2H), 5.67 (s, 1H), 5.64 (q, 1H), 5.21 (m, 1H), 4.93 (dd, 1H), 4.67 (m, 2H), 4.30 (d, 1H), 4.04 (m, 1H), 3.85 (s, 3H), 2.87 (m, 1H), 2.66-2.40 (m, 3H), 2.51 (s, 3H), 2.22 (q, 1H), 1.95-0.82 (m, 15H).

[0319] 화합물 201: MS: m/z 814.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.41 (s, 1H), 7.98 (m, 3H), 7.60 (s, 1H), 7.43 (d, 1H), 7.33 (d, 1H), 7.16 (s, 1H), 6.98 (d, 2H), 5.64 (m, 2H), 5.29 (m, 2H), 4.93 (dd, 1H), 4.69 (m, 1H), 4.36 (m, 1H), 4.01 (m, 1H), 3.84 (s, 3H), 3.42 (s, 3H), 2.87 (m, 1H), 2.66 (m, 2H), 2.50 (m, 1H), 2.49 (s, 3H), 2.25 (q, 1H), 1.94-0.82 (m, 15H).

[0320] 화합물 202: MS: m/z 838.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.23 (s, 1H), 8.26 (d, 1H), 8.00 (d, 2H), 7.60 (m, 2H), 7.44 (m, 2H), 7.23 (m, 2H), 7.01 (d, 2H), 5.73 (s, 1H), 5.67 (q, 1H), 4.94 (dd, 1H), 4.68 (m, 2H), 4.32 (d, 1H), 4.07 (m, 1H), 3.86 (s, 3H), 2.86 (m, 1H), 2.67 (m, 2H), 2.41 (m, 1H), 2.23 (q, 1H), 1.94-1.08 (m,13H), 0.94-0.87 (m,2H).

[0321] 화합물 203: MS: m/z 842.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.28 (d, 1H), 7.63 (s, 1H), 7.57 (m, 3H), 7.42 (m, 2H), 7.25 (m, 1H), 7.08 (s, 1H), 6.97 (dd,1H), 5.71 (m, 2H), 5.22 (d, 1H), 4.92 (dd, 1H), 4.64 (m, 2H), 4.31 (m, 1H), 4.00 (m, 1H), 3.91 (s, 3H), 2.89 (m, 1H), 2.69 (m,2H), 2.55 (m, 1H), 2.29 (q, 1H), 1.85-0.83 (m, 15H), 1.19 (s, 9H).

[0322] 화합물 204: MS: m/z 784.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 8.26 (d, 1H), 7.62 (s, 1H), 7.58 (m, 3H), 7.41 (m, 2H), 7.25 (m, 2H), 6.96 (dd,1H), 6.13 (d, 1H), 5.71 (q, 1H), 5.68 (s, 1H), 4.95 (dd, 1H), 4.63 (t, 1H), 4.59 (m, 1H), 4.41 (d, 1H), 4.04 (m, 1H), 3.90 (s, 3H), 2.88 (m, 1H), 2.71 (m,2H), 2.52 (m, 1H), 2.29 (q, 1H), 1.92-1.1.05 (m, 13H), 1.91 (s, 3H), 0.97-0.84 (m, 2H).

[0323] 화합물 205: MS: m/z 801.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.34 (s, 1H), 8.25 (d, 1H), 7.61 (s, 1H), 7.57 (m, 3H), 7.39-7.25 (m, 4H), 6.93 (dd,1H), 5.70 (m, 2H), 5.44 (d, 1H), 4.94 (dd, 1H), 4.70 (m, 1H), 4.39 (d, 1H), 4.32 (m, 1H), 4.03 (m, 1H), 3.90 (s, 3H), 3.48 (s, 3H), 2.88 (m, 1H), 2.70 (m,2H), 2.52 (m, 1H), 2.26 (q, 1H), 1.89-0.82 (m, 15H).

[0324] 화합물 206: MS: m/z 838.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 1H), 8.27 (d, 1H), 7.62 (s, 1H), 7.58 (m, 3H), 7.41 (m, 2H), 7.25 (m, 3H), 6.97 (dd,1H), 5.71 (s, 1H), 5.63 (q,1H), 4.92 (dd, 1H), 4.64 (m, 2H), 4.33 (d, 1H), 4.05 (m, 1H), 3.90 (s, 3H), 2.88 (m, 1H), 2.69 (m,2H), 2.46 (m, 1H), 2.23 (q, 1H), 1.94-1.1.03 (m, 13H), 0.95-0.84 (m, 2H).

[0325] 화합물 207: MS: m/z 800.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.24 (s, 1H), 8.27 (d,1H), 7.86 (d, 1H), 7.55 (m, 2H), 7.42 (m, 3H), 7.12 (m, 2H), 7.00 (d, 1H), 5.68 (q, 1H), 5.62 (s, 1H), 5.47 (d, 1H), 4.92 (dd, 1H), 4.68 (m, 1H), 4.40 (m, 2H), 4.04 (m, 1H), 3.87 (s, 3H), 3.50 (s, 3H), 2.89 (m,1H), 2.68 (m, 2H), 2.50 (m, 1H), 2.25 (q, 1H), 1.91-1.03 (m, 13H), 0.98-0.82 (m, 2H).

[0326] 화합물 208: MS: m/z 838.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.19 (s, 1H), 8.27 (d,1H), 7.82 (d, 1H), 7.57 (m, 2H), 7.39 (m, 5H), 7.12 (dd, 1H), 7.02 (d, 1H), 5.63 (q, 1H), 5.60 (s, 1H), 4.90 (dd, 1H), 4.70 (m, 2H), 4.32 (d, 1H), 4.03 (m, 1H), 3.85 (s, 3H), 2.86 (m,1H), 2.71-2.52 (m, 2H), 2.39 (m, 1H), 2.20 (q,

1H), 1.94-0.84 (m, 15H).

[0327] 화합물 209: MS: m/z 896.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H), 8.31 (d, 1H), 7.99 (d, 2H), 7.58 (m, 2H), 7.42 (m, 1H), 7.30-7.22 (m, 2H), 7.01 (d, 2H), 5.68 (s, 1H), 5.66 (q, 1H), 5.37 (d, 1H), 4.96 (dd, 1H), 4.78-4.51 (m, 4H), 4.37 (m, 1H), 4.06 (m, 1H), 2.69 (m, 2H), 2.51 (m, 1H), 2.28 (q, 1H), 1.94-0.83 (m, 23H), 1.46 (s, 3H), 1.37 (d, 6H).

[0328] 화합물 210: MS: m/z 882.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.24 (s, 1H), 8.27 (d, 1H), 7.98 (d, 2H), 7.58 (m, 2H), 7.42 (m, 1H), 7.24 (m, 1H), 7.01 (d, 2H), 6.89 (s, 1H), 5.68 (s, 1H), 5.66 (q, 1H), 5.22 (d, 1H), 4.97 (dd, 1H), 4.78-4.52 (m, 4H), 4.36 (m, 1H), 4.04 (m, 1H), 2.88 (m, 1H), 2.68 (m, 2H), 2.54 (m, 1H), 2.29 (q, 1H), 1.94-1.05 (m, 21H), 1.37 (d, 6H), 0.97-0.83 (m, 2H).

[0329] 화합물 211: MS: m/z 922.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.13(s, 1H), 8.26(d, 1H), 8.10(d, 2H), 7.59(m, 2H), 7.42(m, 1H), 7.35-7.25(m, 3H), 7.03(s, 1H), 5.77(s, 1H), 5.66(q, 1H), 5.20(d, 1H), 4.99(dd, 1H), 4.71(m, 2H), 4.56(d, 1H), 4.35(m, 1H), 4.03(m, 1H), 2.70(m, 2H), 2.50(m, 1H), 2.29(q, 1H), 1.90-0.84(m, 23H), 0.85 (s, 3H).

[0330] 화합물 212: MS: m/z 892.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.59 (s, 1H), 8.25 (d, 1H), 8.18 (d, 2H), 7.73 (d, 2H), 7.58 (m, 2H), 7.45 (m, 1H), 7.34 (s, 1H), 5.74 (s, 1H), 5.68 (q, 1H), 5.39 (d, 1H), 4.94 (dd, 1H), 4.72 (m, 2H), 4.55 (d, 1H), 4.31 (m, 1H), 4.04 (m, 1H), 2.86 (m, 1H), 2.67 (m, 2H), 2.49 (m, 1H), 2.26 (q, 1H), 1.91-1.05 (m, 23H).

[0331] 화합물 213: MS: m/z 880.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.26 (d, 1H), 8.16 (d, 2H), 7.74 (d, 2H), 7.59 (m, 2H), 7.45 (m, 1H), 7.30 (m, 2H), 5.71 (s, 1H), 5.66 (q, 1H), 5.25 (d, 1H), 4.95 (dd, 1H), 4.71 (m, 1H), 4.65 (d, 1H), 4.28 (m, 1H), 4.03 (m, 1H), 2.87 (m, 1H), 2.70 (m, 2H), 2.51 (m, 1H), 2.27 (q, 1H), 1.92-1.06 (m, 13H), 1.19 (s, 9H), 0.97-0.82 (m, 2H).

[0332] 화합물 214: MS: m/z 780.2 (M^++1).

[0333] 화합물 215: MS: m/z 822.2 (M^++1).

[0334] 화합물 216: MS: m/z 910.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.15 (d, 2H), 7.75 (d, 2H), 7.61 (s, 1H), 7.47 (d, 1H), 7.25-7.15 (m, 3H), 5.72 (s, 1H), 5.68 (q, 1H), 5.18 (d, 1H), 4.98 (dd, 1H), 4.67 (m, 2H), 4.28 (m, 1H), 4.04 (m, 1H), 3.93 (s, 3H), 2.89 (m, 1H), 2.69 (m, 2H), 2.52 (m, 1H), 2.28 (q, 1H), 1.91-0.85 (m, 15H), 1.20 (s, 9H).

[0335] 화합물 217: MS: m/z 922.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 8.17 (m, 3H), 7.74 (d, 2H), 7.26 (m, 1H), 7.17 (s, 1H), 7.02 (m, 2H), 5.77 (s, 1H), 5.69 (q, 1H), 5.20 (d, 1H), 4.96 (dd, 1H), 4.77 (s, 1H), 4.69 (m, 1H), 4.54 (d, 1H), 4.33 (m, 1H), 4.04 (m, 1H), 3.92 (s, 3H), 2.89 (m, 1H), 2.71 (m, 2H), 2.52 (m, 1H), 2.28 (q, 1H), 1.90-1.05 (m, 21H), 0.97-0.83 (m, 2H).

[0336] 화합물 218: MS: m/z 892.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.35 (s, 1H), 8.28 (d, 1H), 8.24 (d, 1H), 7.59 (m, 4H), 7.44 (m, 1H), 7.33 (s, 1H), 7.15 (s, 1H), 5.80 (s, 1H), 5.67 (q, 1H), 5.27 (d, 1H), 4.95 (dd, 1H), 4.70 (m, 2H), 4.58 (d, 1H), 4.30 (m, 1H), 4.06 (m, 1H), 2.88 (m, 1H), 2.70 (m, 2H), 2.54 (m, 1H), 2.28 (q, 1H), 1.92-0.83 (m, 23H).

[0337] 화합물 219: MS: m/z 880.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 8.34 (s, 1H), 8.28 (d, 1H), 8.20 (d, 1H), 7.60 (m, 4H), 7.45 (m, 1H), 7.29 (s, 1H), 7.13 (s, 1H), 5.77 (s, 1H), 5.67 (q, 1H), 5.19 (m, 1H), 4.94 (dd, 1H), 4.67 (m, 2H), 4.26 (m, 1H), 4.05 (m, 1H), 2.88 (m, 1H), 2.71 (m, 2H), 2.53 (m, 1H), 2.29 (q, 1H), 1.90-0.83 (m, 15H), 1.18 (s, 9H).

[0338] 화합물 220: MS: m/z 892.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.39 (d, 1H), 8.06 (d, 2H), 7.88 (s, 1H), 7.71 (d, 1H), 7.45 (m, 3H), 7.36 (s, 1H), 7.18 (s, 1H), 5.68 (s, 1H), 5.65 (q, 1H), 5.33 (d, 1H), 4.93 (dd, 1H), 4.72 (m, 2H), 4.67 (d, 1H), 4.36 (m, 1H), 4.05 (m, 1H), 2.88 (m, 1H), 2.70 (m, 2H), 2.53 (m, 1H), 2.28 (q, 1H), 1.92-0.84 (m, 23H).

[0339] 화합물 221: MS: m/z 880.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.39 (d, 1H), 8.04 (d, 2H), 7.87 (s, 1H), 7.69 (d, 1H), 7.48 (m, 3H), 7.33 (s, 1H), 7.25 (s, 1H), 5.67 (m, 2H), 5.21 (d, 1H), 4.94 (dd, 1H), 4.68 (m, 2H), 4.30 (m, 1H), 4.04 (m, 1H), 2.88 (m, 1H), 2.69 (m, 2H), 2.52 (m, 1H), 2.28 (q, 1H), 1.93-0.84 (m, 15H), 1.17 (s, 9H).

[0340] 화합물 222: MS: m/z 814.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 8.46 (s, 1H), 8.27 (d,1H), 7.47 (m, 3H), 7.41 (m, 1H), 7.33 (s, 1H), 7.16 (d, 1H), 7.05 (s, 1H), 6.56 (d, 1H), 5.69 (m, 2H), 5.24 (d, 1H), 4.95 (dd, 1H), 4.66 (m, 1H), 4.58 (d, 1H), 4.38 (m, 1H), 4.05 (m, 1H), 2.89 (m, 1H), 2.70 (m, 2H), 2.34 (m, 1H), 2.29 (q, 1H), 1.90-1.06 (m, 21H), 0.96-0.83 (m, 2H).

[0341] 화합물 223: MS: m/z 802.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.28 (d,1H), 7.54 (m, 3H), 7.42 (m, 1H), 7.29 (s, 1H), 7.20 (d, 1H), 7.08 (s, 1H), 6.56 (d, 1H), 5.66 (m, 2H), 5.15 (d, 1H), 4.95 (dd, 1H), 4.69 (m, 2H), 4.30 (m, 1H), 4.05 (m, 1H), 2.89 (m, 1H), 2.68 (m, 2H), 2.35 (m, 1H), 2.29 (q, 1H), 1.89-1.04 (m, 13H), 1.19 (s, 9H), 0.97-0.83 (m, 2H).

[0342] 화합물 224: MS: m/z 848.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1H), 8.08 (d,1H), 7.58 (d, 1H), 7.39 (d, 1H), 7.14 (s, 1H), 7.12-6.95 (m, 4H), 5.70 (m, 2H), 5.20 (d, 1H), 4.95 (dd, 1H), 4.66 (m, 1H), 4.59 (d, 1H), 4.33 (m, 1H), 4.03 (m, 1H), 3.91 (s, 3H), 2.90 (m, 1H), 2.66 (m, 2H), 2.52 (m, 1H), 2.28 (q, 1H), 1.89-1.06 (m, 13H), 1.24 (s, 9H), 0.94-0.83 (m, 2H).

[0343] 화합물 225: MS: m/z 760.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 8.25 (d,1H), 7.55 (m, 3H), 7.40 (m, 1H), 7.27 (m, 2H), 7.16 (d, 1H), 6.54 (d, 1H), 5.66 (m, 2H), 5.42 (d, 1H), 4.94 (dd, 1H), 4.67 (m, 1H), 4.46 (d, 1H), 4.35 (m, 1H), 4.04 (m, 1H), 3.50 (s, 3H), 2.89 (m, 1H), 2.66 (m, 2H), 2.33 (m, 1H), 2.26 (q, 1H), 1.92-0.83 (m, 15H).

[0344] 화합물 226: MS: m/z 798.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 1H), 8.25 (d, 1H), 7.55 (m, 3H), 7.41 (m, 1H), 7.27 (m, 3H), 7.16 (d, 1H), 6.56 (d, 1H), 5.66 (m, 2H), 4.94 (dd, 1H), 4.67 (m, 2H), 4.35 (d, 1H), 4.05 (m, 1H), 2.88 (m, 1H), 2.66 (m, 2H), 2.43 (m, 1H), 2.26 (q, 1H), 1.96-0.83 (m, 15H).

[0345] 화합물 227: MS: m/z 744.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 8.21 (d,1H), 7.55 (m, 3H), 7.39 (m, 1H), 7.33-7.25 (m, 2H), 7.12 (d, 1H), 6.56 (d, 1H), 6.16 (d, 1H), 5.66 (q, 1H), 5.62 (s, 1H), 4.94 (dd, 1H), 4.62 (m, 1H), 4.59 (m, 1H), 4.41 (d, 1H), 4.06 (m, 1H), 2.87 (m, 1H), 2.68 (m, 2H), 2.50 (m, 1H), 2.26 (q, 1H), 1.95-0.83 (m, 15H), 1.90 (s, 3H).

[0346] 화합물 228: MS: m/z 857.3 (M^++1).

[0347] 화합물 229: MS: m/z 830.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H), 8.26 (d,1H), 7.59 (m, 2H), 7.43 (m, 2H), 7.25 (m, 2H), 7.19 (m, 1H), 7.06 (m, 1H), 5.76 (s, 1H), 5.72 (q, 1H), 5.18 (m, 1H), 4.97 (dd, 1H), 4.68 (m, 2H), 4.56 (d, 1H), 4.30 (m, 1H), 4.04 (m, 1H), 2.90 (m, 1H), 2.70 (m, 2H), 2.39 (m, 1H), 2.27 (q, 1H), 1.90-0.80 (m, 23H).

[0348] 화합물 230: MS: m/z 860.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 8.10 (d,1H), 7.58 (d, 1H), 7.39 (d, 1H), 7.18 (s, 1H), 7.09-6.97 (m, 4H), 5.72 (s, 1H), 5.68 (q, 1H), 5.24 (d, 1H), 4.95 (dd, 1H), 4.80 (s, 1H), 4.65 (m, 1H), 4.54 (d, 1H), 4.32 (m, 1H), 4.03 (m, 1H), 3.91(s, 3H), 2.94 (m, 1H), 2.68 (m,

2H), 2.54 (m, 1H), 2.28 (q, 1H), 1.90-1.05 (m, 21H), 0.95-0.84 (m, 2H).

[0349] 화합물 231: MS: m/z 848.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 7.64 (d,1H), 7.60 (d, 1H), 7.48 (d, 1H), 7.40 (d, 1H), 7.20 (s, 1H), 7.15 (m, 2H), 6.88 (s, 1H), 5.65 (m, 2H), 5.10 (d, 1H), 4.96 (dd, 1H), 4.63 (m, 2H), 4.31 (m, 1H), 4.04 (m, 1H), 3.94 (s, 3H), 2.86 (m, 1H), 2.68 (m, 2H), 2.56 (m, 1H), 2.29 (q, 1H), 1.94-0.83 (m, 15H), 1.22 (s, 9H).

[0350] 화합물 232: MS: m/z 836.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.29 (s, 1H), 7.89 (dd,1H), 7.60 (d, 1H), 7.50 (dd, 1H), 7.40 (d, 1H), 7.22 (m, 2H), 7.10 (m, 1H), 7.00 (s, 1H), 5.68 (m, 2H), 5.18 (d, 1H), 4.95 (dd, 1H), 4.66 (m, 2H), 4.29 (m, 1H), 4.04 (m, 1H), 2.88 (m, 1H), 2.67 (m, 2H), 2.53 (m, 1H), 2.26 (q, 1H), 1.92-0.83 (m, 15H), 1.20 (s, 9H).

[0351] 화합물 233: MS: m/z 806.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.05 (d,1H), 7.59 (d, 1H), 7.38 (m, 2H), 7.14-6.97 (m, 4H), 5.70 (m, 2H), 5.64 (d, 1H), 4.96 (dd, 1H), 4.65 (m, 1H), 4.58 (m, 2H), 4.04 (m, 1H), 3.90 (s, 3H), 3.58 (s, 3H), 2.89 (m, 1H), 2.68 (m, 2H), 2.53 (m, 1H), 2.25 (q, 1H), 1.88-0.82 (m, 15H).

[0352] 화합물 234: MS: m/z 860.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 7.63 (d,1H), 7.60 (d, 1H), 7.45 (d, 1H), 7.40 (d, 1H), 7.20 (m, 2H), 7.10 (m, 2H), 5.69 (s, 1H), 5.67 (q, 1H), 5.30 (d, 1H), 4.94 (dd, 1H), 4.78 (s, 1H), 4.64 (m, 1H), 4.55 (d, 1H), 4.36 (m, 1H), 4.04 (m, 1H), 3.94 (s, 3H), 2.89 (m, 1H), 2.68 (m, 2H), 2.53 (m, 1H), 2.26 (q, 1H), 1.93-1.04 (m, 21H), 0.97-0.82 (m, 2H).

[0353] 화합물 235: MS: m/z 844.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.24 (s, 1H), 8.04 (d,1H), 7.58 (d, 1H), 7.39 (d, 1H),7.31 (m, 2H), 7.18 (s, 1H), 7.08 (m, 3H), 5.70 (s, 1H), 5.67 (q, 1H), 4.86 (dd, 1H), 4.64 (m, 2H), 4.26 (d, 1H), 4.02 (m, 1H), 3.90 (s, 3H), 2.84 (m, 1H), 2.65 (m, 2H), 2.44 (m, 1H), 2.20 (q, 1H), 1.91-0.83 (m, 15H).

[0354] 화합물 236: MS: m/z 832.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.27 (s, 1H), 8.22 (d,1H), 7.58 (m, 2H), 7.44 (m, 1H), 7.29 (m, 1H), 7.10 (s, 1H), 6.94 (d, 1H), 6.90 (s, 1H), 5.69 (m, 2H), 5.18 (d, 1H), 4.93 (dd, 1H), 4.67 (m, 2H), 4.28 (m, 1H), 4.05 (m, 1H), 2.85 (m, 1H), 2.68 (m, 2H), 2.55 (s, 3H), 2.54 (m, 1H), 2.28 (q, 1H), 1.91-0.83 (m, 15H), 1.19 (s, 9H).

[0355] 화합물 237: MS: m/z 844.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.23 (s, 1H), 8.22 (d,1H), 7.58 (m, 2H), 7.40 (m, 1H), 7.29 (m, 2H), 6.96 (d, 1H), 6.84 (s, 1H), 5.69 (s, 1H), 5.66 (q, 1H), 5.20 (d, 1H), 4.94 (dd, 1H), 4.73 (s, 1H), 4.67 (m, 1H), 4.58 (d, 1H), 4.35 (m, 1H), 4.05 (m, 1H), 2.89 (m, 1H), 2.68 (m, 2H), 2.56 (s, 3H), 2.54 (m, 1H), 2.26 (q, 1H), 1.91-0.83 (m, 23H).

[0356] 화합물 238: MS: m/z 844.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.26 (s, 1H), 8.22 (d,1H), 7.55 (m, 2H), 7.43 (m, 2H), 7.18 (m, 1H), 6.93 (s, 1H), 6.75 (s, 1H), 5.70 (m, 2H), 5.21 (d, 1H), 4.94 (dd, 1H), 4.78 (s, 1H), 4.63 (m, 1H), 4.53 (d, 1H), 4.35 (m, 1H), 4.05 (m, 1H), 2.89 (m, 1H), 2.67 (m, 2H), 2.53 (s, 3H), 2.52 (m, 1H), 2.26 (q, 1H), 1.92-1.04 (m, 21H), 0.95-0.83 (m, 2H).

[0357] 화합물 239: MS: m/z 790.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.34 (s, 1H), 8.20 (d,1H), 7.54 (m, 2H), 7.38 (m, 2H), 7.28 (s, 1H), 7.14 (s, 1H), 6.73 (s, 1H), 5.68 (m, 2H), 5.43 (d, 1H), 4.94 (dd, 1H), 4.65 (m, 1H), 4.39 (m, 2H), 4.04 (m, 1H), 3.58 (s, 3H), 2.89 (m, 1H), 2.68 (m, 2H), 2.51 (s, 3H), 2.50 (m, 1H), 2.28 (q, 1H), 1.93-1.06 (m, 13H), 0.94-0.82 (m, 2H).

[0358] 화합물 240: MS: m/z 828.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.18 (s, 1H), 8.22 (d,1H), 7.56 (m, 2H), 7.40 (m, 2H), 7.20 (s, 2H), 7.08 (s, 1H), 6.76 (d, 1H), 5.71 (s, 1H), 5.66 (q, 1H), 4.94 (dd, 1H), 4.66 (m, 2H), 4.29 (d, 1H), 4.04 (m, 1H), 2.88 (m, 1H), 2.65 (m, 2H), 2.53 (s, 3H), 2.45 (m, 1H), 2.23 (q, 1H),

1.96-1.05 (m, 13H), 0.95-0.83 (m, 2H).

[0359] 화합물 241: MS: m/z 778.1 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 7.89 (dd,1H), 7.58 (d, 2H), 7.44 (dd, 1H), 7.35 (d, 1H), 7.24 (m, 2H), 7.05 (m, 1H), 6.18(d, 1H), 5.71 (q, 1H), 5.62 (s, 1H), 4.95 (dd, 1H), 4.63 (m, 1H), 4.50 (m, 1H), 4.40 (d, 1H), 4.00 (m, 1H), 2.88 (m, 1H), 2.66 (m, 2H), 2.53 (m, 1H), 2.22 (q, 1H), 1.96-0.82 (m, 15H), 1.91 (s, 3H).

[0360] 화합물 242: MS: m/z 846.4 (M^++1).

[0361] 화합물 243: MS: m/z 858.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.28 (s, 1H), 8.24 (d, 1H), 7.57 (m, 2H), 7.42 (m, 2H), 7.19 (s, 1H), 7.08 (s, 1H), 6.79 (d, 1H), 5.66 (m, 2H), 5.24 (d, 1H), 4.96 (m, 1H), 4.78 (s, 1H), 4.67 (m, 1H), 4.55 (d, 1H), 4.35 (m, 1H), 4.03 (m, 1H), 2.85 (m, 3H), 2.67 (m, 2H), 2.53 (m, 1H), 2.28 (q, 1H), 1.94-0.84 (m, 26H).

[0362] 화합물 244: MS: m/z 872.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.13(s, 1H), 8.24(d, 1H), 7.53(m, 2H), 7.41(m, 2H), 7.19(s, 1H), 6.99(s, 1H), 6.79(d, 1H), 5.69(m, 2H), 5.23(d, 1H), 4.98(dd, 1H), 4.77(s, 1H), 4.65(m, 1H), 4.55(d, 1H), 4.35(m, 1H), 4.04(m, 1H), 2.87(q, 2H), 2.68(m, 2H), 2.53(m, 1H), 2.29(q, 1H), 1.94-0.84(m, 26H), 0.83 (s, 3H).

[0363] 화합물 245: MS: m/z 831.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1H), 8.26 (d,1H), 7.90 (d, 2H), 7.58 (m, 2H), 7.46 (d, 2H), 7.00 (s, 1H), 5.69 (m, 2H), 5.09 (d, 1H), 4.99 (dd, 1H), 4.62 (m, 3H), 4.27 (m, 1H), 4.05 (m, 1H), 2.89 (m, 1H), 2.70 (m, 2H), 2.56 (m, 1H), 2.29 (q, 1H), 1.94-0.84 (m, 23H).

[0364] 화합물 246: MS: m/z 761.4 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1H), 8.17 (d,1H), 7.80 (d, 3H), 7.56 (m, 2H), 7.41 (d, 2H), 6.58 (s, 1H), 5.61 (m, 2H), 5.21 (d, 1H), 4.65 (m, 2H), 4.24 (m, 1H), 4.05 (m, 1H), 2.89 (m, 1H), 2.70 (m, 2H), 2.56-2.21 (m, 2H), 1.94-0.84 (m, 15H), 1.87 (s, 3H).

[0365] 화합물 247: MS: m/z 803.4 (M^++1).

[0366] 화합물 248: MS: m/z 845.3 (M^++1).

[0367] 화합물 249: MS: m/z 917.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.22 (s, 1H), 8.08 (d,1H), 7.78 (s, 1H), 7.40 (s, 1H), 7.06 (s, 1H), 6.97 (m, 2H), 5.64 (m, 2H), 5.32 (d, 1H), 4.94 (dd, 1H), 4.70 (m, 2H), 4.54 (d, 1H), 4.34 (dd, 1H), 4.08 (m, 1H), 3.83 (s, 3H), 3.18 (m, 1H), 2.73-2.43 (m, 2H), 2.33 (q, 1H), 2.15-1.20 (m, 30H), 0.83 (s, 3H).

[0368] 화합물 250: MS: m/z 905.4 (M^++1).

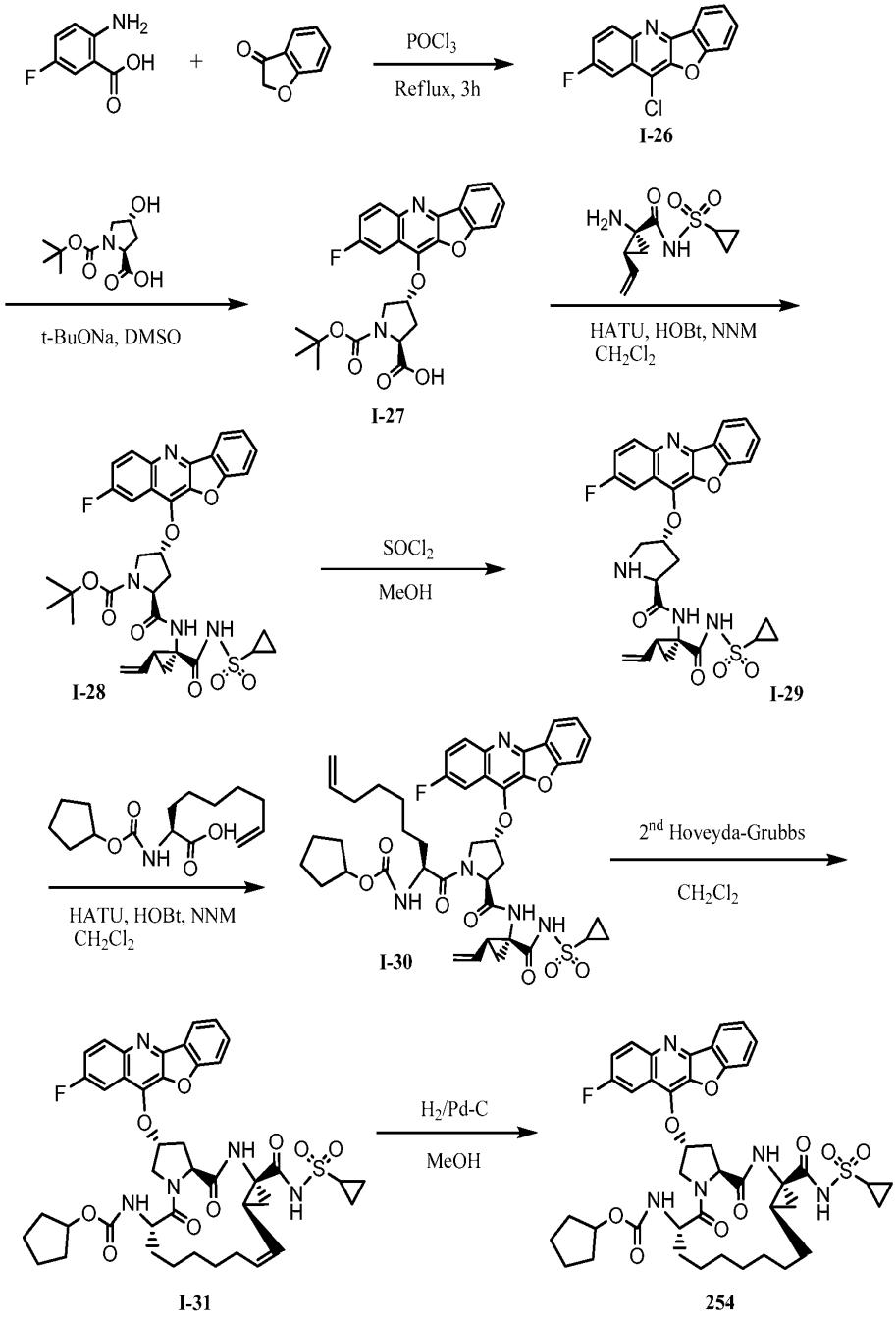
[0369] 화합물 251: MS: m/z 901.3 (M^++1).

[0370] 화합물 252: MS: m/z 917.4 (M^++1).

[0371] 화합물 253: MS: m/z 903.3 (M^++1).

[0372] 실시예 254 : [4-시클로프로판설포닐아미노카보닐-18-(2-플루오로-벤조[4,5]푸로[3,2-b]퀴놀린-11-일옥시)-2,15-디옥소-3,16-디아자-트리시클로[14.3.0.04,6]노나덱-14-일]-카바민산 시클로펜틸 에스터 (화합물 254)의 합성

[0373] 화합물 254는 하기 나타낸 경로를 통해 제조되었다:



[0374]

[0375] DMSO (10 mL) 내 Boc-trans-4-히드록시-L-프롤린 (0.53 g, 2.30 mmol)의 현탁액에 *t*-BuONa (0.49 g, 5.08 mmol)를 0℃에서 가하였다. 실온으로 따뜻하게 하고 1시간 더 교반한 후, 중간체 I-26 (0.62 g, 2.31 mmol)을 10℃에서 천천히 가하였다. 반응 혼합물을 4시간 동안 교반한 다음 10% HCl 수용액으로 pH 6~7로 종결하였다. 미정제 현탁액 고체를 여과하고 물로 세척한 후 진공 하에서 건조하여 화합물 I-27 (0.92 g, 86%)을 얻었다. MS: m/z 467.1 (M^++1).

[0376] CH_2Cl_2 (10 mL) 내 화합물 I-27 (0.90 g, 1.93 mmol), HATU (58.9 g, 1.55 mmol), HOBt (7.0 g, 0.52 mmol) 및 NMM (38.3 g, 3.86 mmol)의 용액에, CH_2Cl_2에 용해된 시클로프로판설폰산 (1-아미노-2-비닐-시클로프로판카보닐)-아미드 (54.0 g, 2.03 mmol) 및 NMM (0.19 g, 1.93 mmol)의 혼합물을 5℃에서 방울방울 가하였다. 실온으로 따뜻하게 하고 16시간 더 교반한 후, 반응 혼합물을 여과하고 농축한 후 실리카겔 컬럼 크로마토그래피로

정제하여 미정제 생성물 I-28 (0.89 g, 80% 수율)을 얻었다. MS: m/z 679.1 (M^++1).

[0377] 화합물 I-28 (1.20 g, 1.77 mmol)을 실온에서 MeOH (18 mL)에 용해시킨 다음 얼음 욕조를 이용하여 용액을 냉각시켰다. 이 반응 혼합물에 티오닐 클로라이드 (0.39 mL, 5.30 mmol)을 방울방울 가하였다. 얼음-욕조 제거 후, 반응 혼합물을 65℃에서 1시간 동안 가열하였다. 결과로 생긴 용액을 40℃로 냉각시키고 여과한 후 차가운 MeOH와 에테르로 세척하여 백색 분말 I-29를 얻었다. 이 화합물은 더 이상 정제 없이 다음 반응 단계에서 사용하였다. MS: m/z 579.1 (M^++1).

[0378] CH_2Cl_2 (10 mL) 내 2-시클로펜틸옥시카보닐아미노-논-8-에노산 (0.87 g, 2.34 mmol), HATU (1.16 g, 3.05 mmol) 및 HOBt (0.14 g, 1.02 mmol)의 용액에, DMF (10 mL)에 용해된 화합물 I-29 (1.18 g, 2.03 mmol)와 NMM (0.49 g, 4.87 mmol)의 혼합물을 5℃에서 방울방울 가하였다. 실온으로 따뜻하게 하고 16시간 더 교반한 후, 10% HCl (1 mL)을 가하고 반응 혼합물을 농축하였다. 잔류물을 5℃로 냉각시키고 5% HCl (aq) (10 mL x 2) 및 $NaHCO_3$(aq) (10 ml x 2)로 순차적으로 세척하여 밝은 노란색 고체를 얻었다. 고체를 MeOH (10 mL)에 용해시키고 소량의 에테르를 천천히 가하여 더 침전시켜 화합물 I-30 (1.51 g, 88% 수율)을 얻었다. MS: m/z 844.3 (M^++1).

[0379] CH_2Cl_2 (120 mL) 내 화합물 I-30 (0.50 g, 0.59 mmol)의 용액을 1시간 동안 질소 버블링에 의해 가스를 제거하였다. Hoveyda-Grubbs 2nd generation catalyst (48mg, 0.076 mmol)을 가한 다음, 반응 혼합물을 40℃에서 16시간 동안 가열하였다. HPLC에 의해 나타낸 반응의 완료 후, 반응 혼합물을 30℃로 냉각시키고 농축한 후 실리카겔 컬럼 크로마토그래피로 정제하여 생성물 I-31 (0.30 g, 62% 수율)을 얻었다. MS: m/z 816.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.33 (s, 1H), 8.30 (d, 1H), 8.11 (dd, 1H), 7.88 (dd, 1H), 7.67-7.56 (m, 2H), 7.46 (dd, 1H), 7.43-7.30 (m, 2H), 6.12 (s, 1H), 5.64 (q, 1H), 5.22 (d, 1H), 4.92 (dd, 1H), 4.77 (d, 1H), 4.66 (dd, 1H), 4.32-4.22 (m, 1H), 4.04 (dd, 1H), 2.93-2.46 (m, 3H), 2.31 (q, 1H), 1.92-0.80 (m, 25H).

[0380] MeOH (10 mL) 내 화합물 I-31 (50 mg, 0.061 mmol)의 용액에 5% Pd-C (5 mg)를 N_2 하에서 실온에서 가하였다. 그 다음, 반응 혼합물을 실온에서 60 psi의 압력 하에 수소 대기에서 4시간 동안 교반하였다. 반응 혼합물을 여과하고 실리카겔 컬럼 크로마토그래피로 정제하여 화합물 254 (27.6 mg, 55%)을 얻었다. MS: m/z 818.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.50 (s, 1H), 8.28 (d, 1H), 8.13 (dd, 1H), 7.80 (dd, 1H), 7.65-7.57 (m, 2H), 7.45 (dd, 1H), 7.39-7.30 (m, 2H), 6.11 (s, 1H), 5.25 (d, 1H), 4.96 (brs, 1H), 4.68 (dd, 1H), 4.60 (d, 1H), 4.37 (dd, 1H), 4.14 (dd, 1H), 3.02-2.57 (m, 3H), 1.92-0.80 (m, 29H).

[0381] 실시예 255~281 : 화합물 255~281의 합성

[0382] 각각의 화합물 255~281을 실시예 254에 기재된 방법과 유사한 방법으로 제조하였다.

[0383] 화합물 255: MS: m/z 764.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.47 (s, 1H), 7.88-7.84 (m, 3H), 7.70 (s, 1H), 7.56 (dd, 1H), 7.37 (m, 1H), 7.18 (m, 1H), 6.20 (d, 1H), 5.97 (s, 1H), 5.64 (q, 1H), 4.94 (dd, 1H), 4.68 (m, 1H), 4.61 (d, 1H), 4.44 (m, 1H), 4.02 (m, 1H), 2.85 (m, 2H), 2.70 (m, 1H), 2.58 (m, 1H), 2.25 (q, 1H), 1.92 (s, 3H), 1.90-1.03 (m, 15H).

[0384] 화합물 256: MS: m/z 815.6 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.31 (s, 1H), 8.32 (d, 1H), 8.25 (m, 1H), 7.81 (dd, 1H), 7.64 (m, 2H), 7.46 (dd, 1H), 7.23-7.12 (m, 2H), 6.20 (s, 1H), 5.66 (q, 1H), 5.16 (d, 1H), 4.98 (dd, 1H), 4.75-4.64 (m, 3H), 4.31 (m, 1H), 4.08 (m, 1H), 2.88 (m, 1H), 2.78 (m, 2H), 2.55 (m, 1H), 2.29 (q, 1H), 1.92-0.84 (m, 23H).

[0385] 화합물 257: MS: m/z 804.1 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.52 (s, 1H), 8.29 (d, 1H), 8.03-7.97 (m, 2H), 7.82 (dd, 1H), 7.63-7.42 (m, 3H), 7.21 (m, 1H), 5.97 (s, 1H), 5.60 (q, 1H), 5.44 (d, 1H), 4.85 (dd, 1H), 4.66 (m, 2H), 4.29 (m, 1H), 4.02 (m, 1H), 3.88-3.62 (m, 2H), 2.87-2.58 (m, 5H), 2.33 (q, 1H), 1.90-0.78 (m, 15H), 0.97 (s, 6H).

[0386] 화합물 258: MS: m/z 806.1 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.28 (d, 1H), 8.07 (m, 1H), 7.84 (s, 1H), 7.62 (m, 3H), 7.44 (m, 2H), 7.18 (m, 1H), 6.06 (s, 1H), 5.67 (q, 1H), 4.96 (dd, 1H), 4.80 (d, 1H), 4.60 (m, 1H), 4.41 (m, 1H), 4.10 (m, 2H), 3.66 (m, 1H), 3.39 (m, 2H), 3.22 (s, 3H), 2.91-2.58 (m, 4H), 2.20 (q, 1H), 1.90-0.86 (m, 15H).

[0387] 화합물 259: MS: m/z 788.1 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.51 (s, 1H), 8.28 (d, 1H), 7.94 (m, 1H), 7.86 (s, 1H), 7.64 (d, 1H), 7.60-7.43 (m, 4H), 7.16 (m, 1H), 6.00 (s, 1H), 5.85 (m, 1H), 5.62 (m, 2H), 5.30-5.19 (m, 2H), 4.93 (dd, 1H), 4.66 (m, 1H), 4.58-4.36 (m, 3H), 4.02 (m, 1H), 2.87-2.56 (m, 4H), 2.26 (q, 1H), 1.86-0.86 (m, 15H).

[0388] 화합물 260: MS: m/z 762.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.63 (s, 1H), 8.26 (d, 1H), 8.10 (s, 1H), 7.88 (d, 1H), 7.67-7.44 (m, 4H), 6.84 (s, 1H), 5.89 (s, 1H), 5.68 (q, 1H), 5.38 (d, 1H), 4.97 (dd, 1H), 4.76 (m, 1H), 4.58 (d, 1H), 4.21 (m, 1H), 3.96 (m, 1H), 3.66 (s, 3H), 2.91-2.60 (m, 4H), 2.25 (q, 1H), 1.89-0.89 (m, 15H).

[0389] 화합물 261: MS: m/z 704.2 (M^++1); ^{1}H NMR (CD_3OD) δ 9.26 (s, 1H), 8.47 (d, 1H), 8.26 (m, 1H), 8.15 (dd, 1H), 7.97-7.82 (m, 3H), 7.66 (m, 1H), 6.54 (s, 1H), 5.74 (q, 1H), 5.13 (dd, 1H), 4.60 (d, 1H), 4.35 (m, 2H), 3.72-3.58 (m, 2H), 2.97-2.81 (m, 3H), 2.51 (m, 1H), 2.33 (q, 1H), 1.99-1.06 (m, 15H).

[0390] 화합물 262: MS: m/z 818.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.42 (s, 1H), 8.30 (d, 1H), 8.12 (m, 1H), 7.86 (m, 1H), 7.49-7.33 (m, 5H), 6.10 (s, 1H), 5.66 (m, 2H), 5.08-4.66 (m, 4H), 4.28 (m, 1H), 4.03 (m, 1H), 3.86-3.58 (m, 4H), 2.86-2.57 (m, 4H), 2.34 (q, 1H), 2.03-0.87 (m, 17H).

[0391] 화합물 263: MS: m/z 780.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.60 (s, 1H), 8.04-7.92 (m, 3H), 7.78 (m, 1H), 7.56 (dd, 1H), 7.38 (m, 1H), 6.94 (m, 1H), 5.89 (s, 1H), 5.67 (q, 1H), 5.40 (d, 1H), 4.95 (dd, 1H), 4.76 (m, 1H), 4.57 (d, 1H), 4.20 (m, 1H), 3.97 (m, 1H), 3.64 (s, 3H), 2.94-2.63 (m, 4H), 2.23 (q, 1H), 1.88-1.09 (m, 15H).

[0392] 화합물 264: MS: m/z 931.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.43 (s, 1H), 8.30 (d, 1H), 8.10 (m, 1H), 7.86 (d, 1H), 7.62-7.34 (m, 5H), 6.08 (s, 1H), 5.60 (q, 1H), 5.38 (s, 1H), 4.90-4.62 (m, 4H), 4.26 (m, 1H), 4.03 (m, 1H), 3.64 (m, 2H), 3.15 (m, 2H), 2.85-2.55 (m, 4H), 2.33 (q, 1H), 1.83-0.86 (m, 19H), 1.44 (s, 9H).

[0393] 화합물 265: MS: m/z 780.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.45 (s, 1H), 8.29 (d, 1H), 8.05 (m, 1H), 7.78 (d, 1H), 7.63-7.25 (m, 4H), 6.04 (m, 2H), 5.63 (q, 1H), 4.91 (dd, 1H), 4.72-4.63 (m, 3H), 4.43-4.32 (m, 2H), 4.02 (m, 1H), 3.78-3.58 (m, 1H), 2.85-2.35 (m, 6H), 2.03-0.86 (m, 15H).

[0394] 화합물 266: MS: m/z 776.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.56 (s, 1H), 8.24 (d, 1H), 8.00 (s, 1H), 7.87-7.79 (m, 2H), 7.61-7.42 (m, 4H), 7.06 (m, 1H), 5.93 (s, 1H), 5.61 (q, 1H), 5.44 (m, 1H), 4.91 (dd, 1H), 4.68 (m, 1H), 4.25-3.96 (m, 4H), 2.86-2.57 (m, 4H), 2.29 (q, 1H), 1.81-0.88 (m, 18H).

[0395] 화합물 267: MS: m/z 812.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.47 (s, 1H), 8.27 (d, 1H), 7.90 (m, 1H), 7.81 (m, 2H), 7.76-7.43 (m, 4H), 7.17 (m, 1H), 6.03-5.85 (m, 2H), 5.61 (q, 1H), 4.88 (dd, 1H), 4.72-4.61 (m, 2H), 4.25-3.98 (m, 4H), 2.86-2.58 (m, 4H), 2.30 (q, 1H), 1.84-0.88 (m, 15H).

[0396] 화합물 268: MS: m/z 832.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.50 (s, 1H), 8.35-8.29 (m, 1H), 8.15-8.01 (m, 1H), 7.84-7.32 (m, 5H), 7.13-7.03 (m, 1H), 6.10 (s, 1H), 5.54 (m, 1H), 5.36 (d, 1H), 5.05-4.83 (m, 2H), 4.74-4.65 (m, 1H), 4.36 (m, 1H), 4.14-4.05 (m, 1H), 2.88-2.51 (m, 4H), 2.12-0.88 (m, 24H).

[0397] 화합물 269: MS: m/z 834.3 (M^++1).

[0398] 화합물 270: MS: m/z 792.2 (M^++1).

[0399] 화합물 271: MS: m/z 822.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.38 (s, 1H), 8.09 (m, 1H), 7.99 (dd, 1H), 7.83 (dd, 1H), 7.58 (dd, 1H), 7.41-7.25 (m, 3H), 6.15 (s, 1H), 5.59 (q, 1H), 5.16 (d, 1H), 4.89 (dd, 1H), 4.78-4.67 (m, 2H), 4.25 (m, 1H), 4.07 (m, 1H), 2.77-2.70 (m, 3H), 2.57 (m, 1H), 2.30 (q, 1H), 1.90-0.82 (m, 15H), 1.23 (s, 9H).

[0400] 화합물 272: MS: m/z 822.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.37 (s, 1H), 8.10 (m, 1H), 7.98 (dd, 1H), 7.83 (dd, 1H), 7.58 (dd, 1H), 7.42-7.27 (m, 2H), 7.19 (s, 1H), 6.16 (s, 1H), 5.62 (q, 1H), 5.11 (d, 1H), 4.92 (dd, 1H), 4.78-4.67 (m, 2H), 4.24 (m, 1H), 4.07 (m, 1H), 2.86-2.77 (m, 3H), 2.56 (m, 1H), 2.32 (q, 1H), 1.90-0.82 (m, 15H), 1.23 (s, 9H).

[0401] 화합물 273: MS: m/z 850.3, 852.3 (M^++1).

[0402] 화합물 274: MS: m/z 834.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.43 (s, 1H), 8.08 (m, 1H), 7.95 (dd, 1H), 7.91 (dd, 1H), 7.56 (dd, 1H), 7.50 (s, 1H), 7.37-7.31 (m, 2H), 6.05 (s, 1H), 5.58 (q, 1H), 5.39 (d, 1H), 4.72-4.67 (m, 4H), 4.27 (m, 1H), 4.03 (m, 1H), 2.89-2.67 (m, 3H), 2.55 (m, 1H), 2.29 (q, 1H), 1.90-0.87 (m, 23H).

[0403] 화합물 275: MS: m/z 780.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.61 (s, 1H), 8.06-7.92 (m, 3H), 7.75 (m, 1H), 7.55 (dd, 1H), 7.39 (m, 1H), 6.90 (m, 1H), 5.89 (s, 1H), 5.66 (q, 1H), 5.44 (d, 1H), 4.94 (dd, 1H), 4.77 (m, 1H), 4.58 (d, 1H), 4.20 (m, 1H), 3.96 (m, 1H), 3.65 (s, 3H), 2.93-2.67 (m, 4H), 2.24 (q, 1H), 1.87-1.09 (m, 15H).

[0404] 화합물 276: MS: m/z 818.1 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.35 (s, 1H), 8.05 (m, 1H), 7.96 (dd, 1H), 7.75 (dd, 1H), 7.57-7.52 (m, 2H), 7.39-7.32 (m, 3H), 6.06 (s, 1H), 5.60 (q, 1H), 4.85-4.73 (m, 2H), 4.55-4.48 (m, 2H), 4.06 (m, 1H), 2.83 (m, 2H), 2.69 (m, 1H), 2.50 (m, 1H), 2.23 (q, 1H), 1.85-1.05 (m, 15H).

[0405] 화합물 277: MS: m/z 856.3 (M^++1).

[0406] 화합물 278: MS: m/z 764.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.49 (s, 1H), 7.94-7.82 (m, 3H), 7.72 (s, 1H), 7.55 (dd, 1H), 7.38 (m, 1H), 7.17 (m, 1H), 6.21 (d, 1H), 5.99 (s, 1H), 5.62 (q, 1H), 4.94 (dd, 1H), 4.68 (m, 1H), 4.61 (d, 1H), 4.45 (m, 1H), 4.02 (m, 1H), 2.85 (m, 2H), 2.71 (m, 1H), 2.56 (m, 1H), 2.27 (q, 1H), 1.92 (s, 3H), 1.90-1.03 (m, 15H).

[0407] 화합물 279: MS: m/z 834.3 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.43 (s, 1H), 8.05 (m, 1H), 7.96 (dd, 1H), 7.91 (dd, 1H), 7.55 (dd, 1H), 7.48 (s, 1H), 7.37-7.32 (m, 2H), 6.05 (s, 1H), 5.57 (q, 1H), 5.39 (d, 1H), 4.79-4.67 (m, 4H), 4.28 (m, 1H), 4.03 (m, 1H), 2.87-2.67 (m, 3H), 2.54 (m, 1H), 2.29 (q, 1H), 1.90-0.87 (m, 23H).

[0408] 화합물 280: MS: m/z 818.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.36 (s, 1H), 8.02 (m, 1H), 7.94 (dd, 1H), 7.71 (dd, 1H), 7.60 (s, 1H), 7.54-7.51 (dd, 1H), 7.42 (d, 1H), 7.36-7.30 (m, 2H), 6.03 (s, 1H), 5.60 (q, 1H), 4.86-4.72 (m, 2H), 4.56-4.48 (m, 2H), 4.05 (m, 1H), 2.84 (m, 2H), 2.68 (m, 1H), 2.48 (m, 1H),

2.23 (q, 1H), 1.88-1.05 (m, 15H).

[0409] 화합물 281은 실시예 1에 기재된 방법과 유사하게 제조되었다:

[0410] 화합물 281: MS: m/z 901.2 (M^++1); ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1H), 8.48 (d, 1H), 7.59 (dd, 1H), 7.39 (d, 1H), 7.32 (dd, 1H), 7.15 (s, 1H), 7.04 (s, 1H), 6.14 (s, 1H), 5.69 (ddd, 1H), 5.04 (m, 2H), 4.72 (m, 1H), 4.56 (m, 2H), 4.24-4.15 (m, 2H), 3.97 (s, 3H), 3.34 (tt, 1H), 2.55 (m, 1H), 2.24-2.26 (m, 1H), 2.01-0.69 (m, 34H).

[0411] 실시예 282: NS3/4A 프로테아제의 저해

[0412] *단백질 발현 및 정제*

[0413] 단백질 과발현을 위해 N-말단 His_6-tagged-$NS4A_{(21-32)}$-GSGS-$NS3_{(3-181)}$을 인코딩하는 유전자를 함유하는 플라스미드를 *E. coli* 균주 BL21(DE3) pLysS (Novagen)로 변형시켰다. 단일 콜로니의 변형된 BL21 (DE3) pLysS를 카나마이신과 클로람페니콜이 있는 200 mL의 Lauria-Bertani (LB) 배지에서 37℃에서 밤새도록 배양하였다. 박테리아 배양물을 항생제를 함유한 6 L LB 배지 (Difco)로 옮기고 22℃에서 흔들면서 배양하였다. 600 nm에서 흡광도가 0.6에 도달한 후, 1 mM 이소프로필-1-티오-β-D-갈락토피라노사이드 (IPTG)로 22℃에서 5시간 동안 배양을 유도하였다. 이후 원심분리(4℃에서 15분 동안 6,000 xg)로 배양물을 수확하였다. 세포 펠렛을 150 mL 완충액 A (50 mM HEPES, pH 7.4, 0.3 M NaCl, 0.1% (w/v) CHAPS, 10 mM 이미다졸, 10% (v/v) 글리세롤)에 재현탁시켰다. 혼합물을 30 psi에서 작동된 초고압 유화기 (Microfluidizer)를 통과한 4개에 의해 분쇄한 후, 세포 부스러기를 원심분리(4℃에서 30분 동안 58,250 xg)로 제거하였다. His_6-태그 단백질을 함유한 세포 용해액은 gradiFrac system (Pharmacia)을 이용하여 10 mM 이미다졸의 존재 하에 25 mL Ni-NTA (Qiagen) 컬럼 위에서 3 mL/min로 충전되었다. 컬럼을 10 컬럼 부피의 용해 완충액(lysis buffer)으로 세척하였다. 결합된 $NS4A_{(21-32)}$-GSGS-$NS3_{(3-181)}$을 300 mM 이미다졸로 보충된 8 컬럼 부피의 완충액 A로 용출시켰다. 합동 분획 (pooled fractions)은 완충액 B (50 mM HEPES, pH 7.4, 0.1% (w/v) CHAPS, 10% (v/v) 글리세롤, 5 mM 디티오트레이톨 (DTT), 및 1M NaCl)로 평형을 유지한 Q-세파로오스 컬럼으로 더 정제하였다. $NS4A_{(21-32)}$-GSGS-$NS3_{(3-181)}$을 함유한 용리액을 모으고, 완충액 C (50 mM HEPES, pH 7.4, 0.1% (w/v) CHAPS, 5 mM DTT, 10% (v/v) 글리세롤)로 미리 평형을 유지한 세파크릴-75 컬럼 (16×100 cm, Pharmacia)을 이용하여 0.5 mL/min의 유속에서 크기-배제 크로마토그래피로 더 정제하였다. 정제된 단백질을 냉동시키고 사용 전에 -80℃에서 저장하였다.

[0414] *HPLC Microbore assay*

[0415] 50 mM Tris, pH 7.4, 100 mM NaCl, 20% 글리세롤, 0.012% CHAPS, 10 mM DTT, 5 μM 기질 Ac-Asp-Glu-Asp(EDANS)-Glu-Glu-Abu-ψ-[COOAla]-Ser-Lys(DABCYL)-NH_2 (RET S1, ANASPEC), 및 10 μM 시험 화합물을 함유하는 용액을 제조하였다. 80 μL의 용액을 96-웰 플레이트의 각 웰에 가하였다. 50 mM Tris 완충액, pH 7.4, 100 mM NaCl, 20% 글리세롤, 및 0.012% CHAPS을 함유한 완충액에서 20 μL의 10 nM NS3/4A 프로테아제를 가하여 반응을 시작하였다. NS3/4A 프로테아제의 최종 농도는 2 nM이고, 이는 Km의 기질 RET S1보다 더 낮았다.

[0416] 어세이 용액은 30℃에서 30분 동안 배양하였다. 그 다음, 100 μL의 1% TFA를 가하여 반응을 종결하였다. 200 μL 분취량을 Agilent 96-웰 플레이트의 각 웰로 옮겼다.

[0417] 하기 기재된 역상 HPLC를 이용하여 반응 생성물을 분석하였다.

[0418] HPLC 시스템은 하기 요소를 포함한다: Agilent 1100, 탈기기(Degasser) G1379A, Binary pump G1312A, Autosampler G1367A, 컬럼 온도조절기 챔버(Column thermostated chamber) G1316A, 다이오드 어레이 검출기 (Diode array detector) G1315B, Column: Agilent, ZORBAX Eclipse XDB-C18, 4.6 mm, 5 μm, P/N 993967-902, 컬럼 온도조절기: 실온, 주입 부피: 100 μL, 용매 A = HPLC 등급 물 + 0.09% TFA, 용매 B = HPLC 등급 아세토니트릴 + 0.09% TFA. 총 HPLC 실행시간 (running time)은 4분 내 25 내지 50% 용매 B, 30초 동안 50% 용매 B, 및 추가 30초 동안 50 내지 25% 용매 B의 선형 기울기와 함께 7.6분 이었다. 컬럼은 다음 시료를 주입하기 전에 2.6분 동안 25% 용매 B와 함께 재-평형을 유지하였다. HPLC 결과를 기준으로 각 시험 화합물의 IC_{50} 값(NS3/4A

활성의 50% 저해가 관찰될 때의 농도)을 계산하였다.

[0419] 화합물 1~281을 상기 저해 어세이에서 시험하였다. 그 결과 274개의 화합물이 20 nM보다 더 낮은 IC_{50} 값을 나타내고, 7개의 화합물이 20~100 nM의 범위의 IC_{50} 값을 나타냄을 보여주었다.

[0420] 또한, 본 발명의 특정 화합물은 효과적인 방법으로 하나 이상의 다른 HCV 약물에 대한 HCV 프로테아제 돌연변이 저항성을 예측하지 못할 정도로 저해함을 발견하였다.

[0421] 실시예 283: HCV 레플리콘(replicon) 세포 어세이 프로토콜

[0422] HCV 레플리콘을 함유한 세포는 10% FBS(fetal bovine serum), 1.0 mg/ml의 G418, 및 적당한 보충물 (배지 A)을 함유한 DMEM에서 유지시켰다.

[0423] 1일째, 레플리콘 세포 모노층을 트립신/EDTA 혼합물로 처리하고 제거한 다음 배지 A를 48,000 cells/ml의 최종 농도로 희석하였다. 24-웰 조직 배양 플레이트의 각 웰에 용액(1 ml)을 가하고, 37℃, 5% CO_2에서 조직 배양 배양기에서 밤새도록 배양하였다.

[0424] 2일째, 시험 화합물 (100% DMSO 내)을 10% FBS 및 적당한 보충물 (배지 B)을 함유한 DMEM에 의해 연속적으로 희석하였다. DMSO의 최종 농도는 희석 내내 0.2%로 유지하였다.

[0425] 레플리콘 세포 모노층 위의 배지를 제거한 다음, 다양한 농도의 화합물을 함유한 배지 B를 가하였다. 어느 화합물이 없는 배지 B를 화합물-없는 대조군으로서 다른 웰에 가하였다.

[0426] 세포를 37℃에서 5% CO_2와 함께 조직 배양 배양기에서 72시간 동안 배지 B 내 화합물 또는 0.2% DMSO와 함께 배양하였다. 그 다음, 배지를 제거하고 레플리콘 세포 모노층을 PBS로 한번 세척하였다. RNeasy 키트로부터 RNA 추출 시약 또는 TRIZOL 시약을 RNA의 분해를 피하기 위해 즉시 세포에 가하였다. 추출 효율 및 일관성을 향상시키기 위해 변형과 함께 제조자에 의해 제공된 지시에 따라 총 RNA를 추출하였다. 마지막으로, HCV 레플리콘 RNA를 포함하는 총 세포 RNA를 용출하고 추가 과정때까지 -80℃에서 저장하였다.

[0427] TaqMan® real-time RT-PCR 정량화 어세이는 2쌍의 특정 프라이머로 설정하였다: 하나는 HCV이고 다른 하나는 ACTB (beta-actin) 이다. 동일한 PCR 웰에서 HCV 및 ACTB RNA의 정량화를 위해 PCR 반응에 총 RNA를 첨가하였다. 실험 실패는 각 웰에서 ACTB RNA의 수준을 기준으로 약해지고 거절되었다. 각 웰에서 HCV RNA의 수준은 동일한 PCR 플레이트에서 실행된 표준 곡선에 따라 계산되었다. 화합물 처리에 의한 HCV RNA 수준의 저해율은 0%의 저해로서 DMSO 또는 화합물-없는 대조군을 이용하여 계산되었다. EC_{50} (HCV RNA 수준의 50% 저해를 이룰 때의 농도)는 어느 정해진 화합물의 적정곡선(titration curve)으로부터 계산되었다.

[0428] 화합물 1~281을 HCV 레플리콘 세포 어세이에서 시험하였다. 그 결과 274개의 화합물이 20 nM보다 더 낮은 EC_{50} 값을 나타내고, 7개의 화합물이 20~100 nM의 범위의 EC_{50} 값을 나타냄을 보여주었다.

[0429] 실시예 284: 약물동태학 연구(Pharmacokinetic study)

[0430] 수컷 스프라구-돌리 랫트 (300~400 g)를 펜토바비탈로 마취시키고 혈액 샘플을 위해 경정맥에 폴리에틸렌 캐눌라와 함께 이식 수술을 하였다. 이들을 임의로 물과 함께 밤새도록 금식시킨 다음, 경구 위관 영양법(oral gavage(PO))으로 시험 화합물과 함께 다음날 복용시켰다. 복용 후 48시간이 될 때까지 연속 혈액 샘플을 모으고 헤파린 처리된 플라즈마를 원심분리하여 회수하였다. 혈액 플라즈마에서 시험 화합물을 추출하고 LC-MS/MS(liquid chromatography-mass spectrometry analysis)로 측정하였다.

[0431] 표준 약물동태학 매개변수는 WinNonlin (Version 4.0, Pharsight, CA, USA)을 이용하여 비의존형 분석(non-compartmental analysis)으로 평가하였다. 혈액 플라즈마에서 시험 화합물 농도 대 시간의 최대 곡선은 C_{max}로 표시된다. 명백한 말기-단계 제거(terminal-phase elimination) ($t_{1/2}$)는 $\ln(2)/\lambda_z$로 계산되었으며, 여기서 λ_z는 제거율 상수이다. 복용시부터 무한까지의 평균 혈중 농도-시간 곡선 하 면적 ($AUC_{(0-inf)}$)은 선형 사다리꼴 규칙에 따라 계산하였다.

[0432] 본 발명의 특정 화합물은 연장된 반감기 및 커다란 AUC 값을 나타내었다.

[0433] **기타 실시예**

[0434] 본 명세서에 개시된 모든 특징은 어느 조합으로 결합될 수 있다. 본 명세서에 개시된 각 특징은 동일, 균등, 또는 유사 목적의 역할로 대안 특징으로 대체될 수 있다. 따라서, 별도의 명백한 언급이 없으면, 개시된 각 특징은 단지 포괄적인 시리즈의 균등 또는 유사 특징의 예이다.

[0435] 상기 설명으로부터, 당업자는 본 발명의 필수 특성을 용이하게 확인할 수 있으며, 이의 정신 및 범위로부터 벗어나지 않고 다양한 사용 및 조건에 순응하기 위해 발명의 다양한 변화 및 변형을 할 수 있다. 따라서, 기타 실시예도 하기 청구항의 범위 내에 있다.