



(19) 대한민국특허청(KR)
(12) 등록특허공보(B1)

(45) 공고일자 2011년12월01일
(11) 등록번호 10-1088922
(24) 등록일자 2011년11월25일

(51) Int. Cl.

C07D 487/04 (2006.01)

- (21) 출원번호 10-2005-7003655
- (22) 출원일자(국제출원일자) 2003년09월03일
심사청구일자 2008년09월02일
- (85) 번역문제출일자 2005년03월03일
- (65) 공개번호 10-2005-0057120
- (43) 공개일자 2005년06월16일
- (86) 국제출원번호 PCT/US2003/027555
- (87) 국제공개번호 WO 2004/022561
국제공개일자 2004년03월18일

(30) 우선권주장

- 60/408,027 2002년09월04일 미국(US)
- 60/421,959 2002년10월29일 미국(US)

(56) 선행기술조사문헌

- EP0628559 A
- US20006107305 A1
- US20026413974 A1
- WO2002050079 A1

전체 청구항 수 : 총 40 항

심사관 : 박종일

(54) 사이클린 의존성 키나제 억제제로서의 피라졸로피리미딘

(57) 요약

본 발명은, 이의 많은 양태에서, 사이클린 의존성 키나제의 억제제로서의 피라졸로[1,5- α]피리미딘 화합물의 신규한 부류, 상기 화합물을 제조하는 방법, 상기 화합물 하나 이상을 함유하는 약제학적 조성물, 상기 화합물 하나 이상을 포함하는 약제학적 제형을 제조하는 방법, 및 상기 화합물 또는 약제학적 조성물을 사용하여 CDK와 관련된 하나 이상의 질환을 치료, 예방, 억제 또는 경감시키는 방법을 제공한다.

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미국 뉴저지 08876 슌머빌 파인 릿지 드라이브 3

호브스 더글라스 월쉬

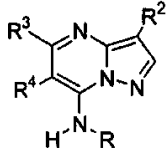
미국 펜실베니아 19067 야들리 유니버시티 드라이브 1330

특허청구의 범위

청구항 1

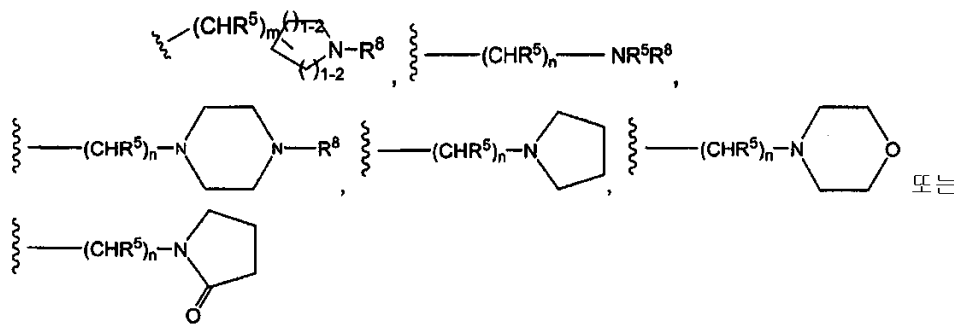
하기 화학식 3의 화합물, 또는 이의 약제학적으로 허용되는 염 또는 용매화물:

화학식 3



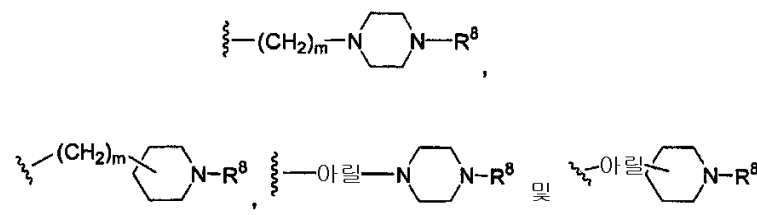
상기식에서,

R은 H, 알킬, 알케닐, 알키닐, 아릴알킬, 아릴알케닐, 사이클로알킬, 사이클로알킬알킬, 알케닐알킬, 알키닐알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴알킬(상기 헤테로아릴의 N-옥사이드를 포함함), $-(CHR^5)_n-$ 아릴, $-(CHR^5)_n-$ 헤테로아릴,



이고, 여기서, 각각의 상기 알킬, 알케닐, 알키닐, 아릴, 사이클로알킬, 헤테로사이클릴 및 헤테로아릴은 치환되지 않거나, 또는 동일하거나 상이할 수 있고, 각각 할로젠, 알킬, 아릴, 사이클로알킬, 헤테로사이클릴알킬, CF_3 , OCF_3 , CN , $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_pR^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 및 $-N(R^5)C(O)NR^5R^{10}$ 로 이루어진 그룹 중에서 독립적으로 선택된 하나 이상의 잔기로 임의 치환될 수 있으며;

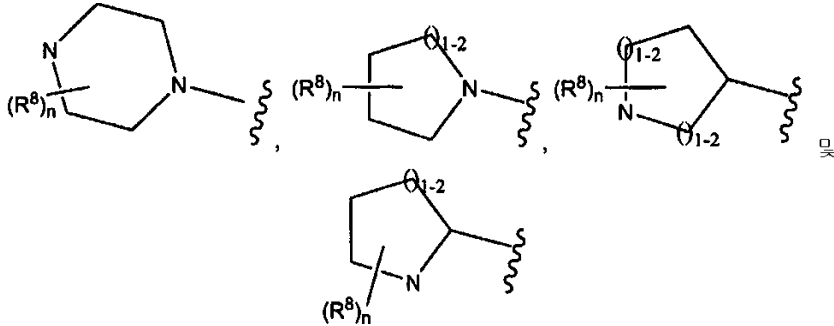
R^2 는 R^9 , 알킬, 알케닐, 알키닐, CF_3 , 헤테로사이클릴, 헤테로사이클릴알킬, 할로젠, 할로알킬, 아릴, 아릴알킬, 헤테로아릴알킬, 알키닐알킬, 사이클로알킬, 헤테로아릴, 동일하거나 상이할 수 있고 하기한 R^9 의 목록으로부터 독립적으로 선택되는 1 내지 6개의 R^9 그룹으로 치환된 알킬; 동일하거나 상이할 수 있고 페닐, 피리딜, 티오펜, 푸라닐 및 티아졸로 그룹 중에서 독립적으로 선택된 1 내지 3개의 아릴 또는 헤테로아릴 그룹으로 치환된 아릴; 아릴 또는 헤테로아릴 그룹과 융합된 아릴; 동일하거나 상이할 수 있고 페닐, 피리딜, 티오펜, 푸라닐 및 티아졸로 그룹 중에서 독립적으로 선택된 1 내지 3개의 아릴 또는 헤테로아릴 그룹으로 치환된 헤테로아릴; 아릴 또는 헤테로아릴 그룹과 융합된 헤테로아릴;



으로 이루어진 그룹 중에서 선택되고, 여기서, R^2 에 대해 위에서 나타난 정의중에서 하나 이상의 아릴 및/또는 하나 이상의 헤테로아릴은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 임의 치환될 수 있고, 각각의 잔기는 할로젠, $-CN$,

$-OR^5$, $-SR^5$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)NR^5R^6$, CF_3 , 알킬, 아릴 및 OCF_3 로 이루어진 그룹 중에서 독립적으로 선택되며;

R^3 은 H, 할로젠, $-NR^5R^6$, $-OR^6$, $-SR^6$, $-C(O)N(R^5R^6)$, 알킬, 알키닐, 사이클로알킬, 아릴, 아릴알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴, 헤테로아릴알킬,



로 이루어진 그룹으로부터 선택되고, 여기서 R^3 에 대한 상기한 알킬, 사이클로알킬, 아릴, 아릴알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬의 각각 및 R^3 에 대해 바로 위에서 나타낸 구조의 헤테로사이클릴 잔기는 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 독립적으로 임의의 치환될 수 있고, 여기서 각각의 잔기는 할로젠, 알킬, 아릴, 사이클로알킬, CF_3 , CN , $-OCF_3$, $-(CR^4R^5)_pOR^5$, $-OR^5$, $-NR^5R^6$, $-(CR^4R^5)_pNR^5R^6$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 및 $-N(R^5)C(O)NR^5R^6$ 로 이루어진 그룹으로부터 독립적으로 선택되고; 단, 헤테로사이클릴 환위의 질소 원자에 인접한 탄소는 $-OR^6$ 잔기를 지니지 않으며;

R^4 는 H, 할로 또는 알킬이고;

R^5 는 H, 알킬, 아릴 또는 사이클로알킬이고;

R^6 은 H, 알킬, 알케닐, 아릴, 아릴알킬, 아릴알케닐, 사이클로알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬로 이루어진 그룹으로부터 선택되고, 여기서 상기 알킬, 아릴, 아릴알킬, 사이클로알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬의 각각은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 임의의 치환될 수 있으며, 여기서 각각의 잔기는 할로젠, 알킬, 아릴, 사이클로알킬, 헤테로사이클릴알킬, CF_3 , OCF_3 , CN , $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_pR^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 및 $-N(R^5)C(O)NR^5R^{10}$ 으로 이루어진 그룹으로부터 독립적으로 선택되고;

R^{10} 은 H, 알킬, 아릴, 아릴알킬, 사이클로알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬로 이루어진 그룹으로부터 선택되고, 여기서 상기 알킬, 아릴, 아릴알킬, 사이클로알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬의 각각은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 임의의 치환될 수 있으며, 여기서 각각의 잔기는 할로젠, 알킬, 아릴, 사이클로알킬, 헤테로사이클릴알킬, CF_3 , OCF_3 , CN , $-OR^5$, $-NR^4R^5$, $-C(R^4R^5)_pR^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 및 $-N(R^5)C(O)NR^4R^5$ 로 이루어진 그룹으로부터 독립적으로 선택되거나;

임의로 (i) 잔기 $-NR^5R^{10}$ 에서 R^5 및 R^{10} 또는 (ii) 잔기 $-NR^5R^6$ 에서 R^5 및 R^6 은, 함께 사이클로알킬 또는 헤테로사이클릴 잔기를 형성할 수 있고, 상기 사이클로알킬 또는 헤테로사이클릴 잔기는 각각 치환되지 않거나, 하나

이상의 R⁹ 그룹에 의해 독립적으로 임의 치환되며;

R⁷은 알킬, 사이클로알킬, 아릴, 아릴알케닐, 헤테로아릴, 아릴알킬, 헤테로아릴알킬, 헤테로아릴알케닐 및 헤테로사이클릴로 이루어진 그룹으로부터 선택되고, 여기서 상기 알킬, 사이클로알킬, 헤테로아릴알킬, 아릴, 헤테로아릴 및 아릴알킬의 각각은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기에 의해 독립적으로 임의 치환될 수 있고, 각각의 잔기는 할로젠, 알킬, 아릴, 사이클로알킬, CF₃, OCF₃, CN, -OR⁵, -NR⁵R¹⁰, -CH₂OR⁵, -C(O₂)R⁵, -C(O)NR⁵R¹⁰, -C(O)R⁵, -SR¹⁰, -S(O₂)R¹⁰, -S(O₂)NR⁵R¹⁰, -N(R⁵)S(O₂)R¹⁰, -N(R⁵)C(O)R¹⁰ 및 -N(R⁵)C(O)NR⁵R¹⁰으로 이루어진 그룹으로부터 독립적으로 선택되고;

R⁸은 R⁶, -OR⁶, -C(O)NR⁵R¹⁰, S(O₂)NR⁵R¹⁰, -C(O)R⁷, -C(=N-CN)-NH₂, -C(=NH)-NHR⁵, 헤테로사이클릴 및 -S(O₂)R⁷로 이루어진 그룹으로부터 선택되고;

R⁹는 할로젠, -CN, -NR⁵R¹⁰, -C(O₂)R⁶, -C(O)NR⁵R¹⁰, -OR⁶, -SR⁶, -S(O₂)R⁷, -S(O₂)NR⁵R¹⁰, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ 및 -N(R⁵)C(O)NR⁵R¹⁰으로 이루어진 그룹으로부터 선택되고;

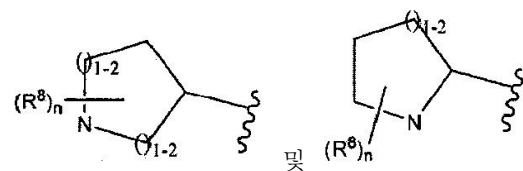
m은 0 내지 4이며;

n은 1 내지 4이고;

p는 1 내지 4이며;

단, R²가 페닐인 경우, R³은 H, -NR⁵R⁶, -OR⁶, -SR⁶, -C(O)N(R⁵R⁶), 사이클로알킬, 아릴, 아릴알킬, 헤테로사이클

릴, 헤테로사이클릴알킬, 헤테로아릴, 헤테로아릴알킬,

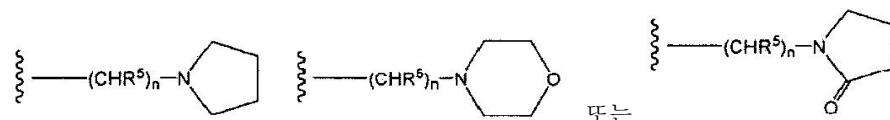


로 이루어진 그룹으로부터 선택되고, 여기서 R³에 대한 상기한 사

이클로알킬, 아릴, 아릴알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬의 각각 및 R³에 대해 바로 위에서 나타난 구조의 헤테로사이클릴 잔기는 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 독립적으로 임의 치환될 수 있고, 여기서 각각의 잔기는 할로젠, 알킬, 아릴, 사이클로알킬, CF₃, CN, -OCF₃, -(CR⁴R⁵)_pOR⁵, -OR⁵, -NR⁵R⁶, -(CR⁴R⁵)_pNR⁵R⁶, -C(O₂)R⁵, -C(O)R⁵, -C(O)NR⁵R⁶, -SR⁶, -S(O₂)R⁶, -S(O₂)NR⁵R⁶, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ 및 -N(R⁵)C(O)NR⁵R⁶로 이루어진 그룹으로부터 독립적으로 선택되고, 단, 헤테로사이클릴 환 위의 질소 원자에 인접한 탄소는 -OR⁵ 잔기를 지니지 않으며;

R²가 아릴인 경우, R은 H, 알킬, 알케닐, 알키닐, 아릴알킬, 아릴알케닐, 사이클로알킬, 사이클로알킬알킬, 알케닐알킬, 알키닐알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴알킬(상기 헤테로아릴의 N-옥사이드를

포함함), -(CHR⁵)_n-아릴, -(CHR⁵)_n-헤테로아릴,



또는

이고, 여기서, 상기 알킬, 알케

닐, 알키닐, 아릴, 사이클로알킬, 헤테로사이클릴 및 헤테로아릴 각각은 치환되지 않거나, 또는 동일하거나 상

이할 수 있는 하나 이상의 잔기로 임의 치환될 수 있으며, 여기서, 각각의 잔기는 할로젠, 알킬, 아릴, 사이클로알킬, 헤테로사이클릴알킬, CF_3 , OCF_3 , CN , $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 및 $-N(R^5)C(O)NR^5R^{10}$ 으로 이루어진 그룹 중에서 독립적으로 선택되고; 추가로, R이 아릴알킬이고 상기 아릴이 헤테로아릴로 치환되는 경우, 상기 헤테로아릴은 3개 이상의 헤테로원자를 함유하며;

단, 상기 치환체들의 정의 중에서, 알킬은 (C_1-C_6) 알킬이고, 알케닐은 (C_2-C_3) 알케닐이고, 알키닐은 (C_2-C_4) 알키닐이고, 아릴알킬은 (C_6-C_{10}) 아릴 (C_1-C_6) 알킬이고, 아릴알케닐은 (C_6-C_{10}) 아릴 (C_2-C_3) 알케닐이고, 사이클로알킬은 (C_5-C_7) 사이클로알킬이고, 사이클로알킬알킬은 (C_5-C_7) 사이클로알킬 (C_1-C_6) 알킬이고, 알케닐알킬은 (C_2-C_3) 알케닐 (C_1-C_6) 알킬이고, 알키닐알킬은 (C_2-C_4) 알키닐 (C_1-C_6) 알킬이고, 헤테로사이클릴은 5개 내지 10개의 환 원자를 포함하는 헤테로사이클릴이고, 헤테로사이클릴알킬은 5개 내지 10개의 환 원자를 포함하는 헤테로사이클릴 (C_1-C_6) 알킬이고, 헤테로아릴알킬은 5개 내지 10개의 환 원자를 포함하는 헤테로아릴 (C_1-C_6) 알킬이고, 헤테로아릴은 5개 내지 10개의 환 원자를 포함하는 헤테로아릴이고, 할로알킬은 할로 (C_1-C_6) 알킬이며, 헤테로아릴알케닐은 5개 내지 10개의 환 원자를 포함하는 헤테로아릴 (C_2-C_3) 알케닐이다.

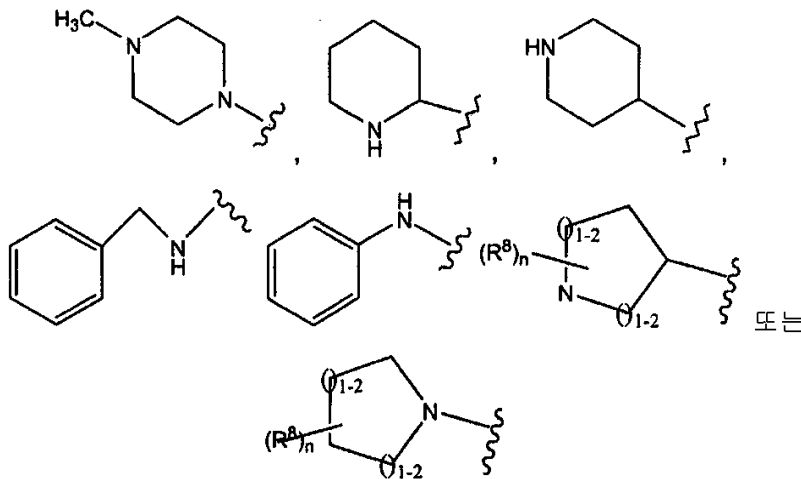
청구항 2

제1항에 있어서,

R이 $-(CHR^5)_n$ -아릴, $-(CHR^5)_n$ -헤테로아릴, 알킬, 사이클로알킬, 헤테로사이클릴 또는 헤테로아릴알킬(상기 헤테로아릴의 N-옥사이드를 포함함)이고, 여기서, 상기 알킬, 아릴, 사이클로알킬, 헤테로사이클릴 및 헤테로아릴의 각각은 치환되지 않거나, 제1항에서 기술한 바와 같은 하나 이상의 잔기에 의해 임의 치환되고;

R^2 가 할로젠, 알킬, 헤테로알킬, CN, 사이클로알킬, 헤테로사이클릴 또는 알키닐이며;

R^3 이 H, C_1-C_6 알킬, 아릴, 헤테로아릴, 사이클로알킬, $-NR^5R^6$,



이며, 여기서 R^3 에 대해 바로 위에서 나타낸 알킬, 아릴, 헤테로아릴, 사이클로알킬 및 헤테로사이클릴 각각은 동일하거나 상이할 수 있는 하나 이상의 잔기에 의해 임의 치환되며, 각각의 잔기는 할로젠, CF_3 , OCF_3 , C_1-C_6 알킬, CN 및 $-C(O)R^5$, $-S(O_2)R^5$, $-C(=NH)-NH_2$, $-C(=CN)-NH_2$, 하이드록시알킬, 알콕시카보닐, $-SR^5$ 및 OR^5 로 이루어진 그룹으로부터 독립적으로 선택되며, 단, 헤테로사이클릴 환상의 질소 원자에 인접한 탄소는 $-OR^5$ 잔기를 지니지 않고;

R^4 가 H 또는 C_1-C_6 알킬이며;

R⁵가 H, C₁-C₆ 알킬 또는 사이클로알킬이며;

n이 1 또는 2이고;

p가 1 또는 2인 화합물.

청구항 3

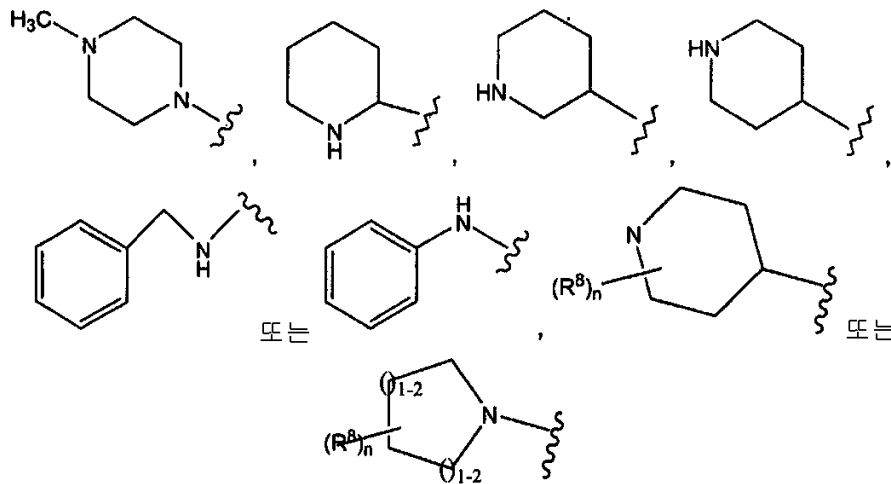
제2항에 있어서, R이 하이드록시알킬, -(CHR⁵)_n-아릴 또는 -(CHR⁵)_n-헤테로아릴이고 여기서, 상기 아릴 및 헤테로아릴의 각각은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 그룹으로 치환되며, 여기서 각각의 그룹은 헤테로아릴, 아민, 헤테로사이클릴, -C(O)N(R⁵R⁶), -S(O₂)R⁵, -S(O₂)N(R⁵R⁶), 알콕시 및 할로로 이루어진 그룹 중에서 독립적으로 선택되는 화합물.

청구항 4

제2항에 있어서, R²가 Br, Cl, CF₃, CN, C₁-C₆ 알킬, 사이클로프로필, 알킬닐, -OR⁶로 치환된 알킬 또는 테트라하이드로푸라닐인 화합물.

청구항 5

제2항에 있어서, R³가 H, C₁-C₆ 알킬, 아릴, 헤테로아릴, 사이클로알킬,



이고, 여기서, R³에 대해 바로 위에서 나타낸 알킬, 아릴, 헤테로아릴, 사이클로알킬 및 헤테로사이클릴의 각각은 동일하거나 상이할 수 있는 하나 이상의 잔기로 임의 치환되며, 여기서, 각각의 잔기는 할로젠, CF₃, OCF₃, C₁-C₆ 알킬, CN 및 OR⁵로 이루어진 그룹 중에서 독립적으로 선택되며, 단, 헤테로사이클릴 환상의 질소 원자에 인접한 탄소는 -OR⁵ 잔기를 지니지 않는다.

청구항 6

제2항에 있어서, R⁴가 H 또는 C₁-C₆ 알킬인 화합물.

청구항 7

제2항에 있어서, R⁵가 H인 화합물.

청구항 8

제2항에 있어서, n이 1인 화합물.

청구항 9

제1항에 있어서, p가 1인 화합물.

청구항 10

제2항에 있어서, R이 벤질 또는 하이드록시알킬인 화합물.

청구항 11

제2항에 있어서, R이 피리드-3-일메틸이고, 여기서, 피리딜은 치환되지 않거나, 제1항에서 정의한 바와 같은 하나 이상의 잔기로 독립적으로 임의 치환될 수 있는 화합물.

청구항 12

제2항에 있어서, R이 피리드-4-일메틸이고, 여기서, 상기 피리딜은 치환되지 않거나, 제1항에서 정의한 바와 같은 하나 이상의 잔기로 독립적으로 임의 치환될 수 있는 화합물.

청구항 13

제2항에 있어서, R이 피리드-2-일메틸, 피리드-3-일메틸, 또는 피리드-4-일메틸의 N-옥사이드이고, 여기서, 상기 피리딜 각각은 치환되지 않거나, 제1항에서 정의한 바와 같은 하나 이상의 잔기로 독립적으로 임의 치환될 수 있는 화합물.

청구항 14

제4항에 있어서, R²가 Br인 화합물.

청구항 15

제4항에 있어서, R²가 Cl인 화합물.

청구항 16

제4항에 있어서, R²가 에틸인 화합물.

청구항 17

제4항에 있어서, R²가 사이클로프로필인 화합물.

청구항 18

제4항에 있어서, R²가 에틸인 화합물.

청구항 19

제2항에 있어서, R³이 C₁-C₆ 알킬, 사이클로알킬, 헤테로사이클릴, 아릴 또는 -N(R⁵R⁶)인 화합물.

청구항 20

제19항에 있어서, R³이 이소프로필인 화합물.

청구항 21

제19항에 있어서, R³이 사이클로헥실 또는 노르보르닐이고, 여기서, 상기 사이클로헥실 또는 노르보르닐의 각각은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 치환될 수 있고, 여기서, 각각의 잔기는 알킬 및 하이드록시알킬로 이루어진 그룹 중에서 독립적으로 선택되는 화합물.

청구항 22

제19항에 있어서, R³이 치환되지 않은 페닐인 화합물.

청구항 23

제19항에 있어서, R³이 동일하거나 상이할 수 있고, 각각 F, Br, Cl 및 CF₃로 이루어진 그룹 중에서 독립적으로 선택된 하나 이상의 잔기로 치환된 페닐인 화합물.

청구항 24

제19항에 있어서, 상기 -N(R⁵R⁶)의 R⁵가 H 또는 하이드록시알킬이고, 상기 -N(R⁵R⁶)의 R⁶이 알킬, 하이드록시알킬, 사이클로알킬 및 메틸렌디옥시로 이루어진 그룹 중에서 선택되며, 여기서, 상기 알킬 및 사이클로알킬의 각각은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 치환될 수 있고, 여기서, 각각의 잔기는 아민, 에톡시카보닐, 아마이드, 하이드록시알킬 및 하이드록시로 이루어진 그룹 중에서 독립적으로 선택되는 화합물.

청구항 25

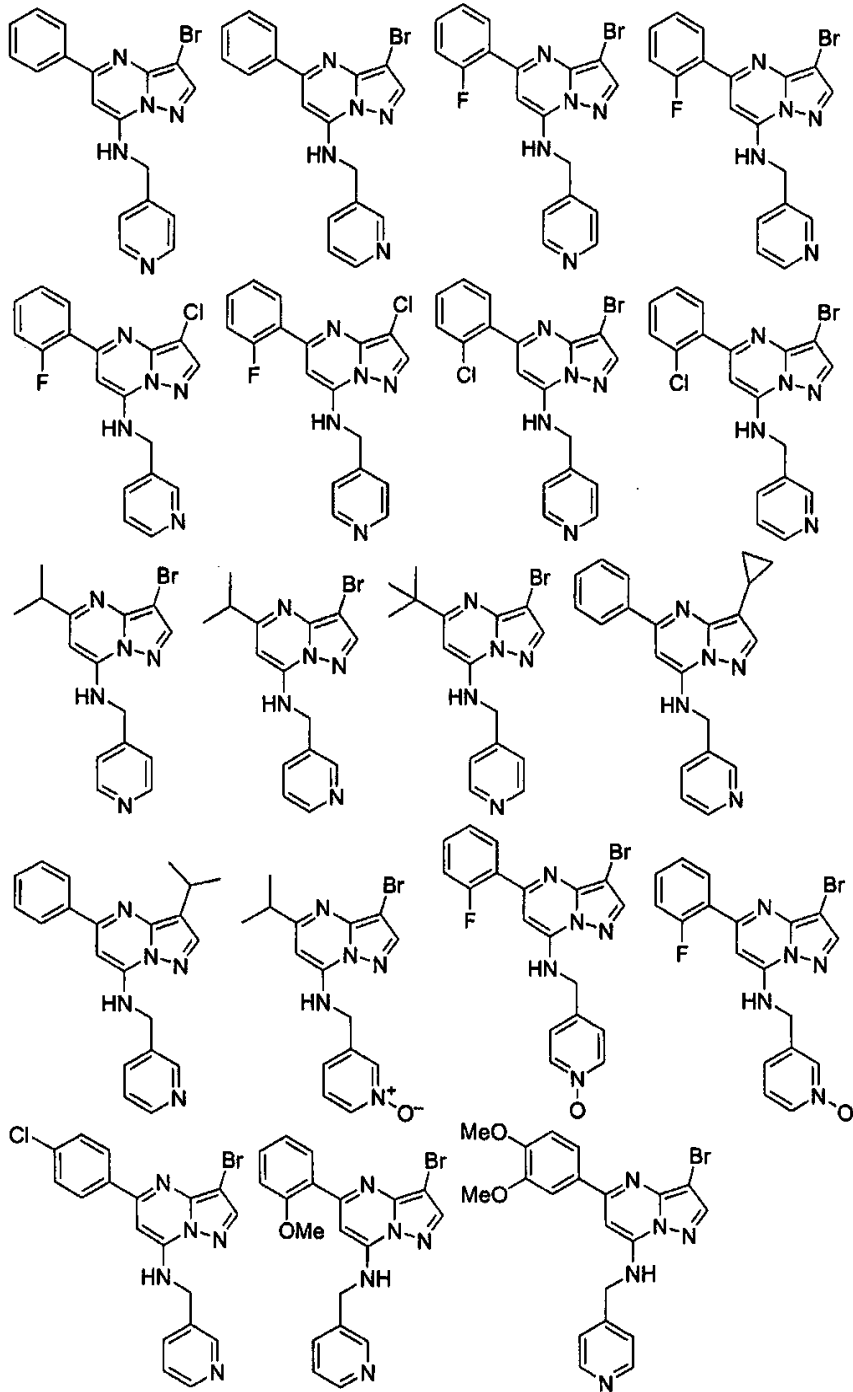
제19항에 있어서, 상기 -N(R⁵R⁶)의 R⁵ 및 R⁶가 함께 결합하여 헤테로사이클릴 잔기를 형성하고, 여기서, 상기 헤테로사이클릴 잔기는 치환되지 않거나 또는 동일하거나 상이할 수 있는 하나 이상의 그룹으로 독립적으로 임의 치환될 수 있으며, 여기서, 각각의 그룹은 하이드록시알킬, 아마이드, -C(O)R⁵, >C(CH₃)₂, -S(O₂)R⁵, -S(O₂)N(R⁵R⁶), -C(=NH)N(R⁵R⁶) 및 -C(=N-CN)N(R⁵R⁶)로 이루어진 그룹 중에서 선택되는 화합물.

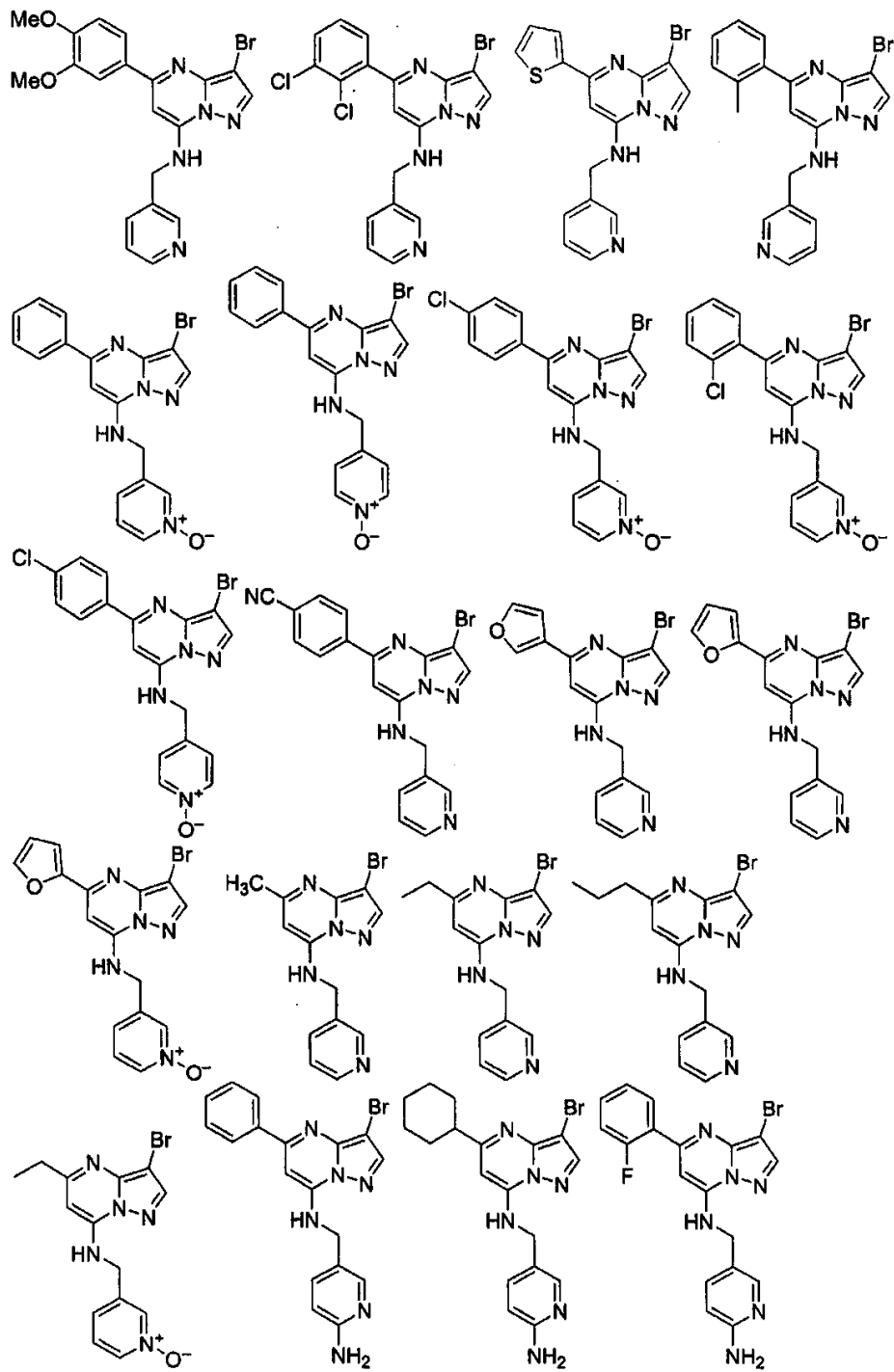
청구항 26

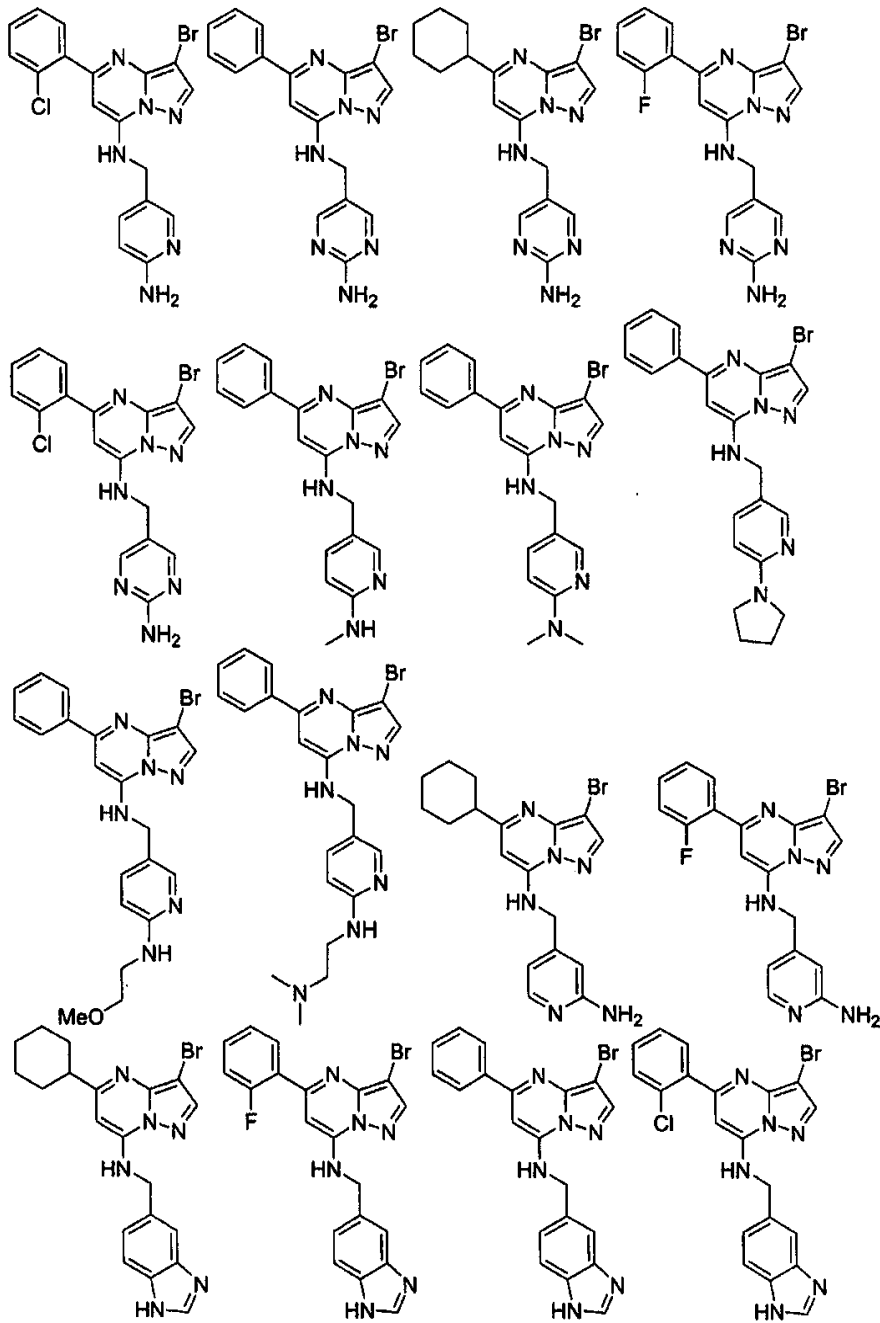
제25항에 있어서, R⁵ 및 R⁶에 의해 형성된 상기 헤테로사이클릴 잔기가 피롤리딘 또는 피페리딘 환인 화합물.

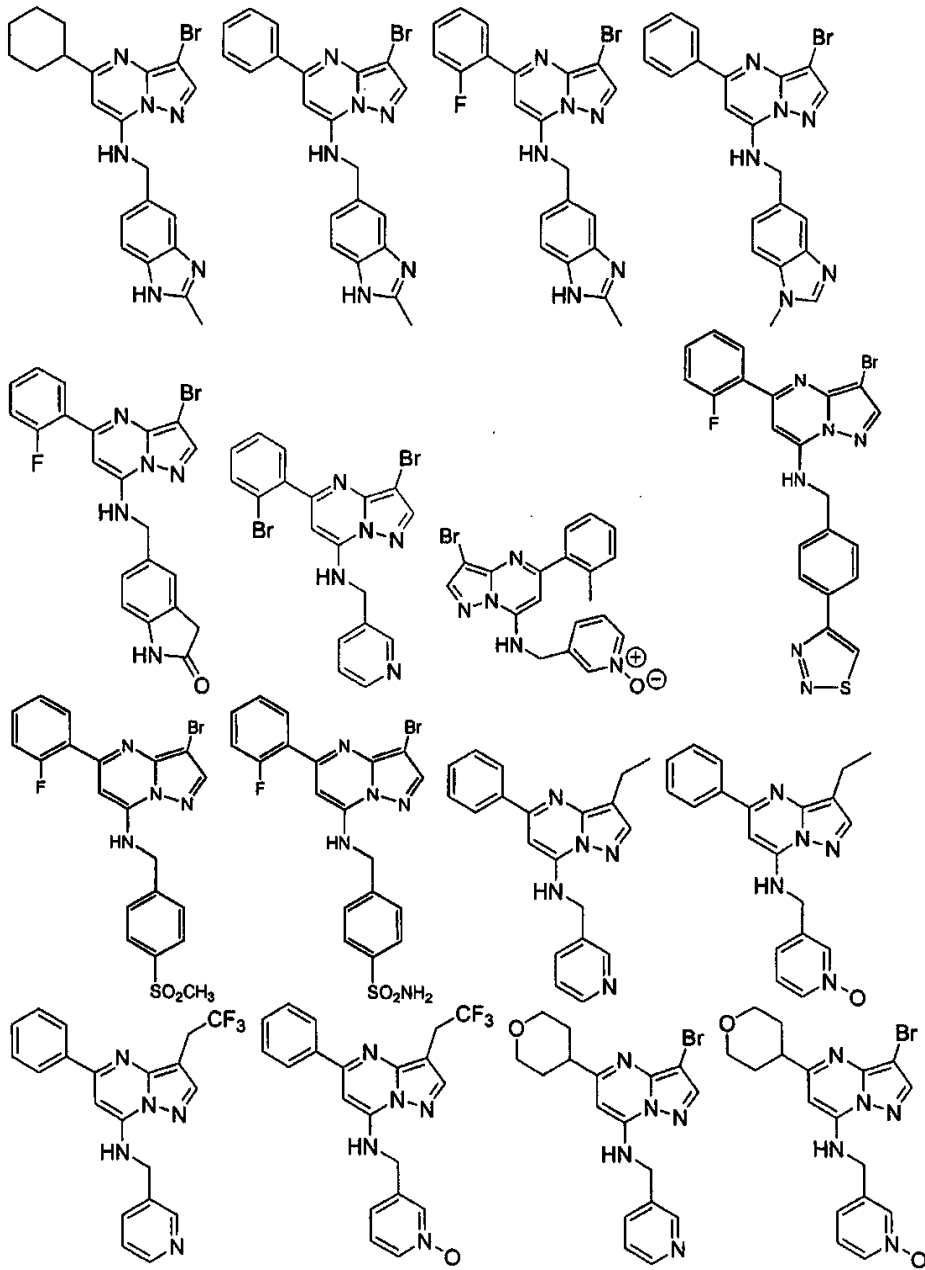
청구항 27

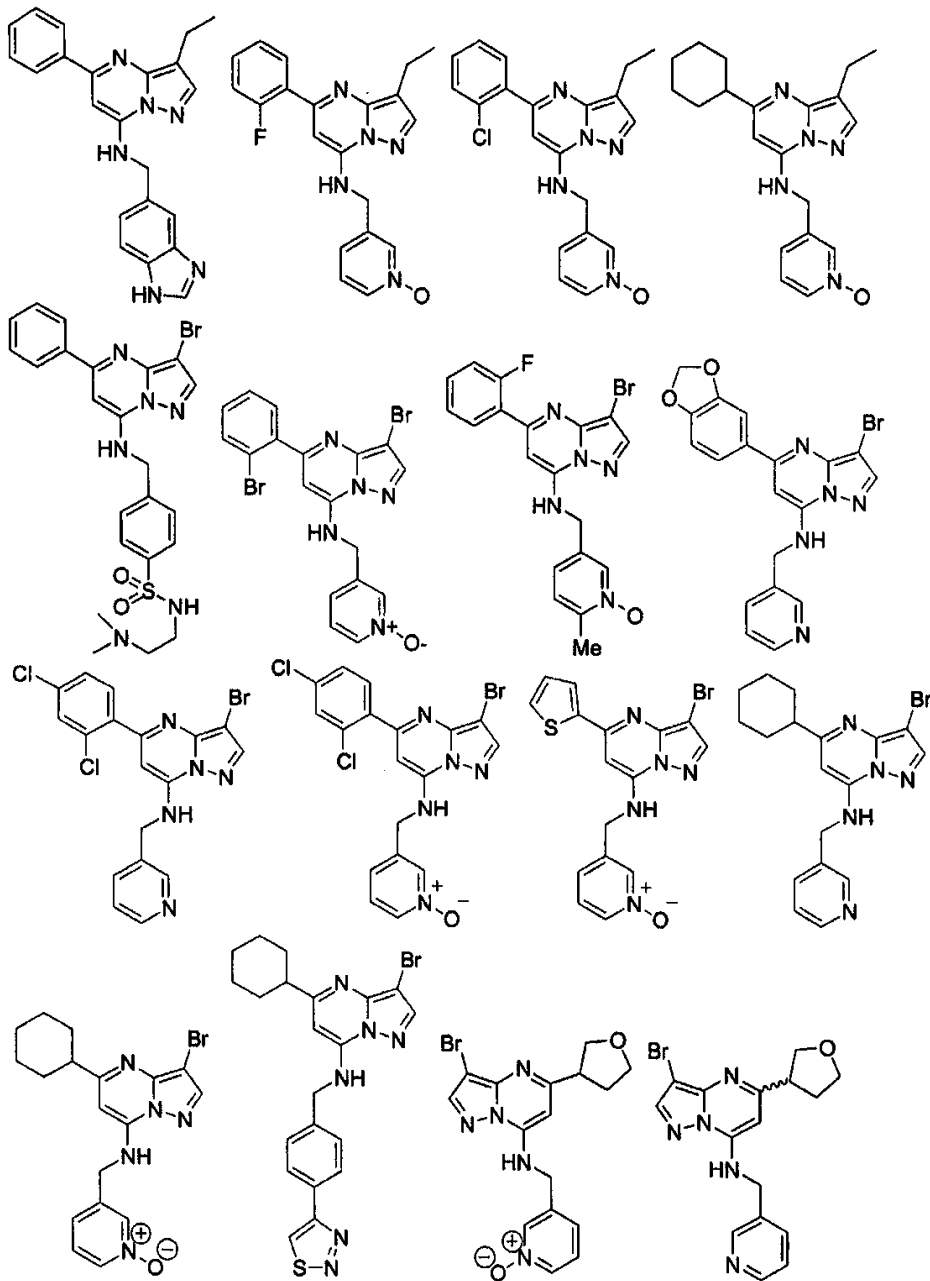
하기 화학식의 화합물, 또는 이의 약제학적으로 허용되는 염 또는 용매화물:

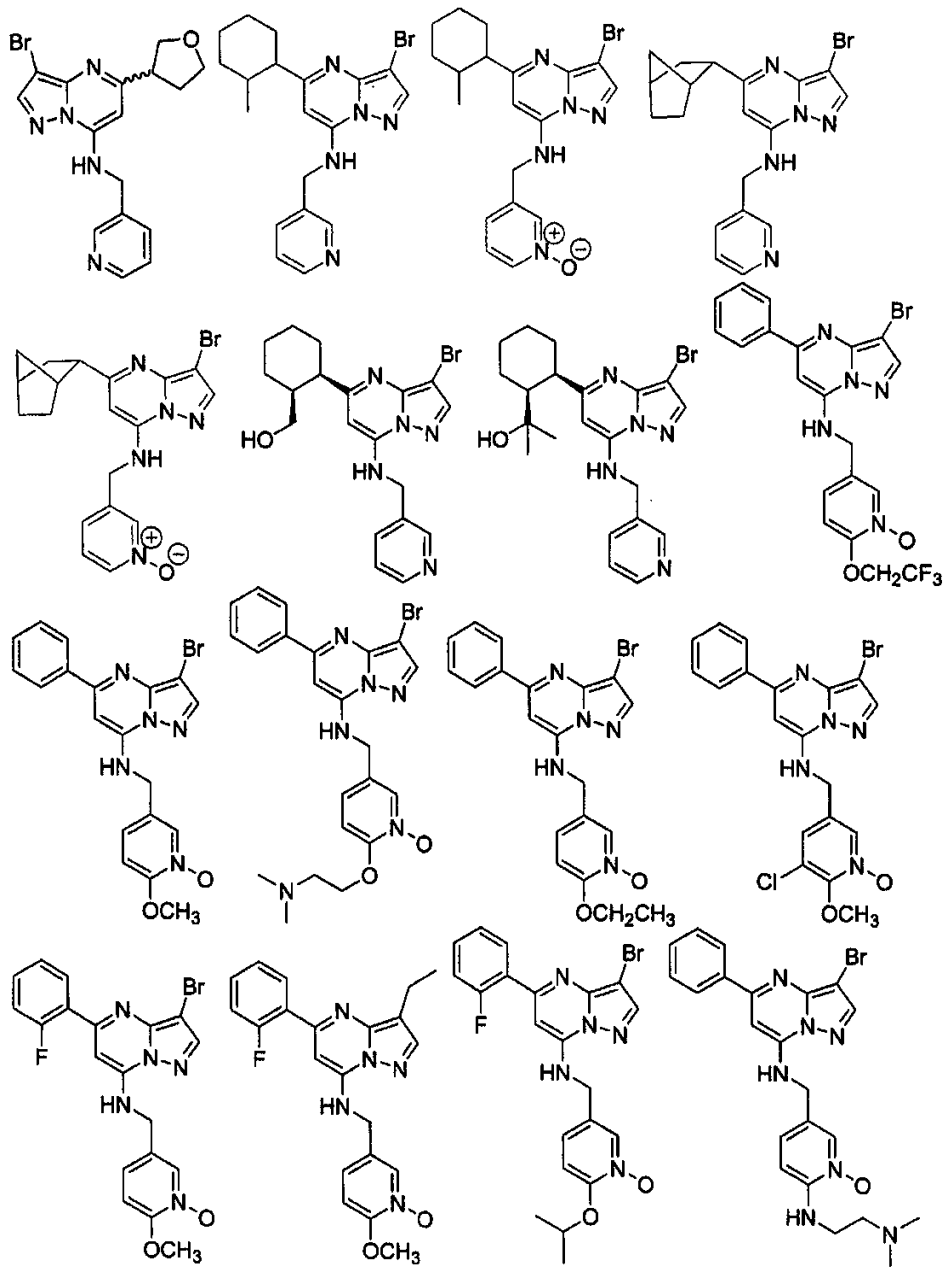


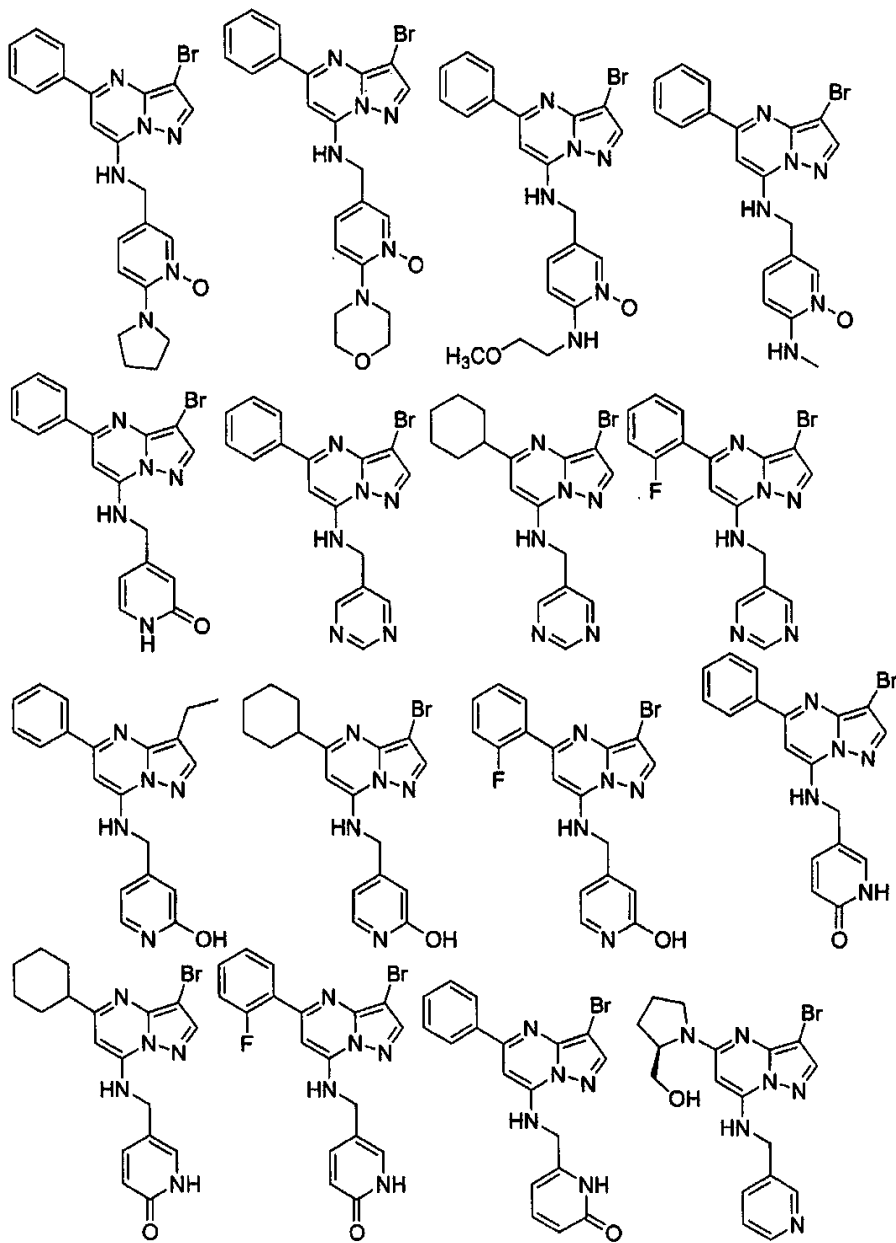


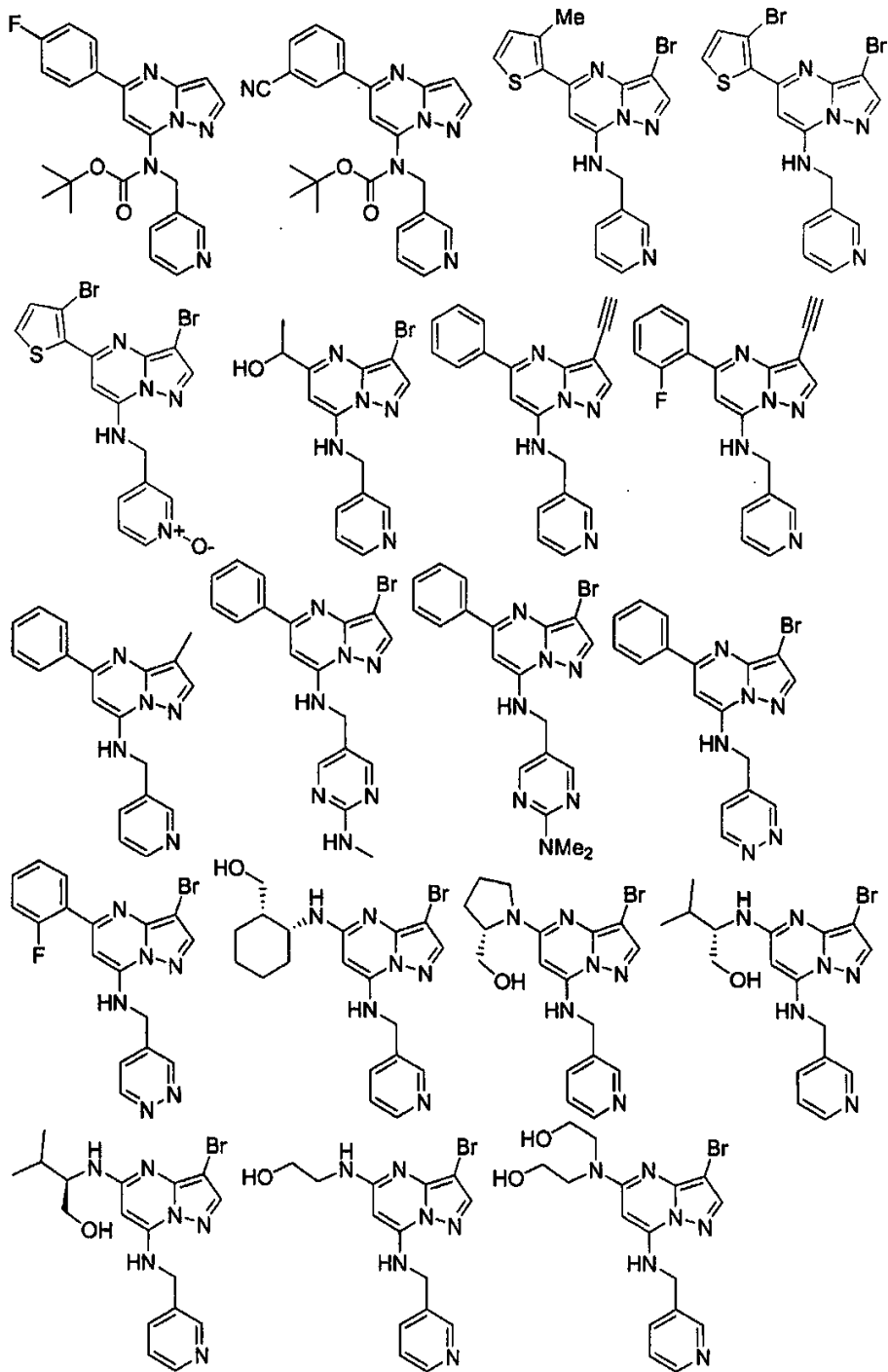


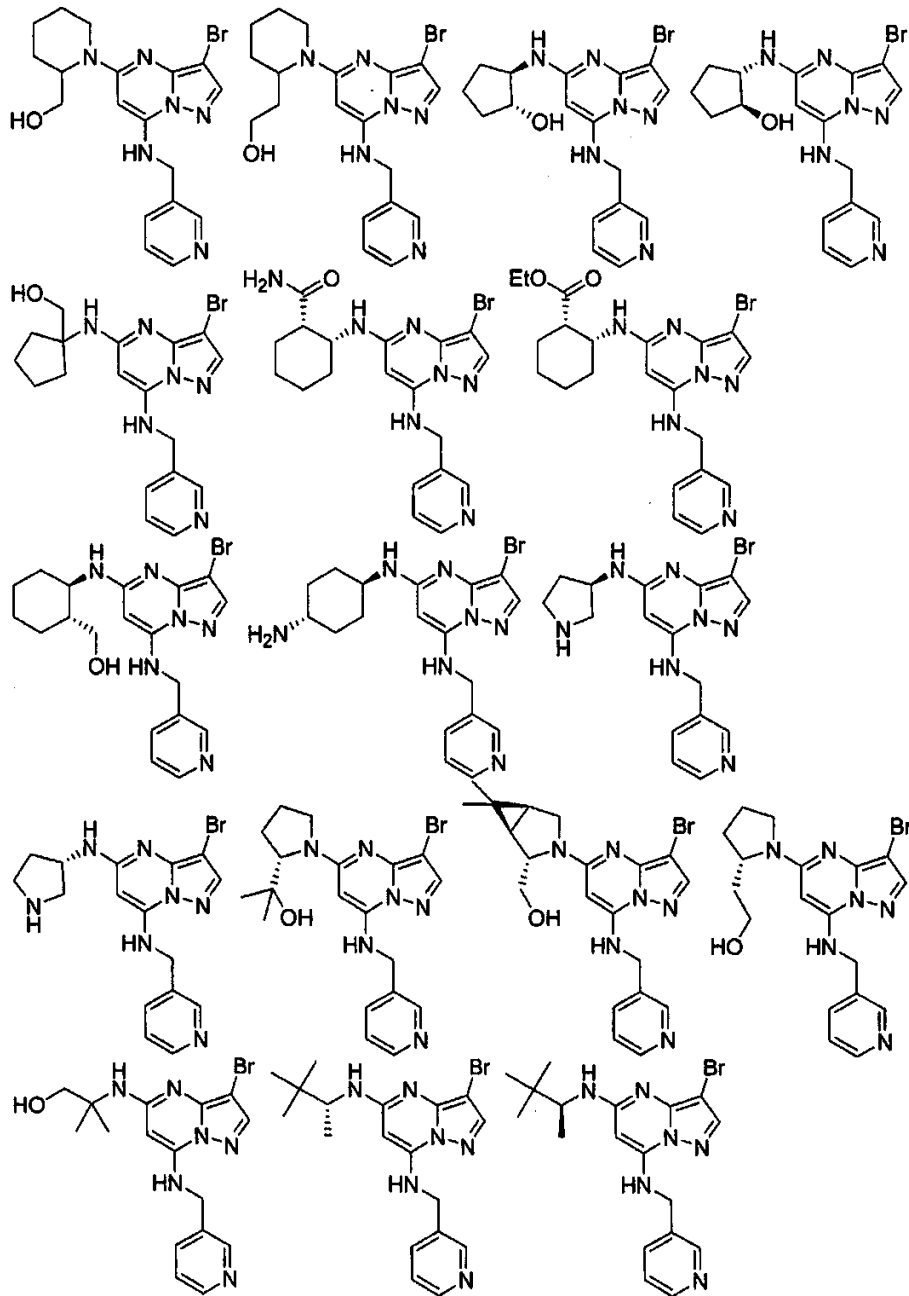


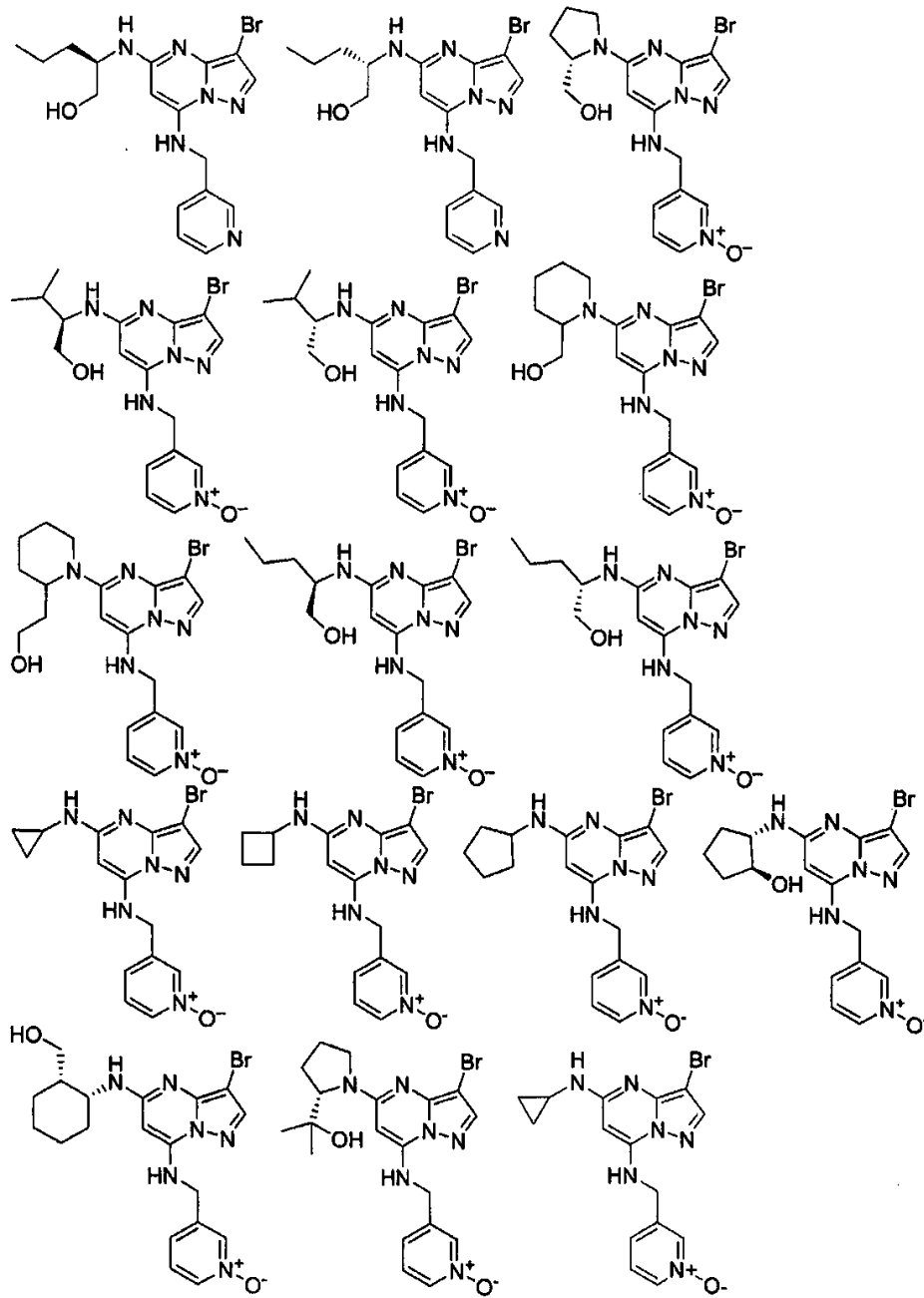


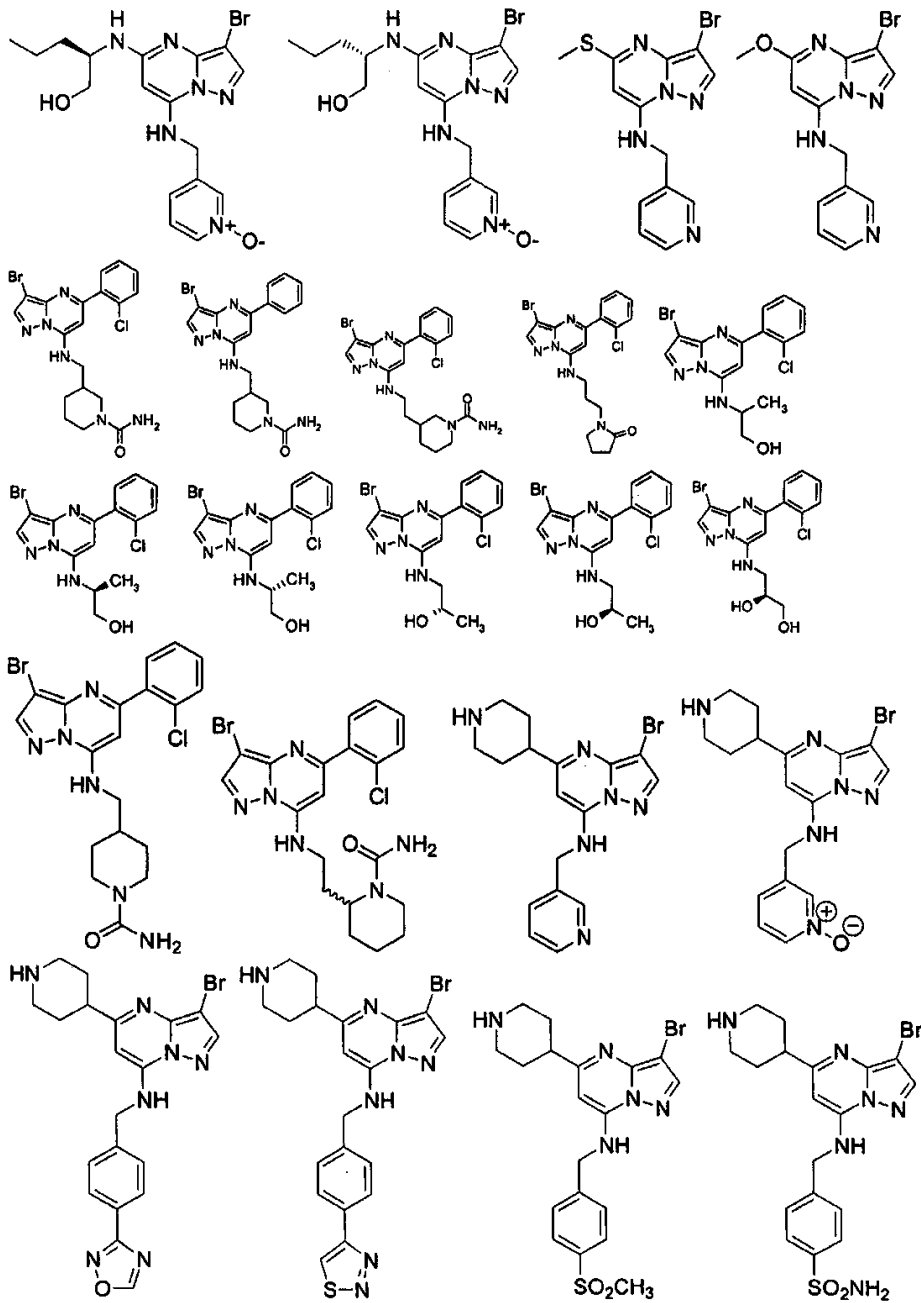


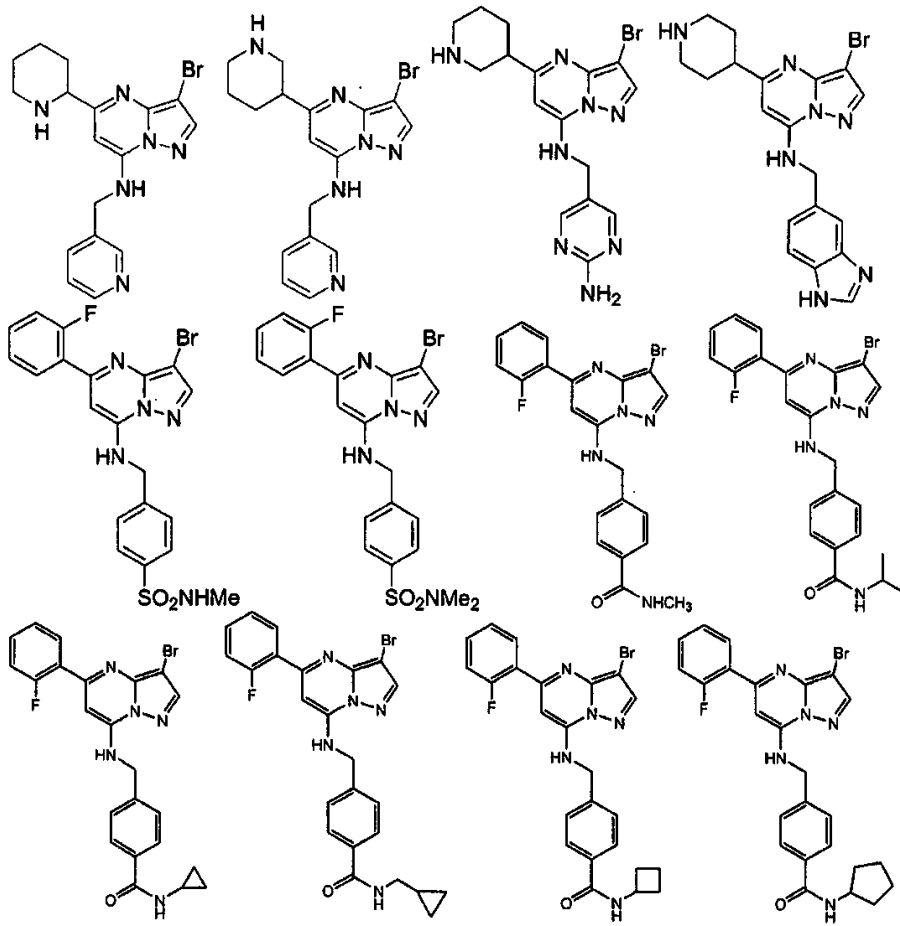


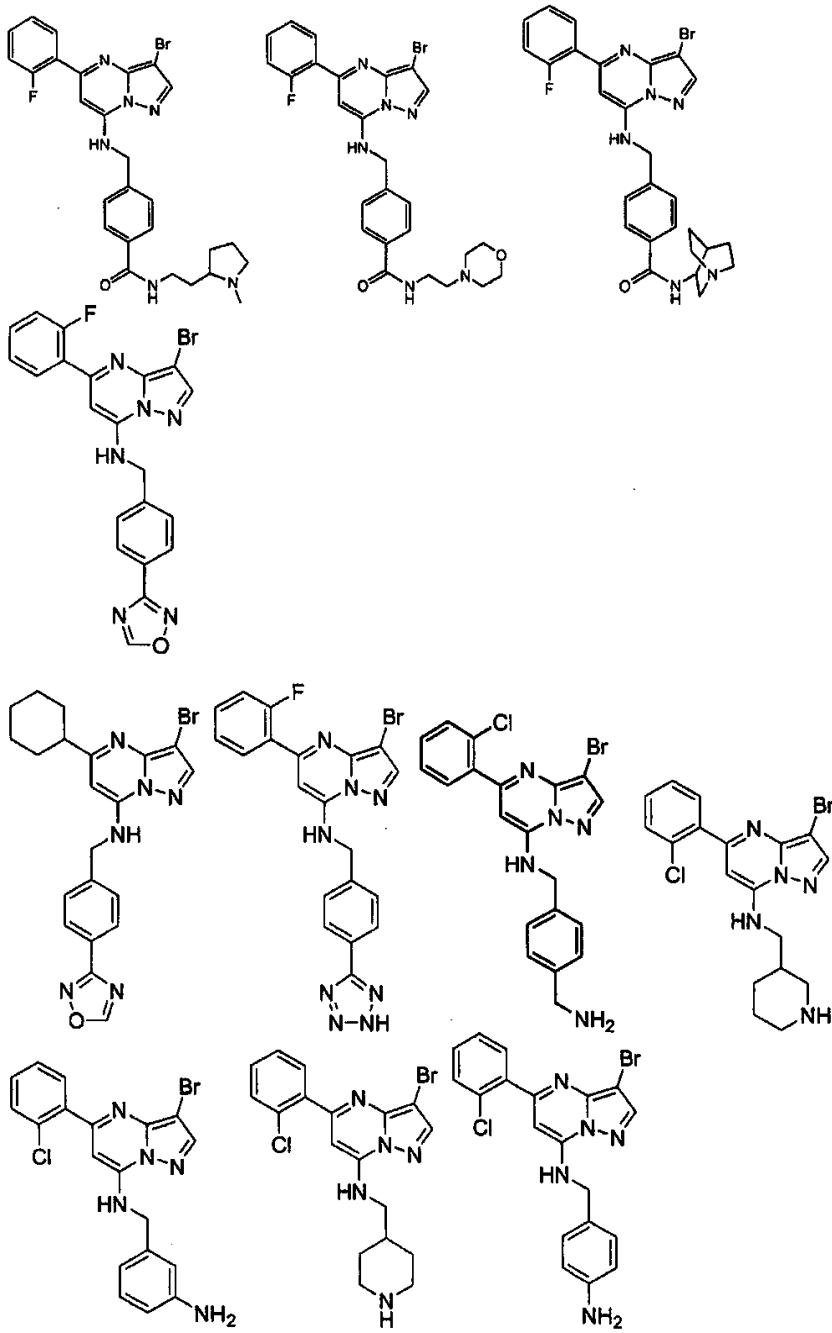


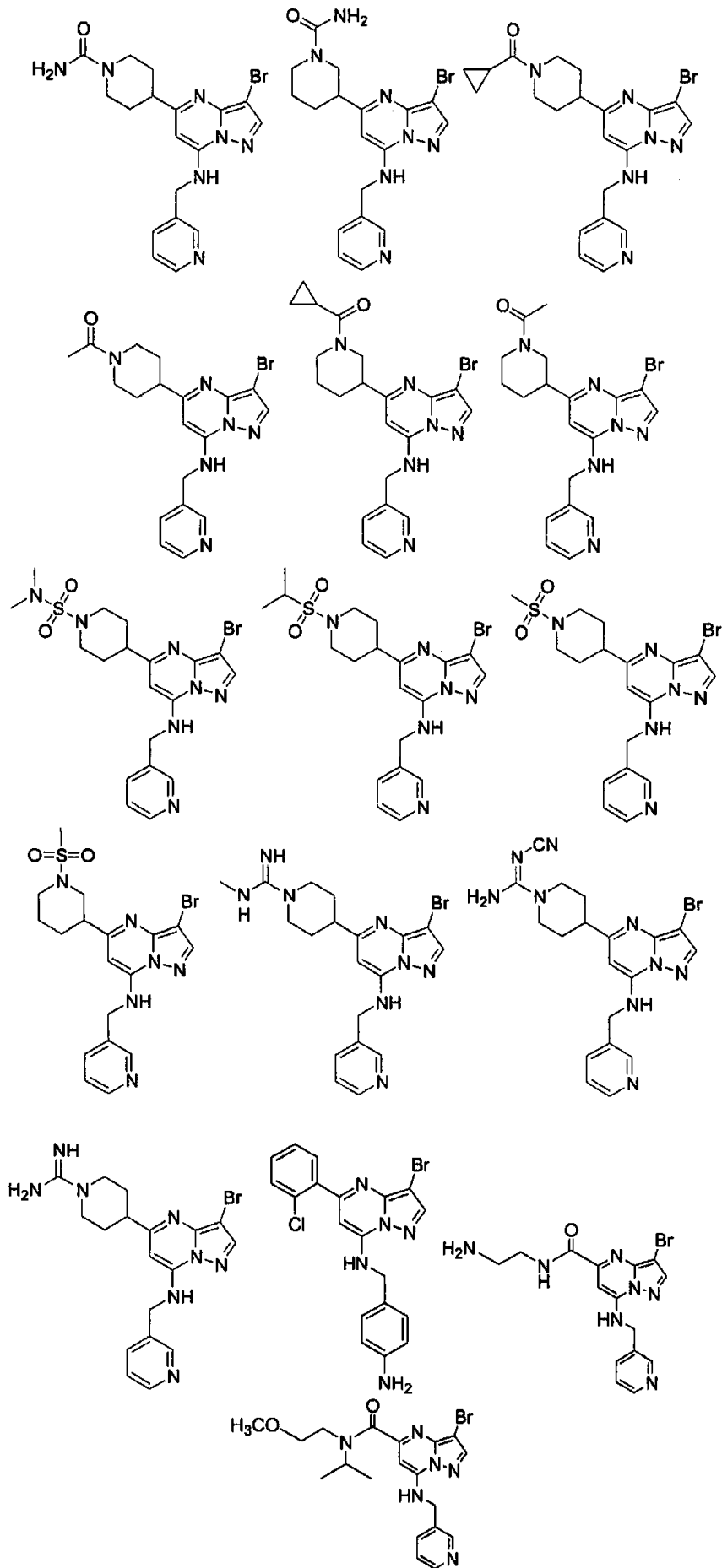






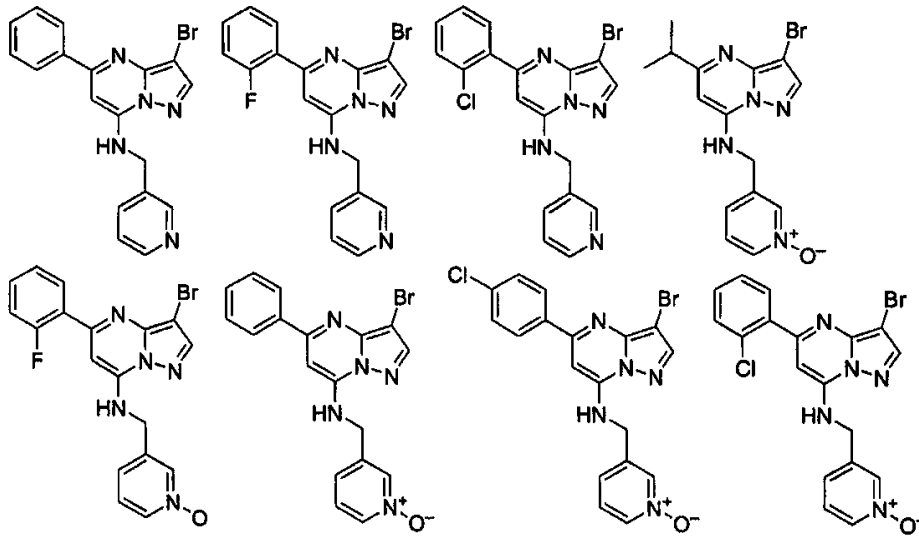


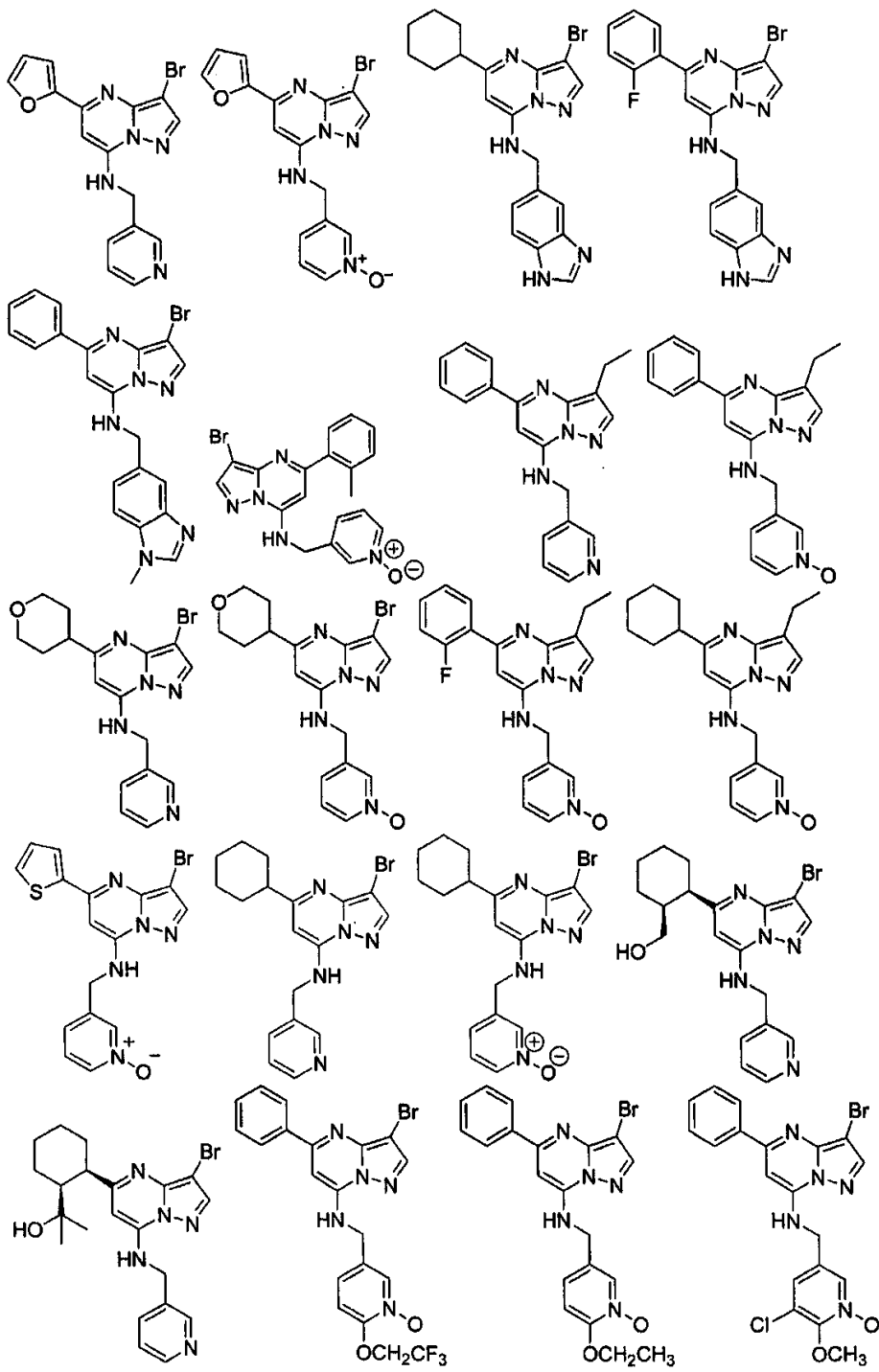


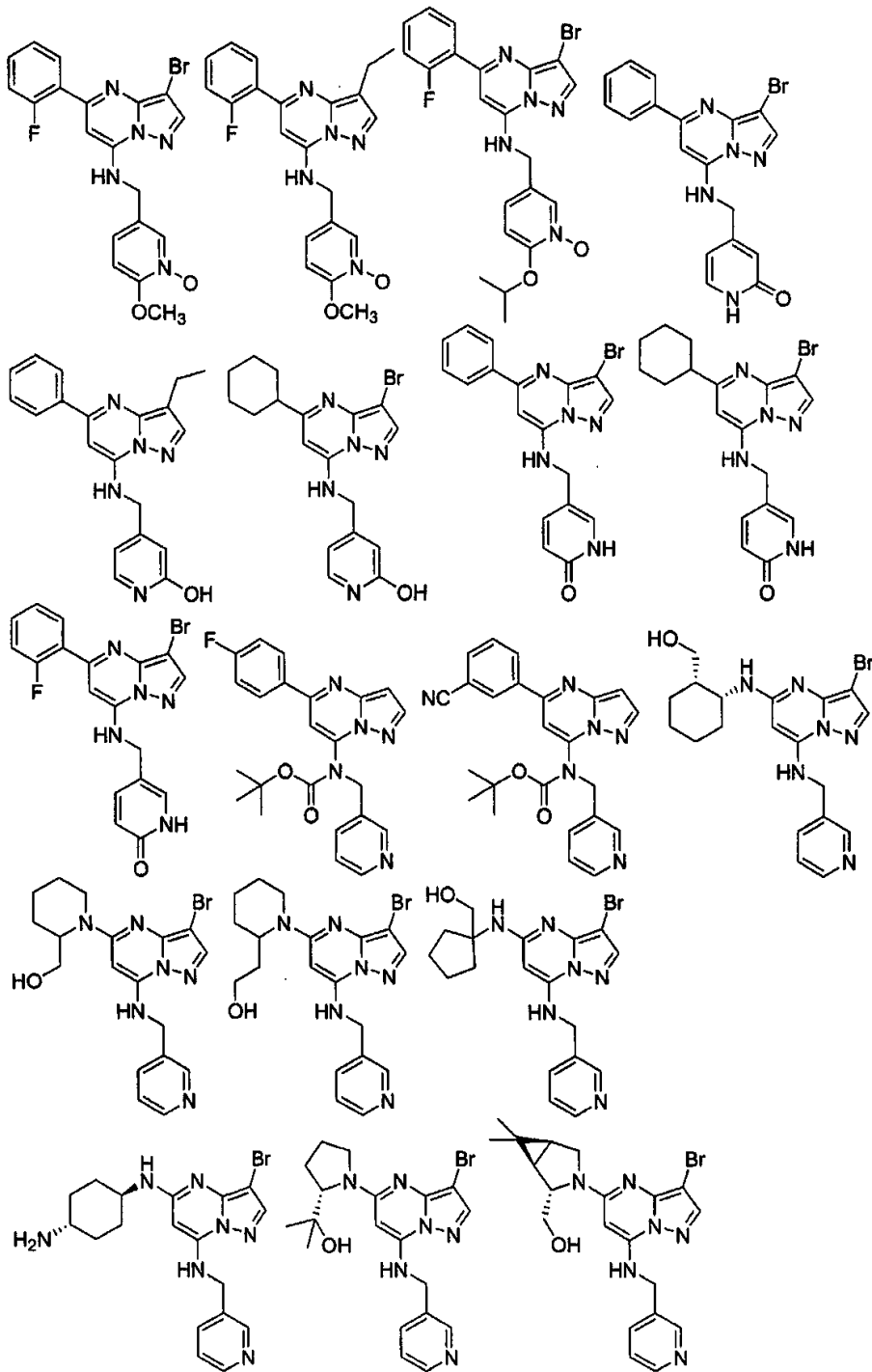


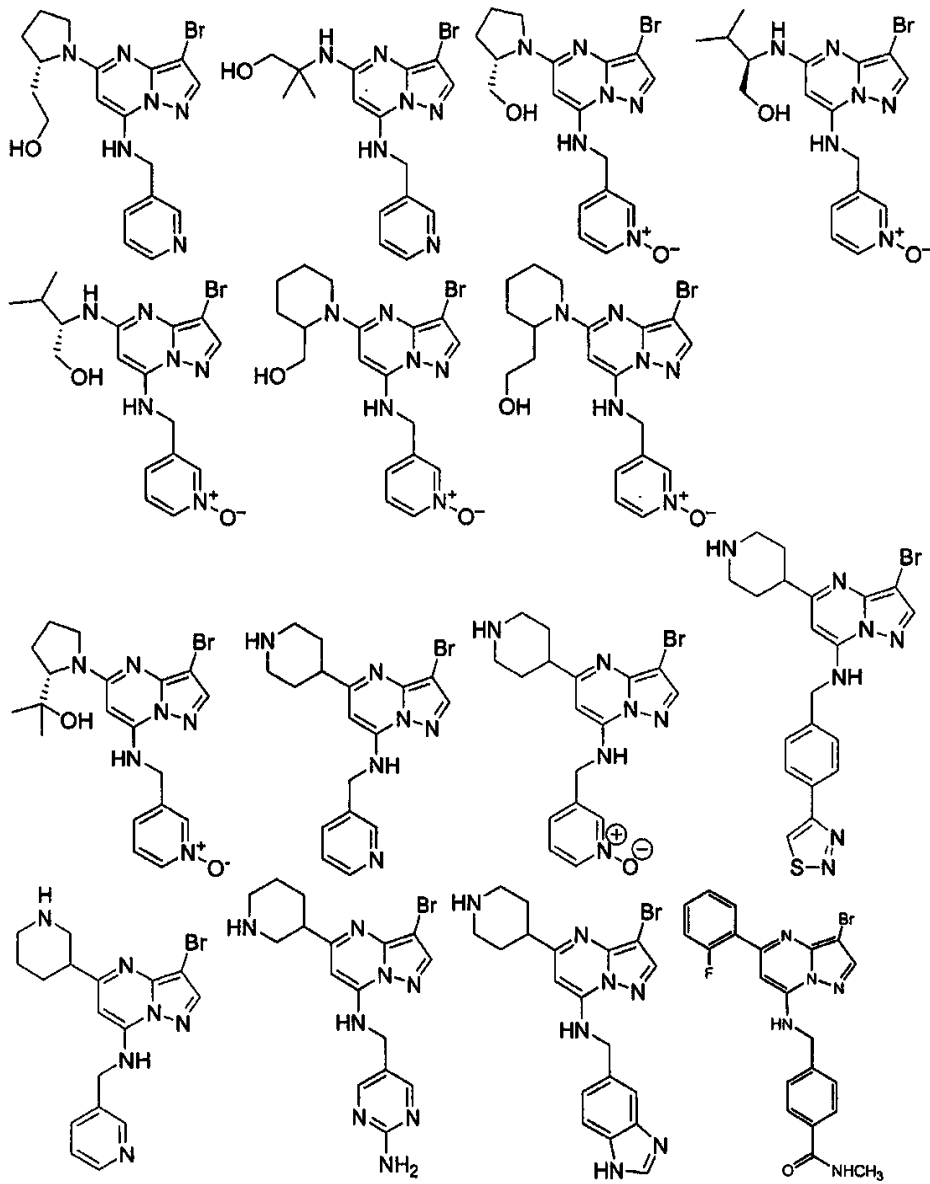
청구항 28

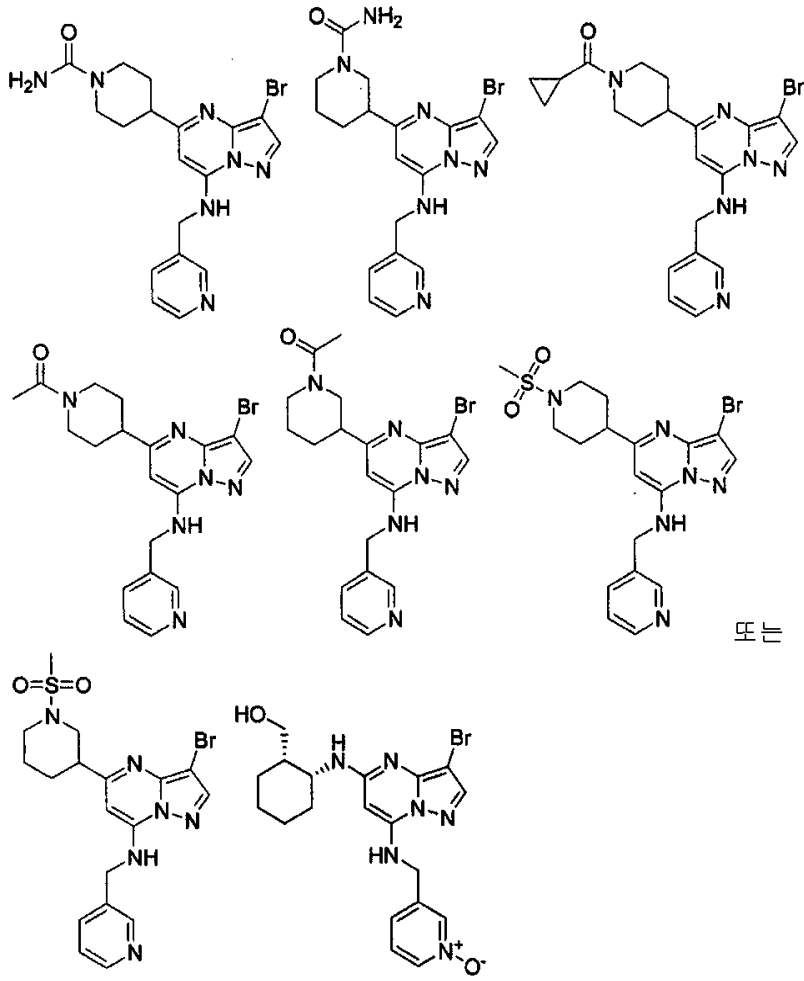
하기 화학식의 화합물, 또는 이의 약제학적으로 허용되는 염 또는 용매화물:





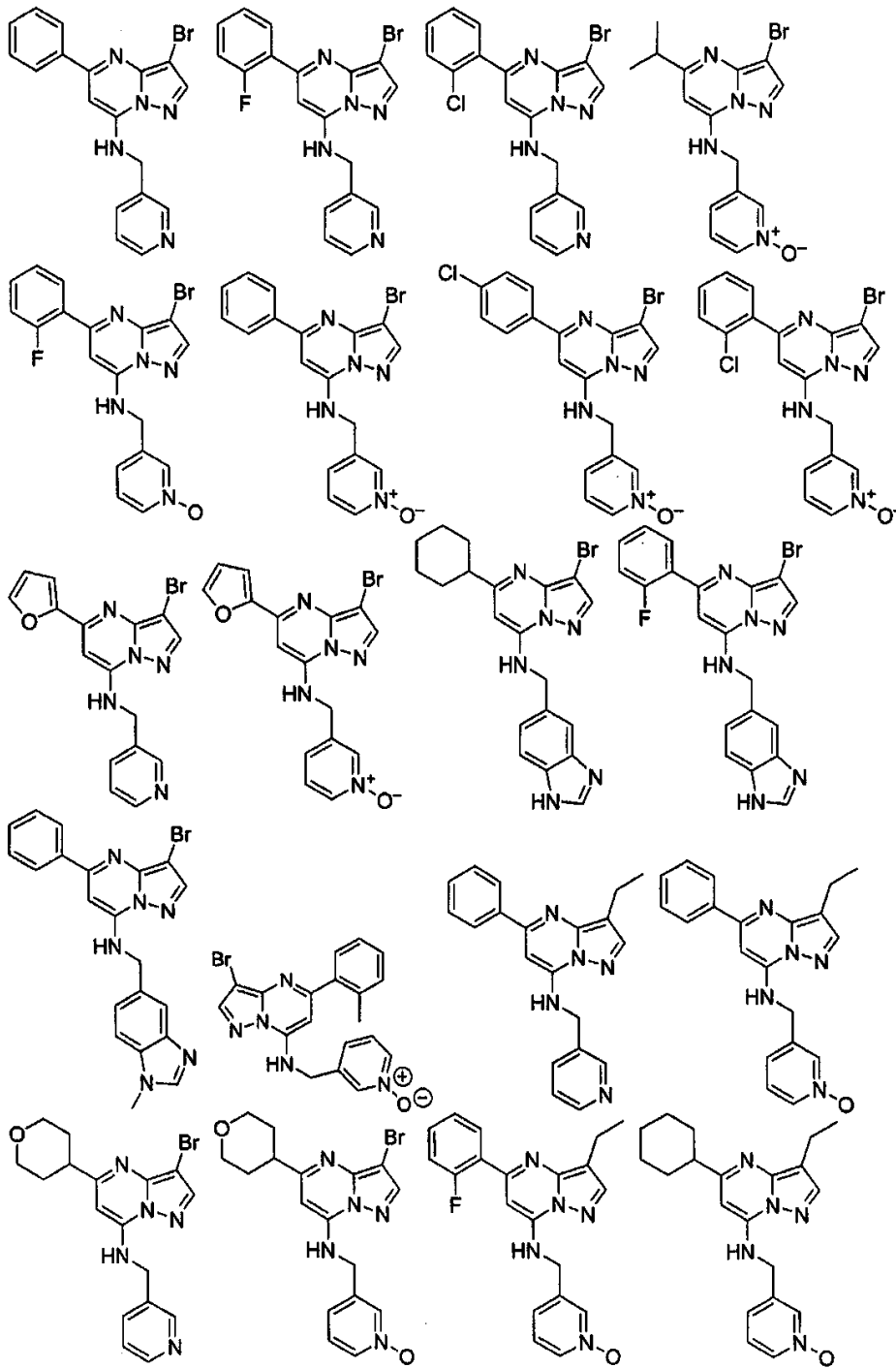


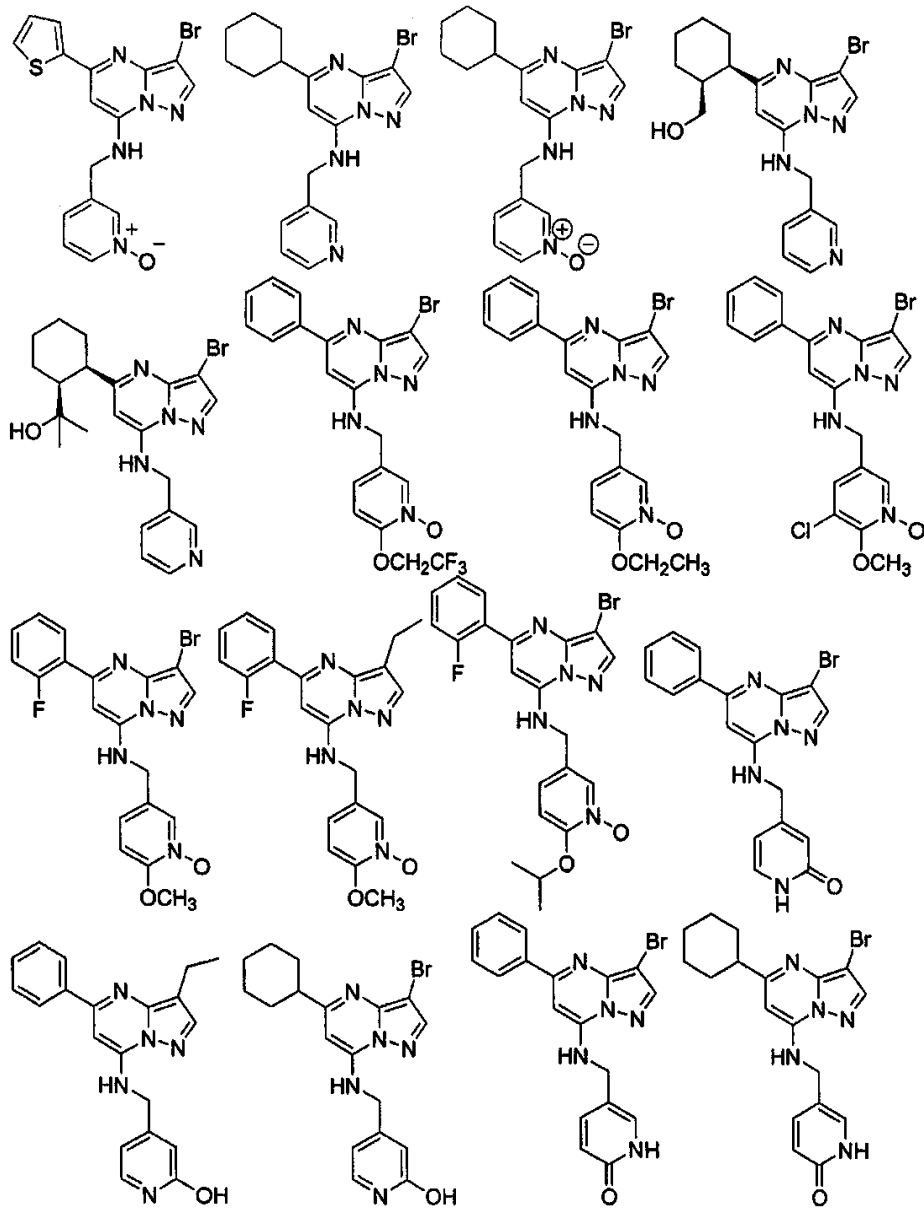


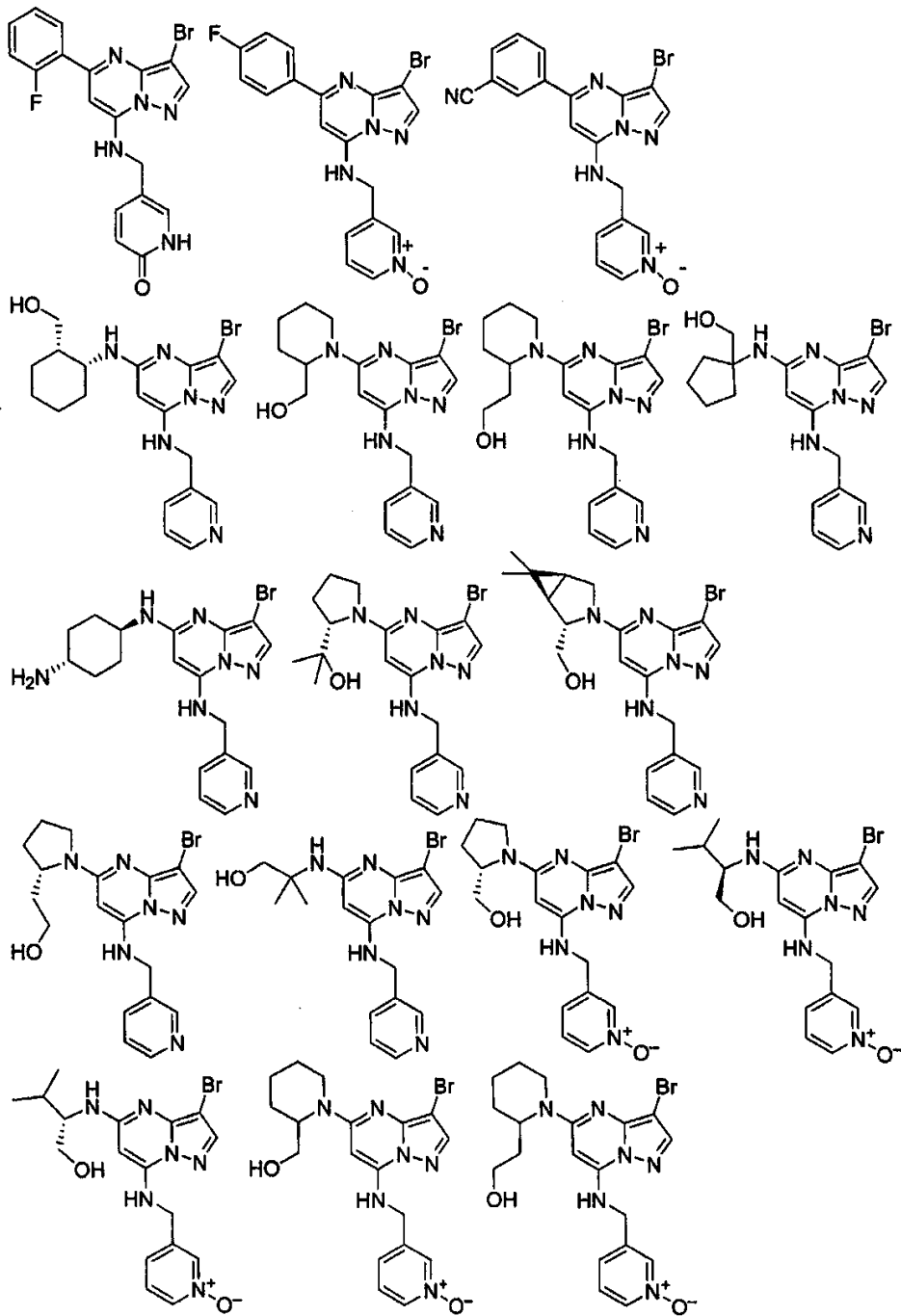


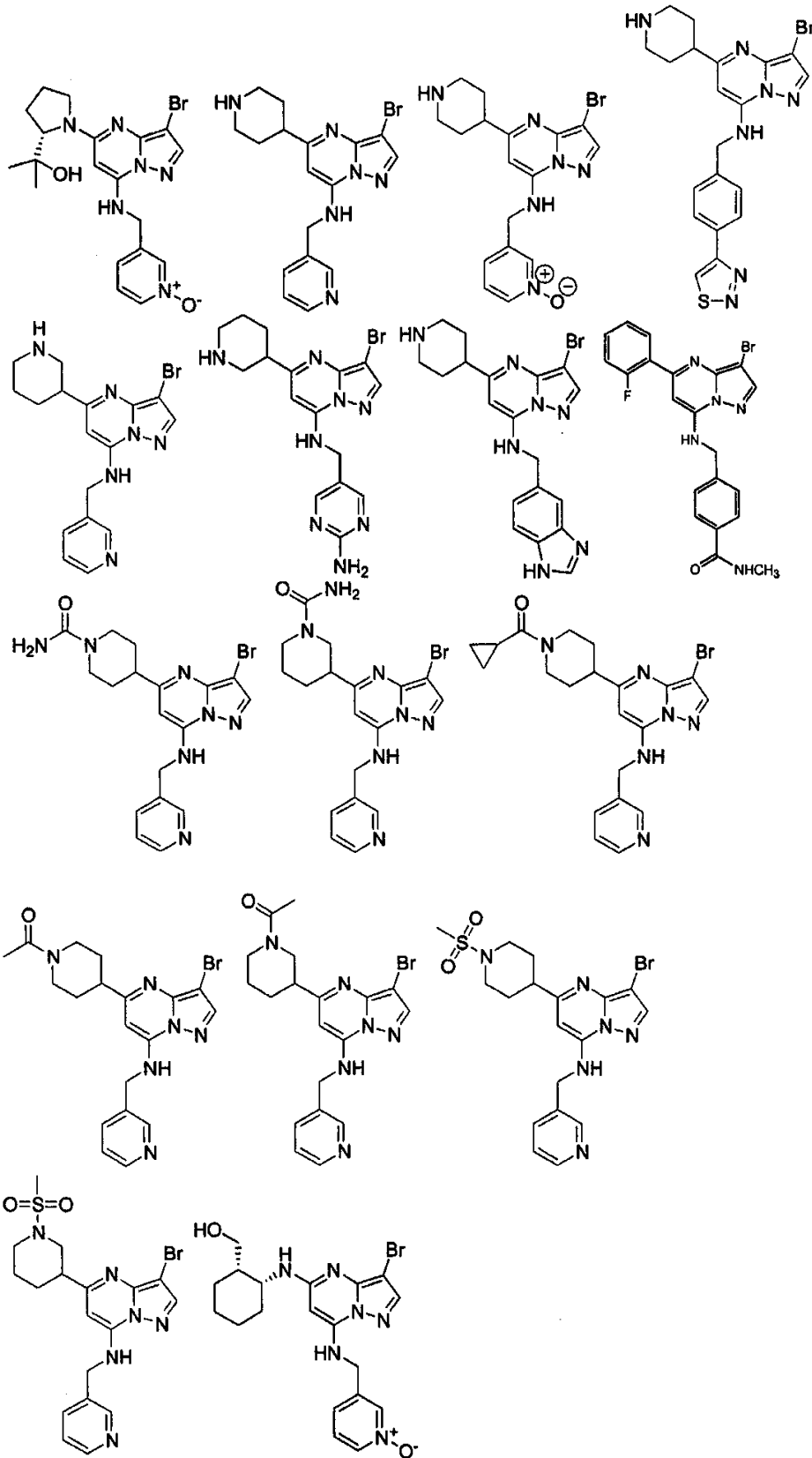
청구항 29

하기 화학식의 화합물, 또는 이의 약제학적으로 허용되는 염 또는 용매화물:



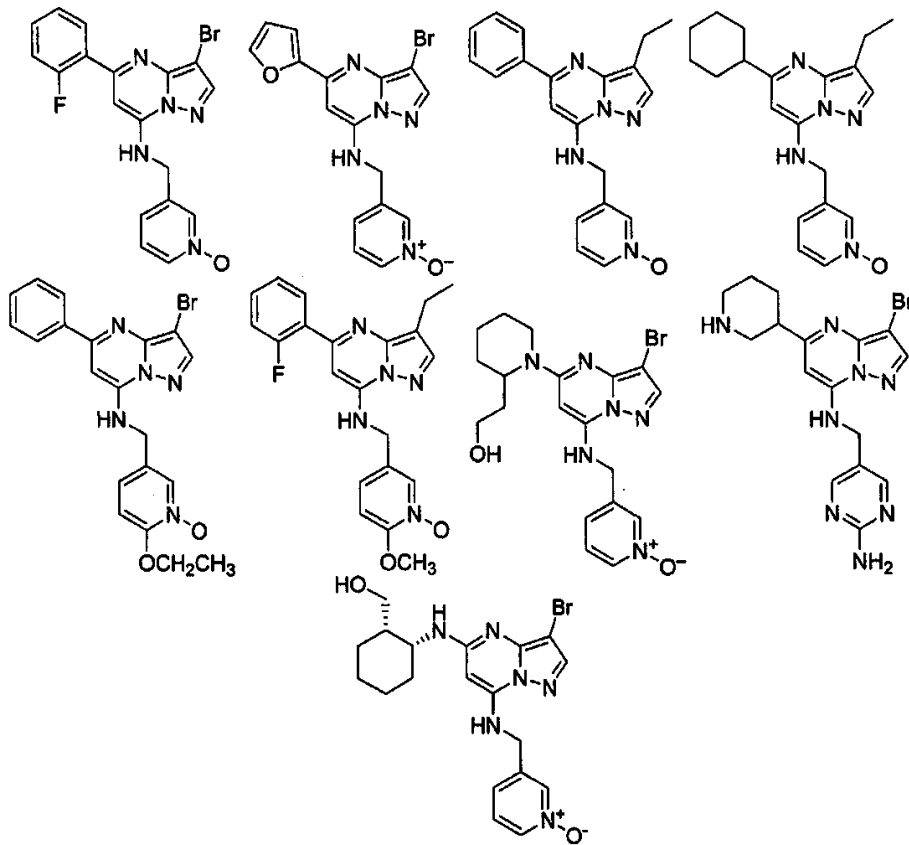






청구항 30

하기 화학식의 화합물, 또는 이의 약제학적으로 허용되는 염 또는 용매화물:



청구항 31

하나 이상의 약제학적으로 허용되는 담체와 배합된, 치료학적 유효량의 하나 이상의 제1항에 따른 화합물을 포함하여, 하나 이상의 사이클린 의존성 키나제를 억제하기 위한 약제학적 조성물.

청구항 32

하나 이상의 약제학적으로 허용되는 담체와 배합된, 치료학적 유효량의 하나 이상의 제1항에 따른 화합물을 포함하여, 사이클린 의존성 키나제와 관련된 하나 이상의 질환을 치료하기 위한 약제학적 조성물.

청구항 33

제32항에 있어서, 사이클린 의존성 키나제가 CDK2인 약제학적 조성물.

청구항 34

제32항에 있어서, 사이클린 의존성 키나제가 유사분열물질 활성화된 단백질 키나제(MAPK/ERK)인 약제학적 조성물.

청구항 35

제32항에 있어서, 사이클린 의존성 키나제가 글리코겐 신타제 키나제 3(GSK3 β)인 약제학적 조성물.

청구항 36

제32항에 있어서, 상기 질환이 편평 세포 암종을 포함하는, 방광, 유방, 결장, 신장, 간, 폐, 소세포 폐암, 식도, 담낭, 난소, 췌장, 위, 자궁경부, 갑상선, 전립선 및 피부의 암;

백혈병, 급성 림프구 백혈병, 급성 림프모구 백혈병, B-세포 림프종, T-세포 림프종, 호지킨 림프종, 비-호지킨 림프종, 모발 세포 림프종 및 버켓 림프종(Burkett's lymphoma);

급성 및 만성 골수 백혈병, 골수형성이상 증후군 및 전골수구 백혈병;

섬유육종 및 횡문근육종;

별아교세포종, 신경모세포종, 신경아교종 및 신경집종; 및

흑색종, 고환종, 기형암종, 골육종, 색소성건피증, 각질가시세포종, 갑상샘소포암 및 카포시 육종으로 이루어진 그룹 중에서 선택되는 약제학적 조성물.

청구항 37

하나 이상의 약제학적으로 허용되는 담체와 배합된, 치료학적 유효량의 제1항에 따른 화합물, 또는 이의 약제학적으로 허용되는 염 또는 용매화물인 제1 화합물; 및 치료학적 유효량의 하나 이상의 항암제인 제2 화합물을 포함하여, 사이클린 의존성 키나제와 관련된 하나 이상의 질환을 치료하기 위한 약제학적 조성물.

청구항 38

제37항에 있어서, 방사선 치료요법을 추가로 포함하는 약제학적 조성물.

청구항 39

제37항에 있어서, 항암제가 세포정지제, 시스플라틴, 독소루비신, 탁소테레, 탁솔, 에토포시드, CPT-11, 이리노테칸, 캄프토스타, 토포테칸, 파클리탁셀, 도세탁셀, 에포틸론, 타목시펜, 5-플루오로우라실, 메톡스트렉세이트, 5FU, 테모졸로마이드, 사이클로포스파미드, SCH66336, R115777, L778,123, BMS 214662, 이레싸(Iressa), 타르세바(Tarceva), EGFR에 대한 항체, 글리벡(Gleevec), 인트론, ara-C, 아드리아마이신, 사이톡산, 잼시타빈, 우라실 무스타드, 클로르메틴, 이포스파미드, 멜팔란, 클로람부실, 피포브로만, 트리에틸렌멜라민, 트리에틸렌티오포스포르아민, 부설판, 카르무스틴, 로무스틴, 스트렙토조신, 다카르바진, 플록수리딘, 사이타라빈, 6-머캅토피린, 6-티오구아닌, 플루다라빈 포스페이트, 옥살리플라틴, 류코비린, 엘록산틴 (ELOXATIN™), 펜토스타틴, 빈블라스틴, 빈크리스틴, 빈데신, 블레오마이신, 닥티노마이신, 다우노루비신, 독소루비신, 에피루비신, 이다루비신, 미트라마이신, 데옥시코포르마이신, 미토마이신-C, L-아스파라기나제, 테니포시드 17 α -에틸닐에스트라디올, 디에틸stil베스트롤, 테스토스테론, 프레드니손, 플루옥시메스테론, 드로모스타놀론 프로피오네이트, 테스톨락톤, 메게스트롤아세테이트, 메틸프레드니솔론, 메틸테스토스테론, 프레드니솔론, 트리암시놀론, 클로로트리아니센, 하이드록시프로게스테론, 아미노글루테쓰이미드, 에스트라무스틴, 메드록시프로게스테론아세테이트, 류프롤라이드, 플루타미드, 토레미펜, 고세렐린, 시스플라틴, 카르보플라틴, 하이드록시우레아, 암사크린, 프로카르바진, 미토탄, 미톡산트론, 레바미솔, 나벨벤, CPT-11, 아나스트라졸, 레트라졸, 카페시타빈, 렐록사핀, 드롤록사핀 또는 헥사메틸멜라민으로 이루어진 그룹 중에서 선택되는 약제학적 조성물.

청구항 40

삭제

청구항 41

삭제

청구항 42

제1항에 있어서, 정제된 형태의 화합물.

명세서

기술분야

본 발명은 단백질 키나제 억제제[예를 들면, 사이클린-의존성 키나제, 유사분열물질-활성화된 단백질 키나제(MAPK/ERK), 글리코겐 신타제 키나제 3(GSK3 β) 등]로서 유용한 피라졸로[1,5-a]피리미딘 화합물, 이를 포함하는 약제학적 조성물, 및 당해 화합물을 사용하는 치료방법 및 예를 들면, 암, 염증, 관절염, 바이러스 질환, 신경변성 질환[예: 알츠하이머병], 심혈관 질환 및 진균 질환과 같은 질환을 치료하기 위한 조성물에 관한 것이다. 본원은 2002년 9월 4일자로 출원된 미국 가특허원 제60/408,027호 및 2002년 10월 29일 출원된 미국

[0001]

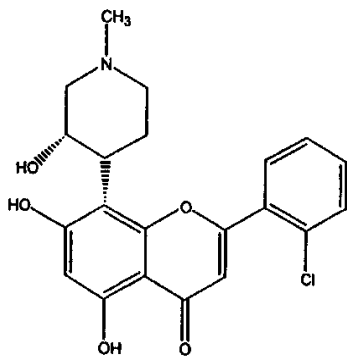
가특허원 제60/421,959호로부터의 우선권의 이익을 청구한다.

배경 기술

[0002] 단백질 키나제 억제제는 예를 들면, 사이클린-의존성 키나제(CDKs), 유사분열물질 활성화된 단백질 키나제(MAPK/ERK), 글리코겐 신타제 키나제 3(GSK3β) 등과 같은 키나제를 포함한다. 단백질 키나제 억제제는 예를 들면 문헌[참조: M. Hale 등의 제WO02/22610 A1호 및 Y. Mettey 등의 J. Med. Chem.,(2003) 46 222-236]에 기술되어 있다. 사이클린-의존성 키나제는 세포 주기 및 세포 증식 이면의 구동력이 되는 세린/트레오닌 단백질 키나제이다. 개개의 CDK, 예를 들면, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 및 CDK7, CDK8 등은 세포 주기 진행에서 분명한 역할을 수행하며, G1, S 또는 G2M 기 효소 중의 하나로 분류할 수 있다. 조절되지 않은 증식은 암세포를 증명하는 것이며, CDK 작용의 부적절한 조절(misregulation)은 다수의 중요한 고형 종양에서 높은 빈도로 발생한다. CDK2 및 CDK4가 특히 중요한데, 그 이유는 이들의 활성이 다양한 종류의 사람 암에서 종종 잘못 조절되기 때문이다. CDK2 활성은 세포 주기의 G1 기를 통해 S 기로 진행시키기 위해 필요하며, CDK2는 G1 체크포인트(checkpoint)의 중요한 성분들 중의 하나이다. 체크포인트는 세포 주기 이벤트의 적절한 순서를 유지하는 작용을 하며, 세포가 공격에 응답하거나 증식성 신호에 응답하도록 하는 반면, 암세포에서의 적절한 체크포인트 조절의 실패는 종양발생을 유발시킨다. CDK2 통로는 종양 억제제 기능(예: p52, RB 및 p27) 및 종양 유전자 활성화(사이클린 E)의 수준에서 종양형성에 영향을 미친다. 많은 보고서에서 CDK2의 억제제 p27과 조활성화제 사이클린 E 둘 다가 유방, 결장, 비소세포 폐, 위, 전립선, 방광, 비-호지킨 림프종(non-Hodgkin's lymphoma), 난소 및 기타 암에서 각각 과발현 또는 저발현되는 것으로 입증되었다. 이들의 변경된 발현은 증가된 CDK2 활성 수준 및 불량한 전체 생존과 상관관계가 있는 것으로 밝혀졌다. 이러한 관찰은, CDK2 및 이의 조절된 통로가 성장 년도(development year) 동안에 표적을 억제시키도록 하고, 다수의 아데노신 5'-트리포스페이트(ATP) 경쟁성인 작은 유기 분자 뿐만 아니라, 펩타이드도 문헌에 암의 잠재적 치료를 위한 CDK 억제제로서 보고되어 왔다. 미국 특허 제6,413,974호의 컬럼 1, 라인 23 내지 컬럼 15, 라인 10에서는 다양한 CDK 및 이들의 각종 형태의 암과의 관계에 대해 잘 기술하고 있다.

[0003] CDK 억제제는 공지되어 있다. 예를 들면, 플라보피리돌(화학식 1)은 사람 임상 시험이 현재 진행되고 있는 비선택적 CDK 억제제이다[참조: A. M. Sanderowicz et al, J. Clin. Oncol.(1998) 16,2986-2999].

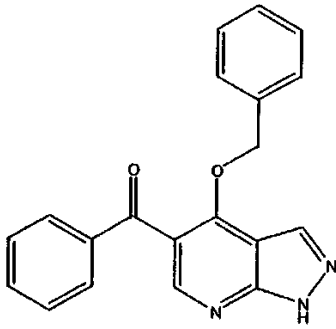
화학식 1



[0004]

[0005] CDK의 기타 공지된 억제제는, 예를 들면, 올로마우신[참조:J. Vesely et al, Eur. J. Biochem.,(1994) 224, 771-786] 및 로스코비틴[참조: I. Meijer et al, Eur. J. Biochem.,(1997) 243, 527-536]을 포함한다. 미국 특허 제6,107,305호에는 CDK 억제제로서의 특정한 피라졸로[3,4-b]피리딘 화합물이 기술되어 있다. 당해 특허로부터의 설명적인 화합물은 다음 화학식 2의 화합물이다:

화학식 2



[0006]

[0007] 문헌[참조: K. S. Kim et al, J. Med. Chem. 45(2002) 3905-3927] 및 WO 02/10162에는 CDK 억제제로서 특정한 아미노티아졸 화합물이 기술되어 있다.

[0008] 피라졸로피리미딘은 공지되어 있다. 예를 들면, WO 92/18504, WO 02/50079, W095/35298, WO 02/40485, EP 94304104.6, EP 0628559(미국 특허 제5,602,136호, 제5,602,137호 및 제5,571,813호와 동일), 미국 특허 제 6,383,790호, 문헌[참조: Chem. Pharm. Bull.,(1999) 47 928, J. Med. Chem.,(1977) 20, 296, J. Med. Chem.,(1976) 19 517 및 Chem. Pharm. Bull.,(1962) 10 620]에는 각종 피라졸로피리미딘이 기술되어 있다.

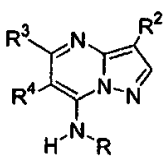
[0009] CDK와 관련된 질환 및 장애를 치료하기 위한 새로운 화합물, 제형, 치료방법 및 치료요법이 필요하다. 따라서, 본 발명의 목적은 이러한 질환 및 장애를 치료하거나 예방하거나 경감시키는데 유용한 화합물을 제공하는 것이다.

[0010] 발명의 요약

[0011] 본 발명의 다수의 양태에서, 본 발명은 사이클린 의존성 키나제의 억제제로서의 신규한 부류의 피라졸로[1,5-a]피리미딘 화합물, 이러한 화합물의 제조방법, 이러한 화합물 하나 이상을 포함하는 약제학적 조성물, 이러한 화합물 하나 이상을 포함하는 약제학적 제형의 제조방법, 및 이러한 화합물 또는 약제학적 조성물을 사용하여 CDK와 관련된 질환 하나 이상을 치료, 예방, 억제 또는 경감하는 방법을 제공한다.

[0012] 하나의 양태에서, 본원은 화학식 3의 화합물, 당해 화합물의 약제학적으로 허용되는 염 또는 용매화물을 기술한다:

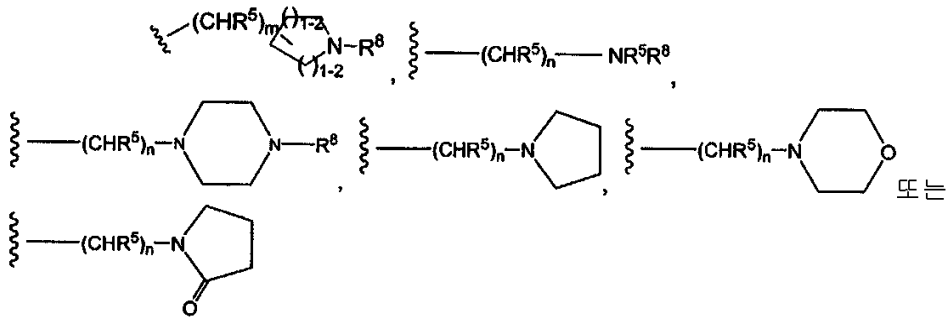
화학식 3



[0013]

[0014] 상기식에서,

[0015] R은 H, 알킬, 알케닐, 알키닐, 아릴알킬, 아릴알케닐, 사이클로알킬, 사이클로알킬알킬, 알케닐알킬, 알키닐알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴알킬(상기 헤테로아릴의 N-옥사이드 포함), $-(CHR^5)_n$ -아릴, $-(CHR^5)_n$ -헤테로아릴,



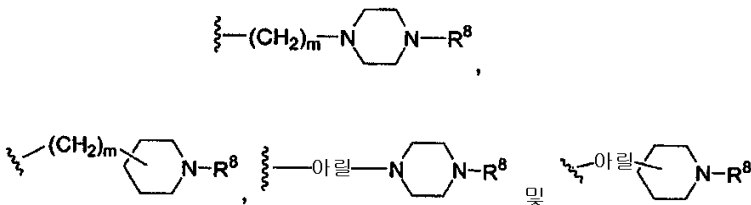
[0016]

[0017]

이고, 여기서, 상기 알킬, 알케닐, 알킬닐, 아릴, 사이클로알킬, 헤테로사이클릴 및 헤테로아릴 각각은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 임의 치환될 수 있으며, 여기서, 잔기 각각은 할로젠, 알킬, 아릴, 사이클로알킬, 헤테로사이클릴알킬, CF₃, OCF₃, CN, -OR⁵, -NR⁵R¹⁰, -C(R⁴R⁵)_p-R⁹, -N(R⁵)Boc, -(CR⁴R⁵)_pOR⁵, -C(O₂)R⁵, -C(O)R⁵, -C(O)NR⁵R¹⁰, -SO₃H, -SR¹⁰, -S(O₂)R⁷, -S(O₂)NR⁵R¹⁰, -N(R⁵)S(O₂)R⁷, -N(R⁵)C(O)R⁷ 및 -N(R⁵)C(O)NR⁵R¹⁰으로 이루어진 그룹 중에서 독립적으로 선택되며;

[0018]

R²는 R⁹, 알킬, 알케닐, 알킬닐, CF₃, 헤테로사이클릴, 헤테로사이클릴알킬, 할로젠, 할로알킬, 아릴, 아릴알킬, 헤테로아릴알킬, 알킬닐알킬, 사이클로알킬, 헤테로아릴; 동일하거나 상이할 수 있고 하기한 R⁹의 목록으로부터 독립적으로 선택되는 1 내지 6개의 R⁹ 그룹으로 치환된 알킬; 동일하거나 상이할 수 있고 페닐, 피리딜, 티오펜, 푸라닐 및 티아졸로 그룹 중에서 독립적으로 선택된 1 내지 3개의 아릴 또는 헤테로아릴 그룹으로 치환된 아릴; 아릴 또는 헤테로아릴 그룹과 융합된 아릴; 동일하거나 상이할 수 있고 페닐, 피리딜, 티오펜, 푸라닐 및 티아졸로 그룹 중에서 독립적으로 선택된 1 내지 3개의 아릴 또는 헤테로아릴 그룹으로 치환된 헤테로아릴; 아릴 또는 헤테로아릴 그룹과 융합된 헤테로아릴,



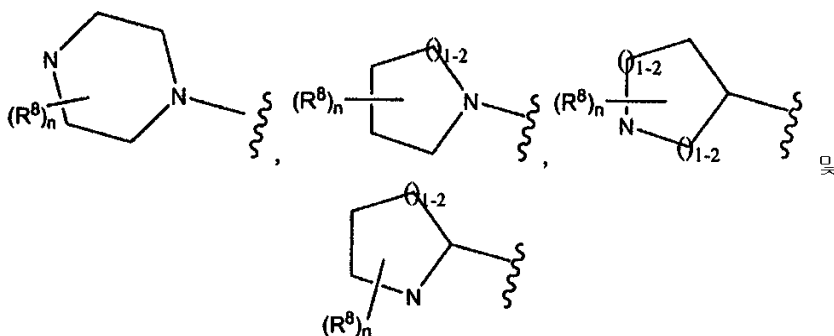
[0019]

[0020]

로 이루어진 그룹 중에서 선택되고, 여기서, R²에 대해 위에서 나타낸 정의중에서 하나 이상의 아릴 및/또는 하나 이상의 헤테로아릴은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 임의 치환될 수 있고, 여기서, 잔기 각각은 할로젠, -CN, -OR⁵, -SR⁵, -S(O₂)R⁶, -S(O₂)NR⁵R⁶, -NR⁵R⁶, -C(O)NR⁵R⁶, CF₃, 알킬, 아릴 및 OCF₃로 이루어진 그룹 중에서 독립적으로 선택되며;

[0021]

R³은 H, 할로젠, -NR⁵R⁶, -OR⁶, -SR⁶, -C(O)N(R⁵R⁶), 알킬, 알킬닐, 사이클로알킬, 아릴, 아릴알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴, 헤테로아릴알킬,



[0022]

[0023] 로 이루어진 그룹으로부터 선택되고, 여기서 R^3 에 대한 상기한 알킬, 사이클로알킬, 아릴, 아릴알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬의 각각 및 R^3 에 대해 바로 위에서 나타낸 구조의 헤테로사이클릴 잔기는 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 독립적으로 임의 치환될 수 있고, 여기서 각각의 잔기는 할로젠, 알킬, 아릴, 사이클로알킬, CF_3 , CN , $-OCF_3$, $-(CR^4R^5)_pOR^5$, $-OR^5$, $-NR^5R^6$, $-(CR^4R^5)_pNR^5R^6$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 및 $-N(R^5)C(O)NR^5R^6$ 로 이루어진 그룹으로부터 독립적으로 선택되고, 단, 헤테로사이클릴 환위의 질소 원자에 인접한 탄소는 $-OR^5$ 잔기를 지니지 않으며;

[0024] R^4 는 H, 할로 또는 알킬이고;

[0025] R^5 는 H, 알킬, 아릴 또는 사이클로알킬이고;

[0026] R^6 은 H, 알킬, 알케닐, 아릴, 아릴알킬, 아릴알케닐, 사이클로알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬로 이루어진 그룹으로부터 선택되고, 여기서, 당해 알킬, 아릴, 아릴알킬, 사이클로알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬의 각각은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 임의 치환될 수 있으며, 여기서 각각의 잔기는 할로젠, 알킬, 아릴, 사이클로알킬, 헤테로사이클릴알킬, CF_3 , OCF_3 , CN , $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_pR^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 및 $-N(R^5)C(O)NR^5R^{10}$ 으로 이루어진 그룹으로부터 독립적으로 선택되고;

[0027] R^{10} 은 H, 알킬, 아릴, 아릴알킬, 사이클로알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬로 이루어진 그룹으로부터 선택되고, 여기서 당해 알킬, 아릴, 아릴알킬, 사이클로알킬, 헤테로사이클릴, 헤테로사이클릴알킬, 헤테로아릴 및 헤테로아릴알킬의 각각은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기로 임의 치환될 수 있으며, 여기서 잔기 각각은 할로젠, 알킬, 아릴, 사이클로알킬, 헤테로사이클릴알킬, CF_3 , OCF_3 , CN , $-OR^5$, $-NR^4R^5$, $-C(R^4R^5)_pR^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 및 $-N(R^5)C(O)NR^4R^5$ 로 이루어진 그룹으로부터 독립적으로 선택되거나;

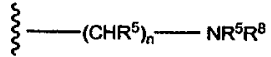
[0028] 임의로 (i) 잔기 $-NR^5R^{10}$ 에서 R^5 및 R^{10} 또는 (ii) 잔기 $-NR^5R^6$ 에서 R^5 및 R^{10} 은, 함께 사이클로알킬 또는 헤테로사이클릴 잔기를 형성할 수 있고, 당해 사이클로알킬 또는 헤테로사이클릴 잔기의 각각은 치환되지 않거나, 하나 이상의 R^9 그룹에 의해 독립적으로 임의 치환되며;

[0029] R^7 은 알킬, 사이클로알킬, 아릴, 아릴알케닐, 헤테로아릴, 아릴알킬, 헤테로아릴알킬, 헤테로아릴알케닐 및 헤테로사이클릴로 이루어진 그룹으로부터 선택되고, 여기서 당해 알킬, 사이클로알킬, 헤테로아릴알킬, 아릴, 헤테로아릴 및 아릴알킬의 각각은 치환되지 않거나, 또는 동일하거나 상이할 수 있는 하나 이상의 잔기에 의해 독립적으로 임의 치환될 수 있고, 여기서, 잔기 각각은 할로젠, 알킬, 아릴, 사이클로알킬, CF_3 , OCF_3 , CN , $-OR^5$, $-NR^5R^{10}$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^{10}$, $-C(O)R^5$, $-SR^{10}$, $-S(O_2)R^{10}$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^{10}$, $-N(R^5)C(O)R^{10}$ 및 $-N(R^5)C(O)NR^5R^{10}$ 으로 이루어진 그룹으로부터 독립적으로 선택되고;

[0030] R^8 은 R^6 , $-OR^6$, $-C(O)NR^5R^{10}$, $-S(O_2)NR^5R^{10}$, $-C(O)R^7$, $-C(=N-CN)-NH_2$, $-C(=NH)-NHR^5$, 헤테로사이클릴 및 $-S(O_2)R^7$ 로 이루어진 그룹으로부터 선택되고;

[0031] R^9 는 할로젠, $-CN$, $-NR^5R^{10}$, $-C(O_2)R^6$, $-C(O)NR^5R^{10}$, $-OR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 및 $-N(R^5)C(O)NR^5R^6$ 로 이루어진 그룹으로부터 선택되고;

- [0032] m은 0 내지 4이며;
- [0033] n은 1 내지 4이고;
- [0034] p는 1 내지 4이며;

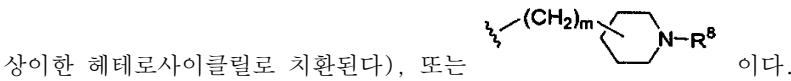
[0035] 단, R²가 페닐인 경우 R³는 알킬, 알킬닐 또는 할로겐이 아니고, R²가 아릴인 경우 R은  이 아니고, 또한 R이 아릴알킬인 경우 상기 아릴알킬중의 아릴상의 어떠한 헤테로아릴 치환체도 3개 이상의 헤테로원자를 함유한다.

[0036] 화학식 3의 화합물은 단백질 키나제 억제제로서 유용할 수 있으며, 증식성 질환, 예를 들면, 암, 염증 및 관절염의 치료 및 예방에 유용할 수 있다. 당해 화합물은 또한 신경변성 질환[예: 알츠하이머병], 심혈관 질환, 바이러스 질환 및 진균 질환의 치료에 유용할 수 있다.

발명의 상세한 설명

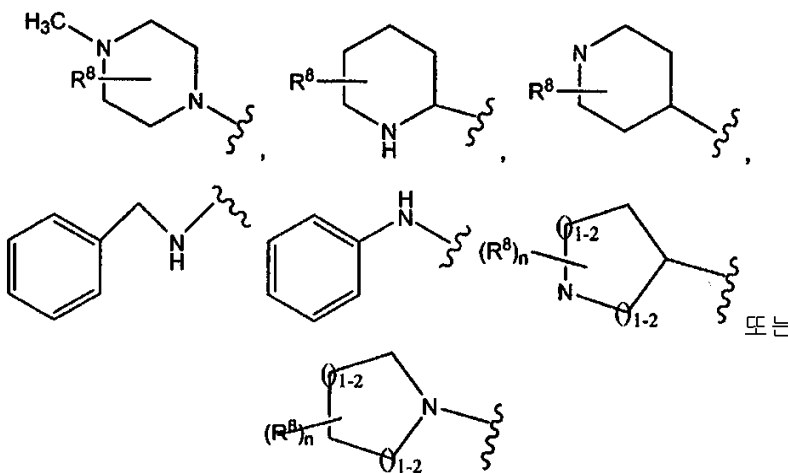
[0037] 한가지 양태에서, 본 발명은 화학식 3으로 나타내어지는 피라졸로[1,5-a]피리미딘 화합물[여기서, 각종 잔기들은 상기한 바와 같다], 또는 이의 약제학적으로 허용되는 염 또는 용매화물에 관한 것이다.

[0038] 다른 양태에서, R은 -(CHR⁵)_n-아릴, -(CHR⁵)_n-헤테로아릴, -(CHR⁵)_n-헤테로아릴(당해 헤테로아릴은 추가의, 동일하거나 상이한 헤테로아릴로 치환된다), -(CHR⁵)_n-헤테로사이클릴(당해 헤테로사이클릴은 추가의 동일하거나



[0039] 또 다른 양태에서, R²는 할로겐, CF₃, CN, 저급 알킬, -OR⁶로 치환된 알킬, 알킬닐, 아릴, 헤테로아릴 또는 헤테로사이클릴이다.

[0040] 또 다른 양태에서, R³은 H, 저급 알킬, 아릴, 헤테로아릴, 사이클로알킬, -NR⁵R⁶,



[0041] 이며, 여기서 R³에 대해 바로 위에서 나타낸 알킬, 아릴, 헤테로아릴, 사이클로알킬 및 헤테로사이클릴 각각은 동일하거나 상이할 수 있는 하나 이상의 잔기에 의해 독립적으로 임의 치환되며, 여기서 잔기 각각은 할로겐, CF₃, OCF₃, 저급 알킬, CN, -C(O)R⁵, -S(O₂)R⁵, -C(=NH)-NH₂, -C(=CN)-NH₂, 하이드록시알킬, 알콕시카보닐, -SR⁵ 및 OR⁵로 이루어진 그룹으로부터 독립적으로 선택되며, 단, 헤테로사이클릴 환위의 질소 원자에 인접한 탄소는 -OR⁵ 잔기를 수반하지 않는다.

[0043] 또 다른 양태에서, R⁴는 H 또는 저급 알킬이다.

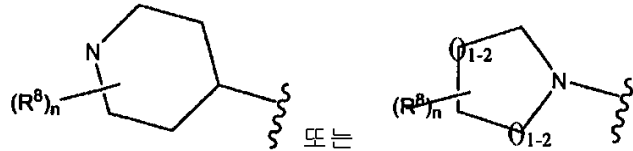
[0044] 또 다른 양태에서, R⁵는 H, 저급 알킬 또는 사이클로알킬이다.

[0045] 또 다른 양태에서, n은 1 또는 2이다.

[0046] 추가의 양태에서, R은 -(CHR⁵)_n-아릴, -(CHR⁵)_n-헤테로아릴이다.

[0047] 추가의 양태에서, R²는 할로젠, CF₃, CN, 저급 알킬, 알킬닐 또는 -OR⁶로 치환된 알킬이다.

[0048] 추가의 양태에서, R²는 저급 알킬, 알킬닐 또는 Br이다.



[0049] 추가의 양태에서, R³는 H, 저급 알킬, 아릴,

여기서, R³에 대해 바로 위에서 나타낸 알킬, 아릴 및 헤테로사이클릴 잔기의 각각은 동일하거나 상이할 수 있는 하나 이상의 잔기로 임의 치환되며, 여기서 잔기 각각은 할로젠, CF₃, 저급 알킬, 하이드록시알킬, 알콕시, -S(O₂)R⁵ 및 CN으로 이루어진 그룹 중에서 독립적으로 선택된다.

[0050] 추가의 양태에서, R⁴는 H이다.

[0051] 추가의 양태에서, R⁵는 H, 에틸, 사이클로프로필, 사이클로부틸, 사이클로펜틸 또는 사이클로헥실이다.

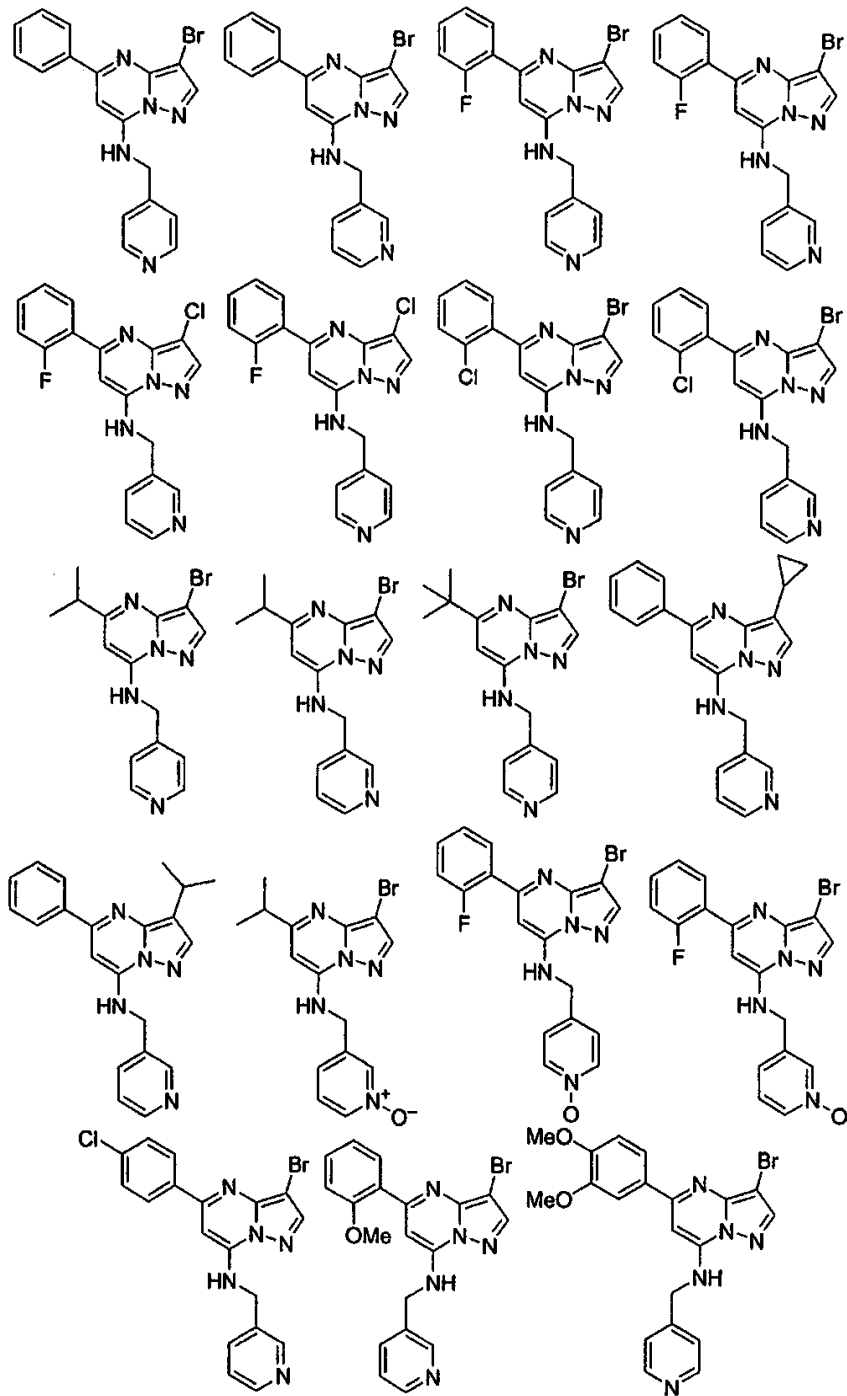
[0052] 추가의 양태에서, R⁸은 알킬 또는 하이드록시알킬이다.

[0053] 추가의 양태에서, n은 1이다.

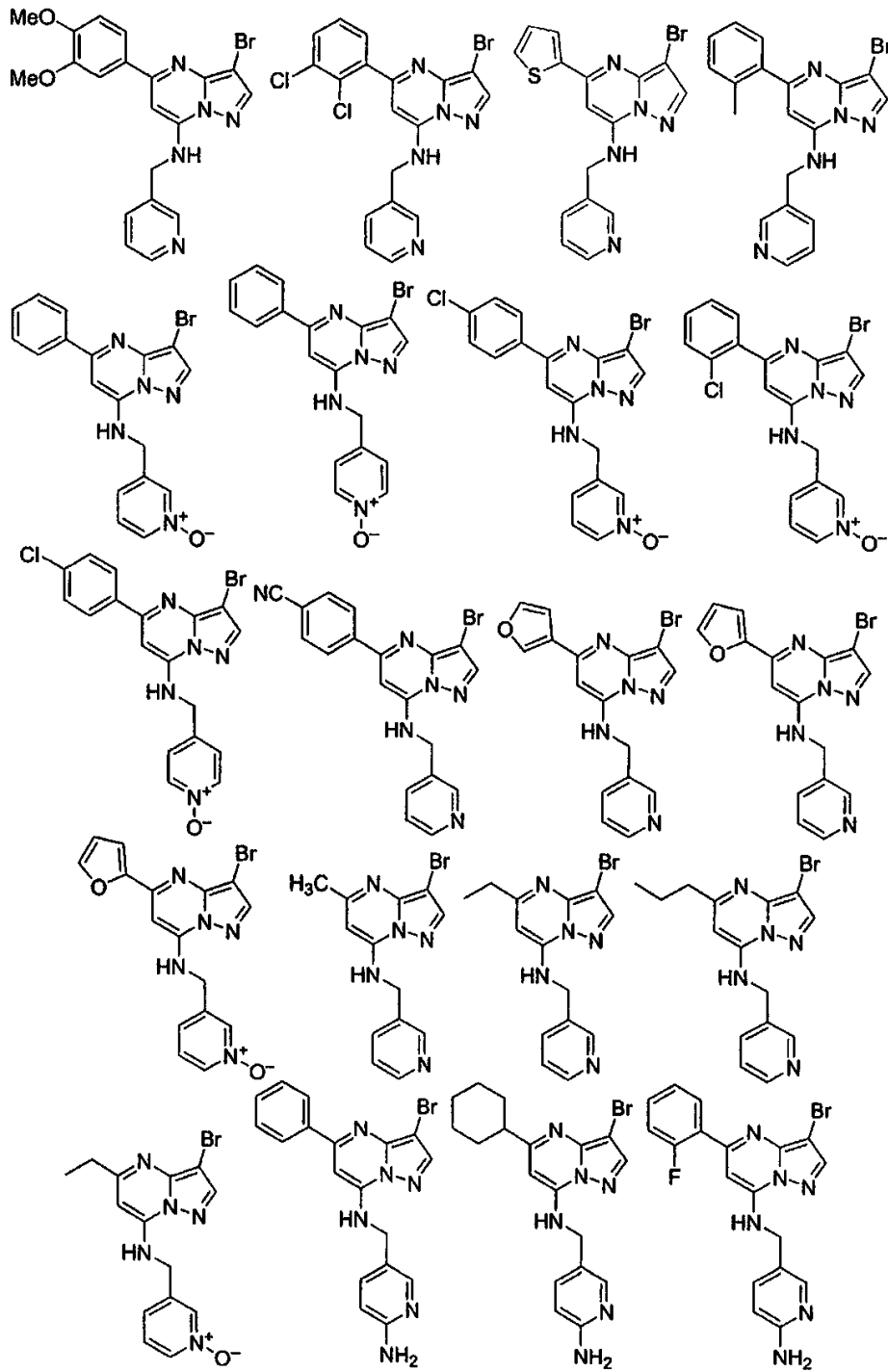
[0054] 추가의 양태에서, p는 1 또는 2이다.

[0055] 또다른 양태는 표 1에 나타낸 본 발명의 화합물을 기술하며, 당해 표 1의 화합물은 약 0.0001 μM 내지 약 5 μM 초과 CDK2 억제 활성을 나타낸다. 검정 방법은 후술한다.

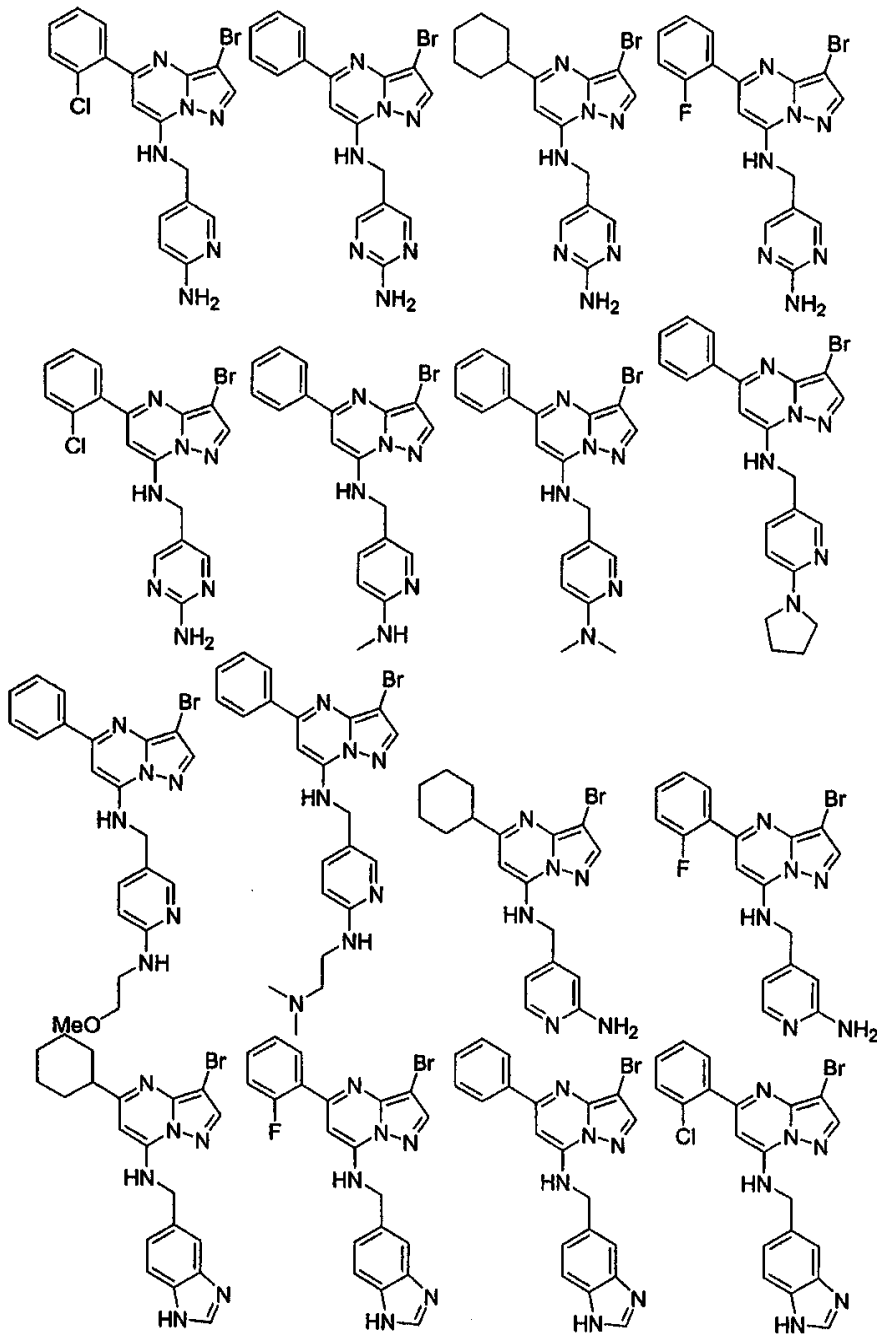
표 1



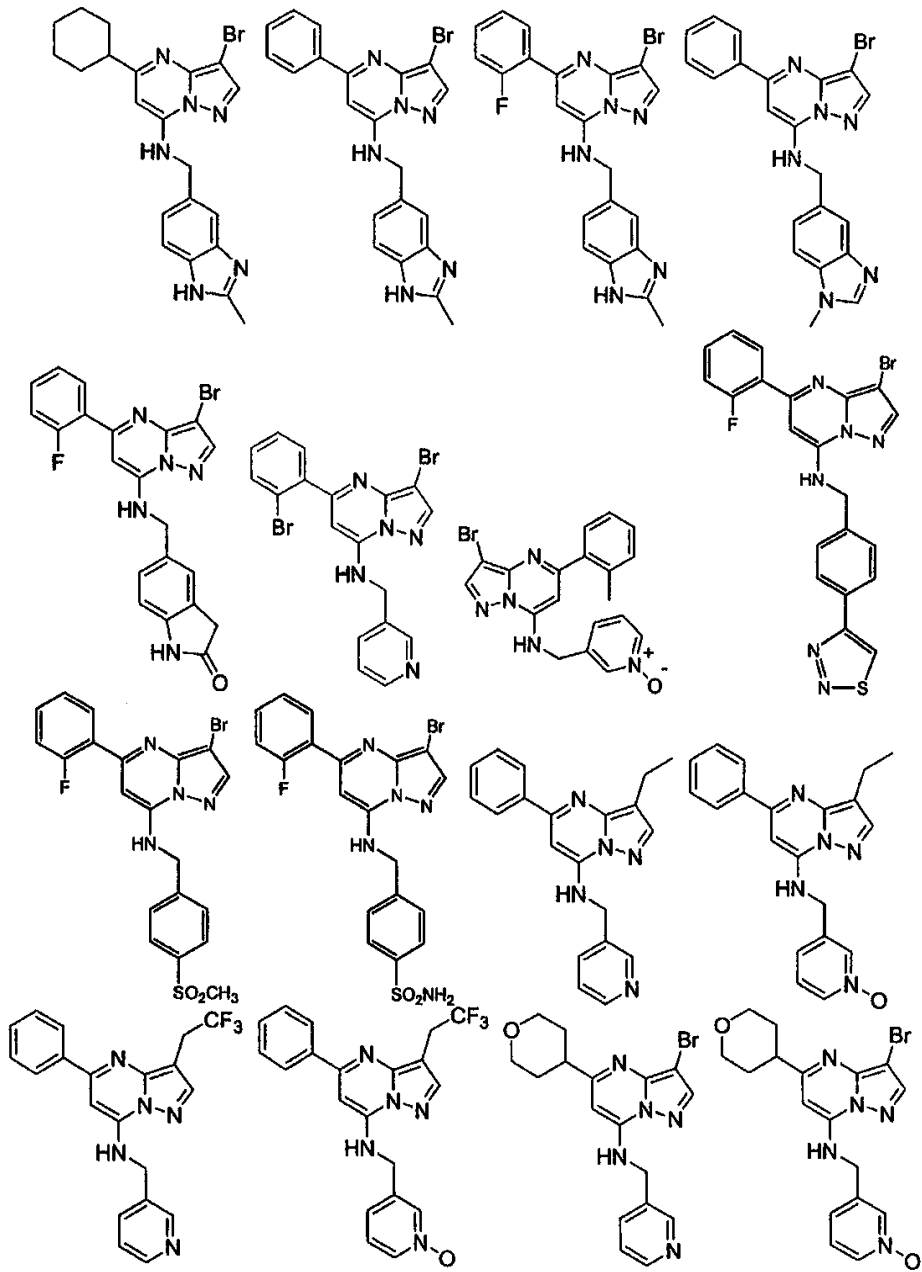
[0056]



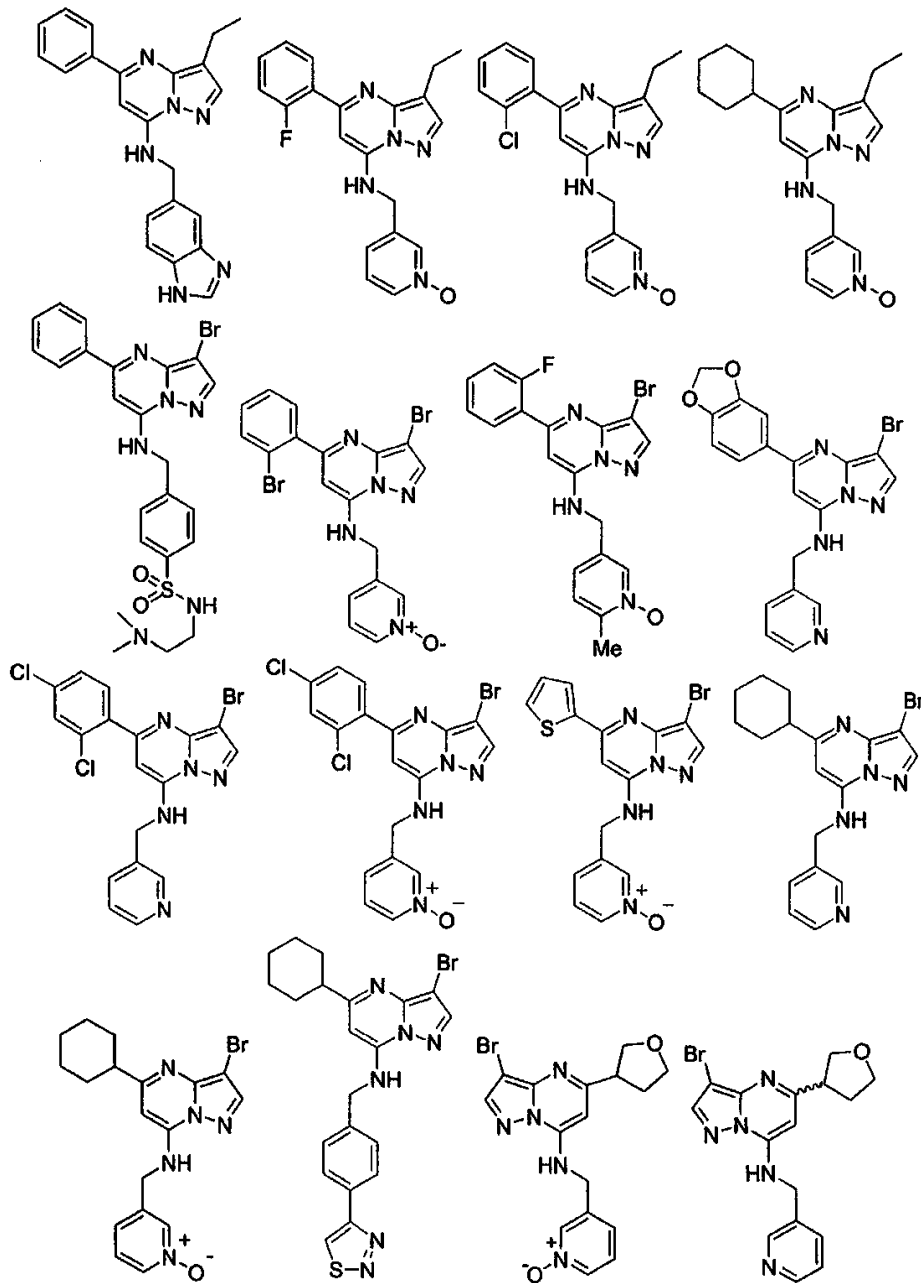
[0057]



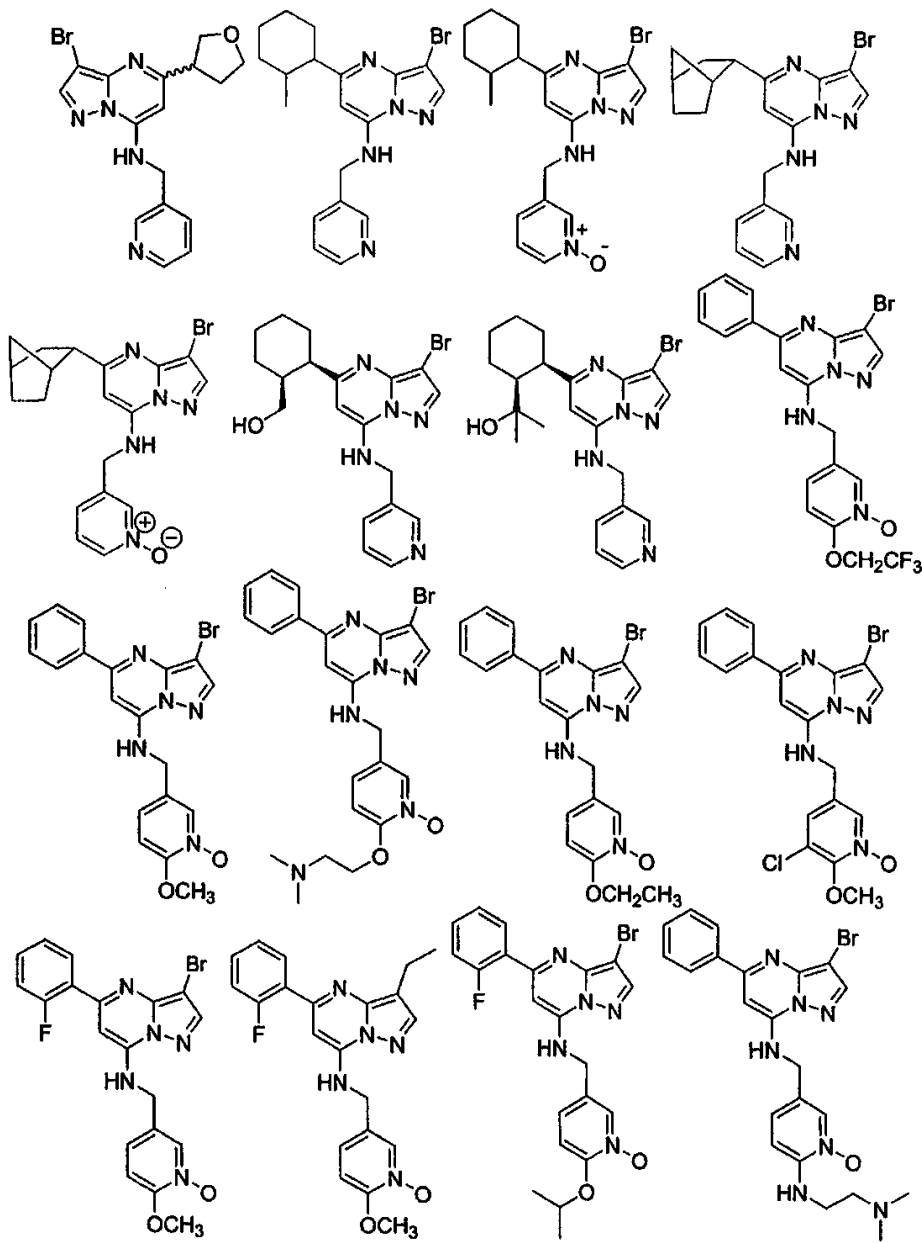
[0058]



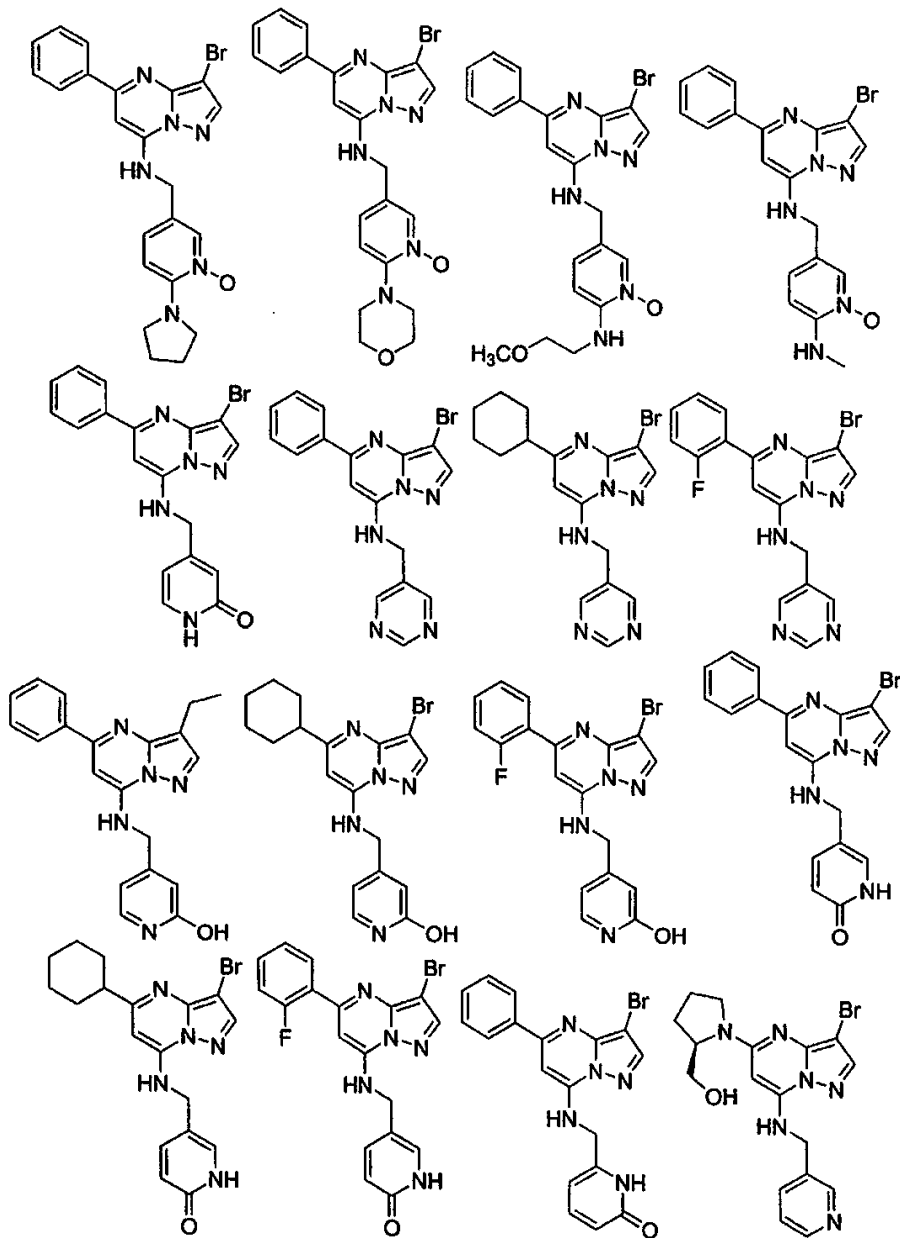
[0059]



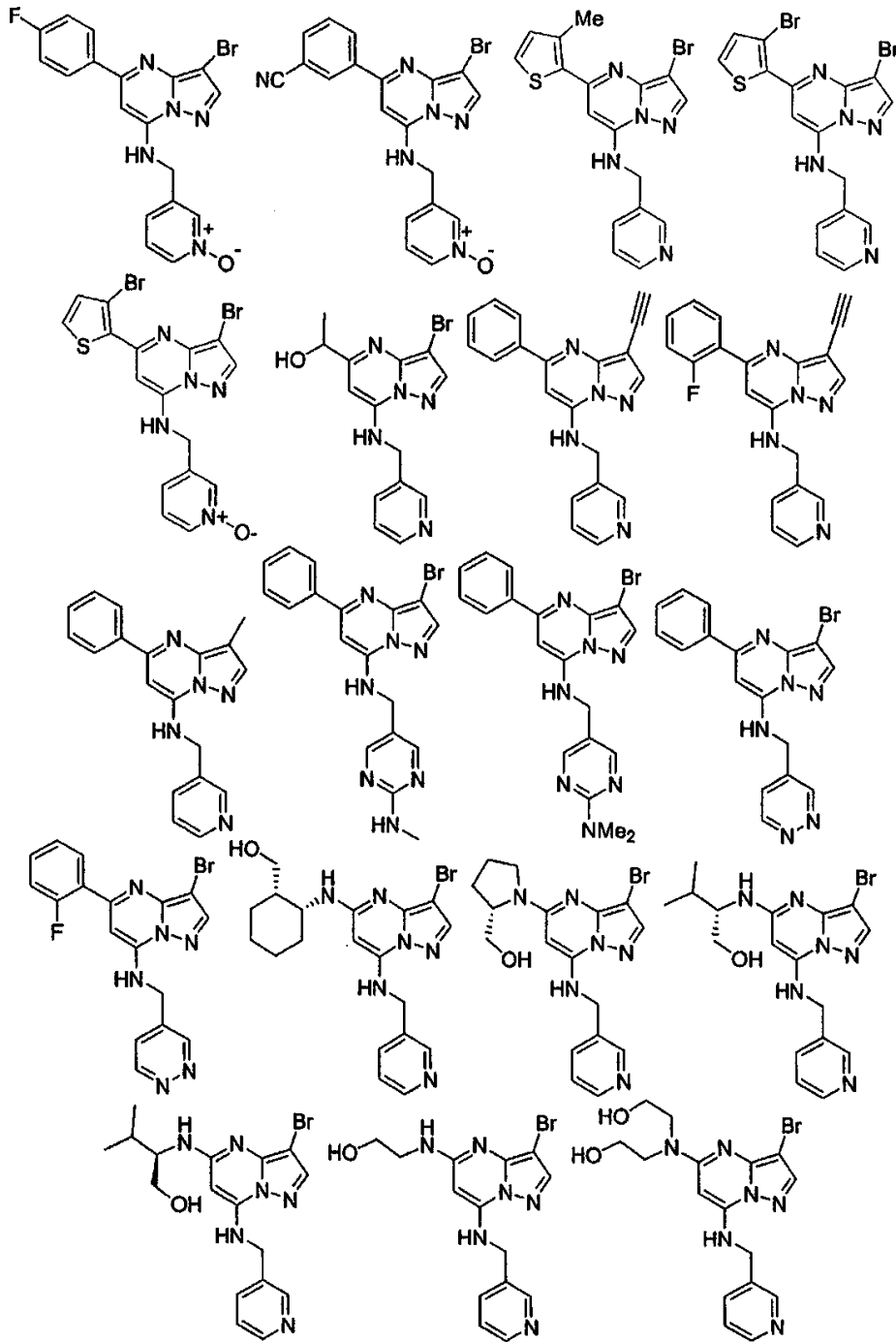
[0060]



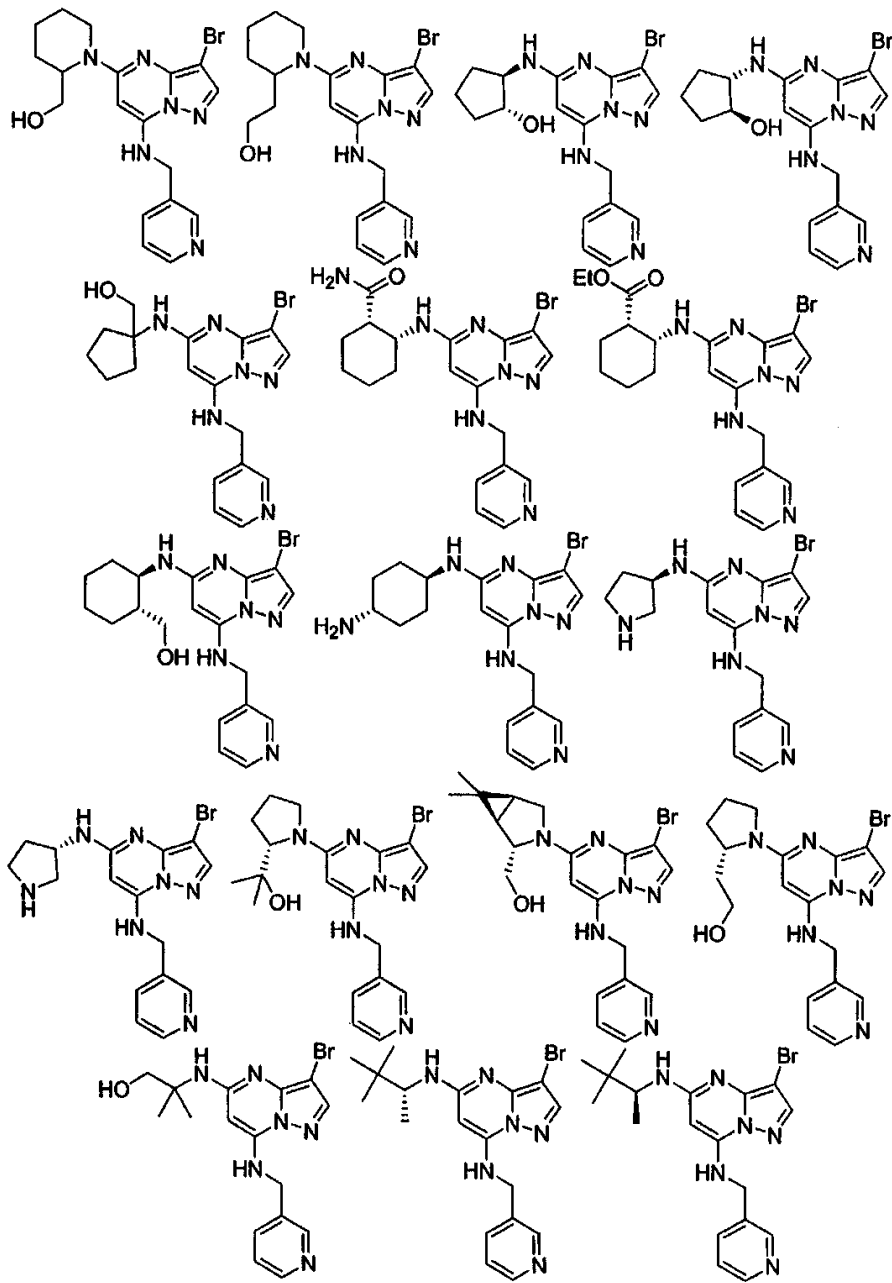
[0061]



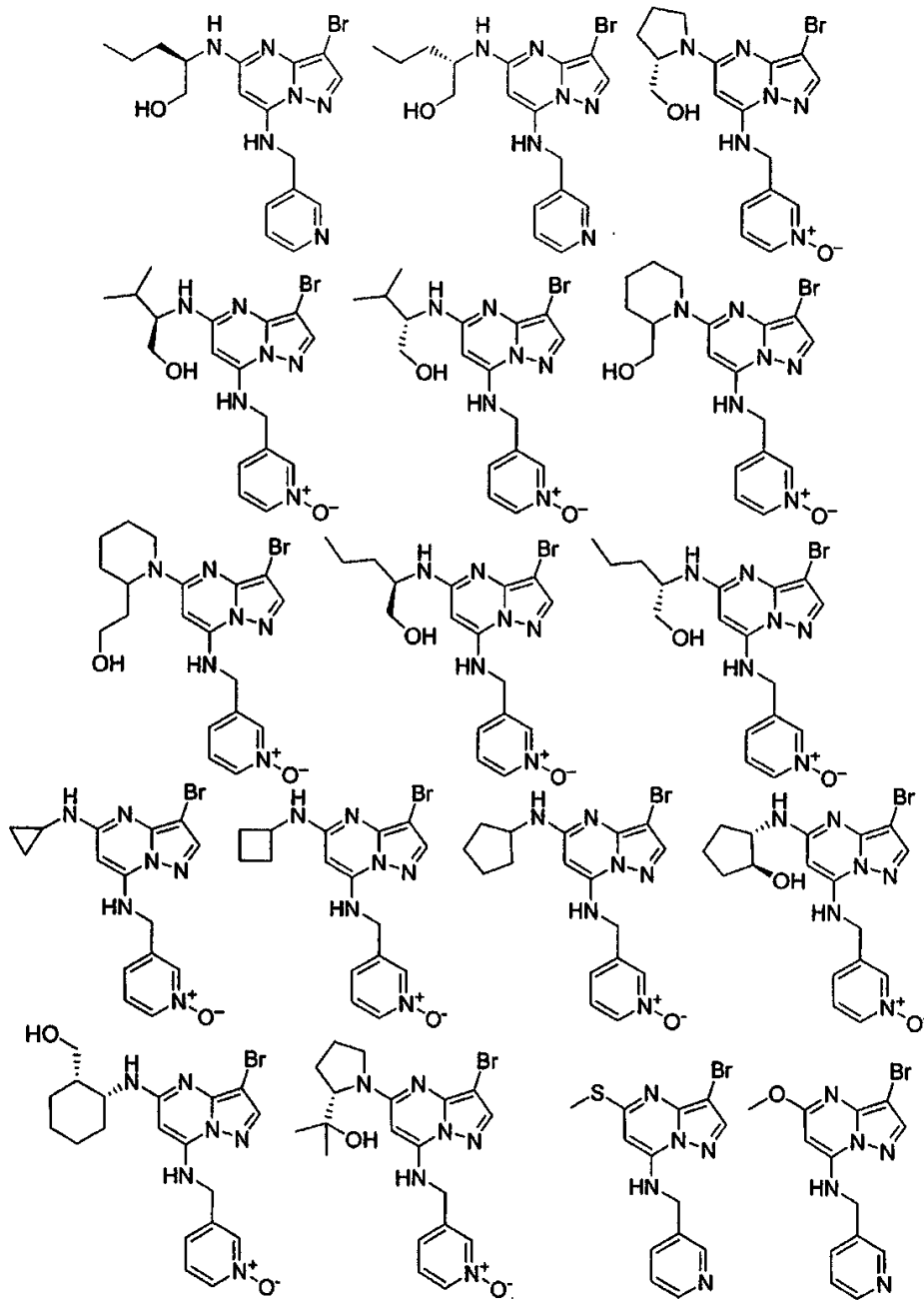
[0062]



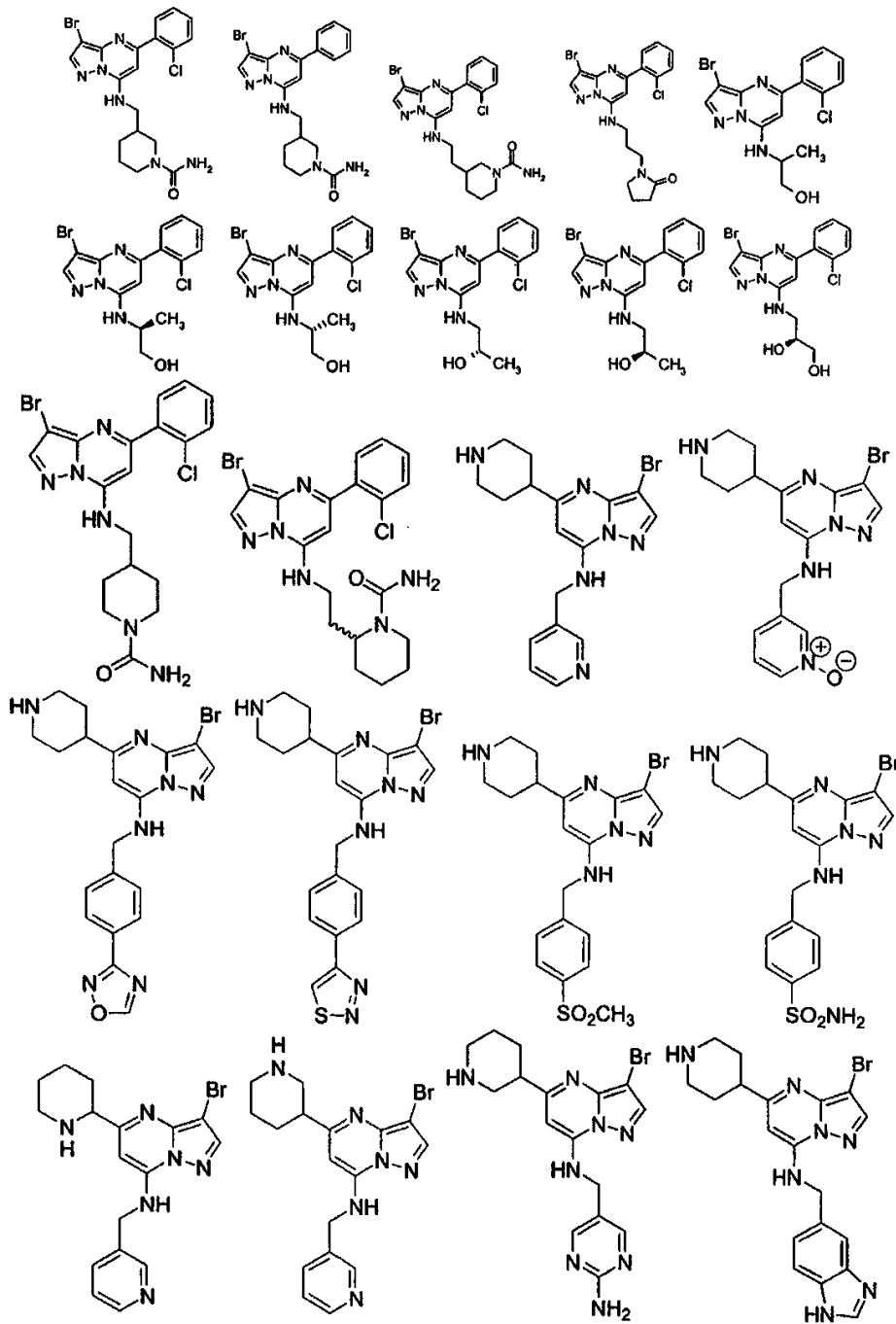
[0063]



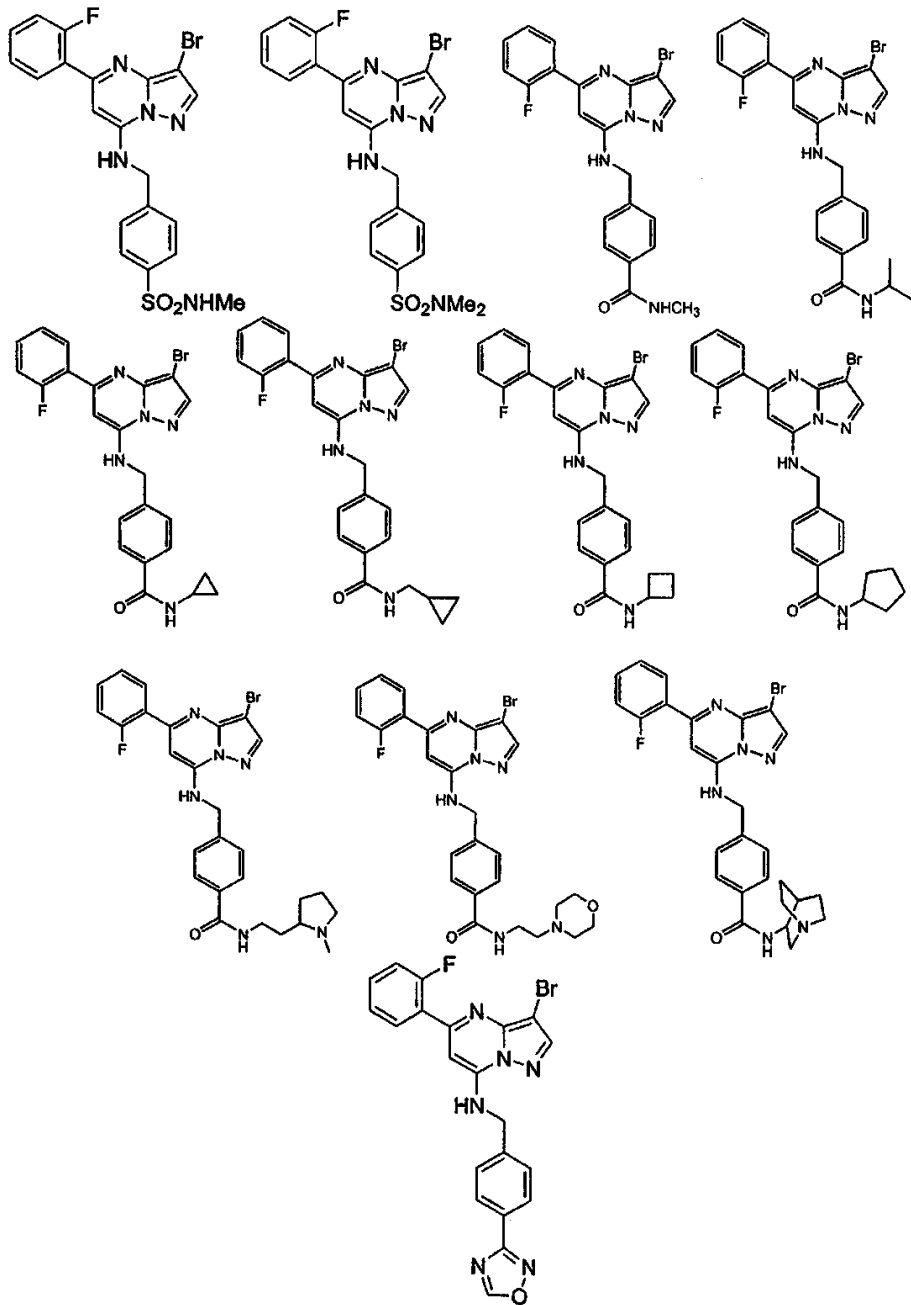
[0064]

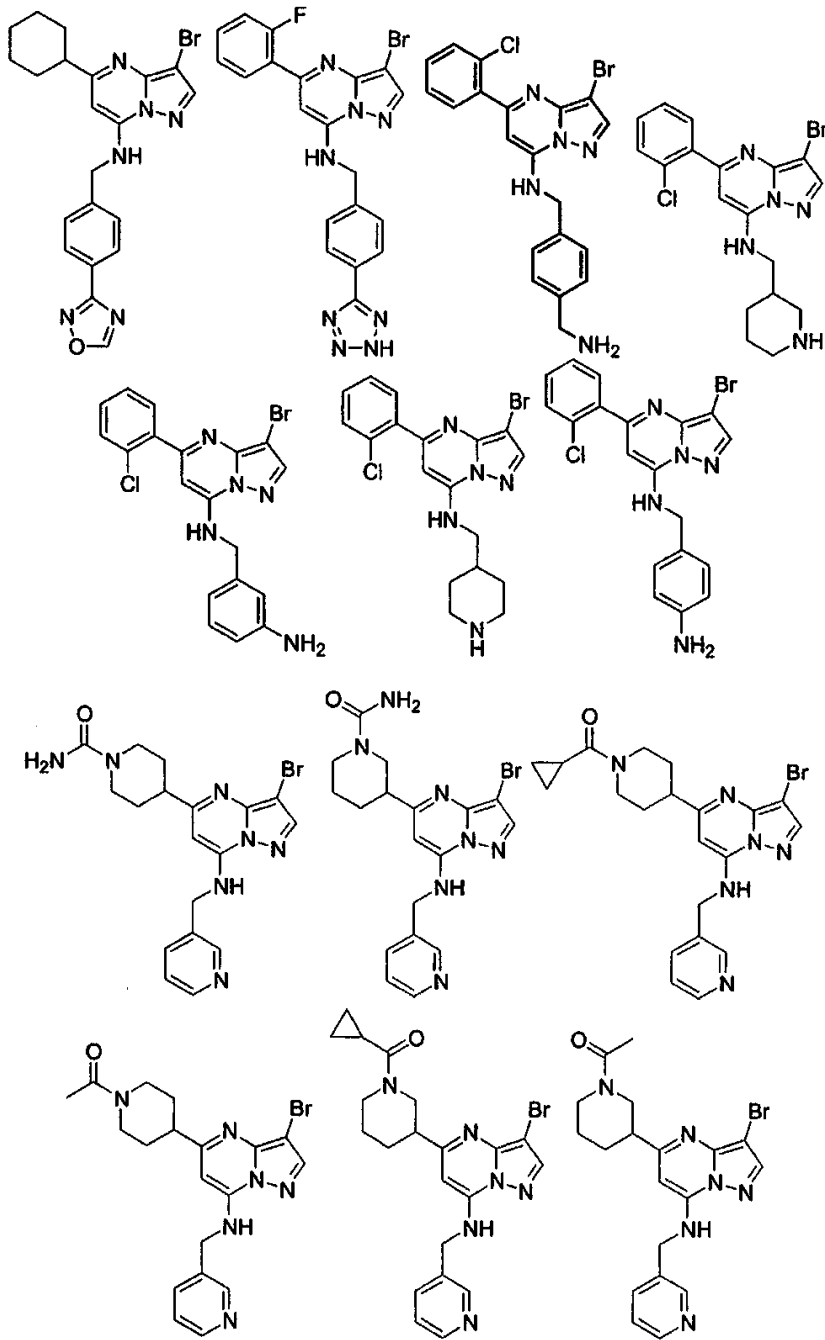


[0065]

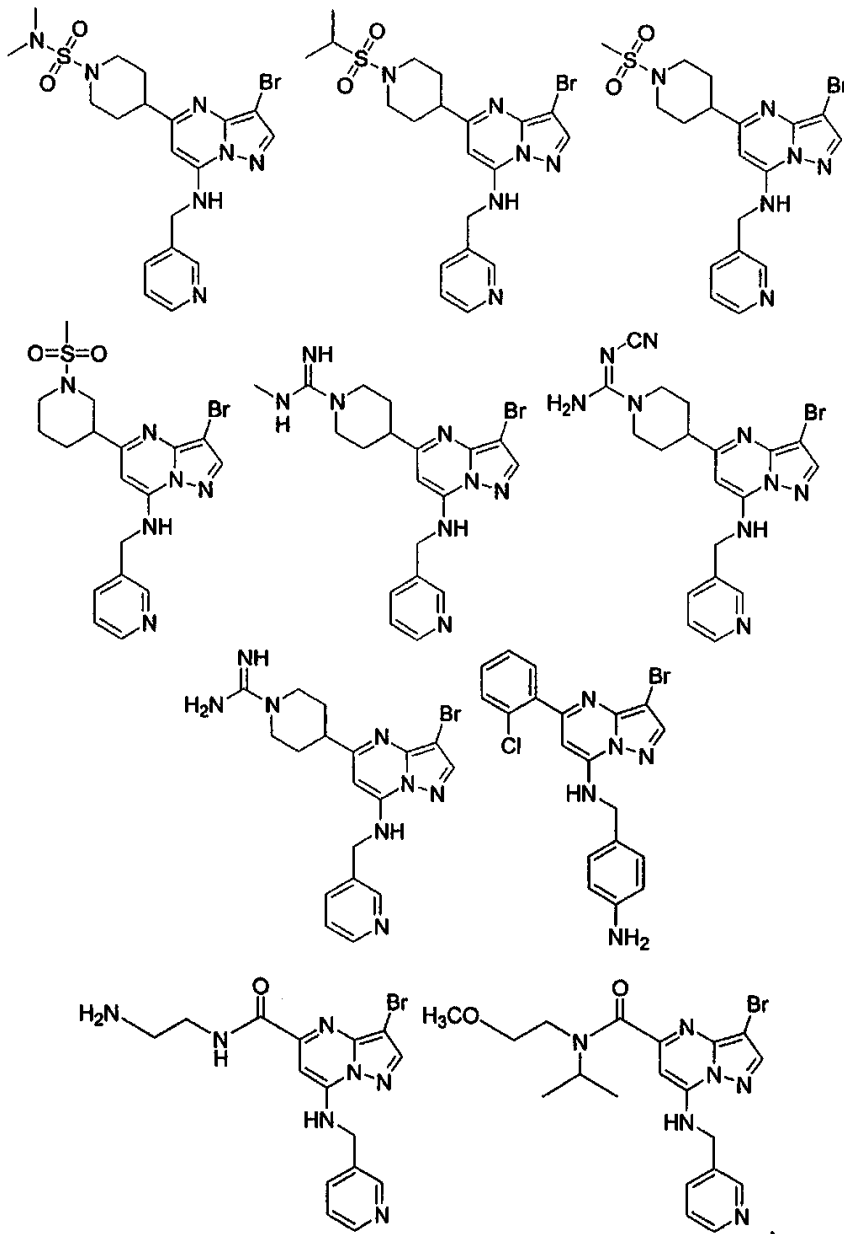


[0066]





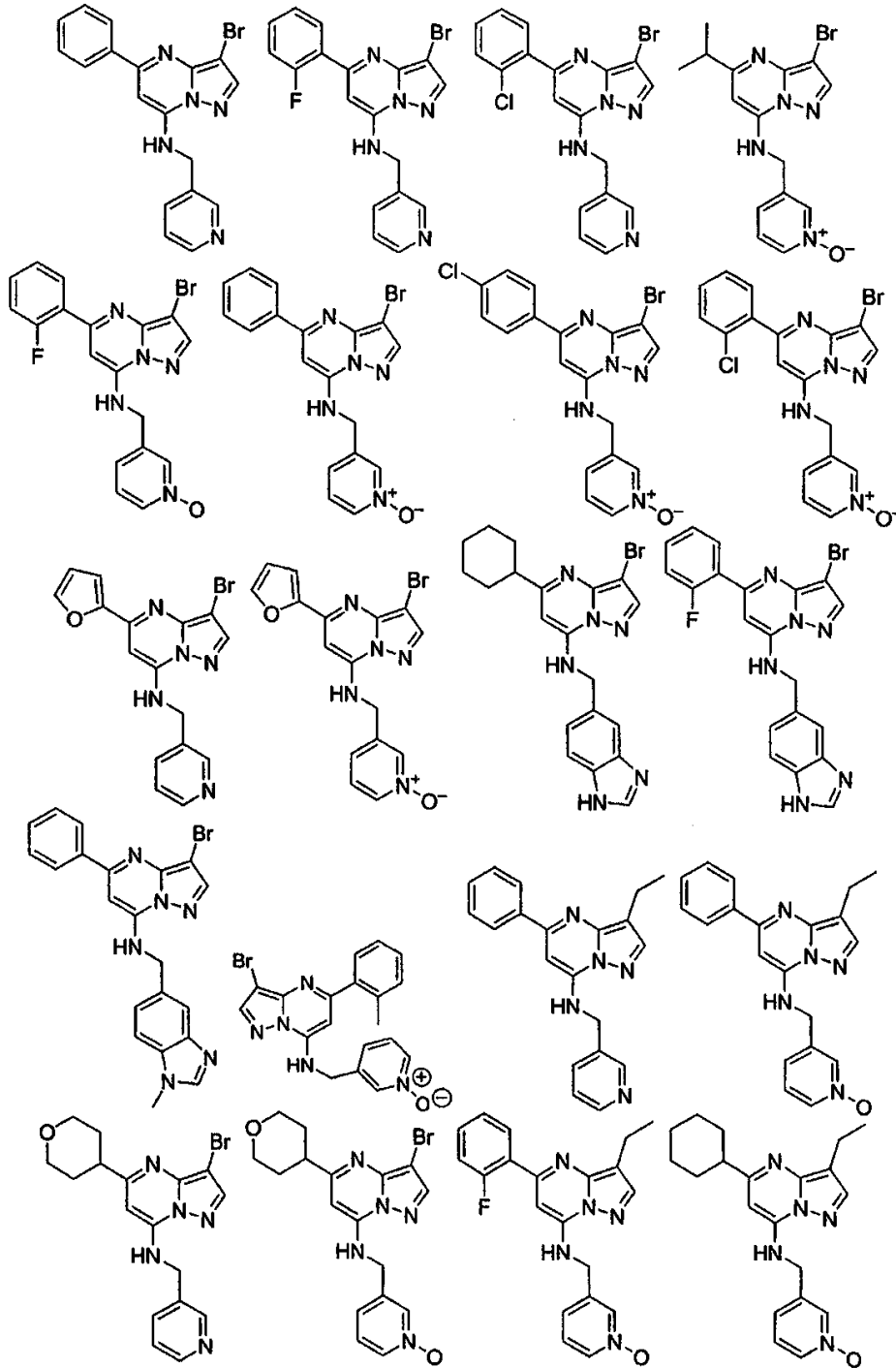
[0068]



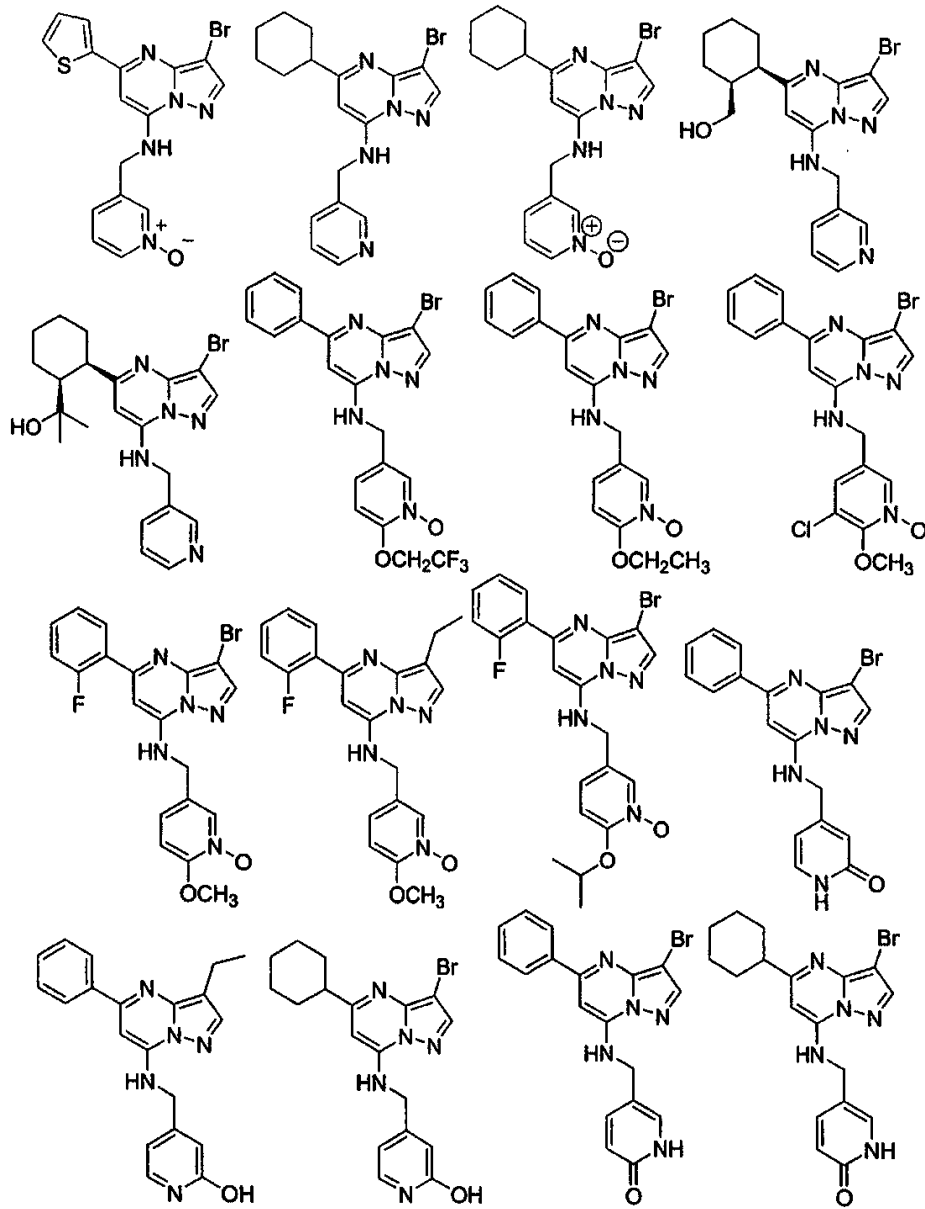
[0069]

[0070]

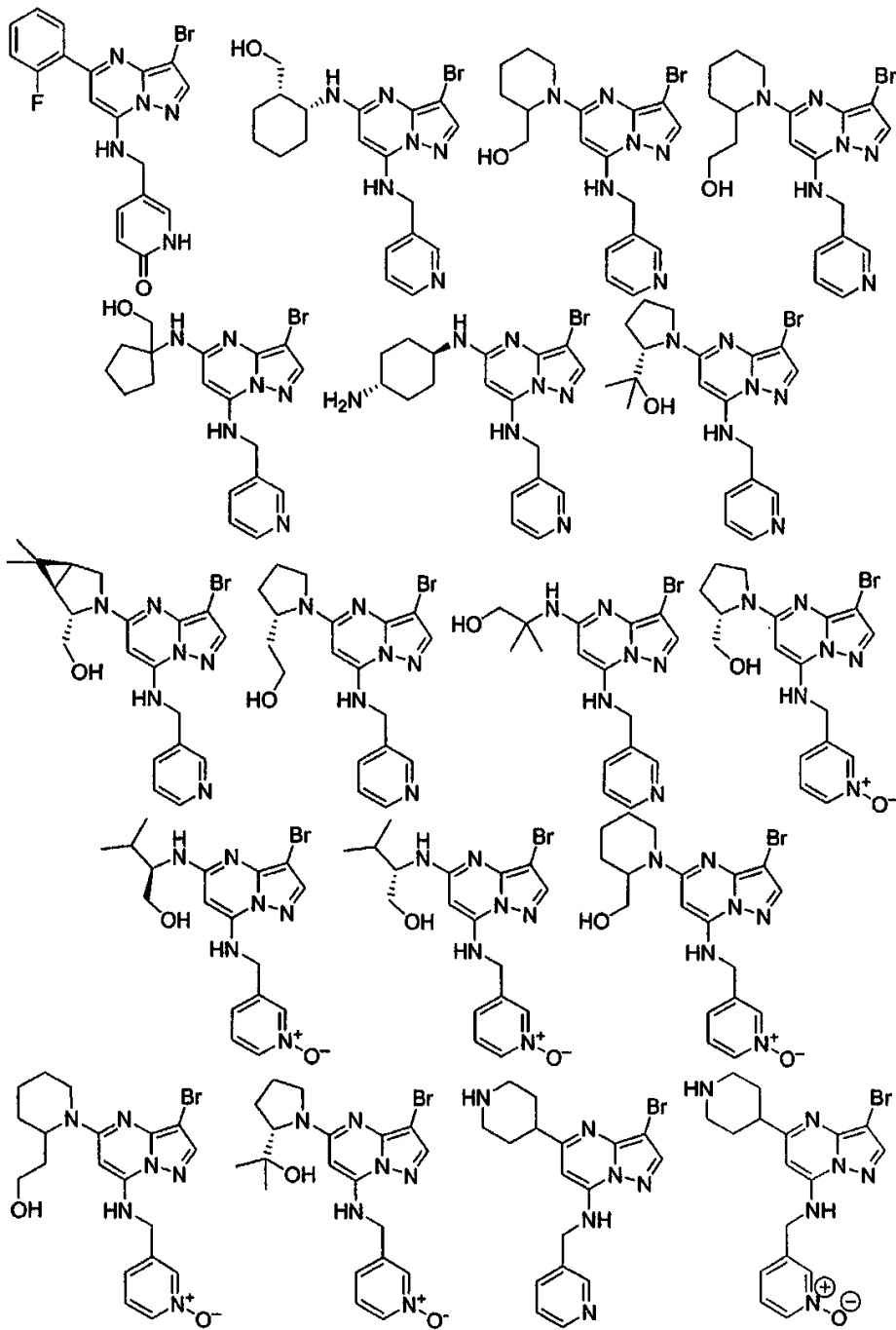
본 발명의 다른 양태는 약 0.0001 μ M 내지 약 0.5 μ M의 CDK2 억제 활성을 나타낸 하기 화합물을 기술한다:



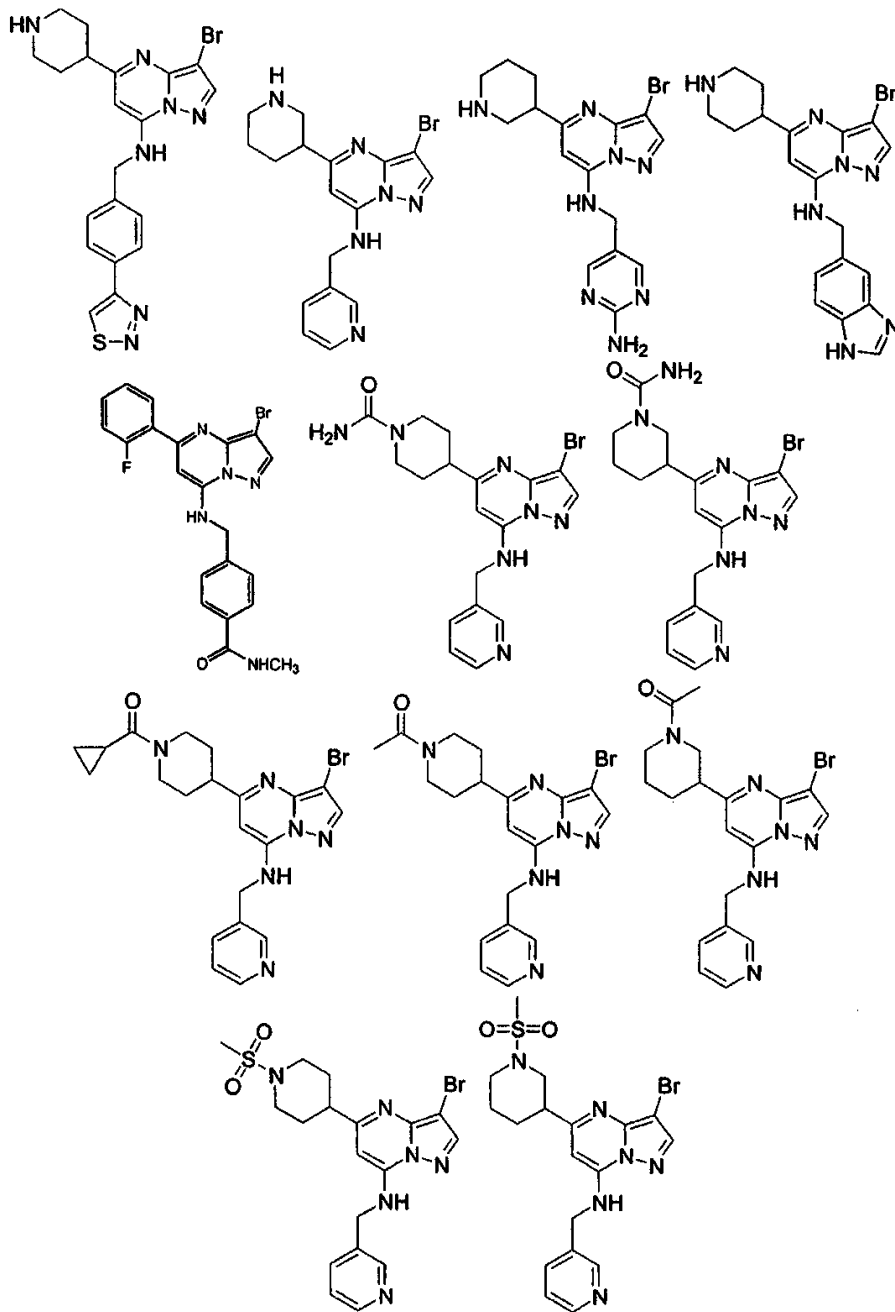
[0071]



[0072]

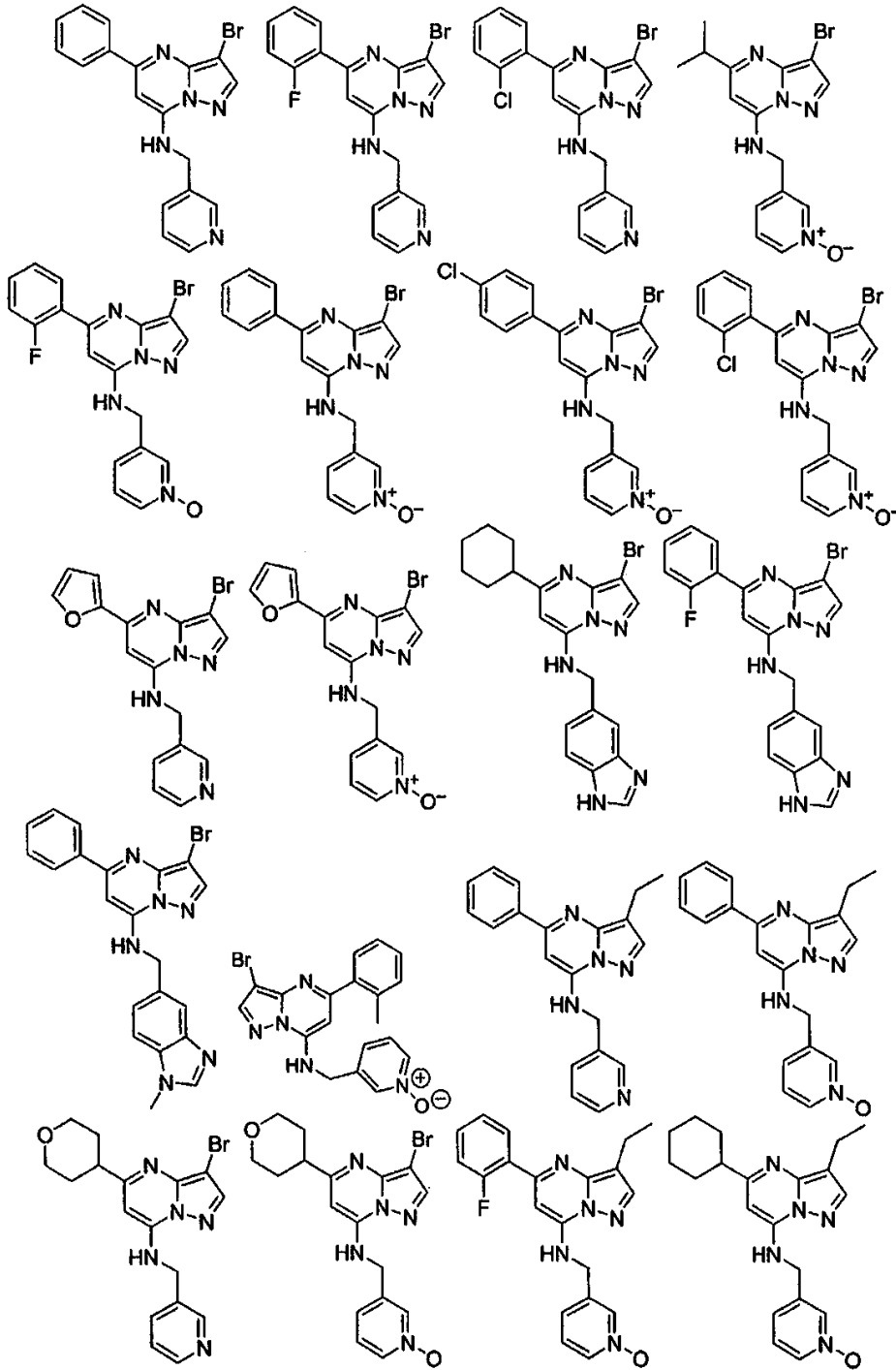


[0073]

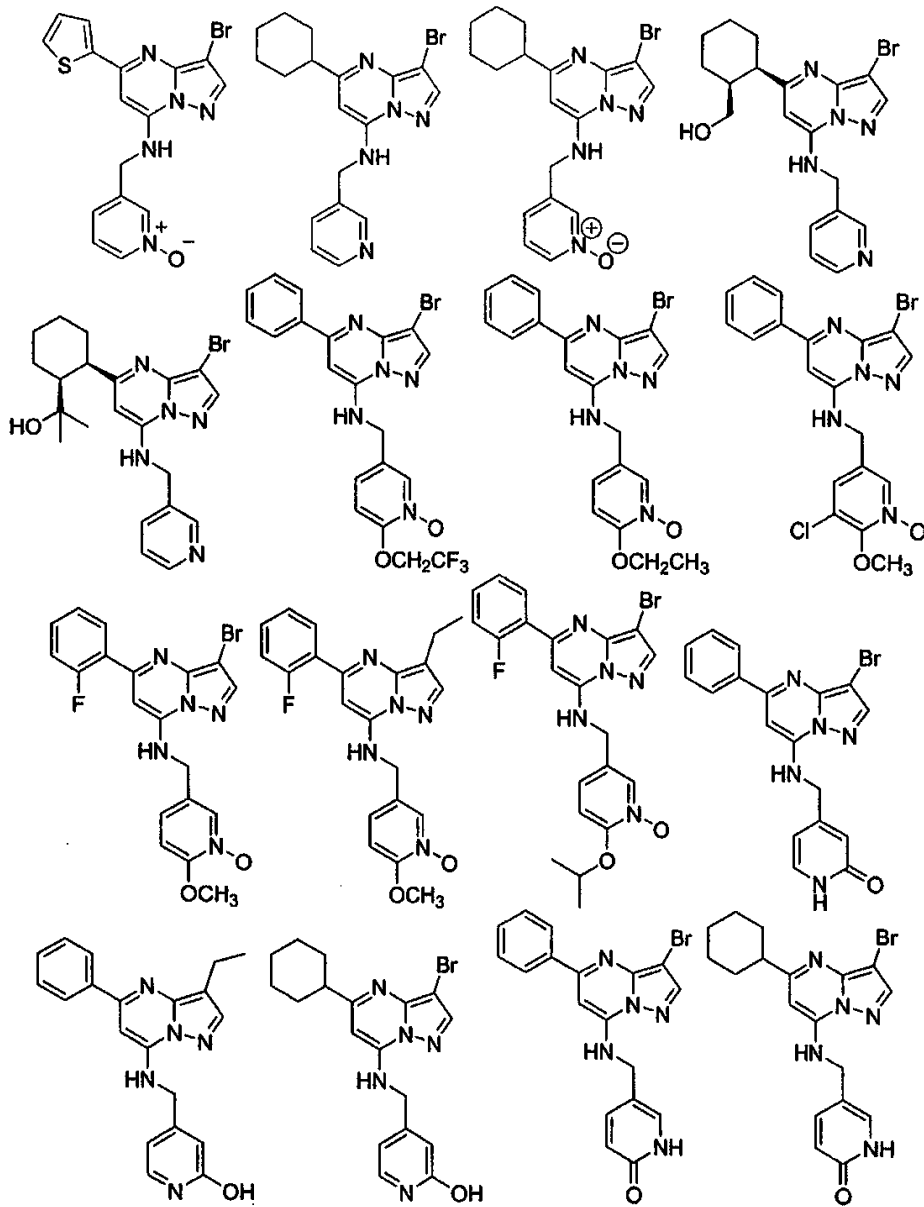


[0074]

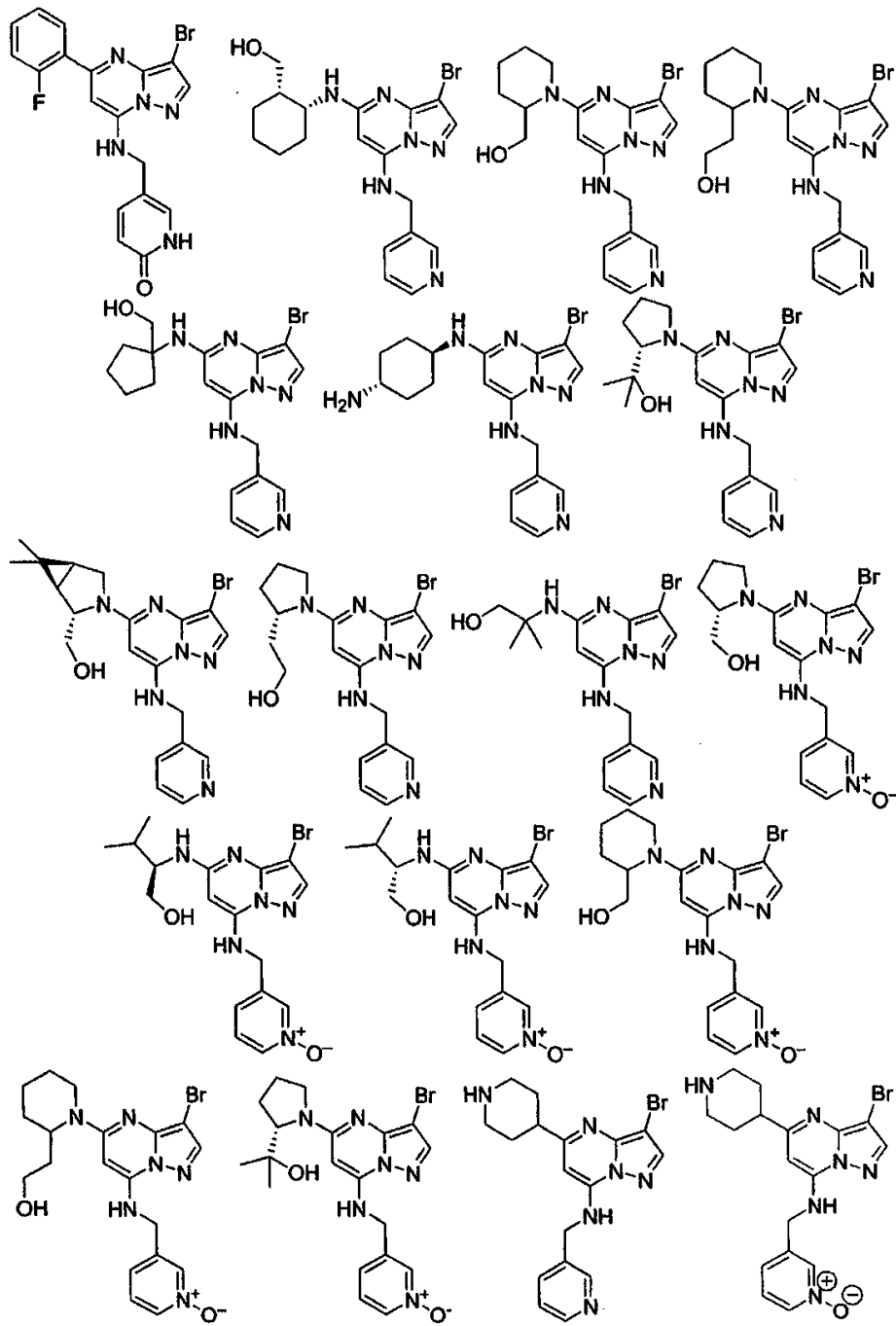
[0075] 본 발명의 다른 양태는 약 0.0001 μ M 내지 약 0.1 μ M의 CDK2 억제 활성을 나타낸 하기 화합물을 기술한다:



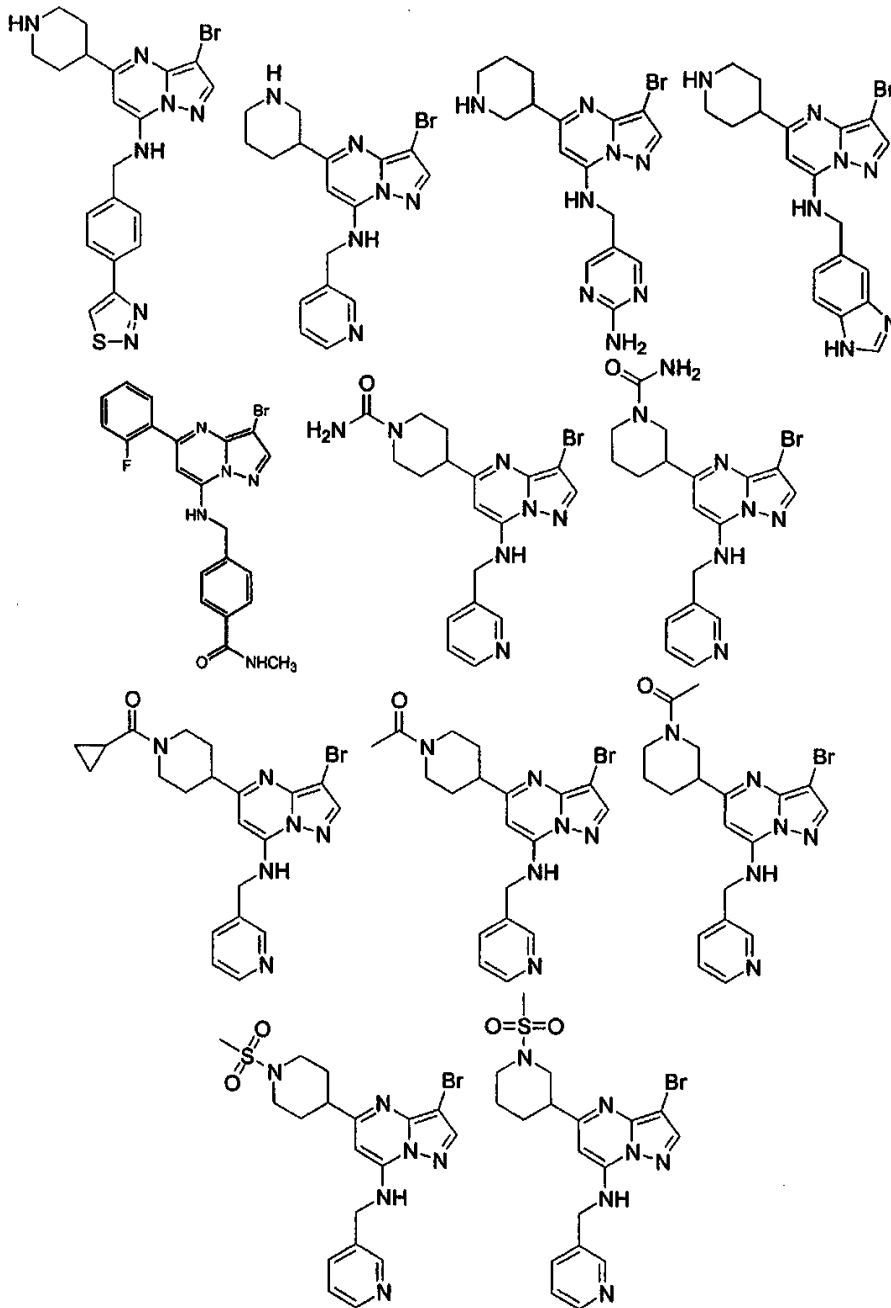
[0076]



[0077]



[0078]



[0079]

[0080]

위에서 사용한 바와 같이, 및 본원 명세서 전반에 걸쳐서, 다음 용어들은, 달리 나타내지 않는 한, 하기한 의미를 갖는 것으로 해석되어야 한다:

[0081]

"환자"는 사람 및 동물 둘 다를 포함한다.

[0082]

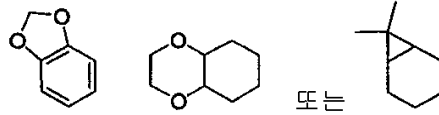
"포유류"는 사람 및 기타 포유동물을 의미한다.

[0083]

"알킬"은쇄중의 탄소수가 약 1 내지 약 20개이고 직쇄 또는 측쇄일 수 있는 지방족 탄화수소 그룹을 의미한다. 바람직한 알킬 그룹은쇄중의 탄소수가 약 1 내지 약 12개이다. 보다 바람직한 알킬 그룹은쇄중의 탄소수가 약 1 내지 약 6개이다. 측쇄는, 메틸, 에틸 또는 프로필과 같은 하나 이상의 저급 알킬 그룹이 선형 알킬 쇠에 부착된 것을 의미한다. "저급 알킬"은 직쇄 또는 측쇄일 수 있는쇄중의 탄소수가 약 1 내지 약 6개인 그룹을 의미한다. 용어 "치환된 알킬"은, 알킬 그룹이 동일하거나 상이할 수 있는 하나 이상의 치환체에 의해 치환될 수 있음을 의미하며, 여기서 각각의 치환체는 할로, 알킬, 아릴, 사이클로알킬, 시아노, 하이드록시, 알콕시, 알킬티오, 아미노, -NH(알킬), -NH(사이클로알킬), -N(알킬)₂, 카복시 및 -C(O)O-알킬로 이루어진 그룹으로부터 독립적으로 선택된다. 적합한 알킬 그룹의 비제한적인 예는 메틸, 에틸, n-프로필, 이소프로필 및 t-부틸을 포함한다.

- [0084] "알킬닐"은 하나 이상의 탄소-탄소 삼중결합을 포함하고 직쇄 또는 측쇄일 수 있으며 쇠중의 탄소수가 약 2 내지 약 15개인 지방족 탄화수소 그룹을 의미한다. 바람직한 알킬닐 그룹은 쇠중의 탄소수가 약 2 내지 약 12 개이며, 보다 바람직하게는 쇠중의 탄소수가 약 2 내지 약 4개이다. 측쇄는, 하나 이상의 저급 알킬 그룹, 예를 들면, 메틸, 에틸 또는 프로필이 선형 알킬닐 쇠에 부착되는 것을 의미한다. "저급 알킬닐"은 직쇄 또는 측쇄일 수 있는 쇠내의 탄소수가 약 2 내지 약 6개임을 의미한다. 적합한 알킬닐 그룹의 비제한적인 예는 에틸닐, 프로필닐, 2-부틸닐 및 3-메틸부틸닐을 포함한다. 용어 "치환된 알킬닐"은, 알킬닐 그룹이 동일하거나 상이할 수 있는 하나 이상의 치환체에 의해 치환될 수 있음을 의미하며, 여기서 치환체 각각은 알킬, 아릴 및 사이클로알킬로 이루어진 그룹으로부터 독립적으로 선택된다.
- [0085] "아릴"은 탄소수가 약 6 내지 약 14개, 바람직하게는 약 6 내지 약 10개인 방향족 단환(모노사이클릭 환) 또는 다환(멀티사이클릭 환) 시스템을 의미한다. 아릴 그룹은 동일하거나 상이할 수 있는 하나 이상의 "환 시스템 치환체"에 의해 임의 치환될 수 있으며, 본원에서 정의한 바와 같다. 적합한 아릴 그룹의 비제한적인 예는 페닐 및 나프틸을 포함한다.
- [0086] "헤테로아릴"은 환 원자수가 약 5 내지 약 14개, 바람직하게는 약 5 내지 약 10개인 단환 또는 다환 시스템을 의미하며, 여기서 환 원자들 중의 하나 이상은 탄소 이외의 원소, 예를 들면, 질소, 산소 또는 황의 단독 또는 조합이다. 바람직한 헤테로아릴은 환 원자수가 약 5 내지 약 6개이다. "헤테로아릴"은 동일하거나 상이할 수 있는 하나 이상의 "환 시스템 치환체"에 의해 임의 치환될 수 있으며, 본원에서 정의한 바와 같다. 헤테로아릴 근(root) 명칭 앞의 접두사인 아자, 옥사 또는 티아는, 적어도 하나의 질소, 산소 또는 황 원자 각각이 환 원자로서 존재함을 의미한다. 헤테로아릴의 질소 원자는 상응하는 N-옥사이드에 임의 산화될 수 있다. 적합한 헤테로아릴의 비제한적인 예는 피리딜, 피라지닐, 푸라닐, 티에닐, 피리미디닐, 피리돈(N-치환된 피리돈 포함), 이속사졸릴, 이소티아졸릴, 옥사졸릴, 티아졸릴, 피라졸릴, 푸라자닐, 피롤릴, 피라졸릴, 트리아졸릴, 1,2,4-티아디아졸릴, 피라지닐, 피라디지닐, 퀴놀살리닐, 프탈라지닐, 옥소인돌릴, 이미다조[1,2-a]피리디닐, 이미다조[2,1-b]티아졸릴, 벤조푸라자닐, 인돌릴, 아자인돌릴, 벤즈이미다졸릴, 벤조티에닐, 퀴놀리닐, 이미다졸릴, 티에노피리딜, 퀴나졸리닐, 티에노피리미딜, 피롤로피리딜, 이미다조피리딜, 이소퀴놀리닐, 벤조아자인돌릴, 1,2,4-트리아지닐, 벤조티아졸릴 등을 포함한다. 용어 "헤테로아릴"은 또한 예를 들면, 테트라하이드로이소퀴놀릴, 테트라하이드로퀴놀릴 등과 같은 부분 포화된 헤테로아릴 잔기를 의미한다.
- [0087] "아르알킬" 또는 "아릴알킬"은, 아릴 및 알킬이 상기한 바와 같은 아릴-알킬 그룹을 의미한다. 바람직한 아르알킬은 저급 알킬 그룹을 포함한다. 적합한 아르알킬 그룹의 비제한적인 예는 벤질, 2-벤에틸 및 나프탈레닐메틸을 포함한다. 모 잔기에 대한 결합은 알킬을 통해 이루어진다.
- [0088] "알킬아릴"은, 알킬 및 아릴이 상기한 바와 같은 알킬-아릴 그룹을 의미한다. 바람직한 알킬아릴은 저급 알킬 그룹을 포함한다. 적합한 알킬아릴 그룹의 비제한적인 예는 톨릴이다. 모 잔기에 대한 결합은 아릴을 통해 이루어진다.
- [0089] "사이클로알킬"은, 탄소수가 약 3 내지 약 10개, 바람직하게는 약 5 내지 약 10개인 비-방향족 단환 또는 다환 시스템을 의미한다. 바람직한 사이클로알킬 환은 약 5 내지 약 7개의 환 원자를 포함한다. 사이클로알킬은 동일하거나 상이할 수 있고 상기한 바와 같은 하나 이상의 "환 시스템 치환체"에 의해 임의 치환될 수 있다. 적합한 단환 사이클로알킬의 비제한적인 예는 사이클로프로필, 사이클로펜틸, 사이클로헥실, 사이클로헥틸 등을 포함한다. 적합한 다환 사이클로알킬의 비제한적인 예는 1-데칼리닐, 노르보르닐, 아다만틸 등 뿐만 아니라, 예를 들면, 인다닐, 테트라하이드로나프틸 등과 같은 부분 포화된 다환 사이클로알킬을 포함한다.
- [0090] "할로겐"은 불소, 염소, 브롬 또는 요오드를 의미한다. 바람직하게는 불소, 염소 및 브롬이다.
- [0091] "환 시스템 치환체"는 방향족 또는 비-방향족 환 시스템[예를 들면, 환 시스템상의 이용 가능한 수소를 대체한다]에 부착된 치환체를 의미한다. 환 시스템 치환체는 동일하거나 상이할 수 있고, 각각 아릴, 알케닐, 알킬닐, 아릴, 헤테로아릴, 아르알킬, 알킬아릴, 헤테로아르알킬, 헤테로아릴알케닐, 헤테로아릴알킬닐, 알킬헤테로아릴, 하이드록시, 하이드록시알킬, 알콕시, 아릴옥시, 아르알콕시, 아실, 아로일, 할로, 니트로, 시아노, 카복시, 알콕시카보닐, 아릴옥시카보닐, 아르알콕시카보닐, 알킬설포닐, 아릴설포닐, 헤테로아릴설포닐, 알킬티오, 아릴티오, 헤테로아릴티오, 아르알킬티오, 헤테로아르알킬티오, 사이클로알킬, 헤테로사이클릭, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(알킬)$, Y_1Y_2N- , $Y_1Y_2N-알킬-$, $Y_1Y_2NC(O)-$, $Y_1Y_2NSO_2-$ 및 $-SO_2NY_1Y_2$ 로 이루어진 그룹으로부터 독립적으로 선택되고, 여기서, Y_1 및 Y_2 는 동일하거나 상이할 수 있고, 수소, 알킬, 아릴, 사이클로알킬 및 아르알킬로 이루어진 그룹으로부터 독립적으로 선택된다. "환 시스템 치환체"는 또한 환 시스템상에 2개

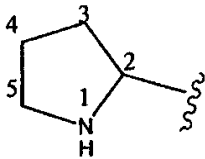
의 인접한 탄소 원자상에 2개의 유용한 수소(각각의 탄소상에 하나의 H)로 동시에 대체된 단일 잔기를 의미할



수 있다. 이러한 잔기의 예는 예를 들면, 메틸렌디옥시, 에틸렌디옥시, $-C(CH_3)_2-$ 등이다.

[0092] "헤테로사이클릴"은, 환 원자수가 약 3 내지 약 10개, 바람직하게는 약 5 내지 약 10개인 비-방향족 포화된 단 환 또는 다환 시스템을 의미하며, 환 시스템내의 원자들 중의 하나 이상은 탄소 이외의 원소, 예를 들면, 질소, 산소 또는 황의 단독 또는 조합이다. 환 시스템내에는 인접한 산소 및/또는 황 원자가 존재하지 않는다. 바람직한 헤테로사이클릴은 약 5 내지 약 6개의 환 원자를 포함한다. 헤테로사이클릴 근 명칭(root name) 앞의 접두사인 아자, 옥사 또는 티아는, 적어도 하나의 질소, 산소 또는 황 원자가 각각 환 원자로서 존재함을 의미한다. 헤테로사이클릴 환내의 특정한 -NH는, 예를 들면, -N(Boc), -N(CBz), -N(Tos) 그룹 등으로서 보호되어 존재할 수 있으며; 이러한 보호된 잔기는 또한 본 발명의 일부로서 고려된다. 헤테로사이클릴은 동일하거나 상이할 수 있고, 본원에서 정의한 바와 같은 하나 이상의 "환 시스템 치환체"에 의해 임의 치환될 수 있다. 헤테로사이클릴의 질소 또는 황 원자는 상응하는 N-옥사이드, S-옥사이드 또는 S,S-디옥사이드로 임의 산화될 수 있다. 적합한 단환 헤테로사이클릴 환의 비제한적인 예는 피페리딘, 피롤리딘, 피페라지닐, 모르폴리닐, 티오모르폴리닐, 티아졸리딘, 1,4-디옥사닐, 테트라하이드로푸라닐, 테트라하이드로티오펜, 락탐, 락톤 등을 포함한다.

[0093] 본 발명의 헤테로원자 함유 환 시스템에서, N, O 또는 S에 인접한 탄소 원자상에는 하이드록시 그룹이 존재하지 않을 뿐만 아니라, 또 다른 헤테로원자에 인접한 탄소상에는 N 또는 S 그룹도 존재하지 않는다. 따라서, 다음 환에서:



[0094]
[0095] 2번 및 5번 탄소에 직접 결합된 -OH 그룹은 존재하지 않는다.



[0096] 예를 들어 잔기: 또는 와 같은 도우도머 형태도 본 발명의 특정 양태에서 동일한 것으로 고려되어야 함을 주목한다.

[0097] "알킬닐알킬"은, 알킬닐 및 알킬이 위에서 기술한 바와 같은 알킬닐-알킬 그룹을 의미한다. 바람직한 알킬닐알킬은 저급 알킬닐 및 저급 알킬 그룹을 포함한다. 모 잔기에 대한 결합은 알킬을 통해 이루어진다. 적합한 알킬닐알킬 그룹의 비제한적인 예는 프로파길메틸을 포함한다.

[0098] "헤테로아르알킬"은, 헤테로아릴 및 알킬이 위에서 기술한 바와 같은 헤테로아릴-알킬 그룹을 의미한다. 바람직한 헤테로아르알킬은 저급 알킬 그룹을 포함한다. 적합한 아르알킬 그룹의 비제한적인 예는 피리딜메틸 및 퀴놀린-3-일메틸을 포함한다. 모 잔기에 대한 결합은 알킬을 통해 이루어진다.

[0099] "하이드록시알킬"은, 알킬이 위에서 정의한 바와 같은 HO-알킬 그룹을 의미한다. 바람직한 하이드록시알킬은 저급 알킬을 포함한다. 적합한 하이드록시 알킬 그룹의 비제한적인 예는 하이드록시메틸 및 2-하이드록시에틸을 포함한다.

[0100] "아실"은, 각종 그룹이 위에서 기술한 바와 같은 H-C(O)-, 알킬-C(O)- 또는 사이클로알킬-C(O)- 그룹을 의미한다. 모 잔기에 대한 결합은 카보닐을 통해 이루어진다. 바람직한 아실은 저급 알킬을 포함한다. 적합한 아실 그룹의 비제한적인 예는 포르밀, 아세틸 및 프로파노일을 포함한다.

[0101] "아로일"은, 아릴 그룹이 상기한 바와 같은 아릴-C(O)- 그룹을 의미한다. 모 잔기에 대한 결합은 카보닐을 통해 이루어진다. 적합한 그룹의 비제한적인 예는 벤조일 및 1-나프토일을 포함한다.

[0102] "알콕시"는, 알킬 그룹이 상기한 바와 같은 알킬-O- 그룹을 의미한다. 적합한 알콕시 그룹의 비제한적인 예는

메톡시, 에톡시, n-프로폭시, 이소프로폭시 및 n-부톡시를 포함한다. 모 잔기에 대한 결합은 에테르 산소를 통해 이루어진다.

- [0103] "아릴옥시"는, 아릴 그룹이 상기한 바와 같은 아릴-O- 그룹을 의미한다. 적합한 아릴옥시 그룹의 비제한적인 예는 페녹시 및 나프톡시를 포함한다. 모 잔기에 대한 결합은 에테르 산소를 통해 이루어진다.
- [0104] "아르알킬옥시"는, 아르알킬 그룹이 상기한 바와 같은 아르알킬-O- 그룹을 의미한다. 적합한 아르알킬옥시 그룹의 비제한적인 예는 벤질옥시 및 1- 또는 2-나프탈렌메톡시를 포함한다. 모 잔기에 대한 결합은 에테르 산소를 통해 이루어진다.
- [0105] "알킬티오"는, 알킬 그룹이 상기한 바와 같은 알킬-S- 그룹을 의미한다. 적합한 알킬티오 그룹의 비제한적인 예는 메틸티오 및 에틸티오를 포함한다. 모 잔기에 대한 결합은 황을 통해 이루어진다.
- [0106] "아릴티오"는, 아릴 그룹이 상기한 바와 같은 아릴-S- 그룹을 의미한다. 적합한 아릴티오 그룹의 비제한적인 예는 페닐티오 및 나프틸티오를 포함한다. 모 잔기에 대한 결합은 황을 통해 이루어진다.
- [0107] "아르알킬티오"는, 아르알킬 그룹이 상기한 바와 같은 아르알킬-S- 그룹을 의미한다. 적합한 아르알킬티오 그룹의 비제한적인 예는 벤질티오이다. 모 잔기에 대한 결합은 황을 통해 이루어진다.
- [0108] "알콕시카보닐"은 알킬-O-CO- 그룹을 의미한다. 적합한 알콕시카보닐 그룹의 비제한적인 예는 메톡시카보닐 및 에톡시카보닐을 포함한다. 모 잔기에 대한 결합은 카보닐을 통해 이루어진다.
- [0109] "아릴옥시카보닐"은 아릴-O-C(O)- 그룹을 의미한다. 적합한 아릴옥시카보닐 그룹의 비제한적인 예는 페녹시카보닐 및 나프톡시카보닐을 포함한다. 모 잔기에 대한 결합은 카보닐을 통해 이루어진다.
- [0110] "아르알콕시카보닐"은 아르알킬-O-C(O)- 그룹을 의미한다. 적합한 아르알콕시카보닐 그룹의 비제한적인 예는 벤질옥시카보닐이다. 모 잔기에 대한 결합은 카보닐을 통해 이루어진다.
- [0111] "알킬설포닐"은 알킬-S(O₂)- 그룹을 의미한다. 바람직한 그룹은, 알킬 그룹이 저급 알킬인 그룹이다. 모 잔기에 대한 결합은 설포닐을 통해 이루어진다.
- [0112] "아릴설포닐"은 아릴-S(O₂)- 그룹을 의미한다. 모 잔기에 대한 결합은 설포닐을 통해 이루어진다.
- [0113] 용어 "치환된"은 지정된 원자상의 하나 이상의 수소가, 나타낸 그룹으로부터 선택된 것으로 대체되는 것을 의미하며, 단 존재하는 상황하의 지정된 원자의 정상 원자가는 초과하지 않으며, 치환은 안정한 화합물을 생성시킨다. 치환체 및/또는 변수의 조합은, 이러한 조합이 안정한 화합물을 생성시키는 경우에만 허용될 수 있다. "안정한 화합물" 또는 "안정한 구조"라는 표현은 반응 혼합물로부터의 유용한 순도로의 분리 및 효과적인 치료제로의 제형화에 견디도록 충분히 견고한 화합물을 의미한다.
- [0114] 용어 "임의 치환된"은 특정한 그룹, 라디칼 또는 잔기로 임의 치환됨을 의미한다.
- [0115] 화합물에 대해 용어 "분리된 또는 분리된 형태"는 합성 과정 또는 이의 천연 공급원 또는 배합물로부터 분리된 후 당해 화합물의 물리적 상태를 말한다. 화합물에 대해 용어 "정제된" 또는 "정제된 형태"는 본원에 기술된 정제 방법 또는 방법들 또는 당해 분야에 공지된 정제 방법 또는 방법들로부터 분리된 후 본원에 기술되거나 당해 분야의 숙련가에게 잘 공지된 표준 정제 기술에 의해 특징화될 수 있도록 충분한 순도인 당해 화합물의 물리적 상태를 말한다.
- [0116] 또한, 본원의 설명, 반응식, 실시예 및 표에서 만족스럽지 않은 원자수를 갖는 어떠한 헤테로 원자도 원자수를 만족시키기 위한 수소원자를 갖는 것으로 추정됨을 주목해야 한다.
- [0117] 화합물에서 작용 그룹은 "보호된"이라고 명명하며, 이는 당해 그룹이, 화합물이 반응에 적용되는 경우 보호된 위치에서 바람직하지 않은 부반응을 방지하도록 변형된 형태임을 의미한다. 적합한 보호 그룹은 당해 기술분야의 통상의 전문가들에게 인지될 것이며, 표준 문헌[참조: 예를 들면, T. W. Greene et al., Protective Groups in organic Synthesis(1991), Wiley, New York]을 참조할 수도 있다.
- [0118] 특정한 변수(예: 아릴, 헤테로사이클, R² 등)가 특정한 구성성분 또는 화학식 3에서 1회 이상 발생하는 경우, 각각의 경우의 이의 정의는 매번 기타의 발생 경우에서의 이의 정의와 독립적이다.
- [0119] 본원에서 사용된 용어 "조성물"은 명시된 양의 특정한 성분을 함유하는 생성물 뿐만 아니라, 명시된 양의 특정

한 성분의 조합으로부터 직접 또는 간접적으로 생성되는 어떠한 생성물도 망라하는 것으로 의도된다.

- [0120] 본 발명의 화합물의 프로드럭(prodrug) 및 용매화물이 또한 본원에서 고려된다. 본원에서 사용된 용어 "프로드럭"은 환자에게 투여하는 경우 대사적 또는 화학 과정에 의해 화학적 전환을 수행하여 화학식 3의 화합물 또는 이의 염 및/또는 용매화물을 생성하는 약물 전구체인 화합물을 나타낸다. 프로드럭의 토의는 문헌[참조: T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems(1987) 14 of the A. C. S. Symposium Series, and in Bioreversible Carriers in Drug Design,(1987) Edward B. Roche, ed. American Pharmaceutical Association and Pergamon Press]에 기술되어 있고, 이들 문헌 둘 다는 본원에서 참조문헌으로 인용된다.
- [0121] "용매화물"은 하나 이상의 용매 분자와 본 발명의 화합물과의 물리적 연합체(physical association)를 의미한다. 이러한 물리적 연합체는 수소 결합을 포함하는 다양한 정도의 이온 결합 및 공유 결합을 포함한다. 특정한 경우에, 용매화물은, 예를 들면, 하나 이상의 용매 분자가 결정성 고체의 결정 격자내에 혼입되는 경우, 분리될 수 있다. "용매화물"은 용매-상 및 분리가능한 용매화물 둘 다를 망라한다. 적합한 용매화물의 비제한적인 예는 에탄올레이트, 메탄올레이트 등을 포함한다. "수화물"은, 용매 분자가 H₂O인 용매화물이다.
- [0122] "유효량" 및 "치료학적 유효량"은 CDK(s)를 억제하여 목적하는 치료, 경감, 억제 또는 예방 효과를 생성하는데 효과적인 본 발명의 화합물 또는 조성물의 양을 기술하기 위한 것을 의미한다.
- [0123] 화학식 3의 화합물은 또한 본 발명의 영역내에 있는 염을 형성할 수 있다. 본원의 화학식 3의 화합물을 언급하는 경우, 달리 제시하지 않는 한 이의 염에 대한 언급도 포함하는 것으로 이해된다. 본원에 사용된 것으로서 용어 "염(들)"은 무기 및/또는 유기 산과 함께 형성된 산성 염, 및 무기 및/또는 유기 염기와 함께 형성된 무기 염을 나타낸다. 또한, 화학식 3의 화합물이 이에 한정되지 않는 피리딘 또는 이미다졸과 같은 염기성 잔기와, 이에 한정되지 않는 카복실산과 같은 산성 잔기를 함유하는 경우, 쓰비터 이온("내부 염")이 형성될 수 있으며 본원에 사용된 것으로서 용어 "염(들)"내에 포함된다. 비록 다른 염도 또한 유용하나, 약제학적으로 허용되는 (예를 들면, 비독성의 생리학적으로 허용되는) 염이 바람직하다. 화학식 3의 화합물의 염은 예를 들면, 화학식 3의 화합물을 염이 침전되는 것과 같은 매질 또는 수성 매질속에서 등량과 같은 양의 산 또는 염기와 반응시킨 후 동결건조시켜 형성시킬 수 있다.
- [0124] 예시적인 산 부가 염은 아세테이트, 아스코르베이트, 벤조에이트, 벤젠설포네이트, 비설페이트, 보레이트, 부티레이트, 시트레이트, 캄포레이트, 캄포르설포네이트, 푸마레이트, 하이드로클로라이드, 하이드로브로마이드, 하이드로요오다이드, 락테이트, 말레이트, 메탄설포네이트, 나프탈렌설포네이트, 니트레이트, 옥살레이트, 포스페이트, 프로피오네이트, 살리실레이트, 석시네이트, 설페이트, 타르타레이트, 티오시아네이트, 툴루엔설포네이트 (또한 토실레이트로 공지됨) 등을 포함한다. 추가로, 염기성 약제학적 화합물로부터 약제학적으로 유용한 염을 형성시키기 위해 적합한 것으로 일반적으로 고려되는 산은 예를 들면, 에스 버지(S. Berge) 등의 문헌[참조: Journal of Pharmaceutical Sciences(1977) 66(1) 1-19 ; P. Gould, International J. of Pharmaceutics(1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry(1996), Academic Press, New York; 및 in The Orange Book(Food & Drug Administration, Washington, D. C., 이들의 웹사이트]에 논의되어 있다. 이들 기제는 본원에 참조로 인용된다.
- [0125] 예시적인 염기성 염은 암모늄 염, 나트륨, 리튬 및 칼륨 염과 같은 알칼리 금속 염, 칼슘 및 마그네슘 염과 같은 알칼리 토금속 염, 디사이클로헥실아민, t-부틸 아민과 같은 유기 염기와의 염(예를 들면, 유기 아민), 및 아르기닌, 라이신 등과 같은 아미노산과의 염을 포함한다. 염기성 질소-함유 그룹은 저급 알킬 할라이드(예를 들면, 메틸, 에틸 및 부틸 클로라이드, 브로마이드 및 요오다이드), 디알킬 설페이트(예를 들면, 디메틸, 디에틸 및 디부틸 설페이트), 장쇄 할라이드(예를 들면, 데실, 라우릴 및 스테아릴 클로라이드, 브로마이드 및 요오다이드), 아르알킬 할라이드(예를 들면, 벤질 및 펜에틸 브로마이드) 등과 같은 제제로 사급화될 수 있다.
- [0126] 모든 이러한 염 및 염기 염은 본 발명의 영역내에 약제학적으로 허용되는 염을 의미하며 모든 산 및 염기 염은 본 발명의 목적에 상응하는 화합물의 유리 형태와 동일한 것으로 고려된다.
- [0127] 화학식 3의 화합물, 이의 염, 용매화물 및 프로드럭은 이의 토우토머 형(예를 들면, 아미드 또는 이미노에테르)으로 존재할 수 있다. 모든 이러한 토우토머 형은 본원에서 본 발명의 일부로 고려된다.
- [0128] 거울상 이성체 형태(이는 비대칭 탄소의 부재하에 존재할 수 있다), 회전이성체 형태, 아트로프이성체(atropisomer) 형태, 및 부분입체이성체 형태를 포함하는 각종 치환체상의 비대칭 탄소에 기인하여 존재할 수 있는 것들과 같은, 본 발명의 화합물(본 발명의 화합물의 염, 용매화물 및 프로드럭, 및 프로드럭의 염 및 용매화물 포함)의 모든 입체이성체(예를 들면, 기하 이성체, 광학 이성체 등)도 위치 이성체(예를 들면, 4-피리딘

및 3-피리딜)과 같이 본 발명의 영역내에서 고려된다. 본 발명의 화합물의 개개의 입체이성체는 예를 들면, 다른 이성체로부터 실질적으로 유리될 수 있거나, 예를 들면, 라세메이트 또는 다른 모든 또는 다른 선택된 입체이성체와 혼합될 수 있다. 본 발명의 키랄 중심은 IUPAC 1974 권고안에 의해 정의된 바와 같은 S 또는 R 배위를 지닐 수 있다. 용어 "염", "용매화물", "전구약물(프로드럭)" 등의 사용은 본 발명의 화합물의 거울상이성체, 입체이성체, 회전이성체, 토우토머, 위치이성체, 라세메이트 또는 프로드럭의 염, 용매화물 및 프로드럭에 동일하게 적용되는 것으로 의도된다.

[0129] 본 발명의 화합물은 약리학적 특성을 지니며, 특히, 화학식 3의 화합물은 예를 들면, 사이클린 의존성 키나제, 유사분열물질-활성화된 단백질 키나제(MAPK/ERK), 글리코젠 신타제 키나제 3(GSK3 β) 등과 같은 단백질 키나제의 억제제일 수 있다. 사이클린 의존성 키나제(CDK)는 예를 들면, CDC2(CDK1), CDK2, CDK4, CDK5, CDK6, CDK7 및 CDK8을 포함한다. 화학식 3의 신규 화합물은 암과 같은 증식성 질환, 자가면역 질환, 바이러스 질환, 진균 질환, 신경/신경변성 질환, 관절염, 염증, 항-증식(예를 들면, 안구 망막병증), 신경, 탈모증 및 심혈관 질환의 치료요법에서 유용한 것으로 기대된다. 많은 이러한 질환 및 장애는 이의 내용이 본원에 앞서 인용된 미국 특허 제6,413,974호에 나열되어 있다.

[0130] 보다 구체적으로, 화학식 3의 화합물은 하기를 포함하나 이에 한정되지 않는 각종 암의 치료에 유용할 수 있다: 방광, 유방, 결장, 신장, 간, 폐의 암을 포함하는 암종, 소세포 폐암, 식도, 담낭, 난소, 췌장, 위, 자궁경부, 갑상선, 전립선 및 피부를 포함하는 암종, 편평 세포 암종을 포함하는 암종; 백혈병, 급성 림프구 백혈병, 급성 림프모구 백혈병, B-세포 림프종, T-세포 림프종, 호지킨 림프종, 비-호지킨 림프종, 모발 세포 림프종 및 버켓 림프종(Burkett's lymphoma)을 포함하는 림프계의 조혈 종양; 급성 및 만성 골수 백혈병, 골수형성이상 증후군 및 전골수구백혈병을 포함하는 골수모양 계통의 조혈 종양; 섬유육종 및 횡문근육종을 포함하는 중간엽세포 기원의 종양; 별아교세포종, 신경모세포종, 신경아교종 및 신경집종을 포함하는 중추 신경계 및 말초 신경계의 종양; 및 흑색종, 고환종, 기형암종, 골육종, 색소성건피증, 각질가시세포종, 갑상샘소포암 및 카포시 육종을 포함하는 기타 종양.

[0131] 일반적으로, 세포 증식의 조절시 CDK의 주요 역할로 인하여, 억제제는 비정상적 세포 증식을 특징으로 하는 어떠한 질환 과정, 예를 들면, 양성 전립샘비대증, 가족섬종폴립증, 신경섬유종증, 죽상경화증, 폐 섬유증, 관절염, 건선, 사구체신염, 혈관성형술 또는 혈관 수술에 이은 재협착, 비대 반흔 형성, 염증성 장 질환, 이식 거부증, 내독소 쇼크 및 진균 감염의 치료에 유용할 수 있는 가역적 세포정지제로서 작용할 수 있다.

[0132] 화학식 3의 화합물은, 또한 CDK5가 tau 단백질의 포스포릴화에 관여한다는 최근의 발견에 의해 제안되는 바와 같이, 알츠하이머 질환의 치료에 유용할 수 있다[참조: J. Biochem,(1995) 117, 741-749].

[0133] 화학식 3의 화합물은 세포사멸을 유발시키거나 억제할 수 있다. 세포사멸 반응은 각종 사람 질환에서 비정상이다. 세포 사멸의 조절인자로서 화학식 3의 화합물은 암(위에서 언급한 유형의 암을 포함하나 이에 한정되지 않는다), 바이러스 감염(헤르페스바이러스, 폭스바이러스, 엡슈타인-바르 바이러스, 신드비스 바이러스 및 아데노 바이러스를 포함하나 이에 한정되지 않는다), HIV에 감염된 개인에서 AIDS 진행의 예방, 자가면역 질환(전신계 낭창, 홍반, 자가면역 중재된 사구체신염, 류마티스 관절염, 건선, 염증성 장 질환 및 자가면역성 당뇨병을 포함하나 이에 한정되지 않는다), 신경변성 질환(알츠하이머 질환, AIDS-관련 치매, 파킨슨 질환, 근위축가쪽 경화증, 망막색소변성, 척수근육위축 및 소뇌 변성을 포함하나, 이에 한정되지 않는다), 골수형성이상질환, 재생 불량빈혈, 심근경색증과 관련된 허혈성 손상, 발작 및 재관류 손상, 부정맥, 죽상경화증, 독소 유발되거나 알콜 관련된 간 질환, 혈액작용 질환(만성 빈혈 및 재생불량성 빈혈을 포함하나 이에 한정되지 않는다), 근육골격 계통의 변성 질환(골다공증 및 관절염을 포함하나 이에 한정되지 않는다), 아스피린 민감성 비부비동염, 낭성유증, 다발성 경화증, 신장 질환 및 암 통증의 치료에 유용할 것이다.

[0134] CDK의 억제제로서 화학식 3의 화합물은 세포 RNA 및 DNA 합성 수준을 조절할 수 있다. 따라서, 이들 제제는 바이러스 감염(HIV, 사람 파필로마 바이러스, 헤르페스바이러스, 폭스바이러스, 엡슈타인-바르 바이러스, 신드비스 바이러스 및 아데노바이러스를 포함하나, 이에 한정되지 않는다)의 치료에 유용하다.

[0135] 화학식 3의 화합물은 암의 화학예방(chemoprevention)에 유용할 수 있다. 화학예방은 돌연변이원성 현상의 개시를 차단하거나, 또는 이미 발생한 전-악성 세포의 진행을 차단하거나 종양 재발을 억제함으로써 침입성 암의 진행을 억제하는 것으로 정의된다.

[0136] 화학식 3의 화합물은 또한 종양 혈관형성 및 전이를 억제하는데 유용할 수 있다.

[0137] 화학식 3의 화합물은 또한 다른 단백질 키나제, 예를 들면, 단백질 키나제 C, her2, raf1, MEK1, MAP 키나제,

EGF 수용체, PDGF 수용체, IGF 수용체, PI3 키나제, wee1 키나제, Src 및 Abl의 억제제로서 작용할 수 있으므로, 다른 단백질 키나제와 관련된 질환을 치료하는데 효과적일 수 있다.

[0138] 본 발명의 다른 측면은 치료학적 유효량의 하나 이상의 화학식 3의 화합물 또는 이의 약제학적으로 허용되는 염 또는 용매화물을 포유동물에게 투여함으로써 CDK와 관련된 질환 또는 상태를 지닌 포유동물(예를 들면, 사람)을 치료하는 방법이다.

[0139] 바람직한 용량은 화학식 3의 화합물 약 0.001 내지 500mg/체중 kg/일이다. 특히 바람직한 용량은 화학식 3의 화합물 또는 이의 약제학적으로 허용되는 염 또는 용매화물 약 0.01 내지 25mg/체중 kg/일이다.

[0140] 본 발명의 화합물은 또한 방사선 치료요법, 및/또는 세포정지제, 세포독성제(예를 들면, DNA 상호작용제(예: 시스플라틴 또는 독소루비신)를 포함하나, 이에 한정되지 않는다); 탁산(예: 탁스테레, 탁솔); 토포이소머라제 II 억제제(예: 에토포시드); 토포이소머라제 I 억제제(예: 이리노테칸(또는 CPT-11), 캄프토스타 또는 토포테칸); 튜불린 상호작용제(예: 파클리탁셀, 도세탁셀 또는 에포틸론); 호르몬 제제(예: 타목시펜); 티미딜레이트 신타제 억제제(예: 5-플루오로우라실); 항-대사제(예: 메톡스트렉세이트); 알킬화제(예: 테모졸로마이드(뉴저지주 케널워쓰에 소재하는 웨링-플라우 코포레이션으로부터의 TEMODARTM), 사이클로포스파미드); 파르네실 단백질 트랜스퍼라제 억제제(예: SARASARTM(4-[2-[4-[(11R)-3,10-디브로모-8-클로로-6,11-디하이드로-5H-벤조[5,6]사이클로헥사[1,2-b]피리딘-11-일]-1-피페리딘일]-2-옥소에틸]-1-피페리딘카복사아미드, 또는 SCH 66336(뉴저지주 케널워쓰에 소재하는 웨링-플라우 코포레이션), 티피파르니브(얀센 파마슈티칼스에서 시판하는 Zarnestra[®] 또는 R115777), L778,123(뉴저지주 화이트하우스 스테이션에 소재하는 머크 앤드 캄파니에서 시판하는 파르네실 단백질 트랜스퍼라제 억제제), 또는 BMS 214662(뉴저지주 프린스턴에 소재하는 브리스톨-마이ер스 스퀴브 파마슈티칼스로부터 시판되는 파르네실 단백질 트랜스퍼라제 억제제)); 신호 전달 억제제(예: 영국에 소재하는 아스트라제네카 파마슈티칼스로부터 시판되는 이레싸(Iressa), 타르세바(Tarceva: EGFR 키나제 억제제), EGFR에 대한 항체(예: C225), 글리벡(GleevecTM)(뉴저지주 이스트 하노버 소재의 노바티스 파마슈티칼스로부터의 C-abl 키나제 억제제)); 인트론(웨링-플라우 코포레이션에서 시판), Peg-인트론(웨링-플라우 코포레이션에서 시판)과 같은 인터페론; 호르몬 치료요법 배합물; 아로마타제 배합물; ara-C, 아드리아마이신, 사이토산 및 겐시타빈으로 이루어진 그룹 중에서 선택된 하나 이상의 항암제와 같은 하나 이상의 항암 치료와 조합(병용)(함께 또는 연속 투여)시 유용할 수 있다.

[0141] 다른 항암제(항-신생물제로서도 공지됨)는 우라실 무스타드, 클로르메틴, 이포스파미드, 펠팔란, 클로람부실, 피포브로만, 트리에틸렌멜라민, 트리에틸렌티오포스포르아민, 부셀판, 카르무스틴, 로무스틴, 스트렙토조신, 다카르바진, 플록수리딘, 사이타라빈, 6-머캅토피린, 6-티오구아닌, 플루다라빈 포스페이트, 옥살리플라틴, 류코비린, 옥살리플라틴(프랑스 소재의 사노피-신테라보 파마슈티칼스에서 시판하는 ELOXATINTM), 펜토스타틴, 빈블라스틴, 빈크리스틴, 빈데신, 블레오마이신, 닥티노마이신, 다우노루비신, 독소루비신, 에피루비신, 이다루비신, 미트라마이신, 데옥시코포르마이신, 미토마이신-C, L-아스파라기나제, 테니포시드 17 α -에틸에스터라디올, 디에틸스티베스트롤, 테스토스테론, 프레드니손, 플루옥시메스테론, 드로모스타놀론 프로피오네이트, 테스톨락톤, 메게스트롤아세테이트, 메틸프레드니솔론, 메틸테스토스테론, 프레드니솔론, 트리암시놀론, 클로로트리아니센, 하이드록시프로게스테론, 아미노글루테스이미드, 에스트라무스틴, 메드록시프로게스테론아세테이트, 류프롤라이드, 플루타미드, 토레미펜, 고세렐린, 시스플라틴, 카르보플라틴, 하이드록시우레아, 암사크린, 프로카르바진, 미토탄, 미톡산트론, 레바미솔, 나벨벤, 아나스트라졸, 레트라졸, 카페시타빈, 렐록사핀, 드롤록사핀 또는 헥사메틸멜라민을 포함하나, 이에 한정되지 않는다.

[0142] 고정 투여량으로 제형화되는 경우, 이러한 배합 산물은 본원에 기술된 용량 범위내의 본 발명의 화합물 및 이의 용량 범위내의 다른 약제학적 활성제 또는 치료제를 사용한다. 예를 들어, CDC2 억제제 올로무신은 세포사멸을 유발하는데 있어서 공지된 세포독성제와 함께 상승적으로 작용하는 것으로 밝혀졌다[참조: J. Cell Sci.,(1995) 108, 2897]. 화학식 3의 화합물은, 또한 배합 제형이 부적절한 경우, 공지된 항암제 또는 세포독성제와 함께 연속적으로 투여될 수 있다. 본 발명은 투여 순서에 제한되지 않으며; 화학식 3의 화합물은 공지된 항암제 또는 세포독성제의 투여 전 또는 투여 후에 투여될 수 있다. 예를 들어, 사이클린-의존성 키나제 억제제인 플라보피리들의 세포독성 활성은 항암제의 투여 순서에 영향을 받는다[참조: Cancer Research,(1997) 57, 3375]. 이러한 기술은 당해 분야의 숙련가 및 주치의의 기술내에 있다.

[0143] 따라서, 하나의 측면에서, 본 발명은 하나 이상의 화학식 3의 화합물 또는 이의 약제학적으로 허용되는 염 또는

용매화물, 및 위에서 나열한 하나 이상의 향암 치료제 및 향암제의 목적인 치료학적 효과를 가져오는 화합물/치료의 양을 포함하는 배합물을 포함한다.

- [0144] 본 발명의 화합물의 약리학적 특성은 다수의 약리학적 검정으로 확인할 수 있다. 후술되는 예시한 약리학적 검정은 본 발명에 따른 화합물 및 이들의 염들을 사용하여 수행하였다.
- [0145] 본 발명은 또한 하나 이상의 화학식 III의 화합물, 또는 이의 약제학적으로 허용되는 염 또는 용매화물 및 하나 이상의 약제학적으로 허용되는 담체를 포함하는 약제학적 조성물에 관한 것이다.
- [0146] 본 발명에서 기술된 화합물로부터 약제학적 조성물을 제조하기 위한, 불활성의 약제학적으로 허용되는 담체는 고체 또는 액체일 수 있다. 고체형 제제는 산제, 정제, 분산성 입제, 캡셀제, 카세트(cachet) 및 좌제를 포함한다. 산제 및 정제는 약 5 내지 약 95%의 활성 성분을 포함할 수 있다. 적합한 고체 담체, 예를 들어, 탄산마그네슘, 스테아르산마그네슘, 활석, 당 또는 락토즈는 당해 분야에 공지되어 있다. 정제, 산제, 카세트 및 캡셀제는 경구 투여에 적합한 고체 용량형으로 사용될 수 있다. 약제학적으로 허용되는 담체 및 각종 조성물의 제조 방법의 예는 문헌[참조: A. Gennaro(ed.), Remington's Pharmaceutical Sciences, 18th Edition,(1990), Mack Publishing Co., Easton, Pennsylvania]에서 찾을 수 있다.
- [0147] 액체형 제제는 액제, 현탁제 및 유제를 포함한다. 예로서 비경구 주사용의 물 또는 물-프로필렌 글리콜 용액, 또는 경구 액제, 현탁제 및 유제용 감미제 및 유백제 첨가제를 언급할 수 있다. 액체형 제제는 또한 비강 투여용 액제를 포함할 수 있다.
- [0148] 흡입에 적합한 에어로졸 제제는 액제 및, 산제 형태의 고체를 포함할 수 있으며, 이들은 불활성의 압착 가스, 예를 들면 질소와 같은 약제학적으로 허용되는 담체와 배합될 수 있다.
- [0149] 또한, 사용 직전에 경구 또는 비경구 투여용 액체형 제제로 전환되도록 의도된 고체형 제제가 포함된다. 이러한 액체형은 액제, 현탁제 및 유제를 포함한다.
- [0150] 본 발명의 화합물은 또한 경피적으로 전달될 수 있다. 경피 조성물은 크림제, 로션제, 에어로졸제 및/또는 유제의 형태를 취할 수 있으며 당해 목적을 위해 당해 기술분야에 통상적인 것으로서 매트릭스 또는 저장소(reservoir) 형태의 경피 패취(patch)속에 포함될 수 있다.
- [0151] 본 발명의 화합물은 또한 피하로 전달될 수 있다.
- [0152] 바람직하게는 당해 화합물은 경구 투여된다.
- [0153] 바람직하게는, 약제학적 제제는 단위 용량형이다. 이러한 형태에서, 당해 제제는 적절한 양, 예를 들면, 바람직한 목적을 달성하기에 효과적인 양의 활성 성분을 함유하는 적합한 크기의 단위 투여량으로 세분(subdividing)된다.
- [0154] 단위 투여량의 제제속의 활성 화합물의 양은 특정 적용에 따라 약 1mg 내지 약 100mg, 바람직하게는 약 1mg 내지 약 50mg, 더욱 바람직하게는 약 1mg 내지 약 25mg으로 변하거나 조절될 수 있다.
- [0155] 사용된 실제 용량은 치료되는 환자의 요구도 및 치료되는 상태의 중증도에 따라 변할 수 있다. 특정 상태에 대한 적절한 용량 섭생(regimen)의 결정은 당해 기술내에 있다. 편의상, 총 일일 용량은 분리될 수 있으며, 필요할 경우, 하루동안에 일부씩 투여할 수 있다.
- [0156] 본 발명의 화합물 및/또는 이의 약제학적으로 허용되는 염의 투여량 및 투여 횟수는 치료되는 환자의 연령, 상태 및 체격, 및 증상의 중증도와 같은 인자를 고려하여 주치의의 판단에 따라 조절될 것이다. 경구 투여용으로 통상 추천되는 일일 용량 섭생은 약 1mg/일 내지 약 500mg/일, 바람직하게는 1mg/일 내지 200mg/일의 2 내지 4 회 분리된 투여량의 범위일 수 있다.
- [0157] 본 발명의 다른 측면은 치료학적 유효량의 하나 이상의 화학식 3의 화합물, 또는 이의 약제학적으로 허용되는 염 또는 용매화물, 및 약제학적으로 허용되는 담체, 비히클 또는 희석제를 포함하는 키트(kit)이다.
- [0158] 본 발명의 또 다른 측면은 목적하는 치료 효과를 가져오는 양의, 하나 이상의 화학식 3의 화합물, 또는 이의 약제학적으로 허용되는 염 또는 용매화물 및 위에서 나열한 하나 이상의 향암 치료요법 및/또는 향암제를 포함하는 키트이다.
- [0159] 본원에 기술된 발명은 기술내용의 범위를 제한하는 것으로 의도되지 않는 하기 제조 실시예 및 실시예에 의해

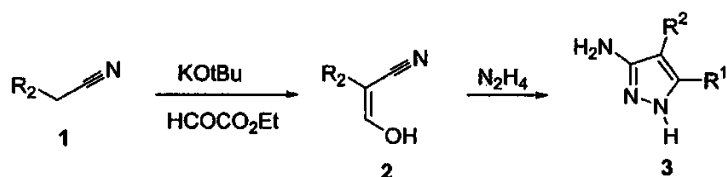
예시된다. 다른 대사 경로 및 유사한 구조는 당해 기술분야의 숙련가들에게 명백할 것이다.

- [0160] NMR 데이터를 나타내는 경우, ¹H 스펙트럼은 바리안(Varian) VXR-200(200MHz, ¹H), 바리안 케미나-300(300 MHz) 또는 XL-400(400 MHz)로 취득되며 Me₄Si로부터의 하부 영역(down field) ppm과 양성자수, 다중선, 및 괄호안에 나타낸 커플링 상수(Herz)로 기록된다. LC/MS 데이터를 나타내는 경우, 분석은 어플라이드 바이오시스템스(Applied Biosystems) API-100 질량 분광계 및 시마즈(Shimadzu) SCL-10A LC 컬럼을 사용하여 수행하였다: 알테크 플라티늄(Altech platinum) C18, 3 마이크론, 33mm x 7mm ID; 구배 속도(gradient flow): 0분 - 10% CH₃CN, 5분 - 95% CH₃CN, 7분 - 95% CH₃CN, 7.5분 - 10% CH₃CN, 9분 - 정지. 보유 시간 및 관측된 모 이온(parent ion)이 제공된다.
- [0161] 하기 용매 및 시약은 괄호안에 이들의 약자로 언급될 수 있다:
- [0162] 박층 크로마토그래피: TLC
- [0163] 디클로로메탄: CH₂Cl₂
- [0164] 에틸 아세테이트: AcOEt 또는 EtOAc
- [0165] 메탄올: MeOH
- [0166] 트리플루오로아세테이트: TFA
- [0167] 트리에틸아민: Et₃N 또는 TEA
- [0168] 부톡시카보닐: n-Boc 또는 Boc
- [0169] 핵자기 공명 분광학: NMR
- [0170] 액체 크로마토그래피 질량 분광분석: LCMS
- [0171] 고 분해능 질량 분광분석: HRMS
- [0172] 밀리리터: mL
- [0173] 밀리몰: mmol
- [0174] 마이크로리터: μ l
- [0175] 그램: g
- [0176] 밀리그램: mg
- [0177] 실온 또는 rt(주위 온도): 약 25°C
- [0178] 디메톡시에탄: DME.

실시예

[0179] 일반적으로, 본 발명의 화합물은 반응식 1에서 후술된 일반적인 경로를 통해 제조할 수 있다.

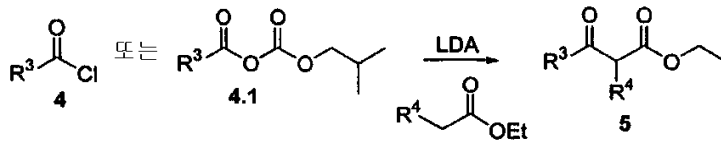
반응식 1



- [0180]
- [0181] 출발물질인 니트릴을 칼륨 3급-부톡사이드와 에틸 포르메이트로 처리하여 중간체 에놀(enol) 2를 취득하고 이를 하이드라진으로 처리하여 목적하는 치환된 3-아미노피라졸을 취득한다. 화합물 3을 적절히 작용화된 케토 에스테르 5와 축합시켜 반응식 3에 나타낸 바와 같은 피리돈 6을 취득한다. 이러한 일반 경로에 사용된 케토 에스

테르는 시판되거나 반응식 2에 나열된 바와 같이 제조할 수 있다.

반응식 2

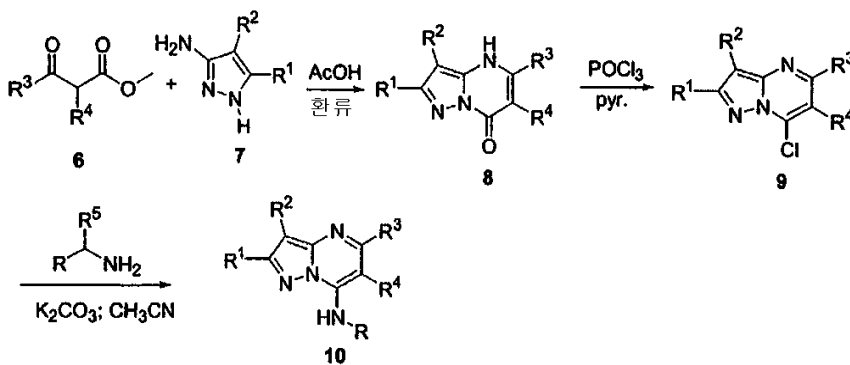


[0182]

[0183] 클로라이드 9는 피리돈 8을 POCl₃로 처리함으로써 제조할 수 있다. R²가 H와 동일한 경우, 이 위치에서의 치환은 친전자성 할로겐화, 아실화, 및 다양한 다른 친전자성 방향족 치환에 의해 화합물 9상에서 가능하다.

[0184] N7-아미노 관능가(functionality)의 도입은 반응식 3에 나타낸 바와 같이 적절한 아민과 반응시킴에 의해 화합물 9의 클로라이드의 치환으로 달성시킬 수 있다.

반응식 3



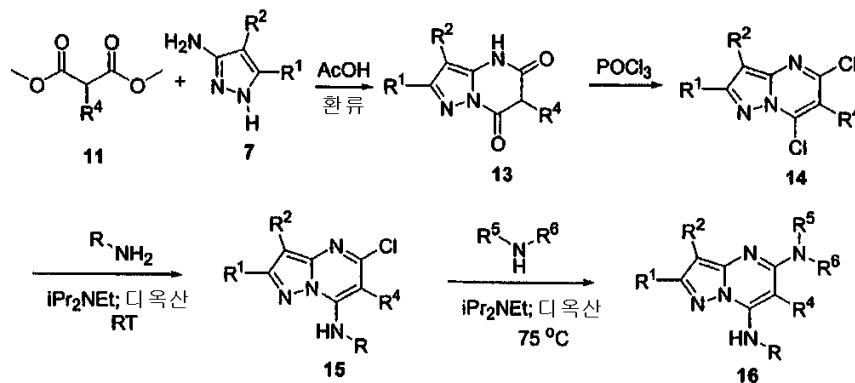
[0185]

[0186] 화합물 7을 적절하게 작용화된 말로네이트 에스테르 11과 축합시켜 반응식 4에 나타낸 피리돈 13을 수득한다.

[0187] 클로라이드 14는, 피리돈 13을 POCl₃로 처리하여 제조할 수 있다. R²가 H인 경우, 당해 위치에서의 치환은 화합물 9에서 친핵성 할로겐화, 아실화, 및 각종의 다른 친핵성 방향족 치환에 의해 가능하다.

[0188] N7-아미노 관능가의 도입은 화합물 클로라이드 14의 입체선택적 치환을 통해 달성할 수 있다. 고온에서 적절한 아민의 도입에 의해 N5-아미노 관능가가 도입된다.

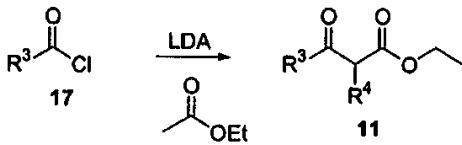
반응식 4



[0189]

[0190] 달리, 반응식 4에 나타낸 바와 같이 아미노피라졸 7을 반응식 5에서 제조된 적절히 작용화된 케토 에스테르와 축합시켜 화합물 13을 수득한다.

반응식 5



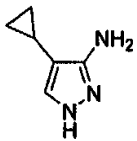
[0191]

[0192] 클로라이드 14는, 피리돈 13을 POCl₃로 처리함으로써 제조할 수 있다. R²가 H와 동일한 경우, 당해 위치에서의 치환은 화합물 14상에서 친핵성 할로젠화, 아실화, 및 각종의 다른 친핵성 방향족 치환에 의해 가능하다.

[0193] N7-아미노 관능가의 도입은 화합물 15의 클로라이드의 치환을 통해 달성할 수 있다.

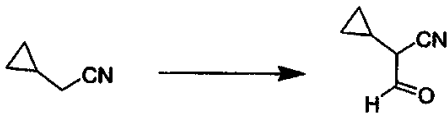
[0194] 제조 실시예:

[0195] 제조 실시예 1:



[0196]

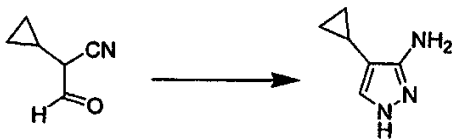
[0197] 단계 A:



[0198]

[0199] 독일 특허 제DE 19834047 A1호, p19에서의 과정은 다음과 같았다. 무수 THF(40mL)중 KOtBu(6.17g, 0.055 mol)의 용액에 무수 THF(4mL)중 사이클로프로필아세트니트릴(2.0g, 0.025 mol) 및 에틸 포르메이트(4.07g, 0.055 mol)의 용액을 적가하였다. 침전물이 즉시 형성되었다. 당해 혼합물을 12시간 동안 교반하였다. 이를 진공하에 농축시키고 잔사를 Et₂O(50mL)로 세척하였다. 수득되는 잔사를 경사분리하고, Et₂O(2 x 50mL)로 세척하고 Et₂O를 진공하에 잔사로부터 제거하였다. 잔사를 냉 H₂O(20mL)속에 용해시키고 pH를 12N HCl을 사용하여 4 내지 5로 조절하였다. 당해 혼합물을 CH₂Cl₂(2 x 50mL)로 추출하였다. 유기 층을 합하고, MgSO₄위에서 건조시키고 진공하에 농축시켜 갈색 액체로서의 알데하이드를 수득하였다.

[0200] 단계 B:



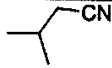
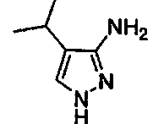

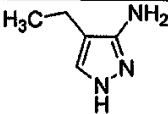
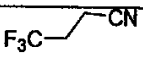
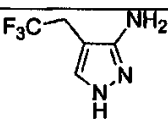
[0201]

[0202] 제조 실시예 1, 단계 A로부터의 생성물(2.12g, 0.0195mol), NH₂NH₂ · H₂O(1.95g, 0.039mol) 및 1.8g(0.029mol)의 빙 CH₃CO₂H(1.8g, 0.029mol)을 EtOH(10mL)에 용해시켰다. 이를 6시간 동안 환류시키고 진공하에 농축시켰다. 잔사를 CH₂Cl₂(150mL)속에서 슬러리화하고 pH를 1N NaOH를 사용하여 9로 조절하였다. 유기 층을 염수로 세척하고, MgSO₄위에서 건조시키며 진공하에 농축시켜 왁스성 오렌지색 고체로서의 생성물을 수득하였다.

[0203] 제조 실시예 2 내지 4:

[0204] 제조 실시예 1에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 2의 컬럼 2에 나타낸 니트릴을 단지 치환시킴으로써, 표 2의 컬럼 3의 화합물을 제조하였다:

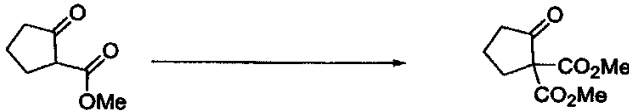
표 2

제조 실시예	컬럼 2	컬럼 3
2		
3		
3.10		

[0205]

[0206]

제조 실시예 4



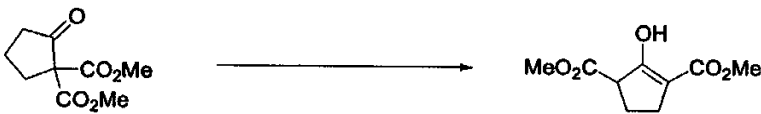
[0207]

[0208]

THF(15ml)중 2-카보메톡시사이클로펜타논(6.6ml, 0.05mol)을 0 내지 10℃에서 THF(100ml)중 NaH(광유중 60%, 4g, 0.1mol)의 격렬히 교반된 현탁액에 적가하였다. 거품 발생이 정지된 때에, 반응 혼합물을 동일한 온도에서 THF(15ml)중 CICOOme(7.8ml, 0.1mol)로 처리하였다. 수득된 회백색 현탁액을 실온에서 30분 및 환류하에 30분 동안 교반하였다. 반응물을 출발하는 물질이 사라지는 동안 TLC로 모니터하였다. 반응 혼합물을 물로 조심스럽게 퀵칭시키고 깔대기속에 에틸 아세테이트 및 염화암모늄의 포화된 용액사이에 분배시켰다. 교반 및 분리하고, 유기 층을 염수로 세척하고 무수 황산나트륨위에서 건조시켰다. 용매를 제거하고, 잔사를 헥산중 5% 및 이후 10% 에틸 아세테이트로 용출시키는 플래쉬 크로마토그래피로 정제하였다. 9.4g의 무색 오일을 94%의 수율로 수득하였다. ¹H NMR(CDC1₃) δ 3.90(s, 3H), 3.73(s, 3H), 2.65(m, 4H), 1.98(m, 2H).

[0209]

제조 실시예 5



[0210]

[0211]

-65℃에서 THF(2.0N, 0.04mol)중 리튬 디이소프로필아민 용액에 THF(60ml)중 2,2-디카보메톡시사이클로펜타논(4g, 0.02mol)을 적가하였다. 수득된 반응 혼합물을 메틸 클로로포르메이트(1.54ml, 0.02mol)를 첨가하기 전에 동일한 온도에서 교반하였다. 반응 혼합물을 1시간 동안 교반하고 염화암모늄 포화된 용액으로 일부 얼음과 함께 부었다. 당해 용액을 에테르로 3회 추출하고, 합한 에테르성 층을 황산나트륨위에서 건조시켰다. 용매를 진공하에 제거하고, 잔사를 헥산중 30%에서 50%로 증가하는 에틸 아세테이트로 용출시키는 플래쉬 크로마토그래피에 의해 정제하였다. 2.3g의 황색 오일은 58% 수율로 수득하였다. ¹H NMR(CDC1₃) δ 3.77(s, 6H), 3.32(t, 1H), 3.60-3.10(m, 4H).

[0212] 제조 실시예 6:



[0213]

[0214] 문헌[참조: K. O. Olsen, J. Org. Chem.,(1987) 52, 4531-4536]에 요약된 바와 같이 반응을 수행하였다. 즉, -65 내지 -70°C에서 THF중 리튬 디소프로필아미드의 출발 용액에 새로이 증류된 에틸 아세테이트를 적가하였다. 수득되는 용액을 30분 동안 교반하고 산 클로라이드를 THF중의 용액으로서 가하였다. 반응 혼합물을 -65 내지 -70°C에서 30분 동안 교반한 후 1N HCl 용액을 첨가하여 종결시켰다. 수득되는 2개 상 혼합물을 주위 온도로 가온되도록 하였다. 수득되는 혼합물을 EtOAc(100mL)로 희석시키고 유기 층을 수집하였다. 수성 층을 EtOAc(100ml)로 추출하였다. 유기 층을 합하고, 염수로 세척하고, 건조(Na₂SO₄)시키며, 진공하에 농축시켜 조악한 β-케토 에스테르를 수득하고, 이를 이후의 축합에 사용하였다.

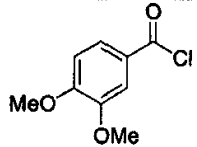
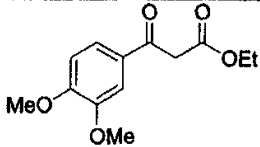
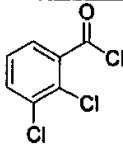
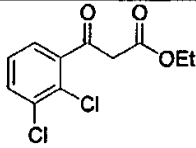
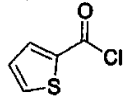
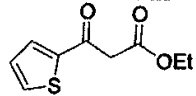
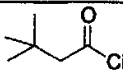
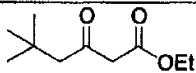
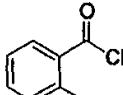
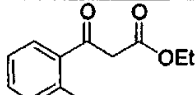
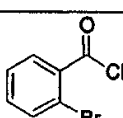
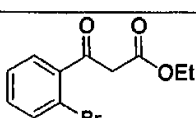
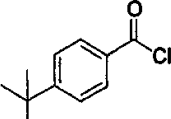
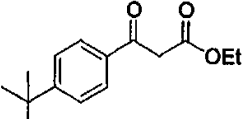
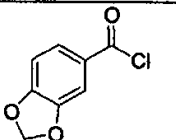
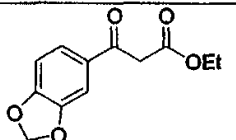
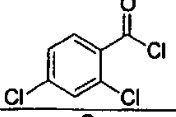
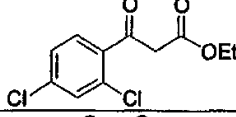
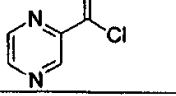
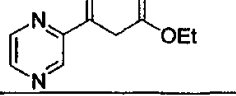
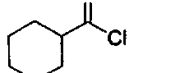
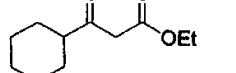
[0215] 제조 실시예 7 내지 19:

[0216] 제조 실시예 6에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 3의 컬럼 2에 나타낸 산 클로라이드를 단지 치환시켜, 표 3의 컬럼 3에 나타낸 β-케토 에스테르를 제조하였다:

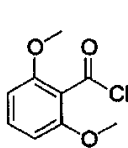
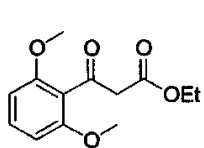
표 3

제조 실시예	컬럼 2	컬럼 3	데이터
7			LCMS: MH ⁺ = 223

[0217]

8			LCMS: MH ⁺ = 253
9			LCMS: MH ⁺ = 261
10			MH ⁺ = 199
11			
12			
13			LCMS: MH ⁺ = 271
14			수율 = 양 MH ⁺ = 249
15			수율 = 양 MH ⁺ = 237
16			수율 = 양 MH ⁺ = 262
17			수율 = 48 MH ⁺ = 195
18			수율 = 99 MH ⁺ = 199

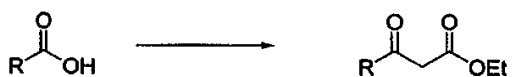
[0218]

19			수율=77% ¹ H NMR (CDCl ₃) δ 7.42(t, 1H), 6.68(d, 2H), 4.29(q, 2H), 3.97(d, 2H), 3.95(s, 3H), 1.38(t, 3H).
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[0219]

[0220] 제조 실시예 20:

[0221]

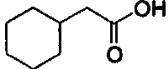
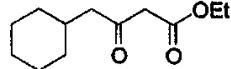
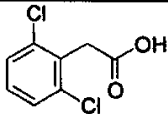
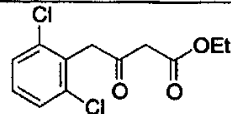
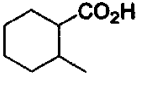
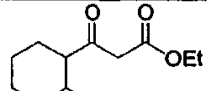


[0222] -20 내지 -30℃에서 THF중 산의 용액에 Et₃N에 이어서 이소부틸 클로로포르메이트를 가하였다. 혼합물을 -20 내지 -30℃에서 30분 동안 교반하고, 트리에틸아민 하이드로클로라이드를 아르곤하에 여과하고, 여액을 -65 내지 -70℃에서 LDA-EtOAc 반응 혼합물(방법 A에서 요약한 바와 같이 제조)에 가하였다. 1N HCl을 첨가한 후, 반응 혼합물을 통상적으로 후처리한 후 용매를 증발시켜, 조악한 β-케토 에스테르를 분리하였다. 조악한 물질을 후속적인 축합에 사용하였다.

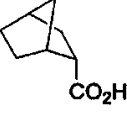
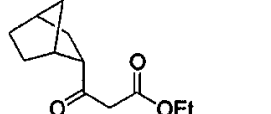
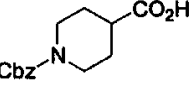
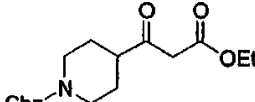
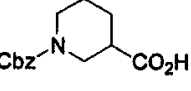
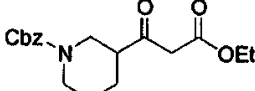
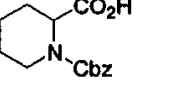
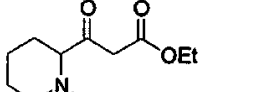
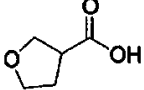
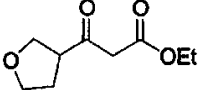
[0223] 제조 실시예 21 내지 28:

[0224] 제조 실시예 20에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 4의 컬럼 2에 나타낸 카복실산을 단지 치환시켜, 표 4의 컬럼 3에 나타낸 화합물을 제조하였다:

표 4

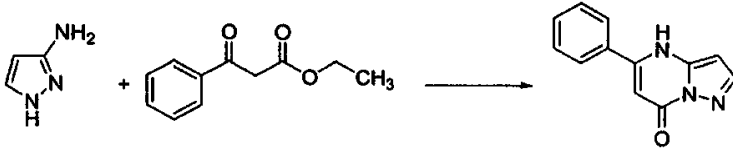
제조 실시예	컬럼 2	컬럼 3	CMPD
21			수율 = 99% MH ⁺ = 213
22			수율 = 70% MH ⁺ = 275
23			수율 = 양 MH ⁺ = 213

[0225]

24			수율 = 양 MH ⁺ = 211
25			수율 = 99 MH ⁺ = 334
26			수율 = 99 MH ⁺ = 334
27			수율 = 99 MH ⁺ = 334
28			수율 = 77% ¹ H NMR (CDCl ₃) δ 4.21(q, 2H), 3.95(d, 2H), 3.93-3.79(m, 4H), 3.52(s, 2H), 2.65(m, 1H), 1.25(t, 3H), 1.23-1.2(m, 2H).

[0226]

[0227] 제조 실시예 29:



[0228]

[0229] AcOH(15mL)중 3-아미노피라졸(2.0g, 24.07mmol) 및 에틸 벤조일아세테이트(4.58mL, 1.1당량)의 용액을 환류하에 3시간 동안 가열하였다. 반응 혼합물을 실온으로 냉각시키고 진공하에 농축시켰다. 수득되는 고체를 EtOAc로 희석시키고 여과하여 백색 고체(2.04g, 40% 수율)를 수득하였다.

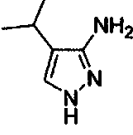
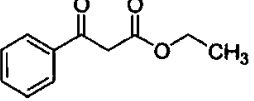
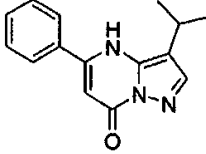
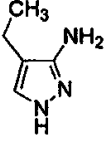
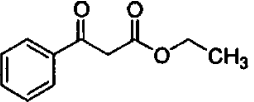
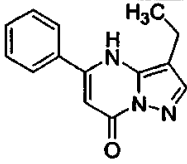
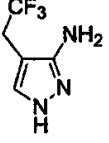
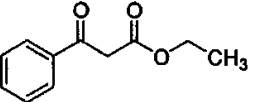
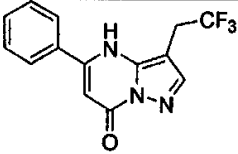
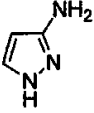
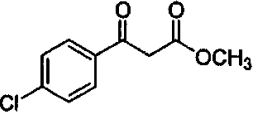
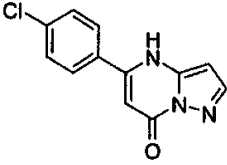
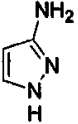
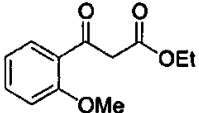
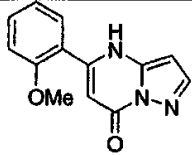
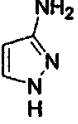
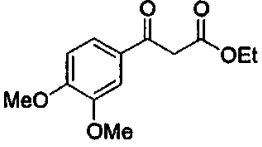
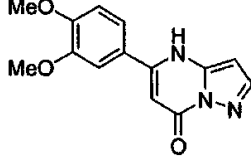
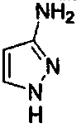
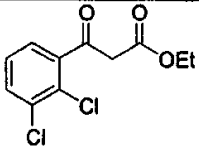
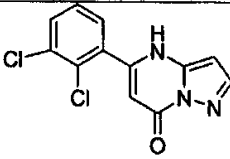
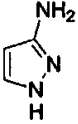
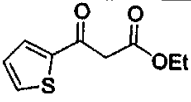
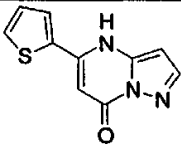
[0230] 제조 실시예 30 내지 73:

[0231] 제조 실시예 29에 나타난 바와 본질적으로 동일한 과정에 의해, 표 5의 컬럼 2에 나타난 아미노피라졸 및 표 5의 컬럼 3에 나타난 에스테르를 단지 치환시켜, 표 5의 컬럼 4에 나타난 화합물을 제조하였다:

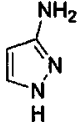
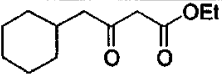
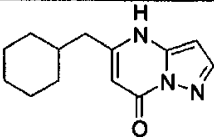
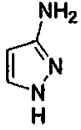
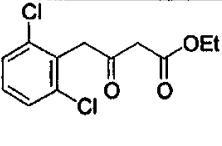
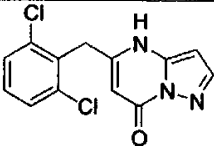
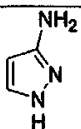
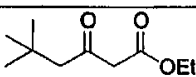
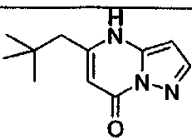
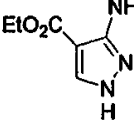
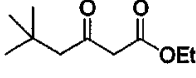
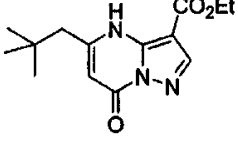
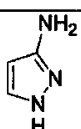
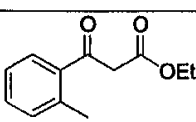
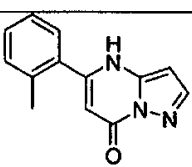
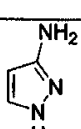
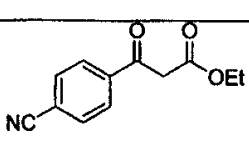
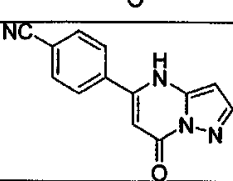
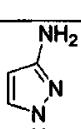
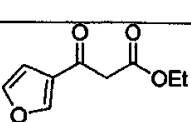
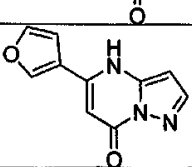
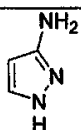
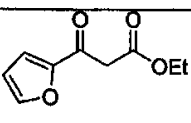
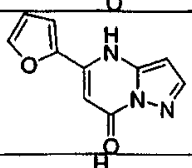
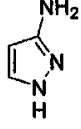
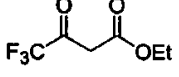
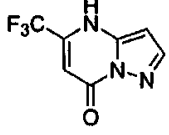
표 5

제조 실시예	컬럼 2	컬럼 3	컬럼 4	컬럼 5
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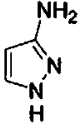

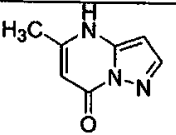
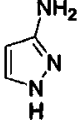
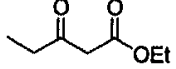
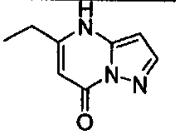
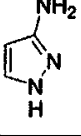
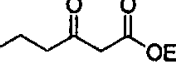
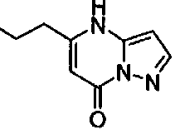
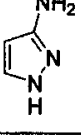
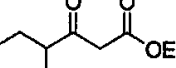
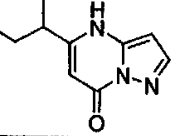
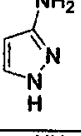

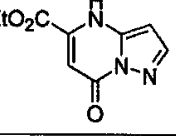
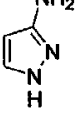
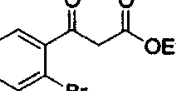
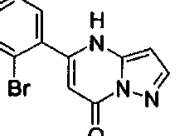
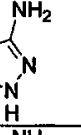

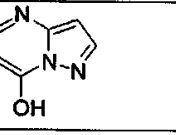
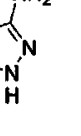
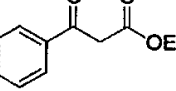
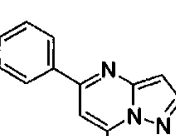
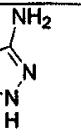
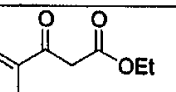
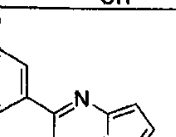
[0232]

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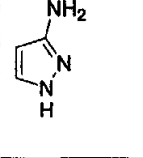
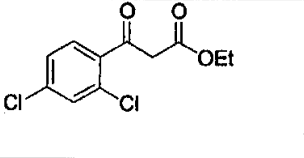
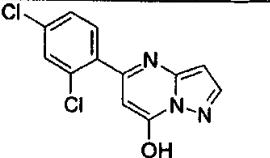
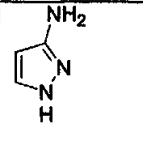
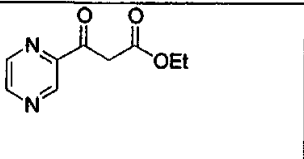
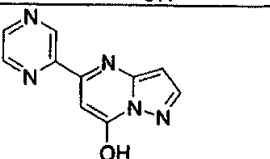
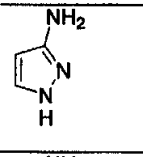
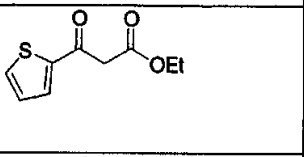
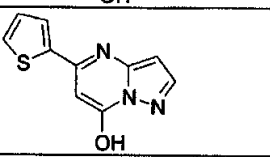
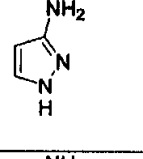
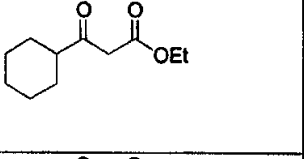
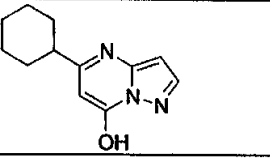
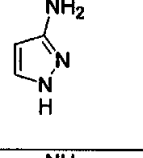
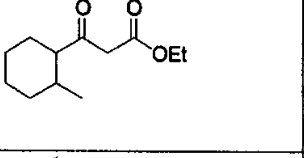
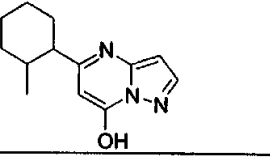
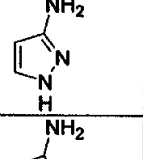
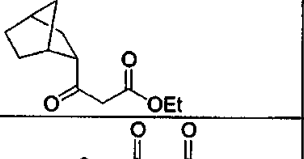
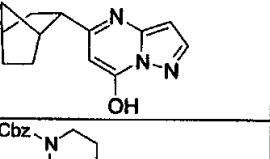
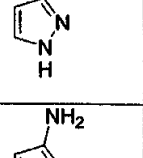
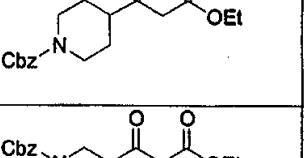
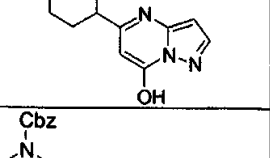
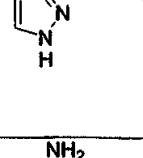
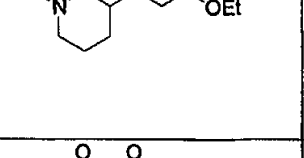
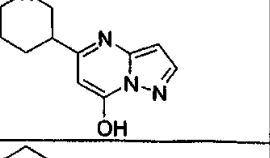
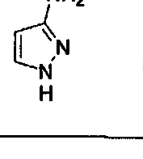
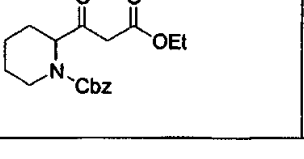
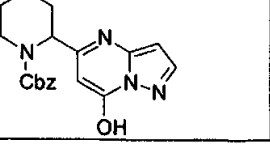
[0233]

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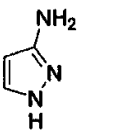
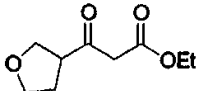
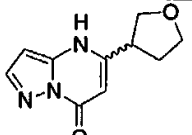
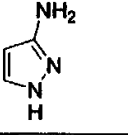
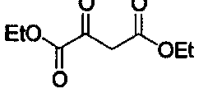
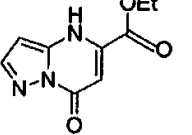
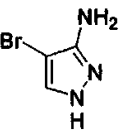
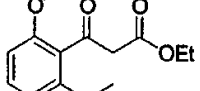
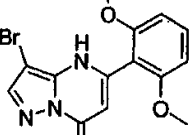
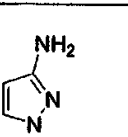
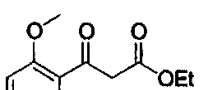
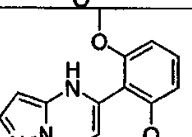
[0234]

52				
53				
54				
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58				수율 = 68 MH ⁺ = 152
59				수율 = 46 MH ⁺ = 268
60				수율 = 63 MH ⁺ = 255

[0235]

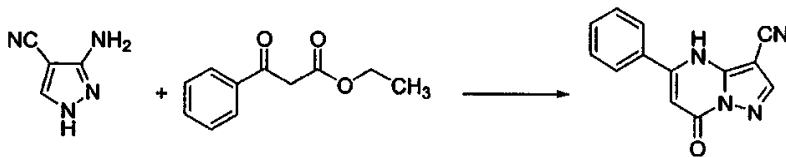
61				수율 = 80 MH ⁺ = 280
62				수율 =72 MH ⁺ = 214
63				수율 = 51 MH ⁺ = 218
64				수율 = 82 MH ⁺ = 218
65				수율 = 39 MH ⁺ = 232
66				수율 = 30 MH ⁺ = 230
67				수율 = 80 MH ⁺ = 353
68				수율 = 49 MH ⁺ = 353
69				수율 = 42 MH ⁺ = 353

[0236]

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71				
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73				

[0237]

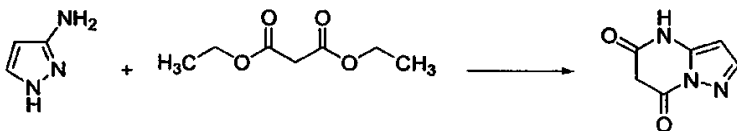
[0238] 제조 실시예 74:



[0239]

[0240] AcOH(5.0mL) 및 H₂O(10mL)중 에틸 벤조일아세테이트(1.76mL, 1.1당량) 및 3-아미노-4-시아노피라졸(1.0g, 9.25mmol)을 환류하에 72시간 동안 가열하였다. 수득되는 용액을 실온으로 냉각시키고, 진공하에 농축시키고, EtOAc로 희석시켰다. 수득되는 침전물을 여과하고, EtOAc로 세척하고 진공하에 건조시켰다(0.47g, 21% 수율).

[0241] 제조 실시예 75



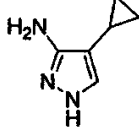
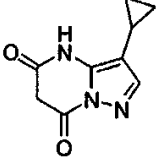
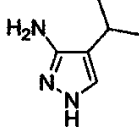
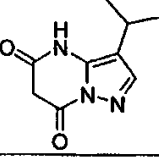
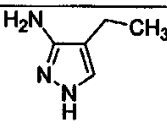
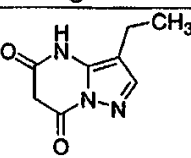
[0242]

[0243] 미국 특허 제3,907,799호의 과정을 수행하였다. 나트륨(2.3g, 2당량)을 EtOH(150mL)에 적가하였다. 나트륨이 완전히 용해되면, 3-아미노피라졸(4.2g, 0.05mol) 및 디에틸 말로네이트(8.7g, 1.1당량)를 가하고 수득되는 용액을 3시간 동안 가열하여 환류시켰다. 수득되는 현탁액을 실온으로 냉각시키고 여과하였다. 여과 케이크를 EtOH(100mL)로 세척하고 수(250mL)중에 용해시켰다. 수득되는 용액을 빙욕속에서 냉각시키고 pH를 진한 HCl을 사용하여 1 내지 2로 조절하였다. 수득되는 현탁액을 여과하고 물(100mL)로 세척하고 감압하에 건조시켜 백색 고체(4.75g, 63% 수율)를 수득하였다.

[0244] 제조 실시예 76 내지 78:

[0245] 제조 실시예 75에 나타난 바와 본질적으로 동일한 과정에 의해, 표 6의 컬럼 2에 나타난 화합물을 단지 치환시켜, 표 6의 컬럼 3에 나타난 화합물을 제조하였다:

표 6

제조 실시예	컬럼 2	컬럼 3
76		
77		
78		

[0246]

[0247] 제조 실시예 79:



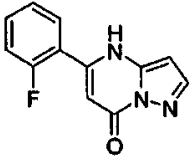
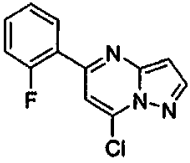
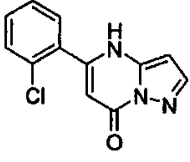
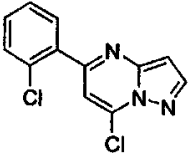
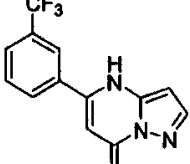
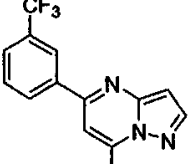
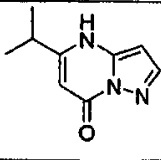
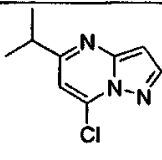
[0248]

[0249] POCl₃(5mL) 및 피리딘(0.25mL)중 제조 실시예 29에서 제조한 화합물(1.0g, 4.73mmol)의 용액을 실온에서 3일동안 교반하였다. 수득되는 슬러리를 Et₂O로 희석시키고, 여과하며, 고체 잔사를 Et₂O로 세척하였다. 합한 Et₂O 세척물을 0℃로 냉각시키고 얼음으로 처리하였다. 격렬한 반응이 중지되면, 수득되는 혼합물을 H₂O로 희석시키고, 분리하고, 수성 층을 Et₂O로 추출하였다. 합한 유기물을 H₂O 및 포화된 NaCl로 세척하고, Na₂SO₄위에서 건조시키고, 여과하고, 농축시켜 담황색 고체(0.86g, 79% 수율)를 수득하였다. LCMS: MH⁺=230.

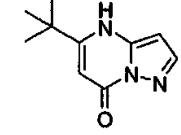
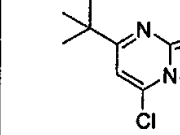
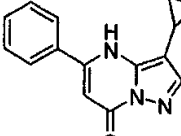
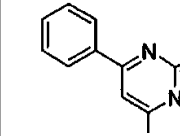
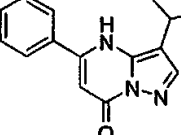
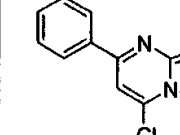
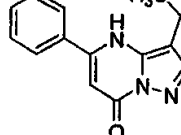
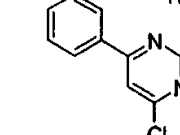
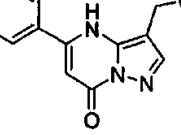
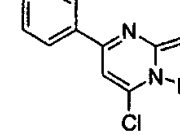
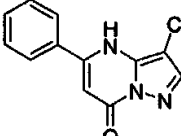
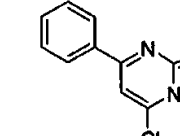
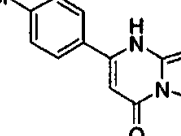
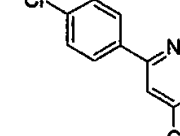
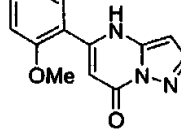
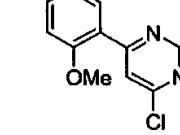
[0250] 제조 실시예 80 내지 122:

[0251] 제조 실시예 79에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 7의 컬럼 2에 나타낸 화합물을 단지 치환시켜, 표 7의 컬럼 3에 나타낸 화합물을 제조하였다:

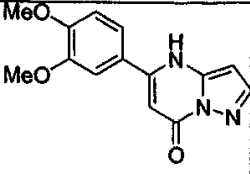
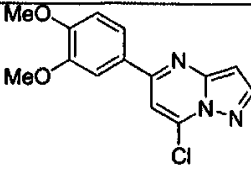
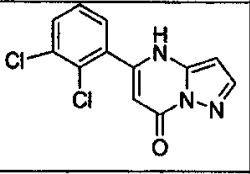
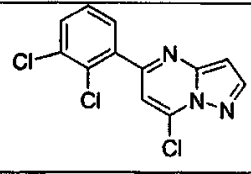
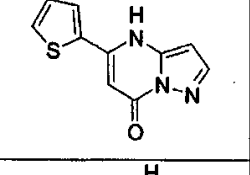
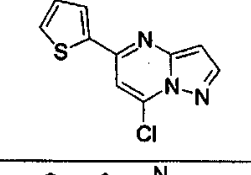
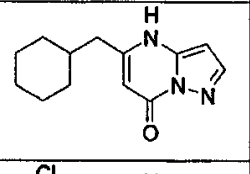
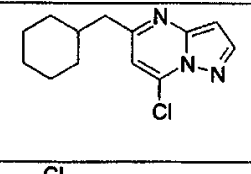
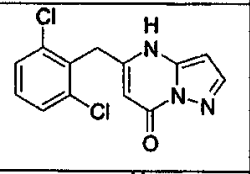
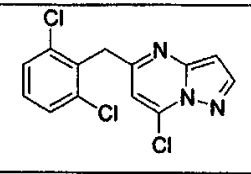
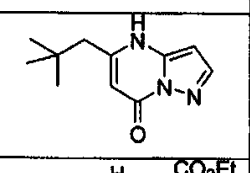
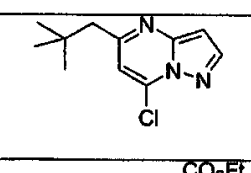
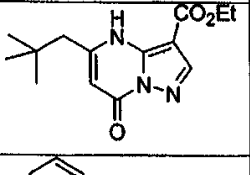
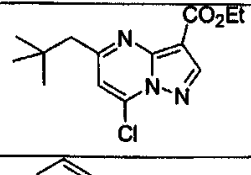
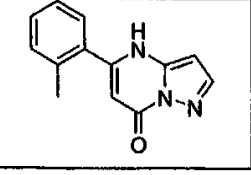
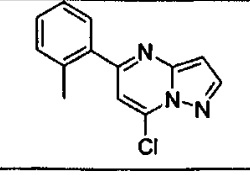
표 7

제조 실시예	컬럼 2	컬럼 3	CMPD
80			MS: MH ⁺ =248
81			
82			MS: MH ⁺ =298
83			MS: MH ⁺ =196

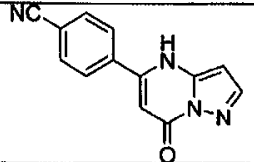
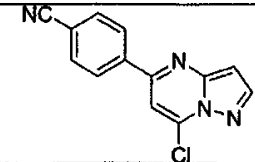
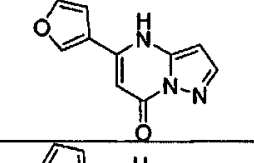
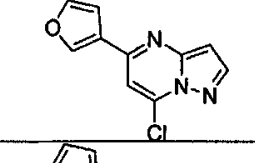
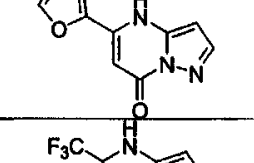
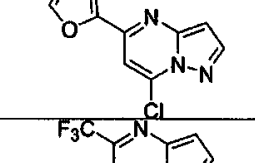
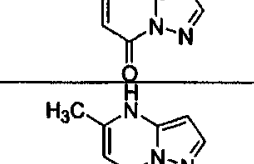
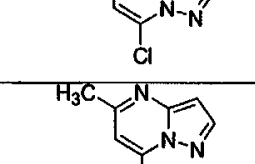
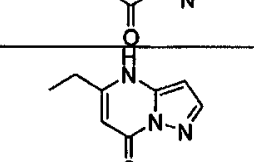
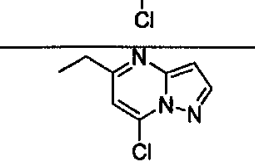
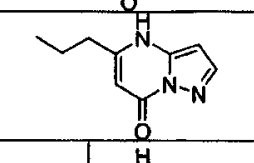
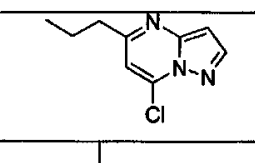
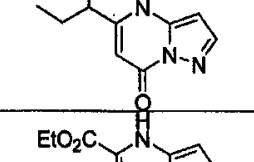
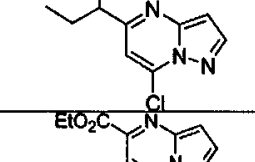
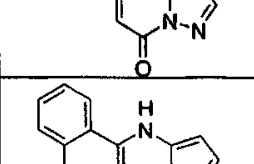
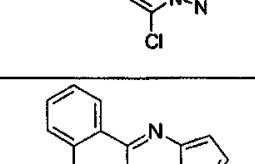
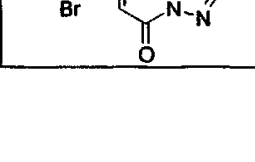
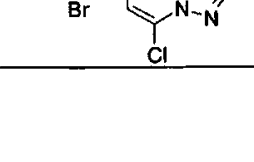


[0252]

84			MS: MH ⁺ =210
85			
86			MS: MH ⁺ =272
87			
87.10			
88			MS: MH ⁺ =255
89			
90			수율 = 65% MS: MH ⁺ = 260

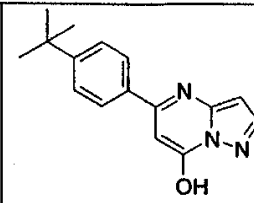
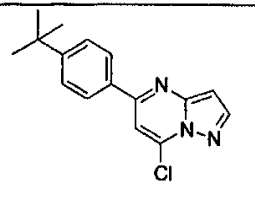
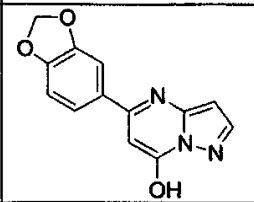
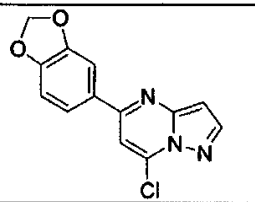
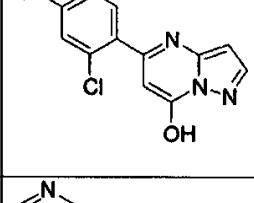
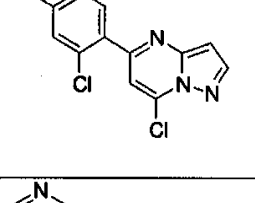
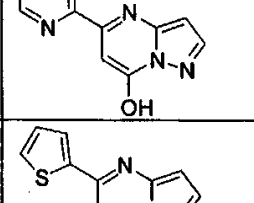
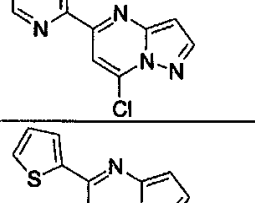
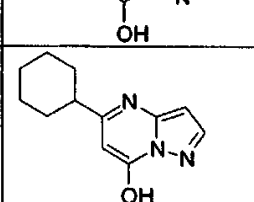
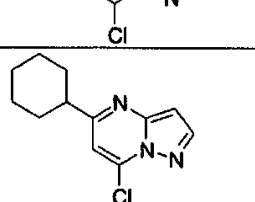
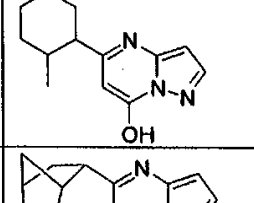
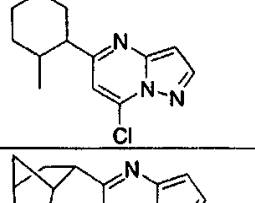
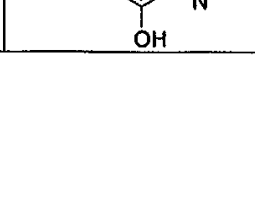
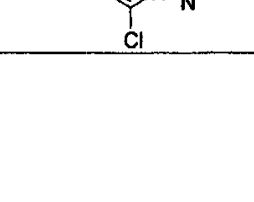


[0253]

91			수율 = 35% MS: MH ⁺ = 290
92			수율 = 32% MS: MH ⁺ = 298
93			수율 = 45% MS: MH ⁺ = 236
94			수율 = 100% LCMS: MH ⁺ = 250
95			수율 = 88% MS: MH ⁺ = 314
96			수율 = 43% MS: MH ⁺ = 223
97			수율 = 30% MS: MH ⁺ = 295
98			수율 = 98% MS: MH ⁺ = 244

[0254]

99			
100			
101			
102			
103			
104			
105			
106			
107			45% 수율; MS: MH ⁺ =226
108			MS: MH ⁺ = 308

[0255]

109			수용 = 양 MH ⁺ = 286
110			수용 = 50 MH ⁺ = 272
111			수용 = 85 MH ⁺ = 299
112			수용 = 97 MH ⁺ = 231
113			수용 = 45 MH ⁺ = 236
114			수용 = 양 MH ⁺ = 236
115			수용 = 57 MH ⁺ = 250
116			수용 = 89 MH ⁺ = 248

[0256]

117			수율 = 96 MH ⁺ = 371
118			수율 = 99 MH ⁺ = 371
119			수율 = 50 MH ⁺ = 371
120			수율 = 57% LCMS: MH ⁺ = 224
121			수율 = 34% LCMS: MH ⁺ = 226
122			수율 = 100% ¹ H NMR (CDCl ₃) δ 8.53(d, 1H), 7.66(t, 1H), 7.51(s, 1H), 7.45(d, 1H), 6.84(d, 2H).

[0257]

[0258] 제조 실시예 123



[0259]

[0260] POCl₃(62mL)를 질소 및 디메틸아닐린(11.4g, 2.8당량)과 제조 실시예 75에서 제조한 화합물(4.75g, 0.032mol)하에 5℃로 냉각시켰다. 반응 혼합물을 60℃로 가온시키고 밤새 교반하였다. 반응 혼합물을 30℃로 냉각시키고 POCl₃를 감압하에 회석시켰다. 잔사를 CH₂Cl₂(300mL)속에 용해시키고 빙상에 부었다. 15분 동안 교반한 후, 혼합물의 pH를 고체 NaHCO₃로 7 내지 8로 조절하였다. 층을 분리하고 유기 층을 H₂O(3x200ml)로 세척하고, MgSO₄ 위에서 건조시키고, 여과하며, 농축시켰다. 조악한 생성물을 50:50 CH₂Cl₂:헥산 용액을 용출제로 사용하는 플래쉬 크로마토그래피에 의해 정제하여 디메틸 아닐린을 용출시켰다. 이후 용출물을 75:25 CH₂Cl₂ : 헥산으로 변경시켜 목적인 생성물(4.58g, 77% 수율)을 용출시켰다. MS: MH⁺=188.

[0261]

제조 실시예 124 내지 126:

[0262]

제조 실시예 123에 나타난 바와 본질적으로 동일한 과정에 의해, 표 8의 컬럼 2에 나타난 화합물을 단지 치환시켜, 표 8의 컬럼 3에 나타난 화합물을 제조하였다:

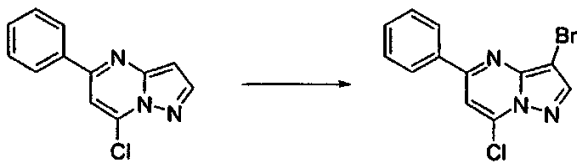
표 8

제조 실시예	컬럼 2	컬럼 3
124		
125		
126		

[0263]

[0264]

제조 실시예 127:



[0265]

[0266]

CH₃CN(3mL)중 제조 실시예 79에서 제조한 화합물(0.10g, 0.435mmol)의 용액을 NBS(0.085g, 1.1당량)으로 처리하였다. 반응 혼합물을 실온에서 1시간 동안 교반하고 감압하에 농축시켰다. 조약한 생성물을 용출제로서 헥산 중 20% EtOAc(0.13g, 100% 수율)를 사용한 플래쉬 크로마토그래피에 의해 정제하였다. LCMS : MH⁺ = 308.

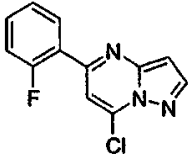
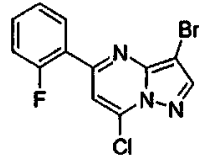
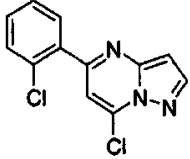
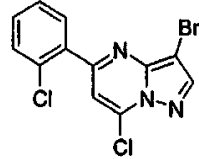
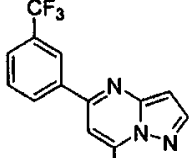
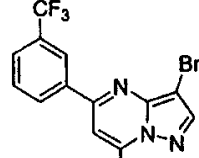
[0267]

제조 실시예 128 내지 164:

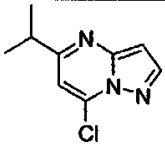
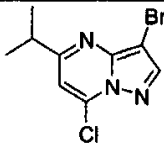
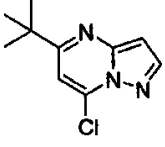
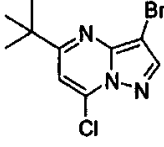
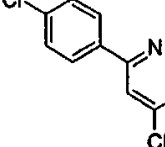
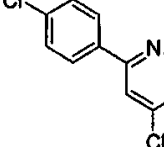
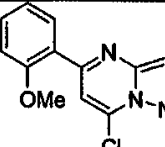
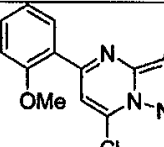
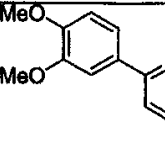
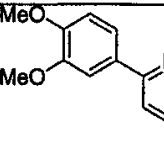
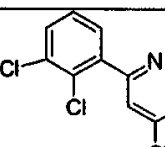
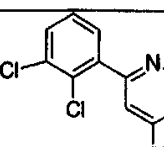
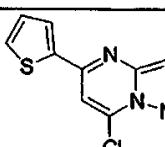
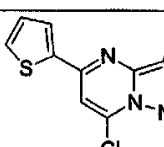
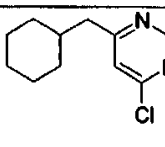
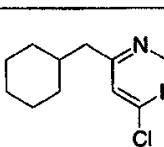
[0268]

제조 실시예 127에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 9의 컬럼 2에 나타낸 화합물을 단지 치환시켜, 표 9의 컬럼 3에 나타낸 화합물을 제조하였다:

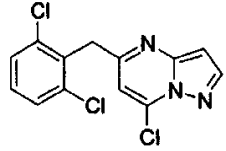
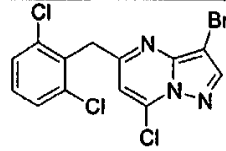
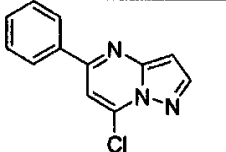
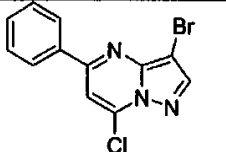
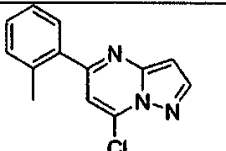
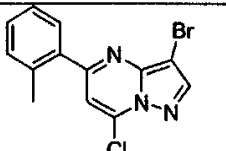
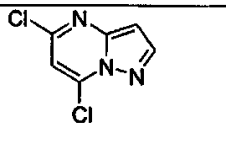
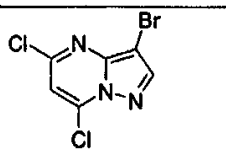
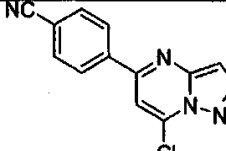
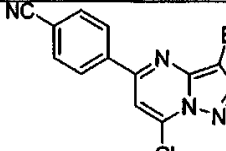
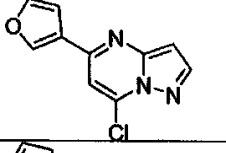
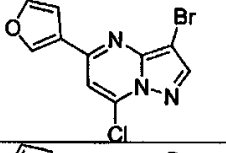
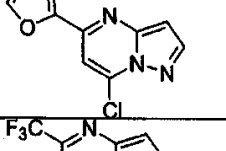
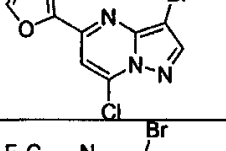
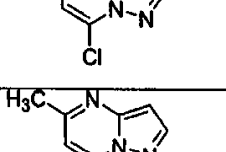
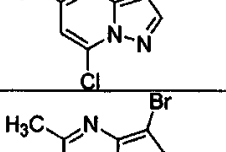
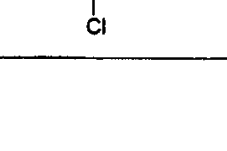
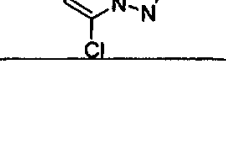
표 9

제조 실시예	컬럼 2	컬럼 3	CMPD
128			MS: MH ⁺ = 326
129			MS: MH ⁺ = 342
130			MS: MH ⁺ = 376

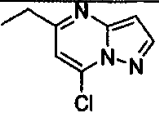
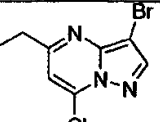
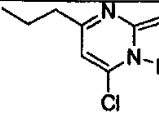
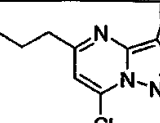
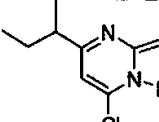
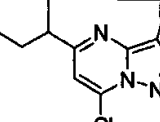
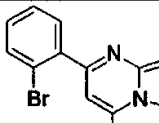
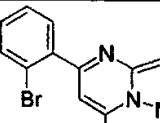
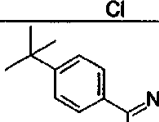
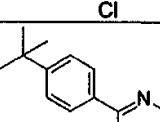
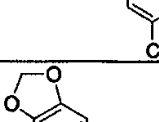
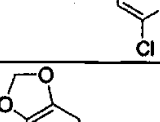
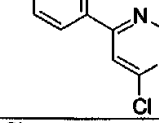
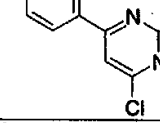
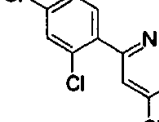
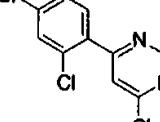
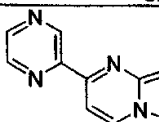
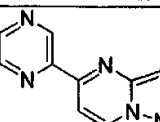
[0269]

131			MS: MH ⁺ =274
132			MS: MH ⁺ =288
133			
134			수율 = 75% MS: MH ⁺ = 338
135			수율 = 52% MS: MH ⁺ = 368
136			수율 = 87% MS: MH ⁺ = 376
137			수율 = 100% MS: MH ⁺ = 316
138			수율 = 92% MS: MH ⁺ = 330

[0270]

139			수율 = 82% MS: MH ⁺ = 395
140			수율 = 88% MS: MH ⁺ = 308
141			수율 = 100% MS: MH ⁺ = 322
142			MH ⁺ = 266
143			
144			
145			
146			
147			

[0271]

148			
149			
150			
151			LCMS: MH ⁺ = 386
152			수율 = 양 MH ⁺ = 364
153			수율 = 양 MH ⁺ = 353
154			수율 = 95 MH ⁺ = 378
155			수율 = 77 MH ⁺ = 311
156			수율 = 양 MH ⁺ = 314

[0272]

157			수율 = 99 MH ⁺ = 328
158			수율 = 98 MH ⁺ = 326
159			수율 = 99 MH ⁺ = 449
160			수율 = 95 MH ⁺ = 449
161			수율 = 72 MH ⁺ = 449
162			수율 = 98% LCMS: MH ⁺ = 302
163			수율 = 95% LCMS: MH ⁺ = 305
164			수율 = 50% ¹ H NMR (CDCl ₃) δ 8.36(s, 1H), 7.72(d, 1H), 7.20(s, 1H), 6.82(d, 1H), 3.99(s, 3H), 3.90(s, 3H),

[0273]

[0274] 제조 실시예 165:



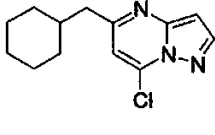
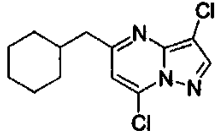
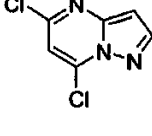
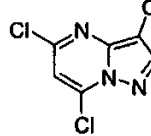
[0275]

[0276] CH₃CN(15mL)중 제조 실시예 80에서 제조한 화합물(0.3g, 1.2mmol)의 용액을 NCS(0.18g, 1.1당량)으로 처리하고 수득되는 용액을 4시간 동안 가열하여 환류시켰다. 추가의 NCS(0.032g, 0.2당량)을 가하고 수득되는 용액을 밤새 환류하에 교반하였다. 반응 혼합물을 실온으로 냉각시키고, 감압하에 농축시키고 잔사를 용출제로서 헥산중 20% EtOAc(0.28g, 83% 수율)를 사용한 플래쉬 크로마토그래피에 의해 정제하였다. LCMS : MH⁺ = 282.

[0277] 제조 실시예 166 내지 167:

[0278] 제조 실시예 165에 나타난 바와 본질적으로 동일한 과정에 의해, 표 10의 컬럼 2에 나타난 화합물을 단지 치환시켜, 표 10의 컬럼 3에 나타난 화합물을 제조하였다:

표 10

제조 실시예	컬럼 2	컬럼 3	CMPD
166			수율 = 82% LCMS: MH ⁺ = 286
167			

[0279]

[0280] 제조실시예 167.10:



[0281]

[0282] 제조 실시예 165에서 나타난 바와 본질적으로 동일한 과정에 의해, N-요도석신이미드를 단지 치환시켜, 상기 화합물을 제조하였다.

[0283] 제조 실시예 168:



[0284]

[0285] DMF(6mL)중 제조 실시예 79에서 제조한 화합물(1.0g, 4.35mmol)의 용액에 POCl₃(1.24mL, 3.05당량)을 가하고 수득되는 혼합물을 실온에서 밤새 교반하였다. 반응 혼합물을 0°C로 냉각시키고 과량의 POCl₃를 추가의 얼음으로 쿨칭시켰다. 수득되는 용액을 1N NaOH로 중화시키고, H₂O로 희석시키고, CH₂Cl₂로 추출하였다. 합한 유기물을 Na₂SO₄위에서 건조시키고, 여과하고, 진공하에 농축시켰다. 조약한 생성물을 용출제로서 CH₂Cl₂ 용액중 5% MeOH를 사용한 플래쉬 크로마토그래피에 의해 정제하였다(0.95g, 85% 수율). LCMS : MH⁺ = 258.

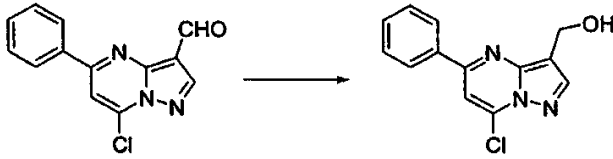
[0286] 제조 실시예 169:



[0287]

[0288] 제조 실시예 168에 나타난 바와 본질적으로 동일한 과정에 의해, 제조 실시예 80에서 제조한 화합물을 단지 치환시켜, 상기 화합물을 제조하였다(0.45g, 40% 수율).

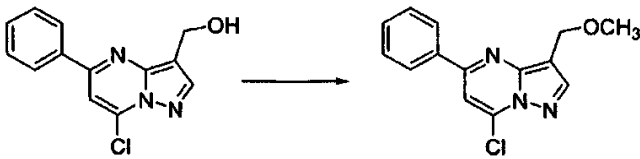
[0289] 제조 실시예 170:



[0290]

[0291] THF중 제조 실시예 169의 생성물(0.25g, 0.97mmol)의 용액에 NaBH₄(0.041g, 1.1당량)을 가하고 수득되는 용액을 실온에서 밤새 교반하였다. 반응 혼합물을 H₂O를 첨가하여 퀀칭시키고 CH₂Cl₂로 추출하였다. 합한 유기물을 Na₂SO₄위에서 건조시키고, 감압하에 농축시켰다. 조약한 생성물을 용출제로서 60 : 40의 헥산 : EtOAc 혼합물을 사용한 플래쉬 크로마토그래피에 의해 정제하였다(0.17g, 69% 수율). MS : MH⁺ = 260.

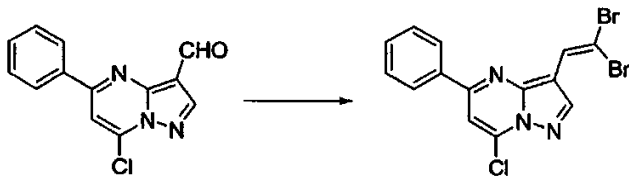
[0292] 제조 실시예 171:



[0293]

[0294] CH₂Cl₂(4ml)중 제조 실시예 170에서 제조한 화합물(0.12g, 0.462mmol), 디메틸 설페이트(0.088mL, 2.0 당량), 50% NaOH(0.26mL) 및 촉매적 Bu₄NBr의 용액을 실온에서 밤새 교반하였다. 반응 혼합물을 H₂O로 희석시키고 CH₂Cl₂로 추출하였다. 합한 유기물을 Na₂SO₄위에서 건조시키고, 여과하고, 감압하에 농축시켰다. 조약한 생성물을 용출제로서 헥산중 30% EtOAc를 사용한 플래쉬 크로마토그래피에 의해 정제하였다(0.062g, 48% 수율).

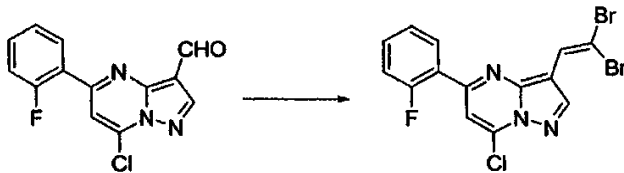
[0295] 제조 실시예 172



[0296]

[0297] 0°C에서 CH₂Cl₂(75ml)중 PPh₃(4.07g, 4.0당량) 및 CBr₄(2.57g, 2.0당량)의 용액에 제조 실시예 168에서 제조한 화합물(1.0g, 3.88mmol)을 가하였다. 수득되는 용액을 0°C에서 1시간 동안 교반하고 감압하에 농축시켰다. 잔사를 용출제로서 헥산 용액중 20% EtOAc를 사용한 플래쉬 크로마토그래피에 의해 정제하였다(1.07g, 67% 수율).

[0298] 제조 실시예 173:



[0299]

[0300] 제조 실시예 172에 나타난 바와 본질적으로 동일한 과정에 의해, 제조 실시예 169에서 제조한 화합물을 단지 치환시켜, 상기 화합물을 제조하였다(0.5g, 70% 수율).

[0301] 제조 실시예 174:



[0302]

[0303] 2-프로판올(50mL, 100.0mmol) 및 37% 수성 NH₃(10.0mL)중 제조 실시예 127에서 제조한 화합물(3.08g, 10.0mmol), 2.0M NH₃를 50°C에서 1일 동안 밀폐된 가압 용기속에서 교반하였다. 용매를 증발시키고 조약한 생성물을 용출제로서 3 : 1 CH₂Cl₂ : EtOAc를 사용한 플래쉬 크로마토그래피에 의해 정제하였다. 담황색 고체 (2.30g, 80%)를 수득하였다. LCMS : M⁺=289.

[0304] 제조 실시예 175 내지 180:

[0305] 제조 실시예 174에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 11의 컬럼 2에 나타낸 화합물을 단지 치환시켜, 표 11의 컬럼 3에 나타낸 화합물을 제조하였다.

표 11

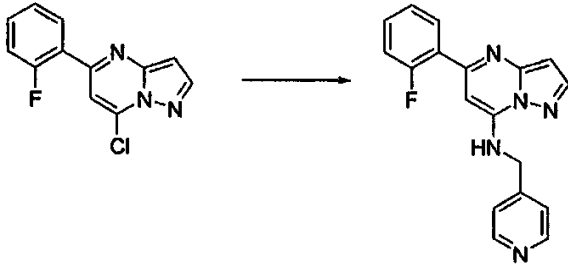
제조 실시예	컬럼 2	컬럼 3
175		
176		

[0306]

177		
178		
179		
180		

[0307]

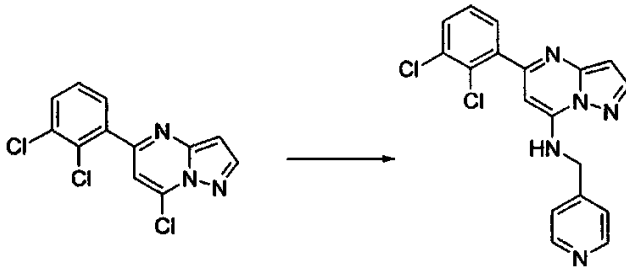
[0308] 제조 실시예 181:



[0309]

[0310] 제조 실시예 80에서 제조한 화합물(0.3g, 1.2mmol), K_2CO_3 (0.33g, 2당량), 및 4-아미노메틸피리딘(0.13mL, 1.1당량)을 밤새 가열하여 환류시켰다. 반응 혼합물을 실온으로 냉각시키고 감압하에 농축시켰다. 잔사를 H_2O 로 희석시키고 CH_2Cl_2 로 추출하였다. 합한 유기물을 Na_2SO_4 위에서 건조시키고, 여과하고, 농축시켰다. 조악한 생성물을 용출제로서 CH_2Cl_2 중 5%(MeOH중 10% NH_4OH) 용액을 사용하여 플래쉬 크로마토그래피로 정제하였다(0.051g, 40% 수율). LCMS : $MH^+ = 320$.

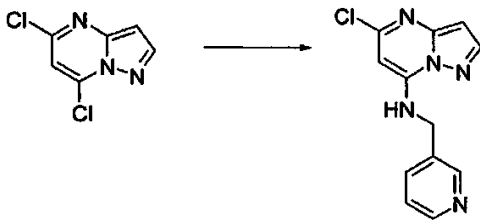
[0311] 제조 실시예 182:



[0312]

[0313] 제조 실시예 181에 나타낸 바와 본질적으로 동일한 과정에 의해, 제조 실시예 92에서 제조한 화합물을 단지 치환시켜, 상기 화합물을 제조하였다. LCMS : $MH^+ = 370$.

[0314] 제조 실시예 183:



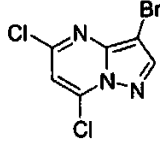
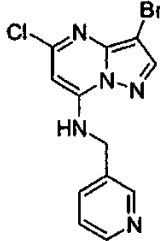
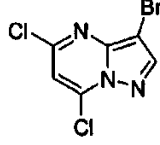
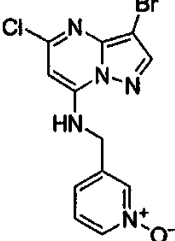
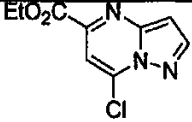
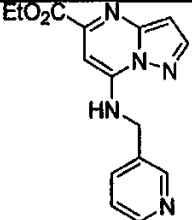
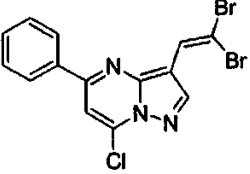
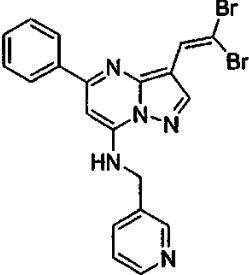
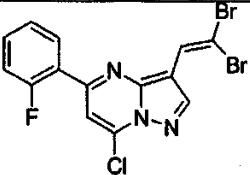
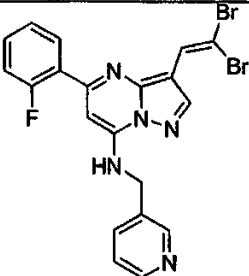
[0315]

[0316] 디옥산(5mL)중 제조 실시예 123에서 제조한 화합물(0.25g, 1.3mmol)의 용액에 iPr_2NEt (0.47mL, 2.0당량) 및 3-아미노메틸피리딘(0.15mL, 1.1당량)을 가하였다. 수득되는 용액을 실온에서 72시간동안 교반하였다. 반응 혼합물을 H_2O 로 희석시키고 EtOAc로 추출하였다. 합한 유기물을 H_2O 및 포화된 NaCl로 세척하고 Na_2SO_4 위에서 건조시키고, 여과하고, 진공하에 농축시켰다. 조악한 생성물을 용출제로서 CH_2Cl_2 중 5% MeOH를 사용하여 플래쉬 크로마토그래피로 정제하였다(0.29g, 83% 수율). MS : $MH^+ = 260$.

[0317] 제조 실시예 184 내지 187:

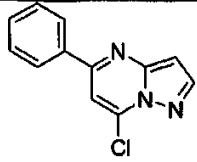
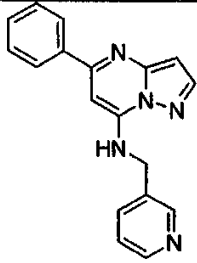
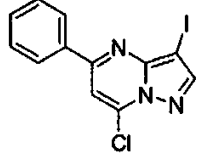
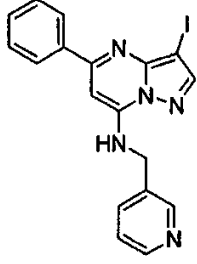
[0318] 제조 실시예 183에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 12의 컬럼 2에 나타낸 화합물을 단지 치환시켜, 표 12의 컬럼 3에 나타낸 화합물을 제조하였다.

표 12

제조 실시예	컬럼 2	컬럼 3
184		
184.1		
185		
186		
187		

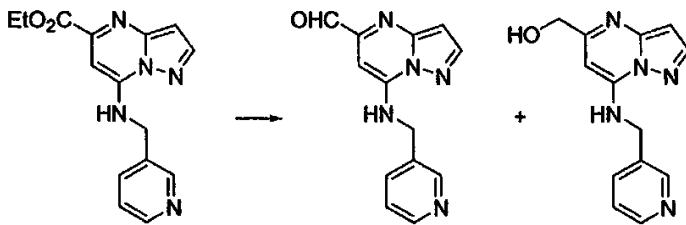
[0319]

[0320]

187.1		
187.11		

[0321]

[0322] 제조 실시예 188 및 제조 실시예 189:



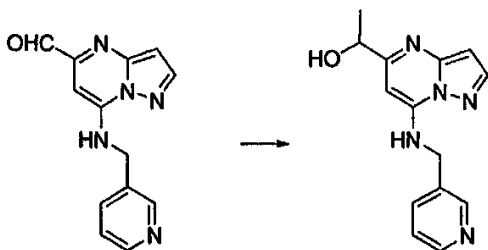
[0323]

[0324] -78℃에서 THF(35mL)중 제조 실시예 185에서 제조한 화합물(1.18g, 3.98mmol)의 용액에 LAH(4.78mL, Et₂O중 1M, 1.0당량)을 적가하였다. 반응 혼합물을 -78℃에서 3시간 동안 교반하고 이때 추가의 LAH(2.0mL, Et₂O중 1M, 0.42당량)를 적가하였다. 반응 혼합물을 추가로 1.25시간 동안 교반하고 포화된 Na₂SO₄(8.5mL)를 첨가하여 퀀칭시켰다. 반응 혼합물을 EtOAc(23mL), H₂O(2mL) 및 CH₃OH(50mL)로 희석시켰다. 수득되는 슬러리를 셀라이트의 플러그를 통해 여과하였다. 셀라이트를 CH₃OH로 세척하고 여액을 Na₂SO₄로 건조시키고, 여과하고, 농축시켰다. 생성물을 용출제로서 CH₂Cl₂ : CH₃OH(93 : 7) 용액을 사용하는 플래쉬 크로마토그래피에 의해 정제하여 제 1 용출 생성물로서의 알데하이드와 제 2 용출 생성물로서의 알콜을 수득하였다.

[0325] 제조 실시예 188:(알데하이드): 0.4g, 39% 수율. MS : MH⁺ = 254.

[0326] 제조 실시예 189:(알콜) : 0.25g, 24% 수율. MS : MH⁺ = 256.

[0327] 제조 실시예 190:

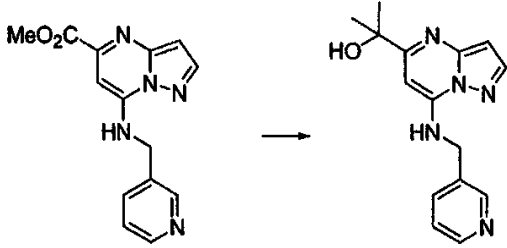


[0328]

[0329] 0℃에서 THF(2.0mL)중 제조 실시예 188(0.075g, 0.30mmol)에서 제조한 화합물의 용액에 CH₃MgBr(0.3mL, Et₂O중 3.0M 용액, 3.0당량)을 적가하였다. 수득되는 용액을 0℃에서 추가로 1.5시간 동안 교반하고, 실온으로 가운하고, 밤새 교반하였다. 추가의 CH₃MgBr(0.15mL, Et₂O중 3.0M, 1당량)을 가하고 수득되는 용액을 추가로 1.5시간 동안 교반하였다. 반응 혼합물을 0℃로 냉각시키고 추가의 포화된 NHC₄를 첨가하여 퀀칭시켰다. 수득되는 용

액을 CH_2Cl_2 및 H_2O 로 희석시키고 CH_2Cl_2 로 추출하였다. 합한 유기물을 포화된 NaCl 로 세척하고 Na_2SO_4 위에서 건조시키고, 여과하고, 농축시켰다. 조약한 생성물을 용출제로서 $\text{CH}_2\text{Cl}_2 : \text{CH}_3\text{OH}(90: 10)$ 용액을 사용하는 플래쉬 크로마토그래피에 의해 정제하였다(0.048g, 60% 수율). MS: $\text{MH}^+ = 270$.

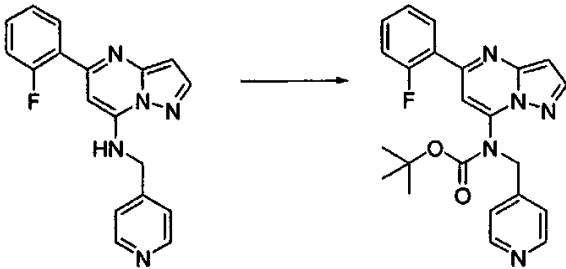
[0330] 제조 실시예 191:



[0331]

[0332] 제조 실시예 190에 나타낸 바와 본질적으로 동일한 과정에 의해, 제조 실시예 185에서 제조한 화합물을 단지 치환하고 과량의 MeMgBr (5당량)을 사용함으로써, 상기 화합물을 제조하였다.

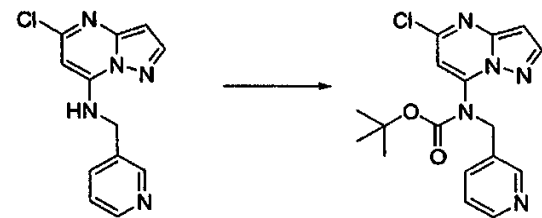
[0333] 제조 실시예 192:



[0334]

[0335] 디옥산(10mL)중 제조 실시예 181에서 제조한 화합물(0.29g, 0.91mmol), BOC_2O (0.22g, 1.1당량), 및 DMAP (0.13g, 1.1당량)을 실온에서 3일동안 교반하였다. 추가의 BOC_2O (0.10g, 0.5당량)을 가하고 반응 혼합물을 4시간동안 교반하였다. 반응 혼합물을 진공하에 농축시키고 포화된 NaHCO_3 (15mL)로 희석시키고, CH_2Cl_2 (2x100mL)로 추출하였다. 합한 유기물을 Na_2SO_4 위에서 건조시키고, 여과하고, 감압하에 농축시켰다. 조약한 생성물을 용출제로서 CH_2Cl_2 중 5%(MeOH 중 10% NH_4OH) 용액을 사용한 플래쉬 크로마토그래피에 의해 정제하였다(0.35g, 91% 수율). LCMS : $\text{MH}^+ = 420$.

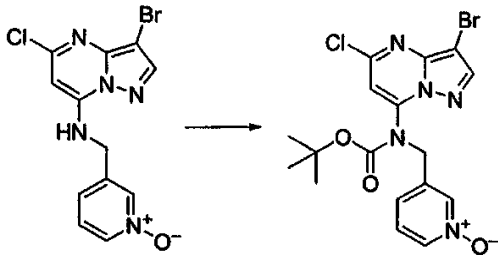
[0336] 제조 실시예 193:



[0337]

[0338] 제조 실시예 192에 나타낸 바와 본질적으로 동일한 과정에 의해, 제조 실시예 183에서 제조한 화합물을 단순 치환함으로써, 상기 화합물을 제조하였다. MS : $\text{MH}^+ = 360$.

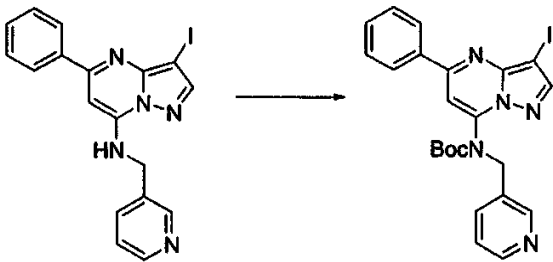
[0339] 제조 실시예 193.10:



[0340]

[0341] 제조 실시예 192에 나타낸 바와 본질적으로 동일한 과정에 의해, 제조 실시예 184.1에서 제조한 화합물을 단지 치환시켜, 상기 화합물을 제조하였다. MS : MH^+ = 454.

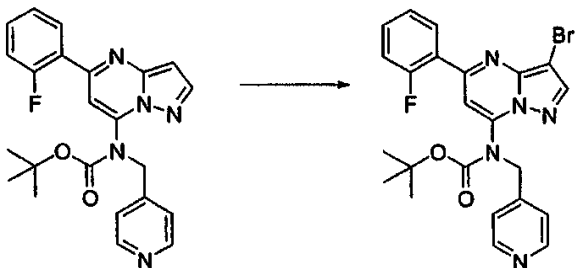
[0342] 제조 실시예 194:



[0343]

[0344] 제조 실시예 192에 나타낸 바와 본질적으로 동일한 과정에 의해, 제조 실시예 187.11에서 제조한 상기 화합물을 단지 치환시켜, 상기 화합물을 제조하였다(0.223g, 88% 수율). MS : MH^+ = 528.

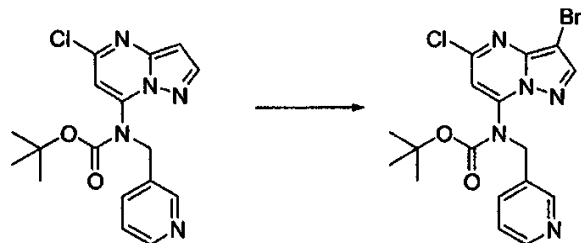
[0345] 제조 실시예 195:



[0346]

[0347] 제조 실시예 127에 나타낸 바와 본질적으로 동일한 과정에 의해, 제조 실시예 192에서 제조한 화합물을 단지 치환시켜, 상기 화합물을 제조하였다(0.38g, 95% 수율). LCMS : MH^+ = 498.

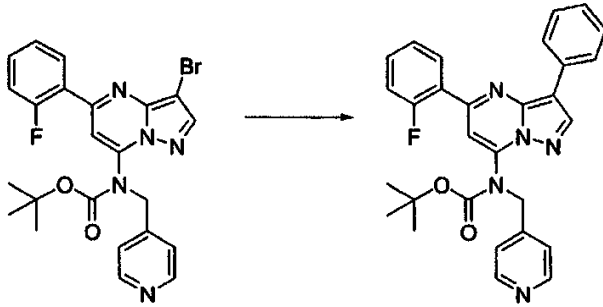
[0348] 제조 실시예 196:



[0349]

[0350] 제조 실시예 195에 나타낸 바와 본질적으로 동일한 과정에 의해, 제조 실시예 193에서 제조한 화합물을 단지 치환시켜, 상기 화합물을 제조하였다(0.3g, 83% 수율). MS : MH^+ = 438.

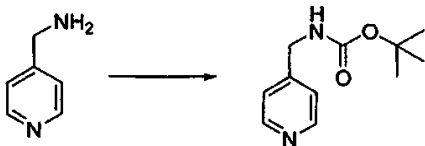
[0351] 제조 실시예 197:



[0352]

[0353] 제조 실시예 195에서 제조한 화합물(0.15g, 0.3mmol), 페닐보론산(0.073g, 2.0당량), K_3PO_4 (0.19g, 3.0당량), 및 $Pd(PPh_3)_4$ (0.017g, 5mol%)의 용액을 DME(16mL) 및 H_2O (4mL)속에서 환류하에 7시간 동안 가열하였다. 수득되는 용액을 실온으로 냉각시키고, H_2O (10mL)로 희석시키고, CH_2Cl_2 (3x50mL)로 추출하였다. 합한 유기물을 Na_2SO_4 위에서 건조시키고, 여과하고, 농축시켰다. 조약한 생성물을 용출제로서 CH_2Cl_2 용액중 2.5%(MeOH중 10% NH_4OH)를 사용하여 플래쉬 크로마토그래피에 의해 정제하였다(0.16g, 100% 수율).

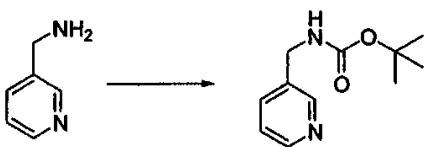
[0354] 제조 실시예 198:



[0355]

[0356] CH_2Cl_2 (50mL)중 4-아미노피리딘(1.41mL, 13.87mmol)의 용액에 BOC_2O (3.3g, 1.1당량) 및 TEA를 가하고 수득되는 용액을 실온에서 2시간 동안 교반하였다. 반응 혼합물을 H_2O (50mL)로 희석시키고 CH_2Cl_2 로 추출하였다. 합한 유기물을 Na_2SO_4 위에서 건조시키고, 여과하고 감압하에 농축시켰다. 조약한 생성물을 용출제로서 CH_2Cl_2 중 5%(MeOH중 10% NH_4OH) 용액을 사용한 플래쉬 크로마토그래피에 의해 정제하여 황색 고체(2.62g, 91% 수율)를 수득하였다. LCMS : $MH^+ = 209$.

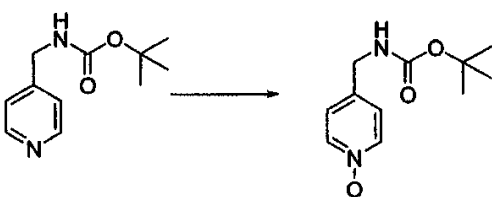
[0357] 제조 실시예 199:



[0358]

[0359] 제조 실시예 198에 나타낸 바와 본질적으로 동일한 과정에 의해, 3-아미노메틸피리딘을 단지 치환시켜, 상기 화합물을 황색 오일로서 제조하였다(2.66g, 92% 수율). LCMS : $MH^+ = 209$.

[0360] 제조 실시예 200:

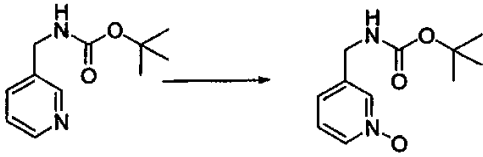


[0361]

[0362] 0°C에서 CH_2Cl_2 (5mL)중 제조 실시예 198에서 제조한 화합물(0.20g, 0.96mmol)의 용액에 m-CPBA(0.17g, 1.0당량)를 가하고 수득되는 용액을 0°C에서 2시간 동안 교반하고 4°C에서 밤새 저장하며 이때 반응 혼합물을 실온으로 가온하고 3시간 동안 교반하였다. 반응 혼합물을 H_2O 로 희석시키고 CH_2Cl_2 로 추출하였다. 합한 유기물을

Na₂SO₄위에서 건조시키고, 여과하고, 농축시켰다. 조악한 생성물을 용출제로서 10%(MeOH중 10% NH₄OH) 용액을 사용한 플래쉬 크로마토그래피에 의해 정제하였다 : LCMS : MH⁺ = 255.

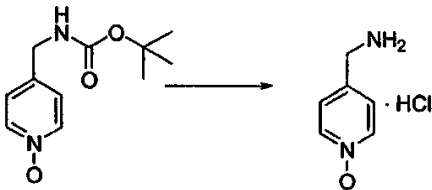
[0363] 제조 실시예 201:



[0364]

[0365] H₂O(250mL)중 옥손(58.6g)의 용액을 MeOH(200mL) 및 H₂O(250mL)중 제조 실시예 199에서 제조한 화합물(27g, 0.13mol) 및 NaHCO₃(21.8g, 2.0당량)에 적가하였다. 수득되는 용액을 실온에서 밤새 교반하였다. 반응 혼합물을 CH₂Cl₂(500mL)로 희석시키고 여과하였다. 층을 분리하고 수성 층을 CH₂Cl₂로 추출하였다. 합한 유기물을 Na₂SO₄위에서 건조시키고, 여과하고, 감압하에 농축시켜 백색 고체(21.0g, 72% 수율)를 수득하였다. MS : MH⁺ = 255.

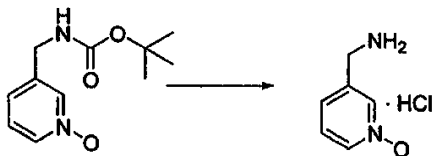
[0366] 제조 실시예 202:



[0367]

[0368] 제조 실시예 200에서 제조한 화합물(0.29g, 1.29mmol)을 디옥산(0.97mL)중 4M HCl속에서 실온으로 2시간 동안 교반하였다. 반응 혼합물을 진공하에 농축시키고 추가의 정제없이 사용하였다. MS : MH⁺ = 125.

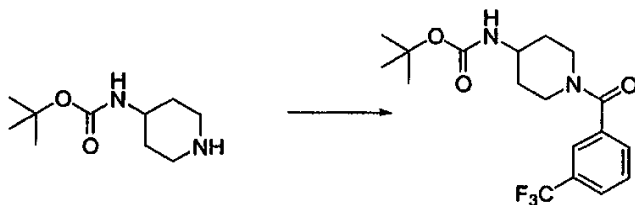
[0369] 제조 실시예 203:



[0370]

[0371] 제조 실시예 202에 나타난 바와 본질적으로 동일한 과정에 의해, 제조 실시예 201에서 제조한 화합물을 단지 치환시켜, 상기 나타난 화합물을 제조하였다. LCMS : MH⁺ = 125.

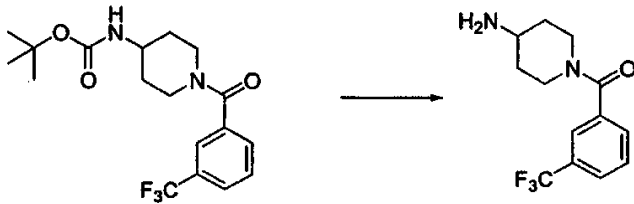
[0372] 제조 실시예 204:



[0373]

[0374] 0°C에서 CH₂Cl₂(10mL)중 4-N-t-부톡시카보닐아미노피페리딘(0.8g, 4.0mmol)에 TEA(1.40mL, 2.5당량) 및 3-트리플루오로메틸 벤조일 클로라이드(1.05g, 1.25 당량)를 가하였다. 수득되는 용액을 15분 동안 교반하고 실온으로 가온하고 3시간 동안 교반하였다. 반응 혼합물을 CH₂Cl₂로 희석시키고 5% Na₂CO₃(2x100mL)로 세척하였다. 유기 층을 Na₂SO₄위에서 건조시키고, 여과시키며 농축시켜, 담황색 고체(정량적 조 수율)를 수득하였다.

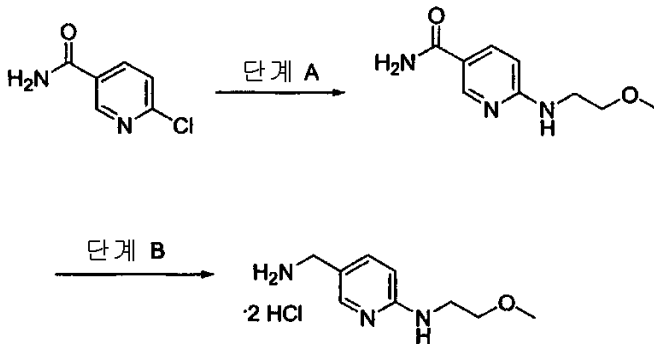
[0375] 제조 실시예 205:



[0376]

[0377] 0°C에서 CH₂Cl₂(15mL)중 제조 실시예 204에서 제조한 화합물(1.0g, 2.76mmol)의 용액에 TFA(8mL)를 가하고 수득되는 용액을 0°C에서 30분 동안 교반하고 실온에서 1시간 동안 교반하였다. 반응 혼합물을 Na₂CO₃(40g)위에 붓고 H₂O(400mL)를 가하고 수득되는 혼합물을 CH₂Cl₂로 추출하였다. 합한 유기물을 Na₂SO₄위에서 건조시키고, 여과시키며 감압하에 농축시켰다. 조약한 생성물을 용출제로서 CH₂Cl₂중 20% 용액(MeOH중 7N NH₃)을 사용하여 플래쉬 크로마토그래피에 의해 정제하였다(0.6g, 82% 수율).

[0378] 제조 실시예 206:



[0379]

[0380] 단계 A:

[0381] 실온에서 이소아밀 알콜(15mL)중 6-클로로니코틴아미드(1g, 6.39mmol)의 용액에 Na₂CO₃(0.81g, 7.67mmol)에 이어서 메톡시에틸아민(0.67 mL, 7.67mmol)을 가하였다. 혼합물을 130°C에서 16시간 동안 가열하고, 실온으로 냉각시키고, 매질 유리 프릿된 여과기를 통해 여과하였다. 수득되는 여액을 감압하에 농축시키고 수득되는 고체를 Et₂O(2x10mL)로 분쇄하였다. 조약한 고체를 고압하에 두어 1.2g(96%)의 담황색 고체를 수득하였다. M + H = 196.

[0382] 단계 B:

[0383] 0°C에서 THF(5mL)중 제조 실시예 206, 단계 A로부터의 아미드(1.2g, 6.12mmol)의 용액에 BH₃-THF(43mL; 43mmol)의 용액을 10분에 걸쳐 적가하였다. 수득되는 용액을 실온으로 가온하고 14시간 동안 교반하였다. 혼합물을 0°C로 냉각시키고 6M HCl(35mL), 물(30mL), 및 MeOH(150mL)로 연속해서 처리하였다. 혼합물을 8시간 동안 교반하고 감압하에 농축시켰다. 조약한 잔사를 MeOH로 분쇄하고, 감압하에 농축시키고 고 진공하에 두어 디하이드로클로라이드 염으로서의 백색 고체1.6g(82%)을 수득하였다. M+H(유리 염기) = 182.0. 당해 물질을 7-Cl 부가물과의 커플링시 조약한 상태로 사용하였다.

[0384] 제조 실시예 207 내지 211:

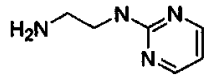
[0385] 제조 실시예 206에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 13의 컬럼 2에 나타낸 아민을 단지 사용함으로써, 표 13의 컬럼 3에 나타낸 아민을 제조하였다:

표 13

제조 실시예	컬럼 2 (아민)	컬럼 3 (아민)	CMPD M+H (유리 염기)
207			M+H = 138
208			M+H = 152
209			M+H = 178
210			M+H = 195
211			M+H = 207

[0386]

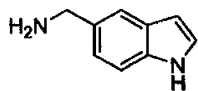
[0387] 제조 실시예 212:



[0388]

[0389] 상기 화합물을 제W091/18904호에 기술된 방법에 따라 제조하였다.

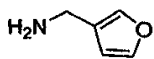
[0390] 제조 실시예 213:



[0391]

[0392] 상기 화합물을 미국 특허 제6,180,627 B1호에 기술된 방법에 따라 제조하였다.

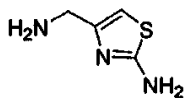
[0393] 제조 실시예 214:



[0394]

[0395] 공지된 아민을 문헌[참조: J. Med. Chem.(2001), 44, 4505-4508]에 기술된 방법에 따라 제조하였다.

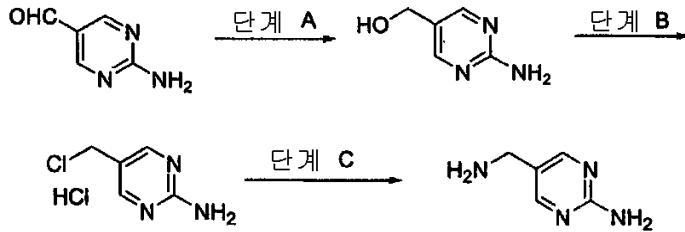
[0396] 제조 실시예 215:



[0397]

[0398] 공지된 아민을 문헌[참조: J. Med. Chem.(1997), 40, 3726-3733]에 기술된 방법에 따라 제조하였다.

[0399] 제조 실시예 216:



[0400]

[0401] 단계 A:

[0402] MeOH(300mL)중 알데하이드(50g, 0.41mol)[참조: 제WO 0232893호]의 용액을 0℃로 냉각시키고 20분에 걸쳐 NaBH₄(20g, 6개 배취중 0.53mol)로 조심스럽게 처리하였다. 이후에 반응물을 20℃로 가온시키고 4시간 동안 교반하였다. 혼합물을 다시 0℃로 냉각시키고, 포화된 수성 NH₄Cl로 조심스럽게 퀀칭시키고 농축시켰다. 플래쉬 크로마토그래피(5-10% 7N NH₃-MeOH/CH₂Cl₂)하여 담황색 고체로서의 1급 알콜(31g, 62%)을 수득하였다.

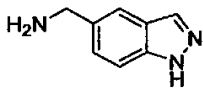
[0403] 단계 B:

[0404] CH₂Cl₂(500mL)중 실시예 216, 단계 A로부터의 알콜(31g, 0.25mol)의 슬러리를 0℃로 냉각시키고 SOCl₂(55mL, 30분에 걸쳐 0.74mol)로 서서히 처리하였다. 이후에 반응물을 20℃에서 밤새 교반하였다. 물질을 농축시키고 아세톤속에서 슬러리화한 후 여과하였다. 수득되는 베이지색 고체를 진공하에 밤새 건조시켰다(38.4g, 52%, HCl 염).

[0405] 단계 C:

[0406] 교반 바가 장착된 15mL 들이 가압 튜브에 제조 실시예 216, 단계 B로부터의 클로라이드(150mg, 0.83mmol)에 이어서 7M NH₃/MeOH(10mL)을 가하였다. 수득되는 용액을 실온에서 48시간 동안 교반하고 혼합물을 감압하에 농축시켜 담황색 고체(0.146g, 83%)를 수득하였다. M+H(유리 염기) = 140.

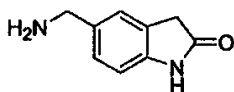
[0407] 제조 실시예 217:



[0408]

[0409] 상기 화합물을 제WO 00/26210호에 기술된 방법에 따라 제조하였다.

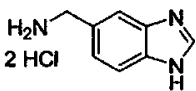
[0410] 제조 실시예 218:



[0411]

[0412] 상기 화합물을 제WO 99/10325호에 기술된 방법에 따라 제조하였다.

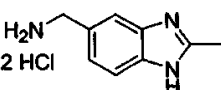
[0413] 제조 실시예 219:



[0414]

[0415] 공지된 아민 디하이드로클로라이드를 제WO 02/64211호에 기술된 방법에 따라 제조하였다.

[0416] 제조 실시예 220:



[0417]

[0418] 상기 화합물을 제W0 02/64211호에 기술된 방법에 따라 제조하였다.

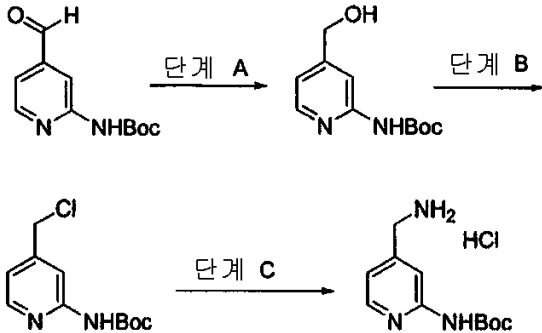
[0419] 제조 실시예 221:



[0420]

[0421] 공지된 1급 알콜을 제W0 00/37473호에 따라 제조하고 제W0 02/064211호에 따라 제조 실시예 220에서와 유사한 양식으로 목적인 아민 디하이드로클로라이드로 전환시켰다.

[0422] 제조 실시예 222:



[0423]

[0424] 단계 A:

[0425] 0°C에서 MeOH/THF(2mL/2mL)중 알데하이드(제W0 02/32893호)(0.46g, 2.07mmol)의 용액에 NaBH₄(94mg, 2.48mmol)을 한번에 가하였다. 수득되는 혼합물을 실온에서 12시간 동안 교반하고 포화된 수성 NH₄Cl(3mL)로 희석시켰다. 혼합물을 감압하에 농축시키고 수득되는 수성 층을 CH₂Cl₂(3x5mL)로 추출하였다. 유기 층을 합하고, 염수(1x5mL)로 세척하고, 건조(Na₂SO₄)시키고, 여과하였다. 유기 층을 감압하에 농축시켜 백색 고체 417mg(90% 수율)을 수득하였다. M+H = 225.

[0426] 단계 B:

[0427] CH₂Cl₂(4mL)중 제조 실시예 222, 단계 A로부터의 조악한 알콜(0.4g, 1.78mmol)을 SOCl₂(0.65mL, 8.91mmol)에 가하고 혼합물을 실온에서 2시간 동안 교반하였다. 혼합물을 감압하에 농축시켜 담황색 고체 407mg(94%)을 수득하였다. M+H = 243. 조악한 생성물을 추가의 정제없이 수득하였다.

[0428] 단계 C:

[0429] 가압 튜브속에서 제조 실시예 222, 단계 B로부터의 조악한 클로라이드 용액(0.33g, 1.36mmol)에 7M NH₃/MeOH(35mL)를 충전시키고 혼합물을 72시간 동안 교반하였다. 혼합물을 감압하에 농축시켜 황색 반고체 257mg(85%)을 수득하였다. M+H(유리 염기) = 224.

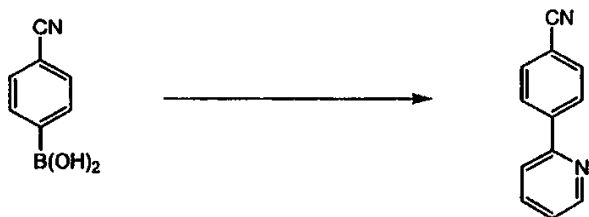
[0430] 제조 실시예 223:



[0431]

[0432] 제조 실시예 222로부터의 아민 하이드로클로라이드(0.24g, 1.1mmol) 및 교반 바아가 충전된 환저 플라스크에 4N HCl/디옥산(10mL)을 가하였다. 수득되는 용액을 실온에서 12시간 동안 교반하고, 감압하에 농축시키고, CH₂Cl₂(3x5mL)로 분쇄하였다. 조악한 생성물을 여과하고, Et₂O(2x5mL)로 세척하고, 고 진공하에 건조시켜 디하이드로클로라이드 염으로서 0.19g(91%)을 수득하였다. M+H(유리 염기) = 124.

[0433] 제조 실시예 224:



[0434]

[0435] Pd(PPh₃)₄(0.404mg, 0.35mmol)을 75mL의 아세토니트릴중 4-시아노벤젠 보론산(1.029g, 7mmol) 및 2-브로모피리딘(1.11g, 7mmol)의 탈기된 용액에 가하였다. 0.4M 탄산나트륨 용액(35mL)을 반응 혼합물에 가하고 수득되는 용액을 90℃에서 Ar하에 24시간 동안 환류시켰다(반응의 진행을 TLC로 모니터하였다). 반응 혼합물을 냉각시키고 수성 층을 분리하였다. 생성물 및 소비된 촉매를 함유하는 유기 층을 실리카 겔(15g)과 혼합하고 농축 건조시켰다. 4-(2-피리딜)-벤조니트릴을 컬럼 크로마토그래피(0.850g, 68%)로 분리하였다. LCMS : MH⁺ = 181; ¹H NMR(CDCl₃) δ 8.85(d, 1H), 8.7(dd, 1H), 7.9(dd, 1H), 7.75(d, 2H), 7.7(d, 2H), 7.4(dd, 1H).

[0436] 제조 실시예 225 내지 228:

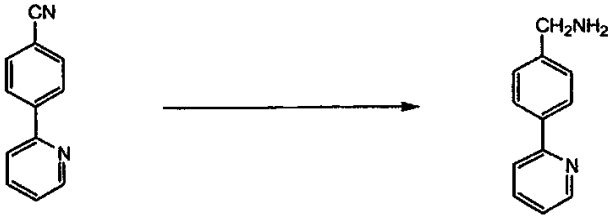
[0437] 제조 실시예 224에 기술된 바와 본질적으로 동일한 과정에 의해, 표 14의 컬럼 2에 나타낸 브로마이드를 단지 치환시켜, 표 14의 컬럼 3의 화합물을 제조하였다.

표 14

제조 실시예	컬럼 2	컬럼 3	컬럼 4
225			수율 = 70% LCMS: MH ⁺ = 187
226			수율 = 60% LCMS: MH ⁺ = 187
227			수율 = 70% LCMS: MH ⁺ = 186
228			수율 = 70% LCMS: MH ⁺ = 200

[0438]

[0439] 제조 실시예 229:



[0440]

[0441] BH₃-THF 용액(1M, 24mL, 5당량)을 무수 THF(25mL)중 4-(2-피리딜)-벤조니트릴(0.85g, 4.72mmol)의 교반 용액에 Ar하에서 서서히 가하고 수득되는 용액을 약 12시간 동안 환류시켰다. 용액을 빙수를 사용하여 0℃로 냉각시켰다. 메탄올(15mL)을 냉 반응 혼합물에 적가하고 1시간 동안 교반하여 과량의 BH₃를 제거하였다. HCl-메탄올(1M, 10mL)를 반응 혼합물에 서서히 가하고 5시간 동안 환류시켰다. 용액을 농축 건조시키고 잔사를 25mL의 물 속에 용해하고 에테르로 추출하여 반응하지 않은 어떠한 물질도 제거하였다. 수용액을 고체 탄산칼륨으로 pH 10 내지 11로 중화시켰다. 이렇게 형성된 유리 아민을 에테르로 추출하고, 탄산칼륨(0.45g, 50%)위에서 건조시켰다. LCMS : MH⁺ = 185; ¹H NMR(CDC₁₃) δ 8.85(d, 1H), 8.7(dd, 1H), 7.9(dd, 1H), 7.75(d, 2H), 7.7(d, 2H), 7.4(dd, 1H), 3.7(t, 2H), 1.7(t, 2H).

[0442] 제조 실시예 230 내지 233:

[0443] 제조 실시예 229에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 15의 컬럼 13의 화합물을 제조하였다.

표 15

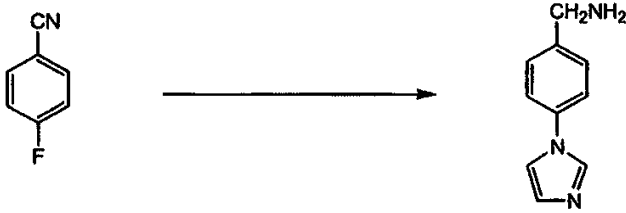
제조 실시예	컬럼 2	컬럼 3	컬럼 4
230			수율 = 60% LCMS: MH ⁺ = 191

[0444]

231			수율 = 60% LCMS: MH ⁺ = 191
232			수율 = 70% LCMS: MH ⁺ = 190
233			수율 = 70% LCMS: MH ⁺ = 204

[0445]

[0446] 제조 실시예 234:



[0447]

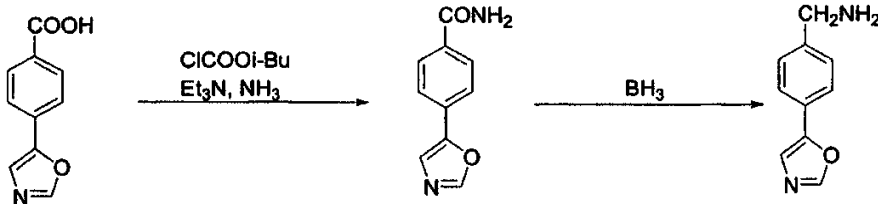
[0448] 단계 A:

[0449] DMF(50ml)중 4-플루오로벤조니트릴(3g, 25mmol) 및 이미다졸릴 나트륨(2.48g, 27.5mmol)의 혼합물을 80℃에서 Ar하에 12시간 동안 교반하였다. 반응의 진행을 TLC로 모니터하였다. 반응 혼합물을 진공하에 농축시키고 잔사를 50mL의 물로 희석시키고 교반하였다. 수성 혼합물을 EtOAc(2x50mL)로 추출하였다. 합한 EtOAc 추출물을 무수 MgSO₄위에서 건조시키고, 농축시키고, 4-(1-이미다졸릴)-벤조니트릴을 컬럼 크로마토그래피에 의해 분리하였다(3.6g, 78%). LCMS : MH⁺ = 170; ¹H NMR(CDC₁₃) δ 8.0(s, 1H), 7.5(d, 2H), 7.4(m, 3H), 7.3(d, 1H)

[0450] 단계 B:

[0451] 4-(1-이미다졸릴)-벤조니트릴(1g, 5.92mmol)을 무수 THF(10mL)속에 용해시키고 실온에서 LAH-THF(THF중 1M, 18mL)의 교반 용액에 적가하였다. 반응 혼합물을 Ar하에 2시간 동안 환류시키고 당해 과정을 TLC로 모니터하였다. 혼합물을 0℃로 냉각시키고 포화된 Na₂SO₄-H₂O 용액을 적가함으로써 퀴청시켰다. 혼합물을 1시간 동안 교반하고 여과하여 리튬 염을 제거하였다. 여액을 무수 MgSO₄위에서 건조시키고 농축시켜 4-(1-이미다졸릴)-벤질아민(0.8g, 80%)을 수득하였다. LCMS : MH⁺ = 174.

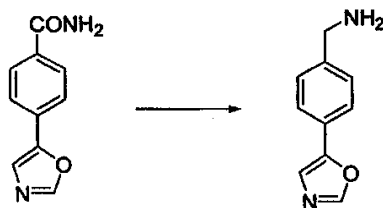
[0452] 제조 실시예 235:



[0453]

[0454] THF 25mL 중의 4-(5-옥사졸릴)벤조산(1.0g, 5.46mmol) 및 Et₃N(552mg, 5.46mmol)의 혼합물을 0℃으로 냉각시키고, CICOOi-Bu(745mg, 5.46mmol)을 적가하였다. 추가의 시간이 경과한 후에, 반응 혼합물을 추가로 5분 동안 교반한 다음, 수성 NH₄OH (0.63mL의 28% 용액, 10.46mmol)를 가하였다. 밤새 교반한 후에, 용매를 증발시키고, 잔사를 물에 용해시키고 pH 9로 염기성화시켰다. 침전된 고체를 여과시키고, 물로 세척하고 진공 건조기 (vacuum desiccator) 속의 P₂O₅ 위에서 건조시켜 4-(5-옥사졸릴)-벤즈아미드 500mg(48%)을 수득하였다: ¹H NMR (DMSO-d₆) δ 8.50 (s, 1H), 8.20-7.80 (m, 5H).

[0455] 제조 실시예 236:



[0456]

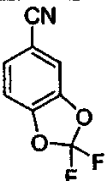
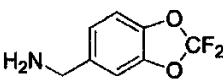
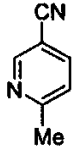
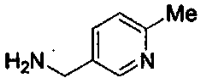
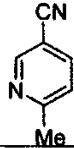
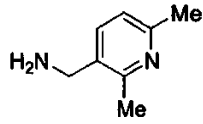
[0457] 무수 THF 10mL 중의 4-(5-옥사졸릴)벤즈아미드(500mg, 2.657mmol)의 현탁액을 0℃로 냉각시키고, 1M BH₃·THF(10.00mmol) 10mL를 가하였다. 내용물을 밤새 환류시키고 과량의 보란을 메탄을 적가하여 분해시켰다. 용매를 증발시키고 잔사를 메탄올성 HCl로 처리하여 아민-보란 착체를 수득하였다. 메탄올을 증발시킨 후에, 잔

사를 물에 용해시키고, pH 10으로 염기성화시키고 생성물을 DCM 속으로 추출시켰다. DCM 층을 건조시키고 (K₂CO₃), 용매를 제거하여 4-(5-옥사졸릴)벤질아민 150mg (32%)을 수득하였다: ¹H NMR (CDCl₃) δ 7.90 (s, 1H), 7.60 (d, 2H), 7.40 (d, 2H), 7.30 (s, 1H), 3.90 (s, 2H).

[0458] 제조 실시예 237 내지 239:

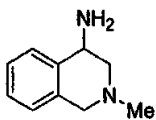
[0459] 상기한 바와 본질적으로 동일한 과정으로, 표 16의 컬럼 2의 화합물을 표 16의 컬럼 3에 나타난 방법을 사용하여 환원시키고, 표 16의 컬럼 4에 나타난 아민을 수득하였다.

표 16

제조 실시예	컬럼 2	컬럼 3	컬럼 4	CMPD
237		BH ₃		¹ H NMR (CDCl ₃) δ 7.15-6.90 (m, 3H), 3.85 (s, 2H), 1.45 (s, 2H)
238		H ₂		¹ H NMR (CDCl ₃) δ 8.40(s, 1H), 7.55 (dd, 1H), 7.10 (d, 1H), 3.85 (s, 2H), 2.50 (s, 3H), 1.70 (bs, 2 H)
239		BH ₃		

[0460]

[0461] 제조 실시예 240



[0462]

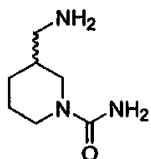
[0463] 문헌[참조: PCT Int. Appl, WO 0105783]에 의해 제조됨:

¹H NMR (CDCl₃) δ 7.35 (d, 1H), 7.24-7.10 (m, 2 H), 7.02 (d, 1H), 3.95 (t, 1H), 3.70 (d, 1H), 3.37 (d, 1H), 2.65 (m, 2H), 2.45 (s, 3H), 1.90 (bs, 2H)

[0464]

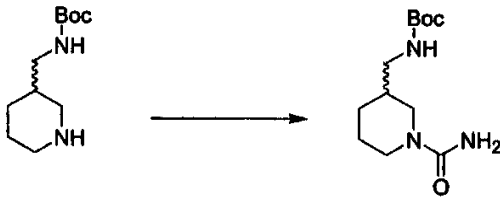
[0465] 제조 실시예 241:

[0466] 3-(아미노메틸)피페리딘-1-카복사미드



[0467]

[0468] A. 3-(3급-부톡시카보닐아미노메틸)피페리딘-1-카복스아미드



[0469]

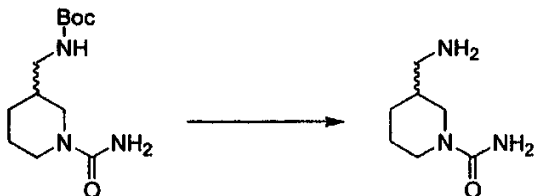
[0470] 3(R/S)-(3급-부톡시카보닐아미노메틸)피페리딘(3g, 14.0mmol)을 무수 디클로로메탄(50mL)에 용해시키고 트리메틸실릴이소시아네이트(9.68g, 11.4mL, 84.0mmol)을 가하였다. 혼합물을 아르곤하에 25℃에서 68시간 동안 교반하였다. 추가의 트리메틸실릴이소시아네이트(4.84g, 5.7mL, 42.0mmol)을 가하고 혼합물을 25℃에서 총 90시간 동안 교반하였다. 혼합물을 증발 건조시키고, 용출제로서 2% (메탄올중의 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(30x5cm) 상에서 크로마토그래피하여 3-(3급-부톡시카보닐아미노메틸)피페리딘-1-카복스아미드(3.05g, 85%)를 수득하였다: [본원에 나타낸 NMR 데이터에서, 용어 Calcd. for는 관련 화합물에 대한 '계산치'를 나타내고, requires는 '필요로 한다'를 의미한다.]

FABMS:

m/z 258.1 (MH⁺); HRFABMS: m/z 258.1816 (MH⁺). Calcd. for C₁₂H₂₄O₃N₃: m/z 258.1818; δ_H (CDCl₃) 1.22 9H, m, CH₃, 1.42 (9H, s, -COOC(CH₃)₃), 1.48 (1H, m, CH₂), 1.67 (2H, m, CH₂), 1.78 (1H, m, CH), 2.80 (1H, m, CH₂), 2.99, 3H, m, CH₂), 3.59 (1H, m, CH₂) 3.69 (1H, m, CH₂), 4.76 (2H, bm, CONH₂) 및 4.98ppm (1H, bm, NH); δ_C (CDCl₃) CH₃: 28.5, 28.5, 28.5; CH₂: 24.0, 28.3, 43.2, 45.1, 47.8; CH: 36.5; C: 79.4, 156.3, 158.5.

[0471]

[0472] B. 3-(아미노메틸)피페리딘-1-카복스아미드



[0473]

[0474] 3-(3급-부톡시카보닐아미노메틸)피페리딘-1-카복스아미드(150mg, 0.583mmol) (상기한 제조 실시예 241, 단계 A에 기술된 바와 같이 제조함)를 메탄올(3mL)에 용해시켰다. 1,4-디옥산(7.9mL)중의 10% 농도의 황산을 가하고 혼합물을 25℃에서 1시간 동안 교반하였다. 혼합물을 메탄올로 희석시키고 BioRad AG1-X8 수지(OH⁻ 형태)를 pH가 염기성이 될 때까지 가하였다. 수지를 여과시키고, 메탄올로 세척하고, 증발 건조시키고 용출제로서 디클로로메탄에 이어서 15% (메탄올중의 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(15 x 2cm) 상에서 크로마토그래피하여 3-(아미노메틸)피페리딘-1-카복스아미드(80mg, 87%)를 수득하였다:

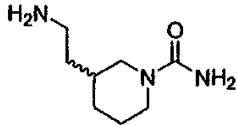
FABMS: m/z 158.1 (MH⁺); HRFABMS: m/z

158.1294 (MH⁺). Calcd. for C₇H₁₆N₃O: m/z 158.1293; δ_H (CDCl₃ + drop CD₃OD) 1.20 (1H, m, CH₂), 1.48 (1H, m, CH₂), 1.60 (1H, m, CH), 1.68 (1H, m, CH₂), 1.83 (1H, m, CH₂), 2.64 (bm, 2H, -CH₂NH₂), 2.82 (1H, m, CH₂), 3.02 (1H, m, CH₂), 2.98 (2H, m, CH₂), 3.70 (1H, m, -CH₂NH₂), 3.78 (1H, m, -CH₂NH₂) 및 5.24 ppm (1H, bs, NH); δ_C (CDCl₃ + drop CD₃OD) CH₂: 24.1, 28.6, 44.0, 44.8, 47.9; CH: 38.3; C: 159.0.

[0475]

[0476] 제조 실시예 242:

[0477] 3-(2-아미노에틸)피페리딘-1-카복스아미드



[0478]

[0479] A. 3-(2-3급-부톡시카보닐아미노에틸)피페리딘-1-카복스아미드



[0480]

[0481] 3-(2-3급-부톡시카보닐아미노에틸)피페리딘(500mg, 2.19mmol)을 무수 디클로로메탄(10mL)에 용해시키고 트리메틸실릴이소시아네이트(2.96mL, 21.9mmol)을 가하였다. 혼합물을 아르곤하에 25℃에서 3.35시간 동안 교반하였다. 혼합물을 디클로로메탄으로 희석시키고 포화된 수성 중탄산나트륨으로 세척하였다. 유기 층을 건조(MgSO₄)시키고, 여과시키고, 증발 건조시키고, 용출제로서 5% (메탄올중의 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(15 x 5cm) 상에서 크로마토그래피하여 3-(2-3급-부톡시카보닐아미노에틸)피페리딘-1-카복스아미드(417.7mg, 70%)를 수득하였다:

FABMS:

m/z 272.0 (MH⁺); HRFABMS: m/z 272.1979 (MH⁺). Calcd. for C₁₃H₂₆O₃: m/z 272.1974; δ_H (CDCl₃) 1.16 (1H, m, CH₂), 1-30-1.60 (5H, m, CH/CH₂), 1.46 (9H, s, -COOC(CH₃)₃), 1.68 (1H, m, CH₂), 1.84 (1H, m, CH₂), 2.54 (1H, dd, CH₂), 2.73 (1H, m, CH₂), 3.08 (1H, m, CH₂), 3.42 (1H, m, CH₂), 4.02 (1H, m, CH₂), 4.10 (1H, m, CH₂), 4.84 (1H, m, NH) 및 4.96 ppm (2H, bm, CONH₂); δ_C (CDCl₃) CH₃: 28.5, 28.5, 28.5; CH₂: 25.2, 31.7, 34.9, 37.3, 44.6, 50.3; CH: 32.9; C: 79.5, 156.4, 158.2.

[0482]

[0483] B. 3-(2-아미노에틸)피페리딘-1-카복스아미드



[0484]

[0485] 3-(2-3급-부톡시카보닐아미노에틸)피페리딘-1-카복스아미드(392.7mg, 1.45mmol) (상기한 제조 실시예 242, 단계 A에 기술된 바와 같이 제조함)를 메탄올 (7.5mL)에 용해시키고 1,4-디옥산 (19.5mL)중의 10%의 농도 황산을 가하였다. 혼합물을 25℃에서 1.25시간 동안 교반하였다. 혼합물을 메탄올로 희석시키고 BioRad AG1-X8 수지 (OH⁻ 형태)를 pH가 염기성이 될때까지 가하였다. 수지를 여과시키고, 메탄올로 세척하고, 증발 건조시키고, 용출제로서 15% (메탄올중의 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(30 x 2.5cm) 상에서 크로마토그래피하여 3-(2-아미노에틸)피페리딘-1-카복스아미드(233mg, 94%)를 수득하였다:

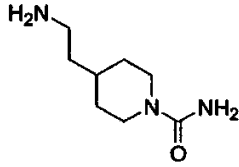
FABMS: m/z

172.1 (MH⁺); HRFABMS: m/z 172.1444(MH⁺). Calcd for C₈H₁₈N₃O requires: m/z 172.1450; δ_H (CDCl₃ + 3% CD₃OD) 1.14 (1H, m, CH₂), 1.40 (2H, m, CH₂), 1.49 (1H, m, CH), 1.58 (1H, m, CH₂), 1.69 (1H, m, CH₂), 1.85 (1H, m, CH₂), 2.55 (1H, m, CH₂), 2.67 (5H, m, CH₂/NH₂), 2.76 (1H, bm, CH₂), 2.84 (1H, m, CH₂) 및 3.82 ppm (2H, m, CONH₂); δ_C (CDCl₃ + 3% CD₃OD) CH₂: 24.8, 30.9, 36.6, 38.9, 44.9, 50.0; CH: 33.4.

[0486]

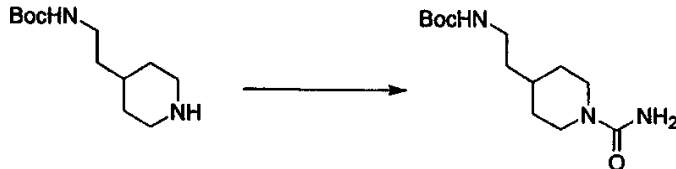
[0487] 제조 실시예 243:

[0488] 4-(2-아미노에틸)피페리딘-1-카복사아미드



[0489]

[0490] A. 4-(2-3급-부톡시카보닐아미노에틸)피페리딘-1-카복사아미드



[0491]

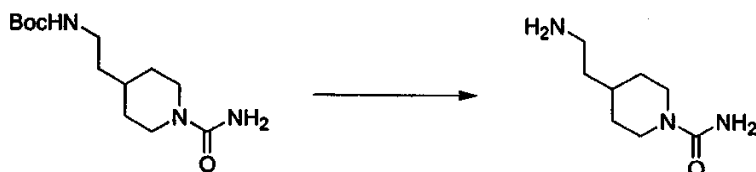
[0492] 4-(2-3급-부톡시카보닐아미노에틸)피페리딘(500mg, 2.19mmol)을 무수 디클로로메탄(10mL)에 용해시키고 트리메틸실릴이소시아네이트(2.96mL, 21.9mmol)를 가하였다. 혼합물을 아르곤하에 25℃에서 3.25시간 동안 교반하였다. 혼합물을 디클로로메탄으로 희석시키고 포화된 수성 중탄산나트륨으로 세척하였다. 유기 층을 건조(MgSO₄)시키고, 여과시키고, 증발 건조시키고, 용출제로서 5%(메탄올중 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카겔 컬럼(15x5cm)상에서 크로마토그래피하여 4-(2-3급-부톡시카보닐아미노에틸)피페리딘-1-카복사아미드(308.2mg, 52%)를 수득하였다:

[0493]

FABMS: m/z 272.0 (MH⁺); HRFABMS: m/z 272.1965 (MH⁺). Calcd. for C₁₃H₂₆O₃N₃: m/z 272.1974; δ_H (CDCl₃) 1.20 (2H, m, CH₂), 1.47 (9H, s, -COOC(CH₃)₃), 1.45-1.55 (3H, m, CH/CH₂), 1.75 (2H, m, CH₂), 2.82 (2H, m, CH₂), 3.19 (2H, m, CH₂), 3.96 (2H, m, CH₂), 4.64 (2H, m, CH₂) 및 4.70 ppm (1H, bm, NH); δ_C (CDCl₃) CH₃: 28.5, 28.5, 28.5; CH₂: 31.8, 31.8, 36.7, 38.0, 44.5, 44.5; CH: 33.4; C: 79.2, 156.7, 158.1.

[0494]

A. 3-(2-아미노에틸)피페리딘-1-카복사아미드



[0495]

[0496] 4-(2-3급-부톡시카보닐아미노에틸)피페리딘-1-카복사아미드(283.3mg, 1.04mmol)(상기 제조 실시예 243, 단계 A에 기술한 바와 같이 제조)를 메탄올(5.4mL)에 용해시키고 1,4-디옥산(14.2mL)중 10% 농도의 황산을 가하고 혼합물을 25℃에서 1.25시간 동안 교반하였다. 혼합물을 메탄올로 희석시키고 BioRad AG1-X8 수지(OH⁻ 형태)를 pH가 염기성이 될 때까지 가하였다. 수지를 여과하고, 메탄올로 세척하고, 증발건조시키고, 용출제로서 15%(메탄올중의 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(30 x 2.5cm) 상에서 크로마토그래피하여 3-(2-아미노에틸)피페리딘-1-카복사아미드(170mg, 95%)를 수득하였다:

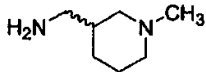
FABMS: m/z

172.1 (MH⁺); HRFABMS: m/z 172.1442. Calcd for C₈H₁₆N₃O requires: m/z 172.1450; δ_H (CDCl₃ + 3% CD₃OD) 1.16 (2H, m, CH₂), 1.43 (2H, m, CH₂), 1.52 (1H, m, CH), 1.70 (2H, m, CH₂), 2.70-2.85 (8H, m, CH₂) 및 3.92 ppm (2H, m, CONH₂); δ_C (CDCl₃ + 3% CD₃OD) CH₂: 31.9, 31.9, 39.0, 39.7, 44.4, 44.4; CH: 33.5; C: 158.7.

[0497]

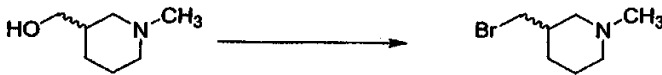
[0498] 제조 실시예 244:

[0499] 3-(아미노메틸)-1-메틸피페리딘



[0500]

[0501] A. 3-(브로모메틸)-1-메틸피페리딘



[0502]

[0503] 3-(하이드록시메틸)-1-메틸피페리딘(2g, 15.5mmol)을 무수 아세트니트릴(32mL)에 용해시키고 무수 피리딘 (2.02mL, 24.8mmol)을 가하고 용액을 0°C로 냉각시켰다. 디브로모트리페닐포스포란(8.49g, 20.2mmol)을 0°C에서 가하고 혼합물을 25° C로 가온시키고 94시간 동안 교반시켰다. 혼합물을 증발 건조시키고 잔사를 용출제로서 디클로로메탄, 디클로로메탄중의 35% 디에틸 에테르 및 디클로로메탄중의 5-10% 메탄올을 사용한 구배 용출을 사용하는 실리카 겔 컬럼(30 x 5cm) 상에서 크로마토그래피하여 3-(브로모메틸)-1-메틸피리딘(3.13g, 100%)을 수득하였다:

[0504]

[0505] A. 3-(디-3급-부톡시카보닐아미노메틸)-1-메틸피페리딘



[0506]

[0507] 3-(브로모메틸)-1-메틸피페리딘(1.5g, 7.81mmol) (상기한 제조 실시예 244, 단계 A로 부터) 및 디-3급-부틸이미노디카복실레이트(1.697g, 7.81 mmol)를 무수 아세트니트릴(25mL)에 용해시켰다. 탄산세슘(5.1g, 15.6mmol) 및 요오드화리튬(52mg, 0.391mmol)을 가하고 혼합물을 70° C에서 20시간 동안 교반하였다. 혼합물을 증발 건조시키고 잔사를 디클로로메탄과 포화된 수성 중탄산나트륨 사이에 분배하였다. 유기 층을 건조(MgSO₄)시키고, 여과하고 증발 건조시키고, 잔사를 용출제로서 디클로로메탄중의 3% 메탄올을 사용하는 실리카 겔 컬럼(30 x 5cm) 상에서 크로마토그래피하여 3-(디-3급-부톡시카보닐아미노)-1-메틸피페리딘(1.331g, 52%)을 수득하였다:

FABMS:

m/z 329.2 (MH⁺); HRFABMS: m/z 329.2438 (MH⁺). Calcd. for C₁₇H₃₃N₂O₄: m/z 329.2440; δ_H (CDCl₃) 1.10 (1H, m, CH₂), 1.54 (18H, s, -COOC(CH₃)₃), 1.86 (2H, m, CH₂), 2.01 (1H, m, CH₂), 2.19 (1H, m, CH), 2.34 (2H, bm, CH₂), 2.59 (3H, -NCH₃), 3.19 (2H, m, CH₂) 및 3.52/3.52 ppm (2H, -CH₂N-); δ_C (CDCl₃) CH₃: 28.5, 28.5, 28.5, 28.5, 28.5, 28.5, 47.2; CH₂: 25.4, 28.3, 50.4, 56.8, 60.8; CH: 37.2; C: 83.0, 83.0, 153.5, 153.5.

[0508]

[0509]

A. 3-(아미노메틸)-1-메틸피페리딘

[0510]



[0511]

3-(디-3급-부톡시카보닐아미노)-1-메틸피페리딘(500mg, 1.52mmol) (상기 제조 실시예 244, 단계 B로부터)을 메탄올(7.5mL)에 용해시키고 1,4-디옥산(19.75mL) 중의 10% (v/v) 농도의 황산을 가하였다. 용액을 25° C에서 0.5시간 동안 교반하였다. 메탄올(300mL)을 가한 다음, BioRad AG1-X8 수지(OH⁻ 형태)를 pH가 ~10이 될 때까지 가하였다. 수지를 여과시키고 메탄올(2 X 200mL)로 세척하였다. 합한 용출물을 증발 건조시키고 잔사를 용출제로서 10% (메탄올 중의 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(30 x 2.5cm) 상에서 크로마토그래피하여 3-(아미노메틸)-1-메틸피페리딘 (69.2mg, 35%)을 수득하였다:

FABMS: m/z 129.1 (MH⁺); HRFABMS: m/z

129.1392 (MH⁺). Calcd. for C₇H₁₇N₂: m/z 129.1392; δ_H (CDCl₃) 0.90 (2H, m, CH₂), 1.65 (2H, m, CH₂), 1.72 (1H, m, CH), 1.79 (1H, m, CH₂), 1.91 (1H, m, CH₂), 2.30 (3H, s, -NCH₃), 2.64 (2H, m, CH₂), 2.82 (1H, m, -CH₂NH₂) 및 2.92 ppm (1H, m, -CH₂NH₂); δ_C (CDCl₃) CH₃: 46.7; CH₂: 25.2, 28.0, 46.3, 56.4, 60.3; CH: 39.9.

[0512]

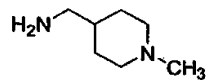
[0513]

제조 실시예 245:

[0514]

4-(아미노메틸)-1-메틸피페리딘

[0515]



[0516]

A. 1-메틸이소니페코트아미드

[0517]



[0518]

이소니페코트아미드(10g, 78.0mmol)을 증류수(100mL)에 용해시키고 37% 수성 포름알데히드(7.6mL, 2.81g HCHO와 동일함, 93.6mmol)를 가하였다. 습윤 10% Pd-C (8개 스푼 압설자)를 아르곤하에 가하고 혼합물을 25° C 및 50psi에서 43시간 동안 수소화시켰다. 촉매를 셀라이트를 통해 여과시키고 후자를 물 및 메탄올로 세척하였다. 합한 여액을 증발 건조시키고 잔사를 용출제로서 8%-10%-20% (메탄올중의 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(60 x 5cm) 상에서 크로마토그래피하여 1-메틸이소니페코트아미드(7.15g, 64%)를 수득하였다:

FABMS: m/z 143.1 (MH⁺);

HRFABMS: m/z 143.1184 (MH⁺). Calcd. for C₇H₁₅N₂O: m/z 143.1184; δ_H (d₆-DMSO) 1.50/1.57 (4H, m, CH₂), 1.76/1.94 (4H, m, CH₂), 2.10 (3H, s, -NCH₃), 2.72 (1H, m, CH) 및 6.68/7.18 ppm (2H, m, CONH₂); δ_C (d₆-DMSO) CH₃: 41.2; CH₂: 28.5, 28.5, 54.9, 54.9; CH: 46.2; C: 176.7.

[0519]

[0520]

B. 4-(아미노메틸)-1-메틸피페리딘



[0521]

[0522]

1-메틸이소니페코트아미드(6.75g, 47.5mmol)(상기한 제조 실시예 245, 단계 A에서 기술한 바와 같이 제조함)를 무수 THF(350mL)에 용해시키고 수득한 혼합물을 질소하에 0℃에서 무수 THF(100mL)중의 수소화알루미늄 리튬(1.8g, 47.5mmoles)의 교반된 슬러리에 한번에 가하였다. 혼합물을 0℃에서 30분 동안 교반한 다음, 질소하에 66℃에서 25시간 동안 가열하였다. 증류수(1.88mL)를 교반된 혼합물에 0℃에서 적가하고, 이어서, 20% 수성 수산화나트륨(1.42mL) 및 증류수(6.75mL)를 적가한 후 혼합물을 15분 동안 교반하였다. 혼합물을 여과하고 고체를 THF 및 디클로로메탄으로 세척하였다. 합한 여액을 증발 건조시키고 용출제로서 15%-20% (메탄올중의 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(30 x 5cm)상에서 크로마토그래피하여 4-(아미노메틸)-1-메틸피페리딘(0.678g, 11%)을 수득하였다:

FABMS: m/z 129.1 (MH⁺); HRFABMS: m/z

129.1389 (MH⁺). Calcd. for C₇H₁₇N₂: m/z 129.1392; δ_H (d₆-DMSO): 2.08ppm (3H, s, -NCH₃); δ_C (d₆-DMSO): CH₃: under DMSO peaks; CH₂: 29.6, 29.6, 46.7, 55.2, 55.2; CH: 46.2.

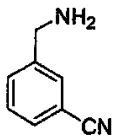
[0523]

[0524]

제조 실시예 246:

[0525]

3-(아미노메틸)벤조니트릴



[0526]

[0527]

A. 3-(디-3급-부톡시카보닐아미노)벤조니트릴



[0528]

[0529]

3-(브로모메틸)벤조니트릴(5g, 25.5mmol) 및 디-3급-부틸이미노디카복실레이트(5.54g, 25.5mmol)을 무수 THF(50mL)에 용해시키고 탄산세슘(16.62g, 25.5mmol) 및 요오드화리튬(170.5mg, 1.275mmol)을 가하였다. 혼합물을 70℃에서 22시간 동안 교반하고 반응을 상기한 제조 실시예 89, 단계 B에 기술된 바와 같이 후처리하였다. 잔사를 용출제로서 헥산중의 5% 에틸 아세테이트를 사용하는 실리카 겔 컬럼(60 x 5cm) 상에서 크로마토그래피하여 3-(디-3급-부톡시카보닐아미노)벤조니트릴(7.39g, 87%)을 수득하였다:

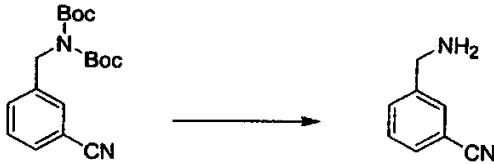
FABMS: m/z 333.2 (MH⁺);

HRFABMS: m/z 333.1815 (MH⁺); Calcd. for C₁₈H₂₅N₂O₄: m/z 333.1814; δ_H (CDCl₃) 1.52 (18H, s, -COOC(CH₃)₃), 4.84 (2H, s, CH₂), 7.48 (1H, m, Ar-H), 7.60 (2H, m, Ar-H) 및 7.65 ppm (1H, m, Ar-H); δ_C (CDCl₃) CH₃: 28.1, 28.1, 28.1, 28.1, 28.1, 28.1; CH₂: 48.4; CH: 129.2, 131.0, 131.0, 131.9; C: 83.2, 83.2, 112.5, 118.8, 140.1, 152.5, 152.5.

[0530]

[0531]

B. 3-(아미노메틸)벤조니트릴



[0532]

[0533]

3-(디-3급-부톡시카보닐아미노)벤조니트릴(2g, 6.0mmol)(상기한 제조 실시예 246, 단계 A에 기술된 바와 같이 제조함)을 메탄올(30mL) 및 10% (v/v) (1,4-디옥산 중의 10% 농도의 황산) (79mL)을 가하였다. 용액을 25℃에서 0.25시간 동안 교반하고 상기한 제조 실시예 89, 단계 C에 기술된 바와 같이 후처리하였다. 잔사를 용출제로서 3% (메탄올 중의 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(15 x 5cm)상에서 크로마토그래피하여 표제 화합물(651.4mg, 82%)을 수득하였다:

[0534]

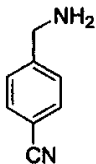
[0535]

[0536]

FABMS: m/z 133.1 (MH⁺); HRFABMS: m/z 133.0762 (MH⁺). Calcd. for C₈H₉N₂: m/z 133.0766 ; δ_H (CDCl₃) 2.57 (2H, s, -CH₂NH₂), 3.92 (2H, s, -CH₂NH₂), 7.46 (1H, m, Ar-H), 7.57 (2H, m, Ar-H) 및 7.64 ppm (1H, m, Ar-H); δ_C (CDCl₃) CH₂: 45.2; CH: 129.4, 130.7, 130.7, 131.8; C: 112.4, 118.8, 143.8.

제조 실시예 247:

4-(아미노메틸)벤조니트릴



[0537]

[0538]

A. 3-(디-3급-부톡시카보닐아미노메틸)벤조니트릴



[0539]

[0540]

4-(브로모메틸)벤조니트릴(5g, 25.5mmol) 및 디-3급-부틸이미노디카복실레이트(5.54g, 25.5mmol)을 무수 THF(50mL)에 용해시키고 탄산세슘(16.62g, 25.5mmol) 및 요오드화리튬(170.5mg, 1.275mmol)을 가하였다. 혼합물을 70℃에서 23시간 동안 교반하고 반응물을 상기한 제조 실시예 244, 단계 B에 기술된 바와 같이 후처리하였다. 잔사를 용출제로서 헥산중의 5% 에틸 아세테이트를 사용하는 실리카 겔 컬럼(50 x 5cm) 상에서 크로마토그래피하여 4-(디-3급-부톡시카보닐아미노메틸)벤조니트릴(7.07g, 83%)을 수득하였다:

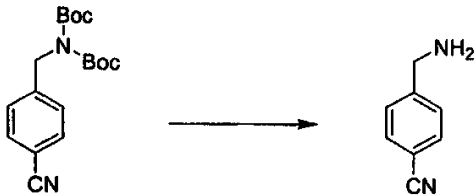
FABMS: m/z 333.2

(MH⁺); HRFABMS: m/z 333.1816 (MH⁺). Calcd. for C₁₈H₂₅N₂O₄: m/z 333.1814; δ_H (CDCl₃) 1.45 (18H, s, -COOC(CH₃)₃), 4.81 (2H, s, CH₂), 7.37 (2H, d, Ar-H) 및 7.62 ppm (2H, d, Ar-H); δ_C (CDCl₃) CH₃: 28.1, 28.1, 28.1, 28.1, 28.1, 28.1; CH₂: 49.2; CH: 127.8, 127.8, 132.3, 132.3; C: 83.2, 83.2, 111.1, 118.9, 144.1, 152.4, 152.4.

[0541]

[0542]

B. 4-(아미노메틸)벤조니트릴



[0543]

[0544]

4-(디-3급-부톡시카보닐아미노메틸)벤조니트릴(2g, 6.0mmol)(상기한 제조 실시예 247, 단계 A에 기술된 바와 같이 제조함)을 TFA(4mL)에 용해시키고 용액을 25℃에서 0.25시간 동안 교반하였다. 반응 혼합물을 디클로로메탄으로 희석시키고 1N 수산화나트륨으로 추출하였다. 유기 층을 건조(MgSO₄)시키고, 여과하고 증발 건조시켰다. 잔사를 용출제로서 3%(메탄올중의 10% 농도의 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(15 x 5cm)상에서 크로마토그래피하여 4-(아미노메틸)벤조니트릴(108mg, 68%)을 수득하였다:

FABMS: m/z 133.1

(MH⁺); HRFABMS: m/z 133.0764 (MH⁺). Calcd. for C₈H₉N₂: m/z 133.0766; δ_H (CDCl₃) 2.04 (2H, s, -CH₂NH₂), 3.89 (2H, s, -CH₂NH₂), 7.40 (2H, d, Ar-H) 및 7.59 ppm (2H, d, Ar-H); δ_C (CDCl₃) CH₂: 45.7; CH: 127.8, 127.8, 132.4, 132.4; C: 110.6, 118.9, 148.0.

[0545]

[0546]

제조 실시예 248



[0547]

[0548]

실온에서 MeOH(50mL)중의 (1S, 2S)-2-벤질옥시사이클로펜틸 아민(1.5g, 7.84mmol)의 용액에 10% Pd/C (50% 습윤, 1.0g)을 가한 다음, 진한 HCl (0.7mL)을 적가하였다. 혼합물을 H₂의 벌룬(balloon)하에 14시간 동안 교반하고 촉매를 셀라이트 패드를 통해 여과하였다. 셀라이트 패드를 MeOH (2 x 10 mL)로 세척하고 수득한 여액을 감압하에 농축시켜 황색 반고체 0.97g (90%)을 수득하였다: M+H (유리 염기) = 102

[0549]

제조 실시예 249 내지 251

[0550]

제조 실시예 248과 유사한 방식으로, 벤질 보호된 사이클로알킬 아민(컬럼 2)을 표 17에 나열된 바와 같은 목적하는 아미노사이클로알칸을 하이드로클로라이드 유도체(컬럼 3)으로 전환시켰다.

표 17

실시예	컬럼 2 (아민)	컬럼 3 (절단 방법)	CMPD M+H
249			M+H = 102 (유리 염기)
250			M+H = 116 (유리 염기)
251			M+H = 116 (유리 염기)

[0551]

[0552]

제조 실시예 252



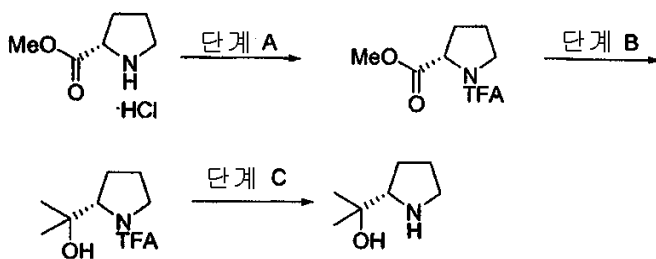
[0553]

[0554]

0°C에서 THF(8mL)중의 에스테르(J. Org. Chem. (1999), 64, 330에 따라 제조함)(0.5 g, 2.43mmol)의 용액에 LiAlH₄ (0.37g, 9.74mmol)을 1부분으로 가하였다. 수득한 혼합물을 환류하에 12시간 동안 가열하고 0°C로 냉각시켰다. 혼합물을 H₂O (1mL), 1M NaOH (1mL) 및 H₂O (3mL)로 순차적으로 처리하였다. CH₂Cl₂(10mL)를 혼합물에 가하고, 이를 30분 동안 격렬하게 교반하였다. 혼합물을 셀라이트 패트를 통해 여과하고, 이를 CH₂Cl₂ (3 x 5mL)로 온화하게 세척하였다. 수득한 여액을 감압하에 농축시켜 황색/오렌지색 고체 0.41g (85%)을 수득하였다. M+H = 142.

[0555]

제조 실시예 253



[0556]

[0557]

단계 A:

[0558]

0°C에서 CH₂Cl₂(15mL) 중의 L-프롤린 메틸 에스테르 하이드로클로라이드(0.50g, 3.0mmol)의 용액에 Et₃N (1.1mL, 7.55mmol)을 가한 다음, TFAA (0.56mL, 3.92mmol)을 가하였다. 혼합물을 실온에서 12시간 동안 교반하고 1N HCl (25mL)을 가하였다. 층을 분리시키고 유기 층을 포화된 수성 NaHCO₃ (1 x 25mL) 및 염수(1 x 25mL)로 순차적으로 세척하였다. 유기 층을 건조(Na₂SO₄)시키고, 여과하고 감압하에 농축시켜 황색 오일 0.72g(100%)을 수득하였다. M+H = 226. 조약한 물질을 추가의 정제 없이 단계 B로 넘겼다.

[0559]

단계 B:

[0560]

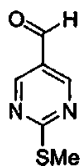
0°C에서 THF(20mL)중의 제조 실시예 253, 단계 A(0.68g, 3.0mmol)에서 제조한 화합물의 용액에 MeMgI(5.1mL, Et₂O 중의 3.0M)을 10분에 걸쳐 적가하였다. 수득한 용액을 실온에서 16시간 동안 교반하고, 혼합물을 포화된

수성 NH₄Cl를 첨가하여 퀀칭시켰다. 혼합물을 농축 건조시키고 수득한 잔사를 EtOAc(100 mL)로 45분 동안 교반하고 여과시켰다. 여액을 감압하에 농축시켜 황색/오렌지색 오일 0.68g (100%)을 수득하였다. M+H = 226. 조약한 물질을 추가의 정제없이 단계 C에 넘겼다.

[0561] 단계 C:

[0562] MeOH(5mL)중의 제조 실시예 253, 단계 B(0.68g, 3.0mmol)에서 제조한 화합물의 용액에 MeOH (5mL)중의 KOH(0.68g, 12.1mmol)의 용액을 가하였다. 혼합물을 환류하에 12시간 및 실온에서 72시간 동안 교반하고, 혼합물을 농축 건조시켰다. 조약한 잔사를 EtOAc (50mL)에 현탁시키고 30분 동안 격렬하게 교반하고 여과시켰다. 이 과정을 2회 이상 반복하고 수득한 여액을 감압하에 농축시켜 적갈색/오렌지색 오일 128mg(33%)을 수득하였다. M+H = 130. 이 물질을 후속적인 커플링 단계에서 추가의 정제없이 사용하였다.

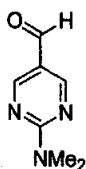
[0563] 제조 실시예 254:



[0564]

[0565] 알데히드를 문헌[참조: Gupton (J. Heterocyclic Chem. (1991), 28,1281)의 과정에 따라 제조하였다.

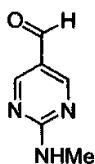
[0566] 제조 실시예 255:



[0567]

[0568] 제조 실시예 254로부터의 알데히드를 사용하여, 문헌[참조: Gupton (J. Heterocyclic Chem. (1991), 28,1281)]의 과정으로 표제 알데히드를 제조하였다.

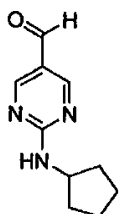
[0569] 제조 실시예 256



[0570]

[0571] 표제 알데히드를 문헌[참조: Ragan et. al Synlett (2000), 8, 1172-1174]의 과정에 따라 제조하였다.

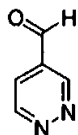
[0572] 제조 실시예 257



[0573]

[0574] 문헌[참조: Ragan (Synlett (2000), 8, 1172- 1174)]의 조건하에 공지된 사이클로펜틸 구아니딘 하이드로클로라이드의 반응[참조: Org. Lett.(2003), 5, 1369-1372])으로 표제 화합물을 제공하였다.

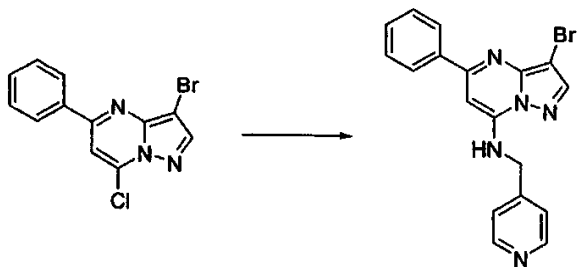
[0575] 제조 실시예 258



[0576]

[0577] 표제 화합물을 공지된 문헌[참조: Monatshefte fur chemie (1973), 104, 1372-1382]에 따라 제조하였다.

[0578] 실시예 1:



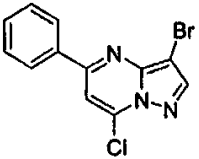
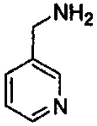
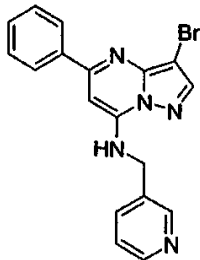
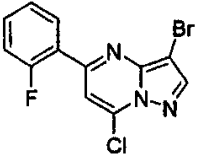
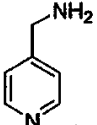
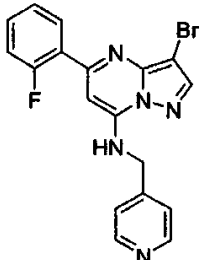
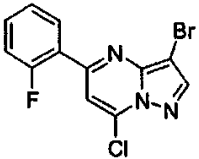
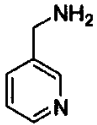
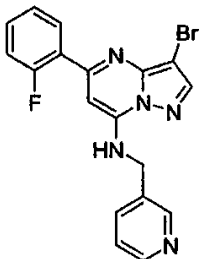
[0579]

[0580] CH₃CN(5mL)중의 제조 실시예 127(0.27g, 0.875mmol)로부터의 생성물, 4-아미노메틸피리딘(0.12g, 1.3 당량) 및 K₂CO₃(0.24g, 2당량)의 용액을 실온에서 48시간 동안 교반하였다. 반응 혼합물을 H₂O로 희석시키고 CH₂Cl₂로 추출하였다. 합한 유기물을 Na₂SO₄ 위에서 건조시키고, 여과하고 농축시켰다. 조약한 생성물을 용출제로서 CH₂Cl₂ 용액중의 4% MeOH를 사용하여 플래쉬 크로마토그래피함으로써 정제하였다(0.28 g, 93% 수율). LCMS: MH⁺ = 380 ; mp = > 205° C (분해).

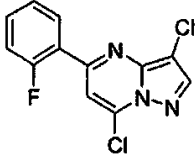
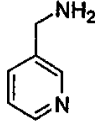
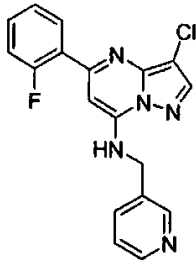
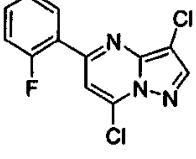
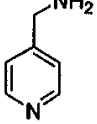
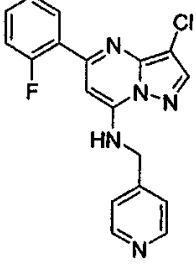
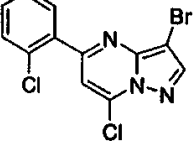
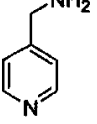
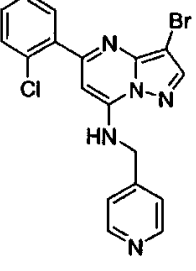
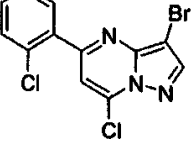
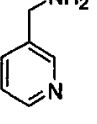
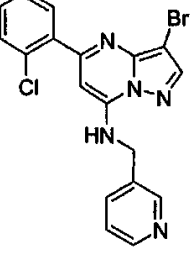
[0581] 실시예 2 내지 210:

[0582] 실시예 1에 나타낸 바와 본질적으로 동일한 과정을 따라, 표 18의 컬럼 2에 나타낸 클로라이드 및 표 18의 컬럼 3에 나타낸 아민을 단지 치환시켜, 표 18의 컬럼 4에 나타낸 화합물을 제조하였다:

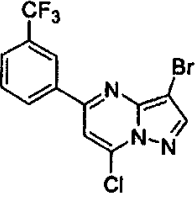
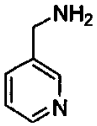
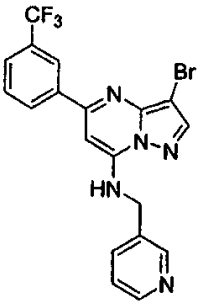
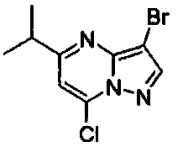
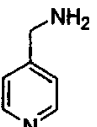
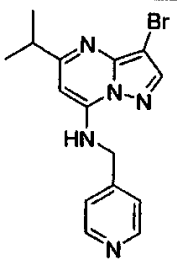
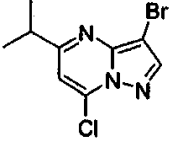
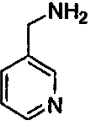
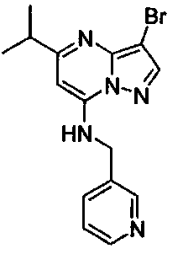
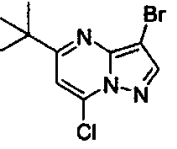
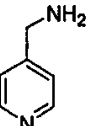
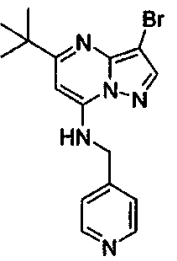
표 18

실시예	컬럼 2	컬럼 3	컬럼 4	데이터
2				LCMS: MH ⁺ = 380; mp=175- 176°C
3				LCMS: MH ⁺ = 398; mp= 156- 157°C
4				LCMS: MH ⁺ = 398; mp= 45-49°C

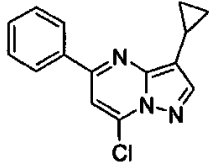
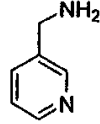
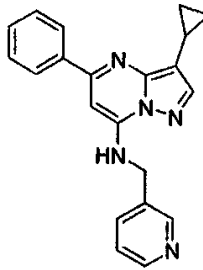
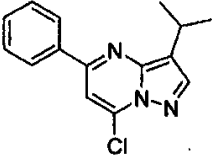
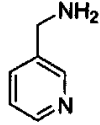
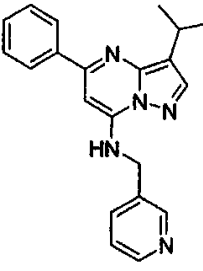
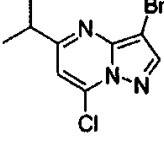
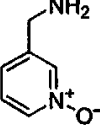
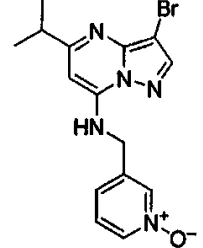
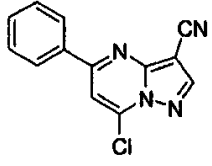
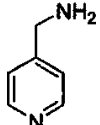
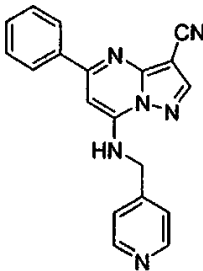
[0583]

5				<p>LCMS: MH⁺= 354; mp= 43-46°C</p>
6				<p>LCMS: MH⁺= 354; mp= 149- 150°C</p>
7				<p>LCMS: MH⁺= 414; mp= 86-92°C</p>
8				<p>LCMS: MH⁺= 414; mp= 185- 186°C</p>

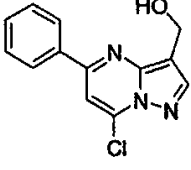
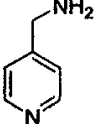
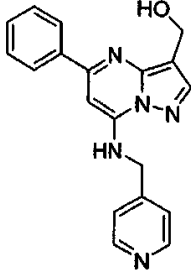
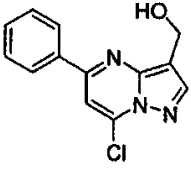
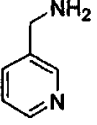
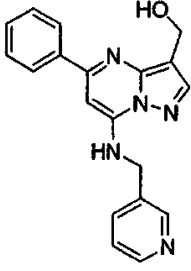
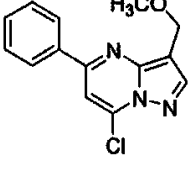
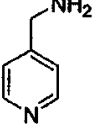
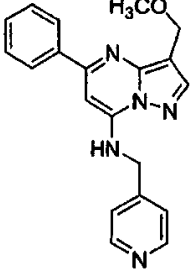
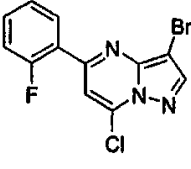
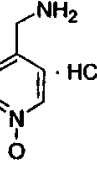
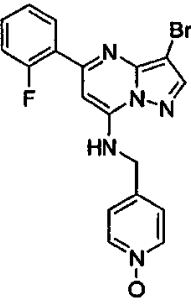
[0584]

9				<p>LCMS: MH⁺= 448; mp= 167- 168°C</p>
10				<p>LCMS: MH⁺= 346; mp= 57-58°C</p>
11				<p>LCMS: MH⁺= 347; mp=122. 9-125.3 °C</p>
12				<p>LCMS: MH⁺= 360; mp= 127- 128°C</p>

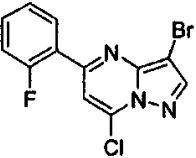
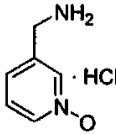
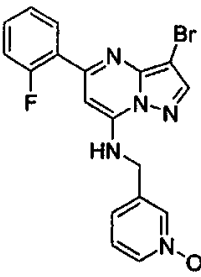
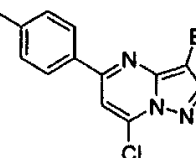
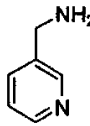
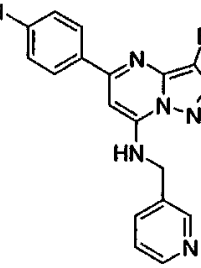
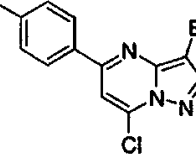
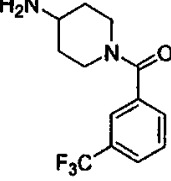
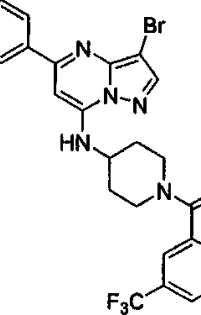
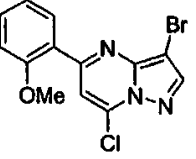
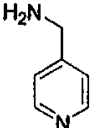
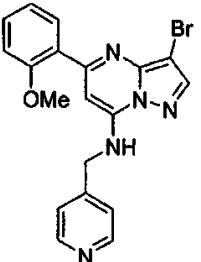
[0585]

13				<p>LCMS: MH⁺= 342; mp= 133- 135°C</p>
14				<p>LCMS: MH⁺= 344; mp= 152- 155°C</p>
15				<p>LCMS: MH⁺= 362; mp= 164- 167°C</p>
16				<p>LCMS: MH⁺= 327; mp= 146- 155°C</p>

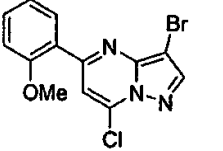
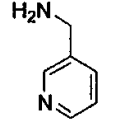
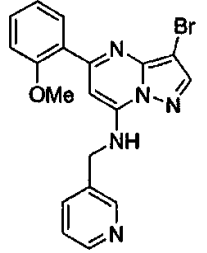
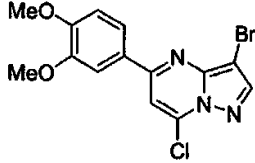
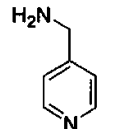
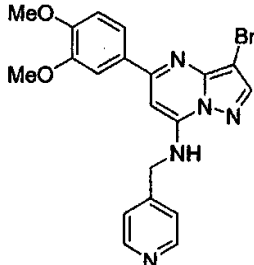
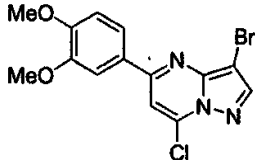
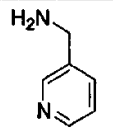
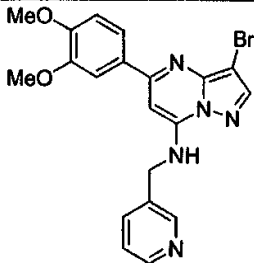
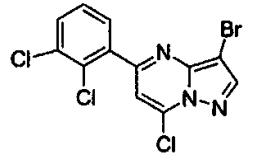
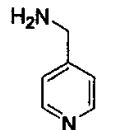
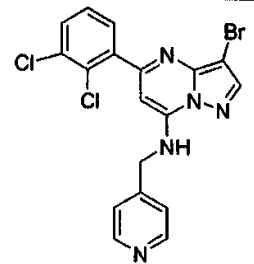
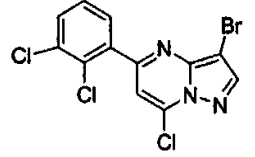
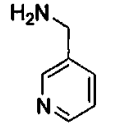
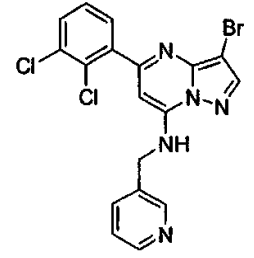
[0586]

17				<p>LCMS: MH⁺= 332; mp= 71-82°C</p>
17. 1				<p>MS: MH⁺ = 332.</p>
18				<p>LCMS: MH⁺= 346; mp= 58-65°C</p>
19				<p>LCMS: MH⁺= 414; mp= 211- 213°C</p>

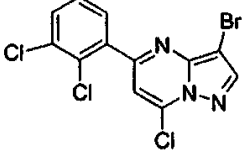
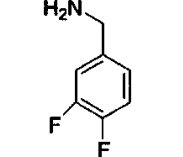
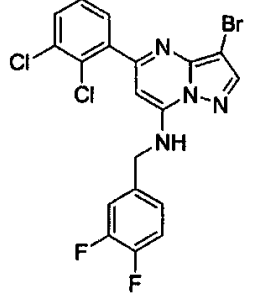
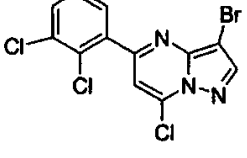
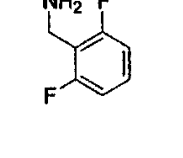
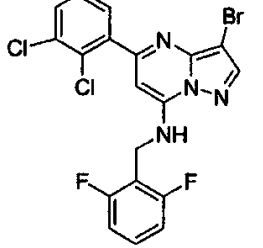
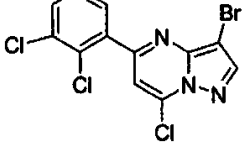
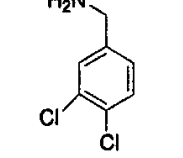
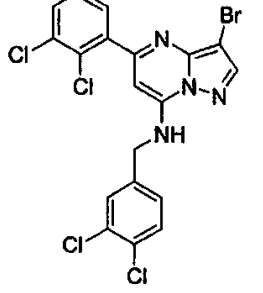
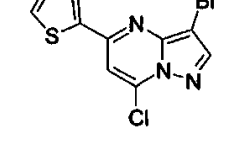
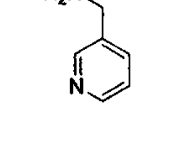
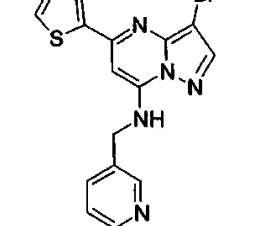
[0587]

20				<p>LCMS: MH⁺= 414; mp= 194- 197°C</p>
21				<p>MS: MH⁺ = 414 m.p. 211 -216°C</p>
22				<p>LCMS: MH⁺= 544; mp= 104- 107°C</p>
23				<p>수율 = 83% LCMS: MH⁺ = 410.</p>

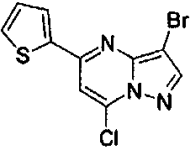
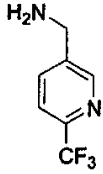
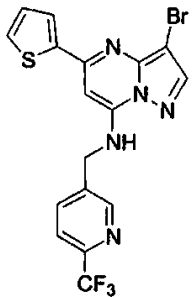
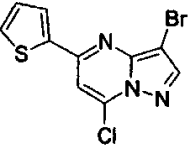
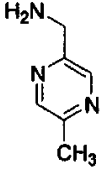
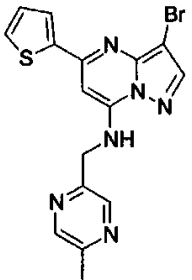
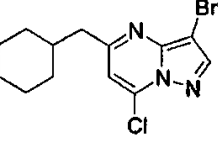
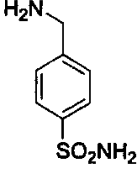
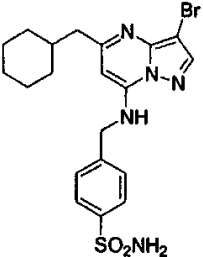
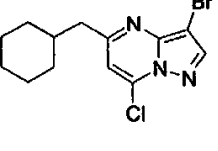
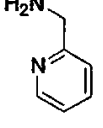
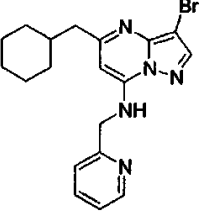
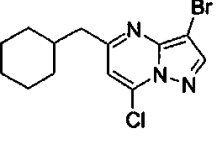
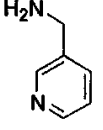
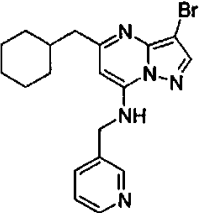
[0588]

24				수율 = 84% LCMS: MH ⁺ = 410.
25				수율 = 96% LCMS: MH ⁺ = 440.
26				수율 = 99% LCMS: MH ⁺ = 440.
27				수율 = 89% LCMS: MH ⁺ = 448.
28				수율 = 78% LCMS: MH ⁺ = 448.

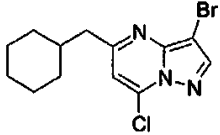
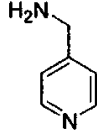
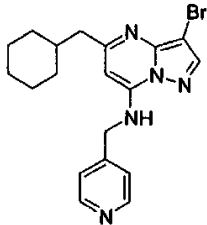
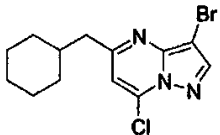
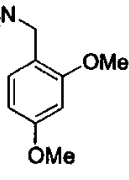
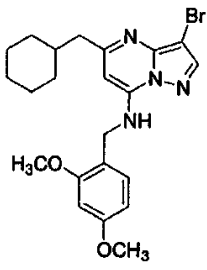
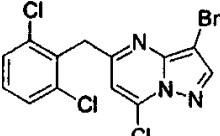
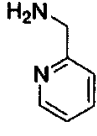
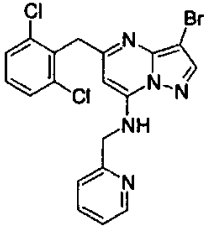
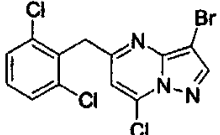
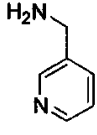
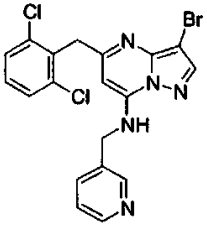
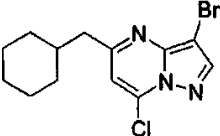
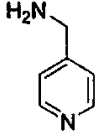
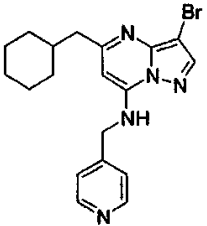
[0589]

30				수율 = 96% LCMS: MH ⁺ = 483.
31				수율 = 35% LCMS: MH ⁺ = 483.
32				수율 = 77% LCMS: MH ⁺ = 515.
33				수율 = 100% m.p. 179°C LCMS: MH ⁺ = 388

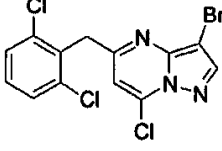
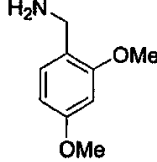
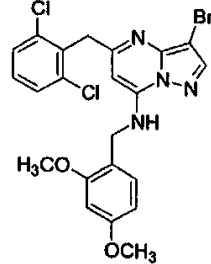
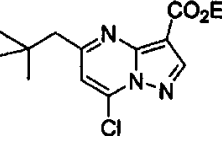
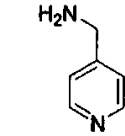
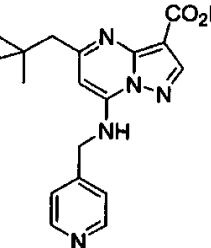
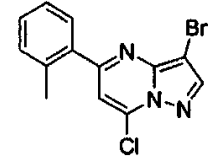
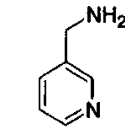
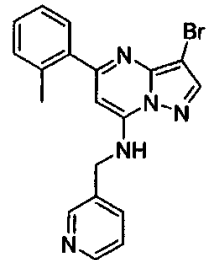
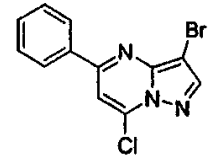
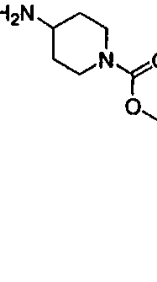
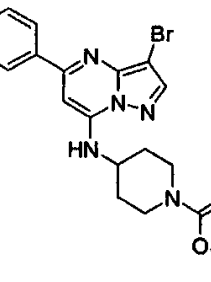
[0590]

34				수율 = 99% m.p. 186°C LCMS: MH ⁺ = 456
35				수율 = 98% m.p. 181°C LCMS: MH ⁺ = 401
36				수율 = 63% m.p. 192°C LCMS: MH ⁺ = 480
37				수율 = 75% m.p. 126 - 127°C LCMS: MH ⁺ = 400
38				수율 = 94% m.p. 132 -133°C LCMS: MH ⁺ = 400

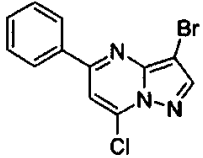
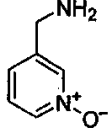
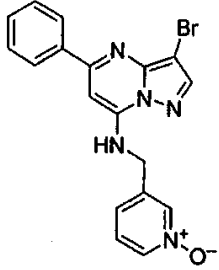
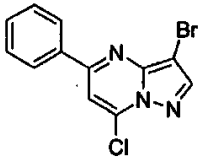
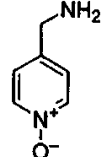
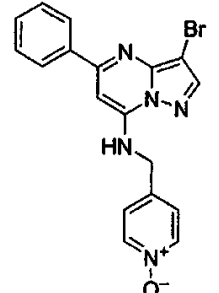
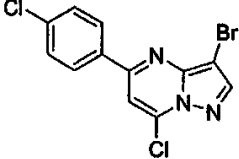
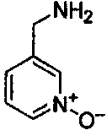
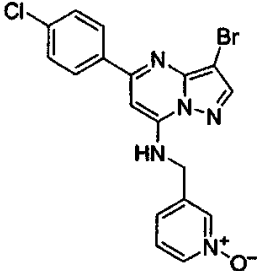
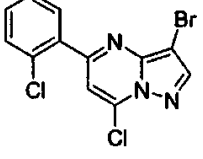
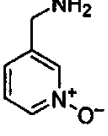
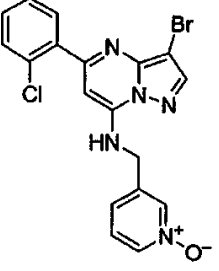
[0591]

39				<p>수율 = 95% m.p. 121 - 122°C LCMS: MH⁺ = 400</p>
40				<p>수율 = 98% LCMS: MH⁺ = 460</p>
41				<p>수율 = 87% m.p. 170 - 171°C LCMS: MH⁺ = 464</p>
42				<p>수율 = 84% m.p. 216 - 217°C LCMS: MH⁺ = 464</p>
43				<p>수율 = 96% m.p. 214°C LCMS: MH⁺ = 464</p>

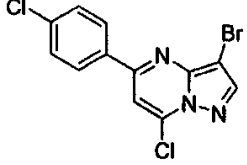
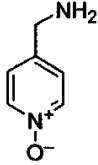
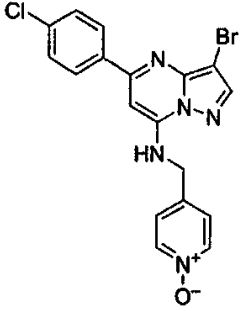
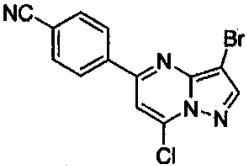
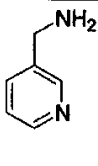
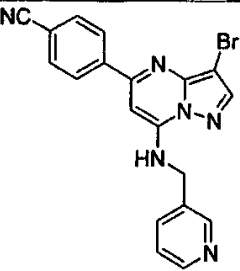
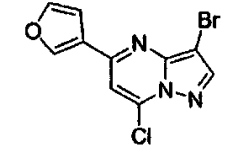
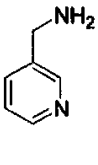
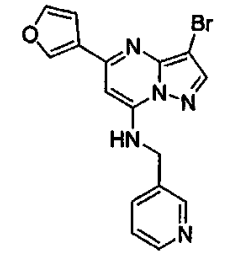
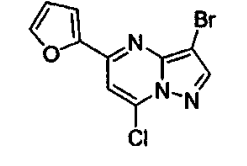
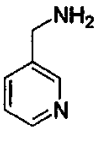
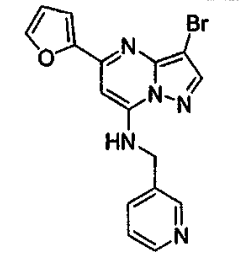
[0592]

44				수율 = 95% m.p. 158°C LCMS: MH ⁺ = 522
45				수율=90 % LCMS: MH ⁺ = 278
46				수율=10 0% ; LCMS: MH ⁺ =394
47				LCMS: MH ⁺ = 473 m.p. 84 - 87°C

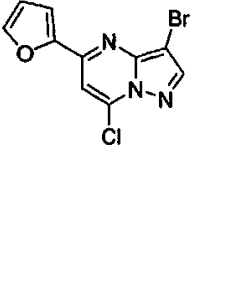
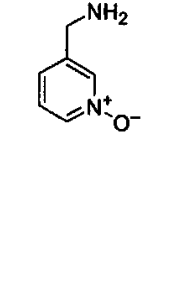
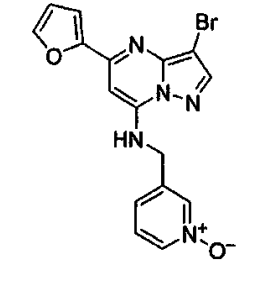
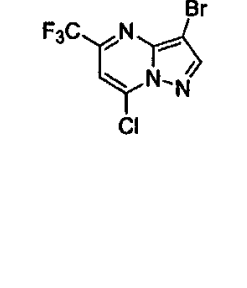
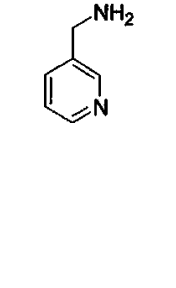
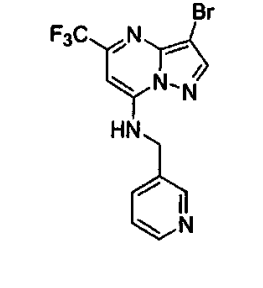
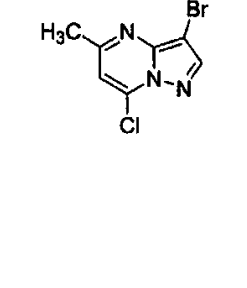
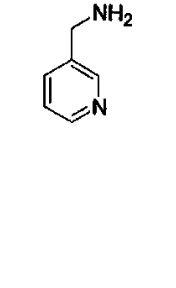
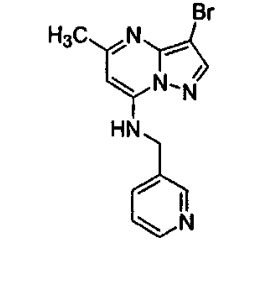
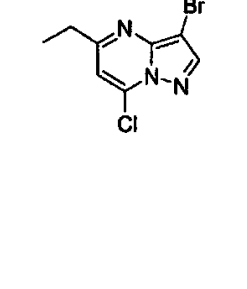
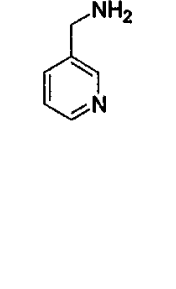
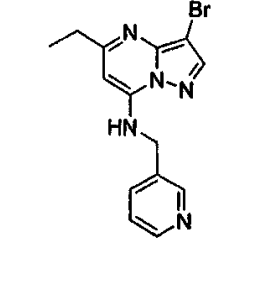
[0593]

48				<p>MS: MH⁺ = 396 m.p. 91.5 - 93.3°C</p>
49				<p>MS: MH⁺ = 396 m.p. 196 - 199°C</p>
50				<p>MS: MH⁺ = 430 m.p. 242 - 244°C</p>
51				<p>MS: MH⁺ = 430 m.p. 218°C</p>

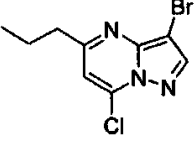
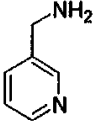
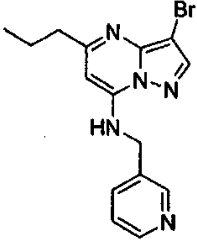
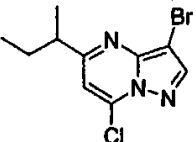
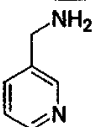
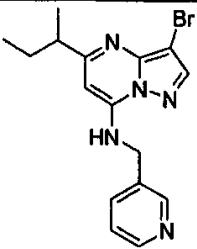
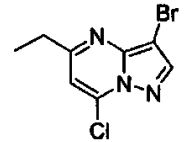
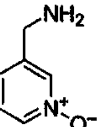
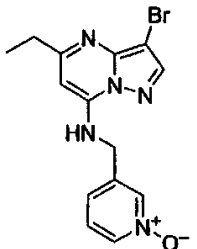
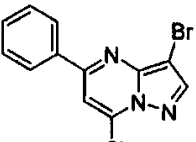

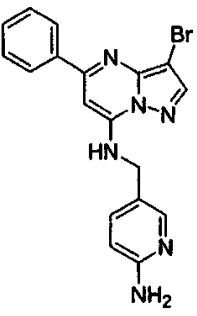
[0594]

52				<p>MS: $MH^+ = 430$ m.p. 230 - 233°C</p>
54				<p>MS: $MH^+ = 405$ m.p. 185 - 188°C</p>
55				<p>MS: $MH^+ = 370$ m.p. 229 - 232°C</p>
56				<p>MS: $MH^+ = 370$ m.p. 85 - 90°C</p>

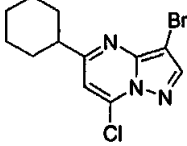
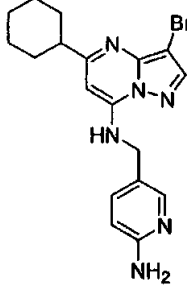
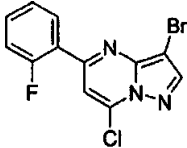
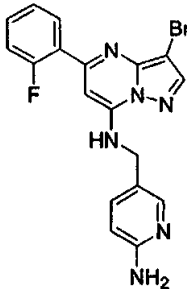
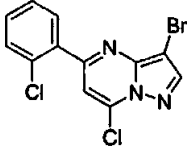
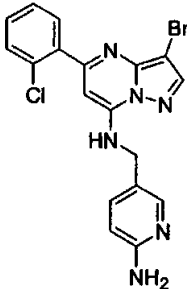
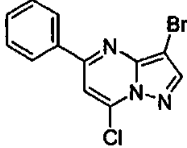
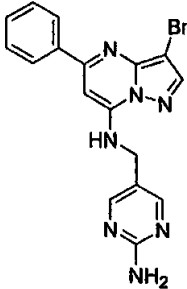
[0595]

57				<p>MS: MH⁺ = 386 m.p. 227 - 230°C</p>
58				<p>MS: MH⁺ = 372 m.p. 212 - 215°C</p>
59				<p>MS: MH⁺ = 318 m.p. 169 - 171°C</p>
60				<p>MS: MH⁺ = 332 m.p. 170 - 173°C</p>

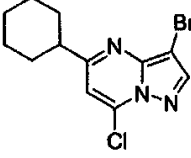
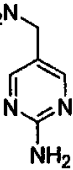
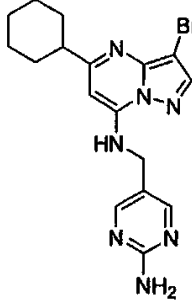
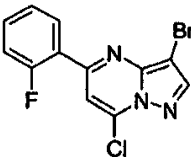
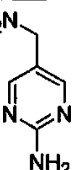
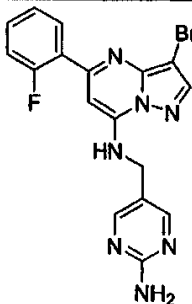
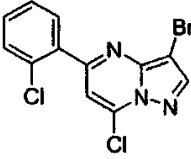
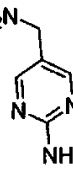
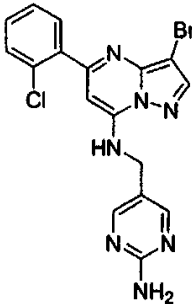
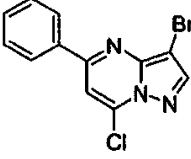
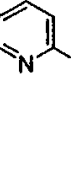
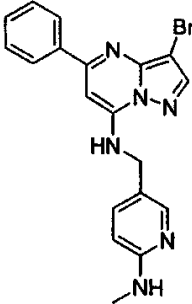
[0596]

61				<p>MS: MH⁺ = 346 m.p. 156 - 159°C</p>
62				<p>MS: MH⁺ = 360 m.p. 114 - 116°C</p>
63				<p>MS: MH⁺ = 348 m.p. 197 - 200°C</p>
64		<p>H₂N-CH₂-NH- 2 HCl</p>		<p>1. mp = 230-232 2. M+H = 396</p>

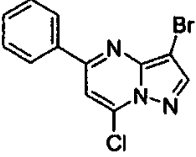
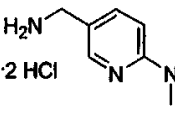
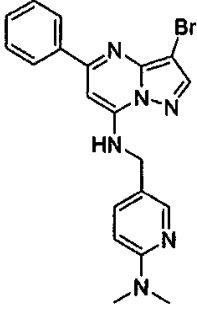
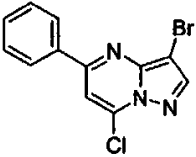
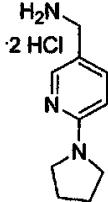
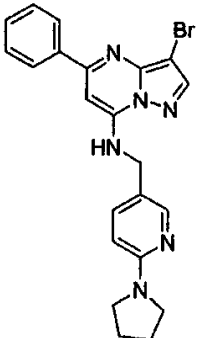
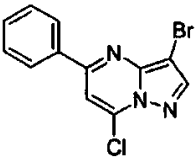
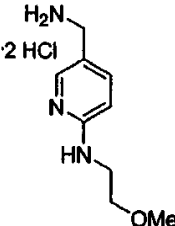
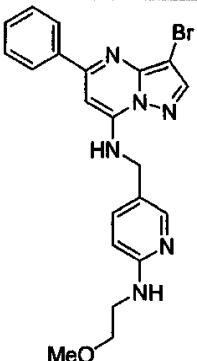
[0597]

65		$\text{H}_2\text{N}-\text{CH}_2-\text{C}_5\text{H}_3\text{N}_2-\text{NH}$ $\cdot 2 \text{HCl}$		1. mp = 205-207 2. M+H = 402
66		$\text{H}_2\text{N}-\text{CH}_2-\text{C}_5\text{H}_3\text{N}_2-\text{NH}$ $\cdot 2 \text{HCl}$		1. mp = 220-223 2. M+H = 414
67		$\text{H}_2\text{N}-\text{CH}_2-\text{C}_5\text{H}_3\text{N}_2-\text{NH}$ $\cdot 2 \text{HCl}$		1. mp = 191-193 2. M+H = 431
68		$\text{HCl} \cdot \text{H}_2\text{N}-\text{CH}_2-\text{C}_5\text{H}_3\text{N}_2-\text{NH}$		1. mp = 235-237 2. M+H = 397

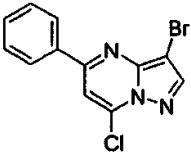
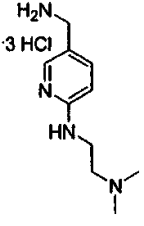
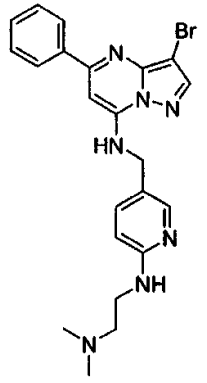
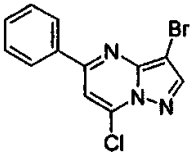
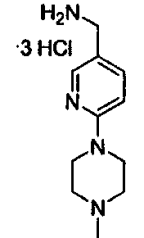
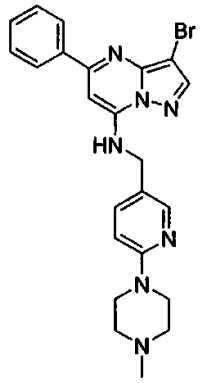
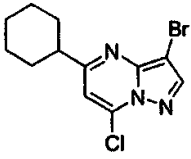
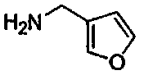
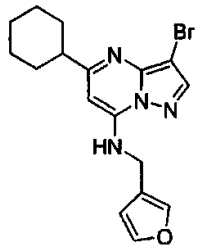
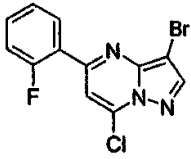
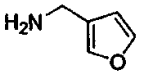
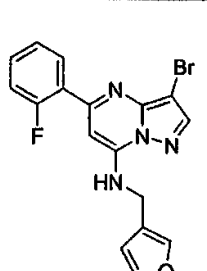
[0598]

69		$\text{HCl} \cdot \text{H}_2\text{N}$ 		<p>1. mp = >250 2. M+H = 403</p>
70		$\text{HCl} \cdot \text{H}_2\text{N}$ 		<p>1. mp = 230-232 2. M+H = 415</p>
71		$2\text{HCl} \cdot \text{H}_2\text{N}$ 		<p>1. mp = 235-238 2. M+H = 431</p>
72		H_2N  $\cdot 2\text{HCl}$		<p>1. mp = 186-188 2. M+H = 410</p>

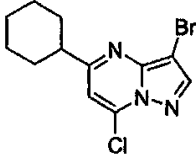
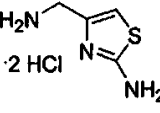
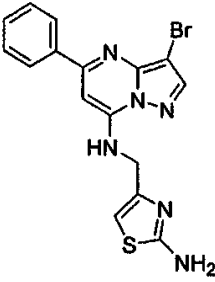
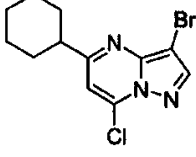
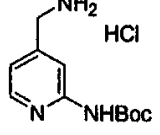
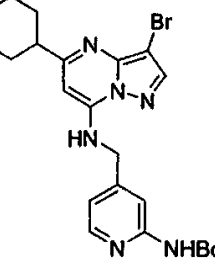
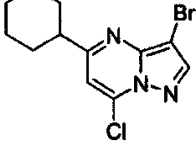
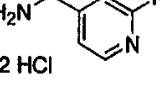
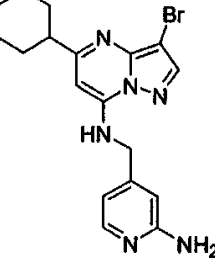
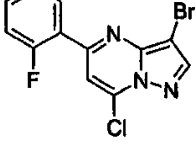
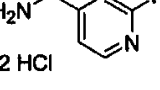
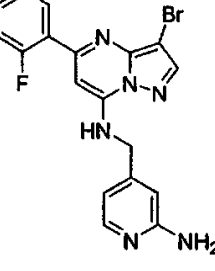
[0599]

73				<p>1. mp = 136-138 2. M+H = 424</p>
74				<p>1. mp = 192-195 2. M+H = 450</p>
75				<p>1. mp = 88-90 2. M+H = 454</p>

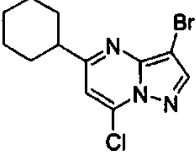
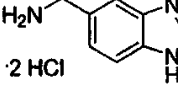
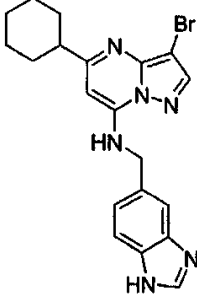
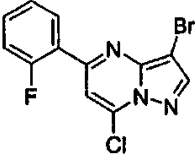
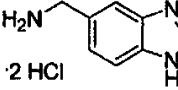
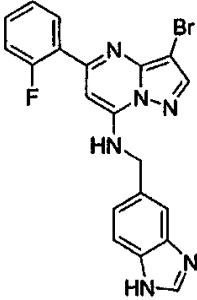
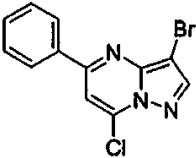
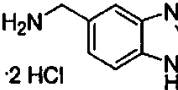
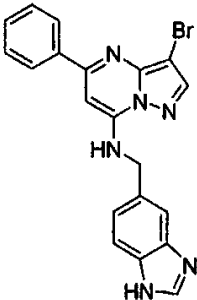
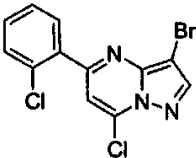
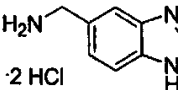
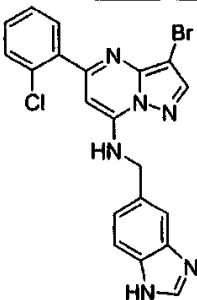
[0600]

76				<p>1. mp = 230-232 2. M+H = 467</p>
77				<p>1. mp = 131-133 2. M+H = 479</p>
78				<p>1. mp = 85-88 2. M+H = 376</p>
79				<p>1. mp = 131-133 2. M+H = 388</p>

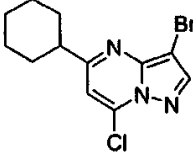
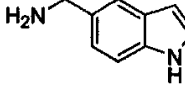
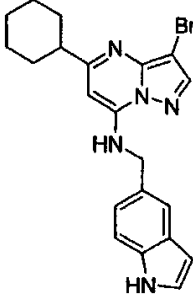
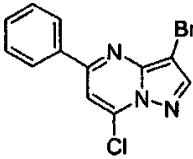
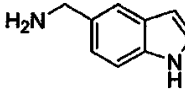
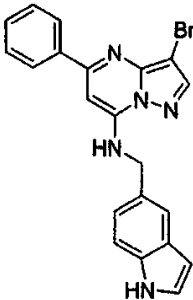
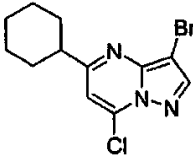
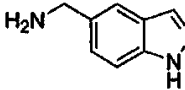
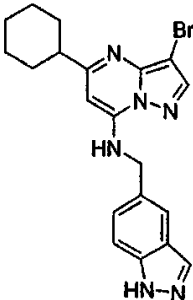
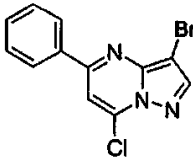
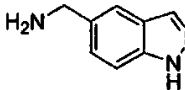
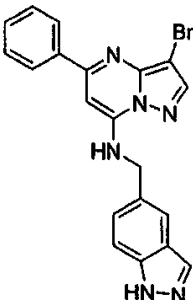
[0601]

80				<p>1. mp = 206-208 2. M+H = 408</p>
81				<p>1. mp = 108-110 2. M+H = 502</p>
82				<p>1. mp = 83-85 2. M+H = 402</p>
83				<p>1. mp = 220 2. M+H = 414</p>

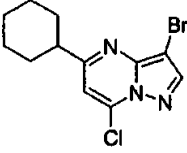
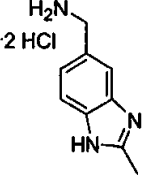
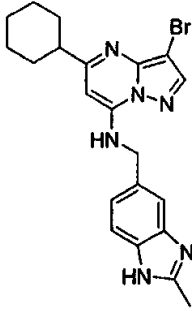
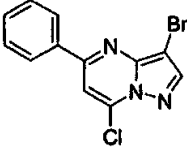
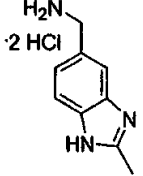
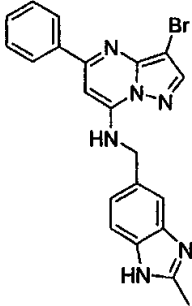
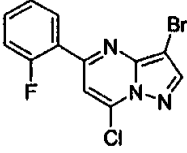
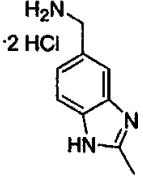
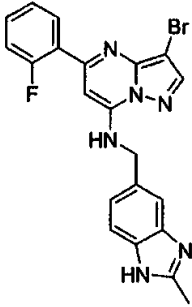
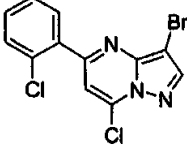
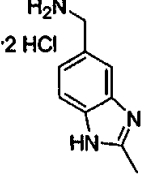
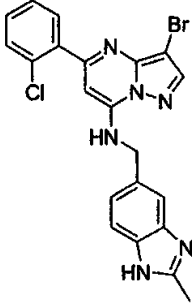
[0602]

84		 H_2N $\cdot 2 \text{HCl}$		<p>1. mp = 154-156 2. M+H = 426</p>
85		 H_2N $\cdot 2 \text{HCl}$		<p>1. mp = 152-153 2. M+H = 438</p>
86		 H_2N $\cdot 2 \text{HCl}$		<p>1. mp = 159-161 2. M+H = 420</p>
87		 H_2N $\cdot 2 \text{HCl}$		<p>1. mp = >220 2. M+H = 455</p>

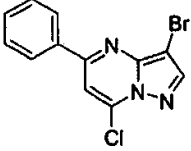
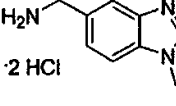
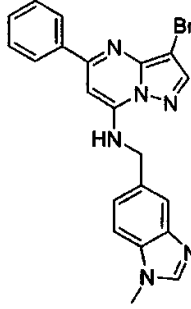
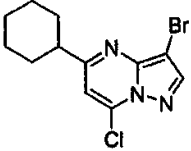
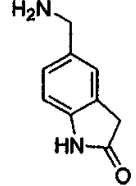
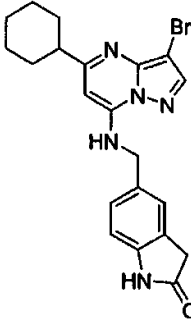
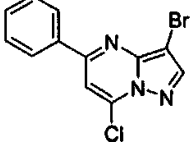
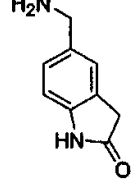
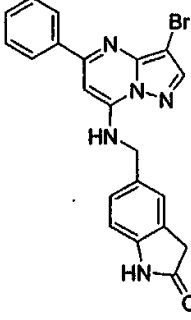
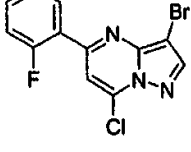
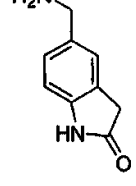
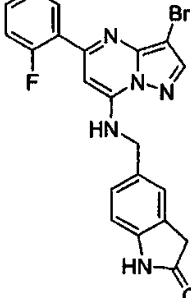
[0603]

88				<p>1. mp = 223-225 2. M+H = 425</p>
89				<p>1. mp = 199-201 2. M+H = 419</p>
90				<p>1. mp = 184-186 2. M+H = 426</p>
91				<p>1. mp = 196-198 2. M+H = 420</p>

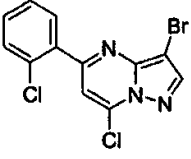
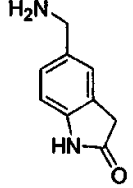
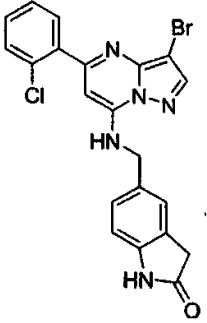
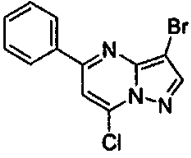
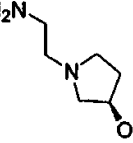
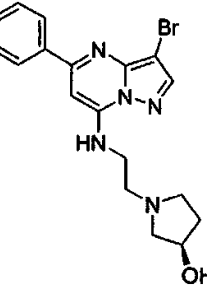
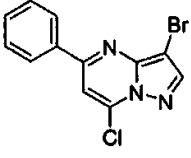
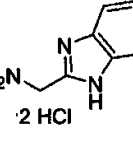
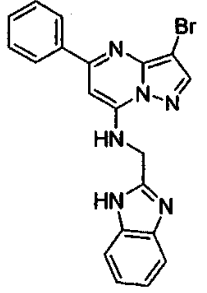
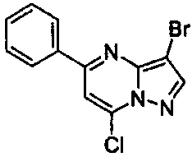
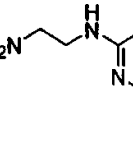
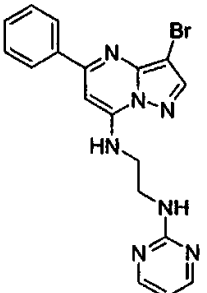
[0604]

92				<p>1. mp = 156-159 2. M+H = 440</p>
93				<p>1. mp = 173-176 2. M+H = 434</p>
94				<p>1. mp = 173-175 2. M+H = 452</p>
95				<p>1. mp = 174-176 2. M+H = 469</p>

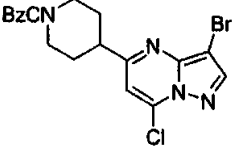
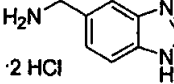
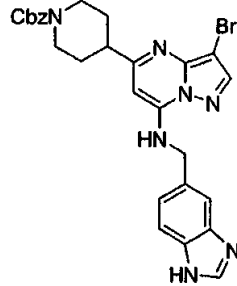
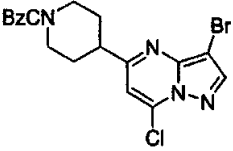
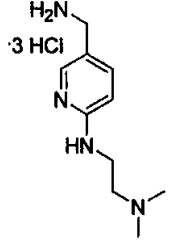
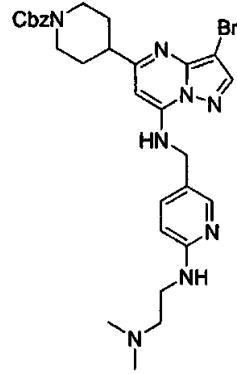
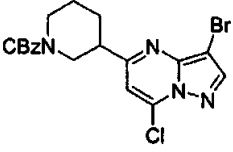
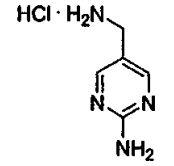
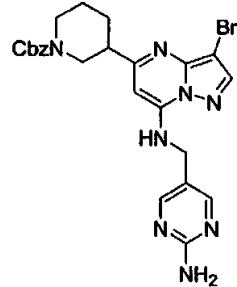
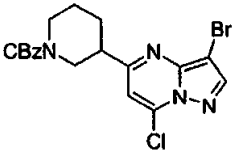
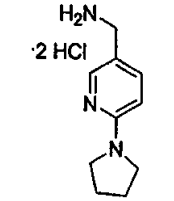
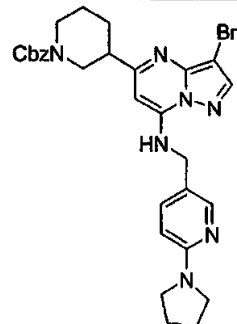
[0605]

96		 <p>$\cdot 2 \text{ HCl}$</p>		<p>1. mp = 230-234 2. M+H = 434</p>
97				<p>1. mp = 191-193 2. M+H = 441</p>
98				<p>1. mp = 202-205 2. M+H = 434</p>
99				<p>1. mp = 209-212 2. M+H = 453</p>

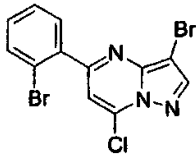
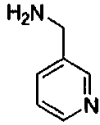
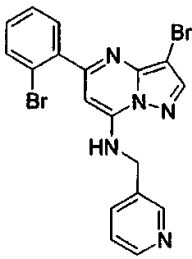
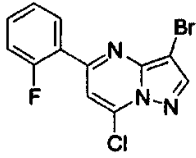
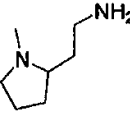
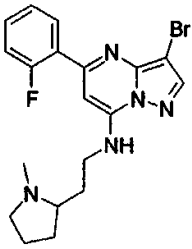
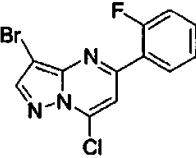
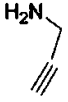
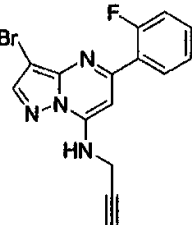
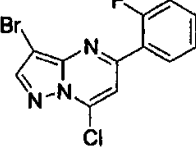
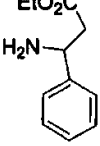
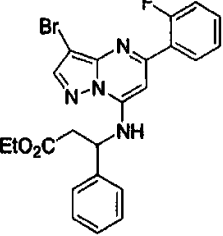
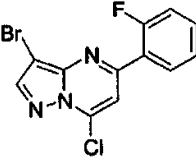
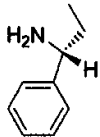
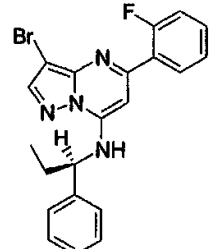
[0606]

100				<p>1. mp = 219-221 2. M+H = 469</p>
101				<p>1. mp = 64-66 2. M+H = 403</p>
102				<p>1. mp = 168-170 2. M+H = 420</p>
103				<p>1. mp = 213-216 2. M+H = 411</p>

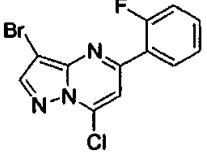
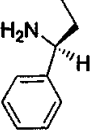
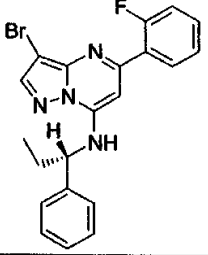
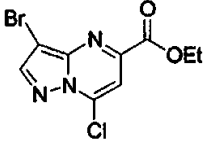
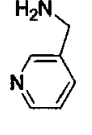
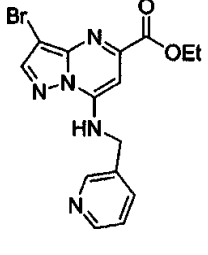
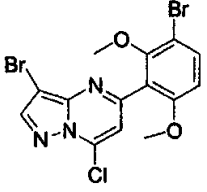
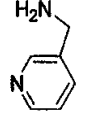
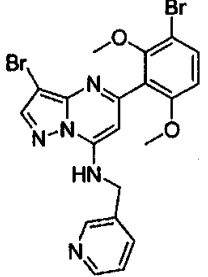
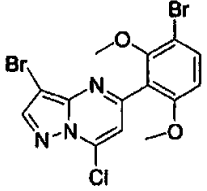
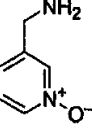
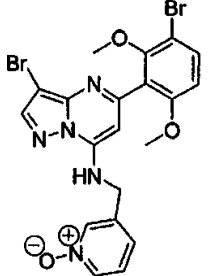
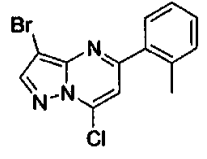
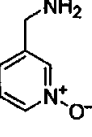
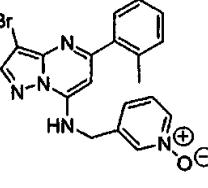
[0607]

104				<p>1. mp = 98-100 2. M+H = 561</p>
105				<p>1. mp 70-72 2. M+H = 608</p>
106				<p>1. mp 168-170 2. M+H = 538</p>
107				<p>1. mp 189-191 2. M+H = 592</p>

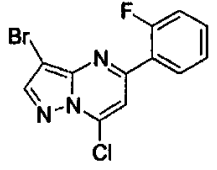

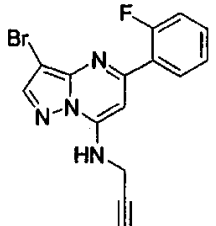
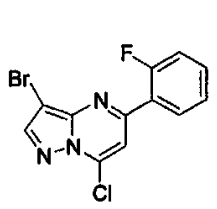
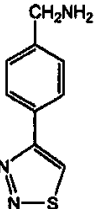
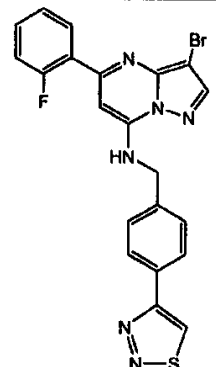
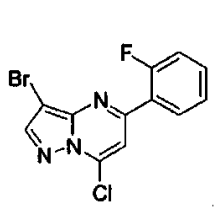
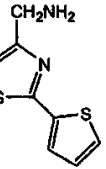
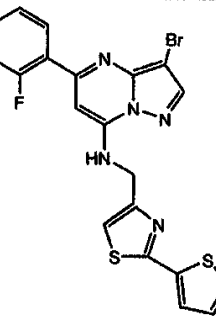
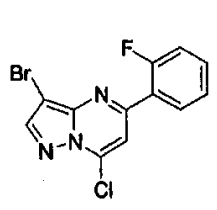
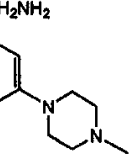
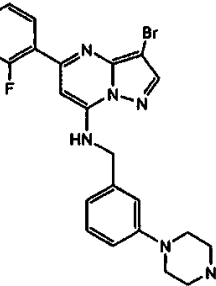
[0608]

108				LCMS: MH ⁺ = 458;
109				수율 = 89 LCMS: MH ⁺ = 418 m. p. = 131-132 °C
110				수율 =95% LCMS: MH ⁺ = 347
111				수율 =91% 3H); LCMS: MH ⁺ = 484
112				수율 =87% LCMS: MH ⁺ = 427

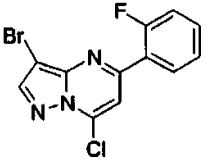
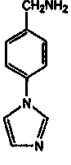
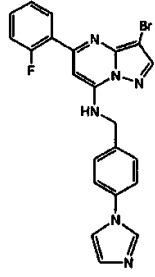
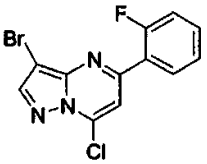
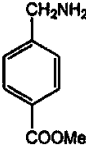
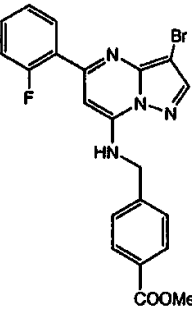
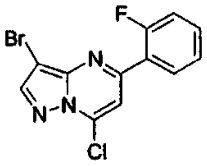
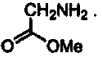
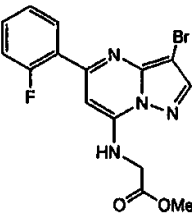
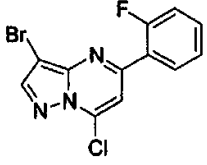
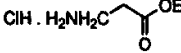
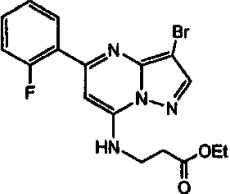
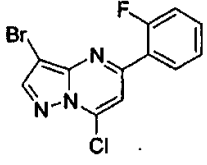
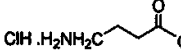
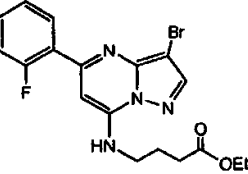
[0609]

113				수율 =80% LCMS: MH ⁺ = 427
114				수율 =91% LCMS: MH ⁺ = 378
115				수율 =92% , 3H); LCMS: MH ⁺ =520
116				수율 =98% LCMS: MH ⁺ =536
117				수율 =82% LCMS: MH ⁺ =410

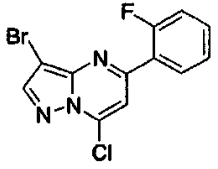
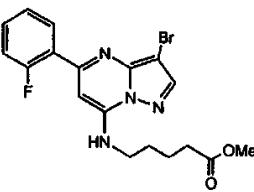
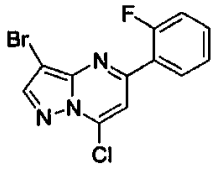
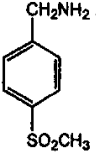
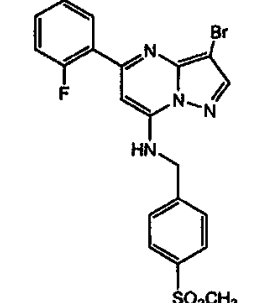
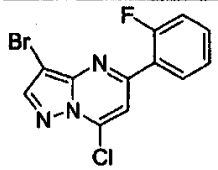
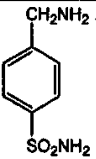
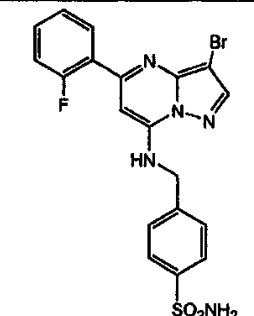
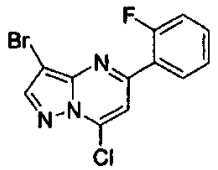
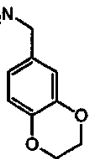
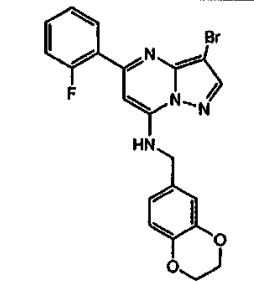
[0610]

118				수율 = 95% LCMS: MH ⁺ = 347
121				수율 = 65% LCMS: MH ⁺ = 481.02
126				수율 = 71% MH ⁺ = 486
127				수율 = 71% MH ⁺ = 495.1

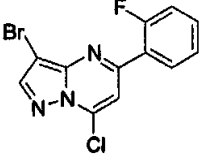
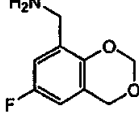
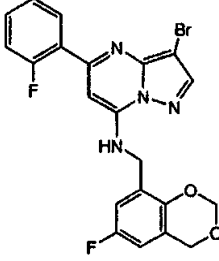
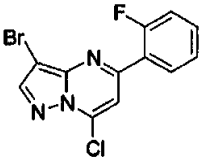
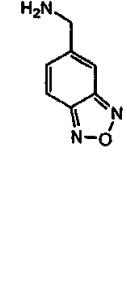
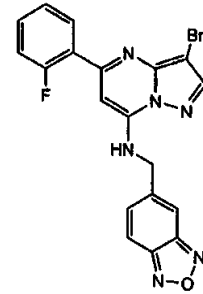
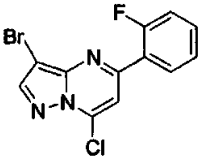
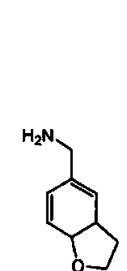
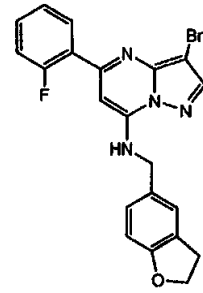
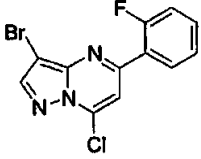
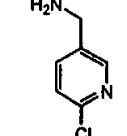
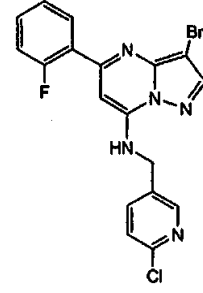
[0611]

128				수율 = 55% MH ⁺ = 463
129				수율 = 77% LCMS: MH ⁺ = 455
130				¹ H NMR (수율 = 75%) LCMS: MH ⁺ = 379
131				수율 = 75% LCMS: MH ⁺ = 407
132				수율 = 75% LCMS: MH ⁺ = 421

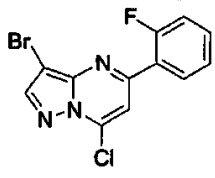
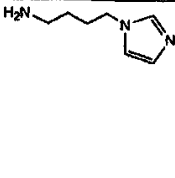
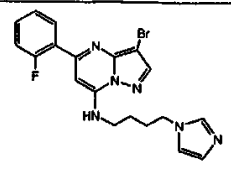
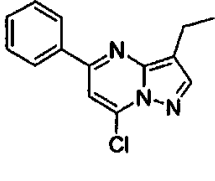
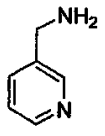
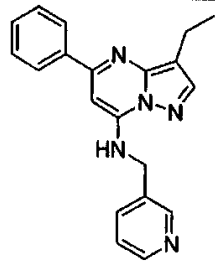
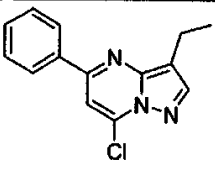
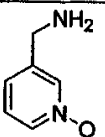
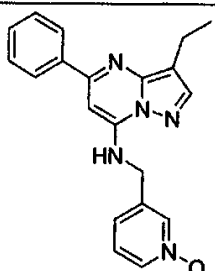
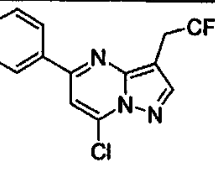
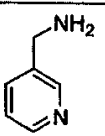
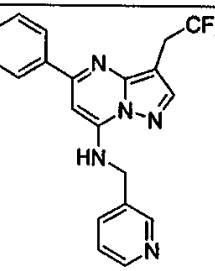
[0612]

133		$\text{ClH}_2\text{N}(\text{CH}_2)_4\text{COOMe}$		수율 = 70% LCMS: MH ⁺ = 421
134		$\text{CH}_2\text{NH}_2 \cdot \text{HCl}$ 		수율 = 78% LCMS: MH ⁺ = 475
135		$\text{CH}_2\text{NH}_2 \cdot \text{HCl}$ 		수율 = 75% LCMS: MH ⁺ = 476
136		H_2N 		수율 = 65% LCMS: MH ⁺ = 455

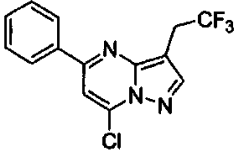
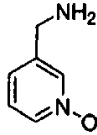
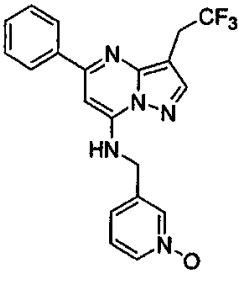
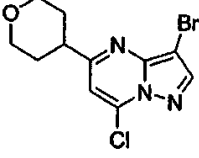
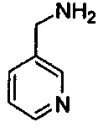
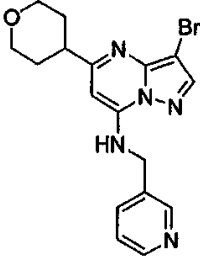
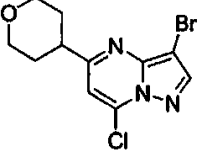
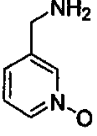
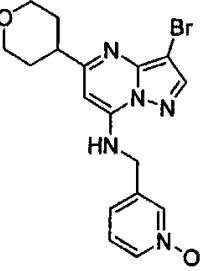
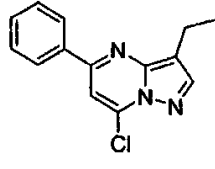
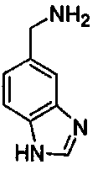
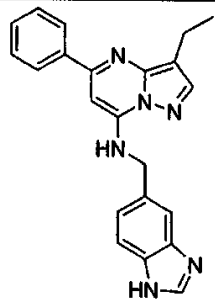
[0613]

137				수율 = 55% LCMS: MH ⁺ = 473)
138				수율 = 60% LCMS: MH ⁺ = 439
139				수율 = 65% LCMS: MH ⁺ = 441
140				수율 = 80% LCMS: MH ⁺ = 432

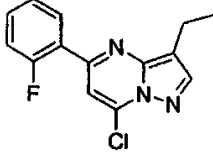
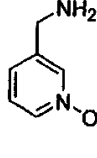
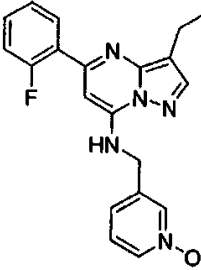
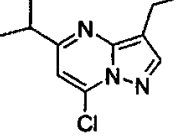
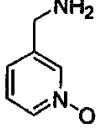
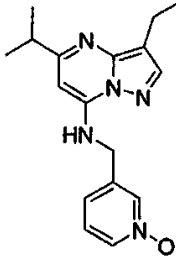
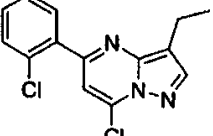
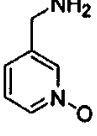
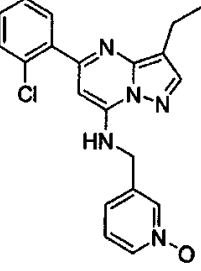
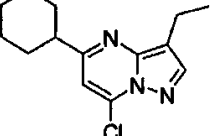
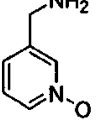
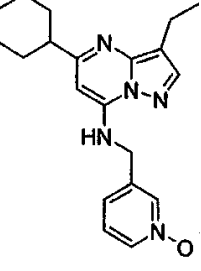
[0614]

141				<p>수율 = 60% LCMS: MH⁺ = 429</p>
142				<p>LCMS: MH⁺=330 ; mp=109- 111°C</p>
143				<p>LCMS: MH⁺=346 ; mp=186- 188°C</p>
144				<p>LCMS: MH⁺=384 ; mp=148- 150°C</p>

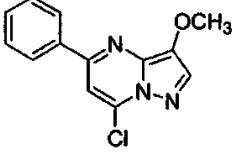
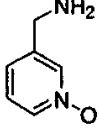
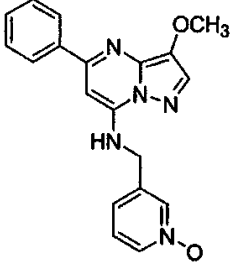
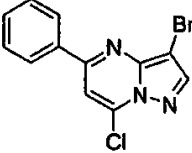
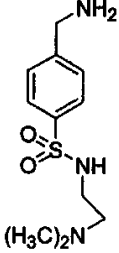
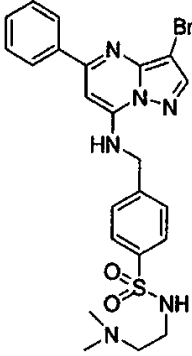
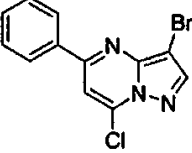
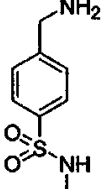
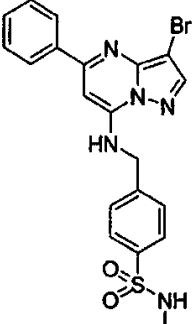
[0615]

145				<p>LCMS: $MH^+ = 400$; mp=186-188°C</p>
146				<p>LCMS: $M2H^+ = 390$; mp=192-194°C</p>
147				<p>LCMS: $M^+ = 404$; mp=220-222°C</p>
148				<p>LCMS: $MH^+ = 369$; mp>230°C</p>

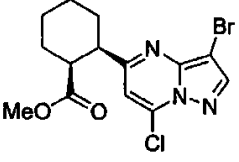
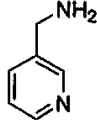
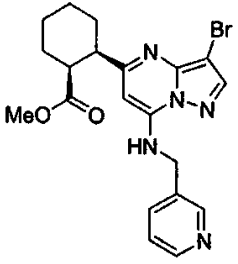
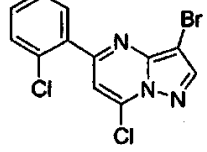
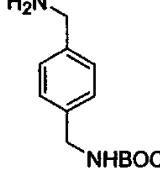
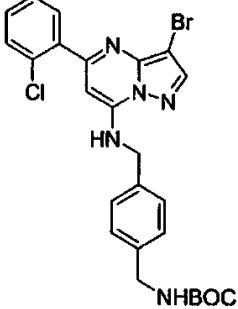
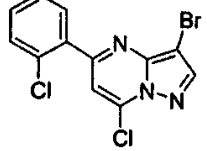
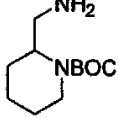
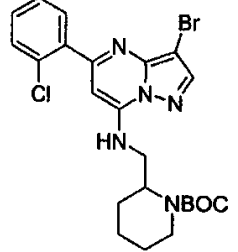
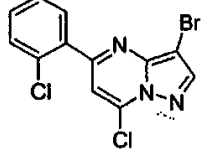
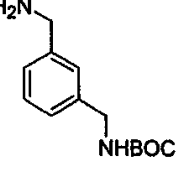
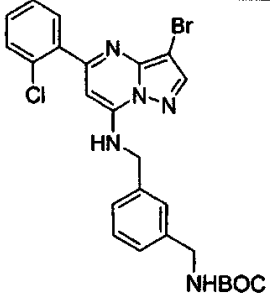
[0616]

149				<p>LCMS: MH⁺=364 ; mp=186-188°C</p>
150				<p>LCMS: MH⁺=312 ; mp=138-140°C</p>
151				<p>LCMS: M⁺=380; mp=172-174°C</p>
152				<p>LCMS: MH⁺=352 ; mp=201-203°C</p>

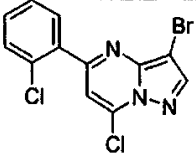

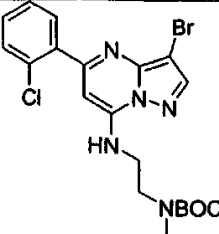
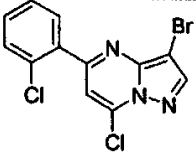
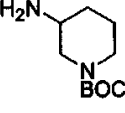
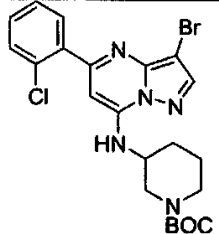
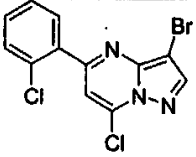
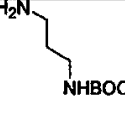
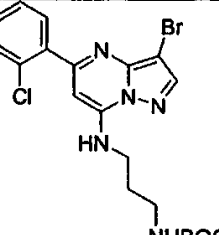
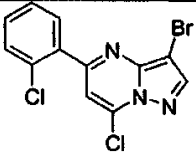
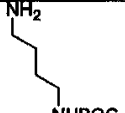
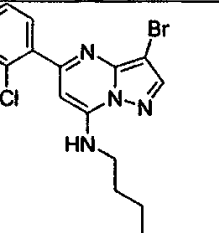
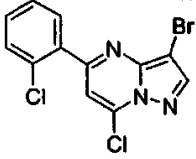

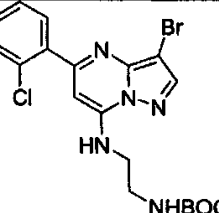
[0617]

153				<p>LCMS: MH⁺=348 ; mp=166- 168°C</p>
154				<p>LCMS: M2H⁺=53 1; mp=78- 80°C</p>
155				<p>LCMS: M2H⁺=47 4; mp=161- 163°C</p>

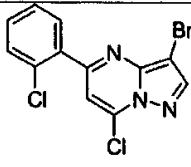
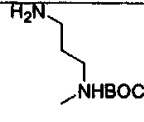
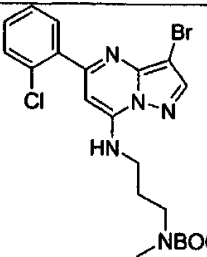
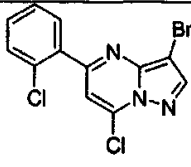
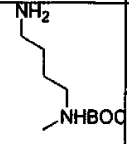
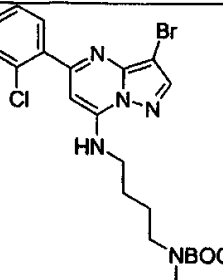
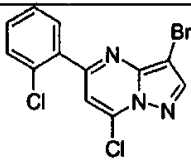
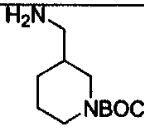
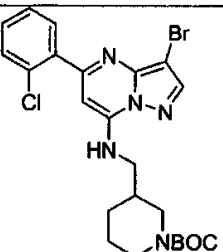
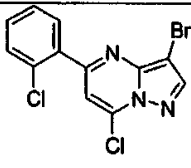
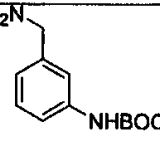
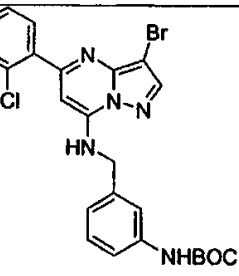
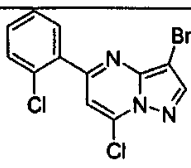
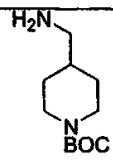
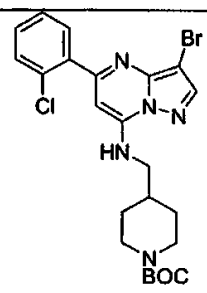
[0618]

156				<p>LCMS: M⁺=444; mp=48-51°C</p>
157				<p>MH⁺ = 542.1</p>
158				<p>MH⁺ = 520.1</p>
159				<p>MH⁺ = 542.1</p>

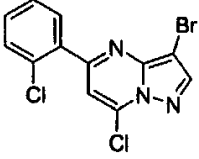
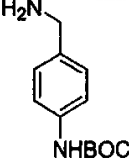
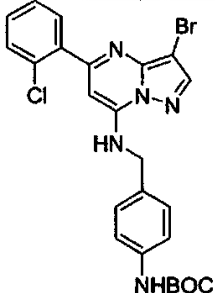
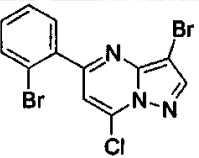
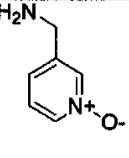
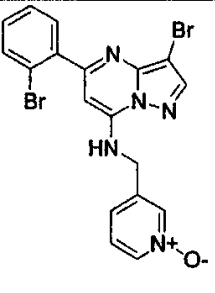
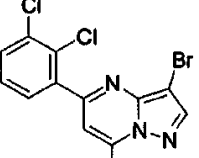
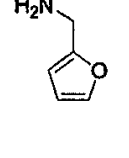
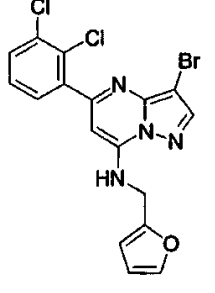
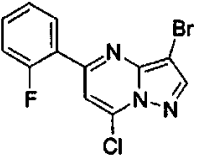
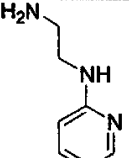
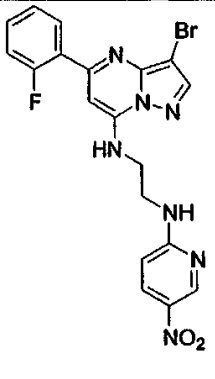
[0619]

160				MH ⁺ = 480.1
161				MH ⁺ = 506.1
162				MH ⁺ = 480.1
163				MH ⁺ = 494.1
164				MH ⁺ = 466.1

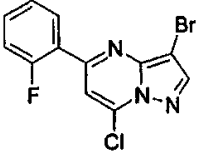
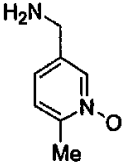
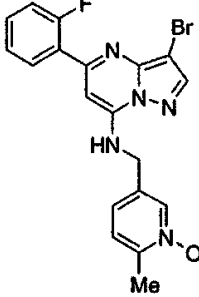
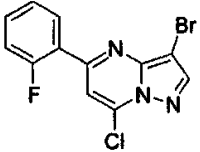
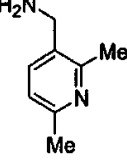
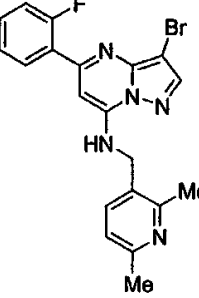
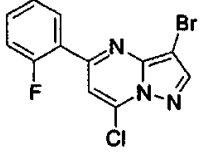
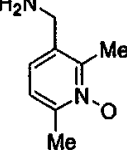
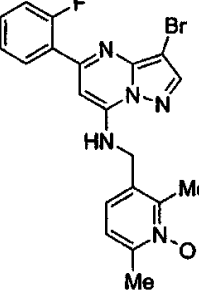
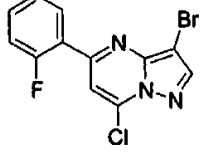
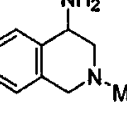
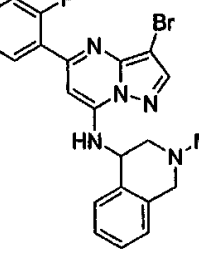
[0620]

165				$MH^+ = 494.1$
166				$MH^+ = 508.1$
167				$MH^+ = 520.1$
168				$MH^+ = 528.1$
169				$MH^+ = 520.1$

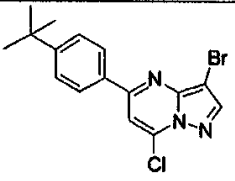
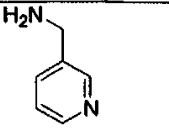
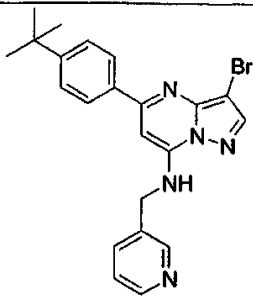
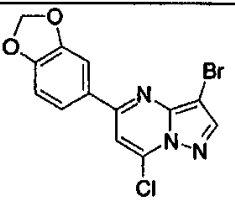
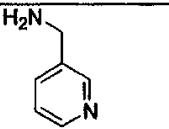
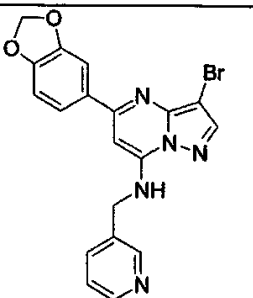
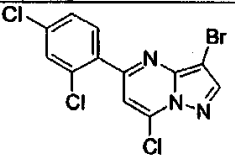
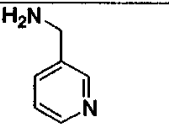
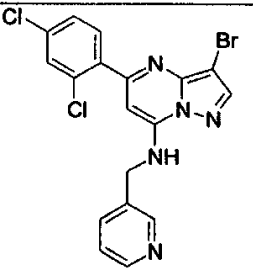
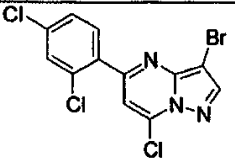
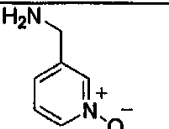
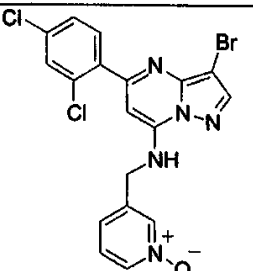
[0621]

170				$MH^+ = 528.1$
171				LCMS: $MH^+ = 474;$
172				LCMS: $MH^+ = 437;$
173				LCMS: $MH^+ = 472;$

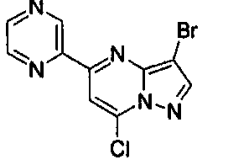
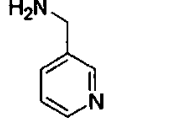
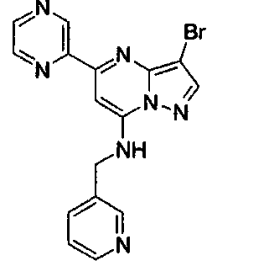
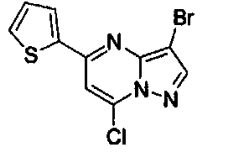

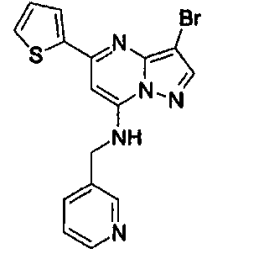
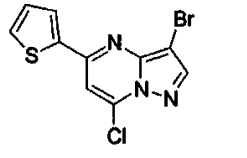
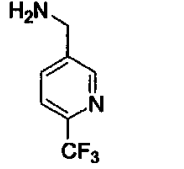
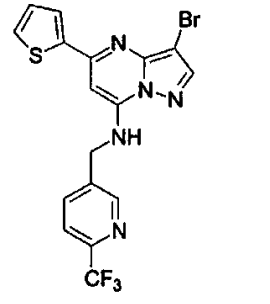
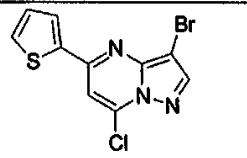
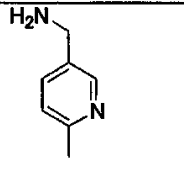
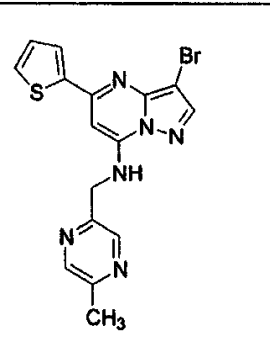
[0622]

174				LCMS: $MH^+ = 428.1$
175				LCMS: $MH^+ = 426.2$
176				LCMS: $MH^+ = 442.0$
177				LCMS: $MH^+ = 452.0$

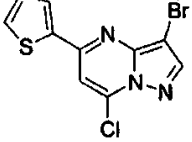
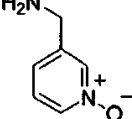
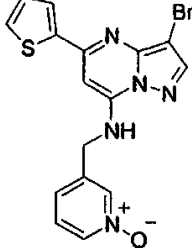
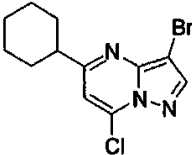
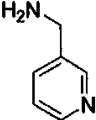
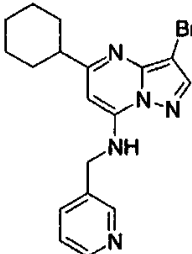
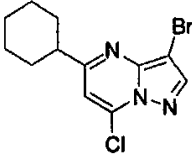
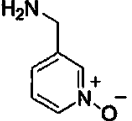
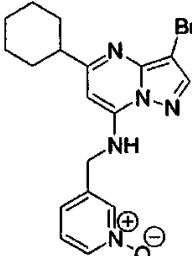
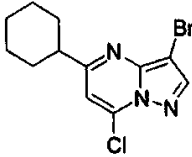
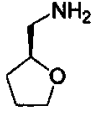
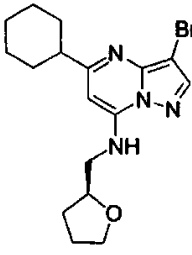
[0623]

178				수올 = 90 MH ⁺ =436 m. pt. = 89.1 °C
179				MH ⁺ =424 m. pt. = 188.2 °C
180				MH ⁺ =448 m. pt. = 211.3 °C
181				수올 = 양 MH ⁺ = 464

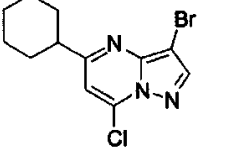
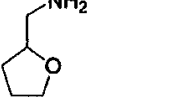
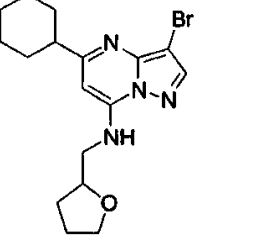
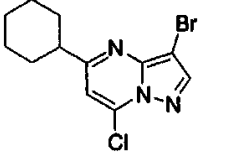
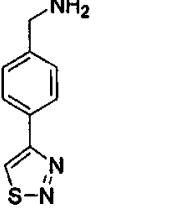
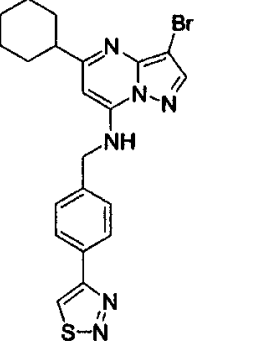
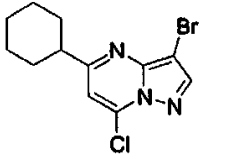
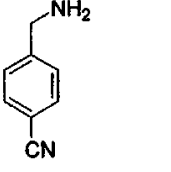
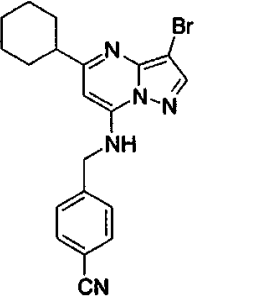
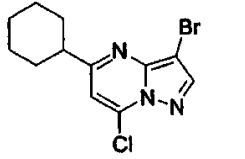
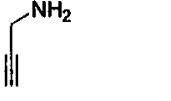
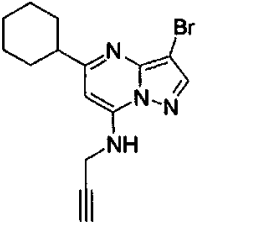
[0624]

182				<p>MH⁺ = 382 m. pt. = 185.8 °C</p>
183				<p>MH⁺ = 387 m. pt. = 181 - 182 °C</p>
184				<p>MH⁺ = 453</p>
185				<p>MH⁺ = 401 m. pt. = 178.3 °C</p>

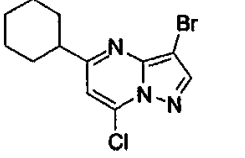
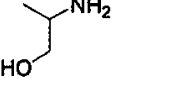
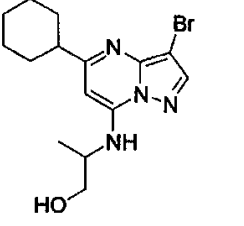
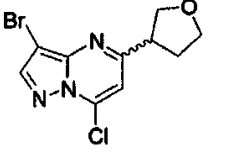
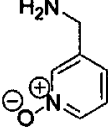
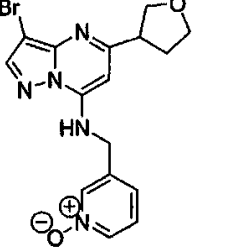
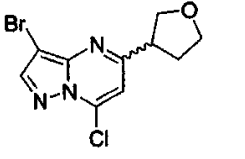
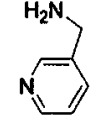
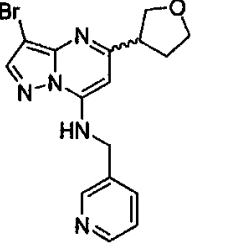
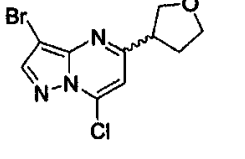
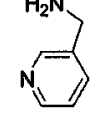
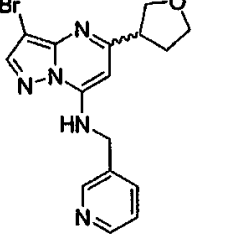
[0625]

186				<p>MH⁺ = 402</p>
187				<p>수용 = 91 MH⁺ = 386 m. pt. = 148.3 °C</p>
188				<p>수용 = 65 MH⁺ = 402 m. pt. = 174.5 °C</p>
189				<p>MH⁺ = 379 m. pt. = 82 - 83 °C</p>

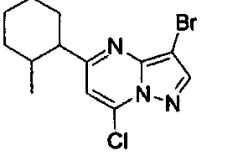
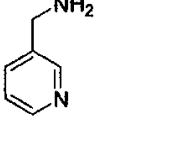
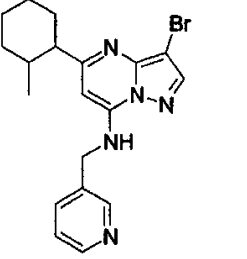
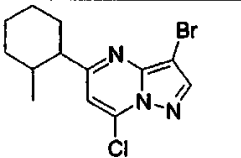
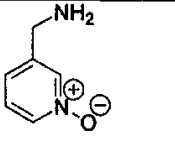
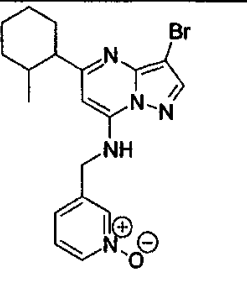
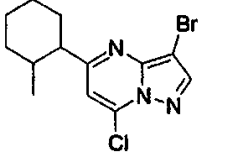
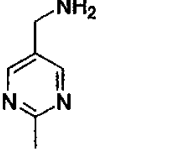
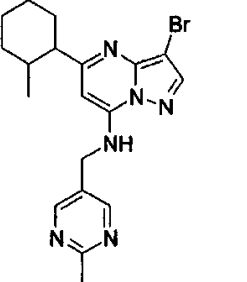
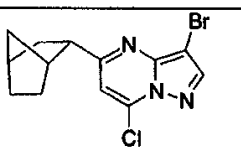
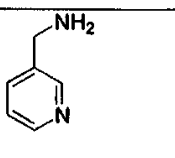
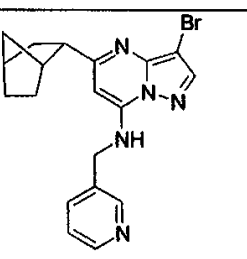
[0626]

190				<p>MH⁺ = 379 m. pt. = 50.7 °C</p>
191				<p>수율 = 89 MH⁺ = 469 m. pt. = 186.7 °C</p>
192				<p>수율 = 93 MH⁺ = 410 m. pt. = 86.7 °C</p>
193				<p>수율 = 76 MH⁺ = 333 m. pt. = 120.3 °C</p>

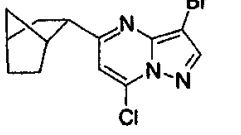
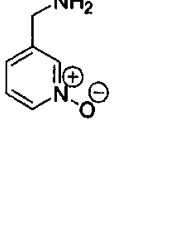
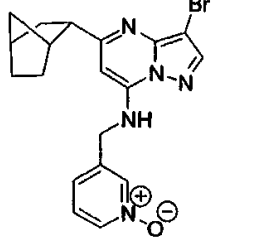
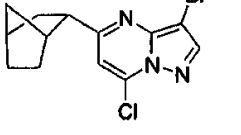
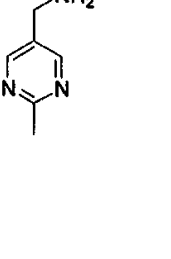
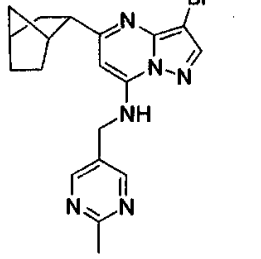
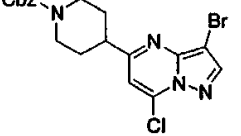
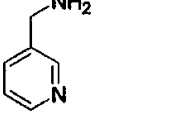
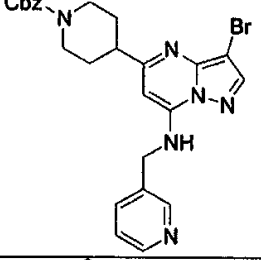
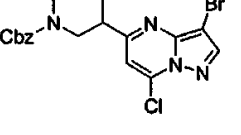
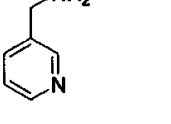
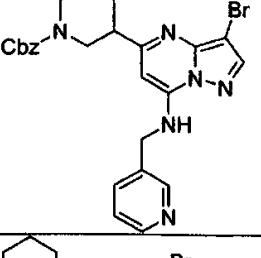
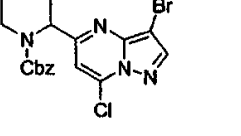
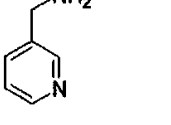
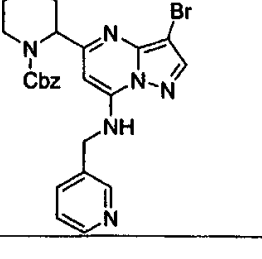
[0627]

194				수율 = 86 MH ⁺ = 353 m. pt. = 188.9 °C
195				수율 =11% LCMS:374 MH ⁺ = 390
196				수율 =88% LCMS:374 MH ⁺ = 346
197				수율 =88% LCMS:374 MH ⁺ = 346

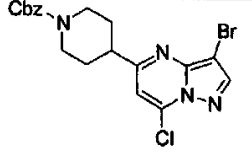
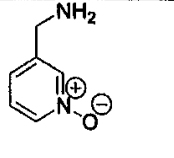
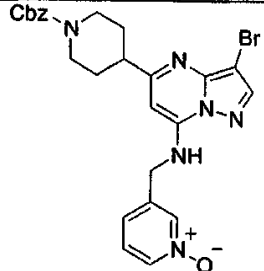
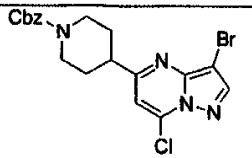
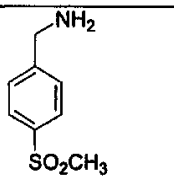
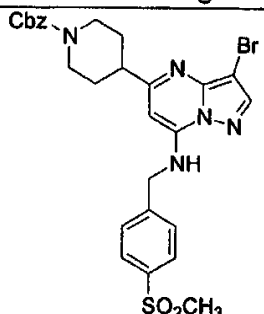
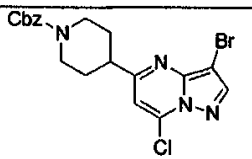
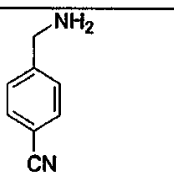
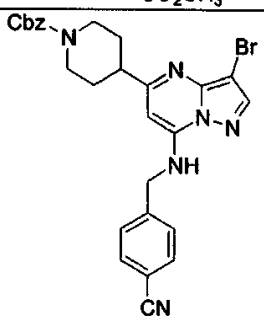
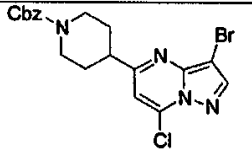
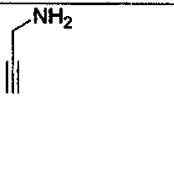
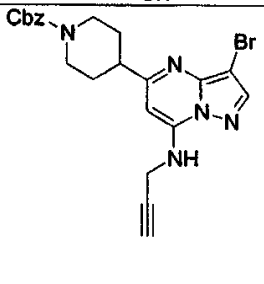
[0628]

198				<p>수용 = MH⁺ = 400 m. pt. = 111.5 – 112.2 °C</p>
199				<p>MH⁺ = 416</p>
200				<p>MH⁺ = 415</p>
201				<p>MH⁺ =398 m.p. = 156.5°C</p>

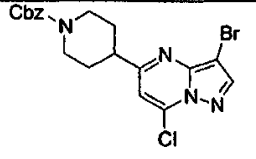
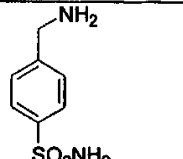
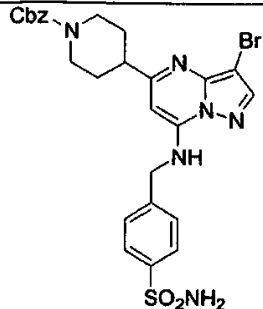
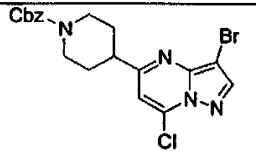
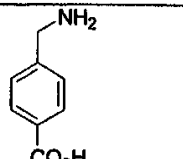
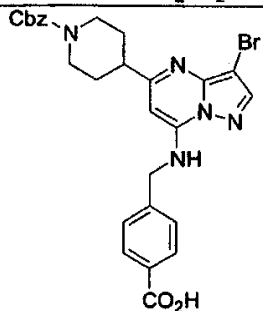
[0629]

202				<p>MH⁺ = 414 m.p. = 89.5 °C</p>
203				<p>MH⁺ = 413</p>
204				<p>수율 = 86 MH⁺ = 521 m.p. = 79.9 °C</p>
204 .10				
204 .11				<p>수율 = 87 MH⁺ = 521 m.p. = 128.6 °C</p>

[0630]

205				수율 = 99 MH ⁺ = 537 m.p. = 83.5 °C
206				수율 = 94 MH ⁺ = 598 m.p. = 110.8 °C
207				수율 = 양 MH ⁺ = 545
208				수율 = 96 MH ⁺ = 468 m.p. = 69.2 °C

[0631]

209				$MH^+ = 498$ m.p. = 226.5 °C
210				$MH^+ = 564$ m.p. = 174.2 °C

[0632]

[0633]

선택 실시예에 대한 추가의 데이터를 다음에 제공하였다:

실시예 23: 1H NMR (CD_3OD) δ 8.63 (d, J = 5.7 Hz, 2H), 8.18 (s, 1H), 7.81 (dd, J = 8.1 Hz, 2.1 Hz, 1H), 7.58 (d, J = 6.0 Hz, 2H), 7.48 (m, 1H), 7.15-7.10 (m, 2H), 6.50 (s, 1H), 4.86 (s, 2H), 3.70 (s, 3H)

실시예 24: 1H NMR ($CDCl_3$) δ 8.82 (s, 1H), 8.73 (d, J = 4.2 Hz, 1H), 8.11 (s, 1H), 8.06 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.53-7.47 (m, 2H), 7.20 (m, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.75 (s, 1H), 4.81 (d, J = 4.5 Hz, 2H), 3.86 (s, 3H)

실시예 25: 1H NMR ($CDCl_3$) δ 8.75 (d, J = 5.7 Hz, 2H), 8.12 (s, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 7.45 (d, J = 6.0 Hz, 2H), 6.96 (t, J = 6.0 Hz, 2H), 6.33 (s, 1H), 4.85 (d, J = 6.0 Hz, 2H), 4.09 (s, 3H), 4.03 (s, 3H)

실시예 26: 1H NMR ($CDCl_3$) δ 8.82 (s, 1H), 8.72 (s, 1H), 8.09 (m, 1H), 7.87-7.83 (m, 2H), 7.60 (m, 1H), 7.45 (m, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.87 (s, 1H), 6.43 (s, 1H), 4.83 (d, J = 4.5 Hz, 2H), 4.11 (s, 3H), 4.04 (s, 3H)

실시예 27: 1H NMR ($CDCl_3$) δ 8.75 (d, J = 4.5 Hz, 2H), 8.19 (s, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.44-7.40 (m, 3H), 7.07 (m, 1H), 6.26 (s, 1H), 4.83 (d, J = 5.1 Hz, 2H)

[0634]

실시예 28: $^1\text{H NMR}$ (CDCl_3) δ 8.86 (s, 1H), 8.74 (m, 1H), 8.17 (s, 1H), 7.97 (m, 1H), 7.66-7.63 (m, 2H), 7.62 (m, 1H), 7.41 (m, 1H), 7.07 (m, 1H), 6.35 (s, 1H), 4.87 (d, $J = 6.0$ Hz, 2H)

실시예 30: $^1\text{H NMR}$ (CDCl_3) δ 8.16 (s, 1H), 7.66-7.62 (m, 2H), 7.41 (m, 1H), 7.33-7.22 (m, 3H), 6.96 (t, $J = 6.0$ Hz, 1H), 6.33 (s, 1H), 4.73 (d, $J = 6.0$ Hz, 2H)

실시예 31: $^1\text{H NMR}$ (CDCl_3) δ 8.13 (s, 1H), 7.66 (d, $J = 7.8$ Hz, 2H), 7.45-7.40 (m, 2H), 7.10-7.04 (m, 2H), 6.93 (t, $J = 6.6$ Hz, 1H), 6.60 (s, 1H), 4.84 (d, $J = 6.6$ Hz, 2H)

실시예 32: $^1\text{H NMR}$ (CDCl_3) δ 8.16 (s, 1H), 7.66-7.62 (m, 2H), 7.57-7.55 (m, 2H), 7.41 (t, $J = 7.8$ Hz, 1H), 7.31 (dd, $J = 7.8, 1.8$ Hz, 1H), 6.99 (t, $J = 6.0$ Hz, 1H), 6.32 (s, 1H), 4.73 (d, $J = 6.0$ Hz, 2H)

실시예 40: $^1\text{H NMR}$ (CDCl_3) δ 8.01 (s, 1H), 7.31 – 7.24 (d, $J = 8.2$ Hz, 1H), 6.72 – 6.64 (br t, $J = 5.4$ Hz, 1H), 6.62 – 6.52 (m, 2H), 6.05 – 6.01 (s, 1H), 5.56 – 4.64 (d, $J = 6.0$ Hz, 2H), 4.03 – 3.93 (s, 3H), 3.94 – 3.86 (s, 3H), 2.79 – 2.70 (d, $J = 8.1$ Hz, 2H), 2.02 – 1.66 (m, 6H), 1.43 – 1.22 (m, 3H), 1.20 – 1.02 (m, 2H)

실시예 45: $^1\text{H NMR}$ (CDCl_3) δ 8.73(d, 2H), 8.54(s, 1H), 7.41(d, 2H), 7.02(br, 1H), 5.90(s, 1H), 4.80(s, 2H), 4.48(q, 2H), 2.75(s, 2H), 1.50(t, 2H), 1.06(s, 9H);

실시예 46: $^1\text{H NMR}$ (CDCl_3) δ 8.79(s, 1H), 8.72(d, 1H), 8.14(s, 1H), 7.84(d, 1H), 7.54-7.33(m, 4H), 6.97(t, 1H), 6.18(s, 1H), 4.79(d, 2H), 2.47(s, 3H)

실시예 108: $^1\text{H NMR}$ (CDCl_3) δ 8.79 (s, 1H), 8.72 (d, $J = 3.0$ Hz, 1H), 8.16 (s, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 7.74 (d, $J = 7.5$ Hz, 2H), 7.55-7.35 (m, 3H), 6.92 (t, $J = 6.3$ Hz, 1H), 6.42 (s, 1H), 4.81 (d, $J = 6.3$ Hz, 2H)

실시예 110: $^1\text{H NMR}$ (CDCl_3) δ 8.18(t, 1H), 8.03(s, 1H), 7.44(m, 1H), 7.30(t, 1H), 7.17(q, 1H), 6.66(s, 1H), 6.56(br, 1H), 4.28(d, 2H), 2.38(s, 1H)

실시예 111: $^1\text{H NMR}$ (CDCl_3) δ 8.72(br, 1H), 8.59(d, 1H), 8.11(t, 1H), 8.06(s, 1H), 7.73(d, 1H), 7.44(d, 1H), 7.42-7.21(m, 3H), 7.07(q, 1H), 6.39(d, 1H), 5.21(q, 1H), 4.16(q, 2H), 3.08(d, 2H), 1.22(t, 3H)

실시예 112: $^1\text{H NMR}$ (CDCl_3) δ 8.22(t, 1H), 8.15(s, 1H), 7.51-7.33(m, 7H), 7.21(q, 1H), 6.82(d, 1H), 6.51(s, 1H), 4.68(q, 1H), 2.18(m, 2H), 1.17(t, 3H)

실시예 113: $^1\text{H NMR}$ (CDCl_3) δ 8.22(t, 1H), 8.14(s, 1H), 7.51-7.33(m, 7H), 7.21(q, 1H), 6.82(d, 1H), 6.51(s, 1H), 4.68(q, 1H), 2.18(m, 2H), 1.17(t, 3H)

[0635]

실시예 114: ^1H NMR (CDCl_3) δ 8.81(s, 1H), 8.75(d, 1H), 8.21(s, 1H), 7.84(d, 1H), 7.47(q, 1H), 6.96(s, 1H), 6.94(t, 1H), 4.85(d, 2H), 4.60(q, 2H), 1.58(t, 3H)

실시예 115: ^1H NMR (CDCl_3) δ 8.77(s, 1H), 8.72(d, 1H), 8.14(s, 1H), 7.83(d, 1H), 7.65(d, 1H), 7.44(q, 1H), 7.80(t, 1H), 7.6(d, 1H), 6.18(s, 1H), 4.75(d, 2H), 3.91(s, 3H), 3.81(s, 3H)

실시예 116: ^1H NMR (CDCl_3) δ 8.67(s, 1H), 8.55(d, 1H), 8.50(s, 1H), 7.92(d, 1H), 7.90(d, 1H), 7.78(t, 1H), 7.10(d, 1H), 6.97(s, 1H), 5.11(s, 2H), 3.77(s, 6H)

실시예 117: ^1H NMR (CDCl_3) δ 8.38(s, 1H), 8.30(d, 1H), 8.17(s, 1H), 7.52-7.37(m, 6H), 6.97(t, 1H), 6.13(s, 1H), 4.77(d, 2H), 2.50(s, 3H)

실시예 118: ^1H NMR (CDCl_3) δ 8.18(t, 1H), 8.03(s, 1H), 7.44(m, 1H), 7.30(t, 1H), 7.17(q, 1H), 6.66(s, 1H), 6.56(br, 1H), 4.28(d, 2H), 2.38(s, 1H);

실시예 121: ^1H NMR (CDCl_3) δ 8.6 (s, 1H), 8.15 (dt, 1H), 8.1 (s, 1H), 8.0 (d, 2H), 7.5 (d, 2H), 7.4 (dd, 1H), 7.2 (d, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.6 (s, 1H), 4.75 (d, 2H).

실시예 126: ^1H NMR (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.5 (d, 1H), 7.42 - 7.35 (m, 2H), 7.3 - 7.2 (m, 2H), 7.15 (dd, 1H), 7.1 (dd, 1H), 7.0 (t, 1H), 6.6 (s, 1H), 4.8 (d, 2H).

실시예 127: ^1H NMR (CDCl_3) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.4 (dd, 1H), 7.3- 7.25 (m, 3H), 7.1 (dd, 1H), 6.9 - 6.85 (m, 2H), 6.7 (t, 1H), 6.6 (s, 1H), 4.6 (d, 2H), 3.2 (m, 4H), 2.6 (m, 4H), 2.3 (s, 3H)

실시예 128: ^1H NMR (CDCl_3) δ 8.15 (dt, 1H), 8.1 (s, 1H), 8.0 (d, 2H), 7.5 (d, 2H), 7.4 (m, 2H), 7.25 (d, 1H), 7.2 (s, 1H), 7.15 (dd, 1H), 7.0 (s, 1H), 6.8 (t, 1H), 6.6 (s, 1H), 4.75 (d, 2H).

실시예 129: ^1H NMR (CDCl_3) δ 8.15 (dt, 1H), 8.05 (s, 1H), 8.0 (d, 2H), 7.5 (d, 2H), 7.4 (m, 1H), 7.3 (dd, 1H), 7.15 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 4.75 (d, 2H), 3.85 (s, 3H)

실시예 130: ^1H NMR (CDCl_3) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.4 (dd, 1H), 7.3 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.4 (s, 1H), 4.2 (d, 2H), 3.8 (s, 3H).

실시예 131: ^1H NMR (CDCl_3) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.4 - 7.15 (m, 3H), 6.7 (t, 1H), 4.2 (q, 2H), 3.8 (dt, 2H), 2.8 (t, 2H), 1.2 (t, 3H)

실시예 132: ^1H NMR (CDCl_3) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.4 – 7.15 (m, 3H), 6.7 (t, 1H), 4.2 (q, 2H), 3.8 (dt, 2H), 2.8 (t, 2H), 2.05 (m, 2H) 1.2 (t, 3H)

실시예 133: ^1H NMR (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.3 (dd, 1H), 7.2 (dd, 1H), 6.5 (s, 1H), 6.4 (t, 1H), 3.7 (s, 3H), 3.5 (dd, 2H), 2.4 (t, 2H), 1.8 (m, 4H)

실시예 134: ^1H NMR (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.95 (d, 2H), 7.6 (d, 2H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 4.8 (d, 2H), 3.0 (s, 3H)

실시예 135: ^1H NMR ($\text{DMSO}-d_6$) δ 9.1 (bs, 2H), 8.4 (s, 1H), 8.0 (t, 1H), 7.85 (d, 2H), 7.7 (d, 2H), 7.6 (m, 1H), 7.4 (m, 2H), 6.6 (s, 1H), 4.8 (bs, 2H)

실시예 136: ^1H NMR (CDCl_3) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.9 (m, 3H), 6.7 (t, 1H), 6.5 (s, 1H), 4.5 (d, 2H), 4.2 (s, 4H)

실시예 137: ^1H NMR (CDCl_3) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.3 (dd, 1H), 7.2 (dd, 1H), 6.9 (dd, 1H), 6.8 (t, 1H), 6.7 (m, 1H), 6.6 (s, 1H), 5.3 (s, 2H), 4.85 (s, 2H), 4.6 (d, 2H).

실시예 138: ^1H NMR (CDCl_3) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 7.4 (m, 2H), 7.3 (dd, 1H), 7.1 (dd, 1H), 6.9 (t, 1H), 6.6 (s, 1H), 4.8 (d, 2H)

실시예 139: ^1H NMR (CDCl_3) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.3 (m, 2H), 7.2 (dd, 1H), 7.1 (dd, 1H), 6.8 (d, 1H), 6.7 (t, 1H), 6.6 (s, 1H), 4.6 (m, 4H), 3.2 (t, 2H)

실시예 140: ^1H NMR (CDCl_3) δ 8.45 (s, 1H), 8.2 (dt, 1H), 8.0 (s, 1H), 7.7 (dd, 1H), 7.4 – 7.3 (m, 3H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.6 (s, 1H), 4.7 (d, 2H)

실시예 141: ^1H NMR (CDCl_3) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.45 – 7.1 (m, 7H), 6.6 (s, 1H), 4.4 (dt, 2H), 2.6 (t, 2H), 1.8 (m, 2H), 1.4 (m, 2H)

실시예 171: ^1H NMR (CD_3OD) δ 8.41 (s, 1H), 8.25 (d, $J = 6.3$ Hz, 1H), 8.15 (s, 1H), 7.67 (d, $J = 7.8$ Hz, 2H), 7.55–7.48 (m, 2H), 7.45 (dd, $J = 7.5, 1.2$ Hz, 1H), 7.34 (dd, $J = 7.5, 1.8$ Hz, 1H), 6.28 (s, 1H), 4.79 (s, 2H).

실시예 172: ^1H NMR (CDCl_3) δ 8.64 (s, 1H), 7.68–7.64 (m, 2H), 7.52 (m, 1H), 7.43 (t, $J = 7.8$ Hz, 1H), 6.89 (t, $J = 6.0$ Hz, 1H), 6.51 (s, 1H), 6.48 (m, 2H), 4.74 (d, $J = 6.0$ Hz, 2H).

[0637]

실시예 173: ^1H NMR ($\text{DMSO}-d_6$) δ 8.86 (s, 1H), 8.46 (s, 1H), 8.32-8.28 (m, 2H), 7.97 (m, 1H), 7.87 (m, 1H), 7.52 (m, 1H), 7.35-7.24 (m, 2H), 6.57 (s, 1H), 6.46 (m, 1H), 3.65 (m, 4H).

실시예 174: ^1H NMR (CDCl_3) d 8.37 (s, 1H), 8.16 (t, J = 7.5 Hz, 1H), 7.45-7.35 (m, 1H), 7.32-7.20 (m, 3H), 7.17-7.07 (m, 1H), 6.92 (t, J = 6 Hz, 1H), 6.48 (s, 1H), 4.65 (d, 2H), 2.50 (s, 3H).

실시예 175: ^1H NMR (CDCl_3) d 8.16 (t, J = 9 Hz, 1H), 8.00 (s, 1H), 7.49 (d, J = 9 Hz, 1H), 7.46-7.36 (m, 1H), 7.18-7.08 (m, 1H), 7.00 (d, J = 9 Hz, 1H), 6.62-6.50 (m, 2H), 2.60 (s, 3H), 2.55 (s, 3H).

실시예 176: ^1H NMR (CDCl_3) d 8.15 (t, J = 9 Hz, 1H), 8.00 (s, 1H), 7.45-7.35 (m, 1H), 7.32-7.20 (m, 1H), 7.20-7.05 (m, 3H), 6.80 (t, 1H), 6.50 (s, 1H), 4.65 (d, 2H), 2.65 (s, 3H), 2.50 (s, 3H).

실시예 177: ^1H NMR (CDCl_3) d 8.20 (t, 1H), 7.90 (s, 1H), 7.50-7.05 (m, 8H), 6.80 (s, 1H), 5.05-4.90 (m, 2H), 3.80 (d, 1H), 3.45 (d, 1H), 3.00 (dd, 1H), 2.90 (dd, 1H), 2.50 (s, 3H).

실시예 181: ^1H NMR (300MHz, CDCl_3) □ 8.41 (s, 1H), 8.28 – 8.23 (d, 1H), 8.15 (s, 1H), 7.69 – 7.60 (d, 1H), 7.62 – 7.50 (m, 3H), 7.50 – 7.47 (dd, 1H); 6.35 (s, 1H), 5.36 (s, 1H), 4.80 (s, 2H).

실시예 184: ^1H NMR (300MHz, CDCl_3) □□ 8.96 - 8.90 (s, 1H), 8.08 (s, 1H), 8.04 (d, 1H), 7.72 (d, 1H), 7.70 – 7.61 (dd, 1H), 7.24 – 7.20 (dd, 1H), 6.92 – 6.84 (t, 1H), 6.36 (s, 1H), 4.96 – 4.89 (d, 2H).

실시예 186: ^1H NMR (300MHz, CDCl_3) □□ 8.96 - 8.90 (s, 1H), 8.08 (s, 1H), 8.44 (s, 1H), 8.27 – 8.24 (d, 1H), 8.02 (s, 1H), 7.78 – 7.76 (d, 1H), 7.73 – 7.70 (d, 1H), 7.58 – 7.51 (m, 2H), 7.13 – 7.08 (dd, 1H), 5.51 (s, 2H).

실시예 195: ^1H NMR (CD_3OD) δ 8.40(s, 1H), 8.27(d, 1H), 8.03(s, 1H), 7.75-7.50(m, 2H), 6.10(s, 1H), 4.76(s, 2H), 4.05(m, 2H), 3.88(m, 2H), 3.52(m, 1H), 2.33(m, 1H), 2.20(m, 1H).

실시예 196: ^1H NMR (CD_3OD) δ 8.73(d, 1H), 8.58(q, 1H), 8.12(s, 1H), 8.00(d, 1H), 7.54(q, 1H), 6.19(s, 1H), 4.86(s, 2H), 4.22-4.08(m, 2H), 4.03-3.93(m, 2H), 3.63(m, 1H), 2.50-2.39(m, 1H), 2.32-2.21(m, 1H).

실시예 197: ¹H NMR (CD₃OD) δ 8.73(d, 1H), 8.58(q, 1H), 8.12(s, 1H), 8.00(d, 1H), 7.54(q, 1H), 6.19(s, 1H), 4.86(s, 2H), 4.22-4.08(m, 2H), 4.03-3.93(m, 2H), 3.63(m, 1H), 2.50-2.39(m, 1H), 2.32-2.21(m, 1H).

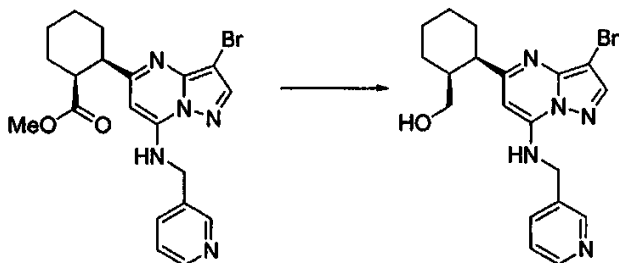
실시예 199: ¹H NMR (300MHz, CDCl₃) □□8.29 (s, 1H), 8.15 (br s, 1H), 7.95 (s, 1H), 7.28 (d, 1H), 7.05 - 6.95 (appt t, 1H), 5.70 (s, 1H), 4.62 (d, 2H), 2.90 (m, 1H), 2.30 (m, 1H), 1.9 - 1.2 (m, 8H), 0.65 (d, 3H).

실시예 200: ¹H NMR (300MHz, CDCl₃) □□ 8.71 (s, 2H), 8.00 (s, 1H), 6.13 (s, 1H), 3.59 (s, 2H), 3.01 - 2.58 (m, 1H), 2.51 - 2.45 (m, 1H), 2.44 - 2.30 (m, 1H), 2.20 (s, 3H), 2.09 - 1.95 (m, 2H), 1.85 - 1.70 (m, 2H), 0.80 - 0.76 (d, 3H).

실시예 203: ¹H NMR (300MHz, CDCl₃) □□8.10 (s, 1H), 8.08 (s, 1H), 6.27 (s, 2H), 4.95 (s, 2H), 3.00 - 2.90 (dd, 2H), 2.60 (m, 2H), 2.48 (br s, 1H), 2.39 (s, 3h), 2.25 m, 1H), 1.95 - 1.70 (m, 3H).

[0639]

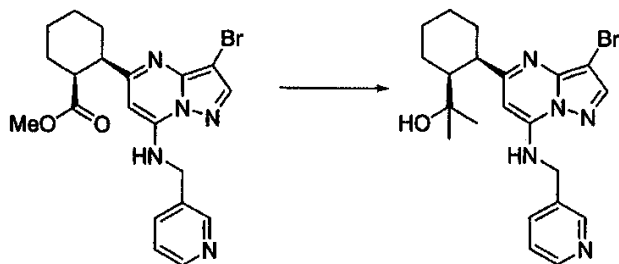
[0640] 실시예 211:



[0641]

[0642] 무수 THF(4mL)중의 실시예 156에서 제조한 화합물(100mg, 0.23mmol)의 용액에 N₂하에 0°C에서 LiAlH₄ (THF중의 1.0M, 0.110mL, 0.110mmol)를 가하였다. 혼합물을 0° C에서 1시간 동안 교반하고, 25° C에서 가온시킨 다음, 추가의 LiAlH₄ (THF중의 1.0M, 0.400mL)를 가하고, 혼합물을 20분 동안 교반한 다음 MeOH (2.0mL)로 퀀칭시켰다. 용매를 증발시키고 조약한 생성물을 용출제로서 10:1 CH₂Cl₂:MeOH를 사용하는 플래쉬 크로마토그래피에 의해 정제하였다. 백색 고체(46mg, 49%)를 수득하였다. LCMS: M⁺ = 416. MP=71-72° C.

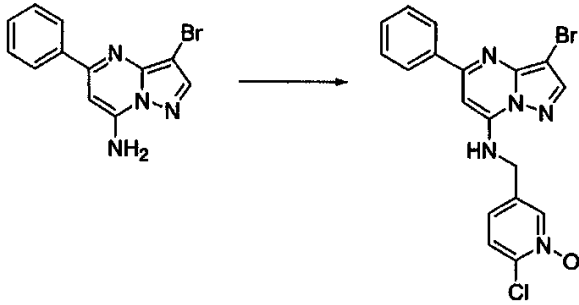
[0643] 실시예 212:



[0644]

[0645] 무수 THF(3mL)중의 실시예 156(70mg, 0.16mmol)에서 제조한 화합물의 용액에 N₂하에 MeMgBr(Et₂O중의 3.0M, 1.10mL, 3.20mmol)을 가하였다. 혼합물을 25°C에서 45분 동안 교반한 다음 포화된 수성 NH₄Cl(5.0mL)로 퀀칭시켰다. 혼합물을 포화된 수성 NH₄Cl(30mL) 속으로 부어넣고 CH₂Cl₂(3 x 20mL)로 추출하였다. 추출물을 Na₂SO₄ 위에서 건조시키고 여과하였다. 용매를 증발시키고 조약한 생성물을 용출제로서 20:1 CH₂Cl₂:MeOH를 사용하는 플래쉬 크로마토그래피에 의해 정제하였다. 백색 고체(25mg, 36%)를 수득하였다. LCMS: M⁺ = 444. MP=76-80°C.

[0646] 실시예 213:



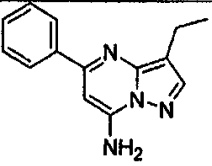
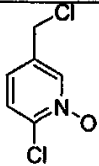
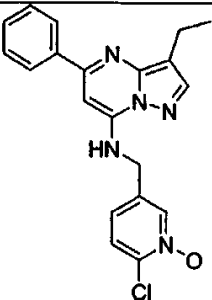
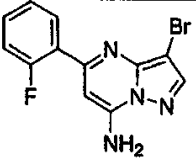
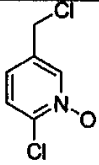
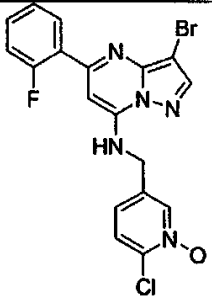
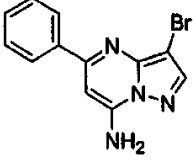
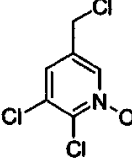
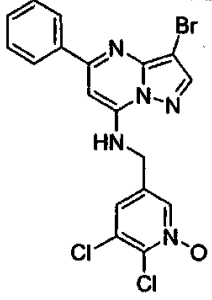
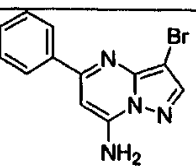
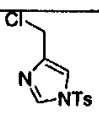
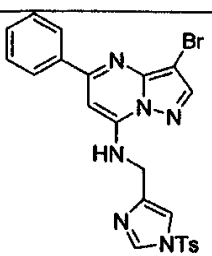
[0647]

[0648] 무수 DMF(40mL)를 N₂하에 가하여 제조 실시예 174(2.50g, 8.65mmol)에서 제조한 화합물 및 무기 오일(346mg, 8.65mmol)중의 60% NaH에 가하였다. 혼합물을 25℃에서 1시간 동안 교반한 다음, 무수 DMF(20mL)중의 2-클로로-5-클로로메틸피리딘 N-옥사이드(1.54g, 8.65mmol)를 서서히 가하였다. 혼합물을 25° C에서 18시간 동안 교반하고, 용매를 증발시키고 조약한 생성물을 용출제로서 30:1 CH₂Cl₂ : MeOH를 사용하는 플래쉬 크로마토그래피로 정제하였다. 이와 같이 수득한 고체를 50mL의 1 : 1 EtOAc:헥산으로 분쇄하였다. 담황색 고체(1.25g, 34%)를 수득하였다. LCMS: MH⁺=432. Mp=224-226℃.

[0649] 실시예 214 내지 217:

[0650] 실시예 213에 나타난 바와 본질적으로 동일한 과정으로, 표 19의 컬럼 2에 나타난 화합물을 표 19의 컬럼 3의 화합물과 조합함으로써, 표 19의 컬럼 3에 나타난 화합물을 제조하였다.

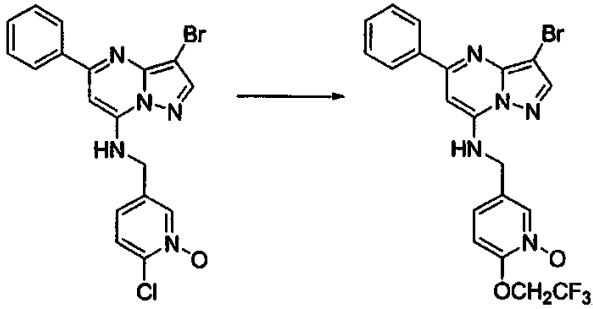
표 19

실시예	컬럼 2	컬럼 3	컬럼 4	COMPD
214				LCMS: MH ⁺ =380; mp=°C
215				LCMS: MH ⁺ =450; mp=218-222°C
216				LCMS: MH ⁺ =466; mp=126-128°C
217				LCMS: M ⁺ =523

[0651]

[0652]

[0653] 실시예 218:



[0654]

[0655] $\text{CF}_3\text{CH}_2\text{OH}$ (3.0mL)를 무기 오일(40mg, 1.0mmol)중의 60% NaH에 N_2 하에 가하고, 혼합물을 20분 동안 교반한 다음, 실시예 213에서 제조한 생성물(50mg, 0.12mmol)을 가하였다. 혼합물을 20분 동안 재환류시키고, 용매를 증발시키고, 잔사를 용출제로서 20:1 CH_2Cl_2 :MeOH를 사용하여 플래쉬 크로마토그래피함으로써 정제하여 담황색 고체(35mg, 61%)를 수득하였다. LCMS: M^+ 496. Mp = 208-210°C.

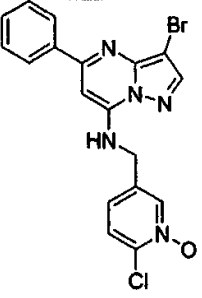
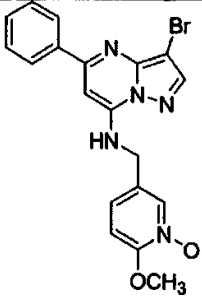
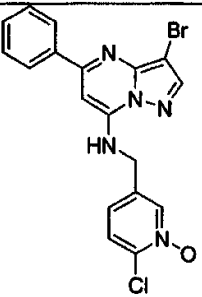
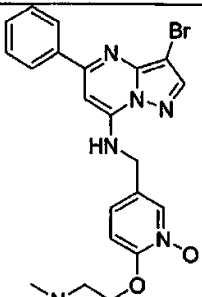
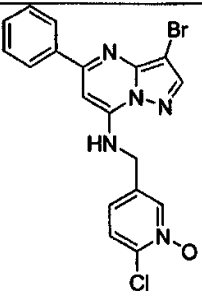
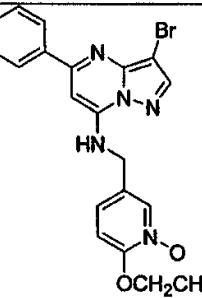
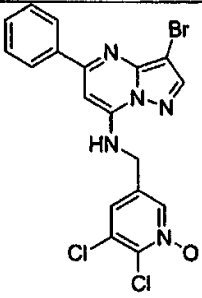
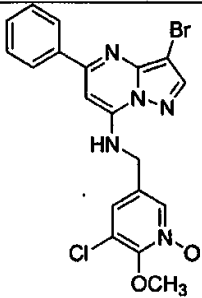
[0656] 실시예 219 내지 225:

[0657] 실시예 218에 나타낸 바와 본질적으로 동일한 과정으로, 표 20의 컬럼 1에 나타낸 화합물을 적합한 알콜과 조합하여, 표 20의 컬럼 2에 나타낸 화합물을 제조하였다.

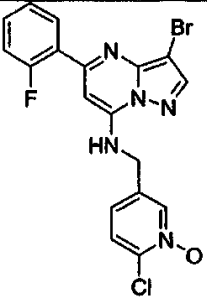
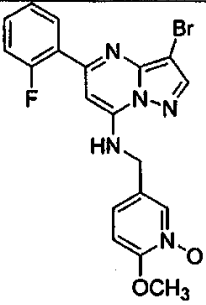
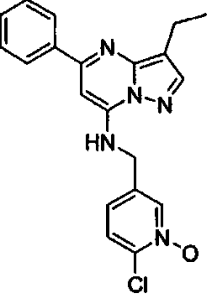
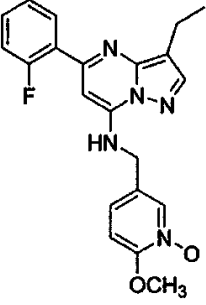
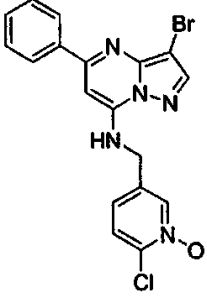
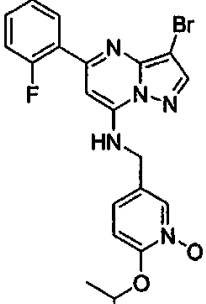
표 20

실시예	컬럼 1	컬럼 2	데이터
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[0658]

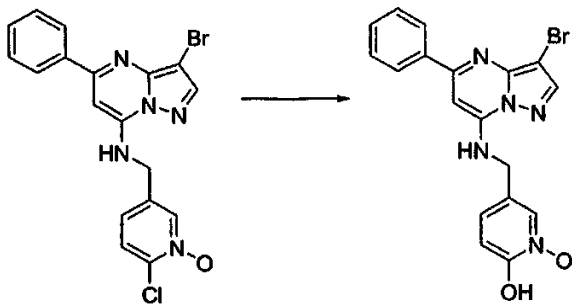
219			<p>LCMS: M⁺=426; mp=126- 128°C</p>
220			<p>LCMS: M⁺=483; mp=89- 91°C</p>
221			<p>LCMS: M2H⁺=442 ; mp=112- 114°C</p>
222			<p>LCMS: MH⁺=462; mp=121- 123°C</p>

[0659]

223			LCMS: MH ⁺ =444; mp=112-114°C
224			LCMS: M ⁺ =376; mp=°C
225			LCMS: MH ⁺ =; mp=°C

[0660]

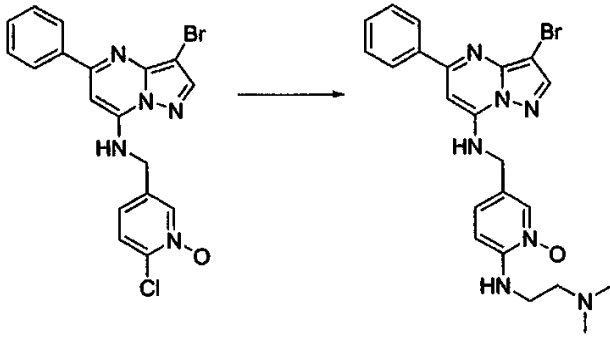
[0661] 실시예 226:



[0662]

[0663] 1,2-디메톡시에탄(3mL) 및 H₂O(1.5mL)중의 실시예 213에서 제조한 생성물(100mg, 0.23mmol) 및 KOH(95mg, 1.70mmol)의 혼합물을 N₂하에 20시간 동안 환류시키고, 아세트산(0.30mL)로 킁칭시키고, 용매를 증발시켰다. 잔사를 H₂O(15mL)에 현탁시키고, 여과하고, 고체를 H₂O(15mL) 및 Et₂O(10mL)로 세척하였다. 이어서, 이를 CH₂Cl₂(2mL) 및 Et₂O(2mL)와 혼합하고 여과하였다. Et₂O(5mL)를 여액에 가하고 혼합물을 밤새 정치시켰다. 고체를 여과하여 제거하고 Et₂O로 세척한 다음, MeOH(5mL)에 용해시켰다. 용액을 여과하고 여액으로부터의 용매를 증발시켰다. 회백색 고체(5mg, 5%)을 수득하였다. LCMS: M⁺ = 412. Mp = 206-208°C.

[0664] 실시예 227:



[0665]

[0666] 무수 N-메틸피롤리딘(0.10mL)중의 실시예 213에서 제조한 생성물(129mg, 0.30mmol), N,N-디메틸에틸렌디아민 (0.165mL, 1.50mmol) 및 디소프로필에틸아민(0.10mL)의 혼합물을 100° C에서 24시간 동안 교반하였다. 용매를 증발시키고, 잔사를 용출제로서 MeOH중의 20:1 CH₂Cl₂:7N NH₃를 사용하여 플래쉬 크로마토그래피함으로써 정제하여 담황색 고체(110mg, 76%)을 수득하였다. LCMS: M⁺ = 482. Mp = 76-78°C.

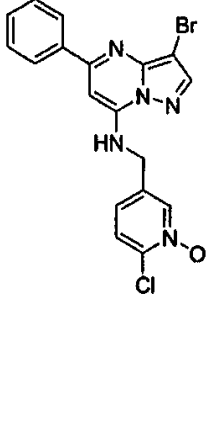
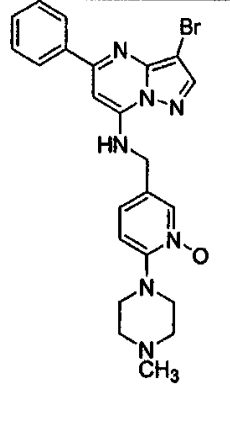
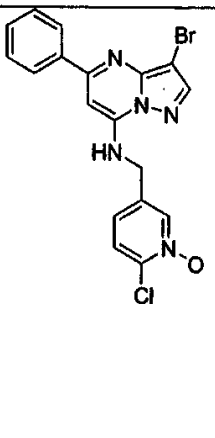
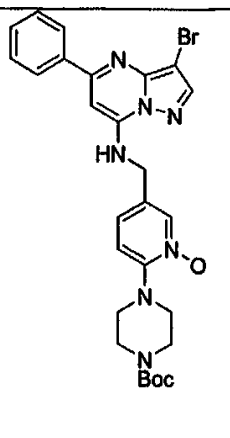
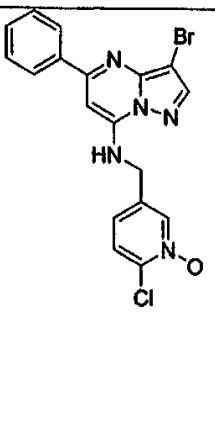
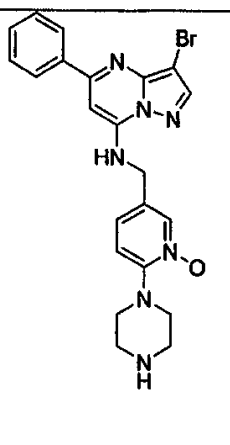
[0667] 실시예 228 내지 233:

[0668] 실시예 227에 나타난 바와 본질적으로 동일한 과정으로, 표 21의 컬럼 1에 나타난 화합물을 적합한 아민과 조합하여, 표 21의 컬럼 2에 나타난 화합물을 제조하였다.

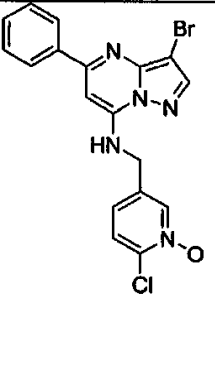
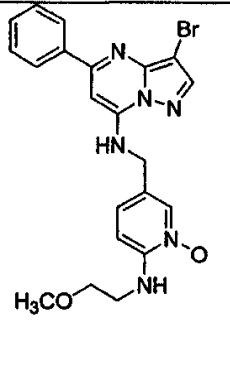
표 21

실시예	컬럼 1	컬럼 2	데이터
228			LCMS: M _{2H⁺} =467 ; mp 126-128=°C
229			LCMS: M ⁺ =481; mp=128-130°C

[0669]

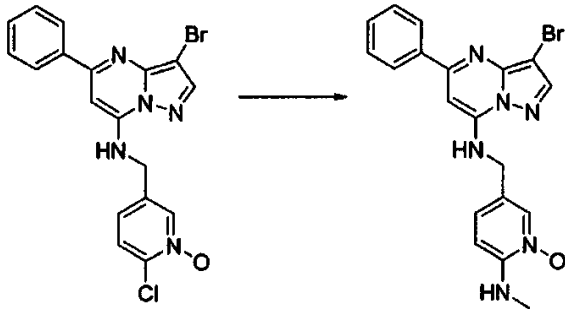
230			<p>LCMS: M⁺=494; mp=108-110°C</p>
231			<p>LCMS: M2H⁺=482 ; mp=129-133°C</p>
232			<p>LCMS: M2H⁺=482 ; mp=124-126°C</p>

[0670]

233			<p>LCMS: M2H⁺=471 ; mp=88-90°C</p>
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[0671]

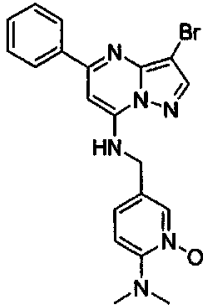
[0672] 실시예 234:



[0673]

[0674] THF중의 실시예 213에서 제조한 생성물(80mg, 0.19mmol) 및 2.0M 메틸아민의 혼합물을 밀폐된 압력 용기 속에서 50°C에서 72시간 동안 교반하였다. 용매를 증발시키고, 잔사를 용출제로서 10:1 CH₂Cl₂:MeOH를 사용하여 플래쉬 크로마토그래피함으로써 정제하여 담황색 고체(40mg, 51%)를 수득하였다. LCMS: M2H⁺=427. MP=217-219°C.

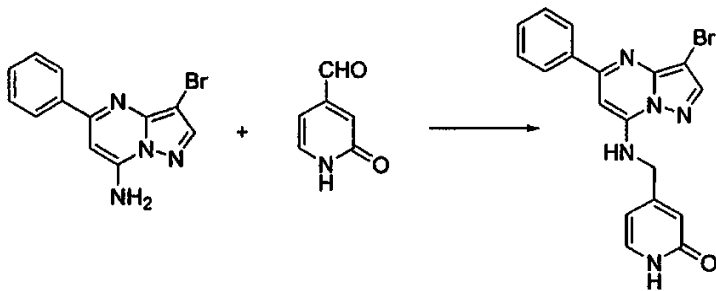
[0675] 실시예 235:



[0676]

[0677] 실시예 234에 나타난 바와 본질적으로 동일한 과정으로, 상기 나타난 화합물을 제조하였다. LCMS: M2H⁺ = 441. Mp = 98-101°C.

[0678] 실시예 236:



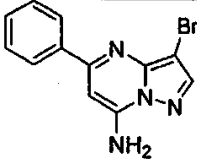
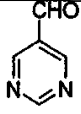
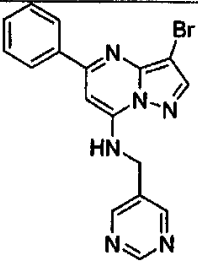
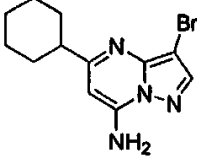
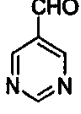
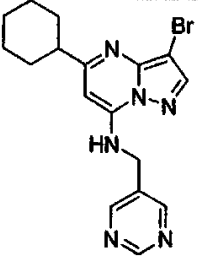
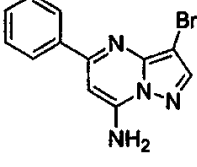
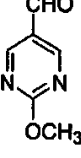
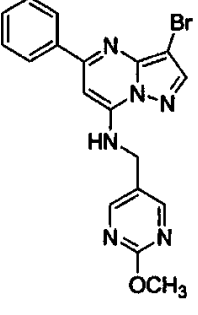
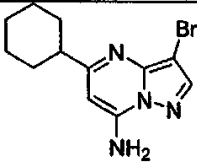
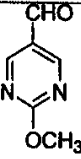
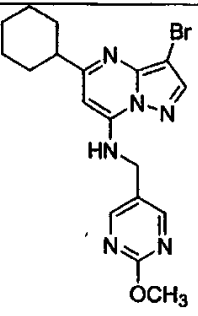
[0679]

[0680] 제조 실시예 174에서 제조한 화합물(140mg, 0.48mmol) 및 알데히드(71mg, 0.58mmol)을 N₂하에 50°C에서 무수 THF(4mL)중에서 교반시켰다. Ti(OiPr)₄(0.574mL, 1.92mmol)을 가하고, 혼합물을 50°C에서 3시간 동안 교반하고, 25°C로 냉각시켰다. NaBH₃CN(181mg, 2.88mmol)을 가하고, 혼합물을 2시간 이상 동안 교반한 다음, 10% 수성 Na₂CO₃ (100mL) 속으로 부어넣고, CH₂Cl₂ (3 x 50mL)로 추출하였다. 합한 추출물을 Na₂SO₄ 위에서 건조시키고, 여과시키고, 용매를 증발시켰다. 잔사를 용출제로서 15:1 CH₂Cl₂:MeOH를 사용하는 플래쉬 크로마토그래피로 정제하여 담황색 고체(40mg, 21%)를 수득하였다. LCMS : MH⁺ = 398. Mp > 230°C.

[0681] 실시예 237 내지 256:

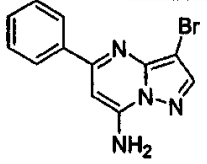

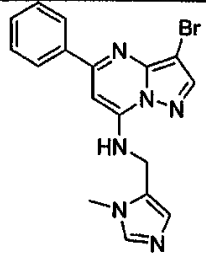
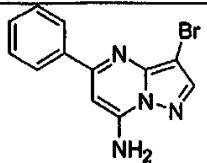
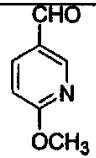
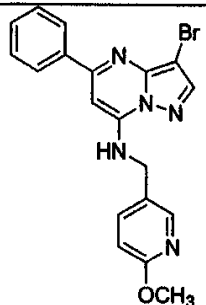
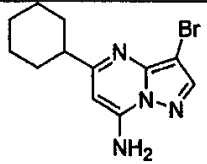
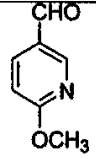
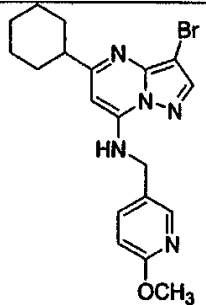
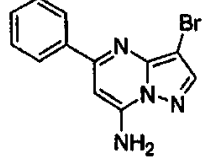

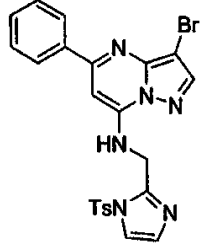
[0682] 실시예 236에 나타난 바와 본질적으로 동일한 과정으로, 표 22의 컬럼 2 및 3에 나타난 화합물을 표 22의 컬럼 4에 나타난 화합물과 조합하여, 표 22의 컬럼 4에 나타난 화합물을 제조하였다.

표 22

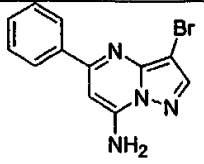
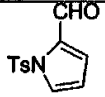
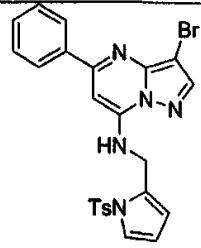
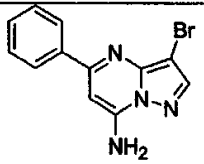
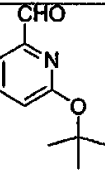
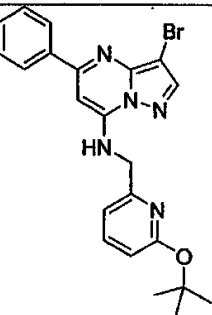
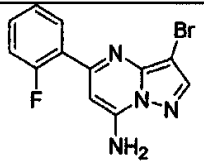
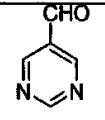
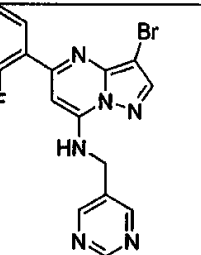
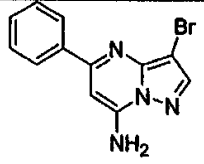
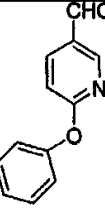
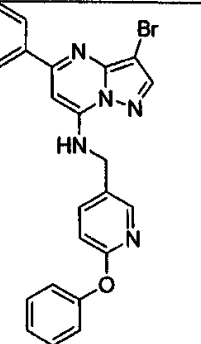
실시예	컬럼 2	컬럼 3	컬럼 4	데이터
237				LCMS: M ⁺ =381; mp>200°C
238				LCMS: M ⁺ =387; mp=°C
239				LCMS: MH ⁺ =413; mp=157-159°C
240				LCMS: M2H ⁺ =419; mp=77-79°C

[0683]

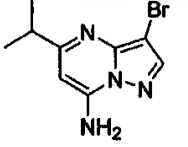
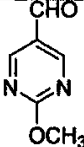
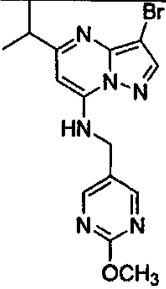
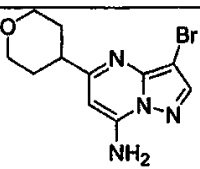
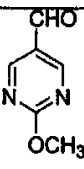
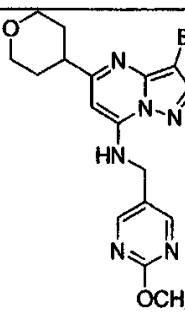
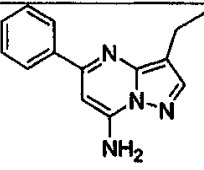
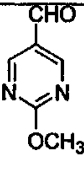
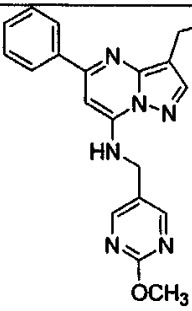
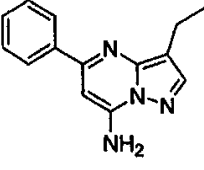
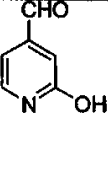
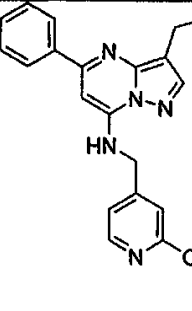
[0684]

241				<p>LCMS: M₂H⁺=385 ; mp=214- 216°C</p>
242				<p>LCMS: MH⁺=; mp=°C</p>
243				<p>LCMS: M⁺=416; mp=80- 82°C</p>
244				

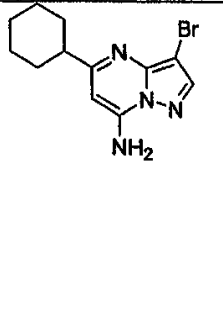
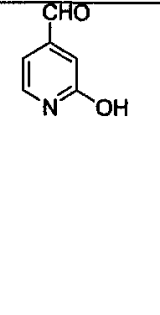
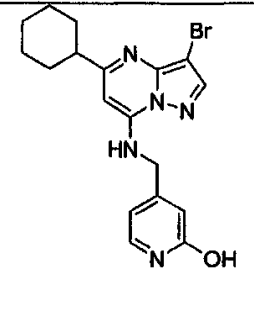
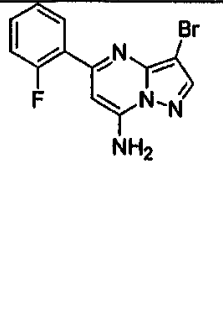
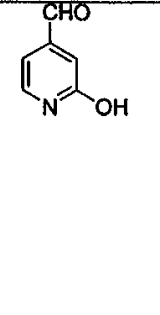
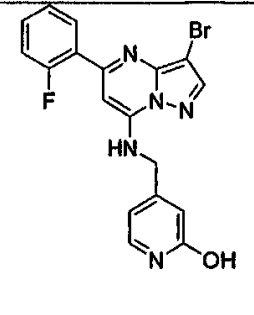
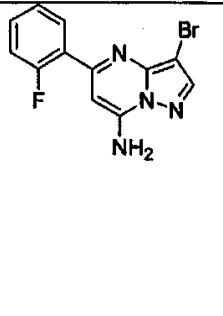
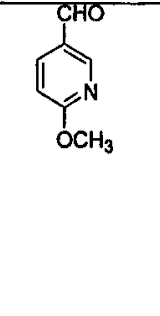
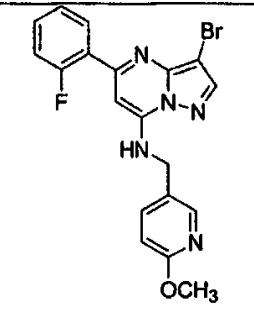
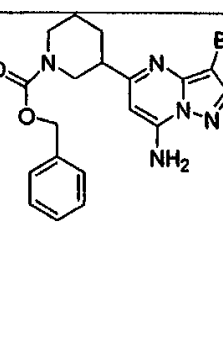
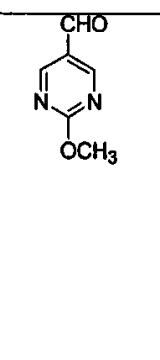
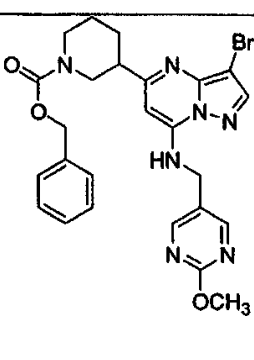
[0685]

245				
246				<p>LCMS: M⁺=452; mp=54-56°C</p>
247				<p>LCMS: MH⁺= 401; mp>200°C</p>
248				<p>LCMS: M2H⁺= 474; mp>200.0. °C dec.</p>

[0686]

249				<p>LCMS: $MH^+ = 377$; mp= 65-67°C</p>
250				<p>LCMS: $M2H^+ = 421$; mp=87-93°C</p>
251				<p>LCMS: $MH^+ = 361$; mp>225°C</p>
252				<p>LCMS: $MH^+ = 346$; mp=270-271°C</p>

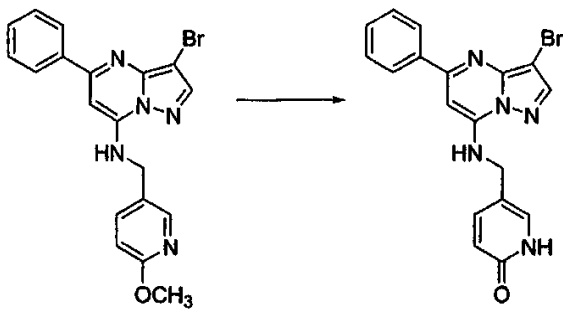
[0687]

253				LCMS: MH ⁺ =402; mp=250-255°C
254				LCMS: MH ⁺ =416; mp=210-215°C
255				LCMS: MH ⁺ =428; mp=145°C
256				LCMS: MH ⁺ =; mp=°C

[0688]

[0689]

실시예 257:



[0690]

[0691]

실시예 242에서 제조한 화합물(100mg, 0.24mmol), 진한 수성 HCl(1.0mL) 및 아세트산(2.0mL)의 혼합물을 N₂하에

2시간 동안 100°C에서 교반한 다음, Na₂CO₃ (15g) 속으로 부어넣고, 1:1 아세톤: CH₂Cl₂ (3 x 30mL)로 추출하였다. 합한 추출물을 여과하고 용매를 증발시켰다. 잔사를 용출제로서 10:1 CH₂Cl₂:MeOH를 사용하는 플래쉬 크로마토그래피로 정제하여 담황색 고체(36mg, 37%)를 수득하였다. LCMS: M⁺2H⁺=398.

[0692] 실시예 258 내지 260:

[0693] 실시예 257에 나타난 바와 본질적으로 동일한 과정으로, 표 23의 컬럼 1에 나타난 화합물로부터 출발하여, 표 23의 컬럼 2에 나타난 화합물을 제조하였다.

표 23

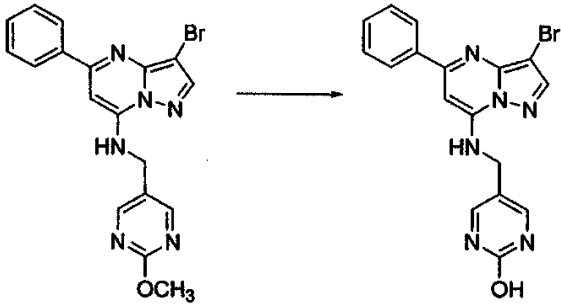
실시예	컬럼 1	컬럼 2	데이터
258			LCMS: M ⁺ =402; mp=229-231°C

[0694]

259			LCMS: MH ⁺ =416; mp=215-218°C
260			LCMS: M ⁺ 2H ⁺ =398 ; mp>230°C

[0695]

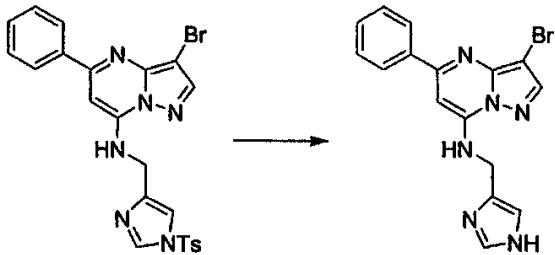
[0696] 실시예 261:



[0697]

[0698] CH_2Cl_2 중의 실시예 239에서 제조한 화합물(41mg, 0.10mmol)의 교반된 용액에 -78°C 에서 CHCl_3 중 1.0M BBr_3 (0.30mL, 0.30mmol)을 가하였다. 혼합물을 -78°C 에서 5분 동안 교반한 다음, 24°C 에서 3시간 동안 교반한 후, MeOH (2.0mL)를 가하고 혼합물을 10분 동안 교반하였다. 용매를 증발시키고, 잔사를 용출제로서 5:1:0.1 CH_2Cl_2 : MeOH :진한 NH_4OH 를 사용하는 플래쉬 크로마토그래피로 정제하여 백색 고체(39mg, 99%)를 수득하였다. LCMS: $\text{M}^+ = 397$. $\text{Mp} > 230^\circ\text{C}$.

[0699] 실시예 262:



[0700]

[0701] MeOH (3.0mL)중의 실시예 217에서 제조한 생성물(40mg, 0.077mmol) 및 5.0M 수성 NaOH (0.8mL)를 N_2 하에 1시간 동안 환류시켰다. NaHCO_3 (700mg)를 가하고, 용매를 증발시키고, 잔사를 용출제로서 10:1:0.1 CH_2Cl_2 : MeOH :진한 NH_4OH 를 사용하여 플래쉬 크로마토그래피함으로써 정제하여 백색 고체(10mg, 35%)를 수득하였다. LCMS: $\text{M}2\text{H}^+ = 371$. $\text{Mp} = 237\text{--}239^\circ\text{C}$.

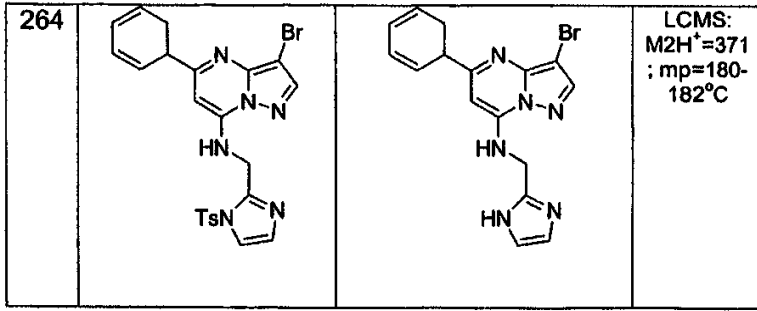
[0702] 실시예 263 및 264:

[0703] 실시예 262에 나타낸 바와 본질적으로 동일한 과정으로, 표 24의 컬럼 1에 나타낸 화합물로부터 출발하여, 표 24의 컬럼 2에 나타낸 화합물을 제조하였다.

표 24

실시예	컬럼 1	컬럼 2	데이터
263			LCMS: $\text{M}2\text{H}^+ = 370$; $\text{mp} = 166\text{--}168^\circ\text{C}$

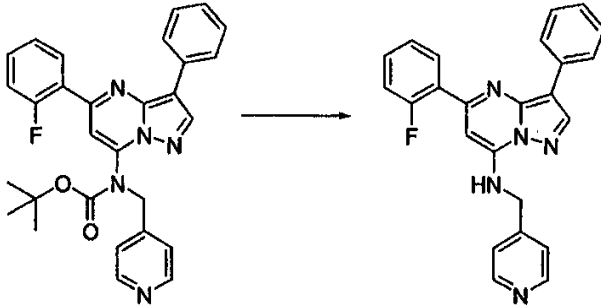
[0704]



[0705]

[0706]

실시예 265:



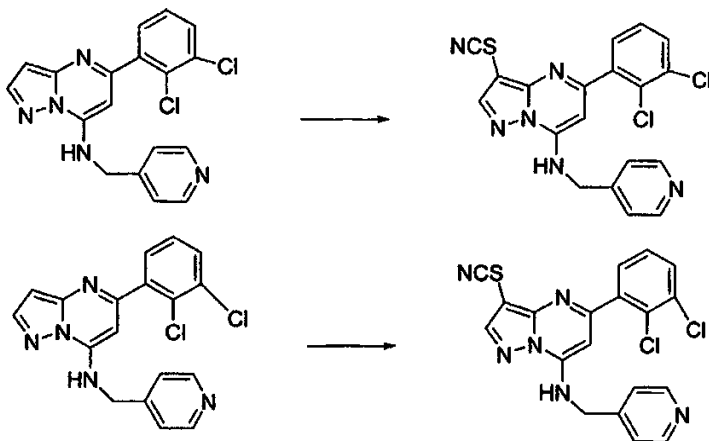
[0707]

[0708]

TFA(0.5mL)를 0°C에서 CH_2Cl_2 (2.0mL)중의 제조 실시예 197에서 제조한 화합물의 용액(0.08g, 0.16mmol)에 가하고, 수득한 용액을 2.5시간 동안 교반하고 4°C에서 밤새 저장하고 이 시점에서 추가의 TFA(0.5mL)를 가하였다. 수득한 용액을 4시간 동안 교반하고 진공하에 농축시켰다. 잔사를 1N NaOH로 중화시키고 CH_2Cl_2 로 추출하였다. 합한 유기물을 Na_2SO_4 위에서 건조시키고, 여과하고, 감압하에 농축시켰다. 조약한 생성물을 용출제로서 CH_2Cl_2 중의 2.5%(MeOH중의 10% NH_4OH)를 사용하여 플래쉬 크로마토그래피함으로써 정제하였다(0.009g, 15% 수율).
 LCMS: $MH^+ = 396$; mp = 53-54°C.

[0709]

실시예 266:



[0710]

[0711]

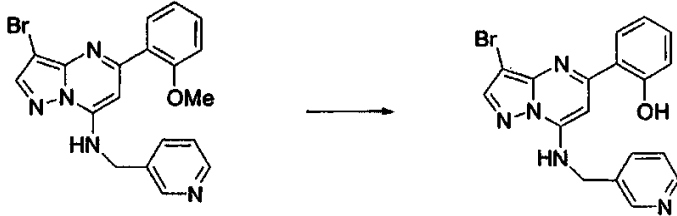
MeOH(1mL)중의 제조 실시예 182에서 제조한 화합물(26mg, 0.070mmol) 및 칼륨 티오시아네이트(13mg, 0.14mmol)의 용액을 냉수 욕 속에서 냉각시켰다. 이에 MeOH (0.7mL)중의 브롬의 용액(22mg, 0.14mmol)을 적가하였다. 수득한 반응 혼합물을 실온에서 4시간 동안 교반하고, 휘발물을 감압하에 제거하였다. 수득한 잔사를 소량의 CH_2Cl_2 중에서 현탁시켰다. 브롬화칼륨을 여과하고 여액의 pH를 수성 암모니아를 가하여 약 7로 조정하였다. 감압하에 농축시키고 잔류 오일을 용출제로서 CH_2Cl_2 중의 15% MeOH를 사용하여 제조 박층 크로마토그래피함으로써 정제하였다(26mg, 87% 수율).

¹H NMR (CDCl₃) δ 8.75 (d, J = 4.2 Hz, 2H), 8.38 (s, 1H), 7.68-7.64 (m, 2H), 7.46-7.39 (m, 3H), 7.22 (t, J = 6.3 Hz, 1H), 6.43 (s, 1H), 4.84 (d, J = 6.3 Hz, 2H);
LCMS: MH⁺ = 427.

[0712]

[0713]

실시예 267:



[0714]

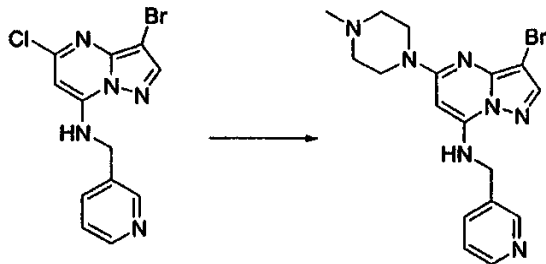
[0715]

삼브롬화벤소(CH₂Cl₂ 중의 1M, 0.60mL, 0.60mmol)을 아르곤 대기하에 CH₂Cl₂(1.5mL)중의 실시예 24에서 제조한 화합물(50mg, 0.12mmol)의 빙냉 교반 용액에 적가하였다. 수득한 반응 혼합물을 0° C에서 30분 동안 교반하고, 실온으로 가온시키고, 밤새 교반시켰다. 혼합물을 소량의 물을 가하여 퀀칭시키고, CH₂Cl₂로 추출하였다. 유기층을 황산마그네슘 위에서 건조시키고 진공하에 농축시켰다(45mg, 94% 수율).

[0716]

[0717]

실시예 268:



[0718]

[0719]

디옥산(1mL)중의 제조 실시예 184로부터의 화합물(0.05g, 0.15mmol), N-메틸피페라진(20 μL, 1.2당량) 및 iPr₂Et(52 μL, 2.0당량)의 용액을 70°C로 밤새 교반하였다. 반응 혼합물을 실온으로 냉각시키고 H₂O 및 포화된 NaHCO₃로 희석시켰다. 수득한 혼합물을 CH₂Cl₂로 추출하고, 합한 유기물을 Na₂SO₄ 위에서 건조시키고, 여과하고 감압하에 농축시켰다. 조악한 생성물을 용출제로서 CH₂Cl₂ 용액중의 5% (MeOH중의 10% NH₄OH)를 사용하여 제조 TLC로 정제하였다(0.028g, 47% 수율). MS:MH⁺ = 402. mp = 210°C (분해).

[0720]

실시예 269 내지 275:


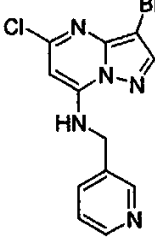
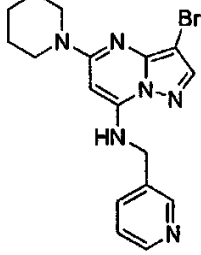

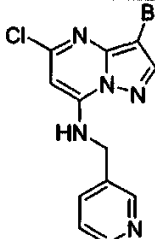
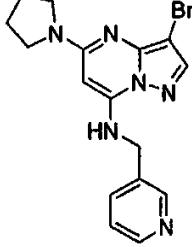
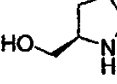
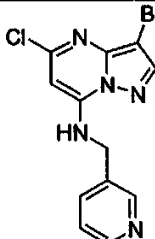
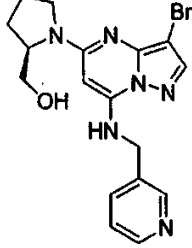
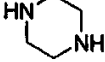
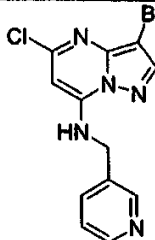
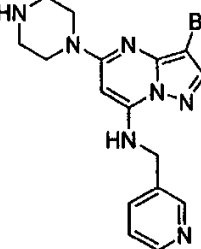
[0721]

실시예 268에서 나타낸 바와 본질적으로 동일한 과정으로, 표 25의 컬럼 2의 아민 및 표 25의 컬럼 3의 클로라이드를 단지 치환시켜, 표 25의 컬럼 4에 나타낸 화합물을 제조하였다:

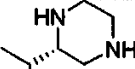
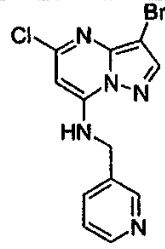
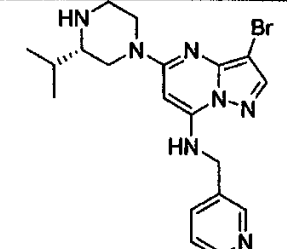
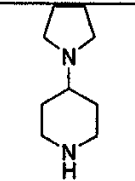
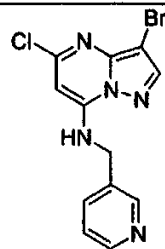
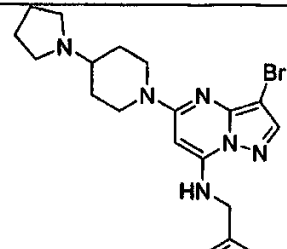
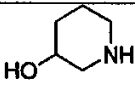
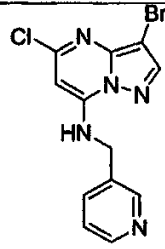
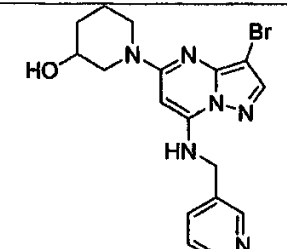
표 25

[0722]

실시예	컬럼 2	컬럼 3	컬럼 4	CMPD
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269				MS: MH^+ = 387 m.p. 182 – 183 °C
270				MS: MH^+ = 373 m.p. 190 – 191 °C
271				MS: MH^+ = 403 m.p. 227 – 230 °C
272				MS: MH^+ = 388 m.p. 198 – 201 °C

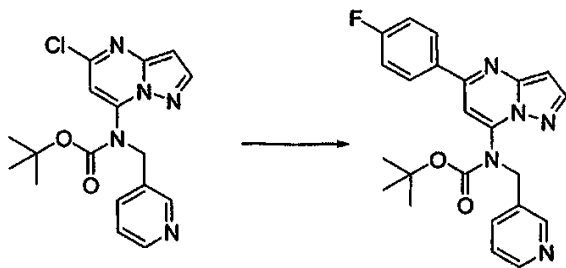
[0723]

273				MS: MH ⁺ = 430 m.p. 100-103 °C
274				MS: MH ⁺ = 456 m.p. 175-178 °C
275				MS: MH ⁺ = 403 m.p. 218 °C

[0724]

[0725] 실시예 276:

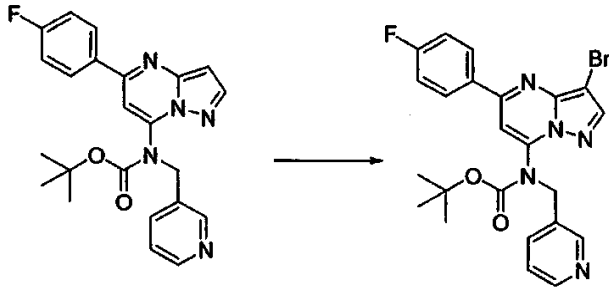
[0726] 단계 A:



[0727]

[0728] 4-플루오로페닐 마그네슘 브로마이드(0.68mL, 1.2당량)를 THF중의 제조 실시예 193에서 제조한 화합물(0.20g, 0.55mmol) 및 PdCl₂(dppf)₂(0.037g, 10mol%)에 가하고 수득한 용액을 실온에서 72시간 동안 교반하였다. 반응 혼합물을 포화된 NH₄Cl로 희석시키고 EtOAc로 추출하였다. 합한 유기물을 포화된 NaCl로 세척하고, Na₂SO₄ 위에서 건조시키고, 여과하고 농축시켰다. 조약한 생성물을 용출제로서 순수한 EtOAc를 사용하여 플래쉬 크로마토그래피함으로써 정제하였다(0.15g, 65% 수율). MS:MH⁺ = 420.

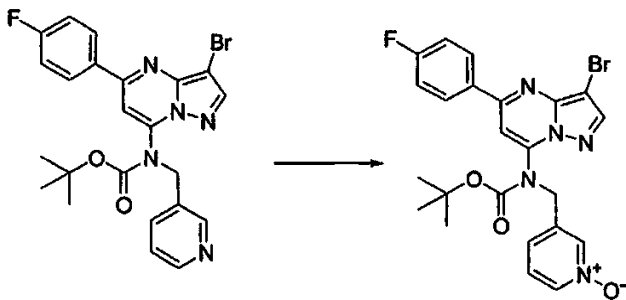
[0729] 단계 B:



[0730]

[0731] 제조 실시예 127에서 나타낸 바와 본질적으로 동일한 과정으로, 실시예 276, 단계 A에서 제조한 화합물을 단지 치환시켜, 상기한 화합물을 제조하였다(0.17g, 94% 수율).

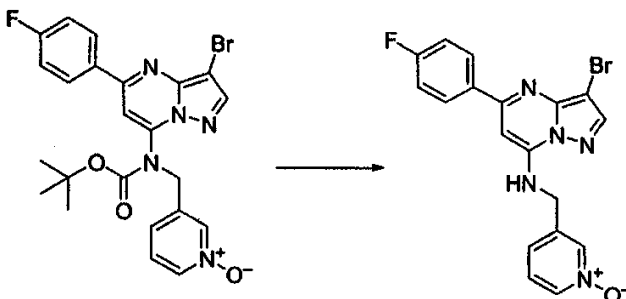
[0732] 단계 C:



[0733]

[0734] 제조 실시예 200에서 나타낸 바와 본질적으로 동일한 과정으로, 실시예 276, 단계 B에서 제조한 화합물을 단지 치환시켜, 상기한 화합물을 제조하였다(0.1g, 100% 수율).

[0735] 단계 D:

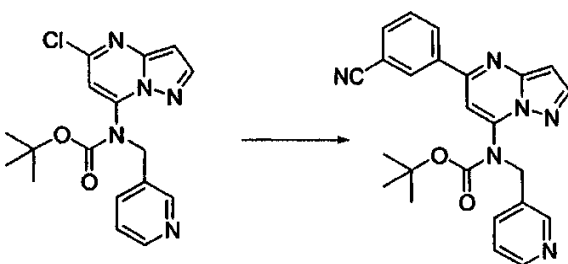


[0736]

[0737] 실시예 265에서 나타낸 바와 본질적으로 동일한 과정으로, 실시예 276, 단계 C에서 제조한 화합물을 단지 치환시켜, 상기한 화합물을 제조하였다(0.049g, 62% 수율). MS:MH⁺ = 414; mp = 110-115 ° C.

[0738] 실시예 277:

[0739] 단계 A:

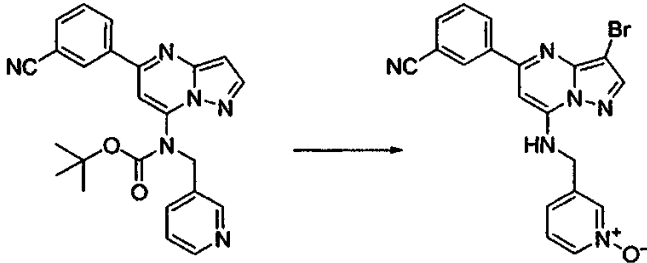


[0740]

[0741] Pd(PPh₃)₄(0.065g, 10mol%)을 DMF(2.0mL)중의 제조 실시예 193에서 제조한 화합물(0.2g, 0.56mmol) 및 3-시아

노페닐 아연 요오다이드(2.2mL, THF중의 0.5M 용액, 2당량)에 가하고, 수득한 용액을 80° C로 144시간 동안 가열하였다. 반응 혼합물을 실온으로 냉각시키고, 포화된 NH₄Cl로 희석시키고 EtOAc로 추출하였다. 합한 유기물을 H₂O 및 염수로 세척하고 Na₂SO₄ 위에서 건조시키고, 여과하고, 감압하에 농축시켰다. 조약한 생성물을 용출제로서 순수한 EtOAc 용액을 사용하여 플래쉬 크로마토그래피함으로써 정제하였다(0.07g, 29% 수율). MS: MH⁺ = 427.

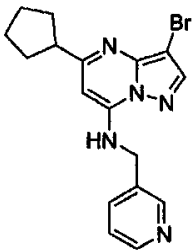
[0742] 단계 B 내지 단계 D:



[0743]

[0744] 실시예 276, 단계 B 내지 단계 D에 나타난 바와 본질적으로 동일한 과정으로, 상기한 화합물을 제조하였다 (0.023g, 53% 수율). MS:MH⁺ = 421; mp = 230°C(분해).

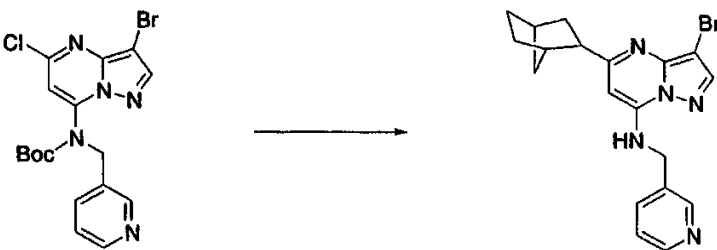
[0745] 실시예 278:



[0746]

[0747] 실시예 276에 나타난 바와 본질적으로 동일한 과정으로, 단계 A에서 적합한 사이클로프로필마그네슘 브로마이드를 단지 치환시켜, 화합물을 제조하였다. MS:MH⁺ = 372; m.p. = 96-98°C.

[0748] 실시예 279:



[0749]

[0750] 팔라듐-촉매된 아연 교차-커플링 반응(palladium-catalyzed zinc cross-coupling reaction)을 문헌[참조: J. Org. Chem. (1999), 453]에 기술된 과정과 유사한 방법으로 수행하였다. DMF(2mL) 중의 클로로피라졸로피리미딘(200mg, 0.458mmol), Pd(PPh₃)₄(53mg, 0.046mmol) 및 엑소-2-노르보닐 브롬화아연(THF중의 0.5M, 0.95mL, 0.47mmol)의 용액을 100°C(오일 욕 온도)에서 밤새 재환류시켰다. 반응 혼합물을 반-포화된 NH₄Cl로 퀀팅시키고 CH₂Cl₂로 추출하였다. 유기 층을 MgSO₄ 위에서 건조시키고, 감압하에 농축시켰다. 잔사를 용출제로서 헥산 용액중의 50% EtOAc를 사용하여 플래쉬 크로마토그래피함으로써 정제하였다. CH₂Cl₂(2mL)중의 수득한 N-Boc-보호된 생성물(121mg, 53% 수율, LCMS:MH⁺ = 498) 및 TFA(1mL)의 용액을 실온에서 2시간 동안 교반하였다. 휘발물을 감압하에 제거하였다. 잔사를 CH₂Cl₂에 용해시키고, 포화된 NaHCO₃로 중화시키고, CH₂Cl₂로

추출하였다. 유기 층을 MgSO₄ 위에서 건조시키고 진공하에 농축시켰다(96mg, 99% 수율).

LCMS: MH⁺ = 398; ¹H NMR (CDCl₃) δ 8.78 (s, 1H), 8.71 (d, J = 4.2 Hz, 1H), 8.04 (d, J = 3.9 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.44 (m, 1H), 6.73 (m, 1H), 5.98 (d, J = 7.5 Hz, 1H), 4.74 (d, J = 5.4 Hz, 2H), 3.40-1.00 (m, 11H).

[0751]

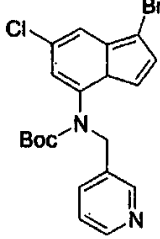
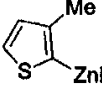
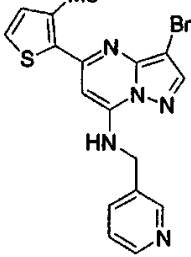
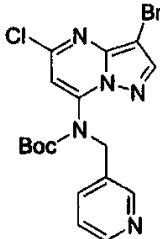
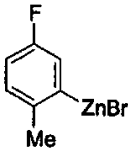
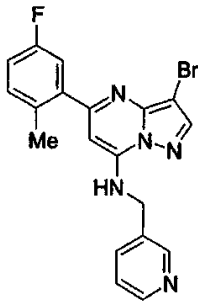
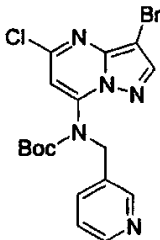
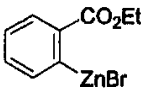
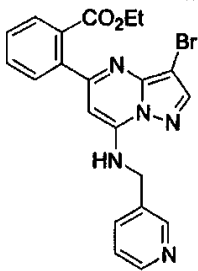
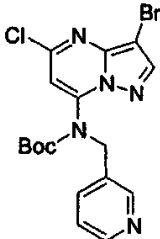
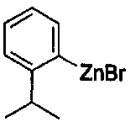
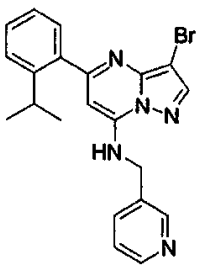
[0752] 실시예 280 내지 294:

[0753] 실시예 279에 나타난 바와 본질적으로 동일한 과정으로, 표 26의 컬럼 2에 나타난 클로라이드 및 표 26의 컬럼 3에 나타난 유기 아연 시약을 단지 치환시켜, 표 26의 컬럼 4의 화합물을 제조하였다:

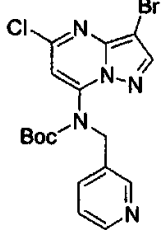
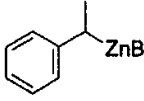
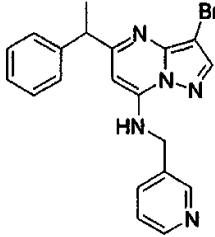
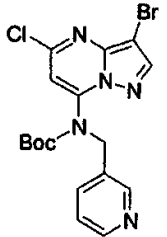
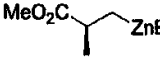
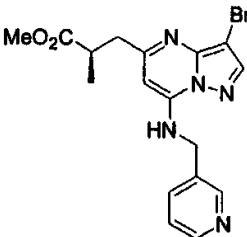
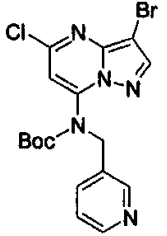
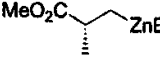
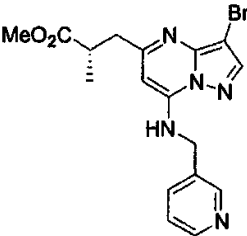
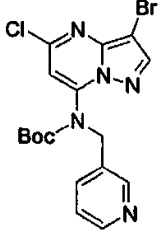
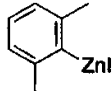
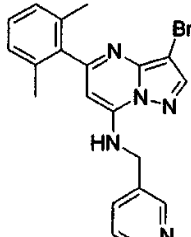
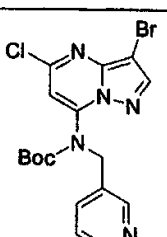
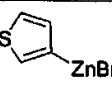
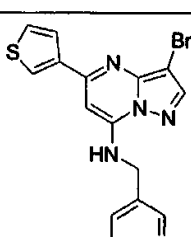
표 26

실시예	컬럼 2	컬럼 3	컬럼 4	데이터
280				LCMS: MH ⁺ = 395

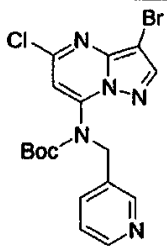
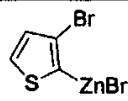
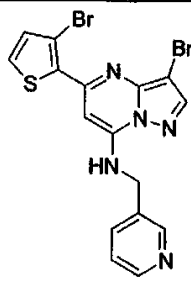
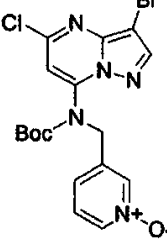
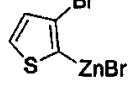
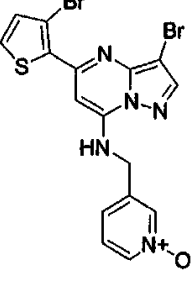
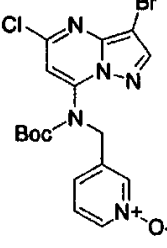
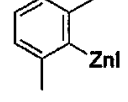
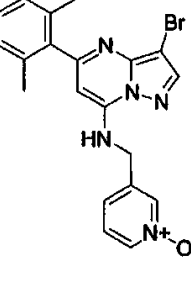
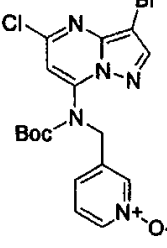
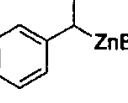
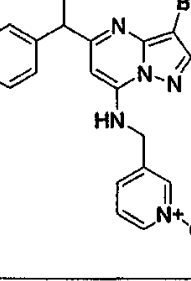
[0754]

281				LCMS: $MH^+ = 400$
282				LCMS: $MH^+ = 412$
283				LCMS: $MH^+ = 452$
284				LCMS: $MH^+ = 422$

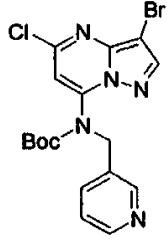

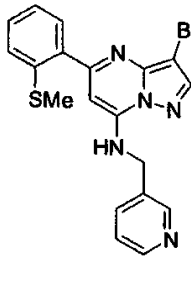
[0755]

285				LCMS: $MH^+ = 408$
286				LCMS: $MH^+ = 404$
287				LCMS: $MH^+ = 404$
288				LCMS: $MH^+ = 408$
289				LCMS: $MH^+ = 386$

[0756]

290				LCMS: $MH^+ = 464$
291				LCMS: $MH^+ = 480$
292				LCMS: $MH^+ = 424$
293				LCMS: $MH^+ = 424$

[0757]

294				LCMS: $MH^+ = 426$
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[0758]

[0759] 선택된 화합물에 대한 추가의 데이터는 하기에 나타낸다.

실시예 280: ^1H NMR (CDCl_3) δ 8.65 (s, 1H), 8.57 (d, $J = 4.2$ Hz, 1H), 8.50 (d, $J = 4.5$ Hz, 1H), 8.01 (s, 1H), 7.69 (d, $J = 7.5$ Hz, 1H), 7.61 (d, $J = 7.8$ Hz, 1H), 7.31-7.22 (m, 2H), 6.77 (m, 2H), 4.71 (d, $J = 5.4$ Hz, 2H), 2.68 (s, 3H).

실시예 281: ^1H NMR (CDCl_3) δ 8.80 (s, 1H), 8.72 (d, $J = 4.8$ Hz, 1H), 8.08 (s, 1H), 7.85-7.40 (m, 3H), 7.02 (d, $J = 5.1$ Hz, 1H), 6.90 (t, $J = 6.0$ Hz, 1H), 6.29 (s, 1H), 4.79 (d, $J = 6.0$ Hz, 2H), 2.61 (s, 3H).

실시예 282: ^1H NMR (CDCl_3) δ 8.67 (s, 1H), 8.61 (d, $J = 3.9$ Hz, 1H), 8.03 (s, 1H), 7.72-7.31 (m, 3H), 7.22-7.00 (m, 2H), 6.81 (t, $J = 6.0$ Hz, 1H), 6.03 (s, 1H), 4.68 (d, $J = 6.0$ Hz, 2H), 2.28 (s, 3H).

실시예 283: ^1H NMR (CDCl_3) δ 8.68 (s, 1H), 8.63 (d, $J = 4.0$ Hz, 1H), 8.00 (s, 1H), 7.80-7.72 (m, 2H), 7.54-7.47 (m, 3H), 7.35 (m, 1H), 6.74 (t, $J = 6.0$ Hz, 1H), 6.19 (s, 1H), 4.67 (d, $J = 6.0$ Hz, 2H), 4.21 (q, $J = 7.2$ Hz, 2H), 1.13 (t, $J = 7.2$ Hz, 3H).

실시예 284: ^1H NMR (CDCl_3) δ 7.97 (s, 1H), 7.65 (d, $J = 7.2$ Hz, 1H), 7.33-7.15 (m, 5H), 6.73 (t, $J = 5.4$ Hz, 1H), 5.99 (s, 1H), 4.61 (d, $J = 5.4$ Hz, 2H), 3.09 (sept, $J = 6.9$ Hz, 1H), 1.11 (d, $J = 6.9$ Hz, 6H).

실시예 285: ^1H NMR (CDCl_3) δ 8.56-8.55 (m, 2H), 7.94 (s, 1H), 7.54 (m, 1H), 7.30-7.22 (m, 6H), 6.59 (t, $J = 5.7$ Hz, 1H), 5.66 (s, 1H), 4.47 (d, $J = 5.7$ Hz, 2H), 4.26 (q, $J = 7.2$ Hz, 1H), 1.68 (d, $J = 7.2$ Hz, 3H).

실시예 286: ^1H NMR (CDCl_3) δ 8.67 (m, 2H), 7.94 (s, 1H), 7.69 (d, $J = 7.8$ Hz, 1H), 7.34 (m, 1H), 6.63 (t, $J = 5.7$ Hz, 1H), 5.87 (s, 1H), 4.62 (d, $J = 5.7$ Hz, 2H), 3.64 (s, 3H), 3.13 (m, 2H), 2.82 (m, 1H), 1.22 (m, 3H).

[0760]

실시예 287: $^1\text{H NMR}$ (CDCl_3) δ 8.66 (m, 2H), 7.94 (s, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 7.34 (m, 1H), 6.62 (t, $J = 6.0$ Hz, 1H), 5.87 (s, 1H), 4.62 (d, $J = 6.0$ Hz, 2H), 3.64 (s, 3H), 3.13 (m, 2H), 2.81 (m, 1H), 1.22 (m, 3H).

실시예 288: $^1\text{H NMR}$ (CDCl_3) δ 8.64 (s, 1H), 8.60 (d, $J = 3.6$ Hz, 1H), 8.04 (s, 1H), 7.68 (m, 1H), 7.31 (m, 1H), 7.16 (m, 1H), 7.07-7.05 (m, 2H), 6.80 (t, $J = 6.3$ Hz, 1H), 5.93 (s, 1H), 4.64 (d, $J = 6.3$ Hz, 2H), 2.08 (s, 6H).

실시예 289: $^1\text{H NMR}$ (CDCl_3) δ 8.72 (s, 1H), 8.62 (d, $J = 4.8$ Hz, 1H), 7.99-7.97 (m, 2H), 7.73-7.69 (m, 2H), 7.40-7.33 (m, 2H), 6.67 (t, $J = 6.0$ Hz, 1H), 6.29 (s, 1H), 4.71 (d, $J = 6.0$ Hz, 2H).

실시예 290: $^1\text{H NMR}$ (CDCl_3) δ 8.73 (s, 1H), 8.62 (d, $J = 4.5$ Hz, 1H), 8.01 (s, 1H), 7.76 (m, 1H), 7.41 (d, $J = 5.1$ Hz, 1H), 7.34 (dd, $J = 8.1, 5.1$ Hz, 1H), 7.05 (d, $J = 5.1$ Hz, 1H), 7.01 (s, 1H), 6.79 (t, $J = 6.0$ Hz, 1H), 4.74 (d, $J = 6.0$ Hz, 2H).

실시예 291: $^1\text{H NMR}$ ($\text{DMSO}-d_6$) δ 9.12 (s, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 8.13 (m, 1H), 7.82 (d, $J = 5.1$ Hz, 1H), 7.40-7.39 (m, 2H), 7.22 (d, $J = 5.1$ Hz, 1H), 6.86 (s, 1H), 4.86 (s, 2H).

실시예 292: $^1\text{H NMR}$ (CDCl_3) δ 8.23 (s, 1H), 8.16 (d, $J = 6.0$ Hz, 1H), 8.06 (s, 1H), 7.31-7.05 (m, 5H), 6.86 (m, 1H), 5.87 (s, 1H), 4.62 (d, $J = 6.3$ Hz, 2H), 2.09 (s, 6H).

실시예 293: $^1\text{H NMR}$ (CDCl_3) δ 8.14 (s, 1H), 8.12 (d, $J = 6.3$ Hz, 1H), 7.94 (s, 1H), 7.29-7.16 (m, 6H), 7.07 (m, 1H), 6.78 (t, $J = 6.0$ Hz, 1H), 5.54 (s, 1H), 4.44 (d, $J = 6.0$ Hz, 2H), 4.24 (t, $J = 7.2$ Hz, 1H), 1.68 (d, $J = 7.2$ Hz, 3H).

실시예 294: $^1\text{H NMR}$ (CDCl_3) δ 8.67 (s, 1H), 8.59 (d, $J = 4.8$ Hz, 1H), 8.01 (s, 1H), 7.71 (m, 1H), 7.52 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.40-7.19 (m, 4H), 6.78 (t, $J = 6.0$ Hz, 1H), 6.32 (s, 1H), 4.67 (d, $J = 6.0$ Hz, 2H), 2.38 (s, 3H).

[0761]

[0762]

실시예 295



[0763]

[0764]

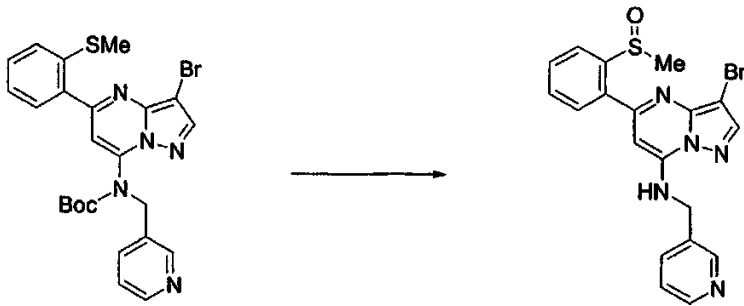
0°C에서 무수 THF(2mL)중 리튬 알루미늄 하이드라이드(10mg, 0.26mmol)의 현탁액에 무수 THF(2mL)중 실시예 283에서 제조한 화합물(20mg, 0.044mmol)의 용액을 적가하였다. 수득되는 혼합물을 1시간 동안 환류시키고 실온에서 밤새 교반하고, 희 황산으로 중화시키고 EtOAc로 추출하였다. 유기 층을 MgSO_4 위에서 건조시키고 감압하에 농축시켰다. 유기 층을 MgSO_4 위에서 건조시키고 감압하에 농축시켰다. 조약한 생성물을 용출제로서 EtOAc 용액중 5% MeOH를 사용하는 제조 박층 크로마토그래피로 정제하였다(15mg, 83% 수율).

LCMS: $\text{MH}^+ = 410$; $^1\text{H NMR}$

(CDCl_3) δ 8.69 (s, 1H), 8.61 (d, $J = 3.9$ Hz, 1H), 8.05 (d, $J = 2.1$ Hz, 1H), 7.74 (d, $J = 7.8$ Hz, 1H), 7.52-7.31 (m, 5H), 6.97 (t, $J = 6.3$ Hz, 1H), 6.55 (d, $J = 2.7$ Hz, 1H), 6.20 (s, 1H), 4.71 (d, $J = 6.3$ Hz, 2H), 4.52 (s, 2H).

[0765]

[0766] 실시예 296:



[0767]

[0768]

-50℃에서 CH₂Cl₂(4mL)중 실시예 294에서 제조한 N-Boc-보호된 화합물(45mg, 0.085mmol)의 용액에 m-CPBA(18mg, 0.10mmol)를 가하였다. -50℃에서 1시간 동안 교반한 후 추가로 m-CPBA(4mg, 0.02mmol)을 가하였다. 혼합물을 추가로 2시간 동안 교반하고, CH₂Cl₂(20mL)로 희석하고, 포화된 NaHCO₃(20mL)로 세척하였다. 유기 층을 MgSO₄위에서 건조시키고 감압하에 농축시켰다. 잔사를 용출제로서 CH₂Cl₂ 용액중 2.5% MeOH를 사용한 제조 박층 크로마토그래피로 정제하였다. CH₂Cl₂(2mL)중 수득된 N-Boc-보호된 생성물(37mg, 80% 수율, LCMS: MH⁺ = 542) 및 TFA(1mL)의 용액을 실온에서 2시간 동안 교반하였다. 휘발물을 감압하에 제거하였다. 잔사를 CH₂Cl₂속에 용해하고 포화된 NaHCO₃로 중화시키며, CH₂Cl₂로 추출하였다. 유기 층을 MgSO₄위에서 건조시키고 감압하에 농축시켰다. 조약한 생성물을 용출제로서 EtOAc 용액중 5% MeOH를 사용한 제조 박층 크로마토그래피로 정제하였다 (26mg, 89% 수율).

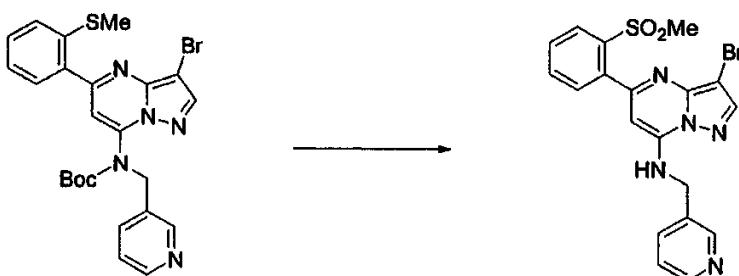
LCMS: MH⁺ = 442; ¹H NMR (CDCl₃) δ 8.71 (s, 1H),

8.64 (d, J = 3.9 Hz, 1H), 8.41 (m, 1H), 8.03 (s, 1H), 7.75-7.54 (m, 4H), 7.36 (dd, J = 8.1, 5.1 Hz, 1H), 6.81 (t, J = 6.0 Hz, 1H), 6.34 (s, 1H), 4.74 (d, J = 6.0 Hz, 2H), 3.25 (s, 3H).

[0769]

[0770]

실시예 297:



[0771]

[0772]

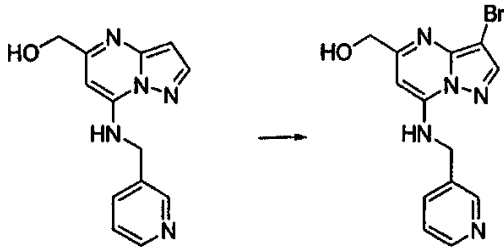
0℃에서 CH₂Cl₂(4mL)중 실시예 294에서 제조한 N-Boc-보호된 화합물의 용액(56mg, 0.11mmol)에 m-CPBA(42mg, 0.24mmol)을 가하였다. 실온에서 2시간 동안 교반한 후 추가의 m-CPBA(13mg, 0.075mmol)를 가하였다. 혼합물을 실온에서 밤새 교반하고, CH₂Cl₂(20mL)로 희석시키고, 포화된 NaHCO₃(20mL)로 세척하였다. 유기 층을 MgSO₄위에서 건조시키고 감압하에 농축시켰다. 잔사를 용출제로서 EtOAc 용액중 2.5% MeOH를 사용하는 제조 박층 크로마토그래피에 의해 정제하였다. 수득된 N-Boc-보호된 생성물(29mg, 49% 수율, LCMS : MH⁺ = 558) 및 TFA(1mL)의 용액을 실온에서 2시간 동안 교반하였다. 휘발물을 감압하에 제거하였다. 잔사를 CH₂Cl₂속에 용해시키고, 포화된 NaHCO₃로 중화시키고, CH₂Cl₂로 추출하였다. 유기 층을 MgSO₄위에서 건조시키고 감압하에 농축시켰다. 조 생성물을 용출제로서 EtOAc 용액중 2.5% MeOH를 사용하는 제조 박층 크로마토그래피로 정제하였다(21mg, 90% 수율).

LCMS: $MH^+ = 458$; 1H NMR ($CDCl_3$) δ 8.64

(s, 2H), 8.20 (m, 1H), 8.01 (s, 1H), 7.73-7.60 (m, 3H), 7.46 (m, 1H), 7.35 (s, 1H), 6.82 (t, $J = 5.9$ Hz, 1H), 6.17 (s, 1H), 4.65 (d, $J = 5.7$ Hz, 2H), 3.60 (s, 3H).

[0773]

[0774] 실시예 298



[0775]

[0776] 제조 실시예 127에 나타난 바와 본질적으로 동일한 과정에 의해, 제조 실시예 189에서 제조한 화합물을 단지 치환시켜, 상기 화합물을 제조하였다. MS : $MH^+ = 334$; mp = 170-173°C.

[0777] 실시예 299 및 300:

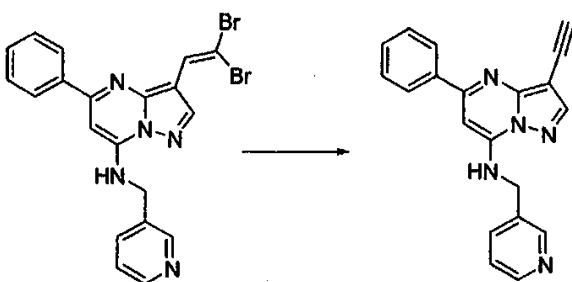
[0778] 실시예 298에 나타난 바와 본질적으로 동일한 과정에 의해, 표 27, 컬럼 2에 나타난 화합물을 단지 치환시켜, 표 27, 컬럼 3에 나타난 화합물을 제조하였다:

표 27

실시예	컬럼 2	컬럼 3	CMPD
299			MS: $MH^+ = 348$ m.p. = 73 - 83 °C
300			MS: $MH^+ = 362$ m.p. = 165 - 175 °C

[0779]

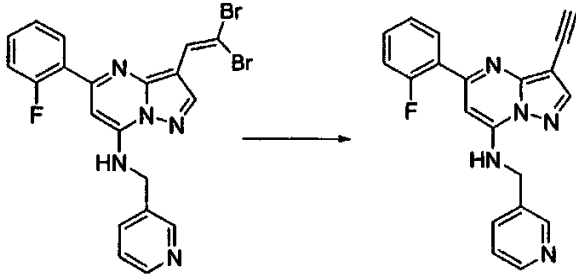
[0780] 실시예 301:



[0781]

[0782] -78℃에서 THF(4.0mL)중 제조 실시예 186에서 제조한 화합물(0.1g, 0.21mmol)의 용액에 nBuLi(0.57mL, 헥산중 2.16M, 5.0당량)를 가하였다. 반응 혼합물을 -78에서 2시간 동안 교반하고, H₂O로 퀀칭시키고, 실온으로 가운하고 EtOAc로 추출하였다. 합한 유기물을 Na₂SO₄위에서 건조시키고, 여과하고, 감압하에 농축시켰다. 조악한 생성물을 용출제로서 CH₂Cl₂중 2.5%(CH₃OH중 10% NH₄OH) 용액을 사용하는 제조 TLC에 의해 정제하였다. MS: MH⁺ = 326; mp = 71-72℃.

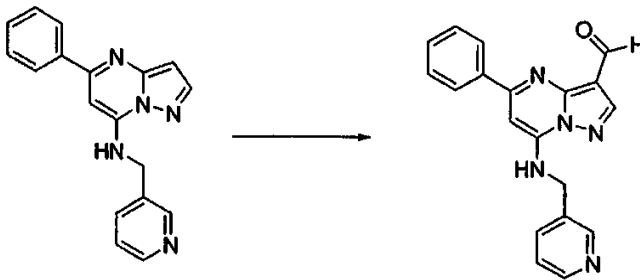
[0783] 실시예 302:



[0784]

[0785] 실시예 301에 나타난 바와 본질적으로 동일한 과정에 의해, 제조 실시예 187로부터의 화합물을 단지 치환시켜, 상기 화합물을 제조하였다(0.049g, 68% 수율). MS : MH⁺ = 334; mp = 69-71℃.

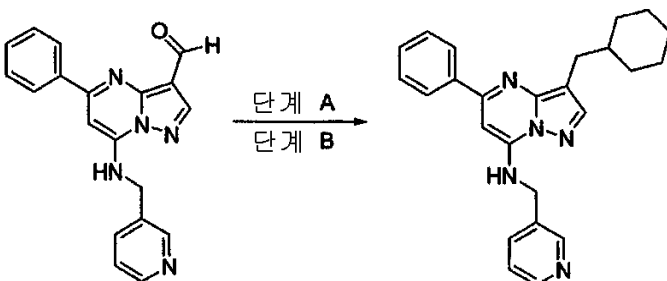
[0786] 실시예 303:



[0787]

[0788] 0℃에서 DMF(4.2mL)중 제조 실시예 187.1로부터의 3-H 부가물의 용액(0.70g, 2.32mmol)에 POCl₃(0.67mL, 7.2mmol)를 적가하였다. 당해 혼합물을 실온에서 14시간 동안 교반하고, 0℃로 냉각시키고 얼음을 첨가하여 퀀칭시켰다. 1N NaOH를 조심스럽게 가하여 pH를 8로 조절하고 혼합물을 CH₂Cl₂(3x25mL)로 추출하였다. 유기 층을 합하고, 건조(Na₂SO₄)시키고, 여과하며, 감압하에 농축시켰다. 조악한 생성물을 EtOAc로부터 재결정화하여 황색 고체 0.43g(56%)을 수득하였다. mp 181-183℃; M + H = 330.

[0789] 실시예 304:



[0790]

[0791] 단계 A:

[0792] 0℃에서 THF(1mL)중 실시예 303으로부터의 알데하이드(100mg, 0.30mmol)의 용액에 사이클로헥실 마그네슘 브로마이드(0.46mL, Et₂O중 2.0M)를 5분에 걸쳐 적가하였다. 수득되는 혼합물을 0℃에서 2시간 동안 교반하고 실온에서 12시간 동안 교반하였다. 혼합물을 0℃로 냉각시키고 포화된 수성 NH₄Cl(3mL) 및 CH₂Cl₂(5mL)로 처리하였

다. 층을 분리하고 수성 층을 CH₂Cl₂(2x5mL)로 추출하였다. 유기 층을 합하고, 염수(1x5mL)로 세척하고, 건조 (Na₂SO₄)시키고, 여과하고, 감압하에 농축시켜 황색 반고체 110mg(89%)을 수득하였다. M + H = 414.

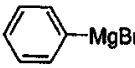
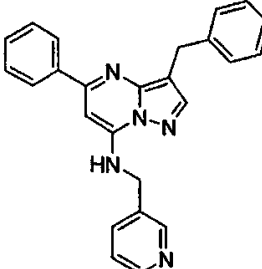
[0793] 단계 B:

[0794] 0℃에서 CH₂Cl₂(0.5mL)중 알콜(53mg, 0.13mmol)의 용액에 Et₃SiH(24μl, 0.15mmol)에 이어 TFA(24μl, 0.30mmol)를 가하였다. 혼합물을 0℃에서 2시간 동안 교반하고 실온에서 2시간 동안 교반한 다음 Et₃SiH(24μl, 0.15mmol) 및 TFA(24μl, 0.30mmol) 일부를 추가로 가하고 당해 혼합물을 실온에서 3시간 동안 교반하였다(TLC로 완료가 확인될 때까지). 혼합물을 감압하에 농축시키고 조약한 잔사를 CH₂Cl₂(5mL) 및 포화된 수성 NaHCO₃(2.5mL)사이 에 분배시켰다. 층을 분리하고 수성 층을 CH₂Cl₂(2x5mL)로 추출하였다. 유기 층을 합하고, 염수(1x5mL)로 세척하 고, 건조(Na₂SO₄)시키고, 여과하며, 감압하에 농축시켰다. 조약한 생성물을 CH₂Cl₂/MeOH(22 : 1)로 용출시키는 제조 TLC(8x1000mM)에 의해 정제하여 황색 반고체 29mg(56%)을 수득하였다. M + H = 398.

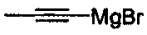
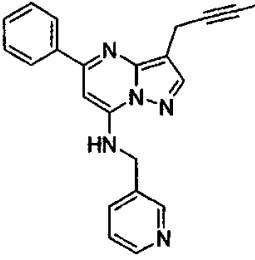

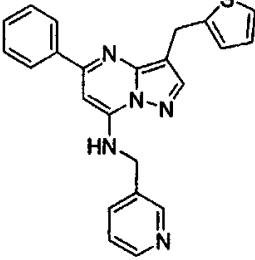
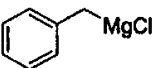
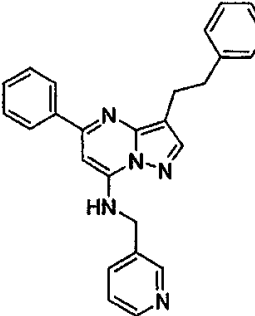
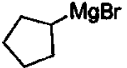
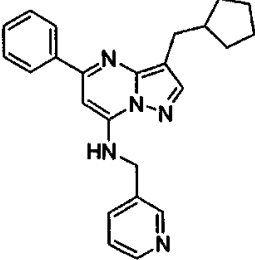
[0795] 실시예 305 내지 312:

[0796] 실시예 304에 나타난 바와 본질적으로 동일한 과정에 의해, 실시예 303으로부터의 알데하이드를 이용하고 그리 나드 또는 표 28의 컬럼 2에 나타난 오가노리튬 시약을 치환시켜, 표 28, 컬럼 3에 나타난 화합물을 제조하였다:


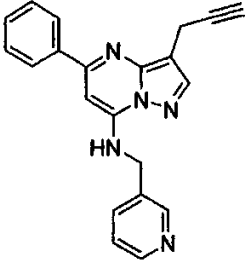

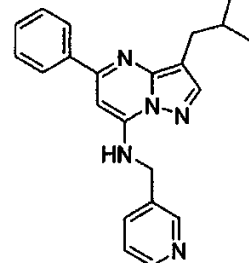

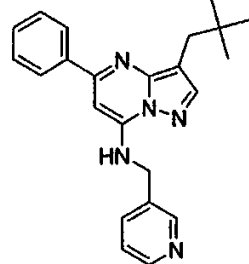
표 28

실시예	컬럼 2 (유기금속성)	컬럼 3 (최종 구조)	CMPD 1. mp (°C) 2. M+H
305			1. 황색 오일 2. M+H = 392

[0797]

306			<p>1. 적색 오일 2. M+H = 353</p>
307			<p>1. 적색 오일 2. M+H = 398</p>
308			<p>1. 황색 오일 2. M+H = 406</p>
309			<p>1. 황색 반고체 2. M+H = 384</p>

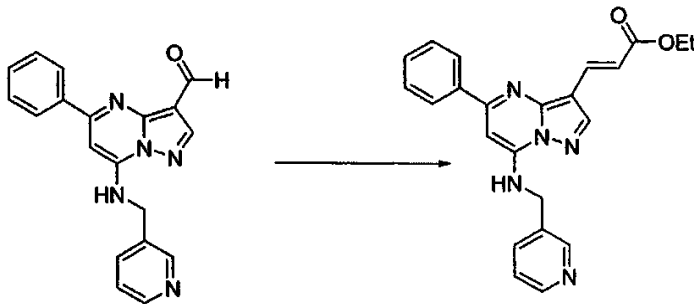
[0798]

310			<p>1. 반고체 2. M+H = 340</p>
311			<p>1. mp = 141-143 2. M+H = 358</p>
312			<p>1. mp = 148-150 2. M+H = 372</p>

[0799]

[0800]

실시예 313:

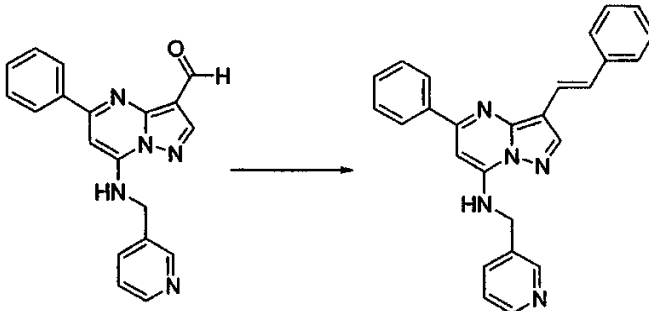


[0801]

[0802]

벤젠(2.5mL)중 실시예 303으로부터의 알데하이드(81mg, 0.25mmol)의 용액에 카보에톡시메틸렌 트리페닐 포스포르산(0.12g, 0.33mmol)을 한번에 가하였다. 혼합물을 환류하에 24시간 동안 가열하고, 실온으로 냉각시키고, 감압하에 농축시켰다. 혼합물을 CH₂Cl₂(5mL)로 희석시키고, 염수(2mL)를 가하고 층을 분리하였다. 수성 층을 CH₂Cl₂(2x4mL)로 추출하였다. 유기 층을 합하고, 건조(Na₂SO₄)시키고, 여과하고 감압하에 농축시켰다. 조약한 생성물을 CH₂Cl₂/MeOH(20 : 1)로 용출시키는 제조 TLC(8x1000 μM)로 정제하여 백색 고체 98mg(100%)를 수득하였다. mp 151-153°C ; M + H = 400.

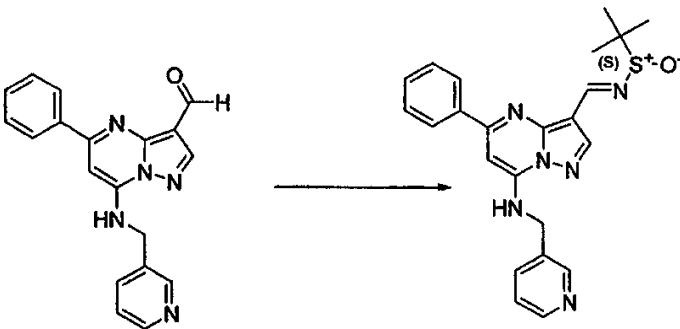
[0803] 실시예 314:



[0804]

[0805] THF(3mL)중 벤질트리페닐포스포늄 브로마이드(0.59g, 1.37mmol)의 혼합물에 NaH(55mg, 1.37mmol)을 가하고 당해 혼합물을 30분 동안 교반하였다. 실시예 303으로부터의 알데하이드(0.15g, 0.46mmol)를 한번에 가하고 혼합물을 36시간 동안 환류하에 가열하였다. 혼합물을 실온으로 냉각시키고 감압하에 농축시켰다. 혼합물을 CH₂Cl₂(5mL)로 희석시키고, 염수(2mL)를 가하고, 층을 분리하였다. 수성 층을 CH₂Cl₂(2x4mL)로 추출하였다. 유기 층을 합하고, 건조(Na₂SO₄)시키고, 여과하며, 감압하에 농축시켰다. 조약한 생성물을 CH₂Cl₂/MeOH(20 : 1)로 용출시키는 제조 TLC(8x1000 μM)에 의해 정제하여 황색 고체 58mg(32%)를 수득하였다. mp 138-141°C ; M + H = 404.

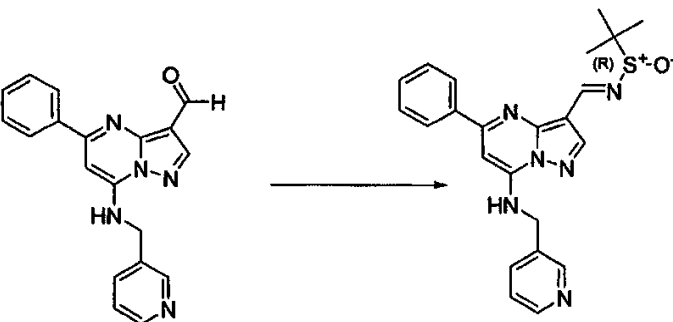
[0806] 실시예 315:



[0807]

[0808] THF(3mL)중 실시예 303으로부터의 알데하이드(0.20g, 0.60mmol)의 용액에 Ti(i-OPr)₄(0.36mL, 1.21mmol)을 적 가하고 이어서 (S)-(-)-2-메틸-2-프로판설피나미드(74mg, 0.61mmol)를 가하였다. 수득되는 혼합물을 환류하에 18시간 동안 교반하고, 실온으로 냉각시키고, 염수(2mL)로 퀴칭시켰다. 혼합물을 EtOAc(2x2mL)로 세척한 셀라이트 패드를 통해 여과하였다. 층을 분리하고 수성 층을 EtOAc(2x4mL)로 추출하였다. 유기 층을 합하고, 건조(Na₂SO₄)시키고, 여과하고, 감압하에 농축시켰다. 조약한 생성물을 CH₂Cl₂/MeOH(20 : 1)로 용출시키는 제조 TLC(8x1000 μM)에 의해 정제하여 황색 고체 0.21g(80%)을 수득하였다. mp 108-110°C ; M + H = 433.

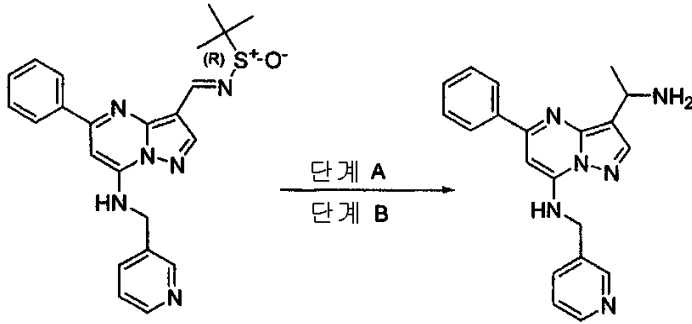
[0809] 실시예 316:



[0810]

[0811] (R)-(-)-2-메틸-2-프로판설피나미드를 치환시키는 것을 제외하고는 실시예 315에서와 동일한 양식으로 제조하여 황색 고체로서의 생성물 0.25g(94%)을 수득하였다. mp 107-109°C ; M + H = 433.

[0812] 실시예 317:



[0813]

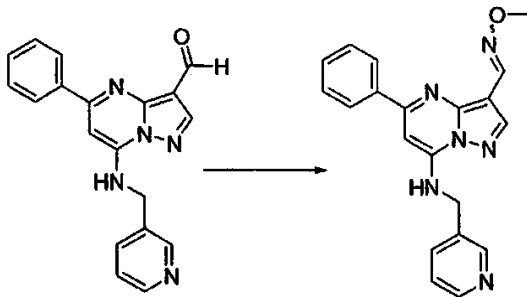
[0814] 단계 A:

[0815] -40℃에서 CH₂Cl₂(2.5mL)중 실시예 316으로부터의 설핀이미드(50mg, 0.12mmol)의 용액에 MeMgBr(96mL, 0.29mmol)을 적가하였다. 혼합물을 -40℃에서 5시간 동안 교반하고 실온에서 12시간 동안 교반하였다. 추가로 일부의 MeMgBr(96mL, 0.29mmol) 및 혼합물을 12시간 동안 교반하였다. 포화된 수성 NH₄Cl(2mL)을 가하고 혼합물을 EtOAc(3x4mL)로 추출하였다. 유기 층을 합하고, 건조(Na₂SO₄)시키며, 여과하고, 감압하에 농축시켜 조약한 잔사 30mg(58%)을 수득하였다. 당해 물질을 정제하지 않고 다음 단계에서 사용하였다.

[0816] 단계 B:

[0817] MeOH(2mL)속에서 단계 A로부터의 조약한 물질(30mg, 0.067mmol)을 진한HCl(2mL)에 가하였다. 혼합물을 실온에서 12시간 동안 교반하고 혼합물을 농축 건조시켰다. 조약한 물질을 CH₂Cl₂(3mL) 및 포화된 수성 NaHCO₃(2mL)사이에 분배하고 층을 분리하였다. 수성 층을 CH₂Cl₂(2x3mL)로 추출하고 유기 층을 합하였다. 유기 층을 건조(Na₂SO₄)시키고, 여과하며, 감압하에 농축시켜 담황색 고체로서의 표제 화합물 6mg(24%)을 수득하였다. mp 100-102℃; M + H = 345.

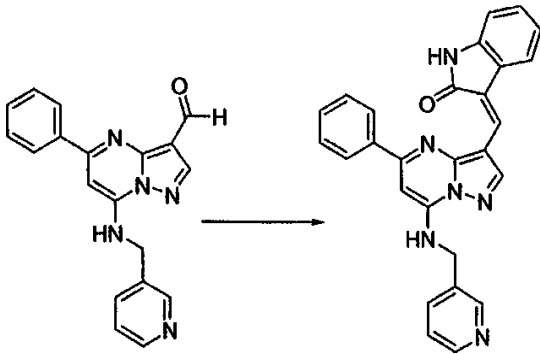
[0818] 실시예 318:



[0819]

[0820] 실온에서 THF/CH₂Cl₂(5mL/1mL)중 실시예 300으로부터의 알데하이드(75mg, 0.23mmol)의 용액에 MeONH₂·HCl(38mg, 0.46mmol)을 가하고 피리딘(46 μL, 0.57mmol)를 적가하였다. 혼합물을 실온에서 72시간 동안 교반한 후 혼합물을 농축 건조시켰다. 조약한 물질을 CH₂Cl₂(3mL) 및 포화된 수성 NaHCO₃(2mL)사이에 분배시키고 층을 분리하였다. 수성 층을 CH₂Cl₂(2x3mL)로 추출하고 유기 층을 합하였다. 유기 층을 건조(Na₂SO₄)시키고, 여과하며, 감압하에 농축시켰다. 조약한 생성물을 CH₂Cl₂/MeOH(22 : 1)로 용출시키는 제조 TLC(3x1000 μM)에 의해 정제하여 담황색 고체 90mg(100%)을 수득하였다. mp 173-175℃; M + H = 359.

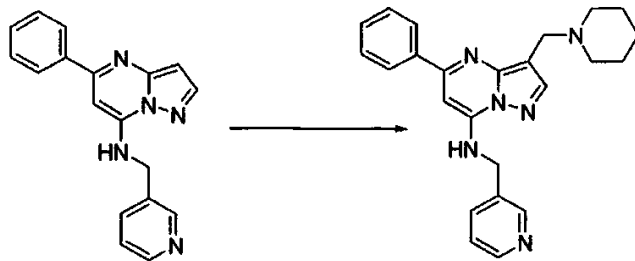
[0821] 실시예 319:



[0822]

[0823] EtOH(2.5mL)에 실시예 303으로부터의 알데하이드(60mg, 0.18mmol)의 용액에 옥스인돌(48mg, 0.37mmol)을 가하고 피페리딘(3 방울)을 적가하였다. 혼합물을 14시간 동안 환류하에 가열하고 혼합물을 실온으로 냉각시켰다. 수득되는 침전물을 여과하고 냉 EtOH(2x2mL)로 세척하였다. 생성물을 고 진공하에 건조시켜 오렌지/갈색 고체로서의 표제 화합물 81mg(100%)을 수득하였다. mp 182-185°C; M + H = 445.

[0824] 실시예 320:



[0825]

[0826] AcOH(2mL)중 제조 실시예 187.10으로부터의 3-H 유사체(106mg, 0.35mmol)의 용액에 37% 수성 포름알데하이드(1.5mL, 1.40mmol)에 이어 피페리딘(100 μL, 0.37mmol)를 적가하였다. 수득되는 혼합물을 실온에서 24시간 동안 교반한 후 AcOH를 감압하에 제거하였다. 혼합물을 물(2mL)로 희석시키고 2M NaOH로 pH = 8이 될 때까지 중화시켰다. 수성 층을 CH₂Cl₂(3x7mL)로 추출하고 유기 층을 합하였다. 유기 층을 염수(1x4mL)로 세척하고, 건조(Na₂SO₄)시키고, 여과하며, 감압하에 농축시켜 회백색 고체 96mg(69%)을 수득하였다. mp 88-90°C; M + H = 399.

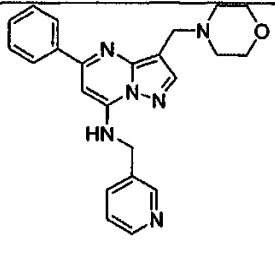
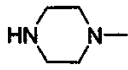
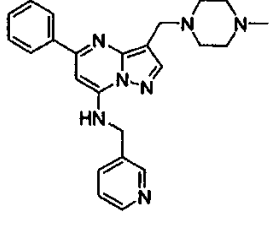
[0827] 실시예 321 및 322:

[0828] 실시예 320에 나타난 바와 본질적으로 동일한 과정에 의해, 표 29의 컬럼 2에 나타난 아민을 단지 치환시키고 제조 실시예 187.10으로부터의 3-H 부가물을 사용함으로써, 표 29, 컬럼 3에 나타난 화합물을 제조하였다:

표 29

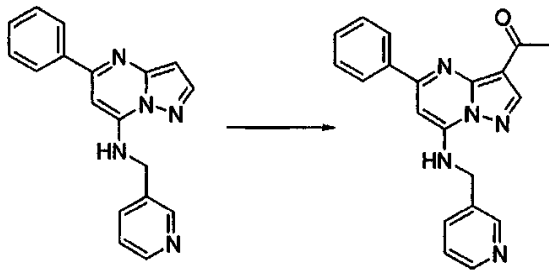
실시예	컬럼 2 (아민)	컬럼 3 (최종 구조)	CMPD 1. mp (°C) 2. M+H
321			1. mp = 178-180 2. M+H = 401

[0829]

			
322			1. mp = 102-104 2. M+H = 414

[0830]

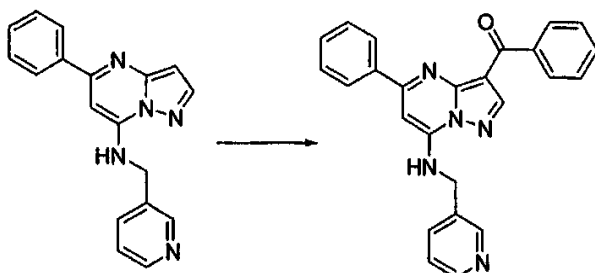
[0831] 실시예 323:



[0832]

[0833] 실온에서 CH_2Cl_2 (5mL)중 제조 실시예 187.10으로부터의 3-H 유사체(113mg, 0.38mmol)의 용액에 AlCl_3 (215mg, 1.61mmol)에 이어서 AcCl (100mL, 1.40mmol)을 가하였다. 혼합물을 환류하에 12시간 동안 가열하고 실온으로 냉각시켰다. 혼합물을 3M HCl (3mL)에 이어서 포화된 수성 NaHCO_3 (pH = 8이 될때까지)로 연속해서 처리하였다. 층을 분리하고, 수성 층을 CH_2Cl_2 (2x5mL)로 추출하였다. 유기 층을 합하고, 건조(Na_2SO_4)시키고, 여과하며, 감압하에 농축시켰다. 조약한 생성물을 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (20:1)로 용출시키는 제조 TLC(8x1000mM)로 정제하여 백색 고체 68mg(52%)을 수득하였다. mp 220-221°C; M + H = 344.

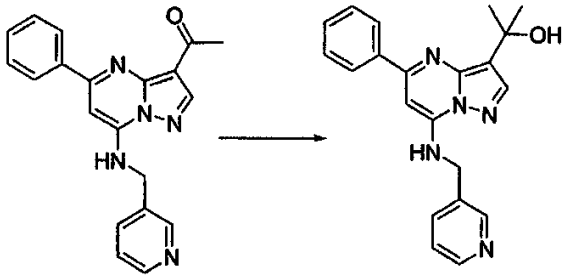
[0834] 실시예 324:



[0835]

[0836] 벤조일 클로라이드를 사용하는 것을 제외하고는, 실시예 323에 기술된 방법을 사용하여, 포제 화합물을 백색 고체로서 61%의 수율로 제조하였다. mp 172-175°C; M + H = 406.

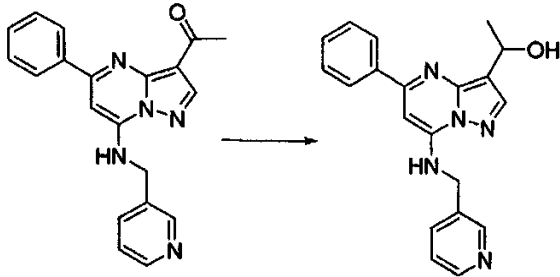
[0837] 실시예 325:



[0838]

[0839] 0°C에서 CH₂Cl₂(2.5mL)중 제조 실시예 323으로부터의 케톤(100mg, 0.29mmol)의 용액에 MeMgBr(0.35mL, Et₂O중 3.0M)을 적가하였다. 수득되는 혼합물을 실온에서 18시간 동안 교반하고 포화된 수성 NH₄Cl(2mL)을 첨가하여 조심스럽게 퀴칭시키고 CH₂Cl₂(2mL)를 가하였다. 층을 분리하고 수성 층을 CH₂Cl₂(2x4mL)로 추출하였다. 유기 층을 합하고, 건조(Na₂SO₄)시키고, 여과하며, 감압하에 농축시켰다. 조약한 생성물을 CH₂Cl₂/MeOH(10 : 1)로 용출시키는 제조 TLC(8x1000 μM)로 정제하여 황색 고체 68mg(52%)을 수득하였다. mp 160-162°C; M + H = 360.

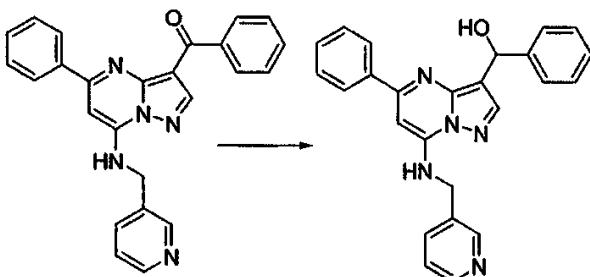
[0840] 실시예 326:



[0841]

[0842] 0°C에서 MeOH/THF(1:1; 총 2mL)중 실시예 323으로부터의 케톤(84mg, 0.24mmol)의 용액에 NaBH₄(12mg, 0.30mmol)을 한번에 가하였다. 수득되는 혼합물을 실온에서 18시간 동안 교반하고 NaBH₄(12mg, 0.30mmol) 일부를 추가로 가하였다. 혼합물을 12시간 동안 교반하고 혼합물을 얼음으로 퀴칭시킨 후 1M NaOH를 첨가하여 pH를 9로 조절하였다. 혼합물을 CH₂Cl₂(5mL)로 희석시켰다. 층을 분리하고 수성 층을 CH₂Cl₂(2x4mL)로 추출하였다. 유기 층을 합하고, 건조(Na₂SO₄)시키고, 여과하며, 감압하에 농축시켰다. 조약한 생성물을 CH₂Cl₂/MeOH(10 : 1)로 용출시키는 제조 TLC(8x1000 μM)로 정제하여 황색 고체 25mg(30%)을 수득하였다. mp 148-150°C; M + H = 346.

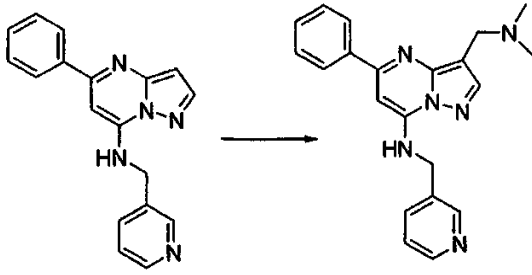
[0843] 실시예 327:



[0844]

[0845] 실시예 326에 요약한 바와 동일한 과정을 사용하여, 케톤(84mg, 0.21mmol)을 담황색 고체 53mg(62%)로 전환시켰다. mp 78-80°C; M + H = 408.

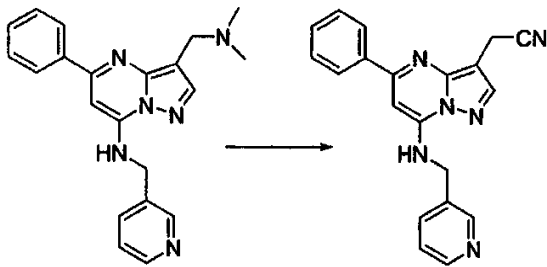
[0846] 실시예 328:



[0847]

[0848] CH_2Cl_2 (50mL)중 제조 실시예 187.10으로부터의 3-H 부가물(1.3g, 4.31mmol)의 용액에 에첸모서 염 (Eschenmoser's salt)(0.79g, 4.31mmol)을 가하고 TFA(0.56mL, 7.33mmol)을 적가하였다. 혼합물을 실온에서 48시간 동안 교반하고 CH_2Cl_2 (250mL)로 희석시켰다. 유기 층을 포화된 수성 NaHCO_3 (2x125mL)로 세척하여 황색 고체 1.41g(92%)을 수득하였다. mp 231-233°C; M + H = 359.

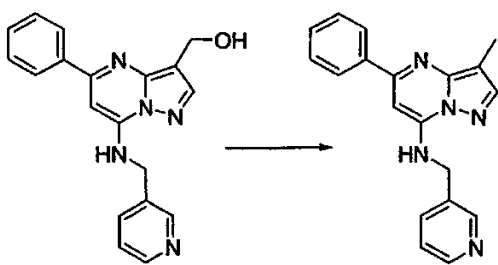
[0849] 실시예 329:



[0850]

[0851] 가압 튜브속에서 50% 수성 DMF(5mL)중 실시예 328로부터의 3급 아민 부가물(100mg, 0.28mmol)의 용액에 KCN(0.15g, 2.32mmol)을 가하였다. 튜브를 밀봉하고 100°C에서 96시간 동안 가열하였다. 혼합물을 실온으로 냉각시키고 EtOAc(25mL)로 희석시켰다. 유기 층을 염수(1x5mL) 및 물(1x5mL)로 세척하였다. 유기 층을 건조 (Na_2SO_4)시키고, 여과하며, 감압하에 농축시켰다. 조약한 생성물을 EtOAc로 용출시키는 제조 TLC(4x1000 μM)로 정제하여 갈색 고체 21mg(30%)을 수득하였다. mp 152-155°C; M + H = 341.

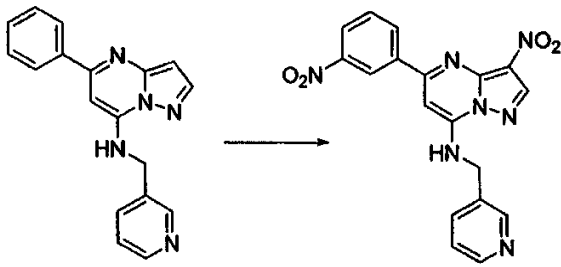
[0852] 실시예 330:



[0853]

[0854] 0°C에서 CH_2Cl_2 (0.7mL)중 실시예 17.10으로부터의 알콜(45mg, 0.14mmol)의 용액에 Et_3SiH (26 μL , 0.16mmol)에 이어서 TFA(25 μL , 0.33mmol)을 가하였다. 혼합물을 0°C에서 2시간 동안 교반하고 실온에서 2시간 동안 교반한 다음 일부의 Et_3SiH (26 μL , 0.16mmol) 및 TFA(25 μL , 0.33mmol)을 추가로 가하고 혼합물을 실온에서 4시간 동안 교반하였다(TLC로 완료된 것이 확인될 때까지). 혼합물을 감압하에 농축시키고 조약한 잔사를 CH_2Cl_2 (3mL) 및 포화된 수성 NaHCO_3 (1.5mL)사이 에 분배시켰다. 층을 분리하고 수성 층을 CH_2Cl_2 (2x4mL)로 추출하였다. 유기 층을 합하고, 염수(1x5mL)로 세척하고, 건조(Na_2SO_4)시키며, 여과하고, 감압하에 농축시켰다. 조약한 생성물을 CH_2Cl_2 /MeOH(20 : 1)로 용출시키는 제조 TLC(4x1000mM)에 의해 정제하여 황색 고체 21mg(48%)을 수득하였다. mp 146-148°C; M + H = 316.

[0855] 실시예 331:

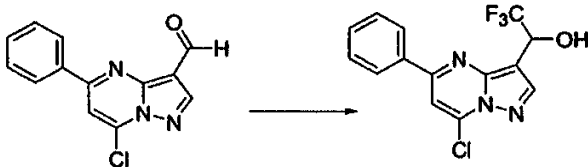


[0856]

[0857] 0℃에서 진한 H₂SO₄(2mL)중 제조 실시예 187.10으로부터의 3-H 부가물(90mg, 0.30mmol)의 용액에 혼연하는 HNO₃(30 μL, 0.72mmol)를 적가하였다. 수득되는 혼합물을 0℃에서 1시간 동안 가열하고 얼음(~1g)을 혼합물에 가하였다. 수득되는 침전물을 수집하고 물(2x2mL) 및 CH₂Cl₂(2x2mL)로 세척하였다. 조약한 생성물을 고 진공하에 건조시켜 황색/오렌지색 고체로서의 모노설페이트 염 67mg(60%)을 수득하였다. mp 250℃; M + H(유리 염기) = 392.

[0858] 실시예 332:

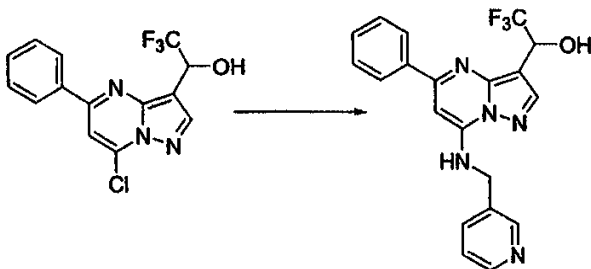
[0859] 단계 A:



[0860]

[0861] 0℃에서 THF(2.5mL)중 제조 실시예 168로부터의 알데하이드(0.10g, 0.39mmol)의 용액에 CF₃TMS(64μL, 0.43mmol)에 이어서 CsF(10mg)을 가하였다. 수득되는 혼합물을 0℃에서 2시간 동안 교반하고 실온에서 2시간 동안 교반하였다. 1M HCl(5mL)을 가하고 혼합물을 CH₂Cl₂(10mL)로 희석시켰다. 층을 분리하고, 수성 층을 CH₂Cl₂(2x10mL)로 추출하고 유기 층을 합하였다. 유기 층을 염수(1x10mL)로 세척하고, 건조(Na₂SO₄)시키며, 여과하고, 감압하에 농축시켜 황색 반 고체 127mg(99%)을 수득하였다. 조약한 생성물을 추가의 정제없이 수행하였다.

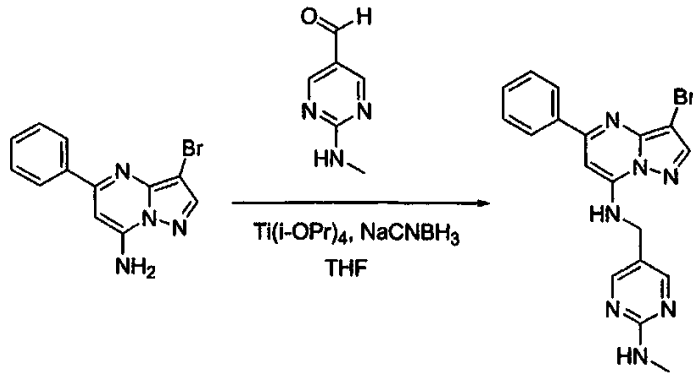
[0862] 단계 B:



[0863]

[0864] 실시예 1에 나타난 일반적인 과정을 이용함으로써, 실시예 332, 단계 A로부터의 7-Cl 부가물(127mg, 0.39mmol)을 3-(아미노메틸)피리딘(73 μL, 0.43mmol)과 반응시켜 담황색 고체로서의 표제 화합물 80mg(51%)을 수득하였다. mp 68-72℃; M + H = 400.

[0865] 실시예 333:



[0866]

[0867] 실온에서 THF(6mL)중 제조 실시예 174로부터의 아닐린(200mg, 0.69mol)의 용액에 제조 실시예 256으로부터의 알데하이드(114mg, 0.83mmol)를 가하고 Ti(i-OPr)₄(0.82mL, 2.77mmol)을 첨가하였다. 혼합물을 4시간 동안 환류하에 가열하고 실온으로 냉각시켰다. NaCNBH₃(347mg, 5.53mmol)를 가하고 혼합물을 실온에서 2시간 동안 교반하였다. 혼합물을 0°C로 냉각시키고, 1M NaOH(4mL) 및 염수(1mL)로 처리하고 30분 동안 교반하였다. 혼합물을 CH₂Cl₂(3x10mL)로 추출하고 유기 층을 합하였다. 유기 층을 염수(1x7mL)로 세척하고, 건조(Na₂SO₄)시키며, 여과하고, 감압하에 농축시켰다. 조악한 생성물을 CH₂Cl₂/MeOH(25:1)로 용출시키는 제조 박층 크로마토그래피(8x1000 μM 플레이트)에 의해 정제하여 황색 고체로서의 표제 화합물 89mg(31%)을 수득하였다. mp 210-213°C; M + H = 411.

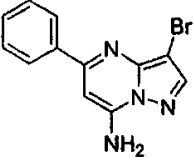
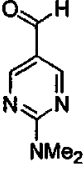
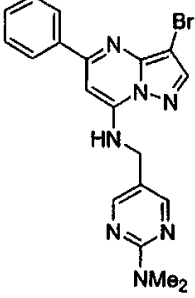
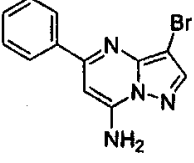
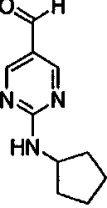
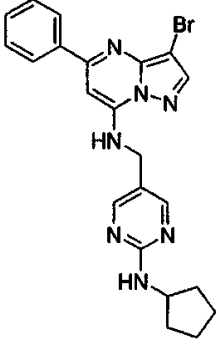
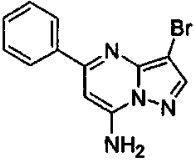
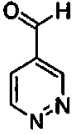
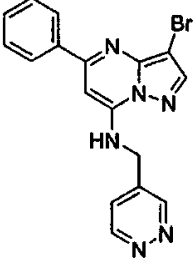
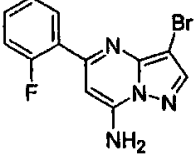
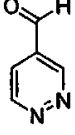
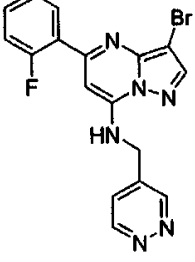
[0868] 실시예 334 내지 337:

[0869] 표 30의 컬럼 2에 나타낸 아닐린 및 표 30의 컬럼 3에 나타낸 알데하이드를 단지 이용함으로써 실시예 333에 나타낸 바와 본질적으로 동일한 과정에 의해 표 30의 컬럼 4의 화합물을 제조하였다:

표 30

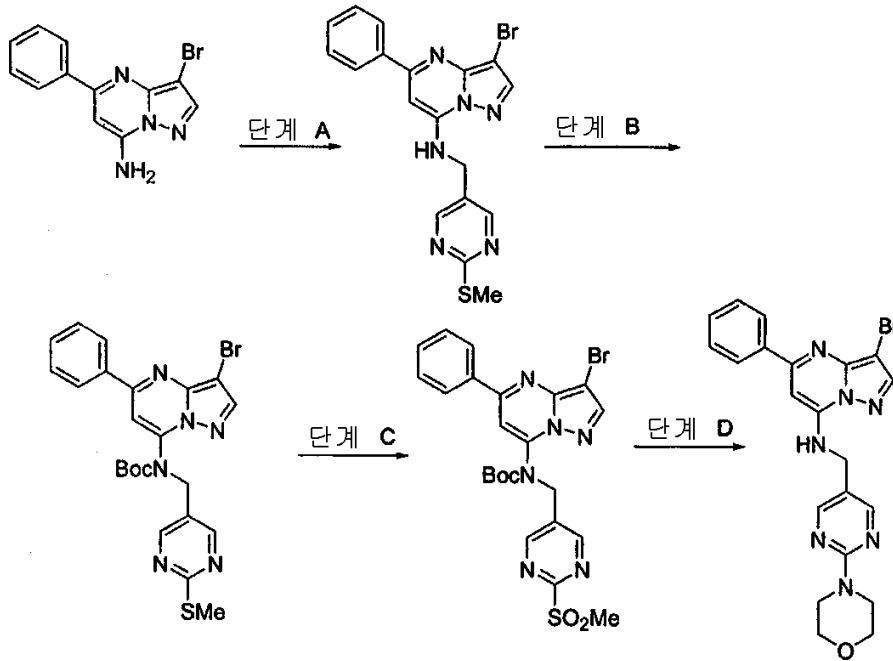
실시예	컬럼 2 (아닐린)	컬럼 3 (알데히드)	컬럼 4 (최종 구조)	CMPD 1. mp (°C) 2. M+H

[0870]

334				<p>1. mp = 85-87 2. M+H = 425</p>
335				<p>1. mp = 160-162 2. M+H = 451</p>
336				<p>1. mp = 117-119 2. M+H = 382</p>
337				<p>1. mp = 171-175 2. M+H = 400</p>

[0871]

[0872] 실시예 338:



[0873]

[0874] 단계 A:

[0875] 실시예 333에 기술된 반응 조건하에서 아닐린(0.20g, 0.69mmol)을 알데하이드(0.13g, 0.83mmol)과 반응시켜 황색 고체로서의 티오메틸 유도체 70mg(23%)를 황색 고체로서 수득하였다. M + H = 428.

[0876] 단계 B:

[0877] 디옥산(2mL)중 실시예 338, 단계 A로부터의 티오닐메틸 유도체(60mg, 0.14mmol)의 용액에 Boc_2O (61mg, 0.28mmol)에 이어 DMAP(21mg, 0.17mmol)를 가하였다. 혼합물을 실온에서 14시간 동안 교반하고 감압하에 농축시켰다. 조약한 생성물을 헥산/EtOAc(4:1)로 용출시키는 제조 박층 크로마토그래피(6x1000 μM 플레이트)로 정제하여 황색 고체로서의 표제 화합물 61mg(83%)을 수득하였다. M + H = 528.

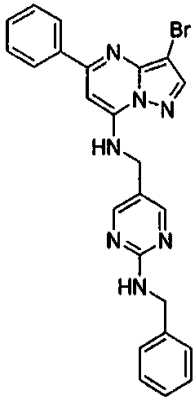
[0878] 단계 C:

[0879] CH_2Cl_2 (2mL)중 실시예 338, 단계 B로부터의 티오메틸 유도체(41mg, 0.078mmol)의 용액에 MCPBA(33mg, 0.19mmol)를 일부씩 가하였다. 수득되는 혼합물을 실온에서 3시간 동안 교반하고, 혼합물을 CH_2Cl_2 (5mL) 및 포화된 수성 NaHCO_3 (2.5mL)로 희석시켰다. 층을 분리하고, 수성 층을 CH_2Cl_2 (2x5mL)로 추출하고, 유기 층을 합하였다. 유기 층을 건조(Na_2SO_4)시키며, 여과하고, 감압하에 농축시켜 담황색 고체로서의 설폰 부가물 40mg(92%)을 수득하였다. M + H = 560.

[0880] 단계 D:

[0881] 실시예 338, 단계 C로부터의 설폰(75mg, 0.13mmol) 및 교반 바아가 충전된 플라스크에 모르폴린(2ml; 22mmol)을 가하였다. 혼합물을 환류하에 12시간 동안 가열하고, 실온으로 냉각시키고 감압하에 농축 건조시켰다. 조약한 생성물을 CH_2Cl_2 /MEOH(40 : 1)로 용출시키는 제조 박층 크로마토그래피(6x1000 μM 플레이트)에 의해 정제하여 황색 고체로서의 표제 화합물 41mg(68%)을 수득하였다. mp 209-210 $^\circ\text{C}$; M+H = 466.

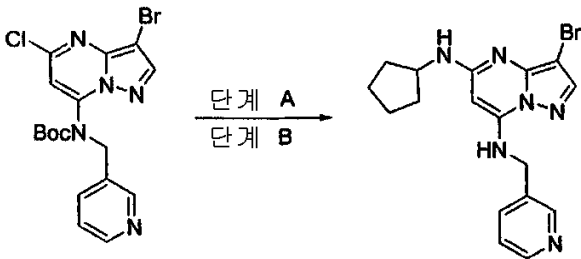
[0882] 실시예 339:



[0883]

[0884] 벤질 아민을 사용하는 것외에는 실시예 338에 요약된 과정에 따라 표제 화합물을 백색 고체로서 12mg(70%)을 수득하였다. mp 194-196°C; M + H = 487.

[0885] 실시예 340:



[0886]

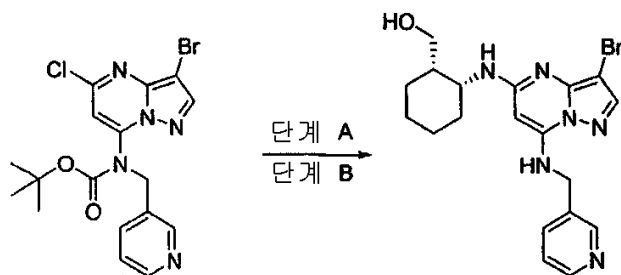
[0887] 단계 A:

[0888] 실온에서 디옥산/DIPEA(2.5mL/1.0mL)중 2-클로로 부가물(0.15g, 0.34mmol)의 용액에 사이클로펜틸아민(0.041μL, 0.41mmol)을 적가하였다. 수득되는 용액을 16시간동안 환류하에 교반하고, 실온으로 냉각시키고 감압하에 농축시켰다. 조약한 물질을 CH₂Cl₂/MeOH(25 : 1)로 용출시키는 제조 박층 크로마토그래피(8x1000 μM)에 의해 정제하여 황색 오일 148mg(89%)을 수득하였다. M + H = 489.

[0889] 단계 B: TFA를 사용한 t-부톡시카보닐 보호 그룹의 제거

[0890] 실온에서 CH₂Cl₂(2mL)중 실시예 340, 단계 A에서 제조한 화합물(135mg, 0.28mmol)의 용액에 TFA(0.54mL, 7.0mmol)를 적가하였다. 수득되는 용액을 실온에서 18시간 동안 교반하고 감압하에 농축시켰다. 조약한 물질을 CH₂Cl₂(5mL)속에 재용해시키고 유기 층을 포화된 수성 NaHCO₃(2x2mL) 및 염수(1x2mL)로 연속해서 세척하였다. 유기 층을 건조(Na₂SO₄)하고, 여과하고 감압하에 농축시켰다. 조약한 물질을 CH₂Cl₂/MeOH(20 : 1)로 용출시키는 제조 박층 크로마토그래피(8x1000 μM)로 정제하여 백색 고체 105mg(97%)을 수득하였다. mp 120-122°C; M + H = 389.

[0891] 실시예 341:

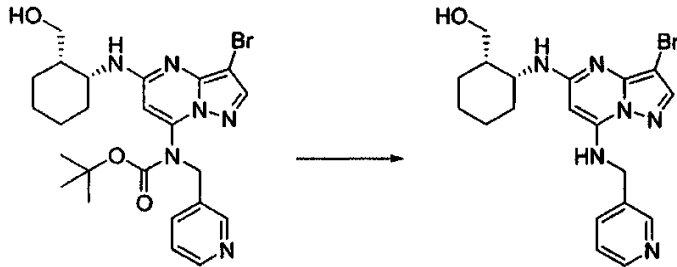


[0892]

[0893] 단계 A:

[0894] 실시예 340에 나타낸 바와 본질적으로 동일한 과정을 사용함으로써, 적절한 아민을 단지 치환시켜 상기 화합물을 제조하였다. MS: $MH^+ = 431$.

[0895] 단계 B: KOH를 사용한 t-부톡시카보닐 보호 그룹에 대한 제거



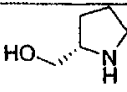
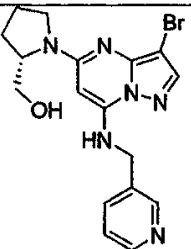
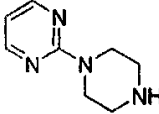
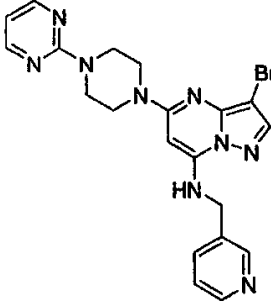
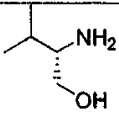
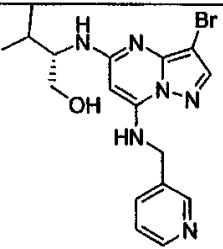
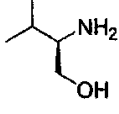
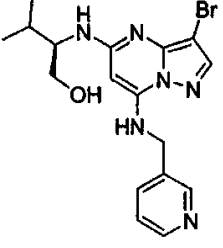
[0896]

[0897] EtOH:H₂O(3mL, 2 : 1)중 실시예 341, 단계 A에서 제조한 화합물(0.14g, 0.26mmol)의 혼합물에 KOH(0.29g, 20당량)을 일부씩 가하였다. 수득되는 용액을 환류하에 14시간 동안 교반하고, 실온으로 냉각시키고, 감압하에 농축시켰다. 잔사를 CH₂Cl₂(5mL)속에 넣고 포화된 NaHCO₃(2mL)로 희석시켰다. 층을 분리하고 수성 층을 CH₂Cl₂(2x4mL)로 추출하였다. 합한 유기물을 염수로 세척하고, Na₂SO₄위에서 건조시키며, 여과하고, 감압하에 농축시켰다. 조약한 생성물을 CH₂Cl₂ 용액중 5% MeOH로 용출시키는 제조 TLC(8x1000 μM)에 의해 정제하였다 (0.066g, 59% 수율). MS : $MH^+ = 432$; mp = 219-221° C.


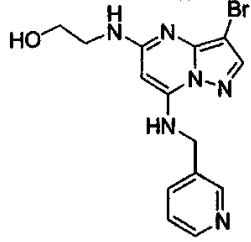
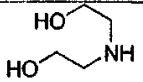
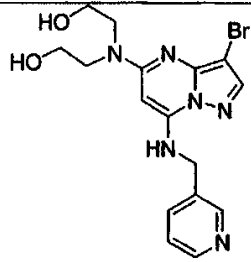
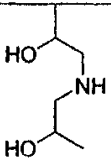
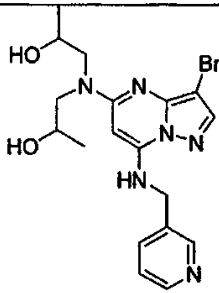
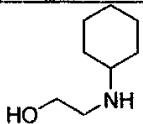
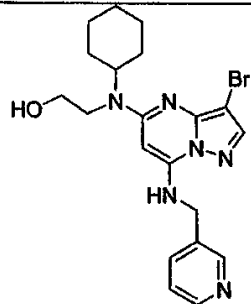
[0898] 실시예 342 내지 397:

[0899] 실시예 340에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 31의 컬럼 2의 클로라이드를 단지 치환하고 t-부톡시카보닐 보호 그룹을 표 31의 컬럼 3에 나타낸 방법에 의해 제거시켜, 표 31의 컬럼 4에 나타낸 화합물을 제조하였다.

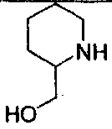
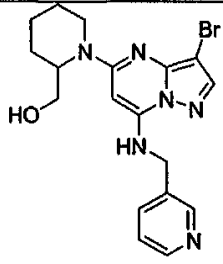
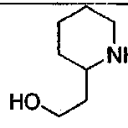
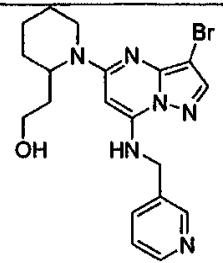
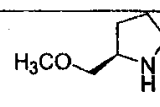
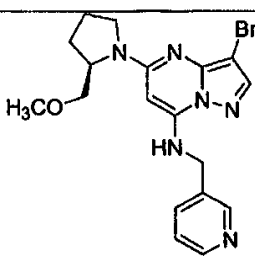
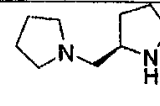
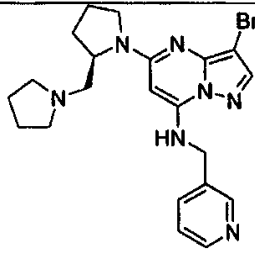
표 31

실시예	컬럼 2	컬럼 3	컬럼 4	CMPD
342		HCl		MS: MH ⁺ = 403 m.p. 151 – 157 °C
343		HCl		MS: MH ⁺ = 466 m.p. 212 – 217 °C
344		HCl		MS: MH ⁺ = 405 m.p. 53 – 58 °C
345		HCl		MS: MH ⁺ = 405 m.p. 63 – 69 °C

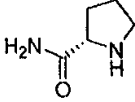
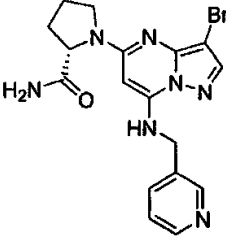
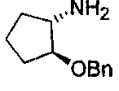
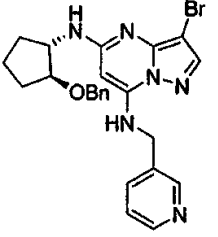
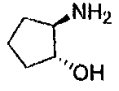
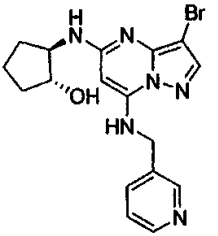
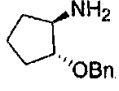
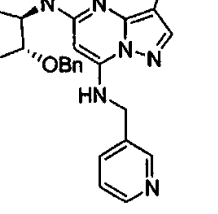
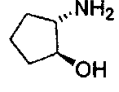
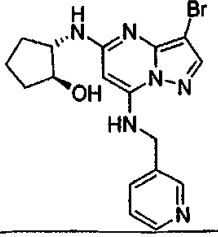
[0900]

346		HCl		MS: MH^+ = 363 m.p. 170 – 171 °C
347		HCl		MS: MH^+ = 407 m.p. 148 – 151 °C
348		HCl		MS: MH^+ = 435 m.p. 56 – 59 °C
349		HCl		MS: MH^+ = 445 m.p. 66 – 68 °C

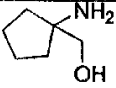
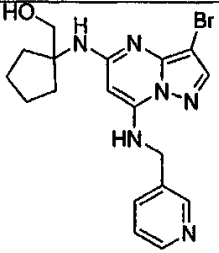
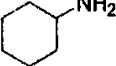
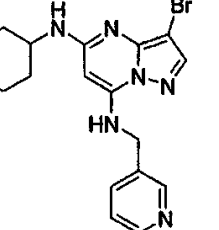
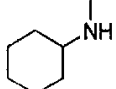
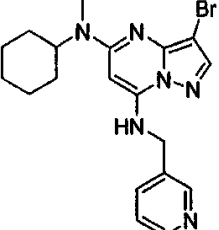
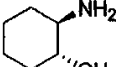
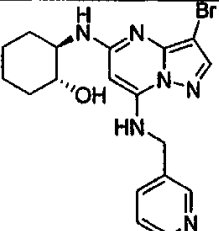
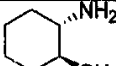
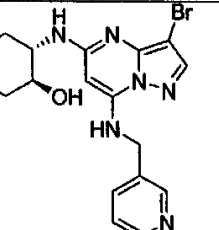
[0901]

350		KOH		MS: MH ⁺ = 417 m.p. 149 – 151 °C
351		KOH		MS: MH ⁺ = 431 m.p. 111 – 114 °C
352		KOH		MS: MH ⁺ = 417 m.p. 53 – 58 °C
353		KOH		MS: MH ⁺ = 456 m.p. 186 – 189 °C

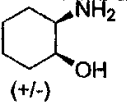
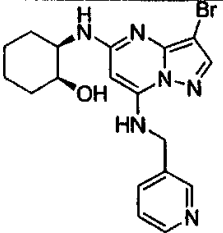
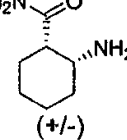
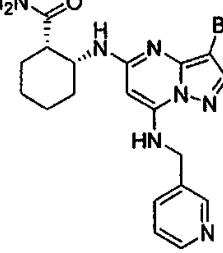
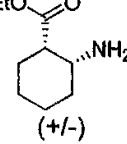
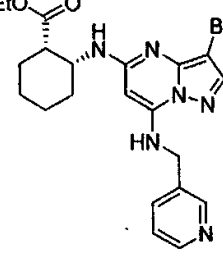
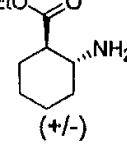
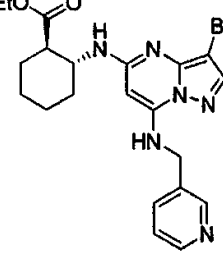
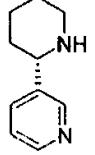
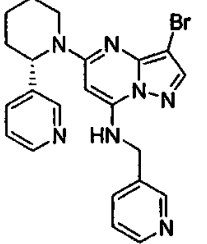
[0902]

354		KOH		MS: MH^+ = 416 m.p. 210 – 213 °C
355		TFA		1. mp = 68-70 2. M+H = 494
356		KOH		1. mp = 181-183 2. M+H = 404
357		TFA		1. mp = 69-71 2. M+H = 494
358		KOH		1. mp = 182-184 2. M+H = 404

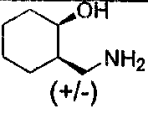
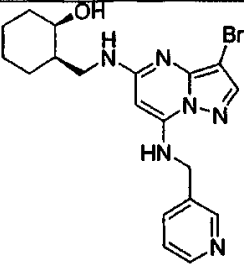
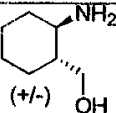
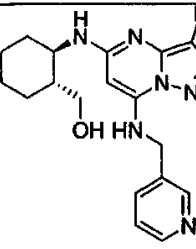
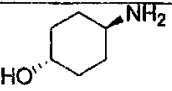
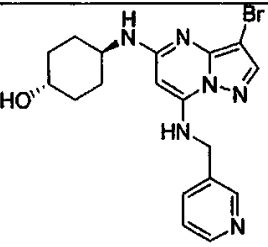
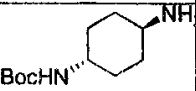
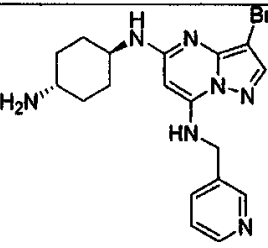
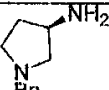
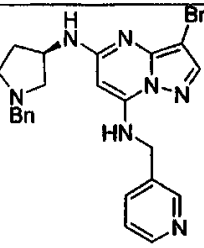
[0903]

359		KOH		<p>1. mp = 202-204 2. M+H = 418</p>
360		TFA		<p>1. mp = 160-162 2. M+H = 402</p>
361		TFA		<p>1. mp = 151-153 2. M+H = 416</p>
362		KOH		<p>1. mp = 140-143 2. M+H = 418</p>
363		KOH		<p>1. mp = 139-142 2. M+H = 418</p>

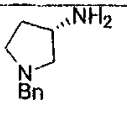
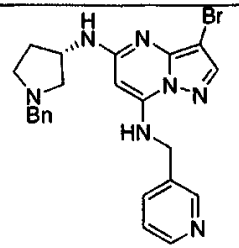
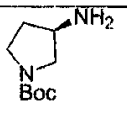
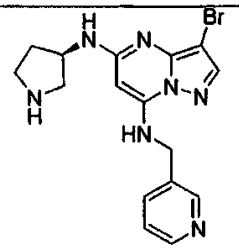
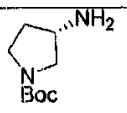
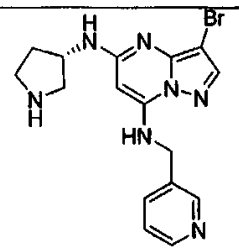
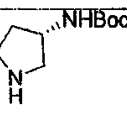
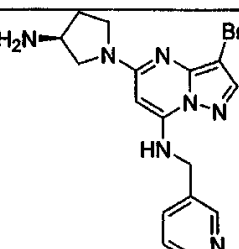
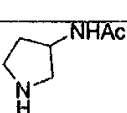
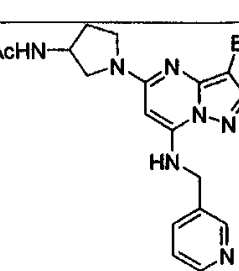
[0904]

364	 <p>(+/-)</p>	KOH		<p>1. mp = 115-117 2. M+H = 418</p>
366	 <p>(+/-)</p>	TFA		<p>1. mp = 102-104 2. M+H = 445</p>
367	 <p>(+/-)</p>	TFA		<p>1. mp = 118-120 2. M+H = 474</p>
368	 <p>(+/-)</p>	TFA		<p>1. mp = 106-108 2. M+H = 474</p>
369		TFA		<p>1. mp = 160-161 2. M+H = 464</p>


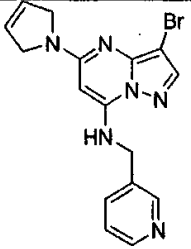
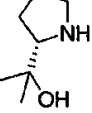
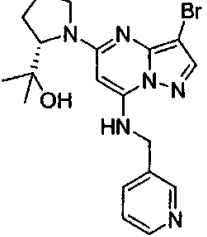
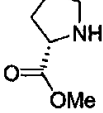
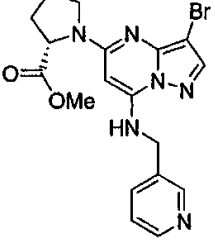
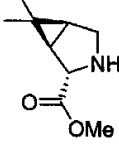
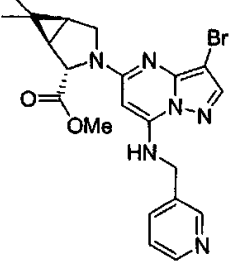
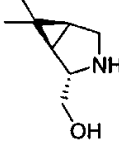
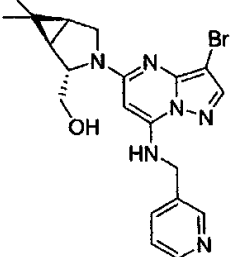
[0905]

370	 <p>(+/-)</p>	TFA		<p>1. mp = 93-95 2. M+H = 432</p>
371	 <p>(+/-)</p>	KOH		<p>1. mp = 108-110 2. M+H = 432</p>
372		KOH		<p>1. mp = 180-182 2. M+H = 418</p>
373		TFA		<p>1. mp = 169-170 2. M+H = 417</p>
374		TFA		<p>1. mp = 77-79 2. M+H = 479</p>

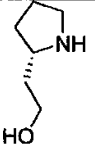
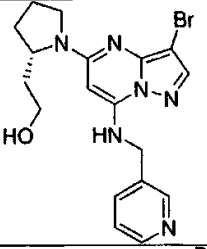
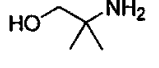
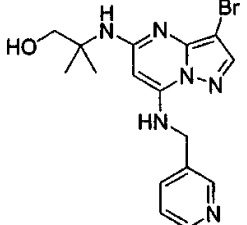
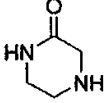
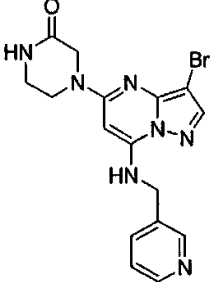
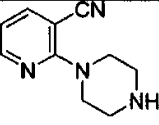
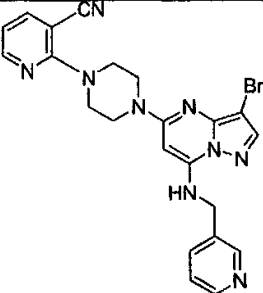
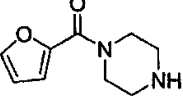
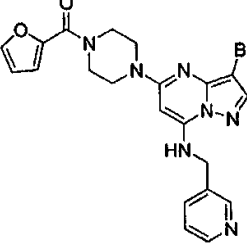
[0906]

375		TFA		<p>1. mp = 76-79 2. M+H = 479</p>
376		TFA		<p>1. mp = 105-107 2. M+H = 389</p>
377		TFA		<p>1. mp = 105-107 2. M+H = 389</p>
378		TFA		<p>1. mp = 130-133 2. M+H = 389</p>
379		TFA		<p>1. mp = 132-135 2. M+H = 431</p>

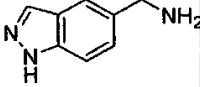
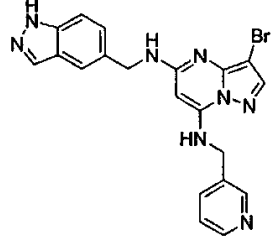
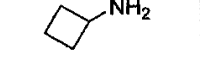
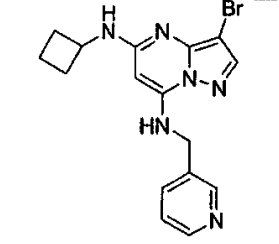
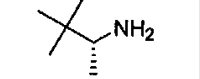
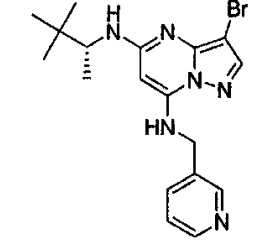
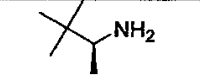
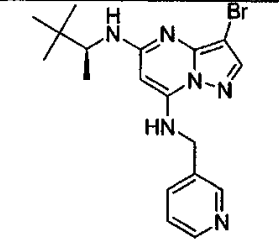
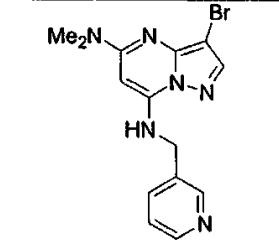
[0907]

380		TFA		1. mp = 135-137 2. M+H = 372
381		KOH		1. mp = 78-82 2. M+H = 432
382		TFA		1. mp = 101-103 2. M+H = 432
383		TFA		1. mp = 92-95 2. M+H = 472
384		TFA		1. mp = 107-111 2. M+H = 444

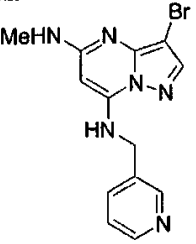

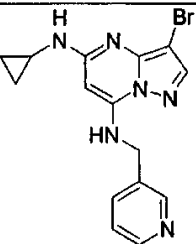
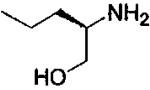
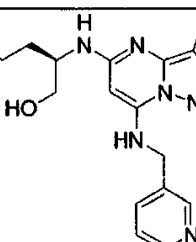
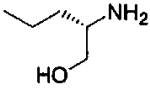
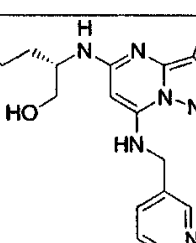
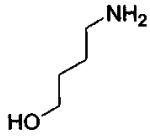
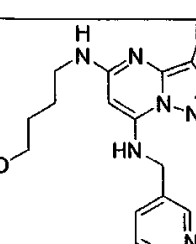
[0908]

<p>384. 10</p>		<p>TFA</p>		<p>1. mp = 2. M+H = 417</p>
<p>384. 11</p>		<p>TFA</p>		<p>1. mp = 210-212 2. M+H = 391</p>
<p>385</p>		<p>TFA</p>		<p>1. mp = 122-124 2. M+H = 403</p>
<p>386</p>		<p>TFA</p>		<p>1. mp = 186-188 2. M+H = 491</p>
<p>387</p>		<p>TFA</p>		<p>1. mp = 173-175 2. M+H = 483</p>

[0909]

388		TFA		1. mp = 167-169 2. M+H = 450
389		TFA		1. mp = 90-92 2. M+H = 374
390		TFA		1. mp = 113-115 2. M+H = 404
391		TFA		1. mp = 114-116 2. M+H = 404
392	HNMe ₂	TFA		LCMS: MH ⁺ = 347;

[0910]

393	<chem>CN</chem>	TFA		LCMS: MH ⁺ = 333;
394		TFA		LCMS: MH ⁺ = 359;
395		TFA		LCMS: MH ⁺ = 405;
396		TFA		LCMS: MH ⁺ = 405;
397		TFA		LCMS: MH ⁺ = 391;

[0911]

[0912] 선택된 실시예에 대한 추가의 데이터를 하기에 나타낸다:

실시예 392: $^1\text{H NMR}$ ($\text{DMSO-}d_6$) δ 8.65 (s, 1H), 8.46 (d, $J = 3.3$ Hz, 1H), 8.21 (t, $J = 6.6$ Hz, 1H), 7.90 (s, 1H), 7.80 (d, $J = 7.8$ Hz, 1H), 7.35 (dd, $J = 7.8, 4.8$ Hz, 1H), 5.46 (s, 1H), 4.61 (d, $J = 6.9$ Hz, 2H), 3.01 (s, 6H).

실시예 393: $^1\text{H NMR}$ (CDCl_3) δ 8.65 (s, 1H), 8.60 (d, $J = 4.8$ Hz, 1H), 7.76 (s, 1H), 7.70 (m, 1H), 7.32 (dd, $J = 8.1, 4.8$ Hz, 1H), 6.43 (t, $J = 6.0$ Hz, 1H), 5.08 (s, 1H), 4.80 (m, 1H), 4.56 (d, $J = 6.0$ Hz, 2H), 2.96 (d, $J = 5.1$ Hz, 3H).

실시예 394: $^1\text{H NMR}$ (CDCl_3) δ 8.68 (s, 1H), 8.60 (d, $J = 4.8$ Hz, 1H), 7.76 (s, 1H), 7.72 (m, 1H), 7.32 (dd, $J = 7.8, 5.4$ Hz, 1H), 6.55 (t, $J = 5.7$ Hz, 1H), 5.53 (s, 1H), 5.35 (s, 1H), 4.62 (d, $J = 5.7$ Hz, 2H), 2.49 (m, 1H), 0.75 (m, 2H), 0.51 (m, 2H).

실시예 395: $^1\text{H NMR}$ (CDCl_3) δ 8.65 (s, 1H), 8.60 (d, $J = 4.0$ Hz, 1H), 7.75 (s, 1H), 7.69 (m, 1H), 7.33 (dd, $J = 8.1, 5.1$ Hz, 1H), 6.45 (t, $J = 6.0$ Hz, 1H), 5.07 (s, 1H), 4.69 (m, 1H), 4.54 (d, $J = 6.0$ Hz, 2H), 3.98 (m, 1H), 3.79 (dd, $J = 10.8, 2.4$ Hz, 1H), 3.59 (dd, $J = 11.1, 7.2$ Hz, 1H), 1.59-1.36 (m, 4H), 0.94 (t, $J = 6.9$ Hz, 3H).

실시예 396: $^1\text{H NMR}$ (CDCl_3) δ 8.60 (s, 1H), 8.56 (d, $J = 4.2$ Hz, 1H), 7.73 (s, 1H), 7.66 (m, 1H), 7.31 (dd, $J = 7.8, 4.8$ Hz, 1H), 6.51 (t, $J = 6.0$ Hz, 1H), 5.05 (s, 1H), 4.86 (d, $J = 6.6$ Hz, 1H), 4.50 (d, $J = 6.0$ Hz, 2H), 3.94 (m, 1H), 3.78 (dd, $J = 11.1, 2.4$ Hz, 1H), 3.57 (dd, $J = 11.1, 7.2$ Hz, 1H), 1.57-1.34 (m, 4H), 0.91 (t, $J = 7.2$ Hz, 3H).

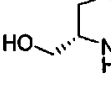
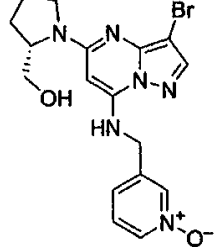
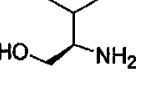
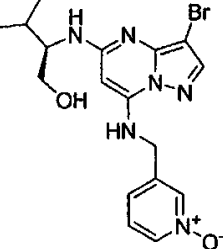
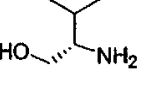
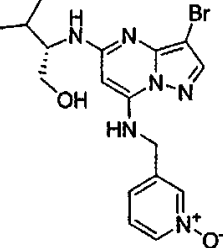
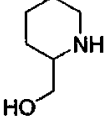
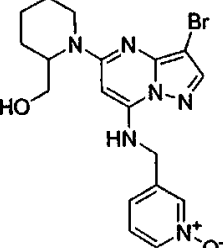
실시예 397: $^1\text{H NMR}$ (CDCl_3) δ 8.65 (s, 1H), 8.59 (d, $J = 4.5$ Hz, 1H), 7.75 (s, 1H), 7.69 (m, 1H), 7.31 (m, 1H), 6.43 (t, $J = 6.0$ Hz, 1H), 5.06 (s, 1H), 4.88 (m, 1H), 4.55 (d, $J = 6.0$ Hz, 2H), 3.70 (m, 2H), 3.38 (m, 2H), 1.79-1.61 (m, 4H).

[0913]

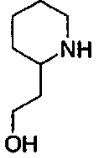
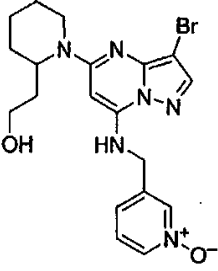
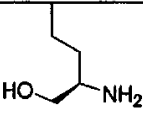
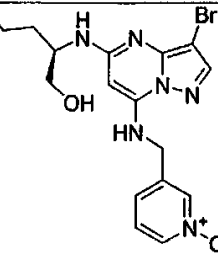
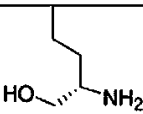
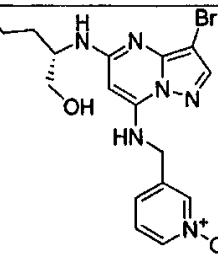

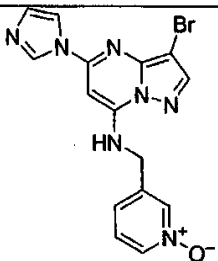
[0914] 실시예 398 내지 416:

[0915] 실시예 341, 단계 A에 나타낸 바와 본질적으로 동일한 과정에 의해, 제조 실시예 193.10에서 제조한 화합물을 단지 치환시켜, 표 32의 컬럼 4에 나타낸 화합물을 제조하였다.


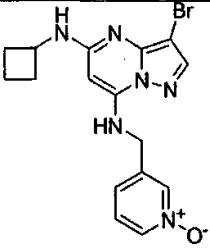
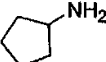
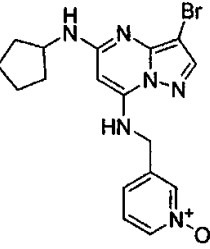
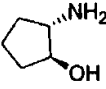
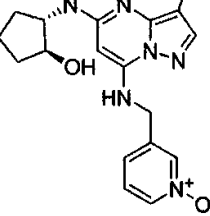
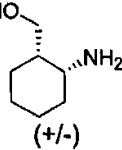
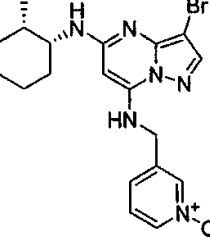

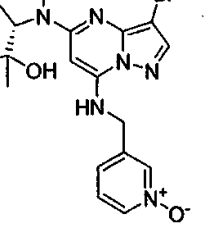
표 32

실시예	컬럼 2	컬럼 3	컬럼 4	CMPD
398				MS: MH ⁺ = 419 m.p. 102 – 105 °C
399				MS: MH ⁺ = 421 m.p. 79 – 81 °C
400				MS: MH ⁺ = 421 m.p. 78 – 79 °C
401				MS: MH ⁺ = 433 m.p. 228-231 °C

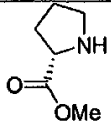
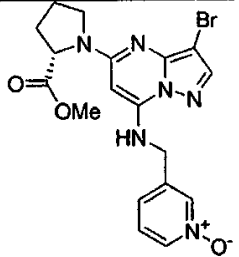
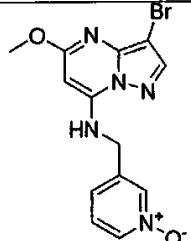
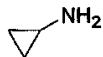
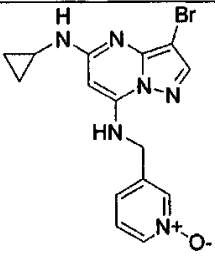
[0916]

402				<p>MS: MH^+ = 447 m.p. 97-102 °C</p>
403				<p>MS: MH^+ = 421 m.p. °C</p>
404				<p>MS: MH^+ = 421 m.p. °C</p>
405				<p>MS: MH^+ = 386 m.p. °C</p>

[0917]

407		KOH		<p>1. mp = 98-100 2. M+H = 390</p>
408		TFA		<p>1. mp = 170-173 2. M+H = 404</p>
409		KOH		<p>1. mp = 219-221 2. M+H = 420</p>
410		KOH		<p>1. mp = 110-112 2. M+H = 448</p>
411		TFA		<p>1. mp = 81-83 2. M+H = 448</p>

[0918]

412		TFA		1. mp = 136-138 2. M+H = 448
413	NaOMe	KOH		1. mp = 107-110 2. M+H = 351
414				LCMS: MH ⁺ = 375;

[0919]

[0920]

선택된 실시예에 대한 추가의 데이터를 하기에 나타낸다:

실시예 414: ¹H NMR (DMSO-*d*₆) δ 8.26 (s, 1H), 8.23 (m, 1H), 8.13 (m, 1H), 7.90 (s, 1H), 7.40-7.27 (m, 3H), 5.34 (s, 1H), 4.49 (d, J = 6.3 Hz, 2H), 2.56 (m, 1H), 0.67 (m, 2H), 0.35 (m, 2H).

실시예 403: ¹H NMR (DMSO-*d*₆+CDCl₃) δ 8.08 (s, 1H), 7.90 (d, J = 6.3 Hz, 1H), 7.49 (s, 1H), 7.34 (t, J = 6.3 Hz, 1H), 7.16-7.09 (m, 2H), 5.65 (d, J = 6.6 Hz, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.29 (d, J = 6.3 Hz, 2H), 3.70 (m, 1H), 3.46 (m, 1H), 3.34 (m, 1H), 1.35-1.17 (m, 4H), 0.71 (t, J = 7.2 Hz, 3H).

실시예 404: ¹H NMR (DMSO-*d*₆) δ 8.21 (s, 1H), 8.12 (d, J = 6.6 Hz, 1H), 8.06 (m, 1H), 7.86 (s, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 5.28 (s, 1H), 4.70 (t, J = 5.1 Hz, 1H), 4.41 (d, J = 6.6 Hz, 2H), 4.00 (s, 1H), 3.39 (m, 1H), 1.53 (m, 1H), 1.36-1.25 (m, 3H), 0.86 (t, J = 7.0 Hz, 3H).

[0921]

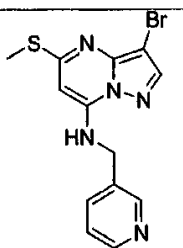
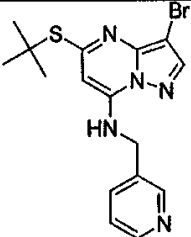
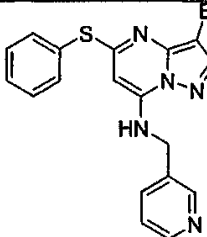
[0922]

실시예 417 내지 421:

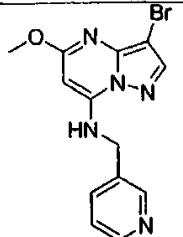
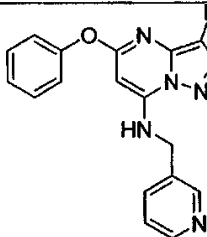
[0923]

문헌(참조: Chem. Pharm. Bull. 1999, 47, 928-938)에 설정된 과정에 의해, 표 33에 기술된 바와 같이 컬럼 2에 나타낸 산소 또는 황 친핵체를 사용하고 표 33의 컬럼 3에 나열된 분해 방법을 사용하여, 표 33의 컬럼 4의 화합물을 제조하였다.

표 33

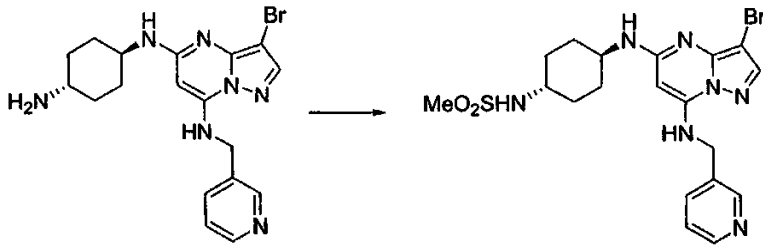
실시예	컬럼 2 (친핵체)	컬럼 3 (절단 방법)	컬럼 4 (최종 구조)	CMPD 1. mp. 2. M+H
417	NaSMe	TFA		1. mp = 172-175 2. M+H = 351
418	NaSt-Bu	TFA		1. mp = 165-168 2. M+H = 392
419	NaSPh	TFA		1. mp = 154-156 2. M+H = 412
420	NaOMe	TFA		1. mp = 161-163 2. M+H = 335

[0924]

				
421	NaOPh	TFA		1. mp = 64-66 2. M+H = 397

[0925]

[0926] 실시예 422:



[0927]

[0928] 실온에서 CH_2Cl_2 (1mL)중 실시예 373으로부터의 아미노 화합물(18mg, 0.043mmol)의 용액에 DIPEA(10 μ l, 0.056mmol)에 이어 MeSO_2Cl (4mL, 0.052mmol)을 가하였다. 혼합물을 실온에서 12시간 동안 교반하고, CH_2Cl_2 (2mL) 및 포화된 수성 NaHCO_3 (2mL)로 희석시켰다. 층을 분리하고 유기 층을 염수(1x2mL)로 추출하였다. 유기층을 건조(Na_2SO_4)시키며, 여과하고, 감압하에 농축시켰다. 조약한 물질을 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (20:1)로 용출시키는 제조 박층 크로마토그래피(8x1000 μ M)에 의해 정제하여 백색 고체 16mg(75%)을 수득하였다. mp = 152-154 $^\circ$ C; M + H = 495.

[0929] 실시예 423 및 424:

[0930] 실시예 422에 대략 나타낸 과정을 이용하여, 아미노 화합물(컬럼 2)을 표 3에서 상응하는 메틸설폰아미드(컬럼 3)로 전환시켰다.

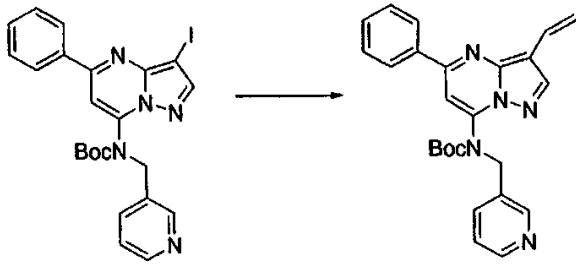
표 34

실시예	컬럼 2 (아민)	컬럼 3 (최종 구조)	CMPD 1. mp. 2. M+H
423			1. mp = 166-168 2. M+H = 467
424			1. mp = 165-168 2. M+H = 467

[0931]

[0932] 실시예 425:

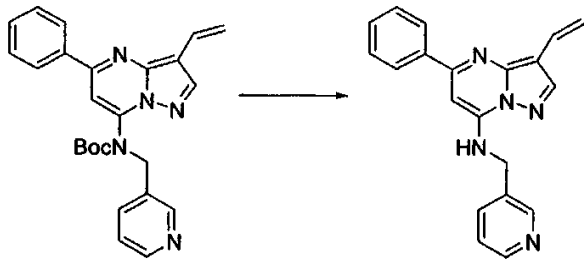
[0933] 단계 A:



[0934]

[0935] 무수 디옥산(5mL) 중의 제조 실시예 194에서 제조한 화합물(132mg, 0.25mmol), 트리부틸비닐틴(95mg, 0.30mmol) 및 테트라키스(트리페닐포스핀) 팔라듐(29mg, 0.025mmol)의 혼합물을 N₂하에 24시간 동안 환류시켰다. 용매를 증발시키고 잔사를 용출제로서 2:1 CH₂Cl₂:EtOAc를 사용하는 플래쉬 크로마토그래피로 정제하여 황색 왁스상 고체(53mg, 50%)를 수득하였다. LCMS: MH⁺ = 428.

[0936] 단계 B:

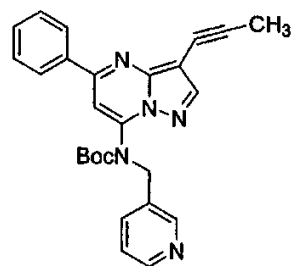


[0937]

[0938] 에탄올(3mL) 및 H₂O(0.6mL) 중의 실시예 425, 단계 A에서 제조한 화합물(50mg, 0.12mmol) 및 KOH(100mg, 1.80mmol)의 혼합물을 70° C에서 N₂하에 24시간 동안 교반하였다. NaHCO₃(1.0g), Na₂SO₄(2.0g) 및 CH₂Cl₂(20mL)를 가하고, 혼합물을 교반한 다음, 여과하였다. 용매를 증발시키고 잔사를 용출제로서 20:1:0.1 CH₂Cl₂:MeOH:진한 NH₄OH를 사용하는 플래쉬 크로마토그래피로 정제하여 황색 왁스상 고체(17mg, 45%)를 수득하였다. LCMS: MH⁺ = 328. Mp = 48-51 ° C.

[0939] 실시예 426:

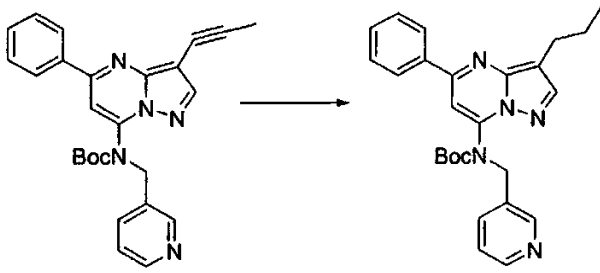
[0940] 단계 A:



[0941]

[0942] 트리부틸메틸에티닐틴을 사용하는 것을 제외하고는 실시예 425, 단계 A에 나타낸 바와 본질적으로 동일한 과정으로, 상기한 화합물을 제조하였다.

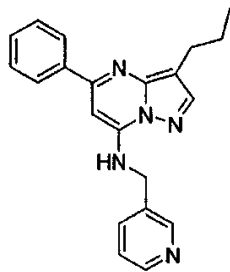
[0943] 단계 B:



[0944]

[0945] 빙초산(5mL)중의 실시예 426, 단계 A에서 제조한 화합물(150mg, 0.34mmol) 및 PtO₂(30mg, 0.13mmol)의 혼합물을 H₂ 1기압하에 20시간 동안 교반하였다. 혼합물을 여과하고 신선한 PtO₂(30mg, 0.13mmol)을 가하고 혼합물을 H₂ 1기압하에 2.5시간 동안 교반하였다. 혼합물을 Na₂CO₃(20g) 및 H₂O(200mL) 속에 붓고 이를 CH₂Cl₂(4 x 20mL)로 추출하였다. 합한 추출물을 Na₂SO₄ 위에서 건조시키고 여과하였다. 용매를 증발시키고 잔사를 용출제로서 1:1 CH₂Cl₂:EtOAc를 사용하는 플래쉬 크로마토그래피로 정제하여 황색 왁스상 고체(68mg, 45%)를 수득하였다.

[0946] 단계 C:

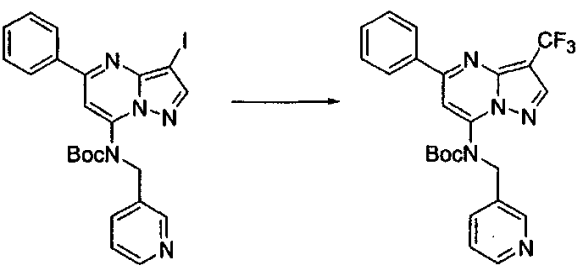


[0947]

[0948] 실시예 426, 단계 B에서 제조한 화합물을 대체시키는 것을 제외하고는 실시예 425, 단계 B에 나타난 바와 본질적으로 동일한 과정으로, 상기한 화합물을 제조하였다. MS: MH⁺ = 344. Mp = 110-112°C.

[0949] 실시예 427:

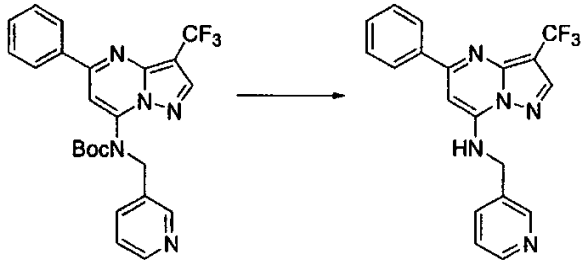
[0950] 단계 A:



[0951]

[0952] 무수 DMF(4mL) 중의 제조 실시예 194에서 제조한 화합물(527mg, 1.00mmol), 트리에틸(트리플루오로메틸)실란(666mg, 3.60mmol), 불화칼륨(210mg, 3.60mmol) 및 CuI(850mg, 4.46mmol)의 혼합물을 80° C에서 72시간 동안 폐쇄 압력 용기 속에서 교반하였다. CH₂Cl₂(80mL)를 가하고 혼합물을 셀라이트를 통해 여과하였다. 용매를 증발시키고 잔사를 용출제로서 2:1 CH₂Cl₂:EtOAc를 사용하는 플래쉬 크로마토그래피로 정제하여 담황색 왁스상 고체(70mg, 15%)를 수득하였다. LCMS: M⁺ = 470.

[0953] 단계 B:

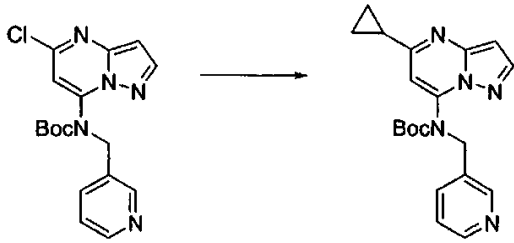


[0954]

[0955] TFA(0.70mL)를 0℃에서 N₂하에 무수 CH₂Cl₂(3mL) 중의 실시예 427, 단계 A에서 제조한 화합물의 교반된 용액에 가하였다. 혼합물을 0℃에서 10분 동안 교반한 다음, 25℃에서 2시간 동안 교반하였다. 이를 10% 수성 Na₂CO₃(50mL) 속으로 넣고, CH₂Cl₂(3 x 15mL)로 추출하고, Na₂SO₄ 위에서 건조시키고, 여과하였다. 용매를 증발시키고 잔사를 용출제로서 EtOAc를 사용하는 플래쉬 크로마토그래피함으로써 정제하여 희백색 고체(40mg, 73%)를 수득하였다. LCMS: M⁺=370. Mp = 156-158 °C.

[0956] 실시예 428:

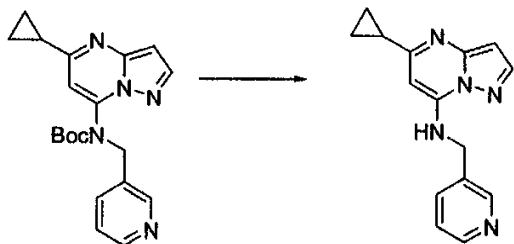
[0957] 단계 A:



[0958]

[0959] 무수 디옥산(3mL) 중의 제조 실시예 193에서 제조한 화합물(100mg, 0.28mmol), 테트라사이클로프로필틴(91mg, 0.32mmol), Pd₂dba₃(8.0mg, 0.009mmol) 및 Pd(PT-Bu₃)₂(9.0mg, 0.017mmol)의 혼합물을 N₂하에 27시간 동안 환류시켰다. 용매를 증발시키고 잔사를 용출제로서 1:1 CH₂Cl₂:EtOAc를 사용하는 플래쉬 크로마토그래피로 정제하여 무색 왁스상 고체(38mg, 38%)를 수득하였다. LCMS:MH⁺ = 366.

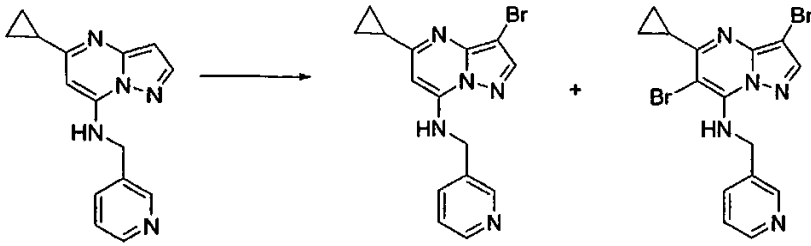
[0960] 단계 B:



[0961]

[0962] 에탄올(3mL), 1,2-디메톡시에탄(3.0mL) 및 H₂O(0.8mL) 중의 실시예 428, 단계 A에서 제조한 화합물(36mg, 0.10mmol) 및 KOH(300mg, 5.40mmol)의 혼합물을 N₂하에 4시간 동안 환류시켰다. 이를 포화된 수성 NaHCO₃(100mL) 속으로 부어넣고, CH₂Cl₂(5 x 10mL)로 추출시키고, Na₂SO₄ 위에서 건조시키고 여과하였다. 용매를 증발시키고 잔사를 용출제로서 30:1 EtOAc:MeOH를 사용하는 플래쉬 크로마토그래피함으로써 정제하여 무색 왁스(18mg, 69%)를 수득하였다. LCMS: MH⁺=266.

[0963] 단계 C:

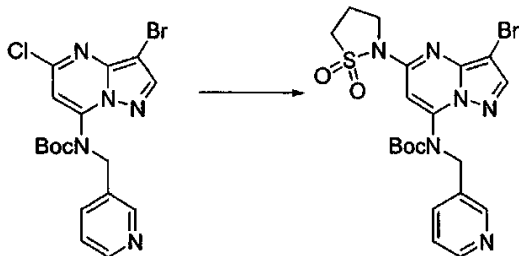


[0964]

[0965] 무수 CH_3CN (2mL) 중의 N-브로모석신이미드(12mg, 0.068mmol)를 N_2 하에 실시예 428, 단계 B(18mg, 0.068mmol)에서 제조한 화합물의 교반 용액에 가하였다. 혼합물을 25°C 에서 2시간 동안 교반하였다. 용매를 증발시키고 잔사를 용출제로서 EtOAc를 사용하는 플래쉬 크로마토그래피함으로써 정제하여 디브로모 화합물 5mg(17%)(백색 고체, LCMS: $\text{M}^+ = 370$, mp= $150\text{-}152^\circ\text{C}$) 및 모노브로모 화합물 8 mg(34%)(무색 고체, LCMS: $\text{M}^+ = 344$, mp = $196\text{-}198^\circ\text{C}$)를 수득하였다.

[0966] 실시예 429:

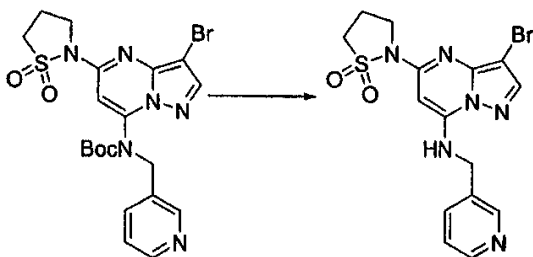
[0967] 단계 A:



[0968]

[0969] 무수 DMF(3mL) 중의 1,3-프로판설파(72mg, 0.60mmol)을 N_2 하에 무기 오일(36mg, 0.90mmol) 중의 60% NaH에 가하였다. 혼합물을 20분 동안 교반한 다음, 제조 실시예 196에서 제조한 화합물(200mg, 0.46mmol)을 가하였다. 혼합물을 100°C 에서 30분 동안 교반하고, 용매를 증발시키고 잔사를 용출제로서 EtOAc를 사용하는 플래쉬 크로마토그래피함으로써 정제하여 무색 고체(150mg, 63%)을 수득하였다. LCMS : $\text{M}^+=523$.

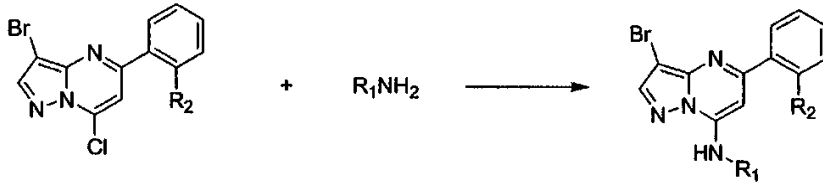
[0970] 단계 B:



[0971]

[0972] TFA(1.5mL)를 N_2 하에 0°C 에서 무수 CH_2Cl_2 (5mL) 중의 제조 실시예 196에서 제조한 화합물(140mg, 0.27mmol)의 교반된 용액에 가하였다. 혼합물을 0°C 에서 10분 동안 교반한 다음, 25°C 에서 2시간 동안 교반하였다. 이를 Na_2CO_3 (10g)에 부어 넣고, CH_2Cl_2 (3 x 50mL)로 추출하고 여과하였다. 용매를 증발시키고 잔사를 용출제로서 40:1 EtOAc:MeOH를 사용하는 플래쉬 크로마토그래피로 정제하여 백색 고체(32mg, 28%)를 수득하였다. LCMS: $\text{M}^+ = 423$. Mp = $218\text{-}220^\circ\text{C}$.

[0973] 실시예 430:

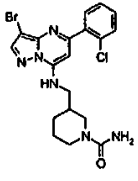
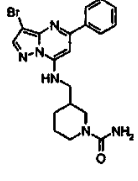
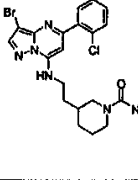
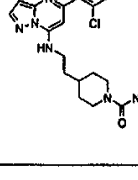
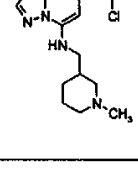


[0974] Where: R₂=H, or Cl

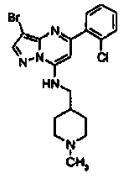
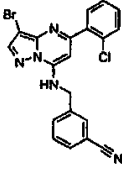
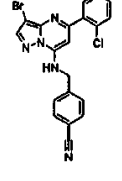
[0975] 3-브로모-7-클로로-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘(1 당량)(제조 실시예 129에 기술된 바와 같이 제조함), 또는 3-브로모-7-클로로-5-페닐피라졸로[1,5-a]피리미딘(1 당량)(제조 실시예 127에 기술된 바와 같이 제조함), R₁NH₂(1.2 당량) 및 디이소프로필 에틸아민(2 당량)을 무수 1,4-디옥산에 용해시키고 혼합물을 75° C 에서 표 97에 나타낸 시간 동안 가열하였다. 용액을 증발 건조시키고 잔사를 표 97에 기술된 바와 같이 실리카 겔 컬럼 상에서 크로마토그래피하여 표제 화합물을 수득하였다.

[0976] 상기한 바와 본질적으로 동일한 과정과 적절한 반응물을 사용하여, 실시예 431 내지 438의 생성물을 제조하였다. 반응 조건의 변화는 표 35에 나타내었다.

표 35

실시예	구조	MW	FABMS MH ⁺	반응 조건	수율	크로마토그래피 데이터
431		463.8	463.0	75°C / 26h	52%	15x2.5cm 0.5-2% (메탄올 중의 10% 농도 수산화 암모늄)- 디클로로메탄
432		429.3	429.2	75°C / 26h 25°C / 39h	53%	15x5cm 디클로로메탄; 1.5% (메탄올 중의 10% 농도 수산화 암모늄)- 디클로로메탄
433		477.8	477.1	75°C / 26h	48%	15x5cm 디클로로메탄; 3.5-15% (메탄올 중의 10% 농도 수산화 암모늄)- 디클로로메탄
434		477.8	477.0	75°C / 26h	50%	15x5cm 디클로로메탄; 3.5-15% (메탄올 중의 10% 농도 수산화 암모늄)- 디클로로메탄
435		434.8	434.1	75°C / 24h 25°C / 65h	53%	15x2.5cm 3% (메탄올 중의 10% 농도 수산화 암모늄)- 디클로로메탄
436		434.8	434.2	75°C / 27h	31%	15x2.5cm 3% (메탄올 중의 10% 농도 수산화 암모늄)- 디클로로메탄

[0977]

						
437		438.7	438.1	75°C / 21h 25°C / 46h	97%	15x2.5cm 0.25% (메탄올 중의 10% 농도 수산화 암모늄)- 디클로로메탄
438		438.7	438.1	75°C / 28h -20°C / 72h	95%	60x2.5cm hexan 중의 20% 에틸 아세테이트

[0978]

[0979]

화합물에 대한 추가의 물리적 데이터를 다음에 나타내었다:

[0980]

실시예 431: 반응물: 3-브로모-7-클로로-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘(110mg, 0.318mmol)(제조 실시예 129에 기술된 바와 같이 제조함); 3-(아미노메틸)피페리딘-1-카복사아미드(60mg, 0.382mmol)(상기한 제조 실시예 241에 기술된 바와 같이 제조함); 디이소프로필 에틸아민(0.111mL, 0.636mmol); 무수 1,4-디옥산(2.5mL). 물리적 특성:

HRFABMS: m/z 463.0628 (MH⁺). Calcd. for C₁₉H₂₁N₆OBrCl: m/z

463.0649: δ_H (CDCl₃) 1.38 (1H, m, CH₂), 1.52 (1H, m, CH₂), 1.73 (1H, m, CH), 1.93 (1H, m, CH₂), 2.02 (1H, m, CH₂), 2.98 (1H, m, CH₂), 3.06 (1H, m, CH₂), 3.37 (2H, m, CH₂), 3.58 (1H, m, CH₂), 3.82 (1H, m, CH₂), 4.87 (2H, bm, CONH₂), 6.28 (1H, s, H₆), 7.02 (1H, m, NH), 7.36 (2H, m, Ar-H), 7.45 (1H, m, Ar-H), 7.68 (1H, m, Ar-H) 및 8.00 ppm (1H, s, H₂); δ_C (CDCl₃) CH₂: 23.7, 28.1, 44.6, 45.5, 47.2; CH: 35.2, 87.4, 127.2, 130.1, 130.3, 131.6, 143.9; C: 83.1, 132.1, 138.6, 145.5, 146.5, 158.0, 158.4.

[0981]

[0982]

실시예 432: 반응물: 3-브로모-7-클로로-5-(페닐)피라졸로[1,5-a]피리미딘(500mg, 1.62mmol)(제조 실시예 127에 기술된 바와 같이 제조함); 3-(아미노에틸)피페리딘-1-카복사아미드(306mg, 1.944mmol)(상기한 제조 실시예 241에 기술된 바와 같이 제조함); 디이소프로필 에틸아민(0.566mL, 3.24mmol); 무수 1,4-디옥산(13mL). 물리적 특성:

HRFABMS:

m/z 429.1031 (MH⁺). Calcd. for C₁₉H₂₂N₆OBr: m/z 429.1038; δ_H (CDCl₃) 1.44 (1H, m, CH₂), 1.59 (1H, m, CH₂), 1.79 (1H, m, CH), 2.01 (1H, m, CH₂), 2.08 (1H, m, CH₂), 3.03 (1H, m, CH₂), 3.13 (1H, m, CH₂), 3.39 (1H, m, CH₂), 3.47 (1H, m, CH₂), 3.63 (1H, m, CH₂), 3.90 (1H, m, CH₂), 4.88 (2H, bm, CONH₂), 6.40 (1H, s, H₆), 6.90 (1H, m, NH), 7.53 (2H, m, Ar-H), 8.02 (1H, s, H₂) 및 8.12 (1H, m, Ar-H); δ_C (CDCl₃) CH₂: 23.7, 28.2, 44.7, 45.5, 47.3; CH: 35.2, 82.9, 127.5, 127.5, 128.7, 128.7, 130.0, 143.9; C: 83.0, 138.5, 145.8, 147.1, 158.3, 158.5.

[0983]

[0984] 실시예 433: 반응물: 3-브로모-7-클로로-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘(347mg, 1.01mmol)(제조 실시예 129에 기술된 바와 같이 제조함); 3-(아미노에틸)피페리딘-1-카복사미드(208mg, 1.21mmol)(상기한 제조 실시예 242에 기술된 바와 같이 제조함); 디이소프로필 에틸아민(0.393mL, 2.02mmol); 무수 1,4-디옥산(9mL). 물리적 특성:

δ_H (CDCl₃) 1.24 (1H, m, CH₂), 1.55 (1H, m, CH), 1.72 (4H, m, CH₂), 1.93 (1H, m, CH₂), 2.69 (1H, m, CH₂), 2.94 (1H, m, CH₂), 3.55 (2H, m, CH₂), 3.73 (1H, m, CH₂), 3.98 (1H, m, CH₂), 4.83 (2H, bm, CONH₂), 6.55 (1H, s, H₆), 6.78 (1H, m, NH), 7.41 (2H, m, Ar-H), 7.50 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) 및 8.04 ppm (1H, s, H₂); δ_C (CDCl₃) CH₂: 24.6, 30.7, 32.6, 39.9, 45.3, 49.3; CH: 33.3, 87.5, 127.4, 130.1, 130.2, 131.6, 143.8; C: 83.2, 132.1, 138.8, 145.7, 146.2, 158.1, 158.1.

[0985]

[0986] 실시예 434: 반응물: 3-브로모-7-클로로-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘(275mg, 0.803mmol)(제조 실시예 129에 기술된 바와 같이 제조함); 4-(아미노에틸)피페리딘-1-카복사미드(165mg, 0.963mmol)(상기한 제조 실시예 243에 기술된 바와 같이 제조함); 디이소프로필 에틸아민(0.311mL, 0.963mmol); 무수 1,4-디옥산(7.2mL). 물리적 특성:

δ_H (d₆-DMSO) 1.00 (2H, m, CH₂), 1.50 (1H, m, CH), 1.59 (2H, m, CH₂), 1.67 (2H, m, CH₂), 2.60 (2H, m, CH₂), 3.48 (2H, m, CH₂), 3.70 (2H, m, CH₂), 5.84 (2H, bs, CONH₂), 6.43 (1H, s, H₆), 7.50 (2H, m, Ar-H), 7.62 (2H, m, Ar-H), 8.30 (1H, s, H₂) 및 8.36 ppm (1H, m, NH); δ_C (d₆-DMSO) CH₂: 31.5, 31.5, 34.8, 43.5, 43.5, 43.5; CH: 32.8, 86.8, 127.1, 129.7, 130.3, 131.0, 143.3; CH: 81.3, 131.0, 138.7, 145.1, 146.4, 157.3, 157.8.

[0987]

[0988] 실시예 435: 반응물: 3-브로모-7-클로로-5-페닐피라졸로[1,5-a]피리미딘(174mg, 0.507mmol)(제조 실시예 129에 기술된 바와 같이 제조함); 3-(아미노에틸)-1-메틸피페리딘(65mg, 0.507mmol)(상기한 제조 실시예 244에 기술된 바와 같이 제조함); 디이소프로필 에틸아민(0.178mL, 1.014mmol); 무수 1,4-디옥산(2.5mL). 물리적 특성:

HRFABMS:

m/z 434.0742 (MH⁺). Calcd. for C₁₉H₂₂N₅BrCl: m/z 434.0747; δ_H (CDCl₃) 1.18 (1H, m, CH₂), 1.68 (1H, m, CH₂), 1.80 (1H, m, CH₂), 1.87 (1H, m, CH₂), 1.96 (1H, m, CH), 2.14 (2H, m, CH₂), 2.32 (3H, s, NCH₃), 2.75 (1H, m, CH₂), 2.29 (1H, m, CH₂), 3.42 (2H, m, -NHCH₂CH), 6.36 (1H, s, H₆), 6.64 (1H, bm, NH), 7.41 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.74 (1H, m, Ar-H) 및 8.06 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 46.6; CH₂: 24.4, 27.9, 46.1, 56.1, 59.6; CH: 36.0, 87.4, 127.1, 130.1, 130.2, 131.6, 143.8; C: 83.2, 132.1, 138.9, 145.6, 146.4, 158.2.

[0989]

[0990] 실시예 436: 반응물: 3-브로모-7-클로로-5-페닐피라졸로[1,5-a]피리미딘(111.4mg, 0.325mmol)(제조 실시예 129에 기술된 바와 같이 제조함); 4-(아미노에틸)-1-메틸피페리딘(50mg, 0.39mmol)(상기한 제조 실시예 245에 기술된 바와 같이 제조함); 디이소프로필 에틸아민(0.1135mL, 0.65mmol); 무수 1,4-디옥산(1.5mL). 물리적 데이터:

HRFABMS: m/z

434.0735 (MH⁺). Calcd. for C₁₉H₂₂N₅BrCl: m/z 434.0747; δ_H (CDCl₃) 1.42 (2H, m, CH₂), 1.72 (1H, m, CH), 1.82 (2H, m, CH₂), 1.93 (2H, m, CH₂), 2.20 (3H, s, NCH₃), 2.89 (2H, m, CH₂), 3.34 (2H, m, -NHCH₂CH), 6.31 (1H, s, H₆), 6.46 (1H, m, NH), 7.36 (2H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.70 (1H, m, Ar-H) 및 8.00 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 46.4; CH₂: 30.2, 30.2, 48.0, 55.3, 55.3; CH: 35.4, 87.5, 127.2, 130.2, 130.2, 131.6, 143.8; C: 83.3, 132.2, 138.9, 145.7, 146.4, 158.1.

[0991]

[0992]

실시예 437: 반응물: 3-브로모-7-클로로-5-페닐피라졸로[1,5-a]피리미딘(191mg, 0.557mmol)(제조 실시예 129에 기술된 바와 같이 제조함); 3-(아미노메틸)벤즈니트릴(88.3mg, 0.668mmol)(상기한 제조 실시예 246에 기술된 바와 같이 제조함); 디이소프로필 에틸아민(0.192ml, 1.114mmol); 무수 1,4-디옥산(4.5mL). 물리적 특성:

HRFABMS: m/z

438.0125 (MH⁺). Calcd. for C₁₉H₁₂N₅BrCl: m/z 438.0121; δ_H (CDCl₃) 4.76 (2H, d, -CH₂NH-), 6.32 (1H, s, H₆), 7.00 (1H, m, -CH₂NH-), 7.40 (2H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.55 (1H, m, Ar-H), 7.67 (2H, m, Ar-H), 7.71 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) 및 8.10 ppm (1H, s, H₂); δ_C (CDCl₃) CH₂: 45.5; CH: 88.2, 127.2, 130.0, 130.2, 130.4, 130.6, 131.4, 131.6, 131.9, 144.1; C: 83.8, 113.4, 118.3, 132.0, 137.8, 138.3, 145.6, 145.9, 158.0.

[0993]

[0994]

실시예 438: 반응물: 3-브로모-7-클로로-5-페닐피라졸로[1,5-a]피리미딘(233.5mg, 0.681mmol)(제조 실시예 129에 기술된 바와 같이 제조함); 4-(아미노메틸)벤즈니트릴(108mg, 0.817mmol)(상기한 제조 실시예 247에 기술된 바와 같이 제조함); 디이소프로필 에틸아민(0.235ml, 1.362mmol); 무수 1,4-디옥산(5.3mL). 물리적 데이터:

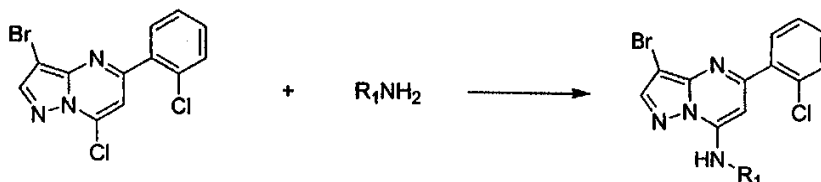
HRFABMS: m/z

438.0117 (MH⁺) Calcd. for C₂₀H₁₄N₅BrCl: m/z 438.0121; δ_H (CDCl₃) 4.80 (2H, d, CH₂), 6.30 (1H, s, H₆), 7.01 (1H, m, NH), 7.40 (2H, m, Ar-H), 7.47 (1H, m, Ar-H), 7.70 (2H, m, Ar-H), 7.72 (2H, m, Ar-H), 7.80 (1H, m, Ar-H) 및 8.10 ppm (1H, s, H₂); δ_C (CDCl₃) CH₂: 45.8; CH: 88.2, 127.2, 127.7, 127.7, 130.2, 130.4, 131.6, 132.9, 132.9, 144.1; C: 83.8, 112.2, 118.4, 132.0, 138.2, 141.5, 145.5, 146.0, 158.0.

[0995]

[0996]

실시예 439:



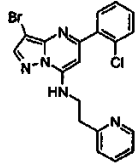
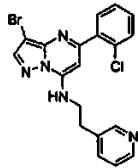
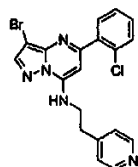
[0997]

[0998]

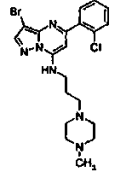
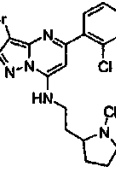
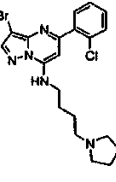
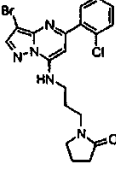
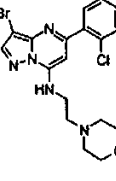
3-브로모-7-클로로-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘(50mg, 0.146mmol)(제조 실시예 129에 기술된 바와 같이 제조함)을 젠박 테크놀로지스 카로우셀 반응 튜브(GeneVac Technologies carousel reaction tube) 속의 무수 디옥산(5mL)에 용해시켰다. PS-디이소프로필 에틸아민 수지(161mg, 0.5828mmol)을 각각의 튜브에 가하였다. 무수 1,4-디옥산(0.2185mL, 0.2185mmol)중의 적합한 아민 R₁NH₂의 새롭게 제조한 1M 용액을 각각의 튜브에 가하고 튜브를 밀봉하고 반응 블록 속에서 자기 교반하면서 70℃에서 78시간 동안 가열하였다. 각각의 튜브를 여과하고 수지를 무수 1,4-디옥산으로 세척한 다음 디클로로메탄으로 세척하였다. 각각의 튜브로부터의 합한 개개 여액을 증발 건조시키고 잔사를 무수 1,4-디옥산(5mL)에 각각 재용해시키고 젠박 반응 튜브 속에 위치시켰다. 각각의 튜브에 PS-이소시아네이트 수지(594mg, 0.8742mmol) 및 PS-트리시아민 수지(129mg, 0.4371mmol)을

가하고 튜브를 25℃에서 20시간동안 반응 블록속에서 교반하였다. 수지를 여과하고 무수 1,4-디옥산 및 디클로로메탄으로 세척하였다. 각각의 튜브로부터의 여액을 증발건조시키고 잔사를 표 36에 나타낸 컬럼 크기 및 용출제를 사용하는 실리카겔 컬럼상에서 각각 크로마토그래피하여 표제 화합물을 수득하였다.

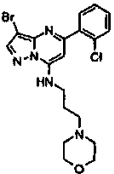
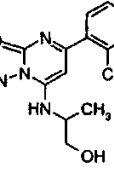
표 36

실시예	구조	MW	FABMS MH ⁺	수율	크로마토그래피 데이터
440		428.7	428.0	81%	15x2.5cm 디클로로메탄; 디클로로메탄 중의 0.5% 메탄올
441		428.7	428.0	48%	20x2cm 디클로로메탄; 디클로로메탄 중의 1.5% 메탄올
442		428.7	428.0	24%	15x2.5cm 디클로로메탄; 디클로로메탄 중의 1.5% 메탄올

[0999]

443		463.8	463.0	44%	15x2.2cm 디클로로메탄; 디클로로메탄 중의 5% 메탄올
444		434.8	434.1	63%	15x2.5cm 디클로로메탄; 디클로로메탄 중의 5% 메탄올
445		448.8	448.2	65%	15x2.5cm 디클로로메탄; 디클로로메탄 중의 5% 메탄올
446		448.8	448.1	40%	15x2.5cm 디클로로메탄; 디클로로메탄 중의 0.5% 메탄올
447		436.7	436.1	72%	15x2.5cm 디클로로메탄; 디클로로메탄 중의 0.5% 메탄올

[1000]

448		450.8	450.0	53%	20x2cm 디클로로메탄; 디클로로메탄 중의 0.5% 메탄올
449		381.7	381.0	44%	20x2cm 디클로로메탄; 디클로로메탄 중의 1.5% 메탄올

[1001]

[1002]

화합물에 대한 추가의 물리학적 데이터를 하기에 나타낸다:

실시예 **440**: 물리적 특성 : HRFABMS: m/z 428.0272 (MH⁺). Calcd. for C₁₉H₁₆N₅BrCl: m/z 428.0278; δ_H (CDCl₃) 3.28 (2H, dd, C₅H₄NCH₂CH₂NH-), 3.94 (2H, ddd, C₅H₄NCH₂CH₂NH-), 6.40 (1H, s, H₆), 7.22-7.29 (3H, m, Ar-H), 7.38-7.44 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.68 (1H, ddd, Ar-H), 7.73 (1H, Ar-H), 8.18 (1H, s, H₂) 및 8.68ppm (1H, NH); δ_C (CDCl₃) CH₂: 36.4, 41.5; CH: 87.3, 122.1, 123.6, 127.1, 130.1, 130.1, 131.6, 137.0, 143.8, 149.5; C: 83.1, 132.1, 138.9, 145.7, 146.3, 158.0, 158.1.

실시예 **441**: 물리적 특성 : HRFABMS: m/z 428.0272 (MH⁺). Calcd. for C₁₉H₁₆N₅BrCl: m/z 428.0278; δ_H (CDCl₃) 3.12 (2H, dd, C₅H₄NCH₂CH₂NH-), 3.77 (2H, ddd, C₅H₄NCH₂CH₂NH-), 6.40 (1H, s, H₆), 6.59 (1H, m, Ar-H), 7.34 (1H, bm, Ar-H), 7.39-7.45 (2H, m, Ar-H), 7.52 (1H, m, Ar-H), 7.62 (1H, m, Ar-H), 7.75 (1H, m, Ar-H), 8.05 (1H, s, H₂) 및 8.63ppm (1H, m, NH); δ_C (CDCl₃) CH₂: 32.7, 43.1; CH: 87.5, 127.2, 130.2, 130.3, 131.6, 136.4, 142.9, 148.3, 149.8; C: 83.5, 132.0, 138.6, 145.6, 145.9, 158.1.

실시예 **442**: 물리적 특성 : HRFABMS: m/z 428.0275 (MH⁺). Calcd. for C₁₉H₁₆N₅BrCl: m/z 428.0278; δ_H (CDCl₃) 3.13 (2H, dd, C₅H₄NCH₂CH₂NH-), 3.80 (2H, ddd, C₅H₄NCH₂CH₂NH-), 6.42 (1H, s, H₆), 6.53 (1H, m, Ar-H), 7.23 (2H, m, Ar-H), 7.40-7.46 (2H, m, Ar-H), 7.62 (1H, m, Ar-H), 7.76 (1H, m, Ar-H), 8.07 (1H,

[1003]

s, H₂) 및 8.63ppm (1H, m, NH); δ_C (CDCl₃) CH₂: 34.7, 42.5; CH: 87.4, 124.5, 124.5, 127.2, 130.2, 130.3, 131.6, 144.0, 150.2, 150.2; C: 83.5, 132.0, 138.6, 145.6, 145.9, 146.6, 158.1.

실시예 443: 물리적 특성 : HRFABMS: m/z 463.1003 (MH⁺). Calcd. for C₂₀H₂₅N₆BrCl: m/z 463.1013; δ_H (CDCl₃) 1.98 (2H, m, =NCH₂CH₂CH₂NH-), 2.43 (3H, s, NCH₃), 2.67 (2H, m, =NCH₂CH₂CH₂NH-), 2.70 (8H, piperazine CH₂), 3.58 (2H, m, =NCH₂CH₂CH₂NH-), 6.32 (1H, s, H₆), 7.37-7.43 (2H, m, Ar-H), 7.50 (1H, m, Ar-H), 7.73 (1H, m, Ar-H), 8.06 (1H, s, H₂) 및 8.60ppm (1H, m, NH); δ_C (CDCl₃) CH₃: 46.1; CH₂: 24.1, 42.8, 53.3, 54.6, 54.6, 57.5, 57.5; CH: 87.1, 127.0, 130.0, 130.1, 131.5, 143.4; C: 82.7, 132.1, 139.2, 145.7, 146.7, 158.0.

실시예 444: 물리적 특성 : HRFABMS: m/z 434.0742 (MH⁺). Calcd. for C₁₉H₂₂N₅BrCl: m/z 434.0747; δ_H (CDCl₃) 1.72 (1H, m, CH/CH₂), 1.78-1.90 (2H, m, CH/CH₂), 2.02 (3H, m, CH/CH₂), 2.50 (1H, m, CH/CH₂), 2.45 (3H, s, NCH₃), 2.51 (1H, m, CH/CH₂), 3.23 (1H, m, CH/CH₂), 3.54 (1H, m, CH/CH₂), 3.60 (1H, m, CH/CH₂), 6.32 (1H, s, H₆), 7.38-7.44 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.75 (1H, m, Ar-H), 7.96 (1H, bm, NH) 및 8.05 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 40.7; CH₂: 22.7, 29.3, 30.1, 39.4, 57.0; CH: 64.2, 87.1, 127.1, 130.0, 130.1, 131.6, 143.8; C: 82.8, 132.1, 139.1, 145.7, 146.4, 158.0.

실시예 445: 물리적 특성 : HRFABMS: m/z 448.0910 (MH⁺). Calcd. for C₂₀H₂₄N₅BrCl: m/z 448.0904; δ_H (CDCl₃) 1.90 (4H, m, CH₂), 2.00 (4H, m, CH₂), 2.84 (2H, m, CH₂), 2.95 (4H, m, CH₂), 3.51 (2H, m, CH₂), 6.32 (1H, s, H₆), 7.05 (1H, bm, NH), 7.37-7.43 (2H, m, Ar-H), 7.50 (1H, m, Ar-H), 7.73 (1H, m, Ar-H) 및 8.04 ppm (1H, s, H₂); δ_C (CDCl₃) CH₂: 23.4, 23.4, 24.8, 26.4, 41.8, 53.9, 53.9, 55.2; CH: 87.3, 127.1, 130.1, 130.2, 131.6, 143.7; C: 83.0, 132.0, 138.9, 145.7, 146.3, 158.1.

실시예 446: 물리적 특성 : HRFABMS: m/z 448.0548 (MH⁺). Calcd. for C₁₉H₂₀N₅OBrCl: m/z 448.0540; δ_H (CDCl₃) 1.94 (2H, m, CH₂), 2.09 (2H, m, CH₂), 2.49 (2H, m, CH₂), 3.45 (2H, m, CH₂), 3.51 (4H, m, CH₂), 6.32 (1H, s, H₆), 7.37-7.44 (3H, m, Ar-H/NH), 7.51 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) 및 8.10 ppm

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(1H, s, H₂); δ_C (CDCl₃) CH₂: 18.0, 26.3, 30.8, 39.2, 39.9, 47.5; CH: 87.0, 127.1, 130.1, 130.1, 131.6, 144.1; C: 82.9, 132.1, 138.9, 145.6, 146.2, 157.9, 176.2.

실시예 447: 물리적 특성 : HRFABMS: m/z 436.0532 (MH⁺). Calcd. for C₁₈H₂₀N₅OBrCl: m/z 436.0540; δ_H (CDCl₃) 2.60 (4H, bm, -N(CH₂CH₂)₂O), 2.83 (2H, m, =NCH₂CH₂NH-), 3.57 (2H, m, =NCH₂CH₂NH-), 3.83 (4H, m, -N(CH₂CH₂)₂O), 6.37 (1H, s, H₆), 6.99 (1H, bm, NH), 7.38-7.45 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) 및 8.09 ppm (1H, s, H₂); δ_C (CDCl₃) CH₂: 38.2, 53.3, 53.3, 56.2, 66.9, 66.9; CH: 87.6, 127.1, 130.1, 130.2, 131.6, 143.9; C: 83.1, 132.1, 138.9, 145.7, 146.2, 158.1.

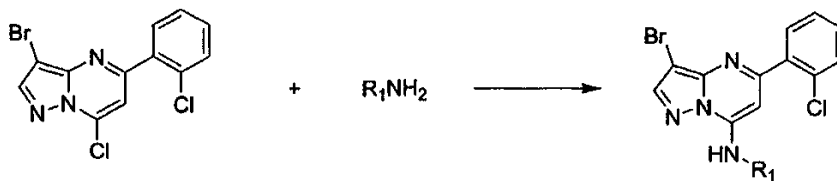
실시예 448: 물리적 특성 : HRFABMS: m/z 450.0688 (MH⁺). Calcd. for C₁₉H₂₂N₅OBrCl: m/z 450.0696; δ_H (CDCl₃) 1.98 (2H, m, =NCH₂CH₂CH₂NH-), 2.58 (4H, m, -N(CH₂CH₂)₂O), 2.67 (2H, m, =NCH₂CH₂CH₂NH-), 3.59 (2H, m, =NCH₂CH₂CH₂NH-), 3.94 (4H, m, -N(CH₂CH₂)₂O), 6.31 (1H, s, H₆), 7.37-7.44 (2H, Ar-H), 7.51 (1H, m, Ar-H), 7.78 (1H, m, Ar-H), 8.08 (1H, s, H₂) 및 8.60 ppm (1H, bm, NH); δ_C (CDCl₃) CH₂: 23.7, 42.7, 52.9, 52.9, 58.0, 66.6, 66.6; CH: 87.0, 127.1, 130.0, 130.1, 131.5, 143.6; C: 82.8, 132.1, 139.1, 145.7, 146.7, 158.0.

실시예 449: 물리적 특성 : HRFABMS: m/z 381.0114 (MH⁺). Calcd. for C₁₅H₁₅N₄OBrCl: m/z 381.0118; δ_H (CDCl₃) 1.39 (3H, d, CHCH₃), 2.76 (1H, bm, -OH), 3.71 (1H, m, =CHCH₂OH), 3.81 (1H, m, =CHCH₂OH), 3.88 (1H, m, =CHCH₂OH), 6.38 (1H, s, H₆), 7.38 (2H, m, Ar-H), 7.48 (1H, m, Ar-H), 7.68 (1H, m, Ar-H) 및 8.02 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 16.9; CH₂: 65.0; CH: 50.0, 88.0, 127.1, 130.1, 130.3, 131.4, 143.8; C: 83.0, 132.0, 138.5, 145.6, 146.0, 158.2.

[1005]

[1006]

실시예 450:



[1007]

[1008]

3-브로모-7-클로로-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘(50mg, 0.146mmoles)(제조 실시예 129에 기술된 바와같이 제조)를 젠백 테크놀로지스 카로우젤(GeneVac Technologies carousel) 반응 튜브속에서 무수 1,4-디옥산(5mL)속에 용해하였다. PS-다이소프로필 에틸아민 수지(161mg, 0.5828mmoles)을 각각의 튜브에 가하였다. 무수 1,4-디옥산(0.3mL)중 적절한 아민 R₁NH₂(0.219mmoles)의 새로이 제조한 용액을, 아민을 1,4-디옥산(0.3mL)중 10% MeOH속에 용해시킨 실시예 99-5를 제외하고는, 각각의 튜브에 가하고, 튜브를 밀봉하고 70°C에서 74시간 동안 반응 블록속에서 자기 교반하면서 가열시킨다. 각각의 튜브를 여과하고 수지를 무수 1,4-디옥산으로 세척한 후 디클로로메탄으로 세척하였다. 각각의 튜브로부터 합한 개개의 여액을 증발 건조시키고 잔사를 각각 무수 1,4-디옥산(5mL)속에 재용해시키고 젠백 반응 튜브속에 위치시켰다. 각각의 튜브에 PS-이소시아네이트 수지(594mg, 0.8742mmoles) 및 PS-트리아민 수지(129mg, 0.4371mmoles)를 가하고 튜브를 25°C에서 20시간 동안 반응 블록속에서 교반하였다. 수지를 여과제거하고 무수 1,4-디옥산 및 디클로로메탄으로 세척하였다. 각각의 튜브로부터의 여액을 증발건조시키고 잔사를 표 37에 나타난 컬럼 크기 및 용출제를 사용하는 실리카 겔 컬럼상

에서 각각 크로마토그래피하여 표제 화합물을 수득하였다.

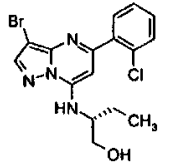
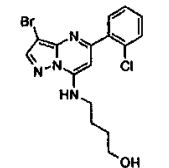
표 37

실시예	구조	MW	FABMS MH ⁺	수율	크로마토그래피 데이터
451		381.7	380.9	66%	15x2.5cm; 디클로로메탄 중의 0.5% 메탄올

[1009]

452		381.7	380.9	60%	20x2cm; 디클로로메탄 중의 0.5% 메탄올
453		381.7	380.9	69%	15x2.5cm; 디클로로메탄 중의 0.35% 메탄올
454		381.7	380.9	75%	15x2.5cm; 디클로로메탄 중의 0.35% 메탄올
455		397.7	397.2	84%	15x2.5cm; 디클로로메탄 중의 1.5% 메탄올
456		397.7			
457		395.7	395.0	60%	15x2.5cm; 디클로로메탄 중의 0.35% 메탄올

[1010]

458		395.7	396.3	50%	15x2.5cm; 디클로로메탄 중의 0.35% 메탄올
459		395.7	396.0	76%	15x2.5cm; 디클로로메탄 중의 0.35% 메탄올

[1011]

[1012]

화합물에 대한 추가의 물리학적 데이터를 하기에 나타낸다:

실시에 **451**: 물리적 특성 : HRFABMS: m/z 381.0115 (MH⁺). Calcd. for C₁₅H₁₅N₄OBrCl: m/z 381.0118; [α]_D^{25°C} +1.4° (c=0.25, MeOH); δ_H (CDCl₃) 1.44 (3H, d, -CHCH₃), 3.77 3.89 (1H, dd, CHCH₂OH), (1H, dd, CHCH₂OH), 3.94 (1H, m, CHCH₂OH), 6.41 (1H, s, H₆), 6.58 (1H, d, NH), 7.41 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.74 (1H, m, Ar-H) 및 8.04 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 17.1; CH₂: 65.5; CH: 49.9, 88.0, 127.1, 130.1, 130.2, 131.6, 143.8; C: 83.2, 132.1, 138.7, 145.6, 145.8, 158.1.

실시에 **452**: 물리적 특성 : HRFABMS: m/z 381.0115 (MH⁺). Calcd. for C₁₅H₁₅N₄OBrCl: m/z 381.0118; [α]_D^{25°C} +6.5° (c=0.32, MeOH); δ_H (CDCl₃) 1.44 (3H, d, -CHCH₃), 3.78 (1H, dd, CHCH₂OH), 3.89 (1H, dd, CHCH₂OH), 3.96 (1H, m, CHCH₂OH), 6.41 (1H, s, H₆), 6.58 (1H, d, NH), 7.41 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) 및 8.04 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 17.1; CH₂: 65.5; CH: 49.9, 88.0, 127.1, 130.1, 130.3, 131.6, 143.8; C: 83.2, 132.1, 138.6, 145.6, 145.8, 158.1.

실시에 **453**: 물리적 특성 : HRFABMS: m/z 381.0115 (MH⁺). Calcd. for C₁₅H₁₅N₄OBrCl: m/z 381.0118; [α]_D^{25°C} +9.4° (c=0.27, MeOH); δ_H (CDCl₃) 1.33 (3H, d, CH₃), 2.25 (1H, bs, OH), 3.37 (1H, dd, CH₂), 3.51 (1H, m, CH₂), 4.16 (1H, m, CH₂OH), 6.35 (1H, s, H₆), 6.93 (1H, m, NH), 7.40 (2H, m, Ar-H), 7.50 (1H, m,

[1013]

Ar-H), 7.70 (1H, m, Ar-H) and 8.04 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 20.8; CH₂: 49.2; CH: 65.7, 87.8, 127.1, 130.1, 130.2, 131.2, 143.9; C: 83.1, 132.1, 138.5, 145.6, 146.6, 158.3.

실시예 454: 물리적 특성 : HRFABMS: m/z 381.0112 (MH⁺). Calcd. for C₁₅H₁₅N₄OBrCl: m/z 381.0118; $[\alpha]_D^{25^\circ C}$ -3.2° (c=0.29, MeOH); δ_H (CDCl₃) 1.32 (3H, d, CH₃), 2.48 (1H, bs, OH), 3.35 (1H, dd, CH₂), 3.49 (1H, m, CH₂), 4.15 (1H, m, CHOH), 6.34 (1H, s, H₆), 6.93 (1H, m, NH), 7.39 (2H, m, Ar-H), 7.49 (1H, m, Ar-H), 7.68 (1H, m, Ar-H) 및 8.03 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 20.8; CH₂: 49.2; CH: 65.7, 87.7, 127.1, 130.1, 130.3, 131.4, 143.9; C: 83.0, 132.0, 138.6, 145.6, 146.6, 158.3.

실시예 455: 물리적 특성 : HRFABMS: m/z 397.0054 (MH⁺). Calcd. for C₁₅H₁₅N₄O₂BrCl: m/z 397.0067; $[\alpha]_D^{25^\circ C}$ -9.5° (c= 0.28, MeOH); δ_H (CDCl₃) 3.18 (2H, bs, OH), 3.47 (1H, dd, CH₂), 3.58 (1H, dd, CH₂), 3.63 (1H, dd, CH₂OH), 3.70 (1H, dd, CH₂OH), 3.98 (1H, m, CH), 6.35 (1H, s, H₆), 7.10 (1H, m, NH), 7.37 (2H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.64 (1H, m, Ar-H) 및 8.01 ppm (1H, s, H₂); δ_C (CDCl₃) CH₂: 44.7, 64.0; CH: 69.7, 87.7, 127.0, 130.1, 130.3, 131.3, 143.9; C: 82.9, 132.0, 138.4, 145.4, 146.7, 158.3.

[1014]

[1015]

실시예 456: 상기한 바와 본질적으로 동일한 과정으로 본 실시예의 거울상 이성체를 제조할 수 있다.

실시예 457: 물리적 특성 : HRFABMS: m/z 395.0260 (MH⁺). Calcd. for C₁₆H₁₇N₄OBrCl: m/z 395.0274; $[\alpha]_D^{25^\circ C}$ -34.3° (c= 0.28, MeOH); δ_H (CDCl₃) 1.08 (3H, dd, CH₃), 1.78 (1H, m, CH₂), 1.86 (1H, m, CH₂), 2.35 (1H, bs, CH₂OH), 3.71 (1H, m, CHNH), 3.81 (1H, dd, CH₂OH), 3.90 (1H, dd, CH₂OH), 6.42 (1H, s, H₆), 6.53 (1H, m, NH), 7.41 (2H, m, Ar-H), 7.51 (1H, Ar-H), 7.75 (1H, m, Ar-H) 및 8.04 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 10.5; CH₂: 24.5, 63.7; CH: 55.9, 88.0, 127.1, 130.1, 130.2, 131.6, 143.8; C: 83.2, 132.1, 138.6, 145.6, 146.3, 158.1.

[1016]

실시예 458: 물리적 특성 : HRFABMS: m/z 395.0274 (MH⁺). Calcd. for C₁₆H₁₇N₄OBrCl: m/z 395.0274; $[\alpha]_D^{25^\circ C}$ +27.5° (c= 0.25, MeOH); δ_H (CDCl₃) 1.05

(3H, dd, CH₃), 1.76 (1H, m, CH₂), 1.85 (1H, m, CH₂), 2.28 (1H, bs, CH₂OH), 3.67 (1H, m, CHNH), 3.77 (1H, dd, CH₂OH), 3.84 (1H, dd, CH₂OH), 6.49 (1H, s, H₆), 6.66 (1H, m, NH), 7.39 (2H, m, Ar-H), 7.49 (1H, Ar-H), 7.71 (1H, m, Ar-H) 및 8.04 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 10.5; CH₂: 24.3, 63.3; CH: 56.1, 88.0, 127.1, 130.1, 130.3, 131.5, 143.8; C: 83.0, 132.1, 138.6, 145.6, 146.3, 158.2.

실시예 459: 물리적 특성 : HRFABMS: m/z 395.0264 (MH⁺). Calcd. for C₁₆H₁₇N₄OBrCl: m/z 395.0274; δ_H (CDCl₃) 1.77 (2H, m, -NHCH₂CH₂CH₂CH₂OH), 1.90 (1H, bm, -NHCH₂CH₂CH₂CH₂OH), 1.93 (2H, m, -NHCH₂CH₂CH₂CH₂OH), 3.54 (2H, m, -NHCH₂CH₂CH₂CH₂OH), 3.77 (2H, m, -NHCH₂CH₂CH₂CH₂OH), 6.37 (1H, s, H₆), 6.72 (1H, m, -NHCH₂CH₂CH₂CH₂OH), 7.41 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) 및 8.06 ppm (1H, s, H₂); δ_C (CDCl₃) CH₂: 25.7, 29.7, 42.2, 62.2; CH: 87.4, 127.1, 130.1, 130.2, 131.6, 143.8; C: 83.1, 132.1, 138.8, 145.6, 146.3, 158.1.

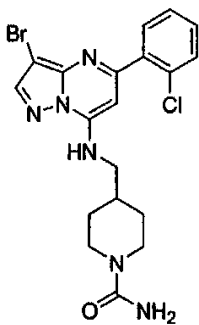
[1017]

[1018]

[1019]

실시예 460:

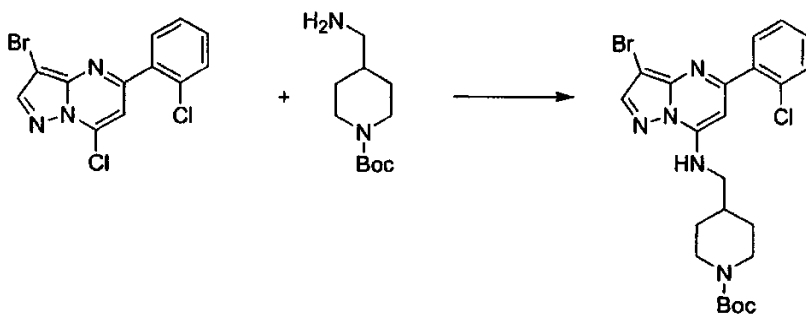
4-{[3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]메틸}피페리딘-1-카복실산 아미드:



[1020]

[1021]

A. 4-{[3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]메틸}피페리딘-1-카복실산 3급-부틸 에스테르:



[1022]

[1023]

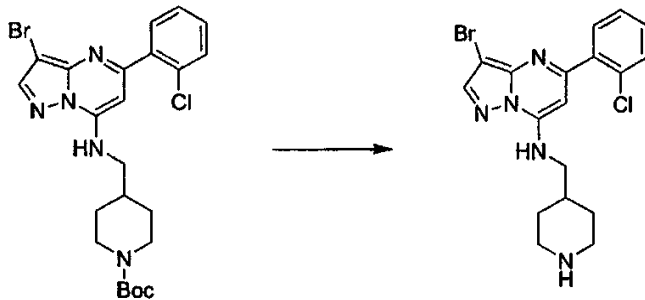
3-브로모-7-클로로-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘(300mg, 0.875mmoles)(제조 실시예 129에 기술된 바와같이 제조)을 무수 1,4-디옥산(6.8mL)속에 용해시켰다. 4-(아미노메틸)피페리딘-1-카복실산 3급-부틸 에스테르(225mg, 1.05mmoles) 및 디이소프로필 에틸아민(0.3055mL, 1.75mmoles)을 가하고 혼합물을 75°C에서 24시간 동안 가열하였다. 용액을 증발 건조시키고 잔사를 용출제로서 디클로로메탄을 사용하는 실리카 겔 컬럼(15x5cm)상에서 크로마토그래피하여 4-{[3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]메틸}피페리딘-1-카복실산 3급-부틸 에스테르(461.2mg, 100%)를 수득하였다: FABMS: m/z 520.1(MH⁺); HRFABMS: m/z 520.1111(MH⁺). C₂₃H₂₈N₅O₂BrCl에 대한 계산치: m/z 520.1115;

δ_H (CDCl₃) 1.30 (2H, m, CH₂), 1.51 (9H, s, -COOC(CH₃)₃), 1.85 (2H, d, CH₂), 1.95 (1H, m, CH), 2.76 (2H, m, CH₂), 3.40 (2H, m, CH₂), 6.37 (1H, s, H₆), 6.55 (1H, m, NH), 7.42 (2H, m, Ar-H), 7.52 (1H, m, Ar-H), 7.76 (1H, m, Ar-H) 및 8.07 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 28.5, 28.5, 28.5; CH₂: 29.1, 29.1, 43.5, 43.5, 47.9; CH: 36.3, 87.5, 127.2, 130.2, 130.3, 131.6, 143.9; C: 79.7, 83.3, 132.1, 138.6, 145.4, 146.3, 154.7, 158.1.

[1024]

[1025]

B. [3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일]피페리딘-4-일메틸아민:



[1026]

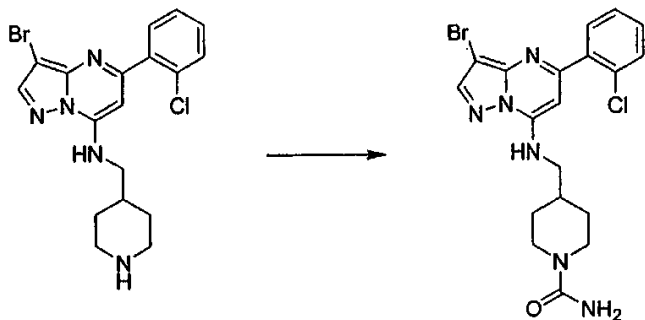
[1027]

4-([3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]메틸)피페리딘-1-카복신산 3급-부틸 에스테르(441mg, 0.847mmoles)(실시예 460, 단계 A에 기술된 바와 같이 제조)를 메탄올(4.5mL)속에 용해시키고 1,4-디옥산(1.46mL)중 10%(v/v) 진한 황산을 가하였다. 혼합물을 25℃에서 0.5시간 동안 교반하였다. 생성물을 제조 실시예 241, 단계 B에 기술된 바와 같이 후처리하고, 용출제로서 8%(메탄올중 10%의 진한 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(15x5cm)상에서 크로마토그래피하여 [3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일]피페리딘-4-일메틸아민(314.4mg, 88%)을 수득하였다: FABMS: m/z 420.0(MH⁺); HRFABMS: m/z 420.0585(MH⁺). C₁₈H₂₀N₅BrCl에 대한 계산치: m/z 420.0591;

[1028]

[1029]

C. 4-([3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]메틸)피페리딘-1-카복실산 아마이드:



[1030]

[1031]

[3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일]피페리딘-4-일메틸아민(57mg, 0.136mmoles)(실시예 460, 단계 B에서 기술한 바와 같이 제조)를 무수 디클로로메탄(1.2mL)속에 용해시키고 트리메틸실릴이소시아네이트(0.091mL, 0.679mmoles)을 가하였다. 혼합물을 25℃에서 2.5시간 동안 교반하였다. 혼합물을 디클로로메탄으로 희석시키고 포화된 수성 중탄산나트륨으로 세척하였다. 유기 층을 건조(MgSO₄)시키고, 여과하며 증발 건조시켰다. 잔사를 용출제로서 3%(메탄올중 10%의 진한 황산)-디클로로메탄을 사용하는 실리카 겔 컬럼

(30x2.5cm)상에서

크로마토그래피하여

4-([3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]메틸)피페리딘-1-카복실산 아마이드(53.7mg, 86%)를 수득하였다: FABMS: m/z 463.1(MH^+); HRFABMS: m/z 463.0647(MH^+). $C_{19}H_{21}N_6OBrCl$ 에 대한 계산치:

m/z 463.0649; δ_H (d_6 -DMSO)

1.09 (2H, m, CH_2), 1.63 (2H, m, CH_2), 1.87 (1H, m, CH), 2.60 (2H, m, CH_2), 3.53 (2H, bm, CONH₂), 3.91 (2H, d, CH_2), 6.52 (1H, s, H₆), 7.50 (2H, m, Ar-H), 7.62 (2H, m, Ar-H), 8.33 (1H, s, H₂) 및 8.52 ppm (1H, m, NH); δ_C (d_6 -DMSO) CH_2 : 30.1, 30.1, 44.2, 44.2, 47.7; CH: 36.4, 88.2, 128.1, 130.7, 131.4, 132.1, 147.9; C: 82.1, 132.1, 139.4, 145.7, 147.9, 158.1, 158.8.

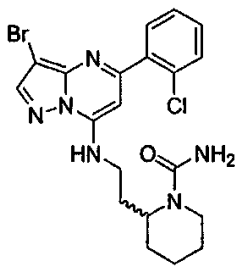
[1032]

[1033]

실시에 461:

[1034]

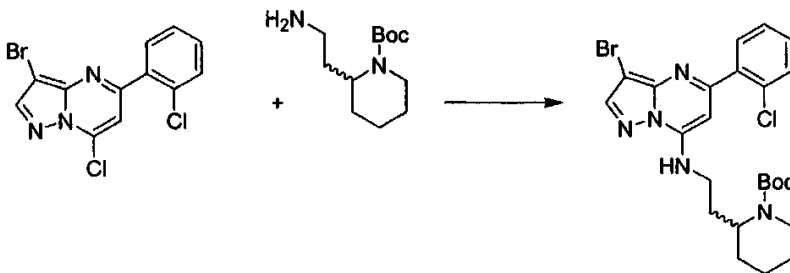
2-(2-[3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]에틸)피페리딘-1-카복실산 아마이드:



[1035]

[1036]

A. 2-(2-[3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]에틸)피페리딘-1-카복실산 3급-부틸 에스테르:



[1037]

[1038]

3-브로모-7-클로로-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘(400mg, 1.166mmoles)(제조 실시예 129에 기술된 바와 같이 제조)을 무수 1,4-디옥산(5.7mL)속에 용해시켰다. 2-아미노에틸피페리딘-1-카복실산 3급-부틸 에스테르(266mg, 1.166mmoles) 및 디이소프로필 에틸아민(0.409mL, 2.33mmoles)을 가하고 혼합물을 75°C에서 48시간 동안 가열하였다. 추가의 디이소프로필 에틸아민(0.204mL, 1.166mmoles)을 가하고 가열을 총 58시간 동안 지속하였다. 용액을 증발 건조시키고 잔사를 용출제로서 디클로로메탄에 이어 0.3%(메탄올중 10%의 진한 수산 화합물)-디클로로메탄을 사용하는 실리카 겔 컬럼(15x5cm)상에서 크로마토그래피하여 2-([3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]에틸)피페리딘-1-카복실산 3급-부틸 에스테르(491.1mg, 79%)를 수득하였다: FABMS: m/z 534.1(MH^+); HRESIMS: m/z 534.12797(MH^+). $C_{24}H_{30}N_5O_2BrCl$ 에 대한 계산치: m/z 534.12714;

δ_H ($CDCl_3$) 1.50 (1H, m, CH_2), 1.51 (9H, s, $COOC(CH_3)_3$), 1.57 (2H, m, CH_2),

1.68 (2H, m, CH_2), 1.76 (2H, m, CH_2), 2.24 (1H, bm, CH_2),

2.82/3.40/3.54/4.08/4.51 (5H, m, CH/ CH_2), 6.34 (1H, s, H₆), 7.41 (2H, m, Ar-H),

[1039]

7.51 (1H, m, Ar-H), 7.76 (1H, m, Ar-H) 및 8.08 ppm (1H, s, H₂); δ_C (CDCl₃) CH₃: 28.5, 28.5, 28.5; CH₂: 19.2, 25.5, 29.2, 29.2, 39.2, 67.1; CH: ~47.4, 87.1, 127.1, 130.1, 130.1, 131.6, 143.9; C: 80.0, 83.0, 132.1, 138.9, 145.7, 146.2, 158.0.

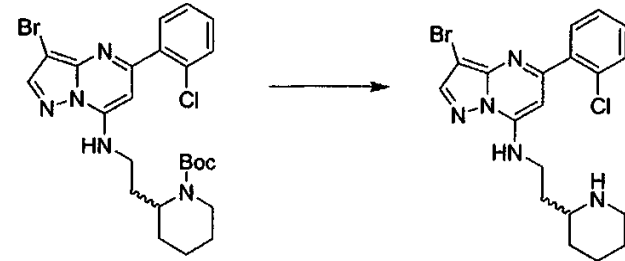
[1040]

[1041]

B. [3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일]-(2-피페리딘-2-일에틸)아민:

[1042]

[1043]



2-([3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]에틸)피페리딘-1-카복실산 3급-에스테르 (465mg, 0.869mmoles)(상기 실시예 461, 단계 A에 기술된 바와 같이 제조)를 메탄올(4.5mL)속에 용해시키고 1,4-디옥산(11.76mL)중 10%(v/v)의 진한 황산을 가하였다. 혼합물을 25℃에서 1.5시간 동안 교반하였다. 생성물을 제조 실시예 241, 단계 B에서 기술한 바와 같이 후처리하고 용출제로서 3.5%(메탄올중 10%의 진한 수산화암모늄)-디클로로메탄을 사용한 실리카 겔 컬럼(15x5cm)상에서 크로마토그래피하여 [3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일]피페리딘-2-일에틸)아민(365.6mg, 97%)을 수득하였다: FABMS: m/z 434.1(MH⁺); HRFABMS: m/z 434.0726(MH⁺). C₁₉H₂₂N₅BrCl에 대한 계산치: m/z 434.0747;

[1044]

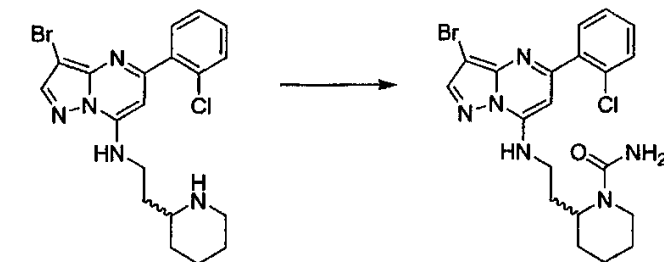
[1045]

δ_H (CDCl₃) 1.24 (1H, m, CH₂), 1.41 (1H, m, CH₂), 1.49 (1H, m, CH₂), 1.66 (1H, m, CH₂), 1.73 (1H, m, CH₂), 1.81 (1H, m, CH₂), 1.88 (2H, m, CH₂), 2.68 (1H, m, CH₂), 2.78 (1H, m, CH₂), 3.20 (1H, m, CH), 3.55 (1H, m, CH₂), 3.60 (1H, m, CH₂), 6.32 (1H, s, H₆), 7.41 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.74 (1H, m, Ar-H), 7.78 (1H, m, NH) 및 8.05 ppm (1H, s, H₂); δ_C (CDCl₃) CH₂: 24.7, 26.8, 33.1, 35.2, 40.3, 47.0; CH: 55.7, 87.2, 127.1, 130.0, 130.1, 131.5, 143.8; C: 82.9, 132.1, 139.0, 145.7, 146.5, 158.1.

C. 2-(2-[3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]에틸)피페리딘-1-카복실산 아마이드:

[1046]

[1047]



[3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일]피페리딘-2-일에틸)아민(200mg, 0.46mmoles)(상기 실시예 461, 단계 B에 기술된 바와 같이 제조)을 무수 디클로로메탄(2mL)속에 용해시키고 트리메틸실릴이소시아네이트(0.31mL, 2.3mmoles)을 가하였다. 혼합물을 25℃에서 1.25시간 동안 교반하였다. 추가의 트리메틸실릴이소시아네이트(0.155mL, 1.15mmoles)를 가하고 교반을 총 3시간 동안 지속하였다. 혼합물을 디클로로메탄으로 희석시키고 포화된 수성 중탄산나트륨으로 세척하였다. 유기 층을 건조(MgSO₄)시키고, 여과하며, 증발 건조시켰다. 잔사를 용출제로서 2%(메탄올중 10%의 진한 수산화암모늄)-디클로로메탄을 사용하는 실리카 겔 컬럼(30x2.5cm)상에서 크로마토그래피하여 2-(2-[3-브로모-5-(2-클로로페닐)피라졸로[1,5-a]피리미딘-7-일아미노]에틸)피페리딘-1-카복실산 아마이드(106.3mg, 48%)을 수득하였다: FABMS: m/z 477.0.(MH⁺) ; HRFABMS: m/z

477.0804(MH⁺). C₂₀H₂₃N₆OBrCl에 대한 계산치: m/z 477.0805;

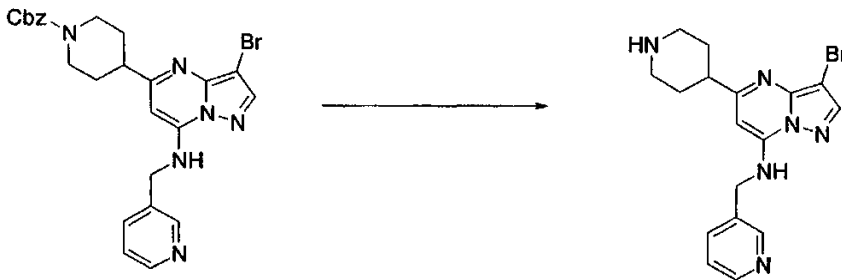
δ_H (d₆-DMSO) 1.29

(1H, m, CH₂), 1.52 (5H, m, CH₂), 1.72 (1H, m, CH₂), 2.05 (1H, m, CH₂), 2.51 (2H, s, CONH₂), 2.79 (1H, dd, CH), 3.31 (1H, m, CH₂), 3.34 (1H, m, CH₂), 3.76 (1H, m, CH₂), 4.30 (1H, bm, CH₂), 6.42 (1H, s, H₆), 7.50 (2H, m, Ar-H), 7.60 (1H, m, Ar-H), 7.63 (1H, m, Ar-H), 8.29 (1H, s, H₂) 및 8.38 ppm (1H, dd, NH); δ_C (d₆-DMSO) CH₂: 18.6, 25.2, 28.2, 38.4, 38.6, 54.8; CH: 46.7, 86.6, 127.1, 129.7, 130.3, 131.0, 143.4; C: 81.2, 131.0, 138.7, 145.1, 146.4, 158.2.

[1048]

[1049]

실시예 462:



[1050]

[1051]

무수 아세트니트릴(20mL)중 실시예 204에서 제조한 화합물(1.11g, 2.12mmol)의 용액에 TMSI(1.70g, 8.52mmol)를 주위 온도에서 적가하였다. 10분 후 아세트니트릴을 진공하에 제거하였다. 수득되는 황색 발포체를 2N HCl 용액(7mL)으로 처리한 후 즉시 Et₂O(5X)로 세척하였다. 수성 상의 pH를 50% NaOH(수성)을 사용하여 10으로 조절하고 생성물을 NaCl을 사용하여 용액을 포화시킴으로써 분리한 후 CH₂Cl₂(5X)로 추출함으로써 결정성 생성물(733mg, 89% 수율)을 수득하였다. MH⁺ = 387; m.p. = 207.5°C

[1052]

실시예 463 내지 472:

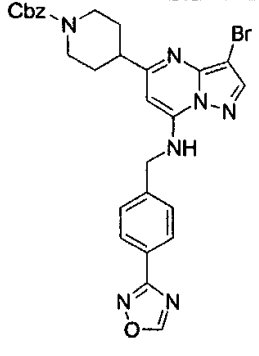
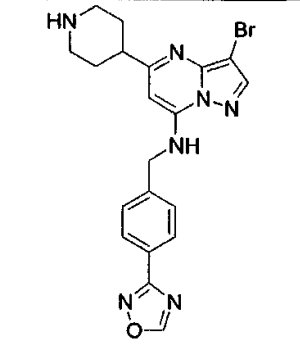
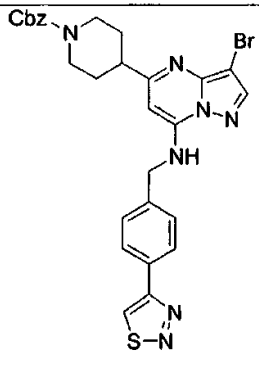
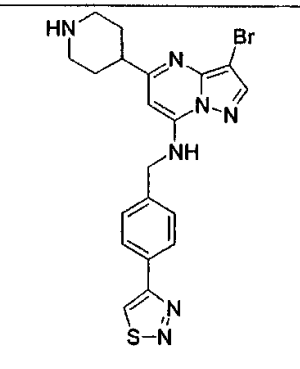
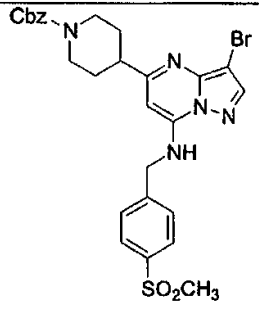
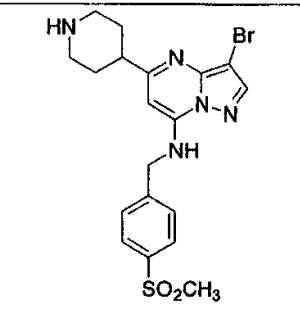
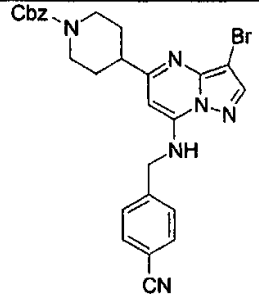
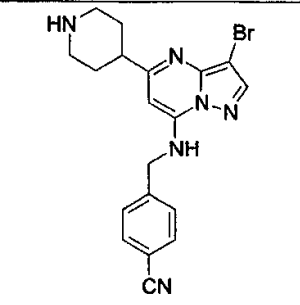
[1053]

실시예 462에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 38의 컬럼 2에 나타낸 화합물을 단지 치환함으로써, 표 38의 컬럼 3에 나타낸 화합물을 제조하였다.

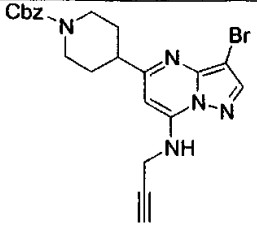
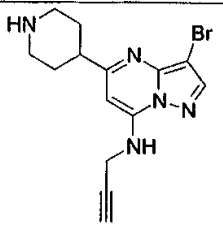
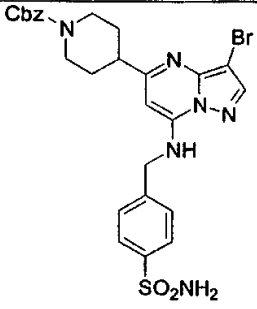
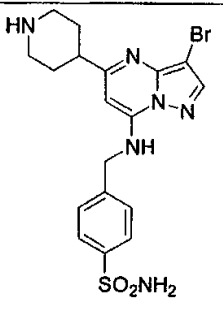
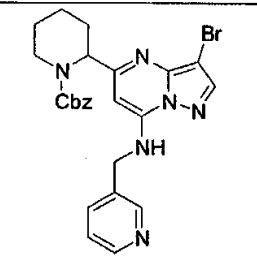
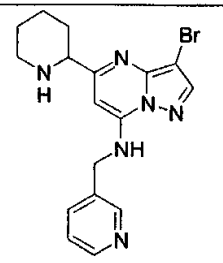
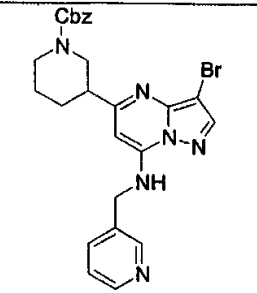
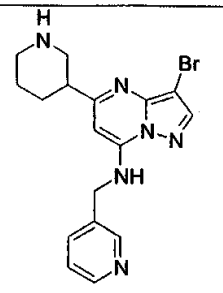
표 38

실시예	컬럼 2	컬럼 3	CMPD
463			MH ⁺ = 403 ¹ H NMR (300MHz, CDCl ₃) δ 8.52 (s, 1H), 8.38 (d, 1H), 8.04 (s, 1H), 7.78 (d, 1H), 7.65 (t, 1H), 6.18 (s, 1H), 4.89 (s, 2H), 3.26-3.21 (d, 2H), 2.96-2.70 (m, 3H), 2.05-1.78 (m, 4H).

[1054]

464			<p>MH⁺ = 454 m. p. = 175.4 °C</p>
465			<p>수용 = 87 MH⁺ = 470 m. p. = 220 °C m. pt (염산 염) = 164.3 °C</p>
466			<p>MH⁺ = 464 m. p. = 206 °C</p>
467			<p>MH⁺ = 411 m. p. = 169.5 °C</p>

[1055]

468			<p>MH⁺ = 334 m. p. = 176.2 °C</p>
469			<p>MH⁺ = 465 m. p. = 250.4 °C</p>
470			<p>MH⁺ = 387 m. p. = 68.5 °C</p>
471			<p>MH⁺ = 387 m. p. = 59.4 °C</p>

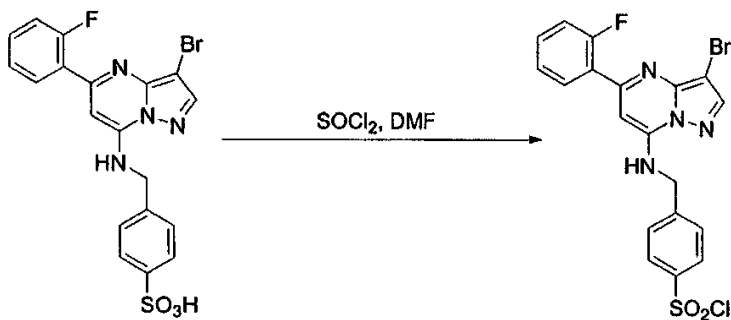
[1056]

472			<p>1. mp = 230-232 2. M+H = 396</p>
472 .10			<p>1. mp = 157-160 2. M+H = 427</p>

[1057]

[1058] 실시예 473:

[1059] 단계 A:



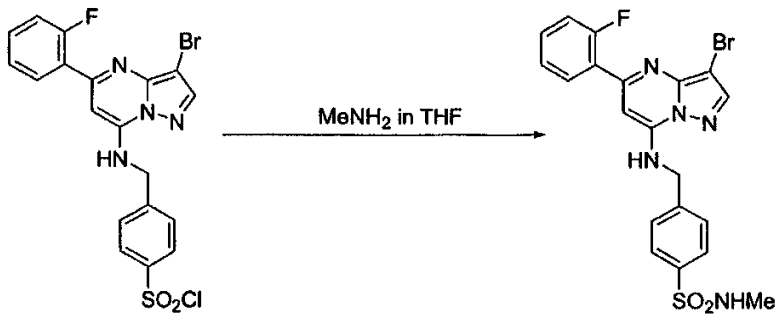
[1060]

[1061] 무수 DMF 5mL중 설푼산(560mg, 1.17mmol)의 용액을 0℃로 냉각시키고 SOCl₂(278mg, 2.34mmol)을 가하였다. 반응 혼합물을 실온으로 되도록 하고 밤새 교반하였다. 다음날 성분들을 얼음위에 붓고 pH를 8로 주의하여 조절하였다. 생성물을 EtOAc로 추출하고 용매를 건조(Na₂SO₄)후 제거함으로써 조약한 설푼닐 클로라이드 240mg(41%)를 수득하고 이를 추가의 정제없이 다음 단계에서 사용하였다.

[1062]

¹H NMR (CDCl₃) δ 8.20-8.10 (m,1H), 8.10-7.95 (m, 3H), 7.65 (d, 2H), 7.45-7.35 (m, 1H), 7.35-7.20 (m, 1H), 7.15-7.05 (m, 1H), 6.95 (t, 1H), 4.85 (d, 2H).

[1063] 단계 B:



[1064]

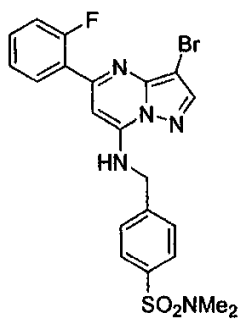
[1065] 10mL의 THF중 실시예 473, 단계 A에서 제조한 화합물(120mg, 0.24mmol)의 용액을 THF중 1M MeNH₂(2.00mmol) 2mL로 실온에서 밤새 처리하였다. 용매를 제거하고 잔사를 크로마토그래피(실리카, 헥산:EtOAc(4:1→1:1))로 정제하여 설폰아미드 56mg(48%)을 수득하였다.

¹H NMR (DMSO-d₆) δ 9.05 (t, J = 9 Hz, 1H), 8.35 (s, 1H), 7.90 (t, J = 7.5 Hz, 1H), 7.75 (d, J = 9 Hz, 2H), 7.62 (d, J = 9 Hz, 2H), 7.55-7.46 (m, 1H), 7.45-7.38 (m, 1H), 7.38-7.25 (m, 1H), 6.50 (s, 1H), 4.80 (d, 2H), 3.30 (s, 3H)

LCMS: MH⁺ = 492.1

[1066]

[1067] 실시예 474:



[1068]

[1069] 실시예 473에 나타낸 바와 본질적으로 동일한 과정에 의해, 디메틸아민을 단지 치환시킴으로써, 상기 화합물을 제조하였다.

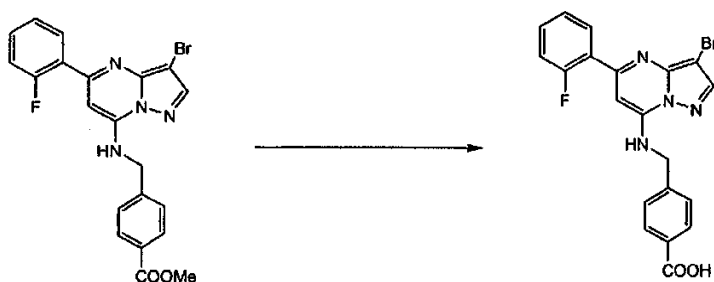
¹H NMR (CDCl₃)

δ 8.14 (t, J = 9 Hz, 1H), 8.00 (s, 1H), 7.76 (d, J = 9 Hz, 2H), 7.54 (d, J = 9 Hz, 2H), 7.34-7.44 (m, 1H), 7.26 (t, J = 9 Hz, 1H), 7.14-7.04 (m, 1H), 6.93 (t, J = 6 Hz, 1H), 6.45 (s, 1H), 4.75 (d, 2H), 2.70 (s, 6H)

LCMS: MH⁺ = 504.2

[1070]

[1071] 실시예 475:



[1072]

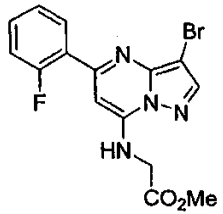
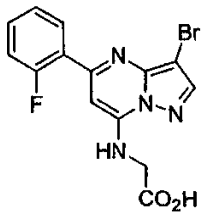
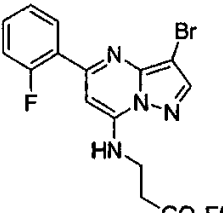
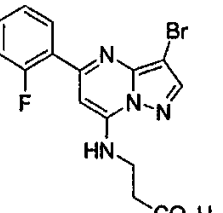
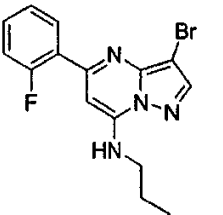
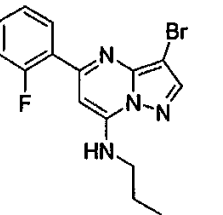
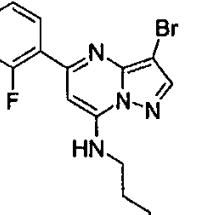
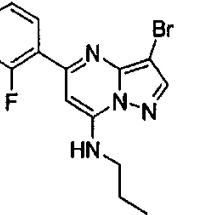
[1073] 실시예 129에서 제조한 화합물(300mg, 0.66mmol), NaOH(5g), CH₃OH-H₂O(100mL, 90:10)의 혼합물을 25°C에서 약

15시간 동안 교반하였다. 가수분해 진행을 TLC로 체크하였다. 반응 혼합물을 농축시켜 메탄올을 제거하였다. 농축물을 50mL 물로 희석시키고, 에테르로 추출하여 반응하지 않은 어떠한 에스테르도 제거하였다. 이렇게 수득된 수용액을 3N HCl을 사용하여 pH 4로 중화시킴으로써 유리 산을 수득하고, 여과하고, 물로 반복적으로 세척하였다. 산을 진공(270mg, 93%)하에 건조시키고 추가의 정제없이 사용하였다.

[1074] 실시예 476 내지 479:

[1075] 실시예 475에 나타난 바와 본질적으로 동일한 과정을 사용하여, 표 39의 컬럼 2의 화합물을 단지 치환시킴으로써, 표 39의 컬럼 3의 화합물을 제조하였다.

표 39

실시예	컬럼 2	컬럼 3	CMPD
476			수율 = 82% LCMS: MH ⁺ = 365
477			수율 = 82% LCMS: MH ⁺ = 379
478			수율 = 72% LCMS: MH ⁺ = 393
479			수율 = 70% LCMS: MH ⁺ = 407

[1077]

[1078] 선택된 실시예에 대한 추가의 데이터를 하기에 나타낸다:

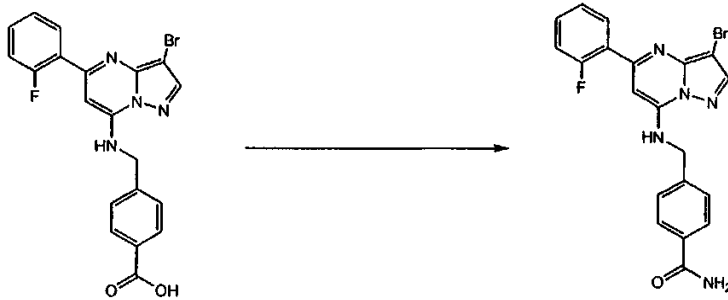
실시예 476: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (m, 2H), 8.0 (m, 1H), 7.6 (m, 1H), 7.3 (m, 2H), 6.6 (s, 1H), 4.2 (d, 2H).

실시예 477: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.0 (t, 1H), 6.5 (s, 1H), 3.8 (dt, 2H), 2.6 (t, 2H).

실시예 479: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 3.5 (dt, 2H), 2.4 (t, 2H), 1.8 (m, 4H).

[1079]

[1080] 실시예 480:



[1081]

[1082] THF(20mL)중 실시예 475로부터의 산(85mg, 0.193mmol) 및 Et_3N (20mg, 0.193mmol)의 혼합물을 25°C에서 15분 동안 교반하였다. 이소부틸릴 클로로포르메이트(28mg, 0.205mmol)을 반응 혼합물에 가하고 10분 동안 교반한 후 NH_4OH 용액(0.5mL)을 첨가하였다. 반응 혼합물을 1시간 동안 교반하고 농축 건조시켰다. 무수 덩어리를 컬럼 크로마토그래피로 정제하였다.

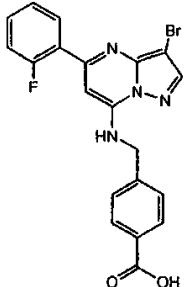
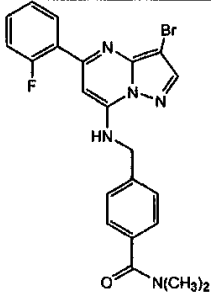
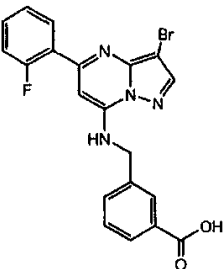
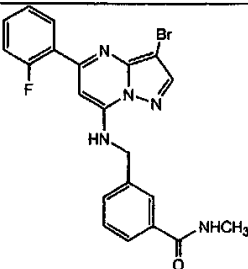
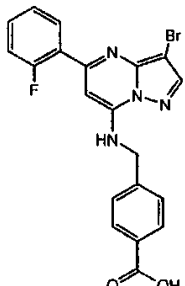

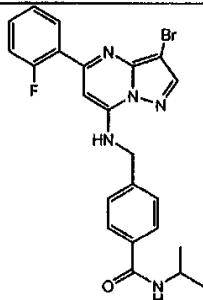
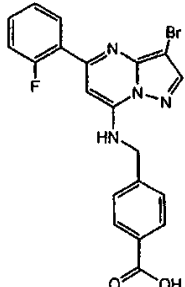

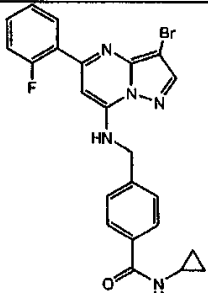
[1083] 실시예 481 내지 508:

[1084] 실시예 480에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 40의 컬럼 2에 나타낸 카복실산 및 표 40의 컬럼 3에 나타낸 아민을 단지 치환시킴으로서, 표 40의 컬럼 4에 나타낸 화합물을 제조하였다.

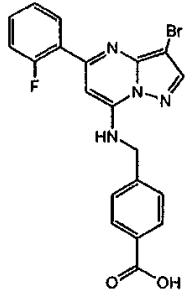

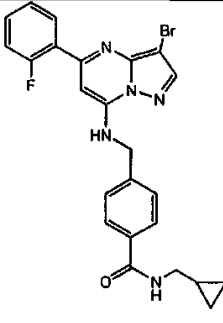
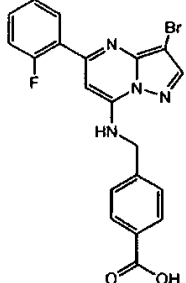

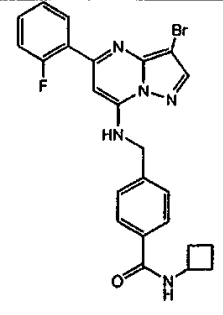
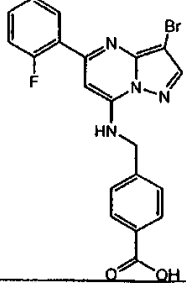

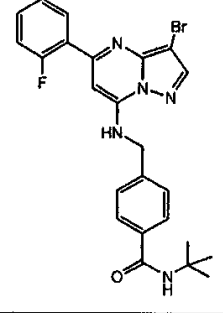
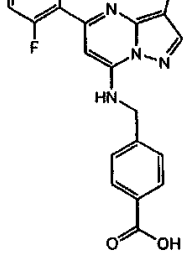

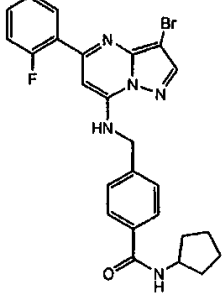
표 40

실시예	컬럼 2	컬럼 3	컬럼 4	CMPD
481		CH_3NH_2		수율 = 88% LCMS: MH^+ = 454

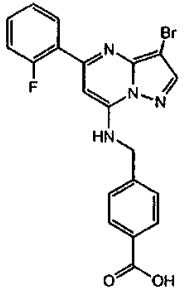
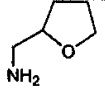
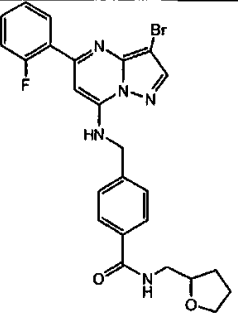
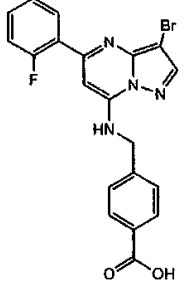

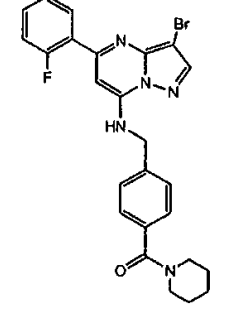
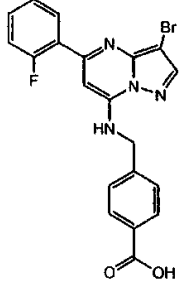

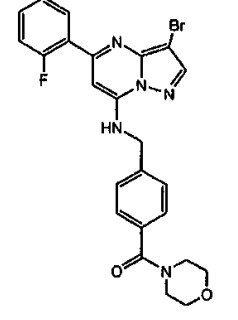
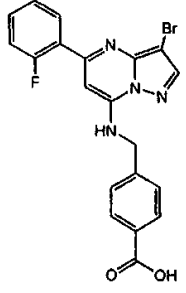

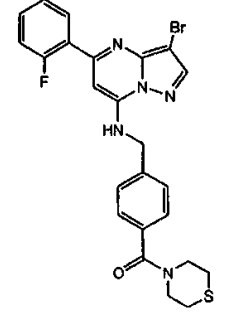
[1085]

482		$(\text{CH}_3)_2\text{NH}$		수율 =80 % LCMS MH ⁺ = 468
483		CH_3NH_2		수율 =70 % LCMS MH ⁺ = 454.
484				수율 =75 % LCMS MH ⁺ = 482.1
485				수율 =71 % LCMS MH ⁺ = 480.1

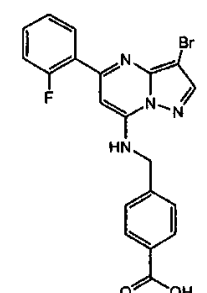
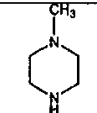
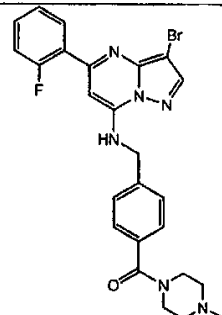
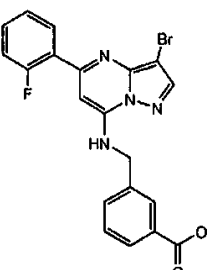
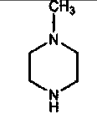
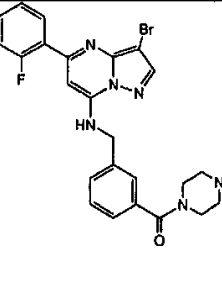
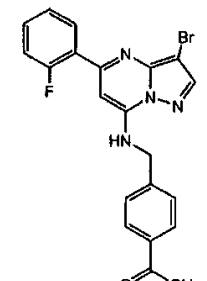
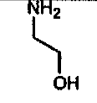
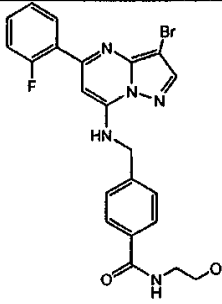
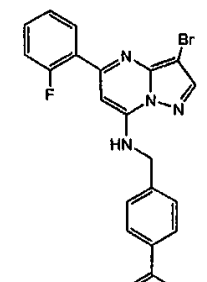
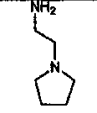
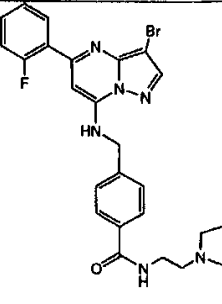
[1086]

486				수율 = 75 % LCMS MH ⁺ = 494.1
487				수율 = 75 % MH ⁺ = 494.1
488				수율 = 75 % MH ⁺ = 496.1
489				수율 = 75 % LCMS MH ⁺ = 508.1

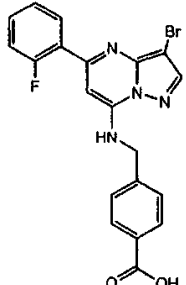
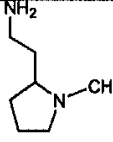
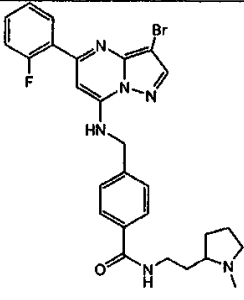
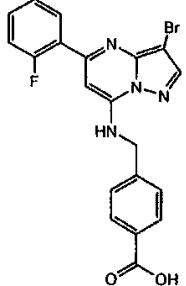
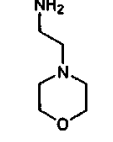
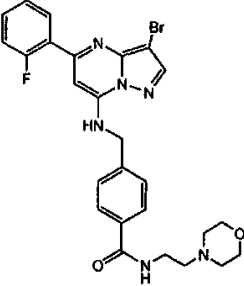
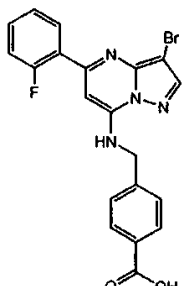

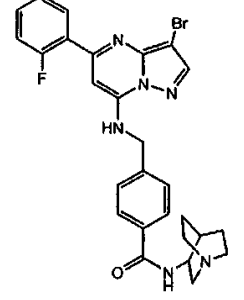
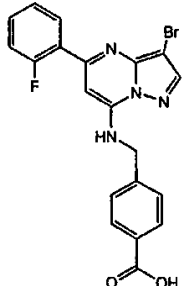
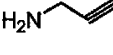
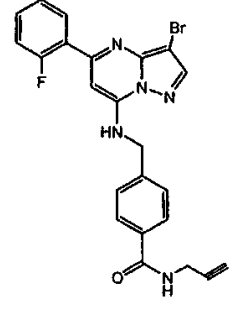
[1087]

490				수율 = 78 % LCMS MH ⁺ = 524.1
491				수율 = 73 % LCMS MH ⁺ = 508.1
492				수율 = 73 % LCMS MH ⁺ = 510.1
493				수율 = 76 % LCMS MH ⁺ = 526.1

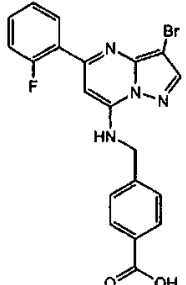
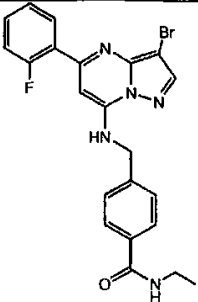
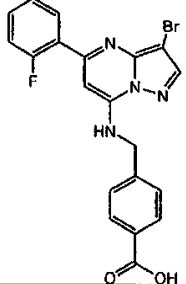
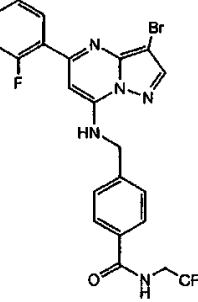
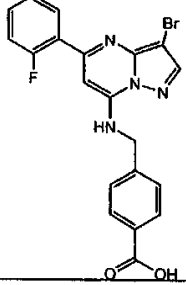
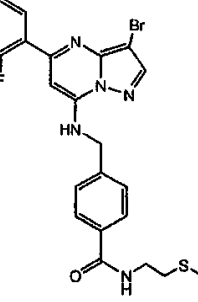
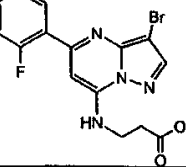
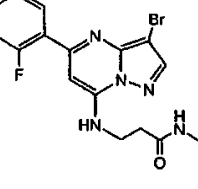
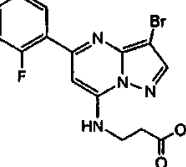

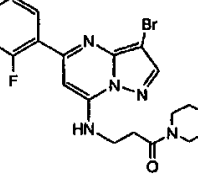
[1088]

494				<p>수율 = 76 % MH⁺ = 523.1</p>
495				<p>수율 = 76 % MH⁺ = 523.1</p>
496				<p>수율 = 51 % LCMS MH⁺ = 484.1</p>
497				<p>수율 = 66 % MH⁺ = 537.1</p>

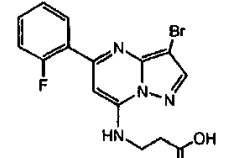

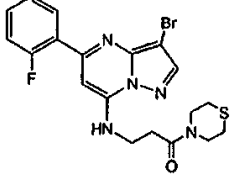
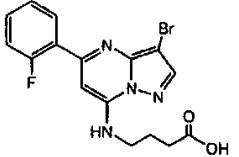
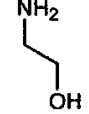
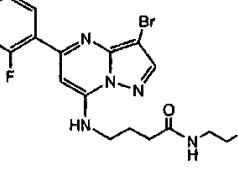
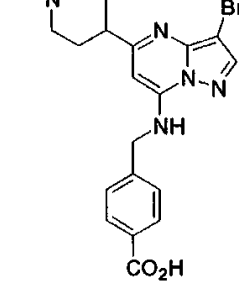
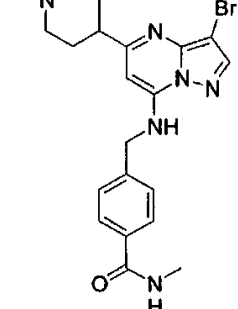
[1089]

498				수율 = 76 % LCMS MH ⁺ = 551.2
499				수율 = 79 % LCMS MH ⁺ = 552.1
500				수율 = 80 % MH ⁺ = 549.1
501				수율 = 80 % LCMS MH ⁺ = 478.1

[1090]

502		$\text{H}_2\text{N}-\text{CH}_2\text{CH}_3$		수율 = 80 % LCMH ⁺ = 468.1
503		$\text{H}_2\text{N}-\text{CH}_2\text{CF}_3$		수율 = 80 % MH ⁺ = 522.1
504		$\text{NH}_2-\text{CH}_2\text{CH}_2\text{S}-\text{CH}_2\text{CH}_3$		수율 = 82 % LCMS MH ⁺ = 528.1
505		CH_3NH_2		수율 = 60 % MH ⁺ = 392
506				수율 = 60 % LCMH ⁺ = 448.1

[1091]

507				수율 =70 % MH ⁺ = 464.1
508				수율 =50 % LCMS MH ⁺ = 436.1
508 .10		CH ₃ NH ₂		수율 = 92 MH ⁺ = 577

[1092]

[1093]

선택된 실시예에 대한 추가의 데이터를 하기에 나타내었다:

실시예 481: ¹H NMR (CDCl₃) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (s, 1H), 7.35 (d, 2H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.95 (t, 1H), 6.5 (s, 1H), 6.25 (bs, 1H), 4.7 (d, 2H), 3.0 (d, 3H).

실시예 482: ¹H NMR (CDCl₃) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.45 – 7.35 (m, 4H), 7.25 (d, 2H), 7.15 (dd, 1H), 6.7 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.1 (s, 3H), 3.0 (s, 3H).

실시예 483: ¹H NMR (CDCl₃) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (bs, 1H), 7.7 (d, 1H), 7.5 – 7.3 (m, 3H), 7.25 (d, 1H), 7.15 (dd, 1H), 6.75 (t, 1H), 6.5 (s, 1H), 6.2 (bs, 1H), 4.7 (d, 2H), 3.0 (d, 3H).

실시예 484: ¹H NMR (CDCl₃) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 6.0 (bs, 1H), 4.7 (d, 2H), 4.25 (m, 1H), 1.2 (d, 6H).

[1094]

실시예 485: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (s, 1H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 6.3 (t, 1H), 4.7 (d, 2H), 2.9 (m, 1H), 0.8 (bt, 2H), 0.6 (bt, 2H).

실시예 486: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (d, 2H), 7.4 (d, 2H), 7.35 (d, 1H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 6.2 (t, 1H), 4.7 (d, 2H), 3.3 (dd, 2H), 1.05 (m, 1H), 0.5 (m, 2H), 0.25 (m, 2H).

실시예 487: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.85 (t, 1H), 6.5 (s, 1H), 6.2 (bs, 1H), 4.7 (d, 2H), 4.6 (m, 1H), 2.4 (m, 2H), 1.95 (m, 1H), 1.75 (m, 2H).

실시예 488: $^1\text{H NMR}$ (CDCl_3) δ 8.5 (t, 1H), 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 5.9 (bs, 1H), 4.7 (d, 2H), 1.4 (s, 9H).

실시예 489: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 6.0 (bs, 1H), 4.7 (d, 2H), 4.4 (m, 1H), 2.05 (m, 2H), 1.7 (m, 4H), 1.4 (m, 2H).

실시예 490: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 6.5 (bs, 2H), 4.7 (d, 2H), 4.1 (m, 1H), 3.9 – 3.7 (m, 3H), 3.3 (m, 1H), 2.0 – 1.9 (m, 4H).

실시예 491: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.45 – 7.35 (m, 5H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.7 (bs, 2H), 3.3 (bs, 2H), 1.7 (bs, 4H), 1.5 (bs, 2H).

실시예 492: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.45 – 7.35 (m, 5H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.85 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.8 – 3.4 (bm, 8H).

실시예 493: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.45 – 7.35 (m, 5H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.80 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 4.0 (m, 2H), 3.6 (m, 2H), 2.8 – 2.45 (m, 4H).

실시예 494: $^1\text{H NMR}$ (CH_3OD) δ 8.15 (s, 1H), 8.0 (dt, 1H), 7.45 – 7.35 (m, 5H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.80 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.7 (bs, 2H), 3.4 (bs, 2H), 2.5 – 2.4 (m, 4H), 2.2 (s, 3H).

[1095]

실시예 495: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.45 – 7.35 (m, 5H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.80 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.75 (bs, 2H), 3.35 (bs, 2H), 2.4 (bs, 2H), 2.3 (s, 3H), 2.2 (bs, 2H).

실시예 496: $^1\text{H NMR}$ (CDCl_3) δ 7.95 (s, 1H), 7.9 (dt, 1H), 7.8 (t, 1H), 7.7 (d, 2H), 7.15 (m, 4H), 7.05 (dd, 1H), 6.9 (dd, 1H), 6.2 (s, 1H), 4.5 (d, 2H), 3.6 (t, 2H), 3.3 (dt, 2H).

실시예 497: $^1\text{H NMR}$ (CH_3OD) δ 8.1 (s, 1H), 7.9 (dt, 1H), 7.8 (d, 2H), 7.5 (d, 2H), 7.4 (m, 1H), 7.3 (dd, 1H), 7.2 (dd, 1H), 6.4 (s, 1H), 4.7 (d, 2H), 3.5 (t, 2H), 2.7 (m, 2H), 2.6 (bs, 4H), 1.8 (bs, 4H).

실시예 498: $^1\text{H NMR}$ (CDCl_3) δ 8.5 (t, 1H), 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.7 – 2.5 (m, 4H), 2.35 (s, 3H), 2.2 (m, 1H), 1.9 – 1.6 (m, 6H).

실시예 499: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.7 (m, 4H), 3.5 (dt, 2H), 2.6 (t, 2H), 2.5 (m, 4H).

실시예 500: $^1\text{H NMR}$ (CH_3OD) δ 8.15 (s, 1H), 7.9 (dt, 1H), 7.8 (d, 2H), 7.45 (d, 2H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.4 (s, 1H), 4.75 (d, 2H), 4.2 (m, 1H), 3.4 – 2.8 (m, 7H), 1.9 – 1.6 (m, 4H).

실시예 501: $^1\text{H NMR}$ (CDCl_3) δ 8.05 (dt, 1H), 8.0 (s, 1H), 7.6 (d, 2H), 7.4 (s, 1H), 7.35 (d, 2H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 6.4 (t, 1H), 4.7 (d, 2H), 4.2 (d, 2H), 2.3 (bs, 1H).

실시예 502: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.75 (d, 2H), 7.45 (s, 1H), 7.4 (d, 2H), 7.3 (dd, 1H), 7.1 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 6.1 (bs, 1H), 4.7 (d, 2H), 3.5 (dq, 2H), 1.2 (t, 3H).

실시예 503: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 6.4 (t, 1H), 4.75 (d, 2H), 4.1 (m, 2H).

실시예 504: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (d, 2H), 7.45 (d, 2H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.8 (t, 1H), 6.6 (t, 1H), 6.5 (s, 1H), 4.7 (d, 1H), 3.6 (m, 2H), 2.8 (t, 2H), 2.6 (q, 2H), 1.3 (t, 3H).

실시예 505: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.0 (t, 1H), 6.5 (s, 1H), 3.8 (m, 2H), 2.7 (t, 2H), 3.0 (d, 3H).

실시예 506: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.0 (t, 1H), 6.5 (s, 1H), 3.8 (m, 2H), 3.6 (m, 6H), 3.4 (m, 2H), 2.7 (t, 2H).

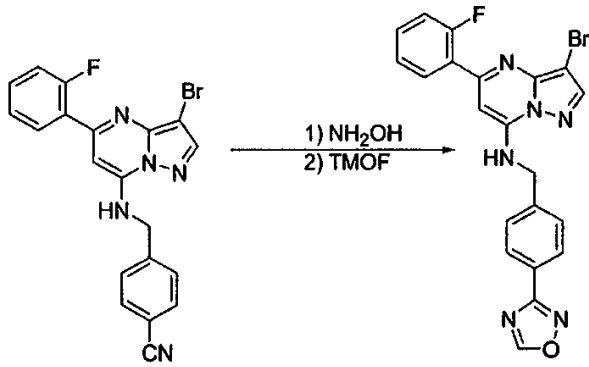
실시예 507: $^1\text{H NMR}$ (CDCl_3) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.0 (t, 1H), 6.5 (s, 1H), 3.9 (t, 2H), 3.8 (dt, 2H), 3.7 (t, 2H), 2.7 (t, 2H), 2.6 (m, 4H).

실시예 508: $^1\text{H NMR}$ (CH_3OD) δ 8.1 (s, 1H), 7.95 (dt, 1H), 7.5 (m, 1H), 7.35 – 7.2 (m, 2H), 6.5 (s, 1H), 3.6 (m, 4H), 3.25 (m, 4H), 2.4 (t, 2H), 2.05 (dt, 2H).

[1096]

[1097]

[1098] 실시예 509:



[1099]

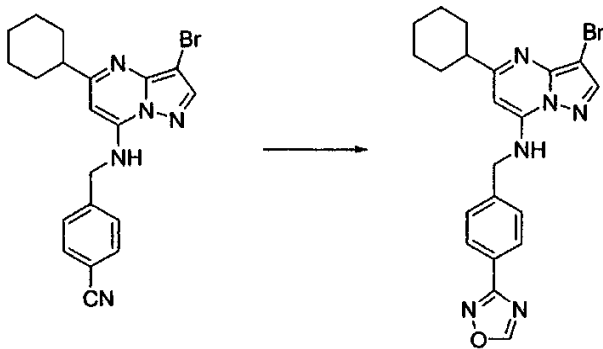
[1100] 물 1mL중 NaOH(59mg, 1.47mmol)의 용액을 0°C에서 메탄올 10mL중 NH₂OH·HCl(102mg, 1.47mmol)의 현탁액에 가하였다. 5분 후에, 실시예 210.10에서 제조한 화합물(208mg, 0.49mmol)을 가하고 반응 혼합물을 밤새 환류시켰다. 용매를 진공하에 제거하고 잔사를 물 및 EtOAc사이에 분배시켰다. EtOAc 층을 건조(Na₂SO₄)시키고 용매를 증발시켰다. 수득되는 조악한 아마이드옥심을 촉매량의 PTS산을 함유하는 트리메틸 오르토포르메이트 속에 현탁시키고 밤새 환류시켰다. 용매를 제거하고 잔사를 EtOAc속에 넣었다. EtOAc 층을 수성 NaHCO₃에 이어서 물 및 염수로 세척하였다. 용매를 증발시키고 잔사를 크로마토그래피(실리카, 헥산:EtOAc(1:1))에 의해 정제하여 옥사디아졸 80mg(35%)을 수득하였다.

¹H NMR (CDCl₃) δ 8.75 (s, 1H), 8.20-8.10 (m, 3H), 8.03 (s, 1H), 7.53 (d, J = 9 Hz, 2H), 7.45-7.36 (m, 1H), 7.30-7.22 (m, 2H), 7.16-7.08 (m, 1H), 6.80 (t, J = 5 Hz, 1H), 6.56 (s, 1H).

LCMS: MH⁺ = 465.2

[1101]

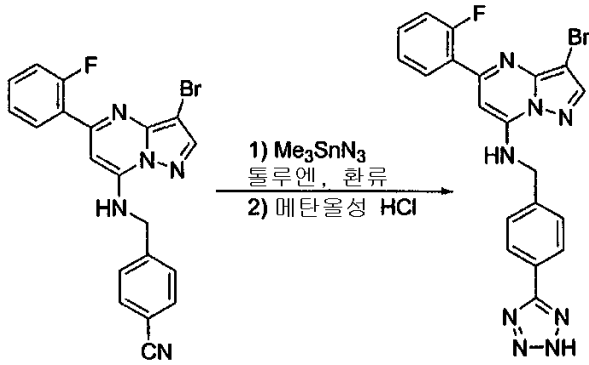
[1102] 실시예 510:



[1103]

[1104] 실시예 509에 나타낸 바와 본질적으로 동일한 과정에 의해, 제조 실시예 192에서 제조한 화합물을 단지 치환시킴으로써, 상기 화합물을 제조하였다. 수율 = 75; MH⁺ = 453; m.p. = 79.3°C.

[1105] 실시예 511:



[1106]

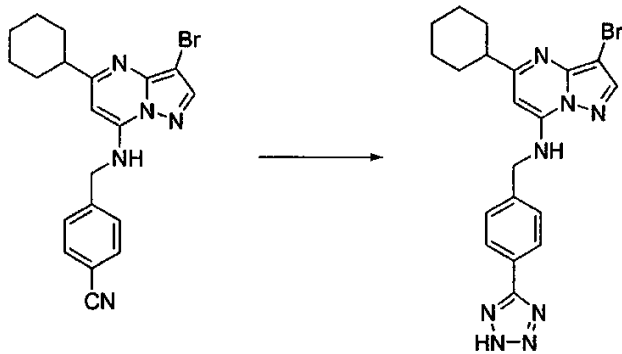
[1107] 20mL의 무수 톨루엔중 니트릴(235mg, 0.56mmol) 및 Me_3SnN_3 (343mg, 1.67mmol)의 혼합물을 Ar하에 2일동안 환류시켰다. 용매를 진공하에 제거하고 잔사를 무수 메탄올속에 용해시켰다. HCl 가스를 용액을 통해 15분 동안 버블링하고 반응 혼합물을 실온에서 밤새 정치시켰다. 다음날, 용매를 제거하고, 잔사를 물에 넣고 pH를 5로 조절하였다. 침전된 생성물을 EtOAc내로 추출하였다. 건조(Na_2SO_4)시킨 후 EtOAc 층을 증발시켜 잔사를 수득하고 이를 크로마토그래피(실리카, DCM:MeOH(98:2→95:5))에 의해 정제하여 순수한 테트라졸 50mg(19%)을 수득하였다.

$^1\text{H NMR (CD}_3\text{OD)} \delta$

8.10 (s, 1H), 8.00 (d, J = 9 Hz, 2H), 7.90 (t, J = 7 Hz, 1H), 7.65 (d, J = 9 Hz, 2H), 7.50-7.40 (m, 1H), 7.30-7.10 (m, 2H), 6.45 (s, 1H), 4.80 (s, 2H); LCMS: $\text{MH}^+ = 465.0$

[1108]

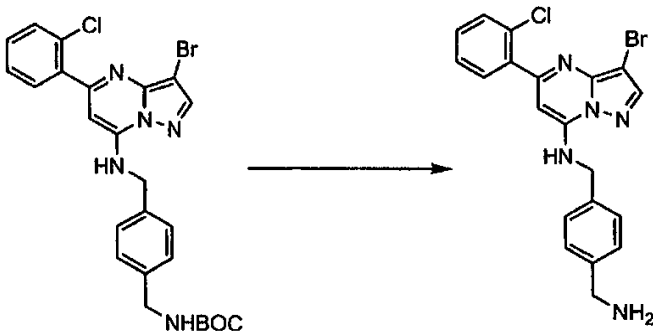
[1109] 실시예 512:



[1110]

[1111] 실시예 511에 나타낸 바와 본질적으로 동일한 과정에 의해, 실시예 192에서 제조된 화합물을 단지 치환시킴으로써, 상기 화합물을 제조하였다. 수율 = 64; $\text{MH}^+ = 453$; m.p. = 238.9°C.

[1112] 실시예 513:



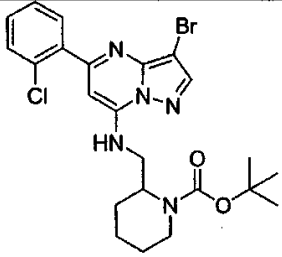
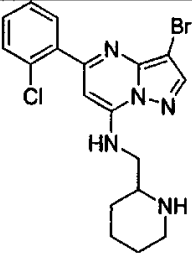
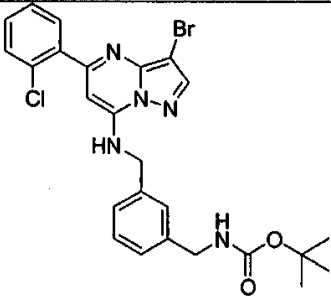
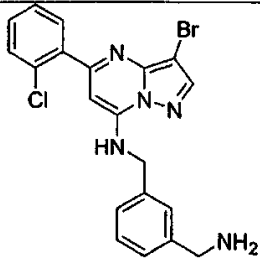
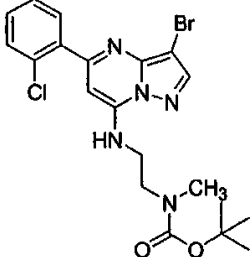
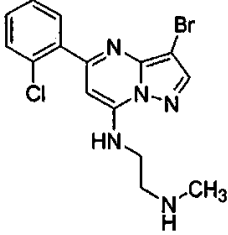
[1113]

[1114] 실시예 157에서 제조한 화합물을 디옥산(30mL)속에 용해시키고 HCl-디옥산 용액(4M, 30mL)을 가하였다. 반응 혼합물을 실온에서 1시간 동안 교반하였다. 반응 혼합물을 감압하에 증발시키고 에틸 아세테이트(200mL)를 가하였다. 유기 용액을 1N 수산화나트륨에 이어 포화된 염수로 세척하였다. 유기 층을 무수 황산나트륨위에서 건조시키고 감압하에 증발시켰다. $MH^+ = 442.1$

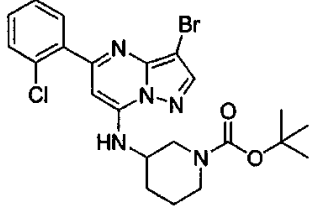
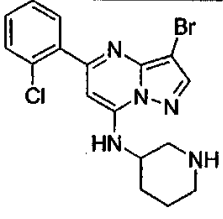
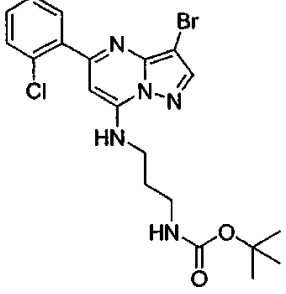
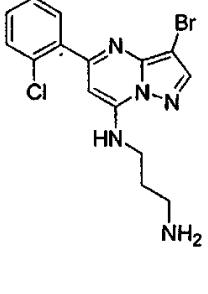
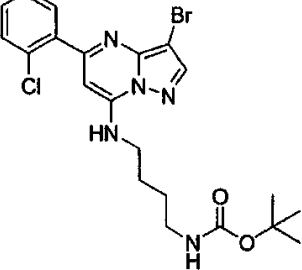
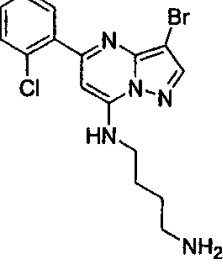
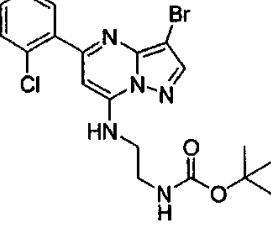
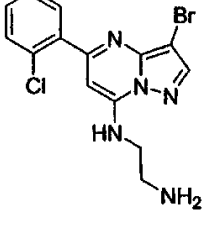
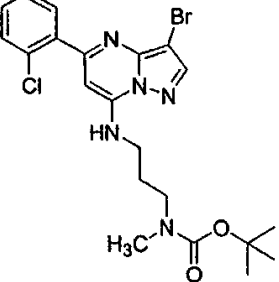
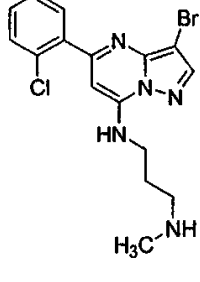
[1115] 실시예 514 내지 526:

[1116] 실시예 513에 나타낸 바와 본질적으로 동일한 과정에 의해, 표 41의 컬럼 2에 나타낸 화합물을 단지 치환시킴으로써, 표 41의 컬럼 3에 나타낸 화합물을 제조하였다.

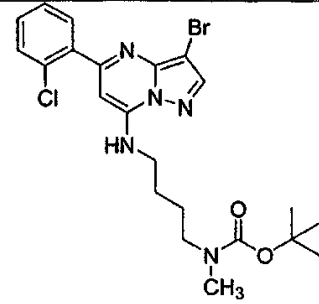
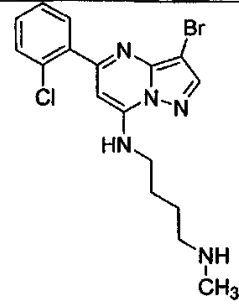
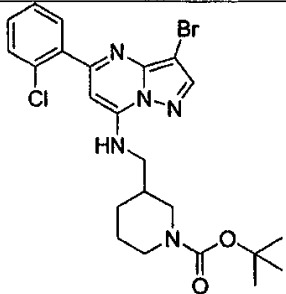
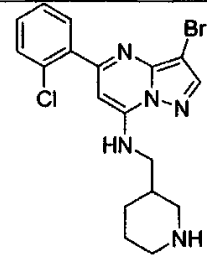
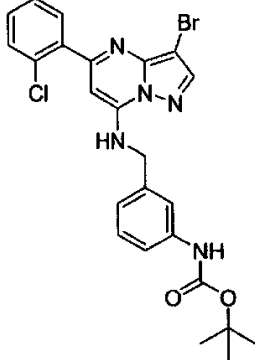
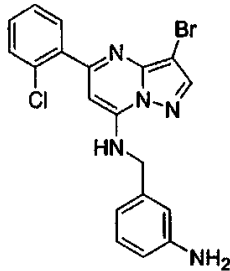
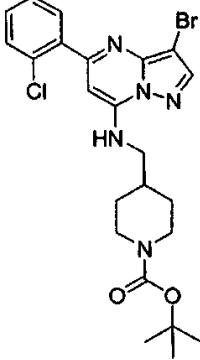
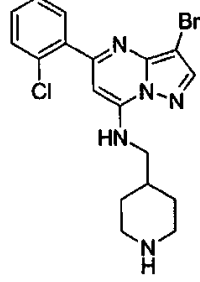
표 41

실시예	컬럼 2	컬럼 3	CMPD
514			$MH^+ = 420.1$
515			$MH^+ = 442.1$
516			$MH^+ = 380.1$

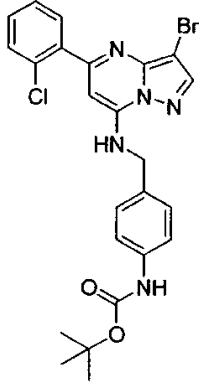
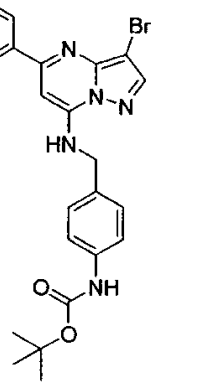
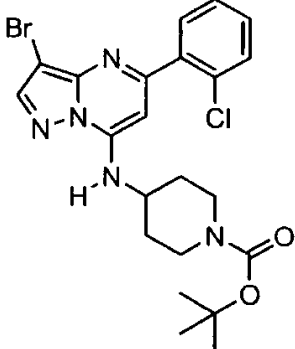
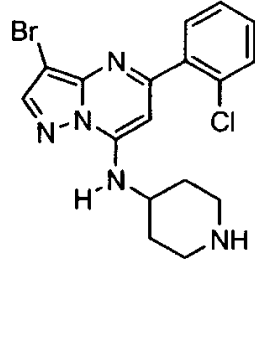
[1117]

517			$MH^+ = 406.1$
518			$MH^+ = 380.1$
519			$MH^+ = 394.1$
520			$MH^+ = 366$
521			$MH^+ = 394$

[1118]

522			$MH^+ = 408.1$
523			$MH^+ = 420.1$
524			$MH^+ = 420.1$
525			$MH^+ = 420.1$

[1119]

526			MH ⁺ = 428.1
526.10			

[1120]

[1121]

실시예 528 내지 564:

[1122]

5-피페리디닐 평행 라이브러리 형성을 위한 일반적인 과정:

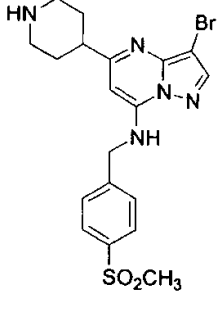
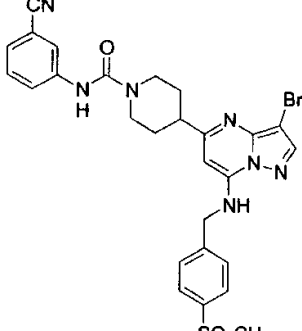
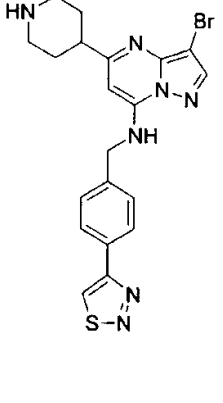
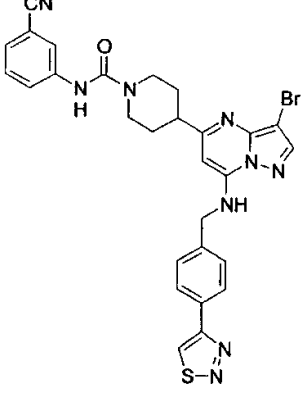
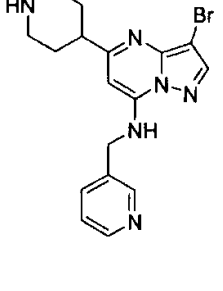
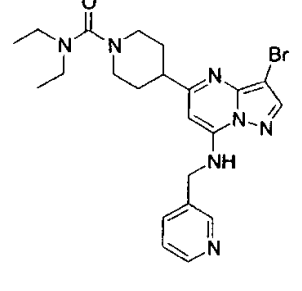
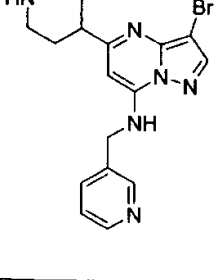
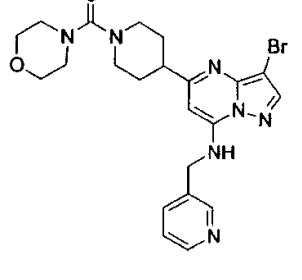
[1123]

무수 CH₂Cl₂(1.5mL) 중의 표 42의 컬럼 2에 나타낸 출발물질(80mg, 0.21mmol)의 혼합물에 DIPEA(75μL, 0.42mmol) 및 적합한 캡핑 시약(capping reagent)(1.1당량, 0.23mmol)을 가하였다. 1 내지 2시간 후에, 반응 혼합물을 1000 마이크로론 제조 TLC 판에 적용시키고 용출제로서 8-10% EtOH-CH₂Cl₂를 사용하여 후속적으로 진행시켜 표 42의 컬럼 3에 나타낸 화합물을 수득하였다.

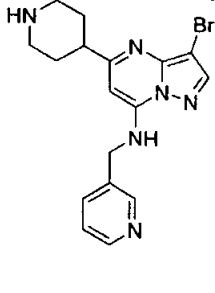
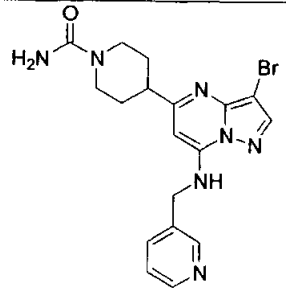
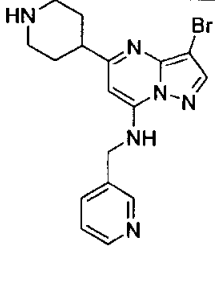
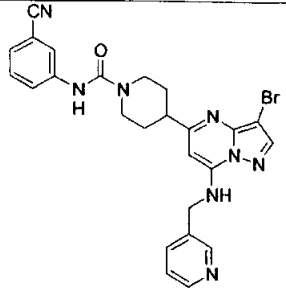
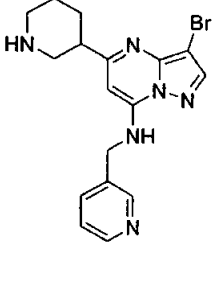
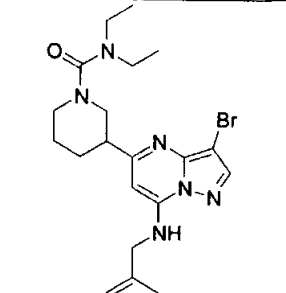
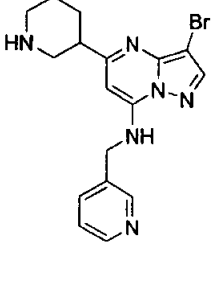
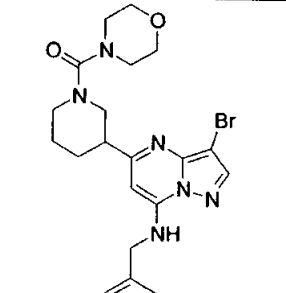
표 42

실시예	컬럼 2	컬럼 3	CMPD
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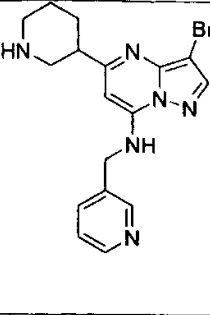
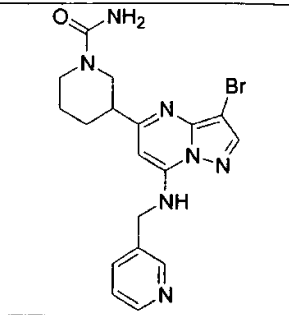
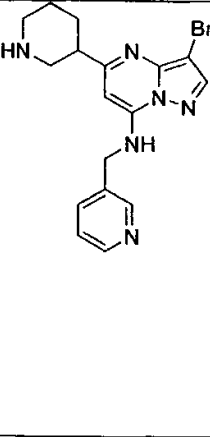
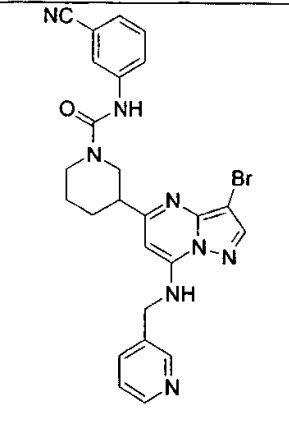
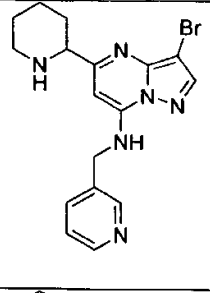
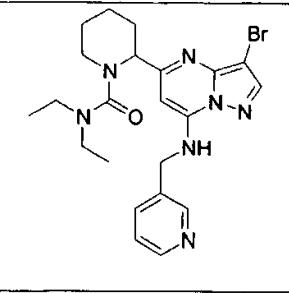
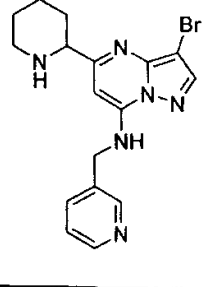
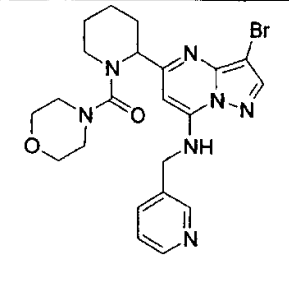
[1124]

528			<p>MH⁺ = 608 m. p. = 230.1 °C</p>
529			<p>Yield = 82 MH⁺ = 614 m. p. = 235.4 °C</p>
530			<p>MH⁺ = 486 m. p. = 60.5 °C</p>
531			<p>MH⁺ = 500 m. p. = 113.6 °C</p>

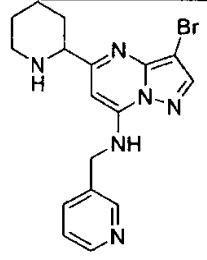
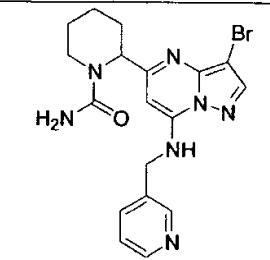
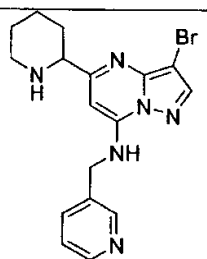
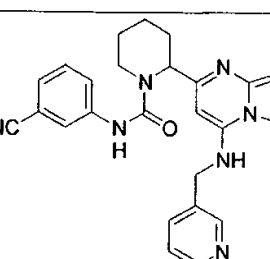
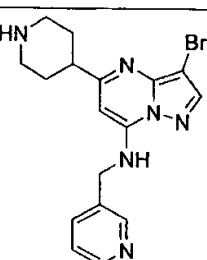
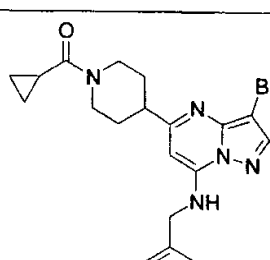
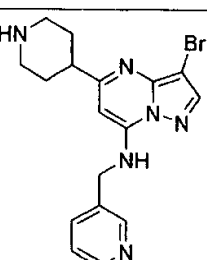
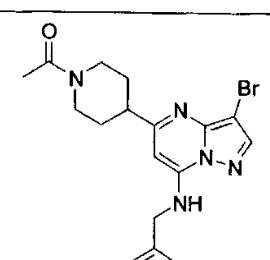
[1125]

532			<p>MH⁺ = 430 m. p. = 158.3 – 159.2 °C</p>
533			<p>MH⁺ = 531 m. p. = 105.9 °C</p>
534			<p>MH⁺ = 486</p>
535			<p>MH⁺ = 500</p>

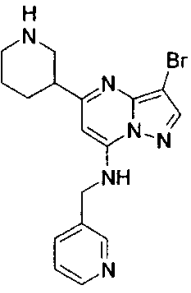
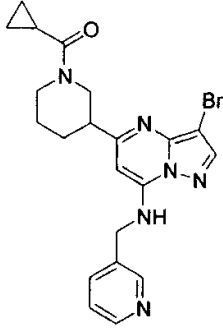
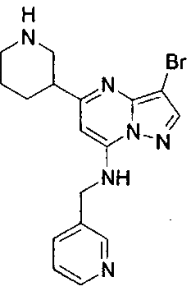
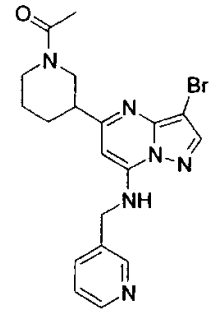
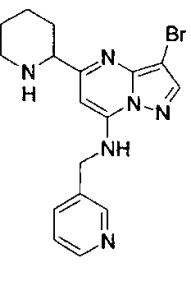
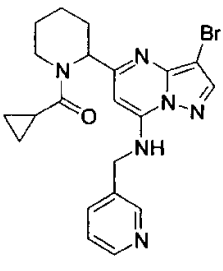
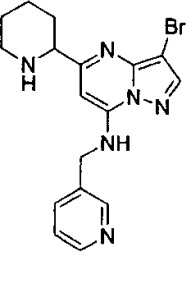
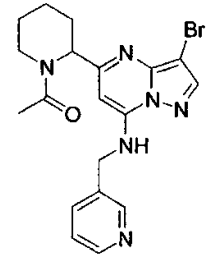
[1126]

536			<p>MH⁺ = 430</p>
537			<p>MH⁺ = 531</p>
538			<p>MH⁺ = 486 m. p. = 69.6 °C</p>
539			<p>MH⁺ = 500 m. p. = 82.3 °C</p>

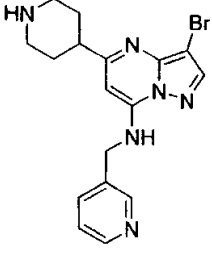
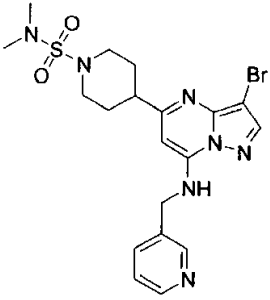
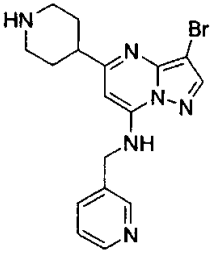
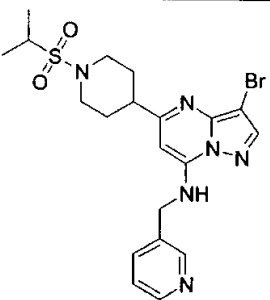
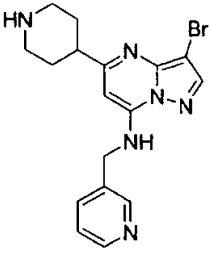
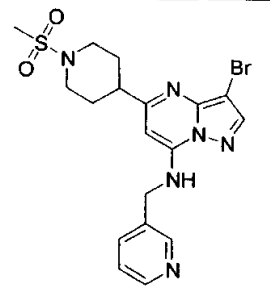
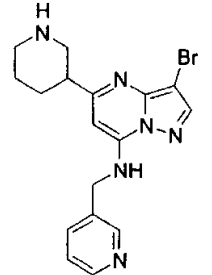
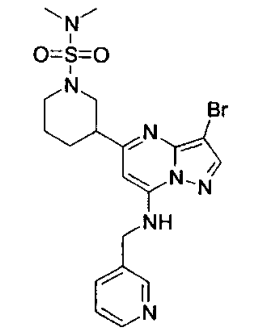
[1127]

540			$MH^+ = 430$ m. p. = 223.6 °C
541			$MH^+ = 531$ m. p. = 118.1 °C
542			$MH^+ = 455$ m. p. = 109 - 110 °C
543			$MH^+ = 429$ m. p. = 111.5 °C

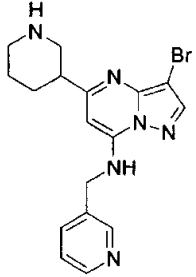
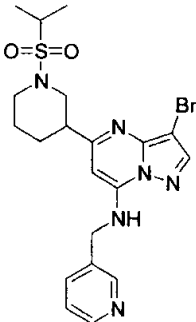
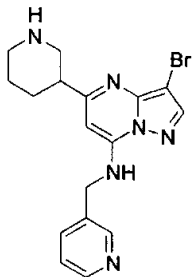
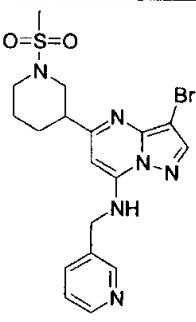
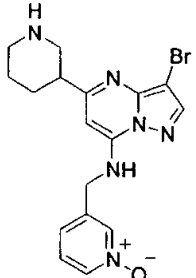
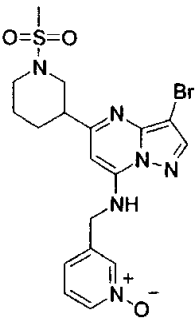
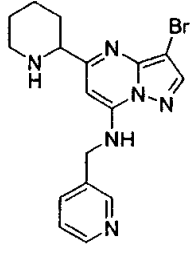
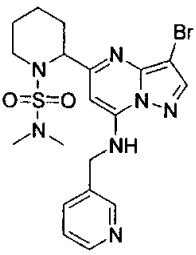
[1128]

544			$MH^+ = 455$
545			$MH^+ = 429$
546			$MH^+ = 455$ m. p. = 80.1 °C
547			$MH^+ = 429$ m. p. = 64.7 °C

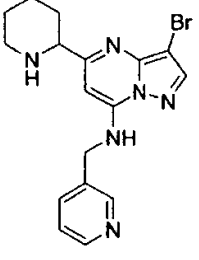
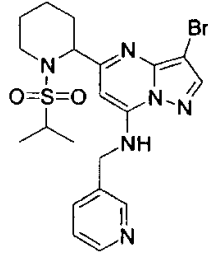
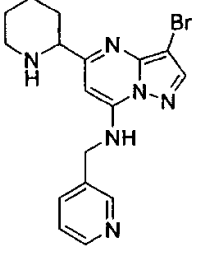
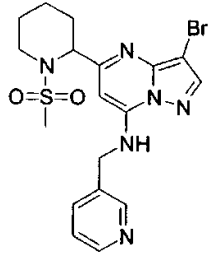
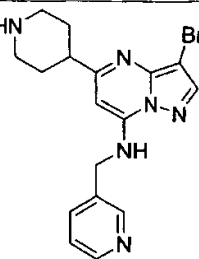
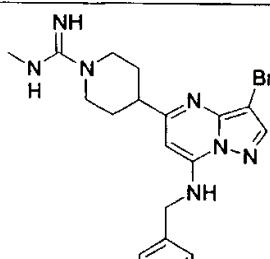
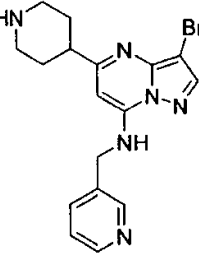
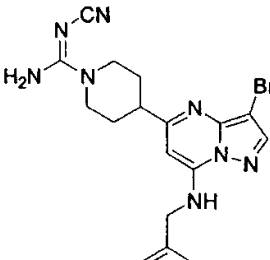
[1129]

548			<p>MH⁺ = 494 m. p. = 76.5 °C</p>
549			<p>MH⁺ = 493 m. p. = 83.6 °C</p>
550			<p>MH⁺ = 465 m. p. = 207.5 °C</p>
551			<p>MH⁺ = 494</p>

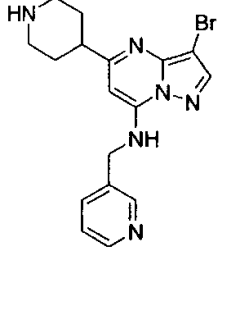
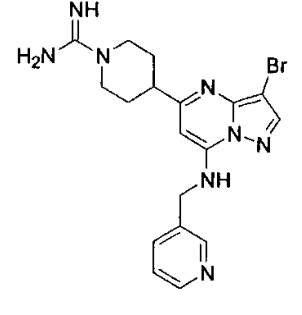
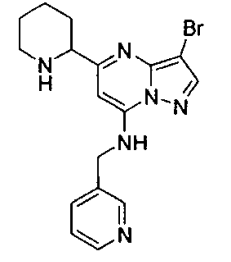
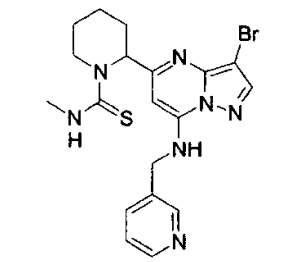
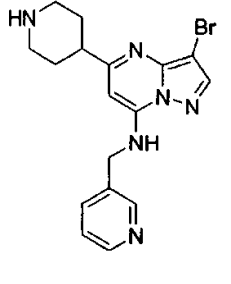
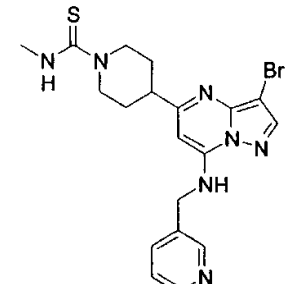
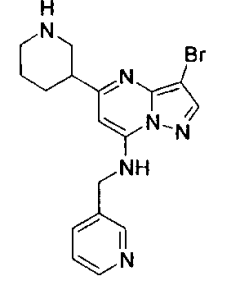
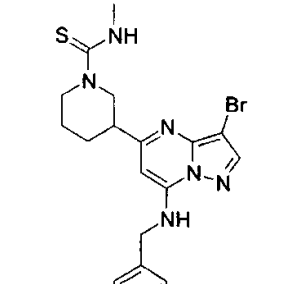
[1130]

552			$MH^+ = 493$
553			$MH^+ = 465$
554			$MH^+ = 481$ m. p. = 102.7 °C
555			$MH^+ = 494$ m. p. = 85.3 °C

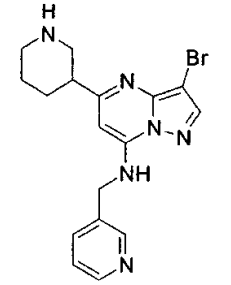
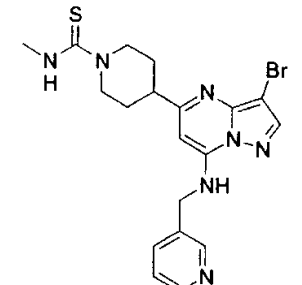
[1131]

556			<p>MH⁺ = 493 m. p. = 89.1 °C</p>
557			<p>MH⁺ = 465 m. p. = 83.8 °C</p>
558			<p>수용액 = 양 MH⁺ = 443 m. p. = 98.3 °C (HCl 염)</p>
559			<p>MH⁺ = 454</p>

[1132]

560			수율 = 양 $MH^+ = 429$ m. p. = 111.5 – 112.6 $^{\circ}C$
561			$MH^+ = 460$ m. p. = 122.7 $^{\circ}C$
562			$MH^+ = 460$ m. p. = 95.4 $^{\circ}C$
563			$MH^+ = 460$

[1133]

564			$MH^+ = 460$ m. p. = 95.4 $^{\circ}C$
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[1134]

[1135] 선택 실시예에 대한 추가의 데이터는 다음에 나타내었다.

실시예 534: $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.66 – 8.62 (s, 1H), 8.62 – 8.58 (d, 1H), 7.95 (s, 1H), 7.72 – 7.68 (d, 1H), 7.36 – 7.31 (dd, 1H), 6.66 – 6.62 (t, 1H), 5.93 (s, 1H), 4.65 – 4.62 (d, 2H), 3.86 – 3.82 (d, 1H), 3.65 – 3.58 (m, 1H), 3.26 – 3.12 (dd, 4H), 3.02 – 2.80 (m, 3H), 2.10 – 2.00 (m, 1H), 1.67 – 1.57 (m, 3H).

실시예 535: $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.66 – 8.62 (s, 1H), 8.62 – 8.58 (d, 1H), 7.95 (s, 1H), 7.72 – 7.67 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.70 – 6.64 (t, 1H), 5.90 (s, 1H), 4.63 – 4.61 (d, 2H), 3.93 – 3.86 (m, 1H), 3.69 – 3.61 (m, 4H), 3.27 – 3.23 (m, 4H), 3.10 – 3.01 (dd, 1H), 2.93 – 2.84 (m, 2H), 2.08 – 2.03 (m, 1H), 1.90 – 1.57 (m, 4H).

실시예 536: $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.67 (s, 1H), 8.62 – 8.58 (d, 1H), 7.96 (s, 1H), 7.72 – 7.68 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.79 – 6.72 (t, 1H), 5.96 (s, 1H), 4.86 (br s, 2H), 4.66 – 4.63 (d, 2H), 3.89 – 3.73 (m, 2H), 3.55 – 3.32 (m, 2H), 3.00 – 2.89 (m, 1H), 2.10 – 1.97 (m, 2H), 1.70 – 1.53 (m, 2H).

실시예 537: $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.66 (s, 1H), 8.62 – 8.58 (d, 1H), 7.98 (s, 1H), 7.77 – 7.76 (t, 1H), 7.72 – 7.69 (d, 1H), 7.63 – 7.59 (m, 1H), 7.56 (s, 1H), 7.36 – 7.29 (dd, 1H), 6.83 – 6.79 (t, 1H), 5.96 (s, 1H), 4.67 – 4.64 (d, 2H), 3.98 – 3.93 (dd, 1H), 3.79 – 3.68 (m, 2H), 3.37 – 3.28 (m, 1H), 3.03 – 2.94 (m, 1H), 2.12 – 1.99 (m, 1H), 1.76 – 1.56 (m, 3H).

실시예 544: $^1\text{H NMR}$ (300MHz, CDCl_3) δ 8.66 – 8.62 (d, 1H), 8.61 – 8.58 (dd, 1H), 7.95 (s, 1H), 7.72 – 7.67 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.80 – 6.62 (br s, 1H), 5.88 (s, 1H), 4.63 (s, 2H), 3.08 – 2.95 (m, 2H), 2.87 – 2.80 (m, 2H), 2.04 (m,

[1136]

1H), 1.85 – 1.78 (m, 4H), 1.52 – 1.44 (m, 1H), 0.87 – 0.82 (m, 2H), 0.72 – 0.66 (m, 2H).

실시예 545: ¹H NMR (300MHz, CDCl₃) δ 8.66 (s, 1H), 8.62 – 8.58 (br t, 1H), 7.97 (s, 1H), 7.73 – 7.68 (d, 1H), 7.36 – 7.30 (br t, 1H), 6.79 – 6.72 (br t, 1H), 5.96 (s, 1H), 4.64 (br s, 2H), 4.59 – 4.46 (br d, 1H), 3.95 – 3.74 (br m, 1H), 3.57 – 3.49 (dd, 1H), 3.10 – 3.01 (dd, 1H), 2.86 – 2.70 (m, 2H), 2.13 (s, 3H), 2.06 – 2.00 (m, 2H), 1.65 – 1.48 (m, 2H).

실시예 551: ¹H NMR (300MHz, CDCl₃) δ 8.67 (s, 1H), 8.63 – 8.59 (d, 1H), 7.96 (s, 1H), 7.74 – 7.69 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.69 – 6.64 (t, 1H), 5.95 (s, 1H), 4.67 – 4.63 (d, 2H), 3.85 3.65 (m, 1H), 3.75 – 3.65 (m, 1H), 3.25 – 3.18 (dd, 1H), 3.03 – 2.90 (m, 2H), 2.81 (s, 6H), 2.03 – 1.95 (m, 1H), 1.89 – 1.68 (m, 3H).

실시예 552: ¹H NMR (300MHz, CDCl₃) δ 8.67 (s, 1H), 8.62 – 8.59 (d, 1H), 7.95 (s, 1H), 7.74 – 7.69 (d, 1H), 7.36 – 7.31 (dd, 1H), 6.67 – 6.60 (t, 1H), 5.98 (s, 1H), 4.67 – 4.63 (d, 2H), 3.92 – 3.86 (m, 1H), 3.85 – 3.75 (m, 1H), 3.40 – 3.30 (dd, 1H), 3.27 – 3.16 (m, 1H), 3.10 – 2.86 (m, 2H), 2.10 – 1.78(m, 3H), 1.40– 1.30 (d, 6H).

실시예 553: ¹H NMR (300MHz, CDCl₃) δ 8.67 (s, 1H), 8.62 (br s, 1H), 7.96 (s, 1H), 7.74 – 7.69 (d, 1H), 7.36 – 7.31 (dd, 1H), 6.70 – 6.66 (t, 1H), 5.98 (s, 1H), 4.67 – 4.63 (d, 2H), 3.88 – 3.81 (m, 1H), 3.71 – 3.65 (m, 1H), 3.20 – 3.11 (dd, 1H), 3.02 – 2.91 (m, 1H), 2.90 – 2.80 (m, 4H), 2.01 – 1.80 (m, 3H).

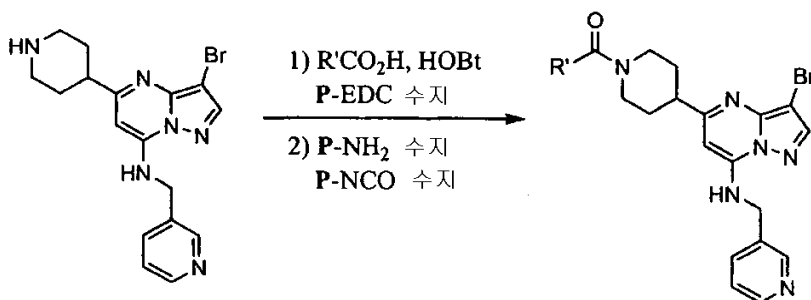
실시예 559: ¹H NMR (300MHz, CDCl₃) δ 8.66–8.60 (d, 1H), 8.50 – 8.44 (dd, 1H), 8.01 (s, 1H), 7.93 (m, 1H), 7.48 – 7.40 (dd, 1H), 6.08 (s, 1H), 4.80 – 7.74 (s, 2H), 4.32 – 4.19 (br d, 2H), 3.10 – 2.86 (m, 2H), 1.95 – 1.68 (m, 4H).

실시예 563: ¹H NMR (300MHz, CDCl₃) δ 8.66 (s, 1H), 8.62 – 8.58 (d, 1H), 7.96 (s, 1H), 7.73 – 7.68 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.96 – 6.86 (br s, 1H), 6.79 – 6.74 (t, 1H), 6.00 (s, 1H), 4.67 – 4.64 (d, 2H), 4.37 – 4.30 (dd, 1H), 4.22 – 4.13 (m, 1H), 3.97 – 3.86 (dd, 1H), 3.73 – 3.64 (m, 1H), 3.17 – 3.14 (d, 3H), 3.07 – 2.99 (m, 1H), 2.20 – 1.97 (m, 2H), 1.68 – 1.48 (m, 2H).

[1137]

[1138]

일반 과정 1: 아마이드 형성 평행 합성을 위한 과정:



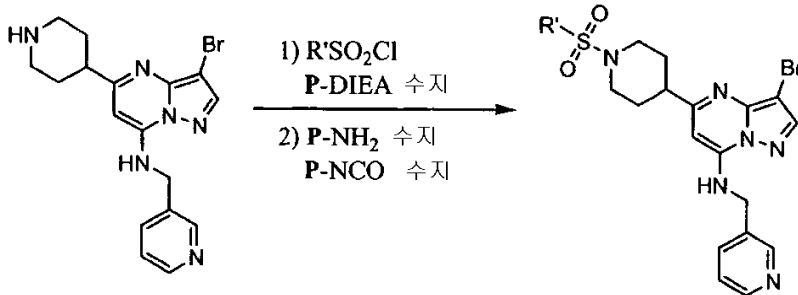
[1139]

[1140]

평행 합성을 제거 가능한 상부 밀봉부를 갖고 고정된 하부 밀봉부를 갖는 폴리프로필렌 96-웰 반응 블럭 속에서 수행하였다. 각각의 반응을 20 마이크로폴리프로필렌 하부 프릿으로 장착하고 최대 용적은 3mL이었다. 회수 블럭은 하부 프릿을 장착시키지 않았다. 각각의 반응 웰에 DMF-THF-MeCN 혼합물(4:3:3 v/v, 0.95mL), EDC 수지(P-EDC, Polymer Laboratories Ltd., 43mg, 0.063mmol), 1-하이드록시벤조트리아졸(HOBt, 5.67mg,

0.042mmol) 및, 디메틸포름아미드 중의 카복실산의 용액(1M, 0.0315mL, 0.0315mmol)에 용해시켰다. 반응 혼합물을 실온에서 16시간 동안 교반하였다. 조악한 생성물 용액을 트리스아민 수지(P-NH₂, Argonaut Tech. Inc., 30mg, 0.126mmol) 및 이소시아네이트 수지(P-NCO, Argonaut Tech. Inc., 35mg, 0.063mmol)이 첨가된 반응 웰 속으로 여과시켰다. 반응 혼합물을 실온에서 16시간 동안 교반시키고, 회수 블럭 속으로 여과시켰다. 생성물 용액을 감압하에 증발시켜 목적하는 아미드 생성물을 수득하였다.

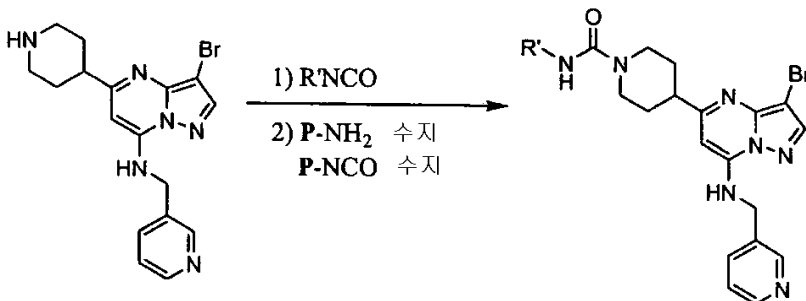
[1141] 일반 과정 2: 설폰아미드 형성 평행 합성을 위한 과정



[1142]

[1143] 평행 합성을 제거 가능한 상부 밀봉부 및 고정된 하부 밀봉부를 갖는 폴리프로필렌 96-웰 반응 블럭 속에서 수행하였다. 각각의 반응 웰을 20마이크론 폴리프로필렌 하부 프릿으로 장착시켰고 최대 용적은 3mL이었다. 회수 블럭은 하부 프릿이 장착되지 않았다. 각각의 반응 웰에 DMF-THF-MeCN 혼합물(3:2:2 v/v, 0.95 mL)에 용해된 아민의 용액(0.021mmol), DIEA 수지(P-DIEA, Argonaut Tech. INC., 18 mg, 0.063 MMOL) 및, 디메틸포름아미드 중의 설폰닐 클로라이드 용액(1M, 0.0315mL, 0.0315mmol)을 가하였다. 반응 혼합물을 실온에서 16시간 동안 교반하였다. 조악한 생성물 용액을 트리스아민 수지(P-NH₂, Argonaut Tech. Inc., 30mg, 0.126mmol) 및 이소시아네이트 수지(P-NCO, Argonaut Tech. Inc., 35mg, 0.063mmol)이 첨가된 반응 웰 속으로 여과시켰다. 반응 혼합물을 실온에서 16시간 동안 교반하고 회수 블럭 속으로 여과시켰다. 생성물 용액을 감압하에 증발시켜 목적하는 설폰아미드 생성물을 수득하였다.

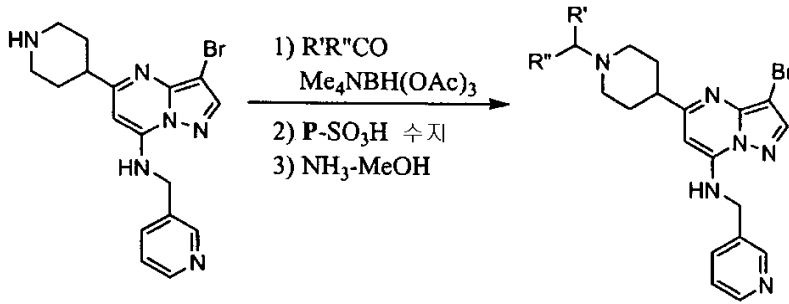
[1144] 일반 과정 3: 우레아 형성 평행 합성을 위한 과정



[1145]

[1146] 평행 합성을 제거 가능한 상부 밀봉부 및 고정된 하부 밀봉부를 갖는 폴리프로필렌 96-웰 반응 블럭 속에서 수행하였다. 각각의 반응 웰을 20마이크론 폴리프로필렌 하부 프릿으로 장착시켰고 최대 용적은 3mL이었다. 회수 블럭은 하부 프릿이 장착되지 않았다. 각각의 반응 웰에 DMF-MeCN 혼합물(1:1 v/v, 0.95 mL)에 용해된 아민의 용액(0.021mmol) 및, 디클로로메탄중의 이소시아네이트 용액(0.33M, 0.126mL, 0.042mmol)을 가하였다. 반응 혼합물을 실온에서 16시간 동안 교반하였다. 조악한 생성물 용액을 트리스아민 수지(P-NH₂, Argonaut Tech. Inc., 30mg, 0.126mmol) 및 이소시아네이트 수지(P-NCO, Argonaut Tech. Inc., 35mg, 0.063mmol)이 첨가된 반응 웰 속으로 여과시켰다. 반응 혼합물을 실온에서 16시간 동안 교반하고 회수 블럭 속으로 여과시켰다. 생성물 용액을 감압하에 증발시켜 목적하는 우레아 생성물을 수득하였다.

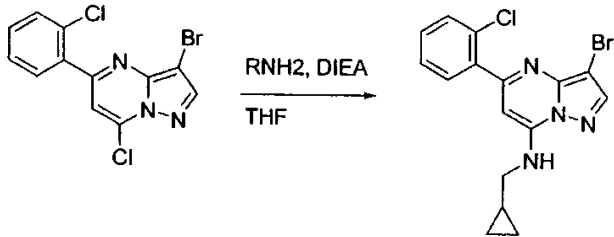
[1147] 일반 과정 4: 환원적 알킬화 평행 합성을 위한 과정



[1148]

[1149] 평행 합성을 제거 가능한 상부 밀봉부 및 고정된 하부 밀봉부를 갖는 폴리프로필렌 96-웰 반응 블록 속에서 수행하였다. 각각의 반응 웰을 20마이크론 폴리프로필렌 하부 프릿으로 장착시켰고 최대 용적은 3mL이었다. 회수 블록은 하부 프릿이 장착되지 않았다. 각각의 반응 웰에 AcOH-DCE 혼합물(1: 99 v/v, 0.5mL)에 용해된 아민의 용액(0.021mmol), 디클로로에탄중의 알데히드 또는 케톤의 용액(1M, 0.147mL, 0.147mmol), 및 AcOH-DCE 혼합물(1: 99 v/v, 0.5mL)에 용해된 테트라메틸암모늄 트리아세톡시보로하이드라이드의 용액(11mg, 0.042mmol)을 가하였다. 반응 혼합물을 실온에서 3일 동안 교반하였다. 조악한 생성물 용액을 설폰산 수지 랜턴(Lantern)(P-SO₃H, Mimotopes Pty Ltd., 0.3mmol)이 담지된 반응 웰 속으로 여과시켰다. 반응 혼합물을 실온에서 2시간 동안 교반하고 경사여과하였다. 생성물 수지 랜턴을 메탄올(1mL)로 3회 세척하였다. 메탄올(2M, 1.2mL) 중의 암모니아의 용액을 가하였다. 반응 혼합물을 실온에서 30분 동안 교반하고, 회수 블록 속으로 여과시켰다. 생성물 용액을 감압하에 증발시켜 목적하는 3급 아민 생성물을 수득하였다.

[1150] 일반 과정 5: 7,N-치환된 피라졸로[1,5a]피리미딘의 평행 합성을 위한 과정



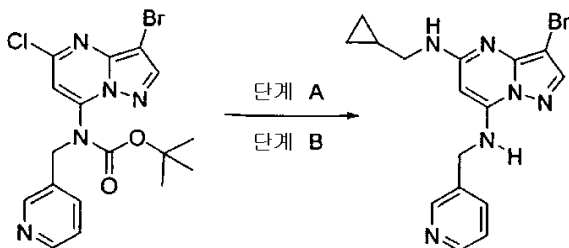
[1151]

[1152] 테트라하이드로푸란 중의 3-브로모-7-클로로-5-(2-(4-클로로-페닐)-피라졸로[1,5a]피리미딘(9.0mg, 0.03mmol)에 디-이소-프로필에틸아민(12μL, 0.07mmol)을 가한 다음, 사이클로프로필메틸아민(70μL, .07mmol ; DMF중의 1M 용액)을 가하였다. 반응 혼합물을 70°C로 36시간 동안 가열한 다음, 실온으로 냉각시켰다. 혼합물을 (P-NCO, Argonaut Tech. Inc, 70mg, 0.12mmol) 및 P-CO₃ (Argonaut Tech. Inc. 70mg, 0.24mmol)로 처리하고 실온에서 12 내지 18 시간 동안 교반하였다. 용액을 여과하고 증발 건조시켜 생성물을 수득하였다. 관찰치: m/z 375.21.

[1153] 일반 과정 6: 5,N-치환된 피라졸로[1,5a]피리미딘의 평행 합성을 위한 과정

[1154] 일반 프로토콜:

[1155] 평행 합성은 상기한 바와 같은 96웰 폴리프로필렌 블록 속에서 수행하였다. 가열이 필요한 경우, 반응은 폴리프로필렌 매트릭스 개별적으로 밀봉된 2.5mL 유리 튜브 속에서 수행하고 96웰 가열 이동 블록으로 가열하였다.



[1156]

[1157] 단계 A:

[1158] p-디옥산중의 3-브로모-5-클로로-7-N-Boc-알킬아미노-피라졸로[1,5-a]피리미딘(17mg, 0.04mmol)에 DIEA(9 μ l, 0.05mmol)를 가한 다음, 사이클로프로필-메틸아민(80 μ l, .08mmol; 이소프로판올 중의 1M 용액)을 가하였다. 반응 혼합물을 90 $^{\circ}$ C 로 36시간 동안 가열한 다음, 실온으로 냉각시켰다. 혼합물을 P-NCO(Argonaut Tech. Inc. 70mg, 0.12mmol) 및 P-CO₃(Argonaut Tech. Inc. 70mg, 0.24mmol)로 처리하고 실온에서 12 내지 18시간 동안 교반하였다. 용액을 여과시키고 증발 건조시켜 생성물을 수득하였다.

[1159] 단계 B (산성):

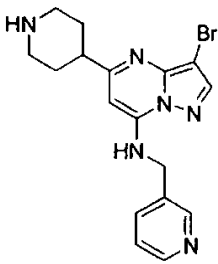
[1160] 단계 A로부터의 생성물을 35% TFA/DCM에 용해시키고 4시간 동안 교반한 다음 고진공하에 농축시켰다. 잔사를 MeOH중의 10% HCl (수성)로 처리하고 2시간 동안 교반한 다음, 농축시켜 목적 생성물을 수득하였다. 관찰치: m/z 375.21.

[1161] 단계 B (염기성):

[1162] 단계 A로부터의 생성물을 EtOH에 용해시키고 Ambersep[®] 900-OH 이온 교환 수지(Acros, 100mg)으로 처리하고, 부드럽게 교반하면서 환류하에 48시간 동안 가열하였다. 반응 혼합물을 실온으로 냉각시키고 여과하고 농축시켜 목적 생성물을 수득하였다.

[1163] 실시예 565:

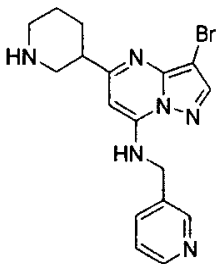
[1164] 일반 과정 1에 나타낸 과정 및 하기한 실시예 462로부터의 화합물을 이용하여, 표 43에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1165]

[1166] 실시예 566:

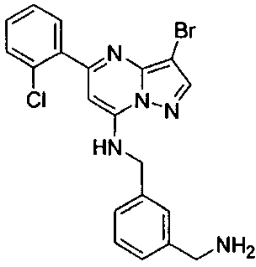
[1167] 일반 과정 1에 나타낸 과정 및 하기한 실시예 471로부터의 화합물을 이용하여, 표 44에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1168]

[1169] 실시예 567:

[1170] 일반 과정 1에 나타낸 과정 및 하기한 실시예 515로부터의 화합물을 이용하여, 표 45에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



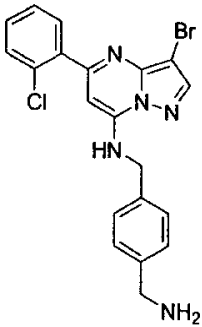
[1171]

[1172]

실시예 568:

[1173]

일반 과정 1에 나타낸 과정 및 하기한 실시예 513으로부터의 화합물을 이용하여, 표 43에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



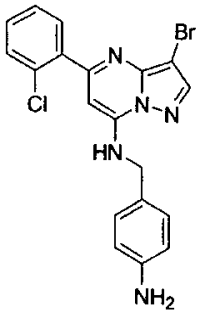
[1174]

[1175]

실시예 569:

[1176]

일반 과정 1에 나타낸 과정 및 하기한 실시예 526로부터의 화합물을 이용하여, 표 47에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



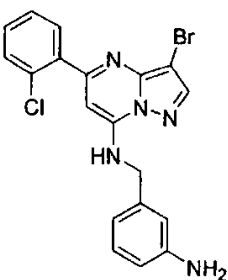
[1177]

[1178]

실시예 570:

[1179]

일반 과정 1에 나타낸 과정 및 하기한 실시예 524로부터의 화합물을 이용하여, 표 48에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



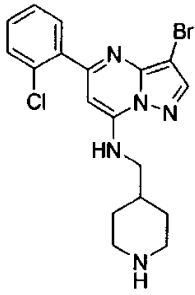
[1180]

[1181]

실시예 571:

[1182]

일반 과정 1에 나타낸 과정 및 하기한 실시예 525로부터의 화합물을 이용하여, 표 49에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



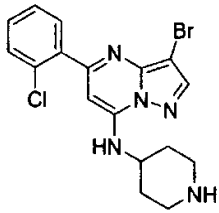
[1183]

[1184]

실시예 572:

[1185]

일반 과정 1에 나타낸 과정 및 하기한 실시예 526.10로부터의 화합물을 이용하여, 표 50에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



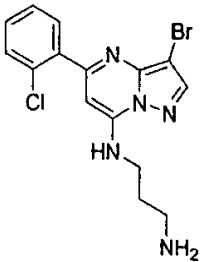
[1186]

[1187]

실시예 573:

[1188]

일반 과정 1에 나타낸 과정 및 하기한 실시예 518로부터의 화합물을 이용하여, 표 51에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



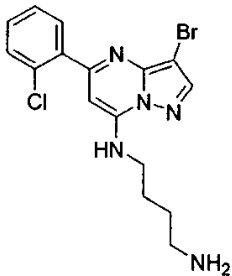
[1189]

[1190]

실시예 574:

[1191]

일반 과정 1에 나타낸 과정 및 하기한 실시예 519로부터의 화합물을 이용하여, 표 52에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



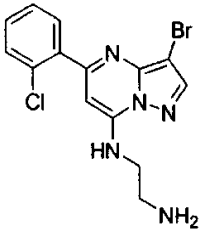
[1192]

[1193]

실시예 575:

[1194]

일반 과정 1에 나타낸 과정 및 하기한 실시예 520로부터의 화합물을 이용하여, 표 53에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



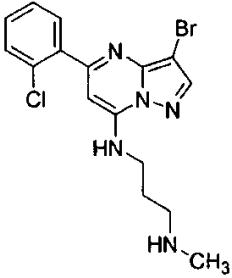
[1195]

[1196]

실시예 576:

[1197]

일반 과정 1에 나타낸 과정 및 하기한 실시예 522로부터의 화합물을 이용하여, 표 54에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



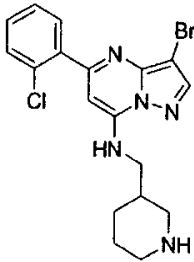
[1198]

[1199]

실시예 577:

[1200]

일반 과정 1에 나타낸 과정 및 하기한 실시예 523로부터의 화합물을 이용하여, 표 55에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



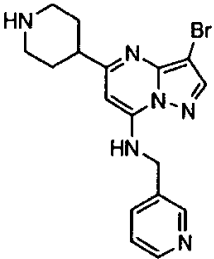
[1201]

[1202]

실시예 578:

[1203]

일반 과정 2에 나타낸 과정 및 하기한 실시예 462로부터의 화합물을 이용하여, 표 56에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



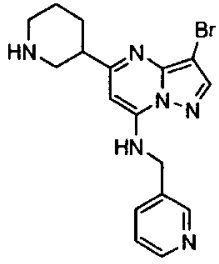
[1204]

[1205]

실시예 579:

[1206]

일반 과정 2에 나타낸 과정 및 하기한 실시예 471로부터의 화합물을 이용하여, 표 57에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



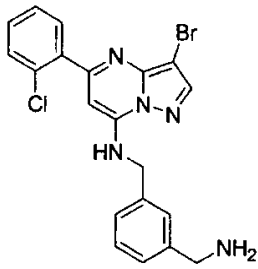
[1207]

[1208]

실시예 580:

[1209]

일반 과정 2에 나타낸 과정 및 하기한 실시예 515로부터의 화합물을 이용하여, 표 58에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



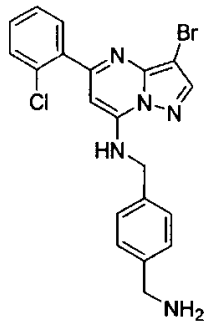
[1210]

[1211]

실시예 581:

[1212]

일반 과정 2에 나타낸 과정 및 하기한 실시예 513로부터의 화합물을 이용하여, 표 59에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



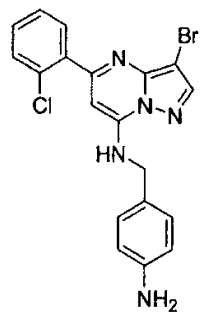
[1213]

[1214]

실시예 582:

[1215]

일반 과정 2에 나타낸 과정 및 하기한 실시예 513로부터의 화합물을 이용하여, 표 60에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



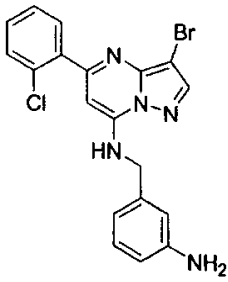
[1216]

[1217]

실시예 583:

[1218]

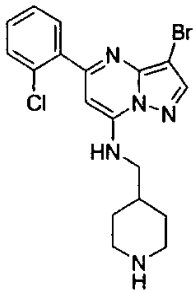
일반 과정 2에 나타낸 과정 및 하기한 실시예 524로부터의 화합물을 이용하여, 표 61에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1219]

[1220] 실시예 584:

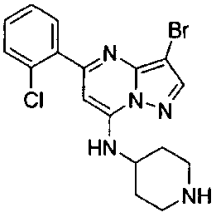
[1221] 일반 과정 2에 나타낸 과정 및 하기한 실시예 525로부터의 화합물을 이용하여, 표 62에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1222]

[1223] 실시예 585:

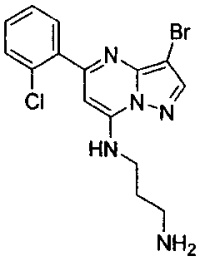
[1224] 일반 과정 2에 나타낸 과정 및 하기한 실시예 526.10로부터의 화합물을 이용하여, 표 63에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1225]

[1226] 실시예 586:

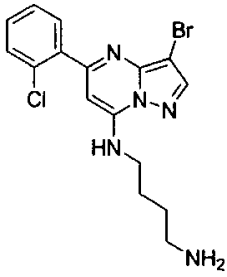
[1227] 일반 과정 2에 나타낸 과정 및 하기한 실시예 518로부터의 화합물을 이용하여, 표 64에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1228]

[1229] 실시예 587:

[1230] 일반 과정 2에 나타낸 과정 및 하기한 실시예 519로부터의 화합물을 이용하여, 표 65에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



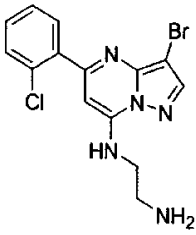
[1231]

[1232]

실시예 588:

[1233]

일반 과정 2에 나타난 과정 및 하기한 실시예 520으로부터의 화합물을 이용하여, 표 67에 나타난 관찰치 m/z을 갖는 화합물을 제조하였다.



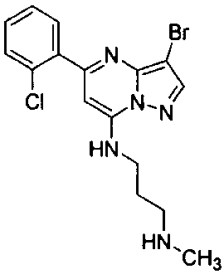
[1234]

[1235]

실시예 589:

[1236]

일반 과정 2에 나타난 과정 및 하기한 실시예 521로부터의 화합물을 이용하여, 표 68에 나타난 관찰치 m/z을 갖는 화합물을 제조하였다.



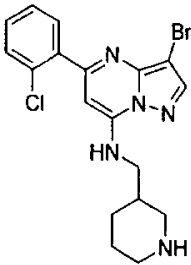
[1237]

[1238]

실시예 590:

[1239]

일반 과정 2에 나타난 과정 및 하기한 실시예 523로부터의 화합물을 이용하여, 표 69에 나타난 관찰치 m/z을 갖는 화합물을 제조하였다.



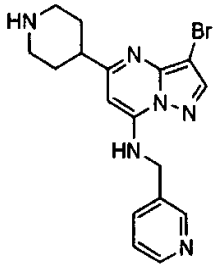
[1240]

[1241]

실시예 591:

[1242]

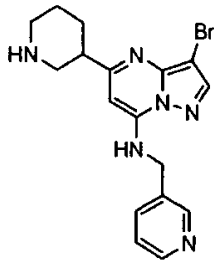
일반 과정 3에 나타난 과정 및 하기한 실시예 462로부터의 화합물을 이용하여, 표 70에 나타난 관찰치 m/z을 갖는 화합물을 제조하였다.



[1243]

[1244] 실시예 592:

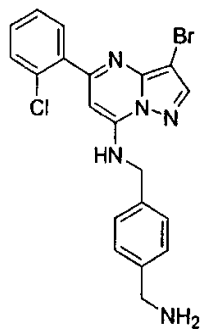
[1245] 일반 과정 3에 나타낸 과정 및 하기한 실시예 471로부터의 화합물을 이용하여, 표 71에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1246]

[1247] 실시예 593:

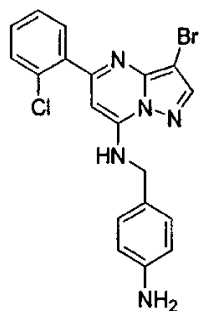
[1248] 일반 과정 3에 나타낸 과정 및 하기한 실시예 513로부터의 화합물을 이용하여, 표 72에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1249]

[1250] 실시예 594:

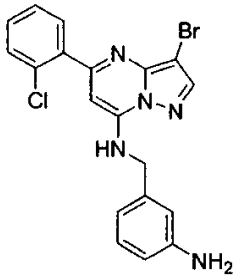
[1251] 일반 과정 3에 나타낸 과정 및 하기한 실시예 524로부터의 화합물을 이용하여, 표 73에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1252]

[1253] 실시예 595:

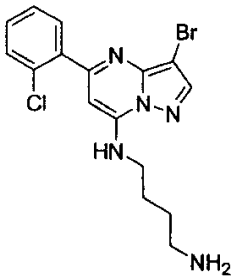
[1254] 일반 과정 3에 나타낸 과정 및 하기한 실시예 524로부터의 화합물을 이용하여, 표 74에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1255]

[1256] 실시예 596:

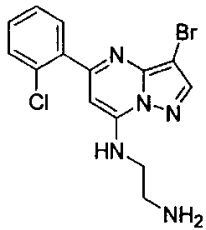
[1257] 일반 과정 3에 나타난 과정 및 하기한 실시예 519로부터의 화합물을 이용하여, 표 75에 나타난 관찰치 m/z을 갖는 화합물을 제조하였다.



[1258]

[1259] 실시예 597:

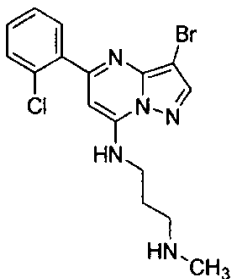
[1260] 일반 과정 3에 나타난 과정 및 하기한 실시예 520로부터의 화합물을 이용하여, 표 76에 나타난 관찰치 m/z을 갖는 화합물을 제조하였다.



[1261]

[1262] 실시예 598:

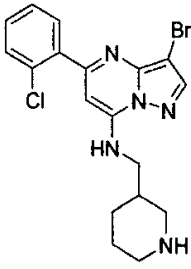
[1263] 일반 과정 3에 나타난 과정 및 하기한 실시예 521로부터의 화합물을 이용하여, 표 77에 나타난 관찰치 m/z을 갖는 화합물을 제조하였다.



[1264]

[1265] 실시예 599:

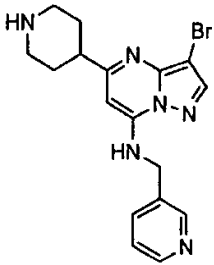
[1266] 일반 과정 3에 나타난 과정 및 하기한 실시예 523로부터의 화합물을 이용하여, 표 78에 나타난 관찰치 m/z을 갖는 화합물을 제조하였다.



[1267]

[1268] 실시예 600:

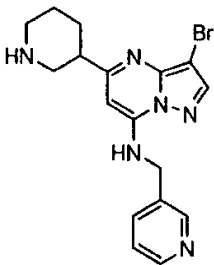
[1269] 일반 과정 4에 나타낸 과정 및 하기한 실시예 462로부터의 화합물을 이용하여, 표 79에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1270]

[1271] 실시예 601:

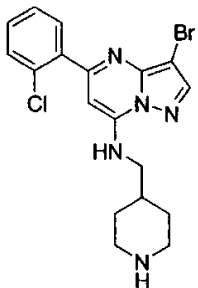
[1272] 일반 과정 4에 나타낸 과정 및 하기한 실시예 471로부터의 화합물을 이용하여, 표 80에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1273]

[1274] 실시예 602:

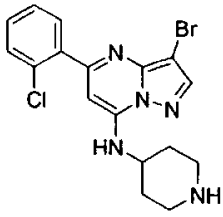
[1275] 일반 과정 4에 나타낸 과정 및 하기한 실시예 525로부터의 화합물을 이용하여, 표 81에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



[1276]

[1277] 실시예 603:

[1278] 일반 과정 4에 나타낸 과정 및 하기한 실시예 526.10로부터의 화합물을 이용하여, 표 82에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



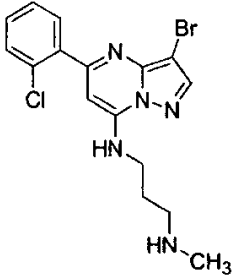
[1279]

[1280]

실시예 604:

[1281]

일반 과정 4에 나타낸 과정 및 하기한 실시예 521로부터의 화합물을 이용하여, 표 83에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



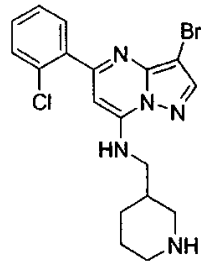
[1282]

[1283]

실시예 605:

[1284]

일반 과정 4에 나타낸 과정 및 하기한 실시예 523로부터의 화합물을 이용하여, 표 84에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



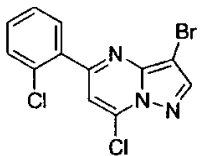
[1285]

[1286]

실시예 606:

[1287]

일반 과정 5에 나타낸 과정 및 하기한 제조 실시예 81로부터의 화합물을 이용하여, 표 85에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



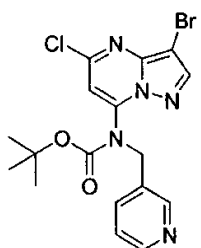
[1288]

[1289]

실시예 607:

[1290]

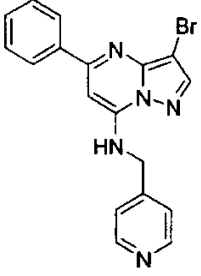
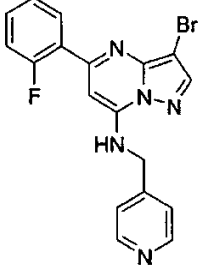
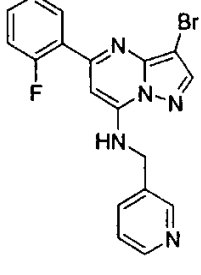
일반 과정 6에 나타낸 과정 및 하기한 실시예 196로부터의 화합물을 이용하여, 표 86에 나타낸 관찰치 m/z을 갖는 화합물을 제조하였다.



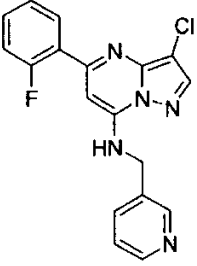
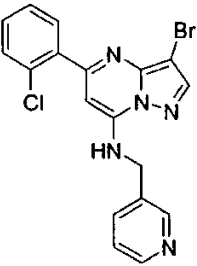
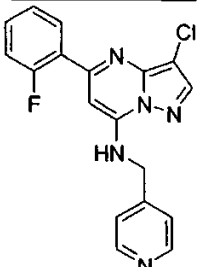
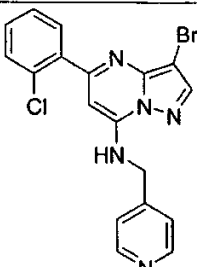
[1291]

- [1292] 검정:
- [1293] 바큘로바이러스(baculovirus) 작제:
- [1294] 사이클린 A 및 E를, 아미노-말단에서 GluTAG 서열(EYMPME)을 가하여 항- GluTAG 친화성 컬럼상에서 정제를 수행하도록 하면서, PCR로 pFASTBAC (인비트로젠)로 클로닝한다. 발현된 단백질의 크기는 대략 46kDa (사이클린 E) 및 50kDa (사이클린 A)이다. CDK2는 또한 카복시-말단(YDVPDYAS)에서 해마글루티닌 에피토프를 첨가하면서, PCR에 의해 pFASTBAC 내로 클로닝하였다. 발현된 단백질의 크기는 대략 34kDa이었다.
- [1295] 효소 생산:
- [1296] 사이클린 A, E 및 CDK2를 발현하는 재조합 바큘로바이러스를 5의 다중 감염도(MOI)에서 SF9 세포내로 48시간 동안 감염시켰다. 세포를 1000RPM에서 10분 동안 원심분리하여 수거하였다. 사이클린을 함유하는(E 또는 A) 펠렛을 CDK2를 함유하는 세포 펠렛과 합하고 30분 동안 빙상에서 용적이 펠렛 용적의 5배인, 50mM 트리스 pH 8.0, 0.5% NP40, 1mM DTT 및 프로테아제/포스파타제 억제제(제조원: 독일 만하임에 소재하는 Roche Diagnostics GmbH)을 함유하는 분해 완충액속에서 분해하였다. 혼합물을 30 내지 60분 동안 교반하여 사이클린-CDK2 복합체 형성을 촉진하였다. 이후에, 혼합된 분해물을 15000RPM에서 10분 동안 회전시키고 상층액을 보유하였다. 5ml의 항-GluTAG 비드(SF9 세포 1리터에 대해)를 사용하여 사이클린-CDK2 복합체를 포획하였다. 결합한 비드를 분해 완충액으로 3회 세척하였다. 단백질을 100 내지 200 μ g/mL의 GluTAG 펩타이드를 함유하는 분해 완충액으로 완전히 용출시켰다. 용출물을 50mM 트리스 pH 8.0, 1mM DTT, 10mM MgCl₂, 100 μ M 나트륨 오르토바나테이트 및 20% 글리세롤을 함유하는 키나제 완충액 2 리터속에서 밤새 투석하였다. 효소를 -70 $^{\circ}$ C에서 분취량으로 저장하였다.
- [1297] 시험관내 키나제 검정:
- [1298] CDK2 키나제 검정(사이클린 A 또는 E-의존성)을 저 단백질 결합 96-웰 플레이트(뉴욕 코닝에 소재하는 Corning Inc.)에서 수행하였다. 효소를 50mM 트리스 pH 8.0, 10mM MgCl₂, 1mM DTT 및 0.1mM 나트륨 오르토바나테이트를 함유하는 키나제 완충액속에서 50 μ g/ml의 최종 농도로 희석시켰다. 당해 반응에 사용된 기질은 히스톤 H1(제조원: 영국 소재의 Amersham)으로부터 기원한 바이오티닐화된 펩타이드였다. 기질을 빙상에서 해동시키고 키나제 완충액속에서 2 μ M로 희석시켰다. 화합물을 10% DMSO 속에서 목적한 농도로 희석시켰다. 각각의 키나제 반응을 위해, 20 μ l의 50 μ g/ml의 효소 용액(1 μ g의 효소) 및 20 μ l의 1 μ M 기질 용액을 혼합한 후, 시험을 위해 각각의 웰에서 희석된 화합물 10 μ l와 합하였다. 키나제 반응을 50 μ l의 4 μ M ATP 및 1 μ Ci의 ³³P-ATP(제조원: 영국 소재의 Amersham)를 첨가하여 개시하였다. 반응을 실온에서 1시간 동안 수행하였다. 0.1% 트리톤 X-100, 1mM ATP, 5mM EDTA 및 5mg/ml의 스트렙타비딘 피복된 SPA 비드(제조원: 영국 소재의 Amersham)을 함유하는 정지 완충액 200 μ l를 15분 동안 가하여 정지시켰다. 이어서, SPA 비드를 필터메이트 유니버설 하베스터(Filtermate universal harvester: 제조원: Packard/Perkin Elmer Life Sciences)를 사용하여 96-웰 GF/B 여과기 플레이트(제조원: Packard/Perkin Elmer Life Sciences)상에 포획시켰다. 비 특이적 신호는, 비드를 2M NaCl로 2회 및 1% 포스폰산과 2M NaCl로 2회 세척하여 제거하였다. 이어서, 방사활성 신호를 TopCount 96 웰 액체 신타레이션 계수기(제조원: Packard/Perkin Elmer Life Sciences)을 사용하여 측정하였다.
- [1299] IC₅₀ 측정:
- [1300] 억제 화합물의 8점 일련 희석물로부터 각각 2회 산출한 억제 데이터로부터 용량-반응 그래프를 도시하였다. 화합물의 농도를 처리한 샘플의 CPM을 처리하지 않은 샘플의 CPM으로 나누어 계산한 키나제 활성 %에 대해 도시하였다. IC₅₀ 값을 생성시키기 위해, 이후에 용량-반응 곡선을 표준 S자 곡선에 대해 조정하고 IC₅₀ 값을 비선형 회귀 분석(nonlinear regression analysis)으로 유도하였다. 본 발명의 화합물에 대해 이렇게 수득한 IC₅₀ 값을 표 87에 나타낸다. 이러한 키나제 활성은 사이클린 A 또는 사이클린 E를 사용함으로써 위에서 기술한 검정을 사용하여 생성시켰다.

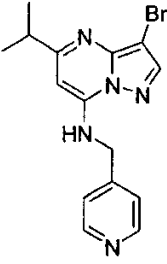
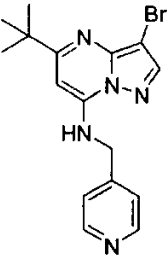
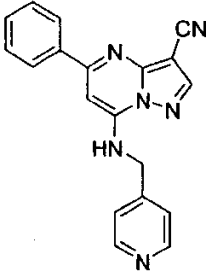
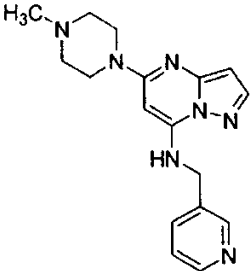
표 87

CMPD	실시예	IC ₅₀ (μM)
	1	0.020 0.029
	3	0.032 0.024
	4	0.011

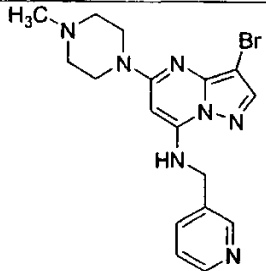
[1301]

	5	0.021
	8	0.003
	6	0.064 0.029
	7	0.01 0.006

[1302]

	10	0.042
	12	0.17
	16	0.62
	1	5.6

[1303]

	3	0.14
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[1304]

[1305]

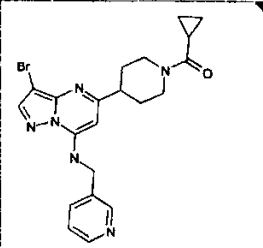
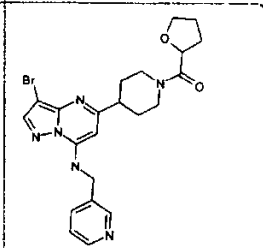
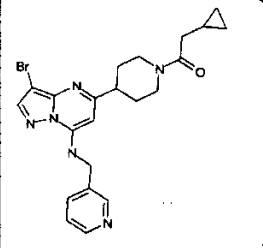
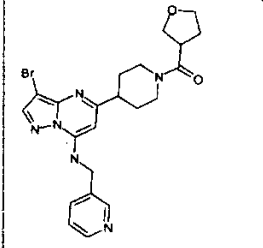
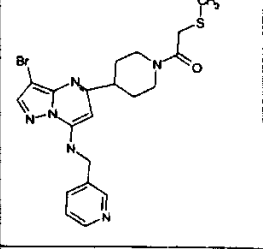
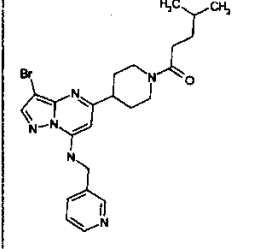
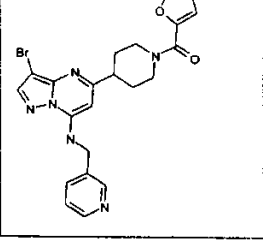
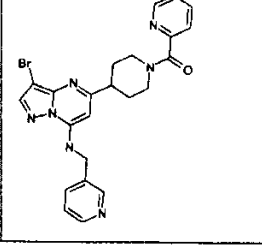
검정 값에 의해 위에서 입증되는 바와 같이, 본 발명의 화합물은 탁월한 CDK 억제 특성을 나타낸다.

[1306]

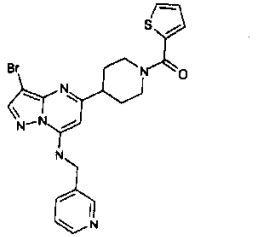
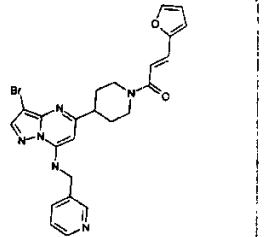
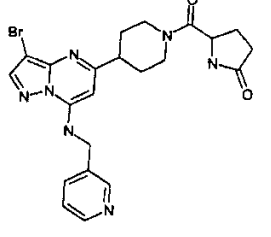
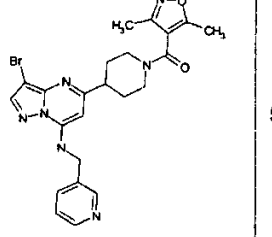
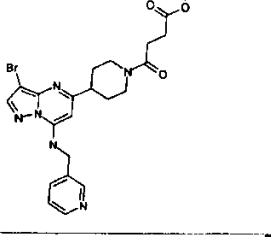
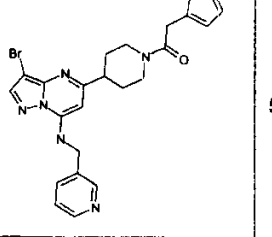
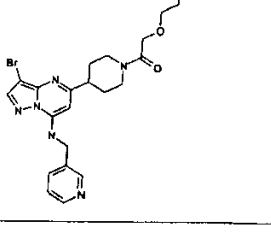
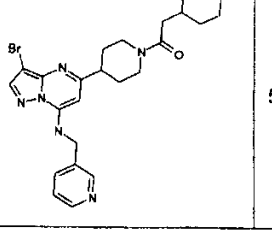
비록 본 발명이 위에 설정한 특정 양태와 함께 기술되었다 하더라도, 이의 많은 변경, 변형 및 기타 변화가 당해 분야의 숙련자들에게는 익숙할 것이다. 모든 이러한 변경, 변형 및 변화는 본 발명의 취지 및 영역내에 있

는 것으로 의도된다.

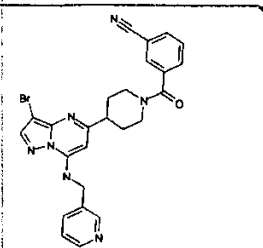
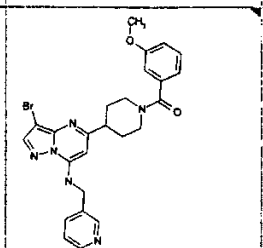
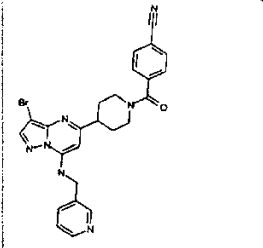
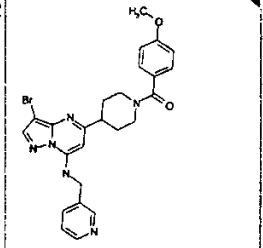
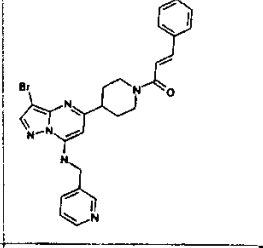
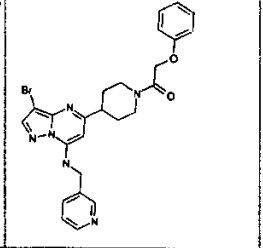
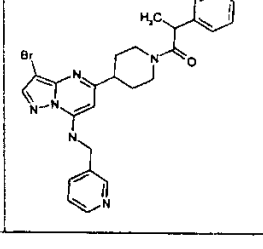
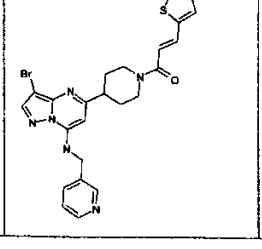
표 43

실시예	화합물	m/z	실시예	화합물	m/z
4301		457.25	4305		487.27
4302		471.26	4306		487.27
4303		477.26	4307		487.27
4304		483.27	4308		494.27

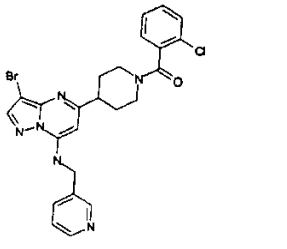
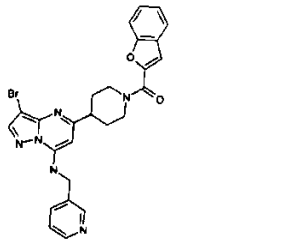
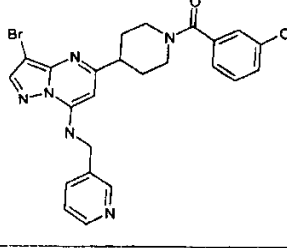
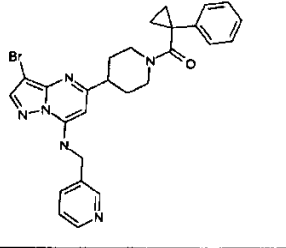
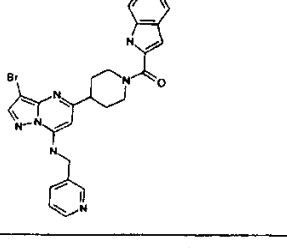
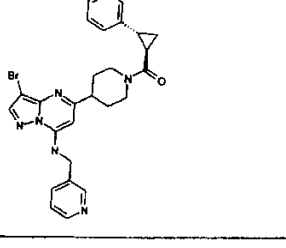
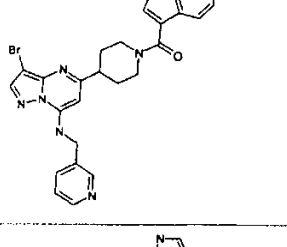
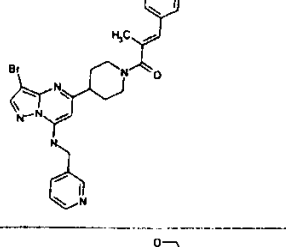
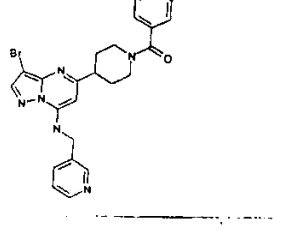
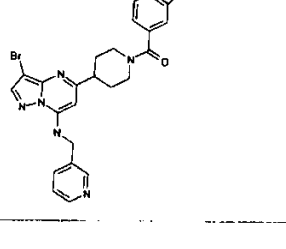
[1307]

실시예	생성물	m/z	실시예	생성물	m/z
4309		499.27	4313		509.28
4310		500.27	4314		512.28
4311		503.28	4315		513.28
4312		505.28	4316		513.28

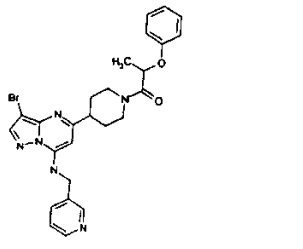
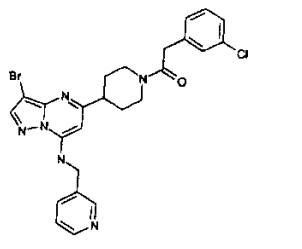
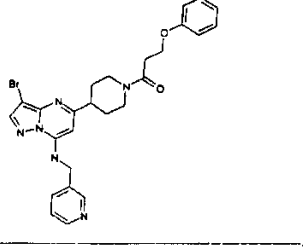
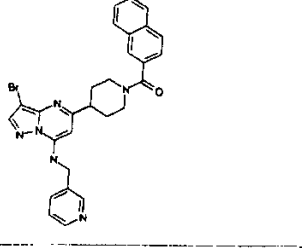
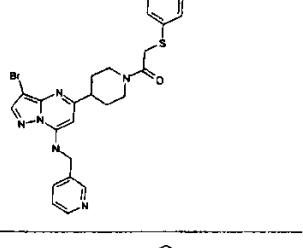
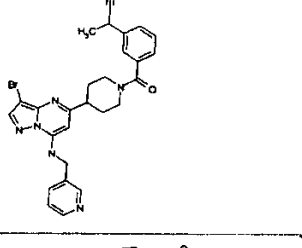
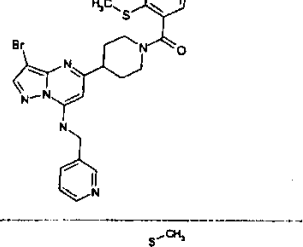
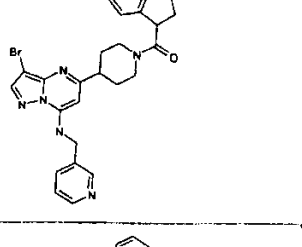
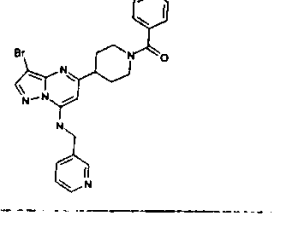
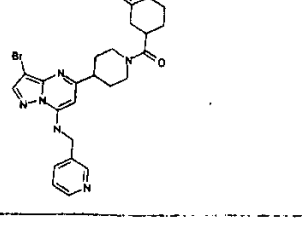
[1308]

실시예	생성물	m/z	실시예	생성물	m/z
4317		518.28	4321		523.29
4318		518.28	4322		523.29
4319		519.29	4323		523.29
4320		521.29	4324		525.29

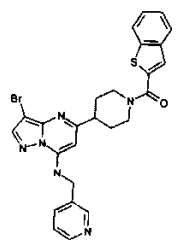
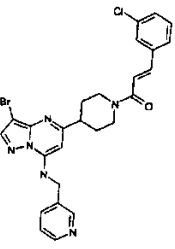
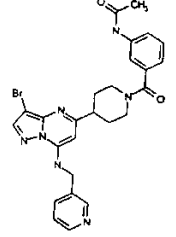
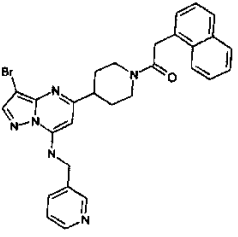
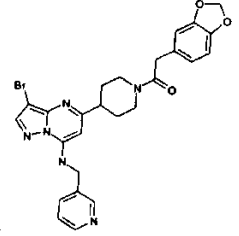
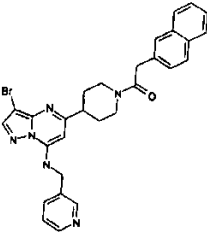
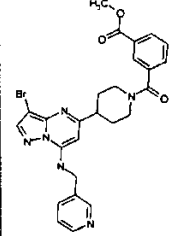
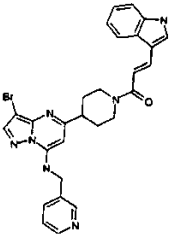
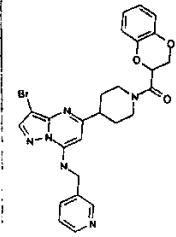
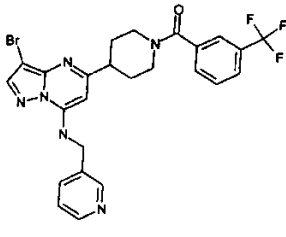
[1309]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4325 2. 527.29		1. 4330 2. 533.29
	1. 4326 2. 527.29		4331
	1. 4327 2. 532.29		1. 4332 2. 533.29
	1. 4328 2. 532.29		1. 4333 2. 533.29
	1. 4329 2. 532.29		1. 4334 2. 537.3

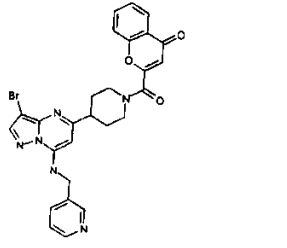
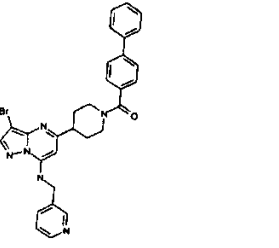
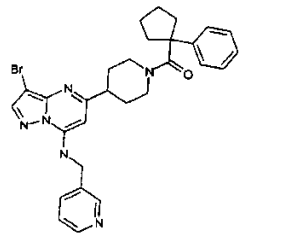
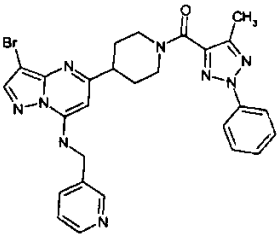
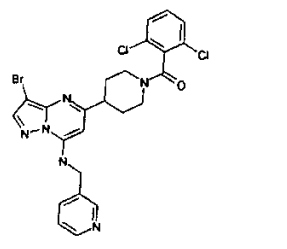
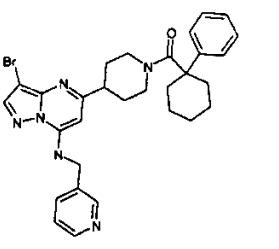
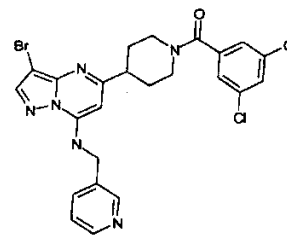
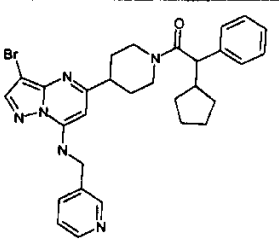
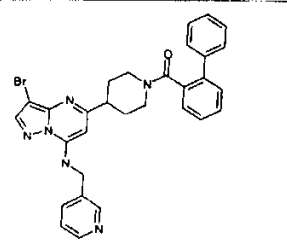
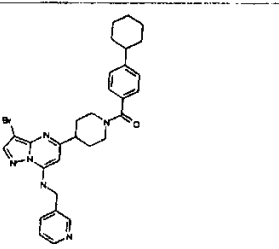
[1310]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4335 2. 537.3		1. 4340 2. 541.3
	1. 4336 2. 537.3		1. 4341 2. 543.3
	1. 4337 2. 539.3		1. 4342 2. 546.3
	1. 4338 2. 539.3		1. 4343 2. 547.3
	1. 4339 2. 539.3		1. 4344 2. 547.3

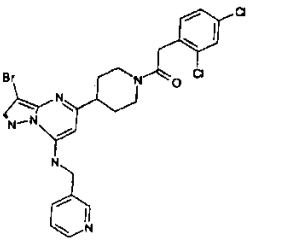
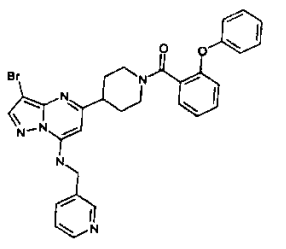
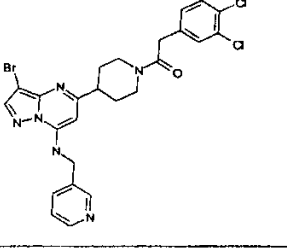
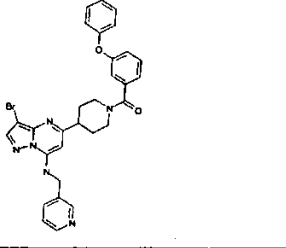
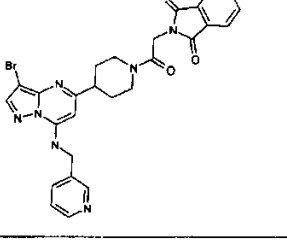
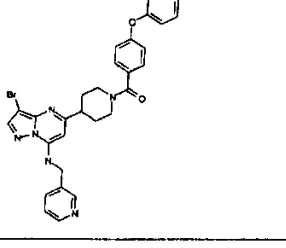
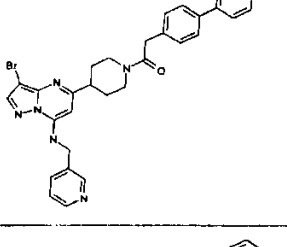
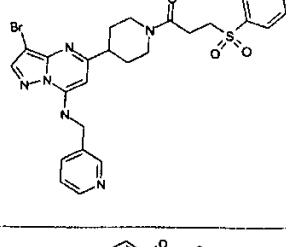
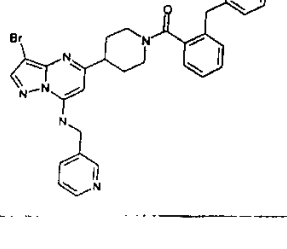
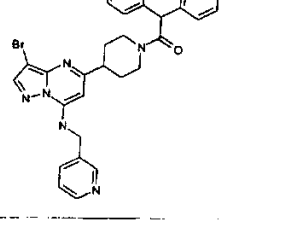
[1311]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	<p>1. 4345 2. 549.3</p>		<p>1. 4350 2. 553.3</p>
	<p>1. 4346 2. 550.3</p>		<p>1. 4351 2. 557.31</p>
	<p>1. 4347 2. 551.3</p>		<p>1. 4352 2. 557.31</p>
	<p>1. 4348 2. 551.3</p>		<p>1. 4353 2. 558.31</p>
	<p>1. 4349 2. 551.3</p>		<p>1. 4354 2. 561.31</p>

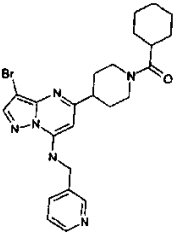
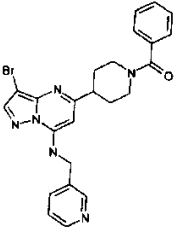
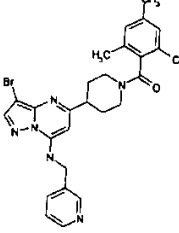
[1312]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	<p>1. 4355 2. 561.31</p>		<p>1. 4360 2. 569.31</p>
	<p>1. 4356 2. 561.31</p>		<p>1. 4361 2. 574.32</p>
	<p>1. 4357 2. 561.31</p>		<p>1. 4362 2. 573.32</p>
	<p>1. 4358 2. 561.31</p>		<p>1. 4363 2. 573.32</p>
	<p>1. 4359 2. 569.31</p>		<p>1. 4364 2. 575.32</p>

[1313]

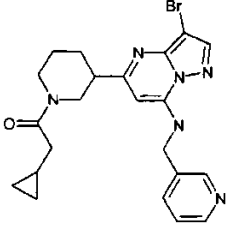
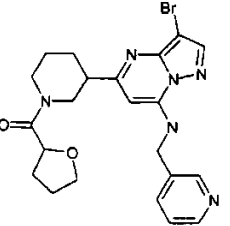
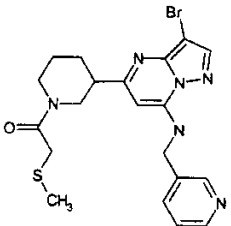
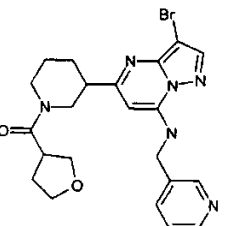
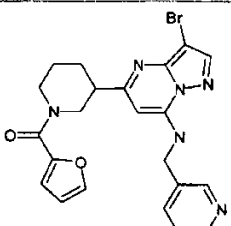
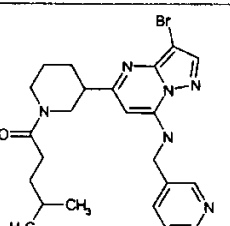
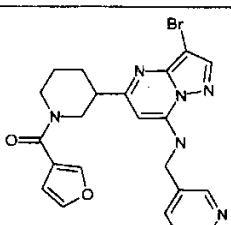
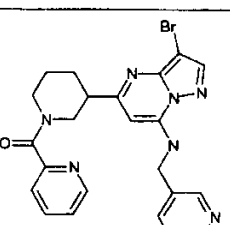
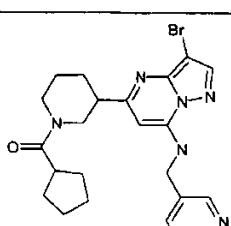
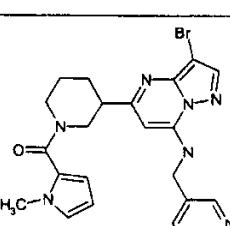
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4365 2. 575.32		1. 43700 2. 585.32
	1. 43666 2. 575.32		1. 4371 2. 583.32
	1. 4367 2. 574.32		1. 4372 2. 585.32
	1. 43688 2. 583.32		1. 4373 2. 585.32
	1. 4369 2. 583.32		1. 4374 2. 597.33

[1314]

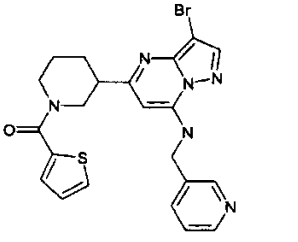
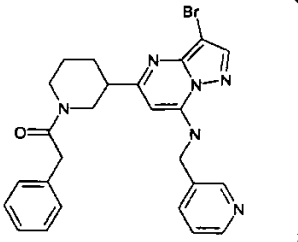
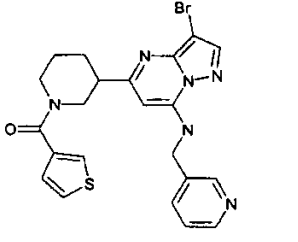
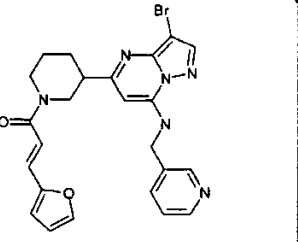
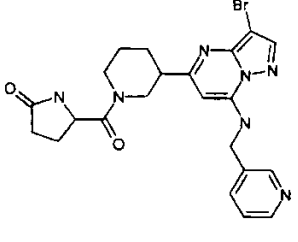
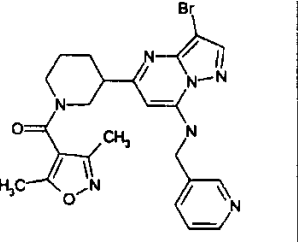
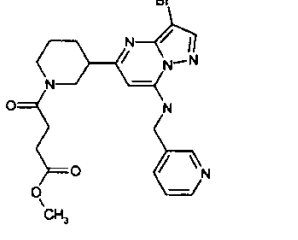
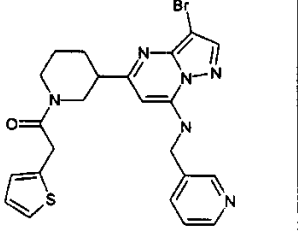
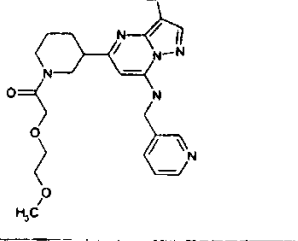
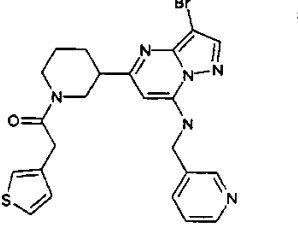
생성물	1.실시예 2. m/z
	<p>1. 4375 2. 499.27</p>
	<p>1. 4376 2. 493.27</p>
	<p>1. 4377 2. 535.29</p>

[1315]

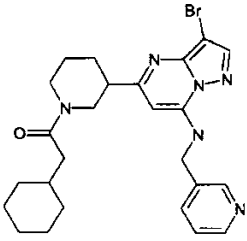
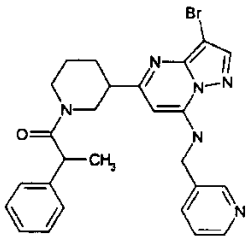
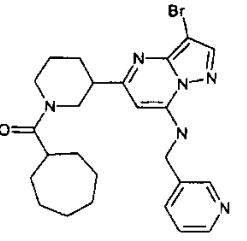
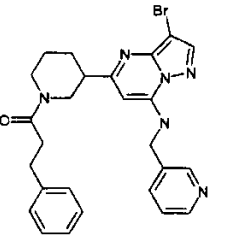
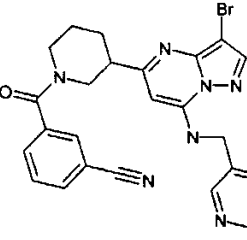
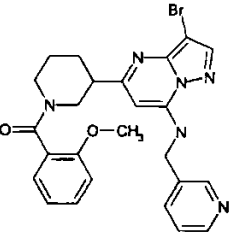
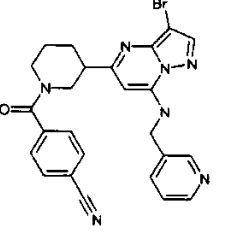
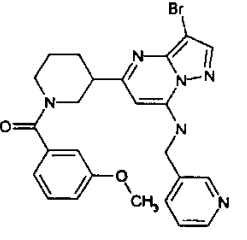
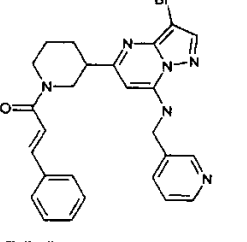
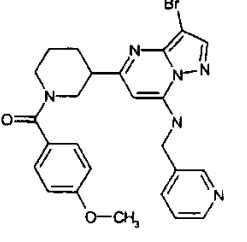
표 44

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4401 2. 471.3		1. 4406 2. 487.27
	1. 4402 2. 475.26		1. 4407 2. 487.27
	1. 4403 2. 483.27		1. 4408 2. 487.27
	1. 4404 2. 481.26		1. 4409 2. 494.3
	1. 4405 2. 485.27		1. 4410 2. 496.27

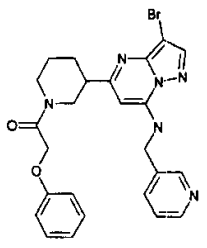
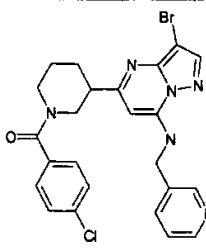
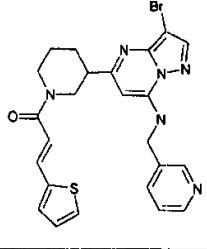
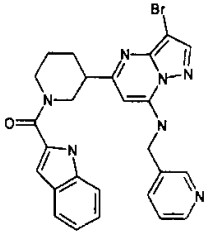
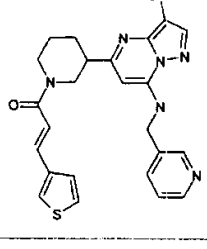
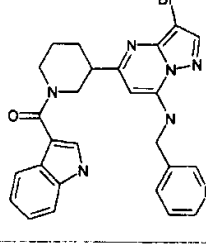
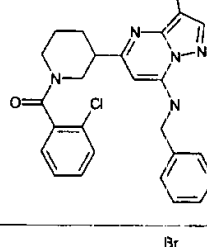
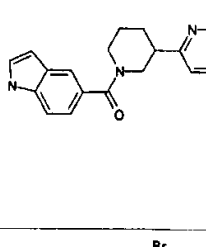
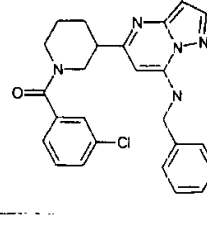
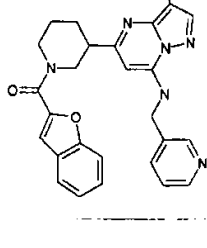
[1316]

생성물	1. 실시예 2. m/z		생성물	1. 실시예 2. m/z
	1. 4411 2. 499.27			1. 4416 2. 507.28
	2. 4412 2. 499.27			1. 4417 2. 509.3
	1. 4413 2. 500.27			1. 4418 2. 512.28
	1. 4414 2. 503.28			1. 4419 2. 513.28
	1. 4415 2. 505.28			1. 4420 2. 513.28

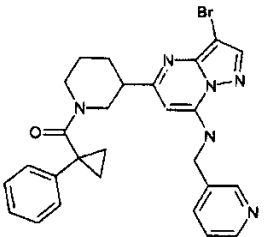
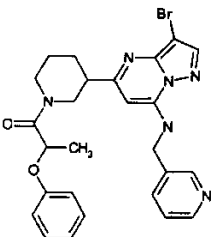
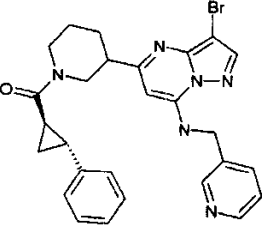
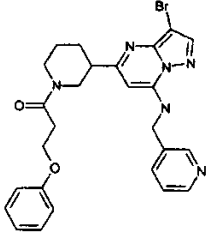
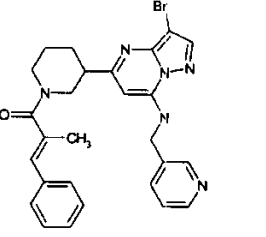
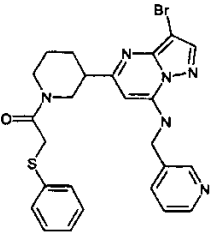
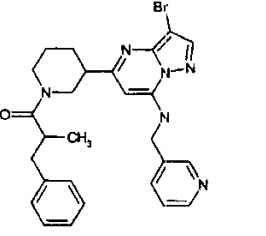
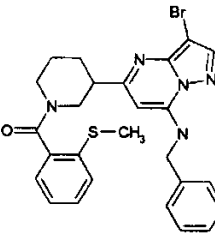
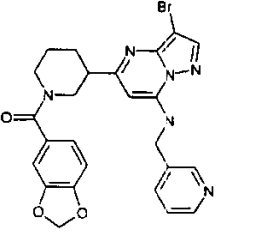
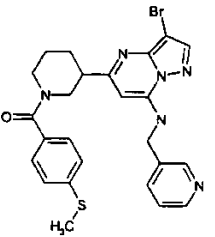
[1317]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4421 2. 513.28		1. 4426 2. 521.29
	1. 4422 2. 513.28		1. 4428 2. 521.29
	1. 4423 2. 518.28		1. 4428 2. 523.29
	1. 4424 2. 518.28		1. 4429 2. 523.29
	1. 4425 2. 519.3		1. 4430 2. 523.29

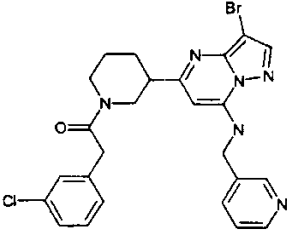
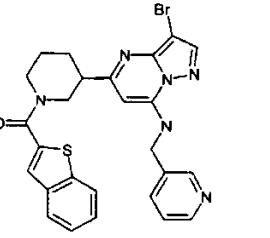
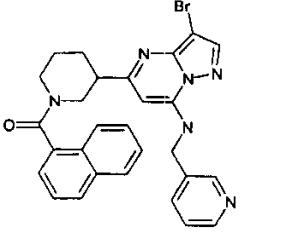
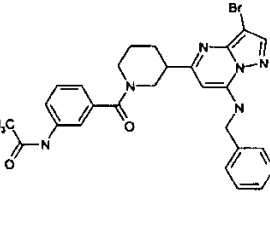
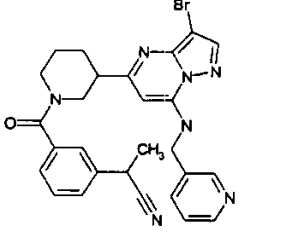
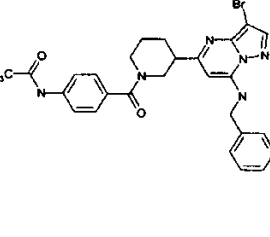
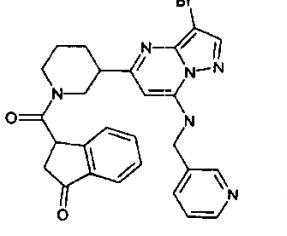
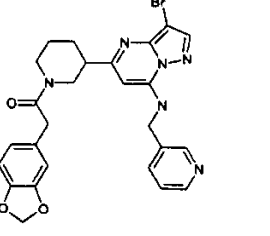
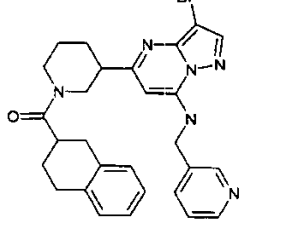
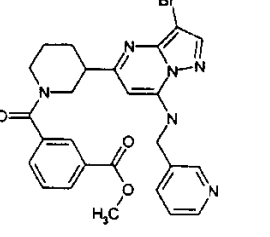
[1318]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4431 2. 523.29		1. 4436 2. 527.29
	1. 4432 2. 525.29		1. 4437 2. 532.29
	1. 4433 2. 525.3		1. 4438 2. 532.29
	1. 4434 2. 527.29		1. 4439 2. 532.29
	1. 4435 2. 527.29		1. 4440 2. 531.29

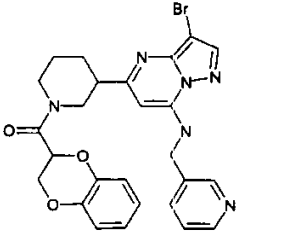
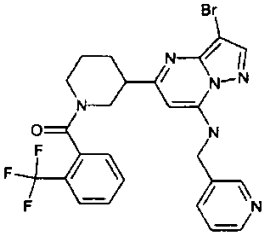
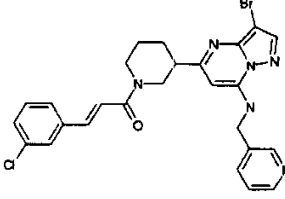
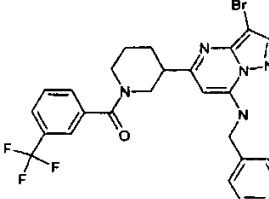
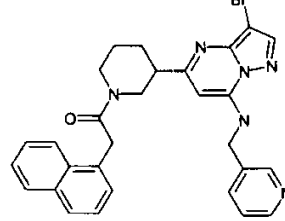
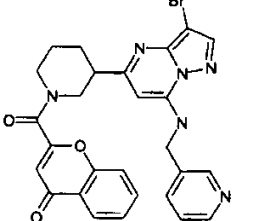
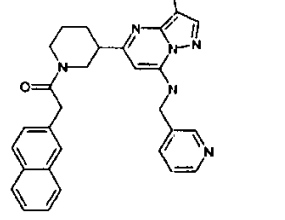
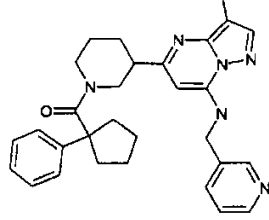
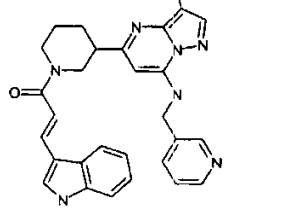
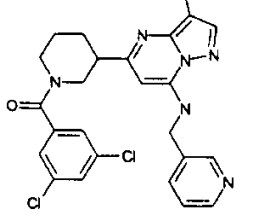
[1319]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4441 2. 533.3		1. 4446 2. 537.3
	1. 4442 2. 531.29		1. 4447 2. 537.3
	1. 4443 2. 533.29		1. 4448 2. 539.3
	1. 4444 2. 535.29		1. 4449 2. 539.3
	1. 4445 2. 537.3		1. 4450 2. 539.3

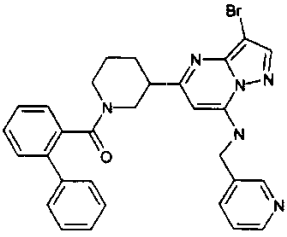
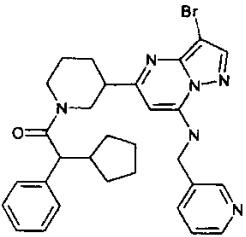
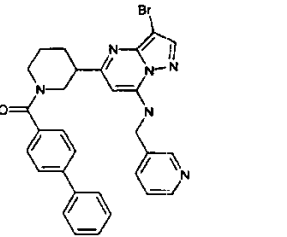
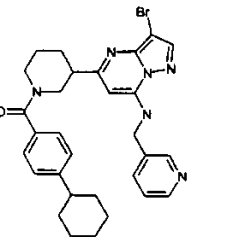
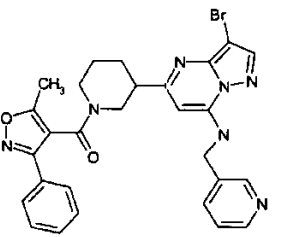
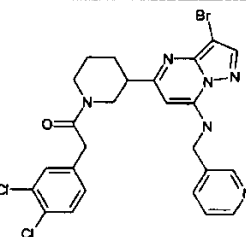
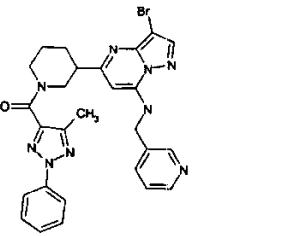
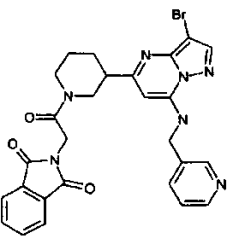
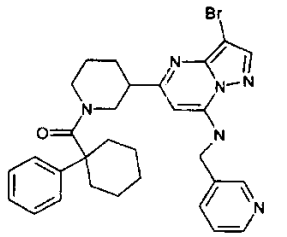
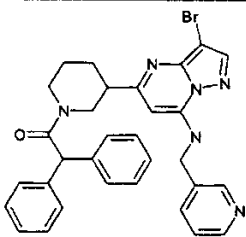
[1320]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	<p>1. 4451 2. 541.3</p>		<p>1. 4456 2. 549.3</p>
	<p>1. 4451 2. 543.3</p>		<p>1. 4457 2. 550.3</p>
	<p>1. 4453 2. 546.3</p>		<p>1. 4458 2. 550.3</p>
	<p>1. 4454 2. 547.3</p>		<p>1. 4459 2. 551.3</p>
	<p>1. 4455 2. 547.3</p>		<p>1. 4460 2. 551.3</p>

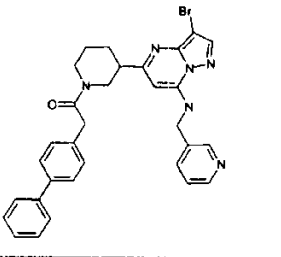
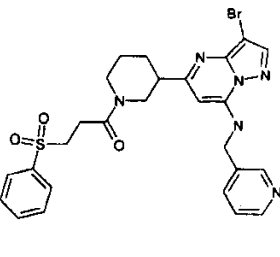
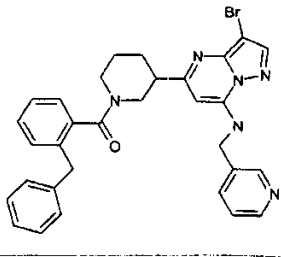
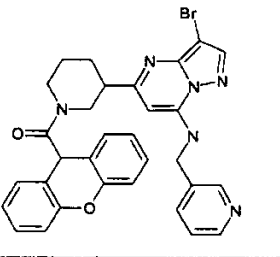
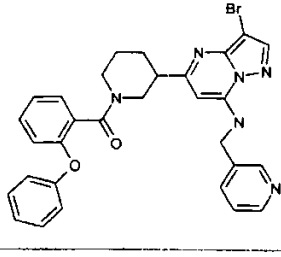
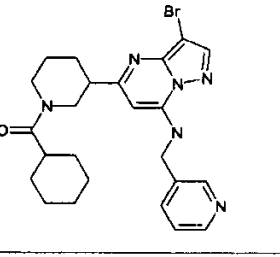
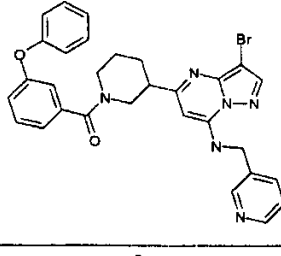
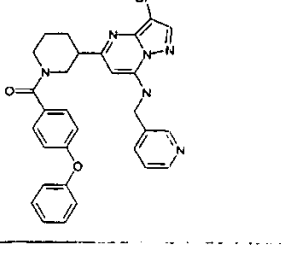
[1321]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	<p>1. 4461 2. 549.3</p>		<p>1. 4466 2. 561.31</p>
	<p>1. 4462 2. 553.3</p>		<p>1. 4467 2. 561.31</p>
	<p>1. 4463 2. 557.3</p>		<p>1. 4468 2. 561.31</p>
	<p>1. 4464 2. 557.31</p>		<p>1. 4469 2. 561.31</p>
	<p>1. 4465 2. 558.31</p>		<p>1. 4470 2. 562.3</p>

[1322]

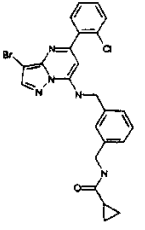
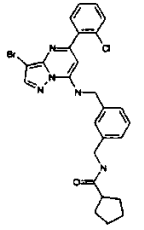
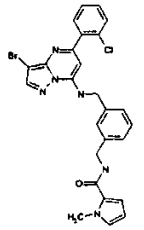
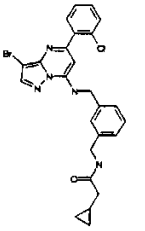
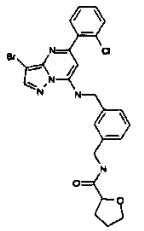
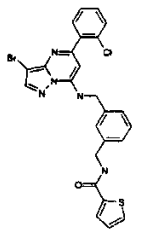
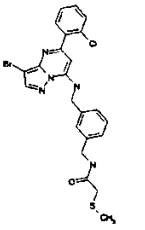
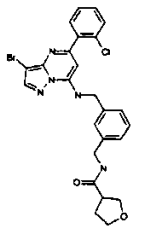
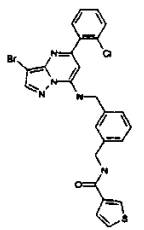
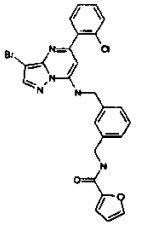
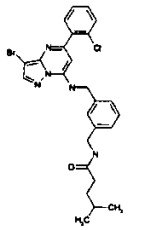
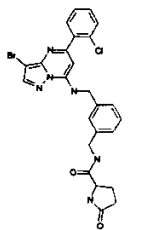
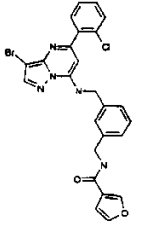
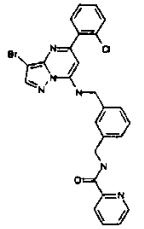
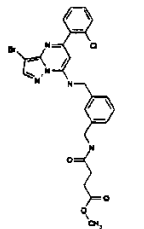
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4471 2. 569.31		1. 4476 2. 572.31
	1. 4472 2. 569.31		1. 4477 2. 573.32
	1. 4473 2. 572.31		1. 4478 2. 574.32
	1. 4474 2. 572.31		1. 4479 2. 576.32
	1. 4475 2. 575.32		1. 4480 2. 583.32

[1323]

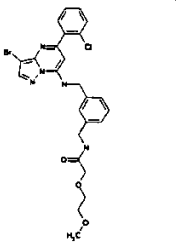
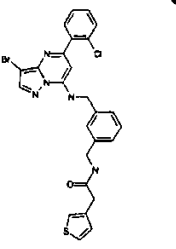
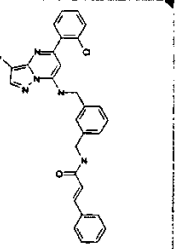
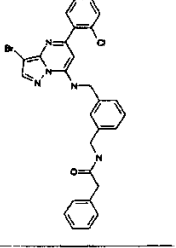
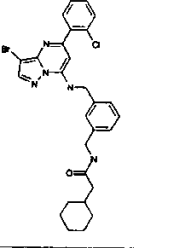
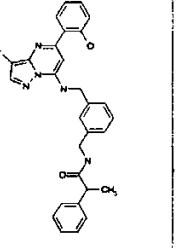
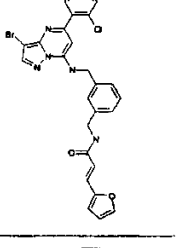
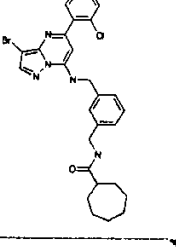
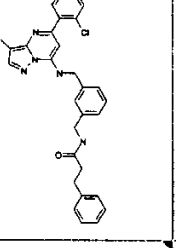
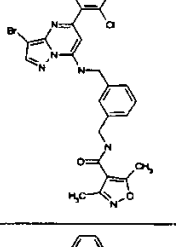
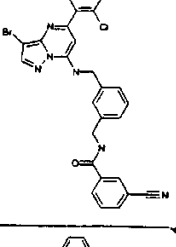
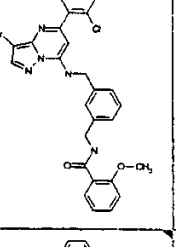
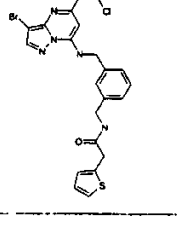
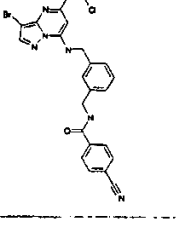
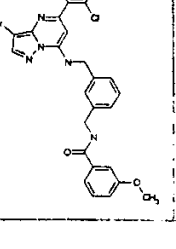
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	<p>1. 4481 2. 583.32</p>		<p>1. 4486 2. 585.32</p>
	<p>1. 4482 2. 583.32</p>		<p>1. 4487 2. 597.33</p>
	<p>1. 4483 2. 585.32</p>		<p>1. 4488 2. 499.27</p>
	<p>1. 4484 2. 585.32</p>		
	<p>1. 4485 2. 585.3</p>		

[1324]

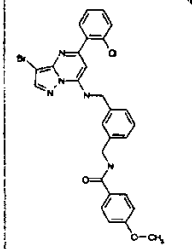
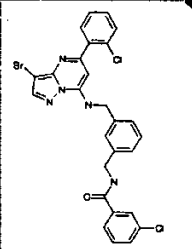
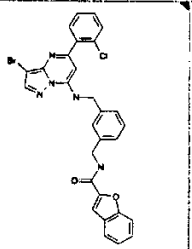
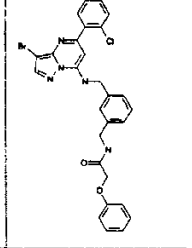
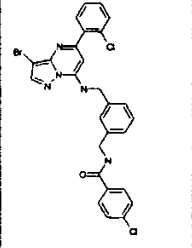
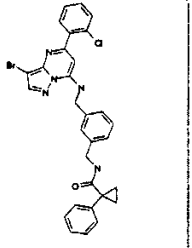
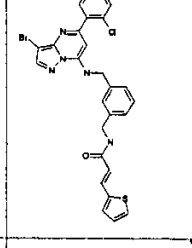
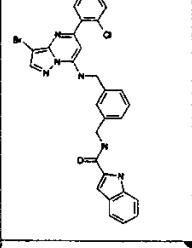
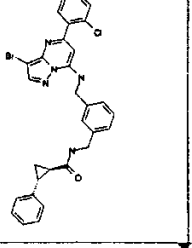
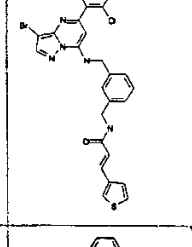
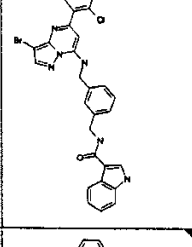
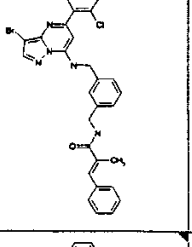
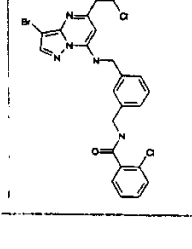
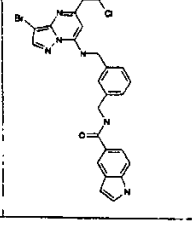
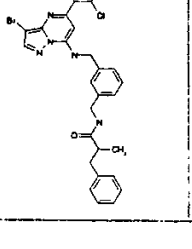
표 45

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4501 2. 512.28		1. 4506 2. 540.3		1. 4511 2. 551.3
	1. 4502 2. 526.29		1. 4507 2. 542.3		1. 4512 2. 554.3
	1. 4503 2. 532.29		1. 4508 2. 542.3		1. 4513 2. 554.3
	1. 4504 2. 538.3		1. 4509 2. 542.3		1. 4514. 2. 555.31
	1. 4505 2. 538.3		1. 4510 2. 549.3		1. 4515 2. 558.31

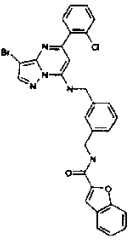
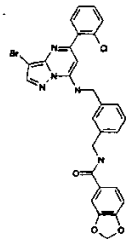
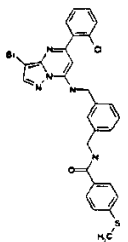
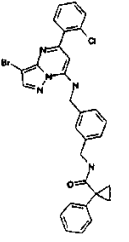
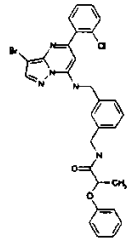
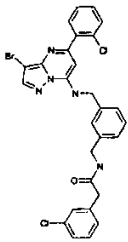
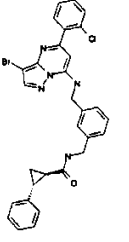
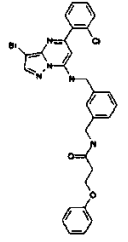
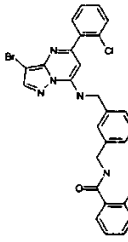
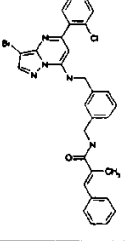
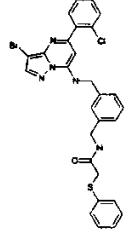
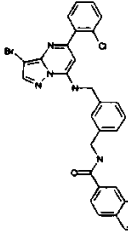
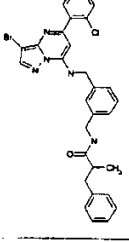
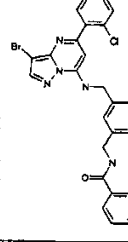
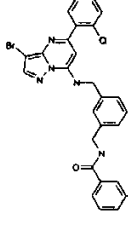
[1325]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4516 2. 560.31		1. 4521 2. 568.31		1. 4526 2. 574.32
	1. 4517 2. 562.31		1. 4522 2. 568.31		1. 4527 2. 576.32
	1. 4518 2. 564.31		1. 4523 2. 568.31		1. 4528 2. 576.32
	1. 4519 2. 567.31		1. 4524 2. 573.32		1. 4529 2. 578.32
	1. 4520 2. 568.31		1. 4525 2. 573.32		1. 4530 2. 578.32

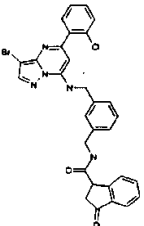
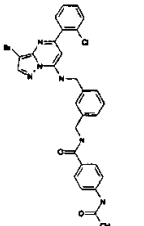
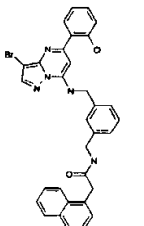
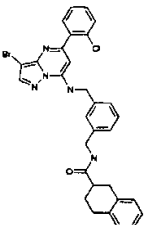
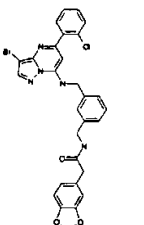
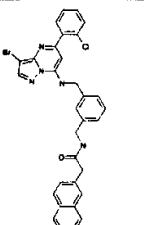
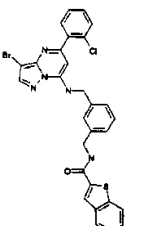
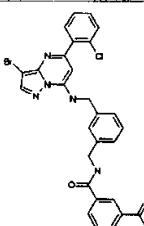
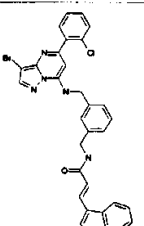
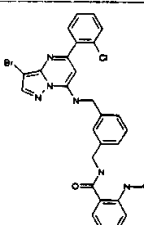
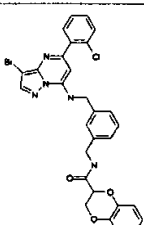
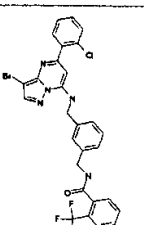
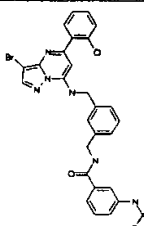
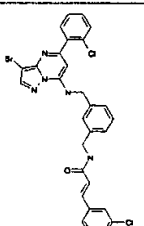
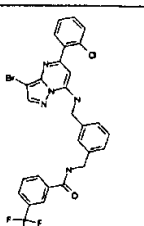
[1326]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4531 2. 578.32		1. 4536 2. 582.32		1. 4541 2. 588.32
	1. 4532 2. 578.32		1. 4537 2. 582.32		1. 4542 2. 588.32
	1. 4533 2. 580.32		1. 4538 2. 587.32		1. 4543 2. 588.32
	1. 4534 2. 580.32		1. 4539 2. 587.32		1. 4544 2. 588.32
	1. 4535 2. 582.32		1. 4540 2. 587.32		1. 4545 2. 590.32

[1327]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4546 2. 588.32		1. 4551 2. 592.33		1. 4556 2. 593.33
	1. 4547 2. 588.32		1. 4552 2. 592.33		1. 4557 2. 596.33
	1. 4548 2. 588.32		1. 4553 2. 592.33		1. 4558 2. 596.33
	1. 4549 2. 588.32		1. 4554 2. 594.33		1. 4559 2. 598.33
	1. 4550 2. 590.32		1. 4555 2. 594.33		1. 4560 2. 601.33

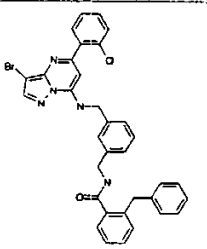
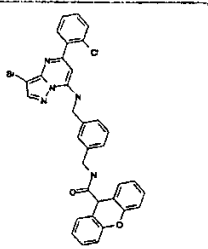
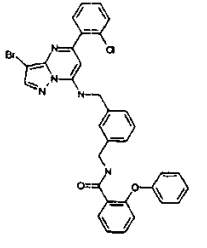
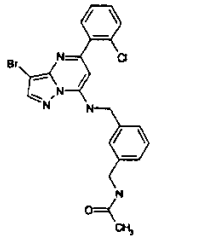
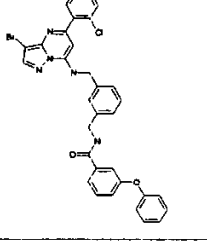
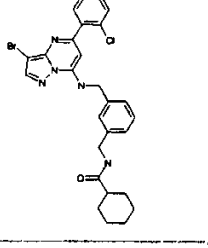
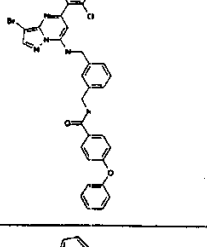
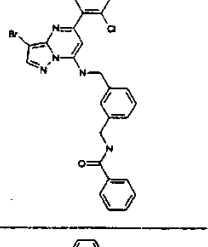
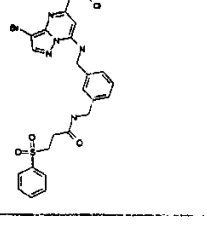
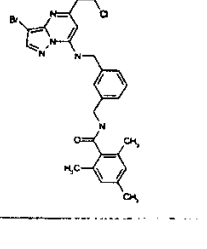
[1328]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4561 2. 602.33		1. 4665 2. 605.33		1. 4571 2. 612.34
	1. 4562 2. 602.33		1. 4567 2. 606.33		1. 4572 2. 612.34
	1. 4563 2. 604.33		1. 4568 2. 606.33		1. 4573 2. 613.34
	1. 4564 2. 603.3		1. 4569 2. 606.33		1. 4574 2. 616.34
	1. 4565 2. 605.33		1. 4570 2. 608.33		1. 4575 2. 616.34

[1329]

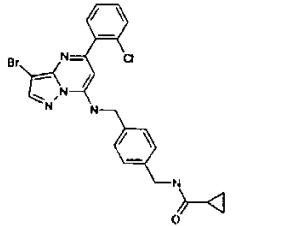
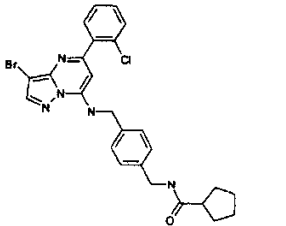
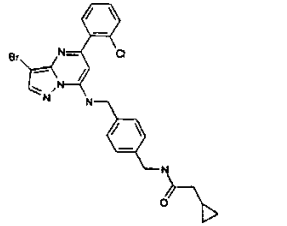
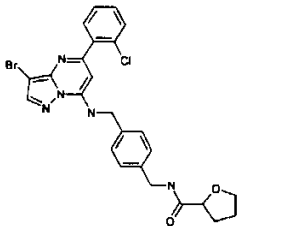
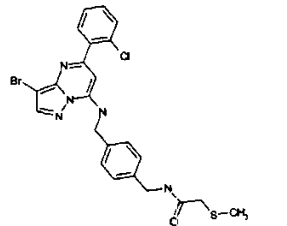
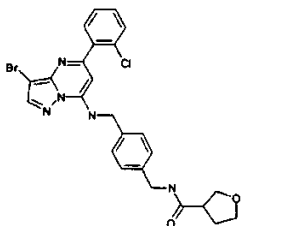
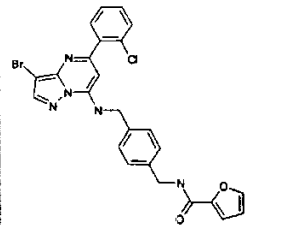
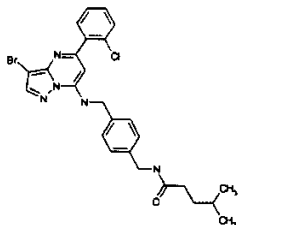
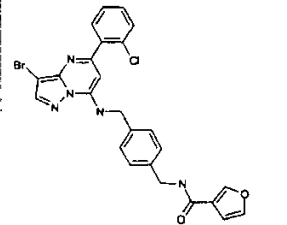
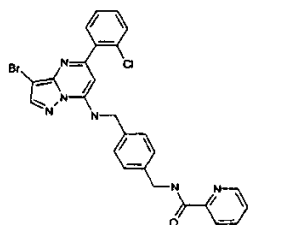
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4576 2. 616.34		1. 4581 2. 624.34		1. 4586 2. 630.35
	1. 4577 2. 616.34		1. 4582 2. 629.35		1. 4587 2. 630.35
	1. 4578 2. 616.34		1. 4583 2. 629.35		1. 4588 2. 630.35
	1. 4579 2. 616.34		1. 4584 2. 630.35		1. 4589 2. 631.35
	1. 4580 2. 624.34		1. 4585 2. 630.35		1. 4590 2. 638.35

[1330]

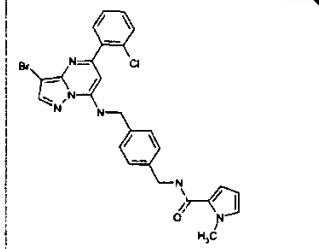
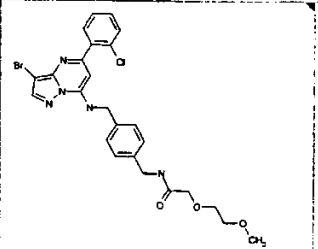
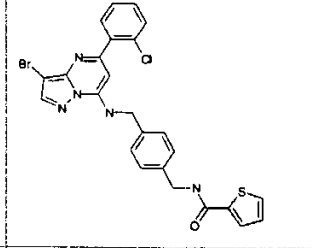
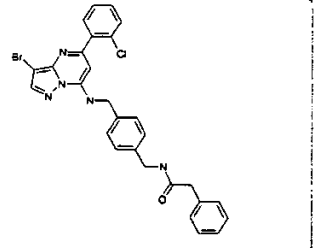
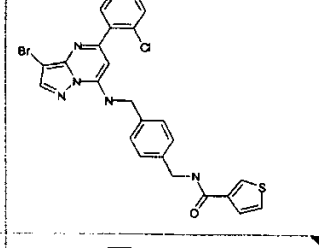
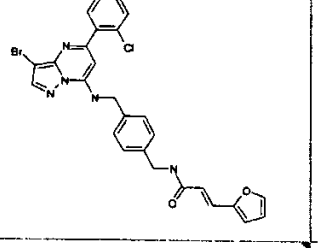
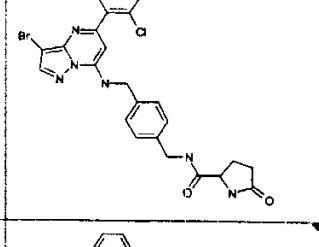
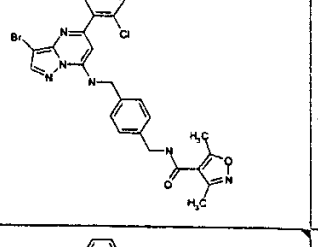
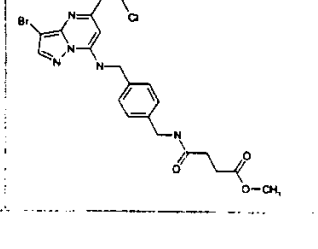
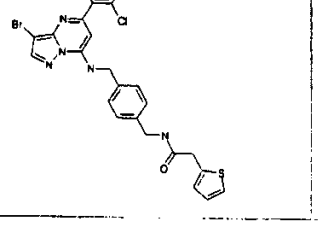
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 4591 2. 638.35		1. 4596 2. 652.36
	1. 4592 2. 640.35		1. 4597 2. 486.27
	1. 4593 2. 640.35		1. 4598 2. 554.3
	1. 4594 2. 640.35		1. 4599 2. 548.3
	1. 4595 2. 640.35		1. 45100 2.

[1331]

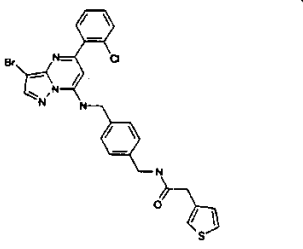
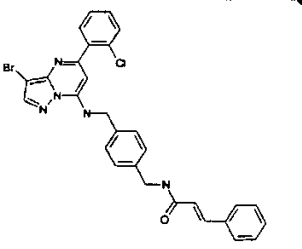
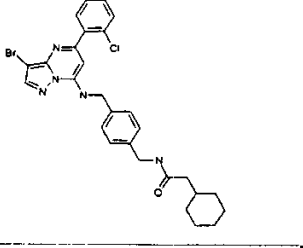
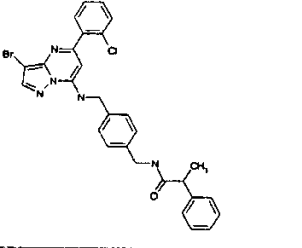
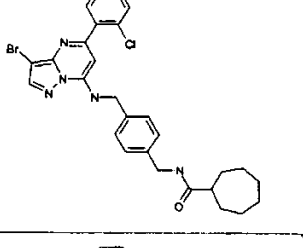
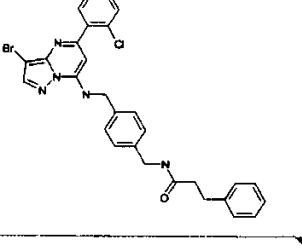
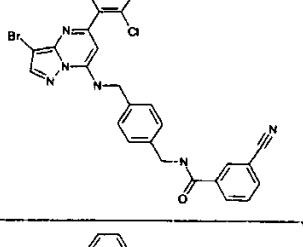
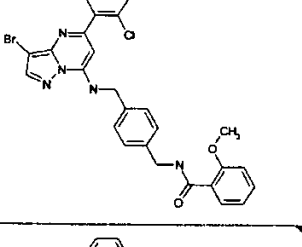
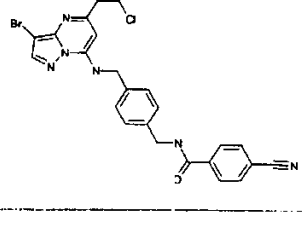
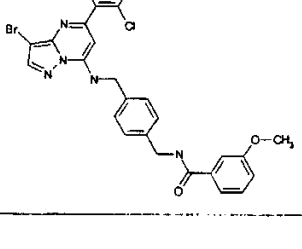
표 46

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4601 2. 512.28		1. 4606 2. 540.3
	1. 4602 2. 526.29		1. 4607 2. 542.3
	1. 4603 2. 532.29		1. 4608 2. 542.3
	1. 4604 2. 538.3		1. 4609 2. 542.3
	1. 4605 2. 536.3		1. 4610 2. 547.3

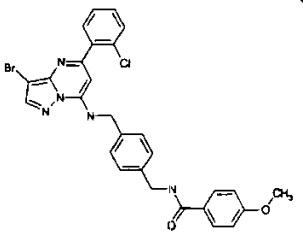
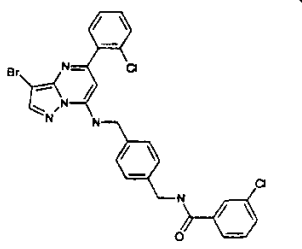
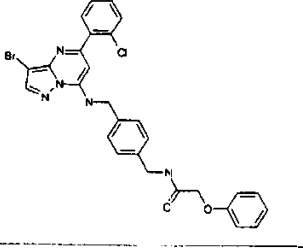
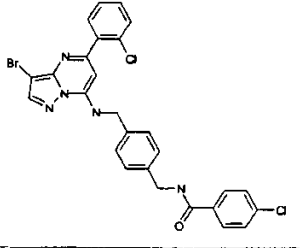
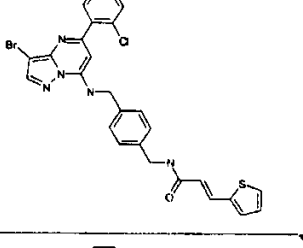
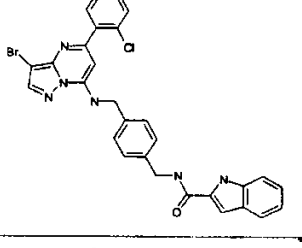
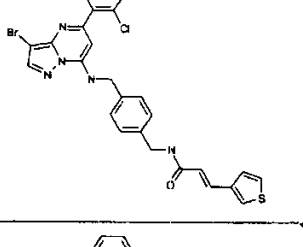
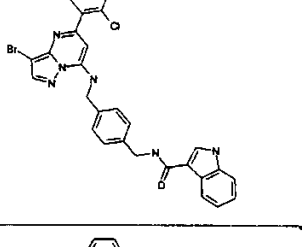
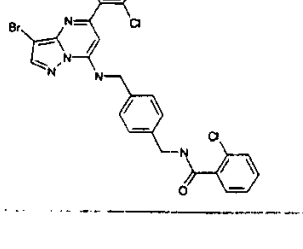
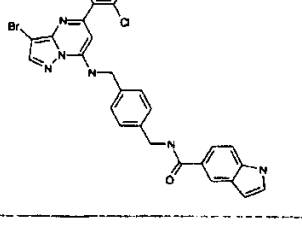
[1332]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4611 2. 551.3		1. 4616 2. 560.31
	1. 4612 2. 552.3		1. 4617 2. 562.31
	1. 4613 2. 552.3		1. 4618 2. 562.3
	1. 4614 2. 555.31		1. 4619 2. 567.31
	1. 4615 2. 558.31		1. 4620 2. 568.31

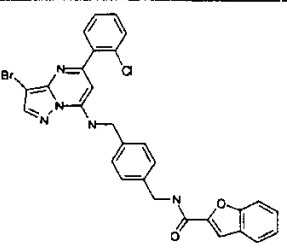
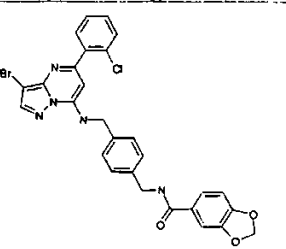
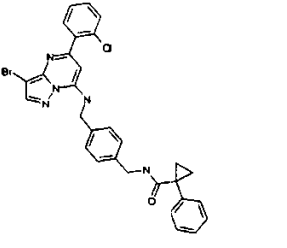
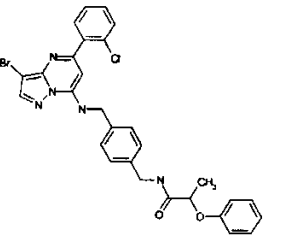
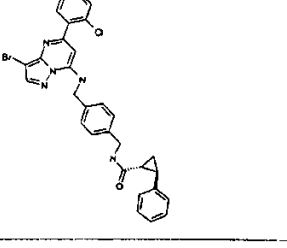
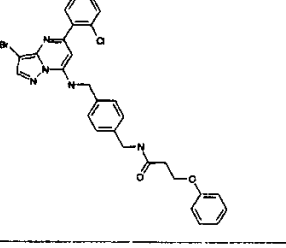
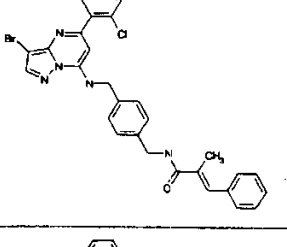
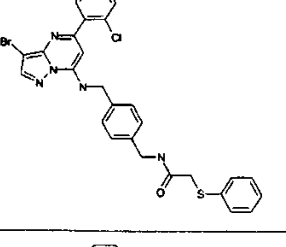
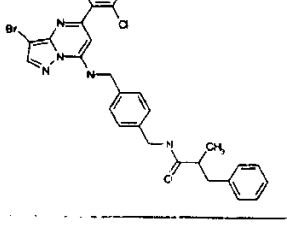
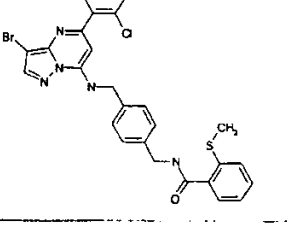
[1333]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4621 2. 568.31		1. 4626 2. 574.32
	1. 4622 2. 568.31		1. 4627 2. 576.32
	1. 4623 2. 568.31		1. 4628 2. 576.32
	1. 4624 2. 573.32		1. 4629 2. 578.32
	1. 4625 2. 573.32		1. 4630 2. 578.32

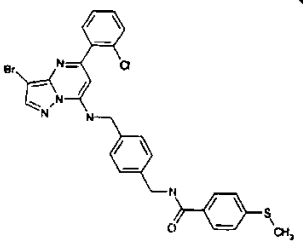
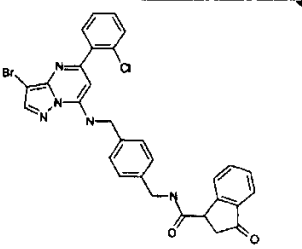
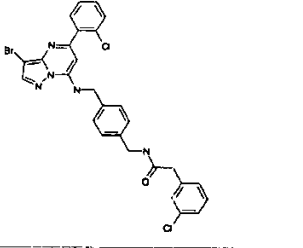
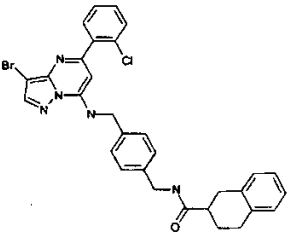
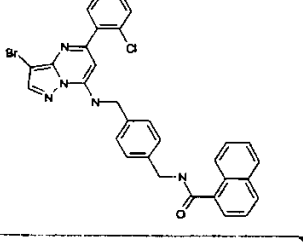
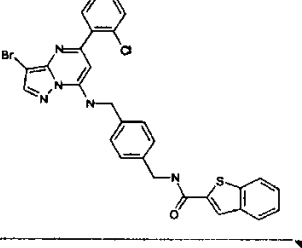
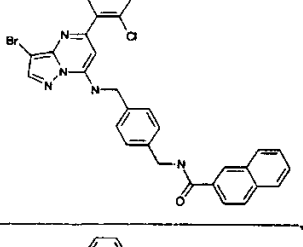
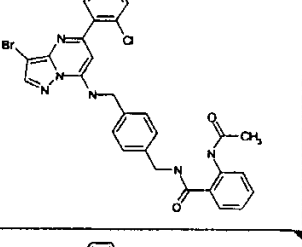
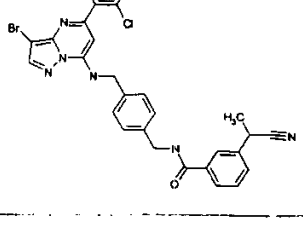
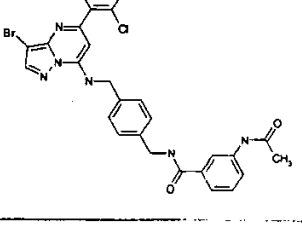
[1334]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4631 2. 578.32		1. 4636 2. 582.32
	1. 4632 2. 578.32		1. 4637 2. 582.32
	1. 4633 2. 580.32		1. 4638 2. 587.32
	1. 4634 2. 580.32		1. 4639 2. 585.3
	1. 4635 2. 582.32		1. 4640 2. 585.3

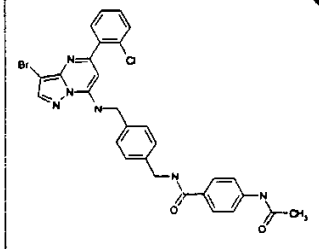
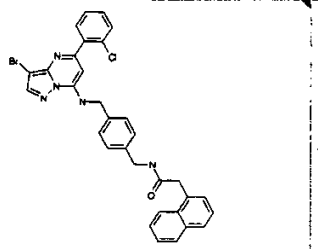
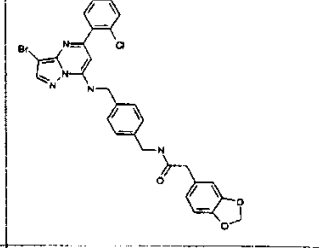
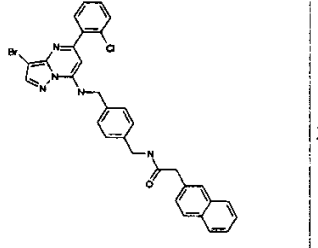
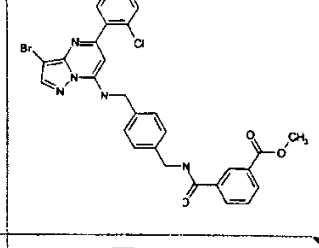
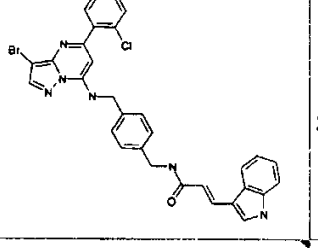
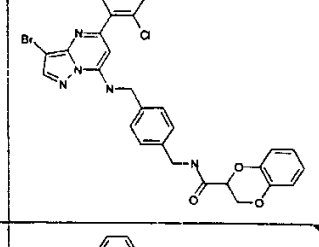
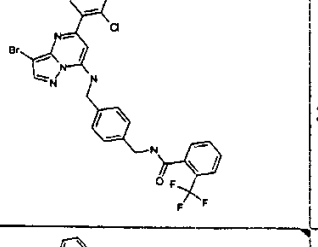
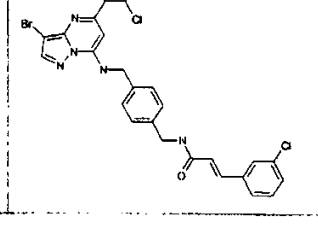
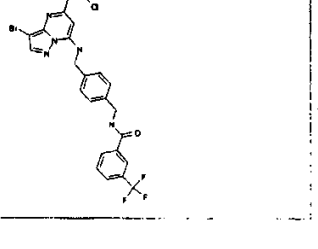
[1335]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4641 2. 588.32		1. 4646 2. 592.33
	1. 4642 2. 588.32		1. 4647 2. 592.33
	1. 4643 2. 588.32		1. 4648 2. 592.33
	1. 4644 2. 588.32		1. 4649 2.
	1. 4645 2. 590.32		1. 4650 2. 594.33

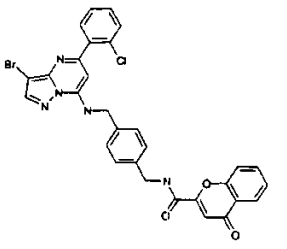
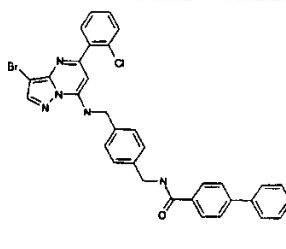
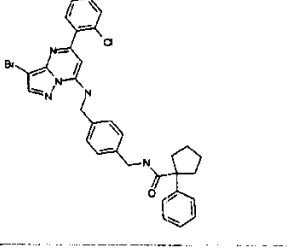
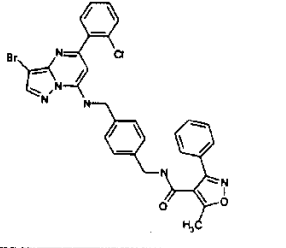
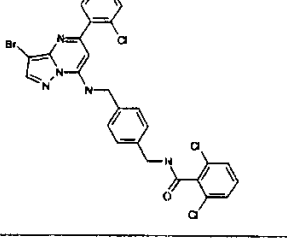
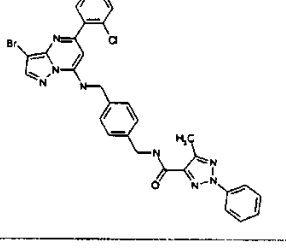
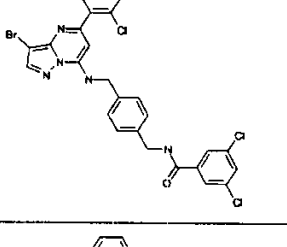
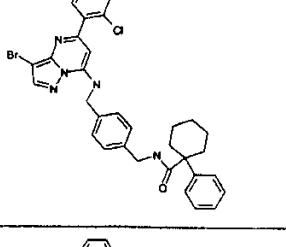
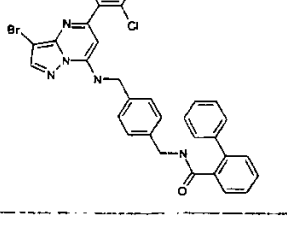
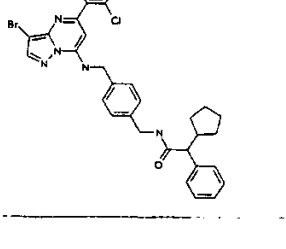
[1336]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4651 2. 594.33		1. 4656 2. 602.33
	1. 4652 2. 596.33		1. 4657 2. 602.33
	1. 4653 2. 596.3		1. 4658 2. 604.33
	1. 4654 2. 598.33		1. 4659 2. 603.3
	1. 4655 2. 601.33		1. 4660 2. 605.33

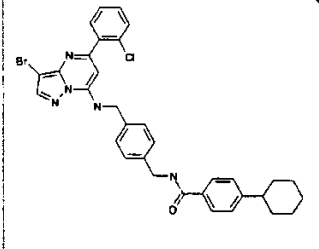
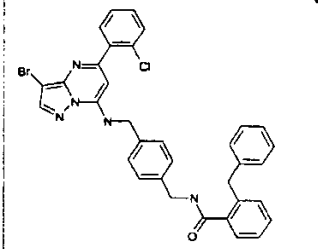
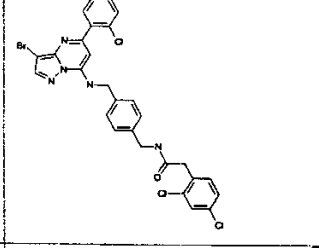
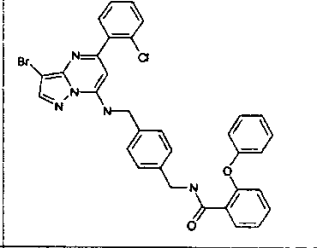
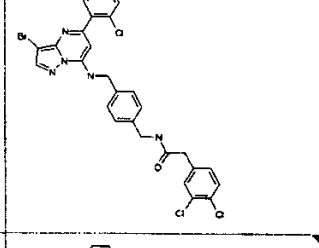
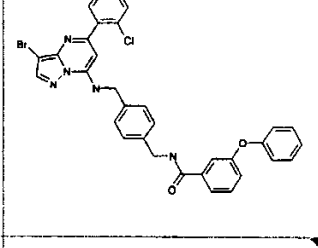
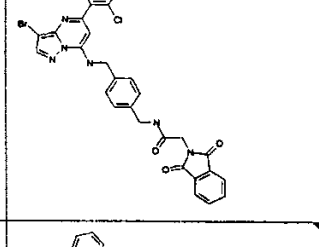
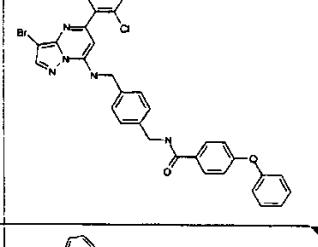
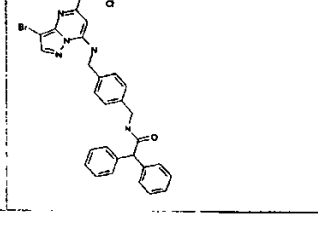
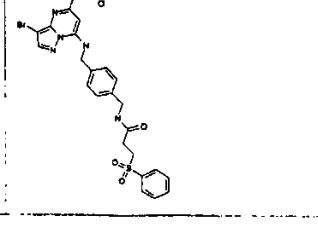
[1337]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4661 2. 605.33		1. 4666 2. 612.34
	1. 4662 2. 606.33		1. 4667 2. 612.34
	1. 4663 2. 606.33		1. 4668 2. 613.34
	1. 4664 2. 606.33		1. 4669 2. 616.34
	1. 4665 2. 608.33		1. 4670 2. 616.34

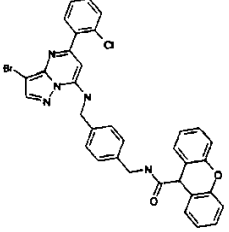
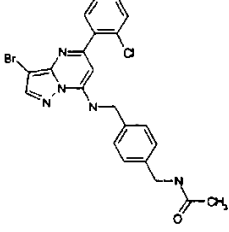
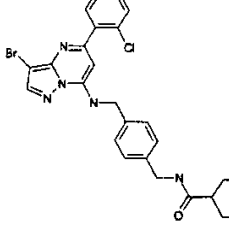
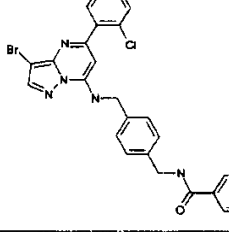
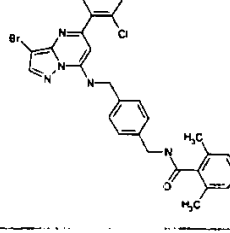
[1338]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4671 2. 616.34		1. 4676 2. 624.34
	1. 4672 2. 616.34		1. 4677 2. 629.35
	1. 4673 2. 616.34		1. 4678 2. 629.35
	1. 4674 2. 616.34		1. 4679 2. 630.35
	1. 4675 2. 624.34		1. 4680 2. 630.35

[1339]

생성물	1.실시예. 2. m/z	생성물	1.실시예 2. m/z
	1. 4681 2. 630.35		1. 4686 2. 638.35
	1. 4682 2. 630.35		1. 4687 2. 640.35
	1. 4683 2. 630.35		1. 4688 2. 640.35
	1. 4684 2. 631.35		4689 2.
	1. 4685 2. 638.35		1. 4690 2. 640.35

[1340]

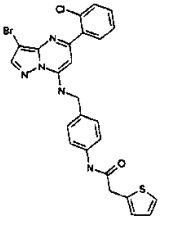
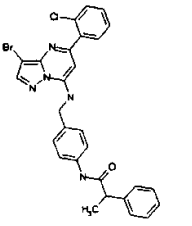
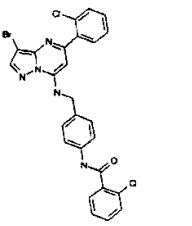
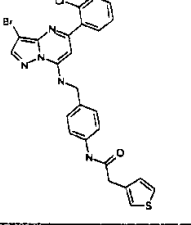
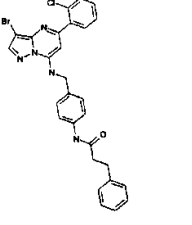
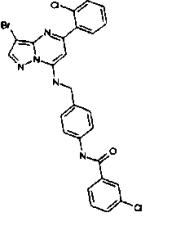
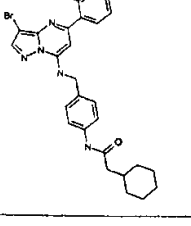
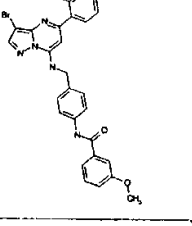
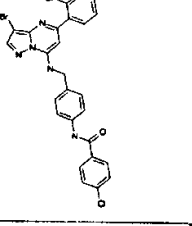
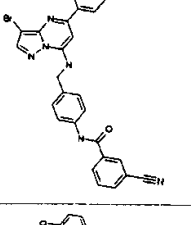
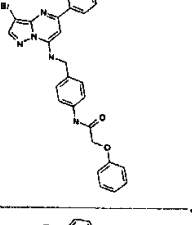
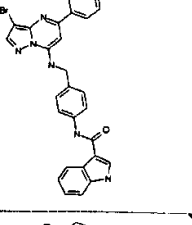
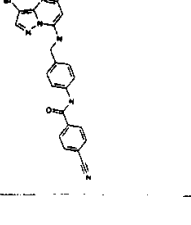
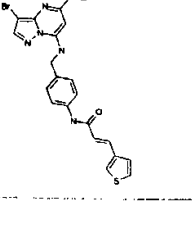
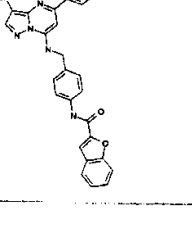
생성물	1.실시에 2. m/z
	<p>1. 4691 2. 652.36</p>
	<p>1. 4692 2. 484.3</p>
	<p>1. 4693 2. 554.3</p>
	<p>1. 4694 2. 548.3</p>
	<p>1. 4695 2. 590.32</p>

[1341]

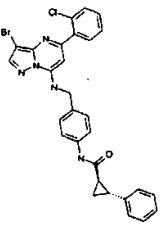
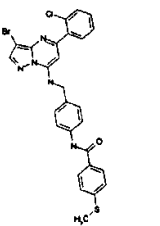
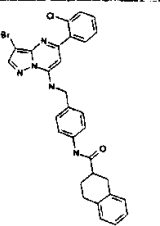
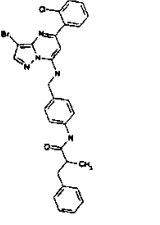
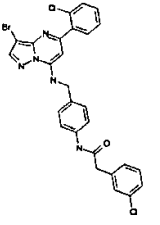
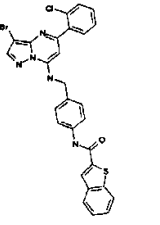
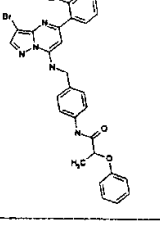
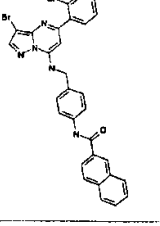
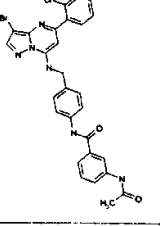
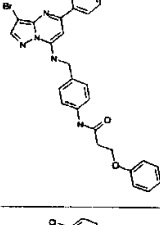
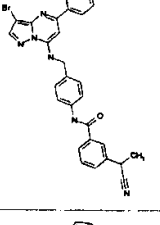
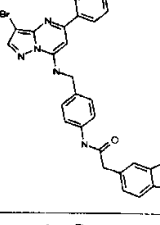
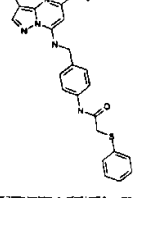
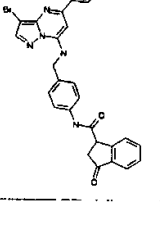
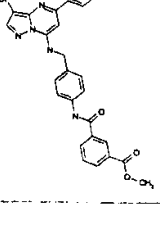
표 47

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4701 2. 498.27		1. 4706 2. 528.29		1. 4711 2. 544.3
	1. 4702 2. 512.28		1. 4707 2. 528.29		1. 4712 2. 546.3
	1. 4703 2. 518.28		1. 4708 2. 535.29		1. 4713 2. 548.3
	1. 4704 2. 524.29		1. 4709 2. 540.3		1. 4714 2. 550.3
	1. 4705 2. 528.29		1. 4710 2. 541.3		1. 4715 2. 553.3

[1342]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4716 2. 554.3		1. 4721 2. 562.31		1. 4726 2. 568.31
	1. 4717 2. 554.3		1. 4722 2. 562.31		1. 4727 2. 568.31
	1. 4718 2. 554.3		1. 4723. 2. 564.31		1. 4728 2. 568.31
	1. 4719 2. 559.31		1. 4724 2. 564.31		1. 4729 2. 573.32
	1. 4720 2. 559.31		1. 4725 2. 566.31		1. 4730 2. 574.32

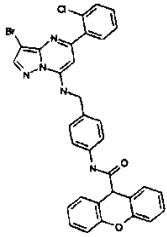
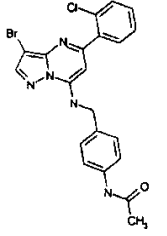
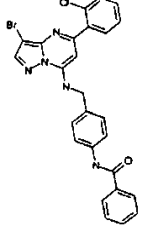
[1343]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4731 2. 574.32		1. 4736 2. 580.32		1. 4741 2. 588.32
	1. 4732 2. 576.32		1. 4737 2. 582.32		1. 4742 2. 590.32
	1. 4733 2. 578.32		1. 4738 2. 584.32		1. 4743 2. 591.33
	1. 4734 2. 578.32		1. 4739 2. 585.32		1. 4744 2. 592.33
	1. 4735 2. 580.32		1. 4740 2. 588.32		1. 4745 2. 592.33

[1344]

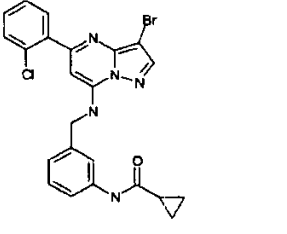
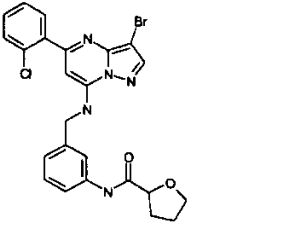
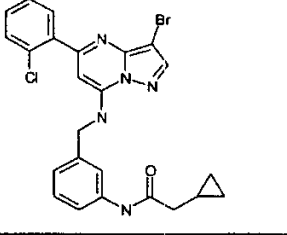
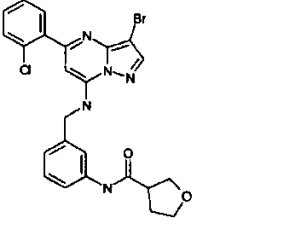
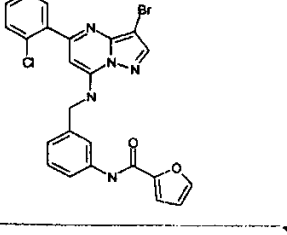
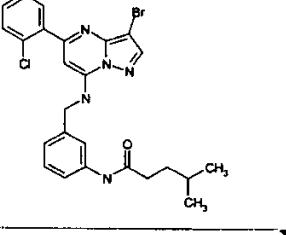
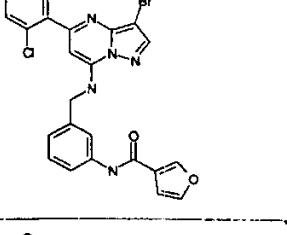
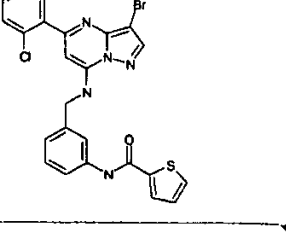
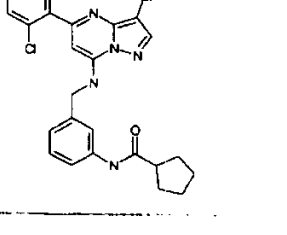
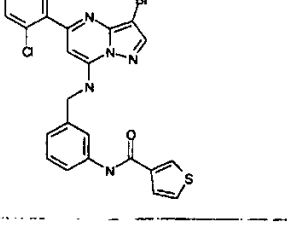
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4746 2. 592.33		1. 4751 2. 602.33		1. 4756 2. 624.34
	1. 4747 2. 598.33		1. 4752 2. 615.34		1. 4757 2. 624.34
	1. 4748 2. 598.33		1. 4753 2. 615.34		1. 4758 2. 626.34
	1. 4749 2. 602.33		1. 4754 2. 616.34		1. 4759 2. 624.34
	1. 4750 2. 602.33		1. 4755 2. 616.34		1. 4760 2. 626.34

[1345]

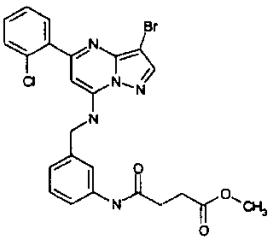
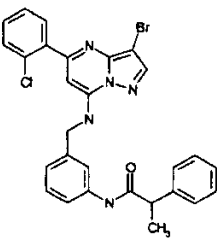
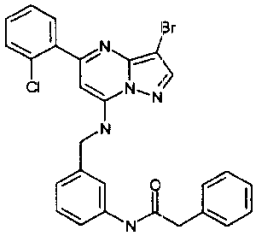
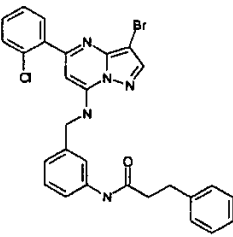
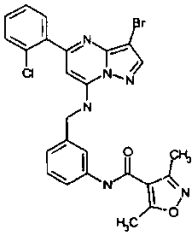
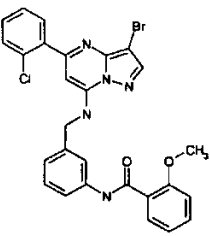
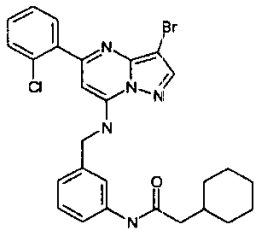
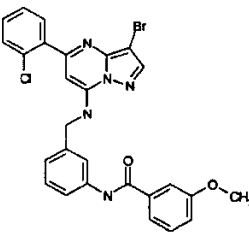
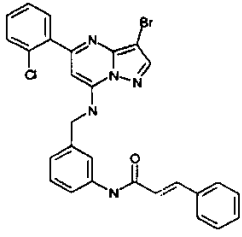
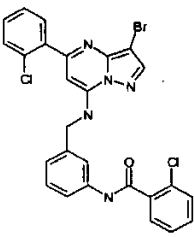
생성물	1.실시에 2. m/z
	<p>1. 4761 2. 638.35</p>
	<p>1. 4762 2. 472.26</p>
	<p>1. 4763 2. 534.29</p>

[1346]

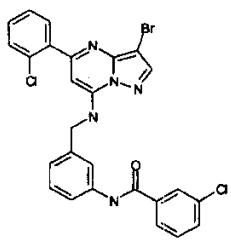
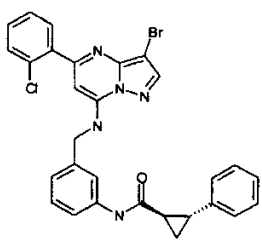
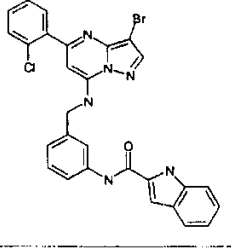
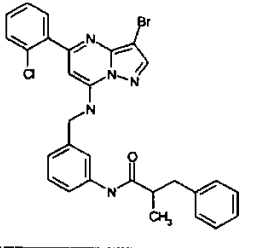
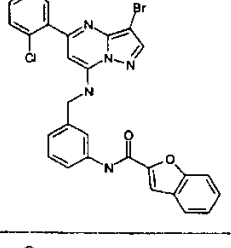
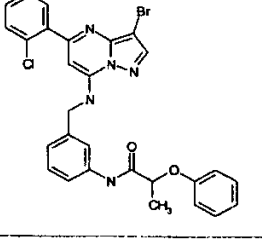
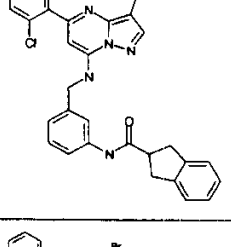
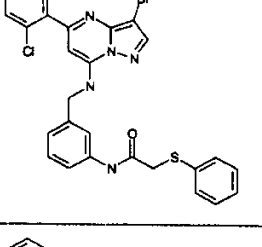
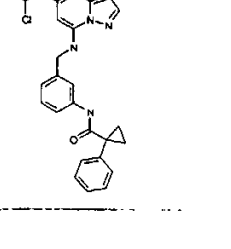
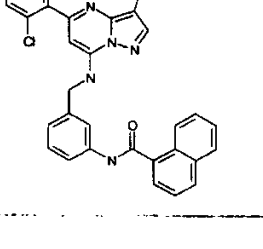
표 48

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 4801 2. 498.27		1.4806 2. 528.29
	1. 4802 2. 512.28		1.. 4807 2. 528.29
	1. 4803 2. 524.29		1. 4808 2. 528.29
	1. 4804 2. 524.29		1. 4809 2. 540.3
	1. 4805 2. 526.29		1. 4810 2. 540.3

[1347]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 4811 2. 544.3		1. 4816 2. 562.31
	1. 4812 2. 548.3		1. 4817 2. 562.31
	1. 4813 2. 553.3		1. 4818 2. 564.31
	1. 4814 2. 554.3		1. 4819 2. 564.31
	1. 4815 2. 560.31		1. 4820 2. 568.31

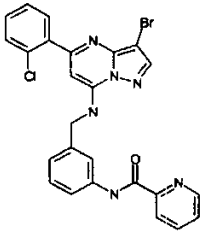
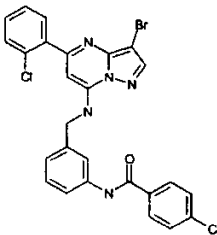
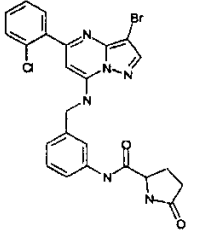
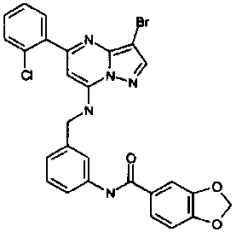
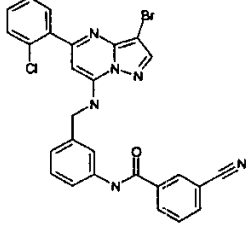
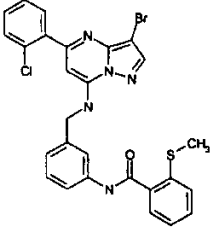
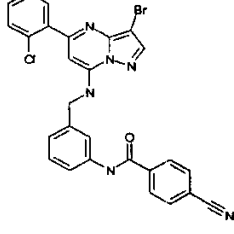
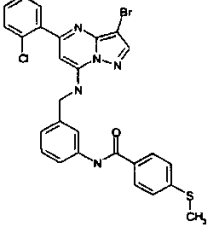
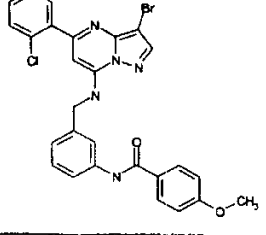
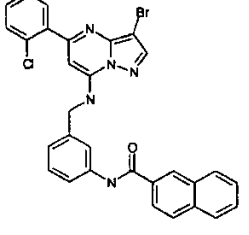
[1348]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 4821 2. 568.31		1. 4826 2. 574.32
	1. 4822 2. 573.32		1. 4828 2. 576.32
	1. 4821 2. 574.32		1. 4829 2. 578.32
	1. 4824 2. 574.32		1. 4829 2. 580.32
	1. 4825 2. 574.32		1. 4830 2. 584.32

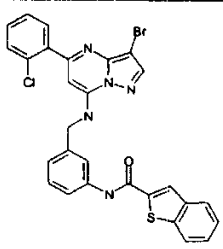
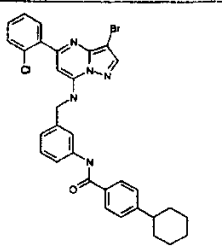
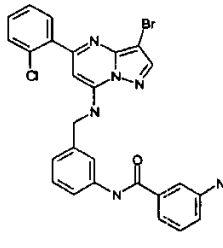
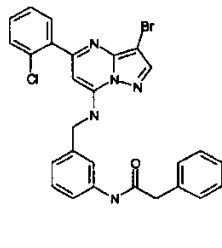
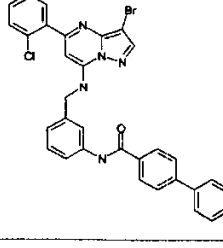
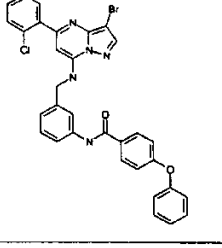
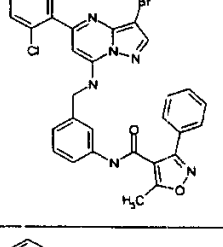
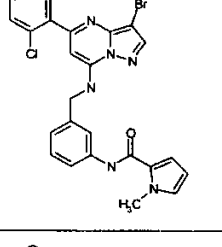
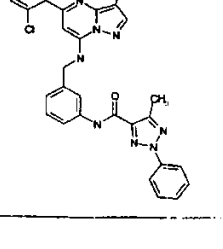
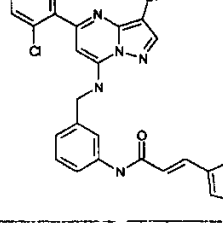
[1349]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 4831 2. 588.32		1. 4836 2. 616.34
	1. 4832 2. 602.33		1. 4837 2. 624.34
	1. 4833 2. 602.33		1. 4838 2. 626.34
	1. 4834 2. 602.33		1. 4839 2. 626.34
	1. 4835 2. 610.34		1. 4840 2. 564.31

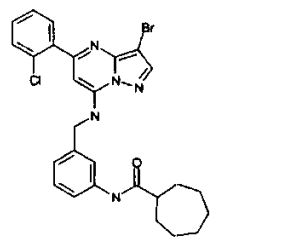
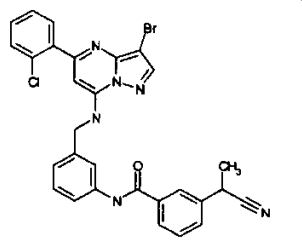
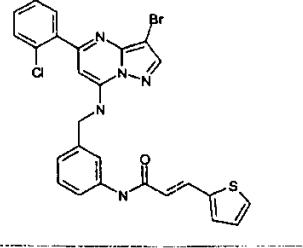
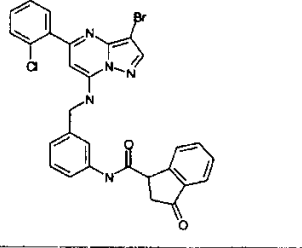
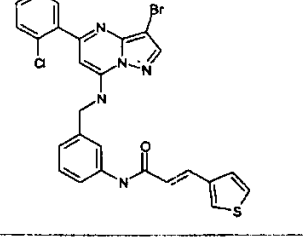
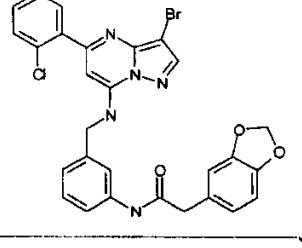
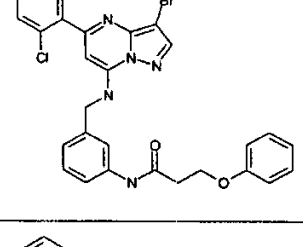
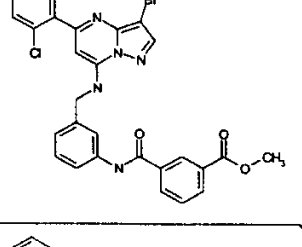
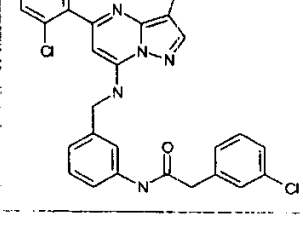
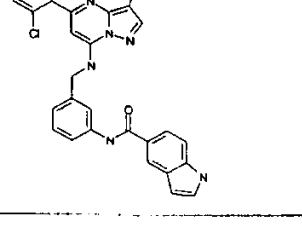
[1350]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 4841 2. 535.29		1. 4846 2. 568.31
	1. 4842 2. 541.3		1. 4847 2. 578.32
	1. 4843 2. 559.31		1. 4848 2. 580.32
	1. 4844 2. 559.31		1. 4849 2. 580.32
	1. 4845 2. 564.31		1. 4850 2. 584.32

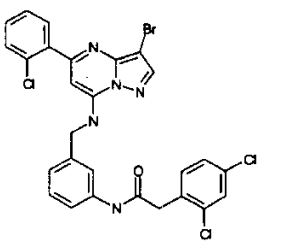
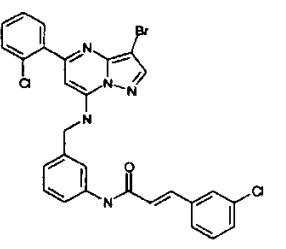
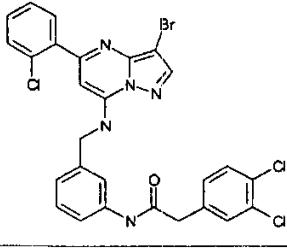
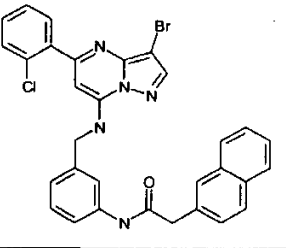
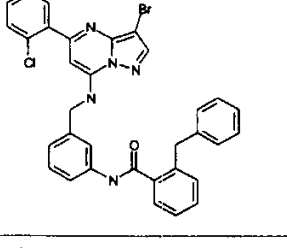
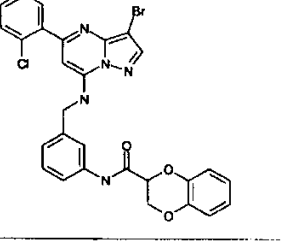
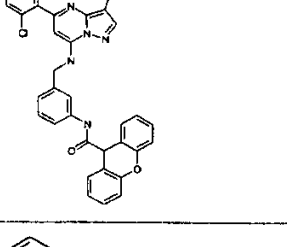
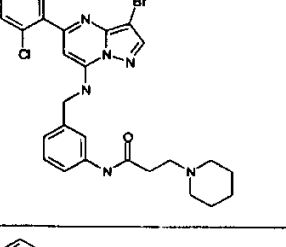
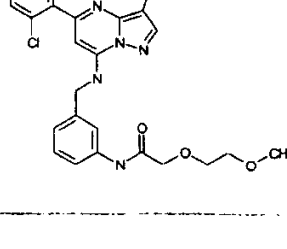
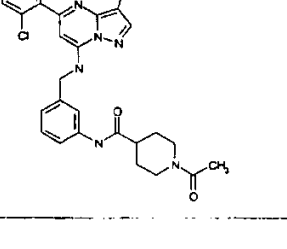
[1351]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4851 2. 590.32		1. 4856 2. 616.34
	1. 4852 2. 591.33		1. 4857 2. 624.34
	1. 4853 2. 610.34		1. 4858 2. 626.34
	1. 4854 2. 615.34		1. 4859 2. 537.3
	1. 4855 2. 615.34		1. 4860 2. 550.3

[1352]

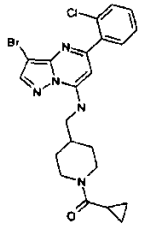
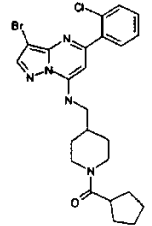
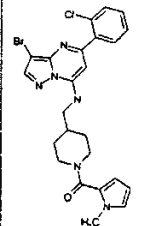
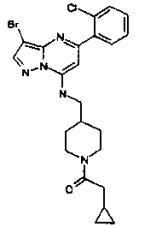
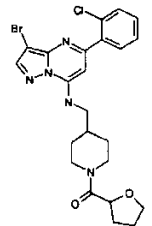
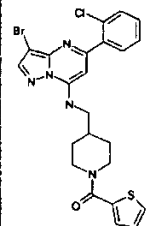
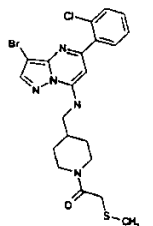
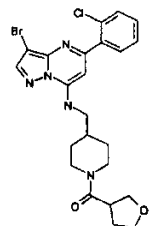
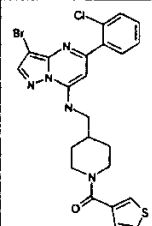
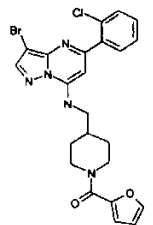
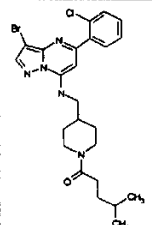
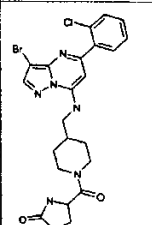
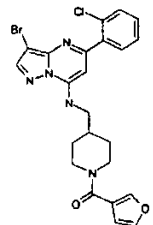
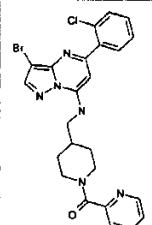
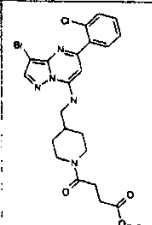
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4861 2. 554.3		1. 4866 2. 587.32
	1. 4862 2. 566.31		1. 4867 2. 588.32
	1. 4863 2. 566.31		1. 4868 2. 592.33
	1. 4864 2. 578.32		1. 4869 2. 592.33
	1. 4865 2. 582.32		1. 4870 2. 573.32

[1353]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 4871 2. 616.34		1. 4876 2. 594.33
	1. 4872 2. 616.34		1. 4877 2. 598.33
	1. 4873 2. 624.34		1. 4878 2. 592.33
	1. 4874 2. 638.35		1. 4879 2. 569.31
	1. 4875 2. 546.3		1. 4880 2. 583.32

[1354]

표 49

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4901 2. 490.27		1. 4906 2. 518.28		1. 4911 2. 529.29
	1. 4902 2. 504.28		1. 4907 2. 520.29		1. 4912 2. 532.29
	1. 4903 2. 510.28		1. 4908 2. 520.29		1. 4913 2. 532.29
	1. 4904 2. 516.28		1. 4909 2. 520.29		1. 4914 2. 533.29
	1. 4905 2. 516.28		1. 4910 2. 527.29		1. 4915 2. 536.29

[1355]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 4916 2. 538.3		1. 4921 2. 546.3		1. 4926 2. 552.3
	1. 4917 2 .540.3		1. 4922 2. 546.3		1. 4927 2. 554.3
	1. 4918 2. 542.3		1. 4923 2. 546.3		1. 4928 2. 554.3
	1. 4919 2. 545.3		1. 4924 2. 551.3		1. 4929 2. 556.31
	1. 4920 2. 546.3		1. 4925 2. 551.3		1. 4930 2. 556.31

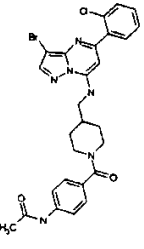
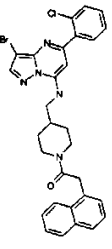
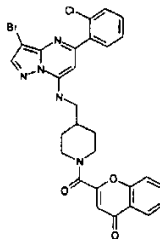
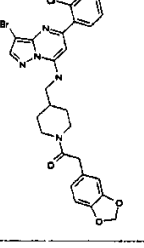
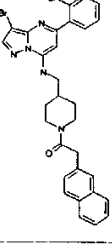
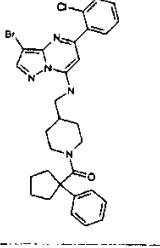
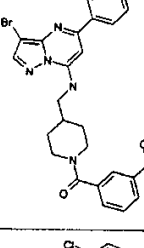
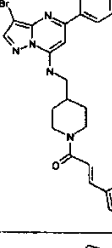
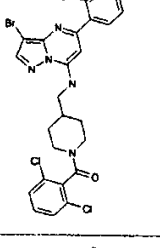
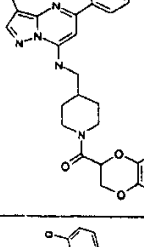
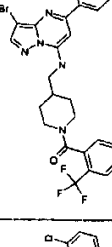
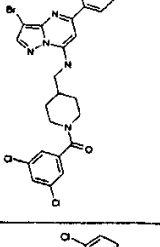
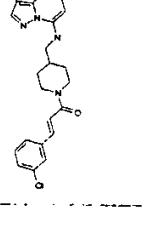
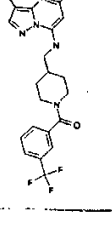
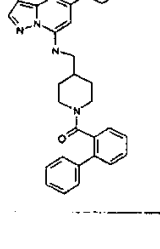
[1356]

생성물	1.실시에. 2.m/z	생성물	1.실시에 2.m/z	생성물	1.실시에. 2.m/z
	1. 4931 2. 556.31		1. 4936 2. 560.31		1. 4941 2. 566.31
	1. 4932 2. 556.31		1. 4937 2. 560.31		1. 4942 2. 566.31
	1. 4933 2. 558.31		1. 4938 2. 565.31		1. 4943 2. 566.31
	1. 4934 3. 558.31		1. 4939 2. 565.3		1. 4944 2. 566.31
	1. 4935 2. 560.31		1. 4940 2. 565.31		1. 4945 2. 568.31

[1357]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4946 2. 570.31		1. 4951 2. 571.31		1. 4956 2. 580.32
	1. 4947 2. 570.31		1. 4952 2. 574.32		1. 4957 2. 580.32
	1. 4948 2. 570.31		1. 4953 2. 576.32		1. 4958 2. 582.32
	1. 4949 2. 572.31		1. 4954 2. 576.32		1. 4959 2. 583.32
	1. 4950 2. 572.31		1. 4955 2. 579.32		1. 4960 2. 583.32

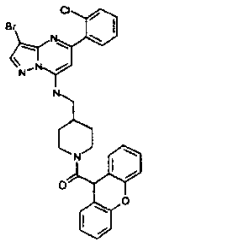
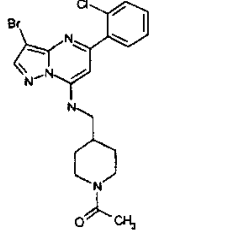
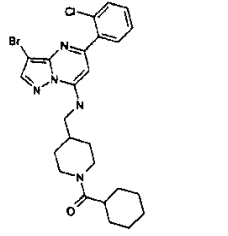
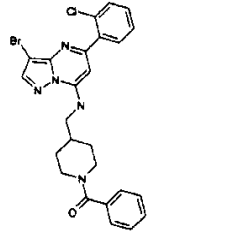
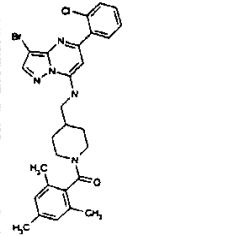
[1358]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4961 2. 583.32		1. 4966 2. 590.32		1. 4971 2. 594.33
	1. 4962 2. 584.32		1. 4967 2. 590.32		1. 4972 2. 594.33
	1. 4963 2. 584.32		1. 4968 2. 591.3		1. 4973 2. 594.33
	1. 4964 2. 584.32		1. 4969 2. 594.33		1. 4974 2. 594.33
	1. 4965 2. 586.32		1. 4970 2. 594.33		1. 4975 2. 602.33

[1359]

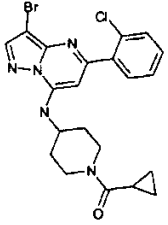
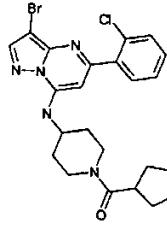
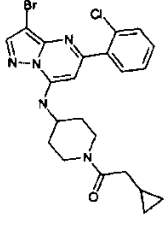
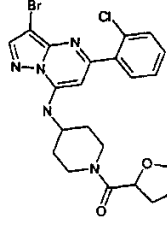
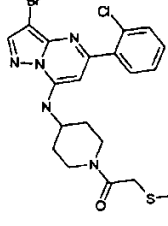
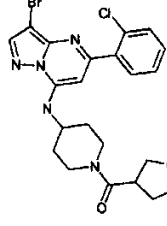
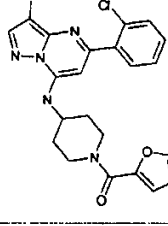
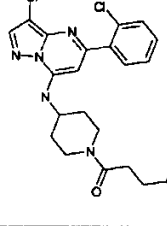
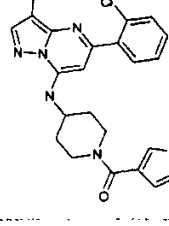
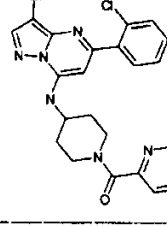
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 4976 2. 602.33		1. 4981 2. 608.33		1. 4986 2. 616.34
	1. 4977 2. 607.33		1. 4982 2. 608.33		1. 4987 2. 618.34
	1. 4978 2. 607.33		1. 4983 2. 608.33		1. 4988 2. 618.34
	1. 4979 2. 605.33		1. 4984 2. 609.33		1. 4089 2. 618.34
	1. 4980 2. 608.33		1. 4985 2. 616.34		1. 4990 2. 618.34

[1360]

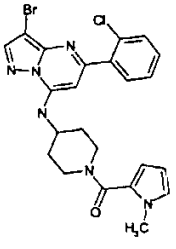
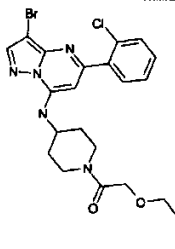
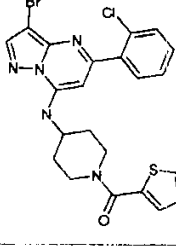
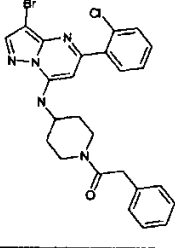
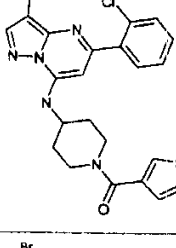
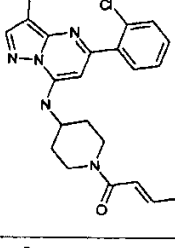
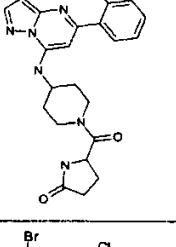
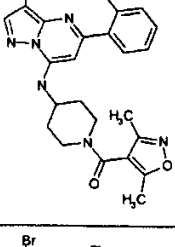
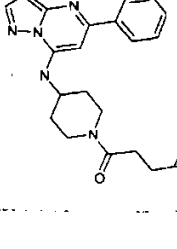
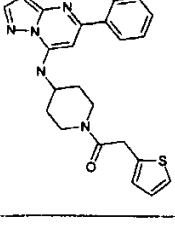
생성물	1.실시예 2.m/z
	<p>1. 4991 2. 630.35</p>
	<p>1. 4992 2. 464.26</p>
	<p>1. 4993 2. 532.29</p>
	<p>1. 4994 2. 526.29</p>
	<p>1. 4995 2. 568.31</p>

[1361]

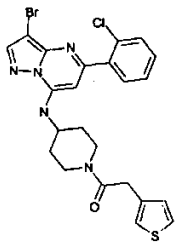
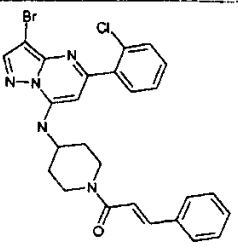
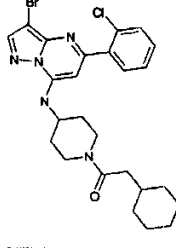
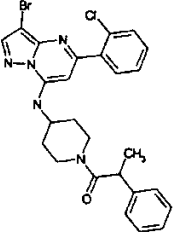
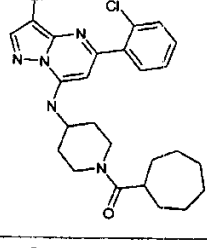
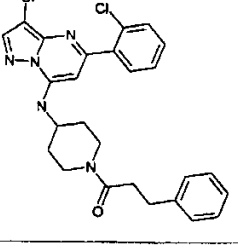
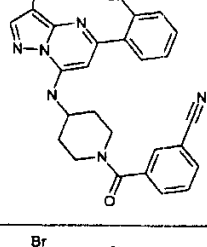
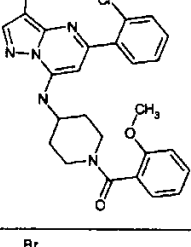
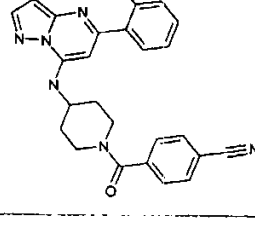
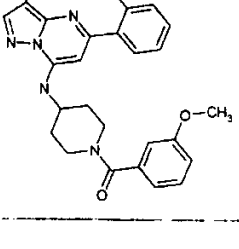
표 50

생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 5001 2. 476.26		1. 5006 2. 504.28
	1. 5002 2. 490.27		1. 5007 2. 506.28
	1. 5003 2. 496.27		1. 5008 2. 506.28
	1. 5004 2. 502.28		1. 5009 2. 506.28
	1. 5005 2. 502.28		1. 5010 2. 513.28

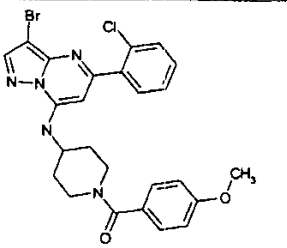
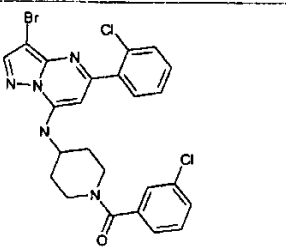
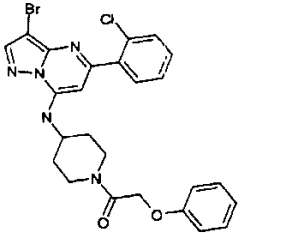
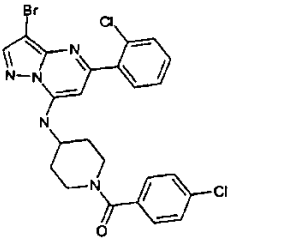
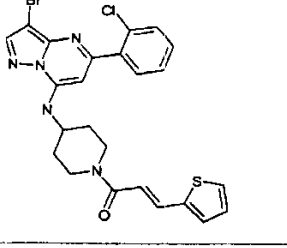
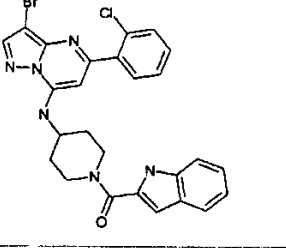
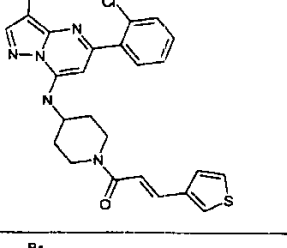
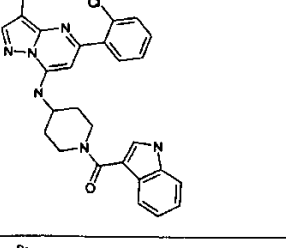
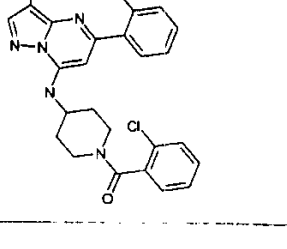
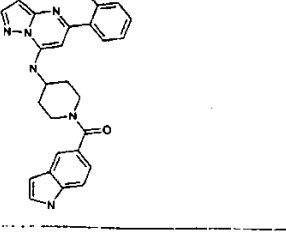
[1362]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 5011 2. 515.28		1. 5016 2. 524.29
	1. 5012 2. 518.28		1. 5017 2. 526.29
	1. 5013 2. 518.28		1. 5018 2. 528.29
	1. 5014 2. 519.29		1. 5019 2. 531.29
	1. 5015 2. 522.29		1. 5020 2. 532.29

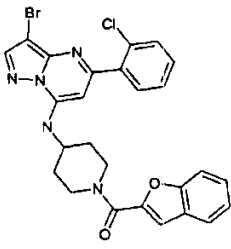
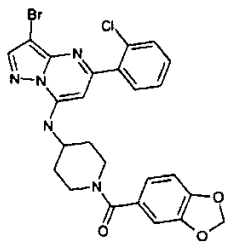
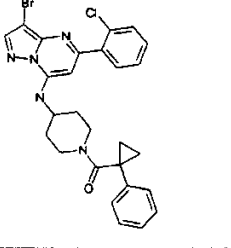
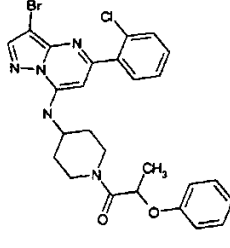
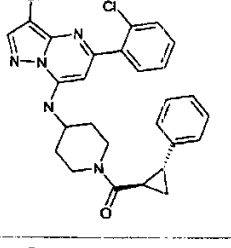
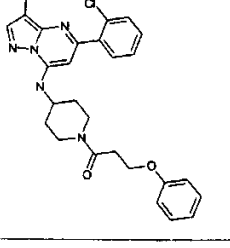
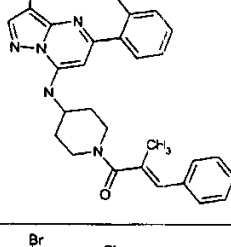
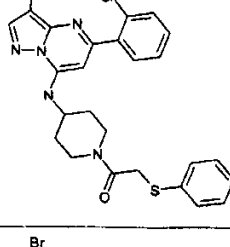
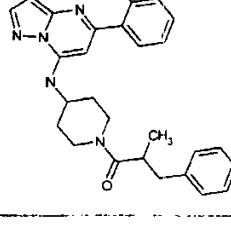
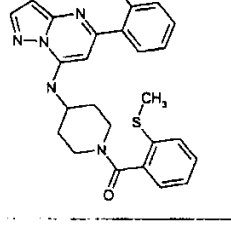
[1363]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 5021 2. 532.29		1. 5026 2. 538.3
	1. 5022 2. 532.29		1. 5027 2. 540.3
	1. 5023 2. 532.29		1. 5028 2. 540.3
	1. 5024 2. 537.3		1. 5029 2. 542.3
	1. 5025 2. 537.3		1. 5030 2. 542.3

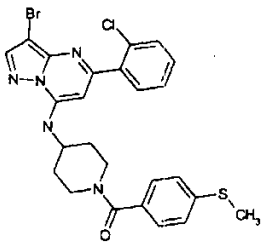
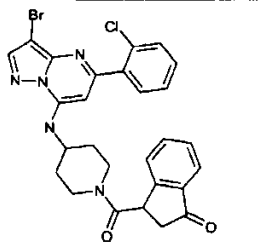
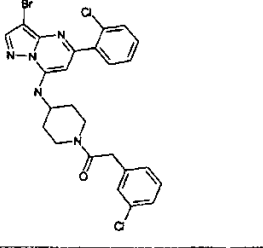
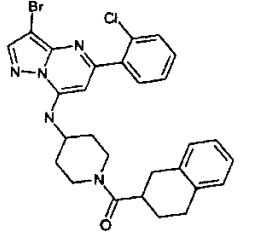
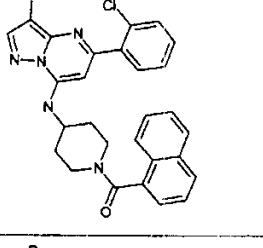
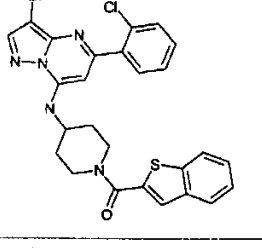
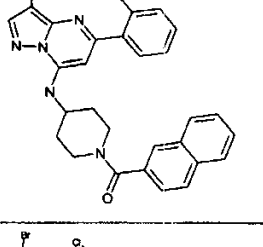
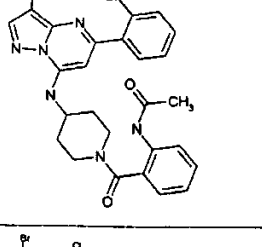
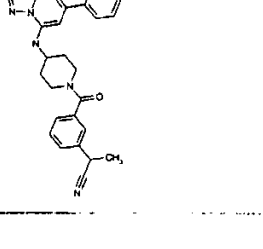
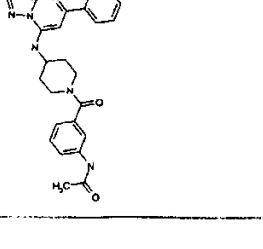
[1364]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 5031 2. 542.3		1. 5036 2. 546.3
	1. 5032 2. 542.3		1. 5037 2 .546.3
	1. 5033 2. 544.3		1. 5038 2. 551.3
	1. 5034 2. 544.3		1. 5039 2. 551.3
	1. 5035 2 .546.3		1. 5040

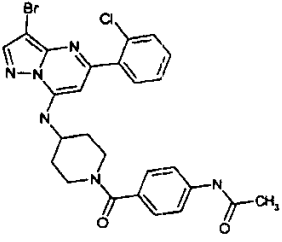
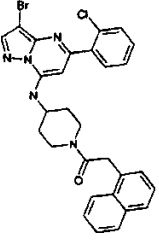
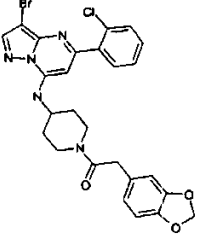
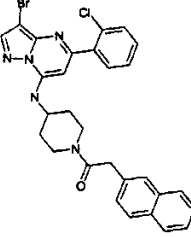
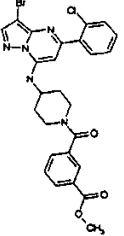
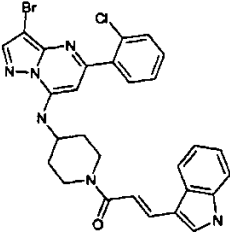
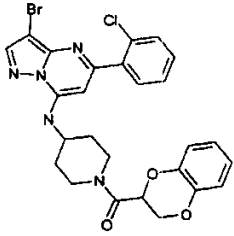
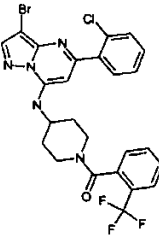
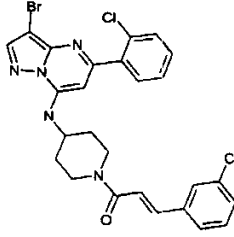
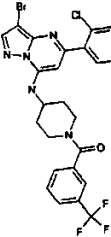
[1365]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 5041 2. 552.3		1. 5046 2. 556.31
	1. 5042 2. 552.3		1. 5047 2. 556.31
	1. 5043 2. 552.3		1. 5048 2. 556.31
	1. 5044 2. 552.3		1. 5049 2. 558.31
	1. 5045 2. 554.3		1. 5050 2. 558.31

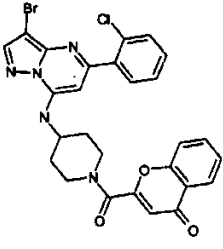
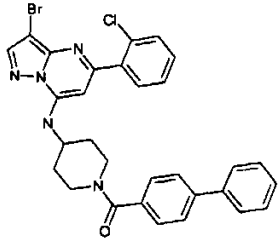
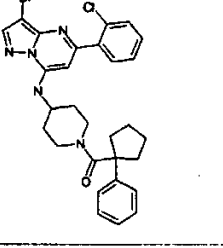
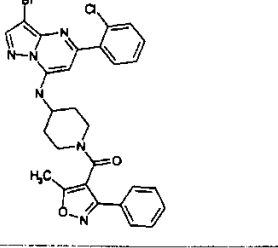
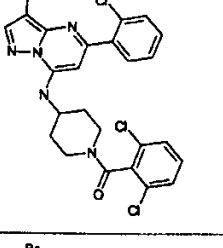
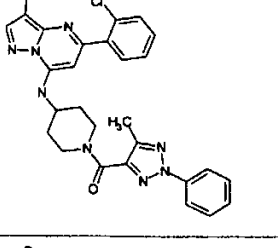
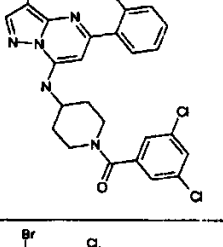
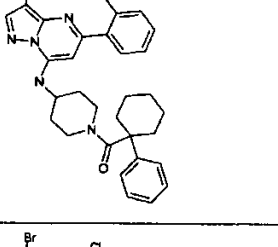
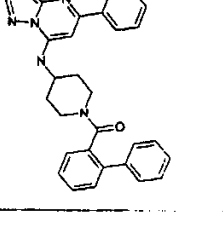
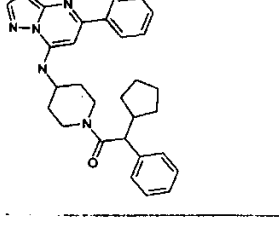
[1366]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5051 2. 558.31		1. 5056 2. 566.31
	1. 5052 2. 560.31		1. 5057 2. 566.31
	1. 5053 2. 562.31		1. 5058 2. 568.31
	1. 5054 2. 562.31		1. 5059 2. 569.31
	1. 5055 2. 565.31		1. 5060 2. 569.31

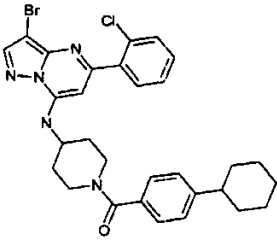
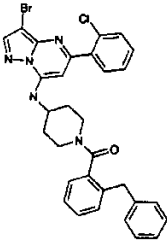
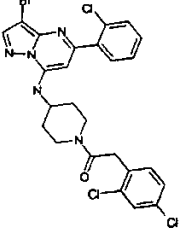
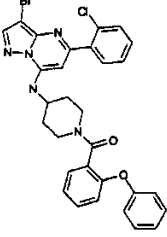
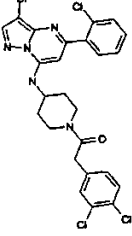
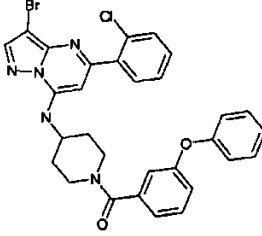
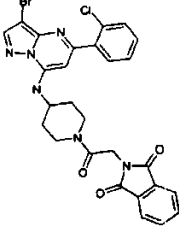
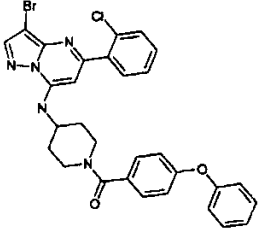
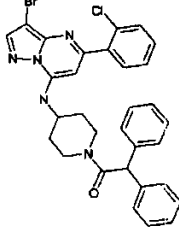
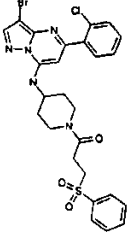
[1367]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5061		1. 5066 2. 576.32
	1. 5062 2. 570.31		1. 5067 2. 576.32
	1. 5063 2. 570.31		1. 5068 2. 577.32
	1. 5064 2. 570.31		1. 5069 2. 580.32
	1. 5065 2. 572.31		1. 5070 2. 580.32

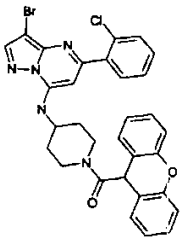
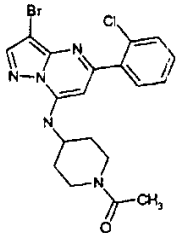
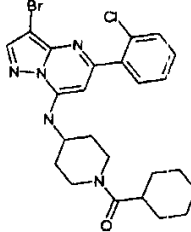
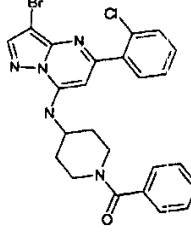
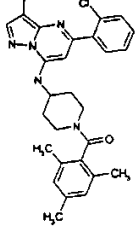
[1368]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 5071 2. 580.32		1. 5076 2. 588.32
	1. 5072 2. 580.32		1. 5077 2. 593.33
	1. 5073 2. 580.32		1. 5078 2. 593.33
	1. 5074 2. 580.32		1. 5079 2. 594.33
	1. 5075 2. 588.32		1. 5080 2. 594.33

[1369]

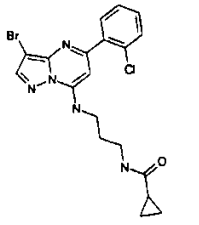
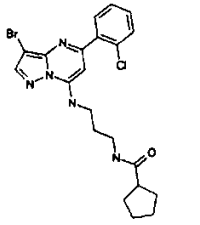
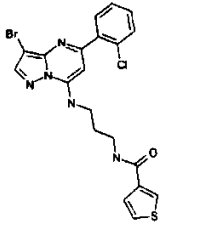
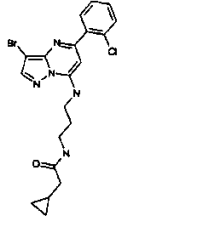
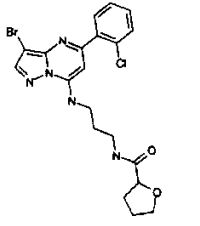
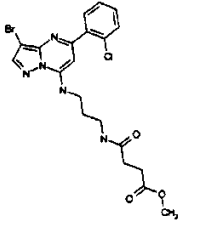
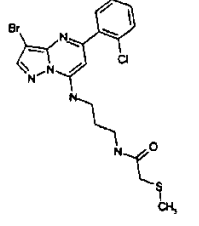
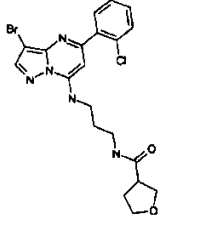
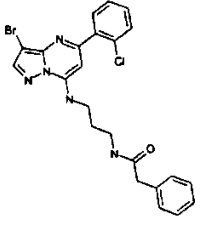
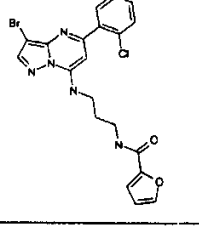
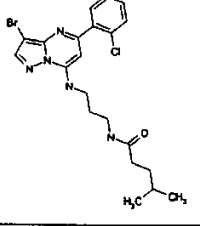
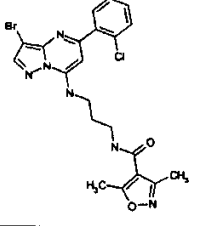
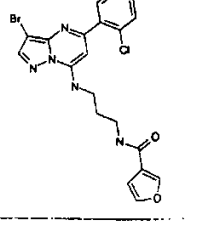
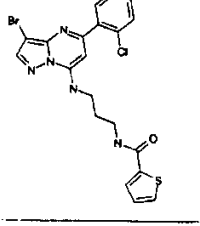
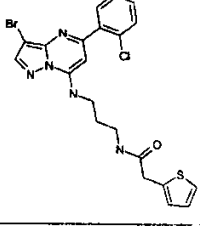
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5081 2. 594.33		1. 5086 2. 602.33
	1. 5082 2. 594.33		1.5087 2. 604.33
	1. 5083 2. 594.33		1. 5088 2. 604.33
	1. 5084 2. 595.33		1. 5089 2. 604.33
	1.5085 2. 602.33		1. 5090 2. 604.33

[1370]

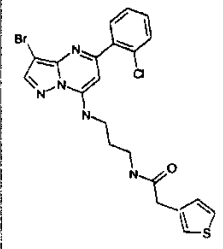
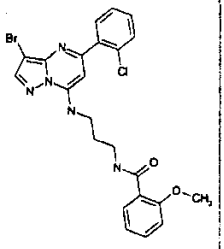
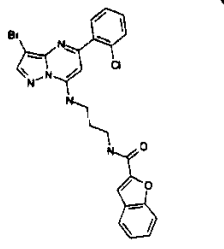
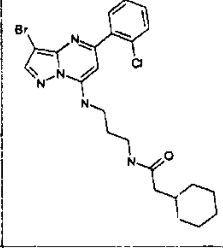
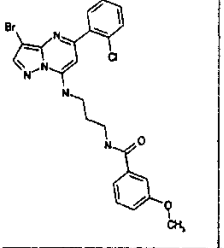
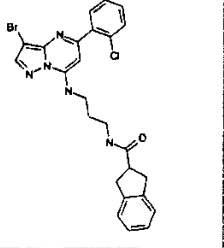
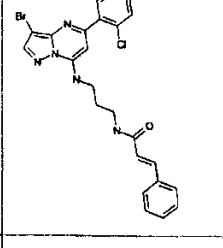
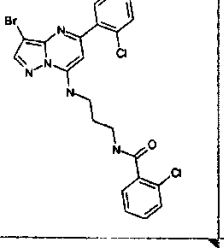
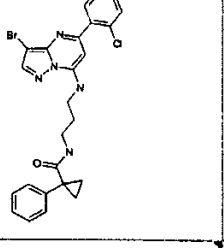
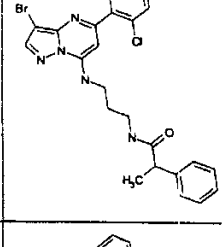
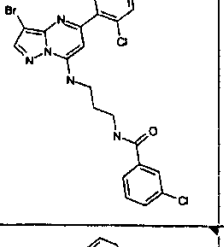
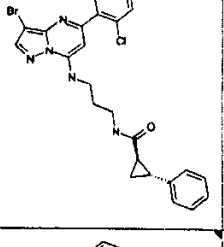
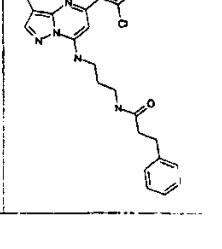
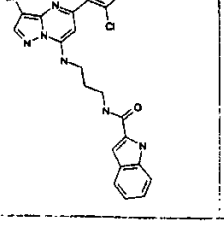
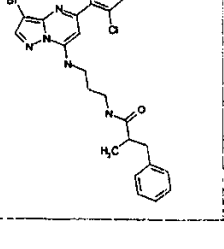
생성물	1.실시예. 2.m/z
	<p>1. 5091 2. 616.34</p>
	<p>1. 5092 2. 450.25</p>
	<p>1. 5093 2. 518.28</p>
	<p>1. 5094 2. 512.28</p>
	<p>1. 5095 2. 554.3</p>

[1371]

표 51

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 5101 2. 448.8		1. 5106 2. 476.8		1. 5111 2. 490.8
	1. 5102 2. 462.8		1. 5107 2. 478.8		1. 5112 2. 494.8
	1. 5103 2. 468.8		1. 5108 2. 478.8		1. 5113 2. 498.8
	1. 5104 2. 474.7		1. 5109 2. 478.8		1. 5114 2. 503.8
	1. 5105 2. 474.7		1. 5110 2. 490.8		1. 5115 2. 504.8

[1372]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 5116 2. 504.8		1. 5121 2. 514.8		1. 5126 2. 524.8
	1. 5117 2. 504.9		1. 5122 2. 514.8		1. 5127 2. 524.9
	1. 5118 2. 510.8		1. 5123 2. 519.2		1. 5128 2. 524.9
	1. 5119 2. 512.8		1. 5124 2. 519.2		1. 5129 2. 524.9
	1. 5120 2. 512.8		1. 5125 2. 523.8		1. 5130 2. 526.9

[1373]

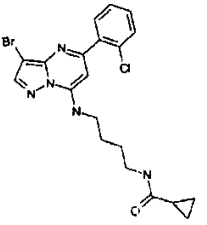
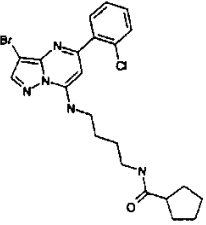
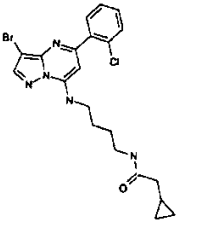
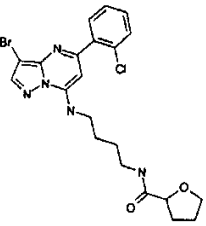
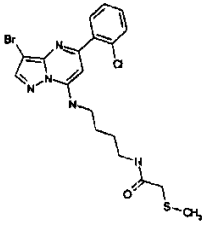
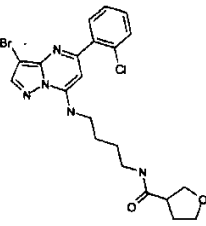
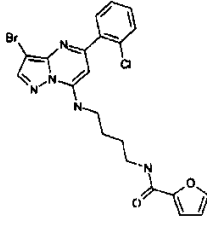
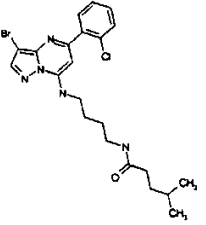
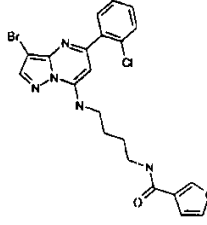
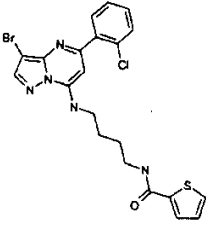
생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 5131 2. 528.8		1. 5136 2. 552.8		1. 5141 2. 567.8
	1. 5132 2. 530.9		1. 5137 2. 553.7		1. 5142 2. 574.9
	1. 5133 2. 534.8		1. 5138 2. 553.7		1. 5143 2. 576.9
	1. 5134 2. 538.9		1. 5139 2. 560.9		1. 5144 2. 576.9
	1. 5135 2. 552.8		1. 5140 2. 566.9		1. 5145 2. 514.8

[1374]

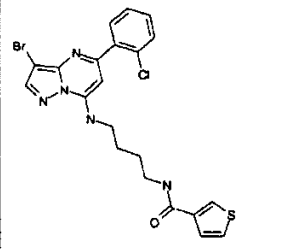
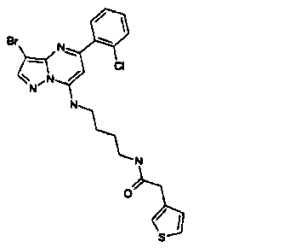
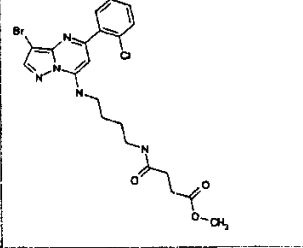
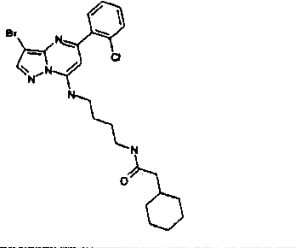
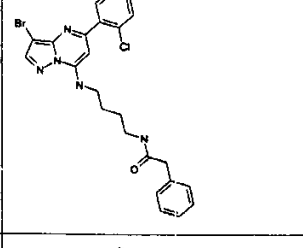
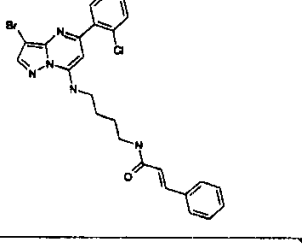
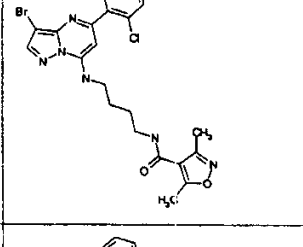
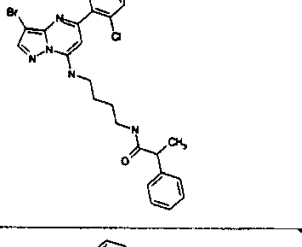
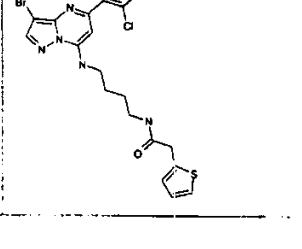
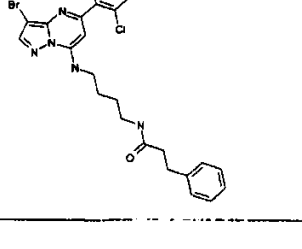
생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 5146 2. 485.8		1. 5151 2. 519.2		1. 5156 2. 534.8
	1. 5147 2. 491.8		1. 5152 2. 523.8		1. 5157 2. 540.9
	1. 5148 2. 509.8		1. 5153 2. 528.8		1. 5158 2. 541.8
	1. 5149 2. 509.8		1. 5154 2. 530.9		1. 5159 2. 541.8
	1. 5150 2. 514.8		1. 5155 2. 530.9		1. 5160 2. 560.9

[1375]

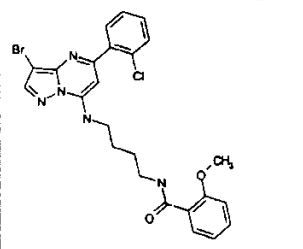
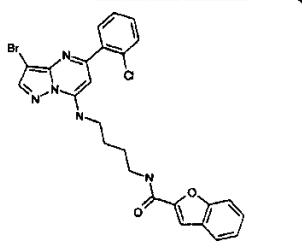
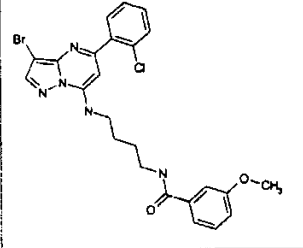
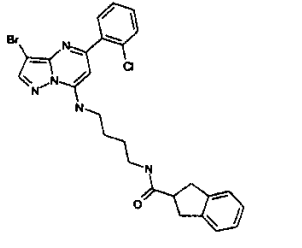
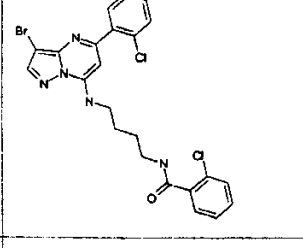
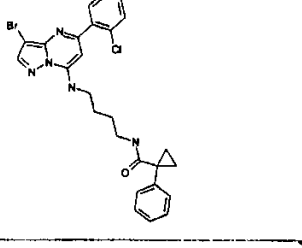
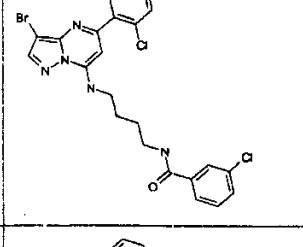
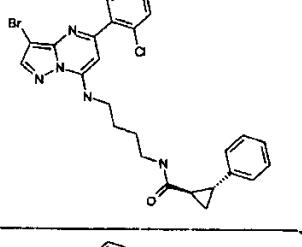
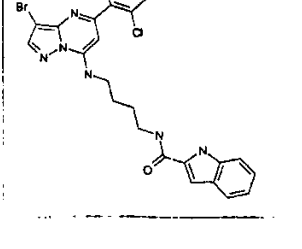
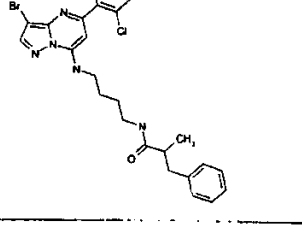
표 52

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5201 2. 462.8		1. 5206 2. 490.8
	1. 5202 2. 476.8		1. 5207 2. 492.8
	1. 5203 2. 482.8		1. 5208 2. 492.8
	1. 5204 2. 488.8		1. 52009 2. 492.9
	1. 5205 2. 488.8		1. 5210 2. 504.8

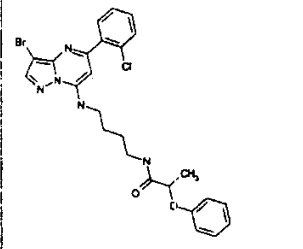
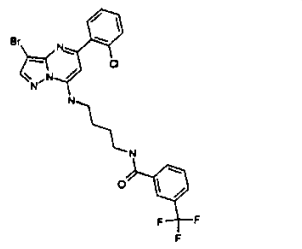
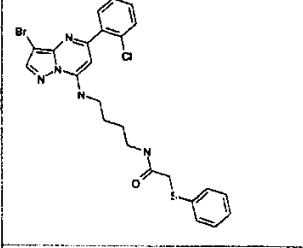
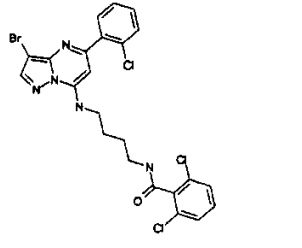
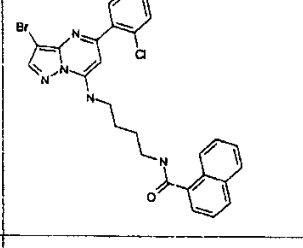
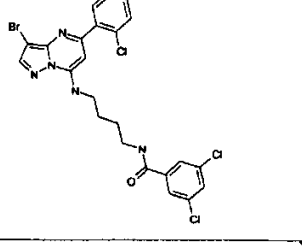
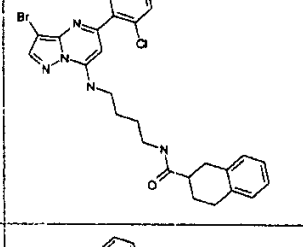
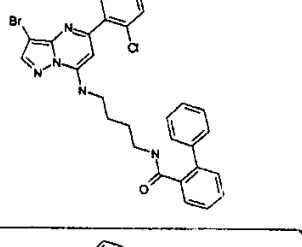
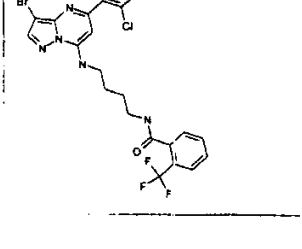
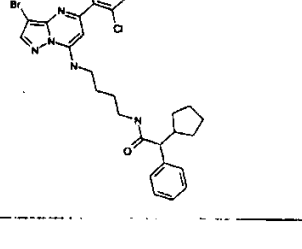
[1376]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 5211 2. 504.8		1. 5216 2. 518.9
	2. 5212 2. 508.8		1. 5217 2. 518.9
	1. 5213 2. 512.8		1. 5218 2. 524.9
	1. 5214 2. 517.8		1. 5219 2. 526.9
	1. 5215 2. 518.9		1. 5220 2. 526.9

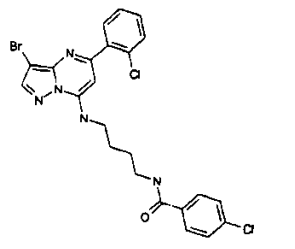
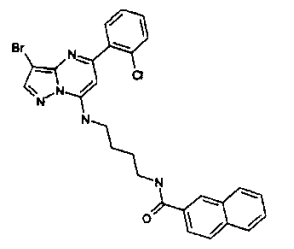
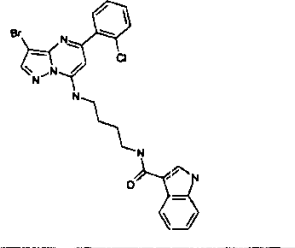
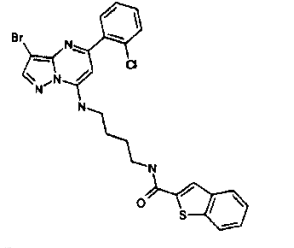
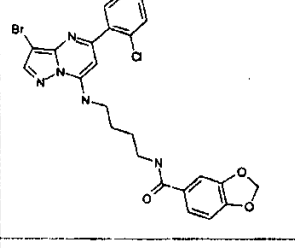
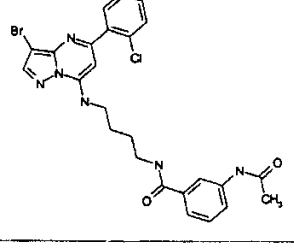
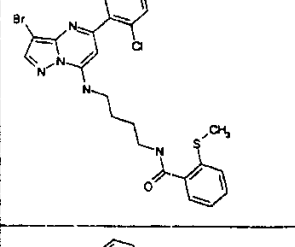
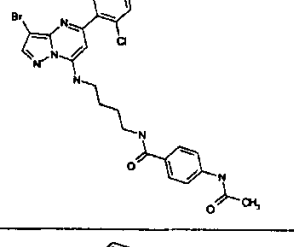
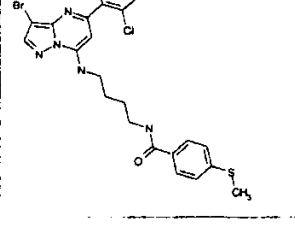
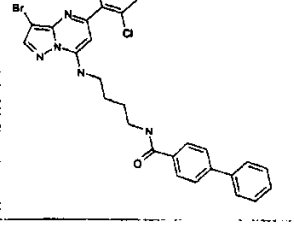
[1377]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 5221 2. 528.8		1. 5226 2. 538.8
	1. 5222 2. 528.8		1. 5227 2. 538.9
	1. 5223 2. 533.3		1. 5228 2. 538.9
	1. 5224 2. 533.3		1. 5229 2. 538.9
	1. 5225 2. 537.9		1. 5230 2. 540.9

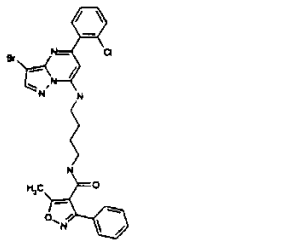
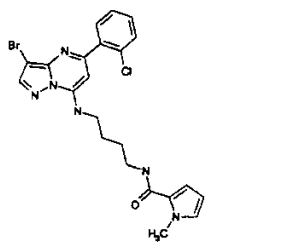
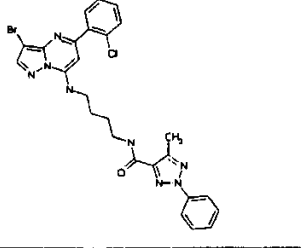
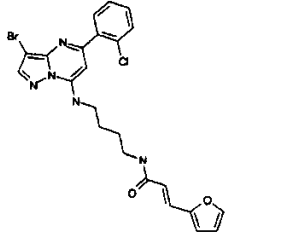
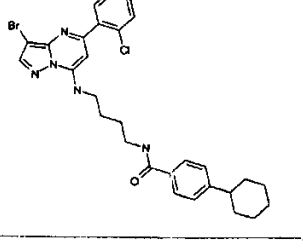
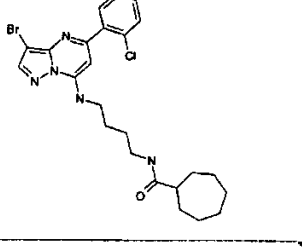
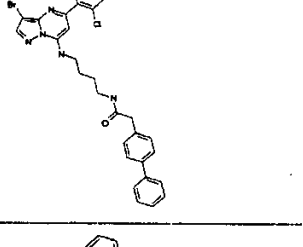
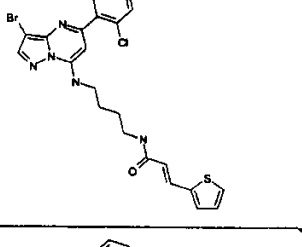
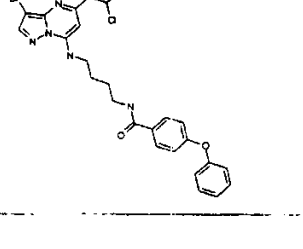
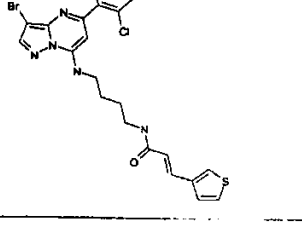
[1378]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5231 2. 542.9		1. 5236 2. 566.8
	1. 5232 2. 544.9		1. 5237 2. 567.7
	1. 5233 2. 548.9		1. 5238 2. 567.7
	1. 5234 2. 552.9		1. 5239 2. 574.9
	1. 5235 2. 566.8		1. 5240 2. 581

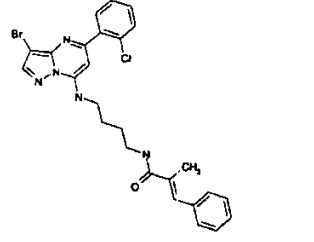
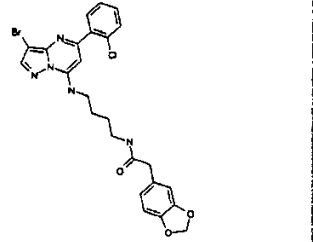
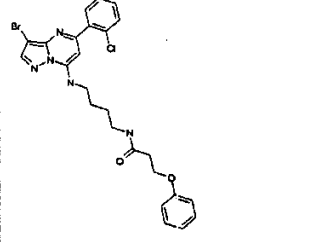
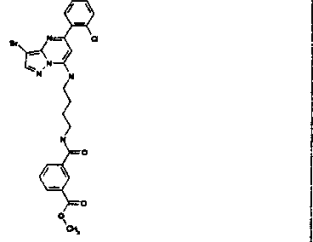
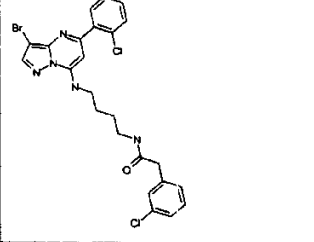
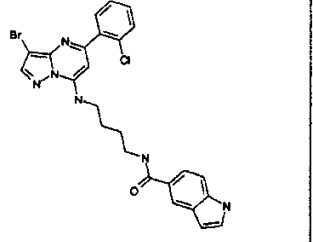
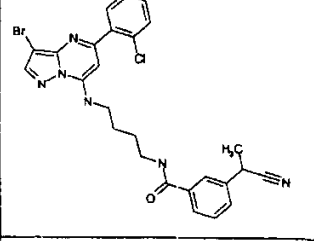
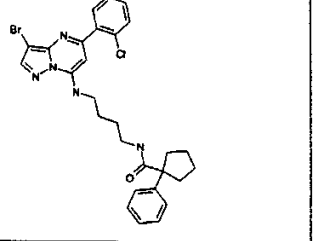
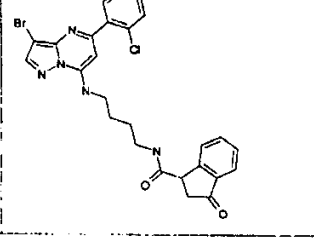
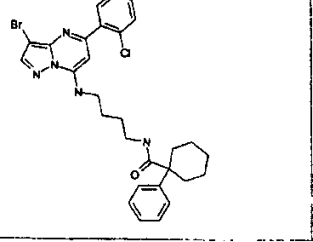
[1379]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5241 2. 533.3		1. 5246 2. 548.9
	1. 5242 2. 537.9		1. 5247 2. 554.9
	1. 5243 2. 542.8		1. 5248 2. 555.9
	1. 5244 2. 544.9		1. 5249 2. 555.9
	1. 5245 2. 544.9		1. 5250 2. 574.9

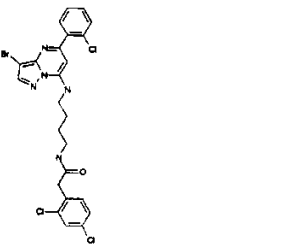
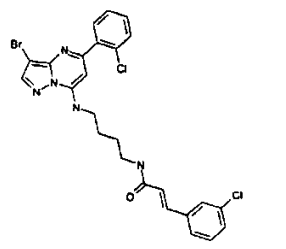
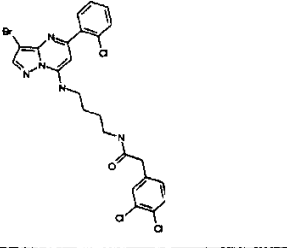
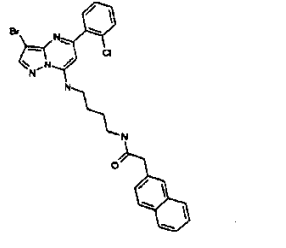
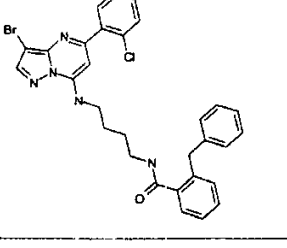
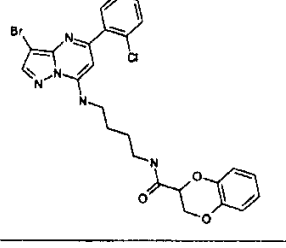
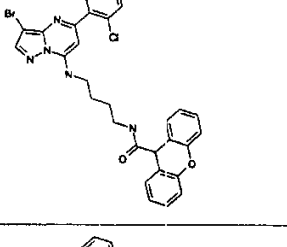
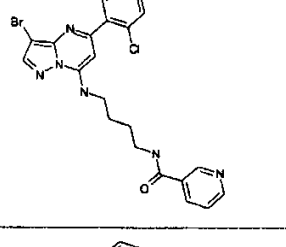
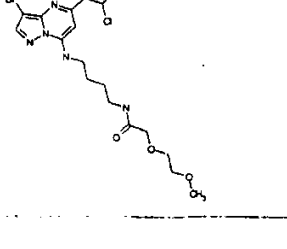
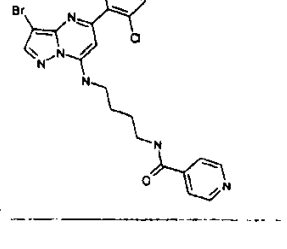
[1380]

생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 5251 2. 579.9		1. 5256 2. 501.8
	1. 5252 2. 579.9		1. 5257 2. 514.8
	1. 5253 2. 581		1. 5258 2. 518.9
	1. 5254 2. 588.9		1. 5259 2. 530.9
	1. 5255 2. 590.9		1. 5260 2. 530.9

[1381]

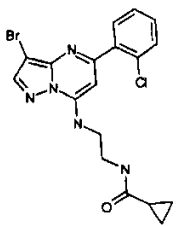
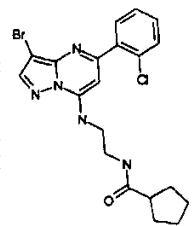
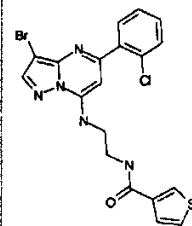
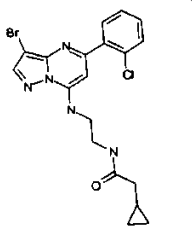
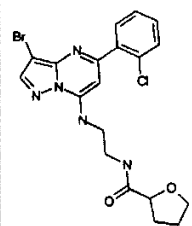
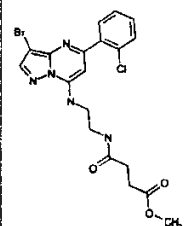
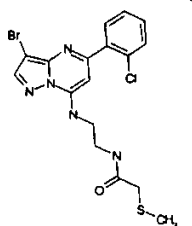
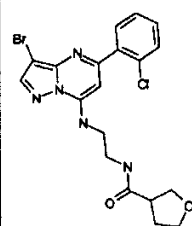
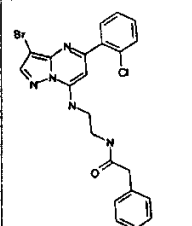
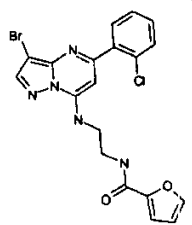
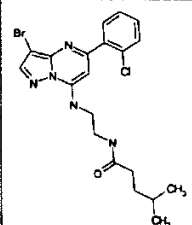
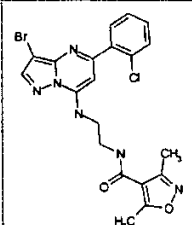
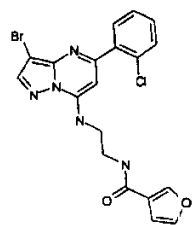
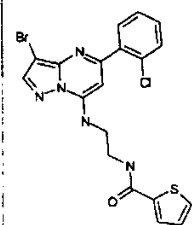
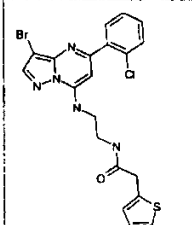
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5261 2. 538.9		1. 5266 2. 556.9
	1. 5262 2. 542.9		1. 5267 2. 556.9
	1. 5263 2. 547.3		1. 5268 2. 537.9
	1. 5264 2. 551.9		1. 5269 2. 566.9
	1. 5265 2. 552.9		1. 5270 2. 581

[1382]

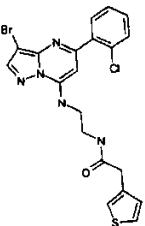
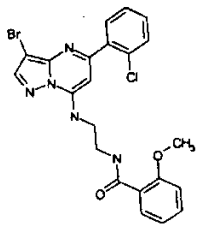
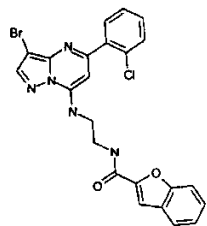
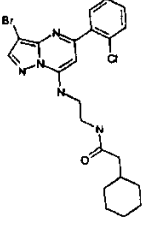
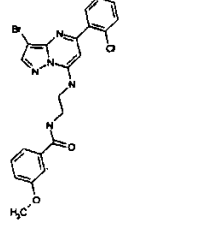
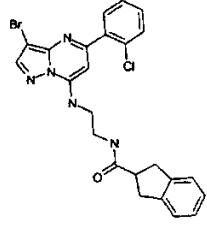
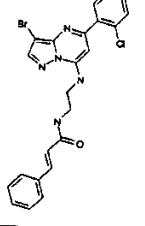
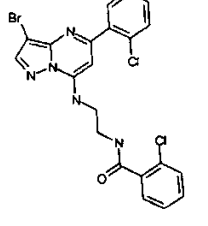
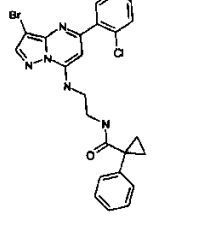
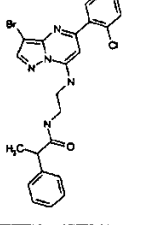
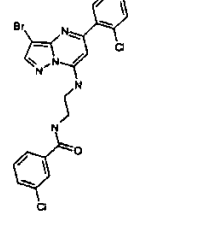
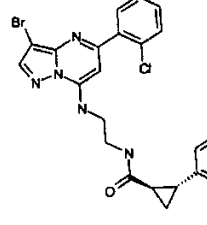
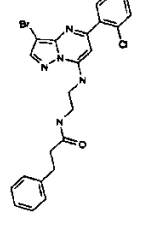
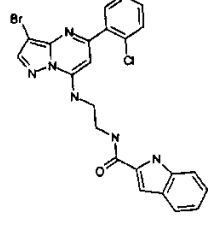
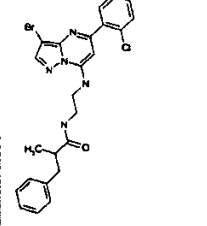
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5271 2. 581.7		1. 5276 2. 559.3
	1. 5272 2. 581.7		1. 5277 2. 562.9
	1. 5273 2. 588.9		1. 5278 2. 556.9
	1. 5274 2. 602.9		1. 5279 2. 499.8
	1. 5275 2. 510.8		1. 5280 2. 499.8

[1383]

표 53

생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 5301 2. 434.7		1. 5306 2. 462.8		1. 5311 2. 476.8
	1. 5302 2. 448.8		1. 5307 2. 464.8		1. 5312 2. 480.8
	1. 5303 2. 454.8		1. 5308 2. 464.8		1. 5313 2. 484.8
	1. 5304 2. 460.7		1. 5309 2. 464.8		1. 5314 2. 489.8
	1. 5305 2. 460.7		1. 5310 2. 476.8		1. 5315 2. 490.8

[1384]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5316 2. 490.8		1. 5321 2. 500.8		1. 5326 2. 510.8
	1. 5317 2. 490.8		1. 5322 2. 500.8		1. 5327 2. 510.8
	1. 5318 2. 496.8		1. 5323 2. 505.2		1. 5328 2. 510.8
	1. 5319 2. 498.8		1. 5324 2. 505.2		1. 5329 2. 510.8
	1. 5320 2. 498.8		1. 5325 2. 509.8		1. 5330 2. 512.8

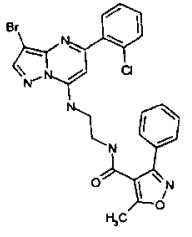
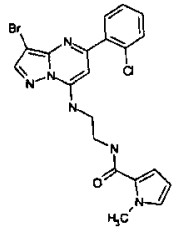
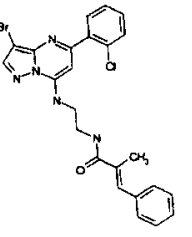
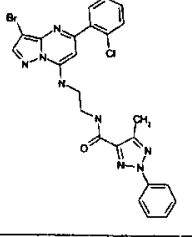
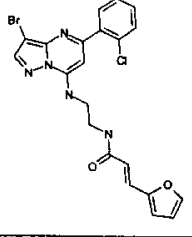
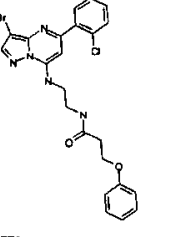
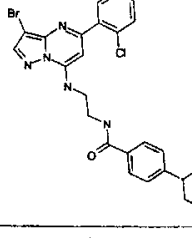
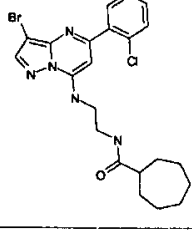
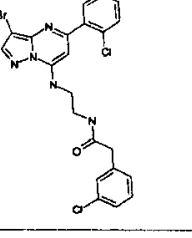
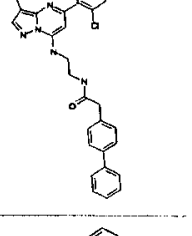
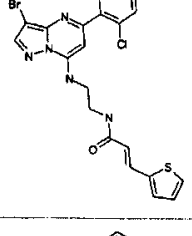
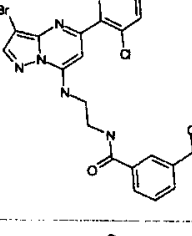
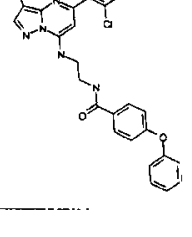
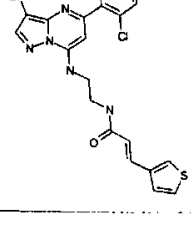
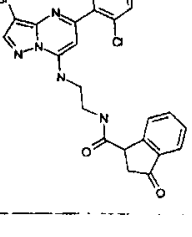
[1385]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5331 2. 514.8		1. 5336 2. 538.8		1. 5341 2. 553.8
	1. 5332 2. 516.9		1. 5337 2. 539.6		1. 5342 2. 560.9
	1. 5333 2. 520.8		1. 5338 2. 539.6		1. 5343 2. 562.9
	1. 5334 2. 524.9		1. 5339 2. 546.9		1. 5344 2. 562.9
	1. 5335 2. 538.8		1.5340 2. 552.9		1. 5345 2. 500.8

[1386]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5346 2. 471.7		1. 5351 2. 505.2		1. 5356 2. 520.8
	1. 5347 2. 477.8		1. 5352 2. 509.8		1. 5357 2. 526.8
	1. 5348 2. 495.8		1. 5353 2. 514.8		1. 5358 2. 527.8
	1. 5349 2. 495.8		1. 5355 2. 516.9		1. 5359 2. 527.8
	1. 5350 2. 500.8		1. 5356 2. 516.9		1. 5360 2. 546.9

[1387]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 5361 2. 551.8		1. 5366 2. 473.8		1. 5371 2. 510.8
	1. 5362 2. 551.8		1. 5367 2. 486.8		1. 5372 2. 514.8
	1. 5363 2. 552.9		1. 5368 2. 490.8		1. 5373 2. 519.2
	1. 5364 2. 560.9		1. 5369 2. 502.8		1. 5374 2. 523.8
	1. 5365 2. 562.9		1. 5370 2. 502.8		1. 5375 2. 524.8

[1388]

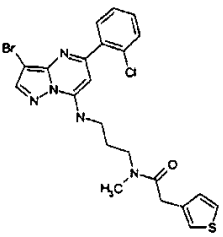
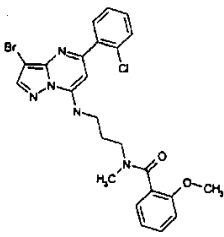
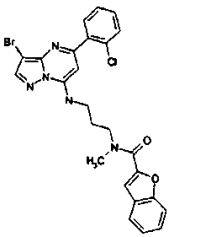
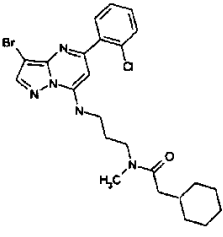
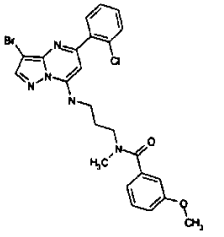
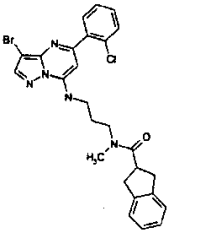
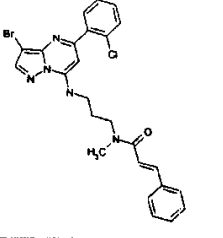
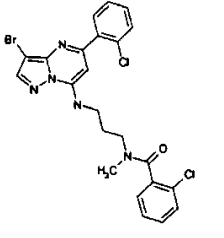
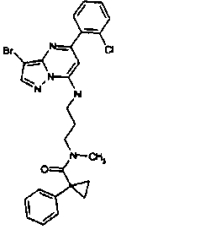
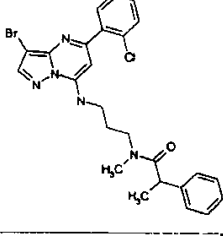
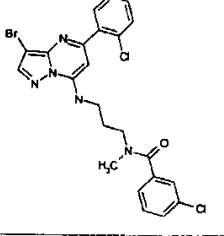
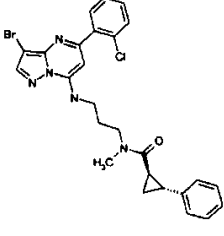
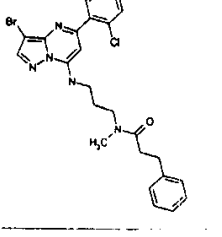
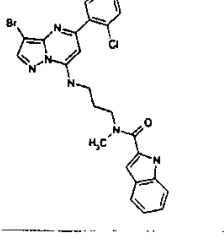
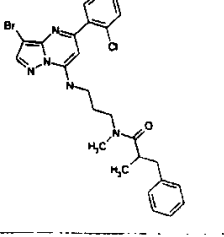
생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 5376 2. 528.8		1. 5381 2. 553.7		1. 5386 2. 531.2
	1. 5377 2. 528.8		1. 5382 2. 553.7		1. 5387 2. 534.8
	1. 5378 2. 509.8		1. 5383 2. 560.9		1. 5388 2. 528.8
	1. 5379 2. 538.9		1. 5384 2. 574.9		1. 5389 2. 538.8
	1. 5380 2. 552.9		1. 5385 2. 482.8		1. 5390 2. 471.7

[1389]

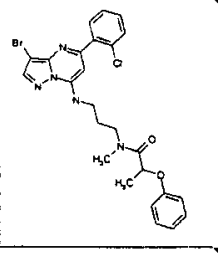
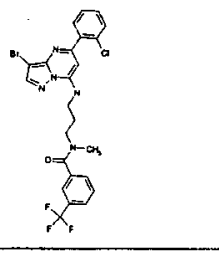
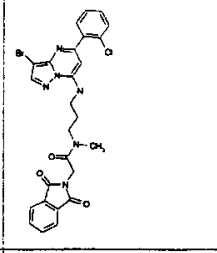
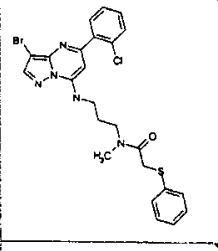
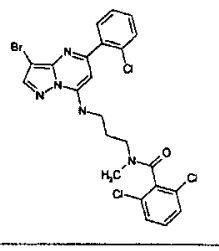
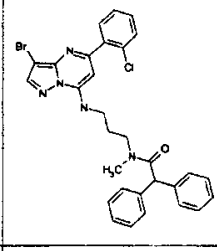
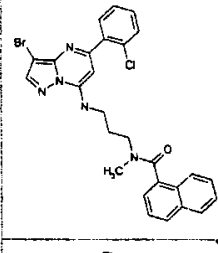
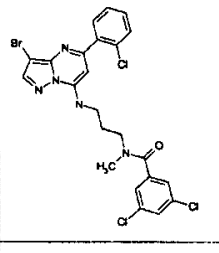
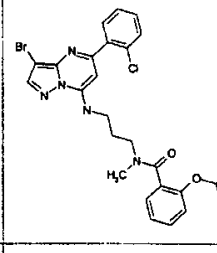
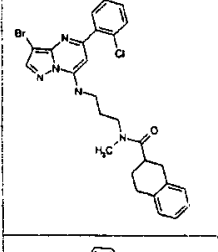
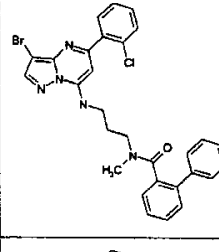
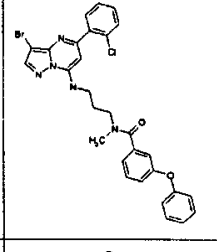
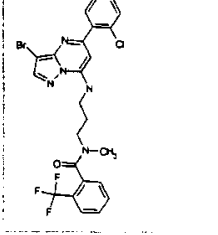
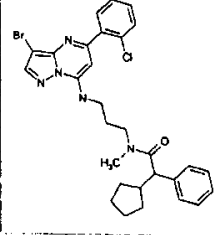
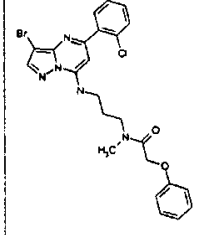
표 54

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5401 2. 463.3		1. 5406 2. 491.3		1. 5411 2. 505.3
	1. 5402 2. 477.3		1. 5407 2. 493.3		1. 5412 2. 509.3
	1. 5403 2. 483.3		1. 5408 2. 493.3		1. 5413 2. 513.3
	1. 5404 2. 489.3		1. 5409 2. 493.3		1. 5414 2. 518.3
	1. 5405 2. 489.3		1. 5410 2. 505.3		1. 5415 2. 519.3

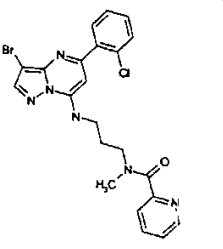
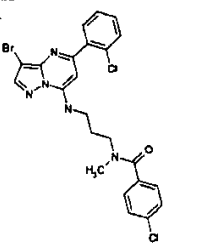
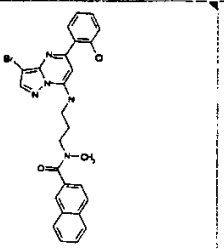
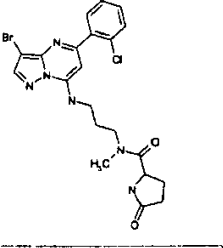
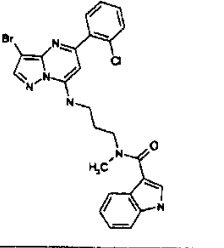
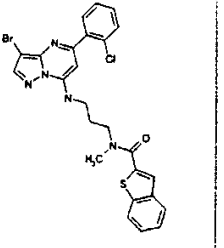
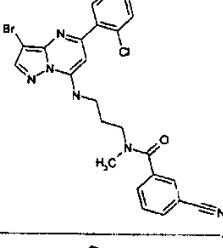
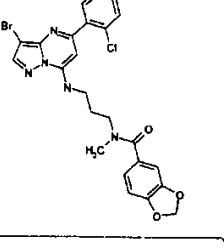
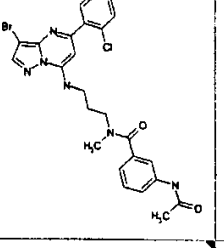
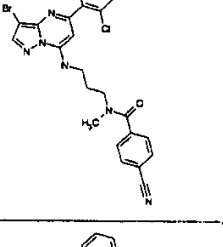
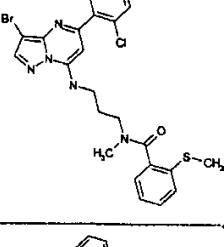
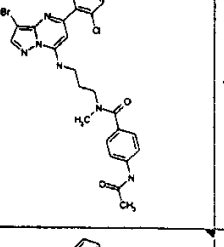
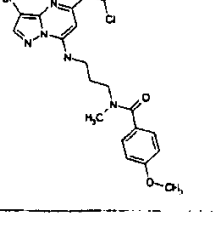
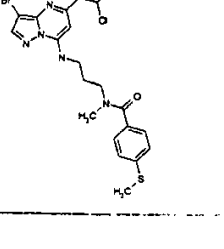
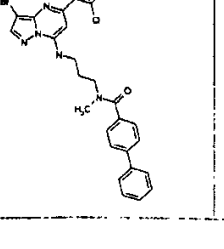
[1390]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5416 2. 519.3		1. 5121 2. 529.3		1. 5426 2. 539.3
	1. 5417 2. 519.3		1. 5422 2. 529.3		1. 5427 2. 539.3
	1. 5418 2. 525.3		1. 5423 2. 533.3		1. 5428 2. 539.3
	1. 5419 2. 527.3		1. 5424 2. 533.3		1. 5429 2. 539.3
	1. 5420 2. 527.3		1. 5425 2. 538.3		1. 5430 2. 541.3

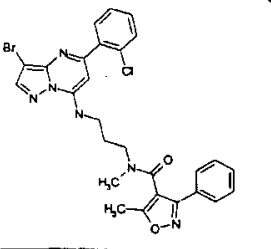
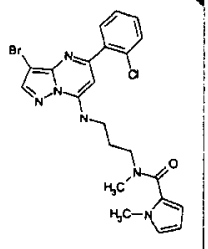
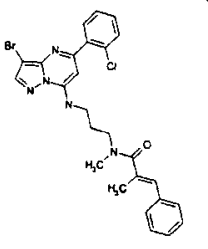
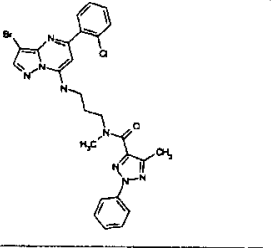
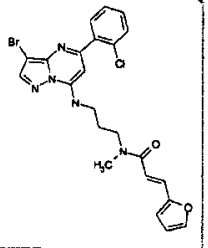
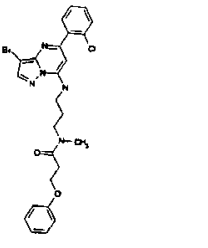
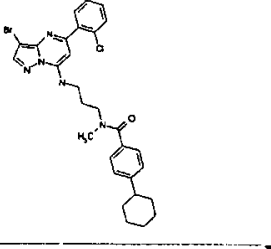
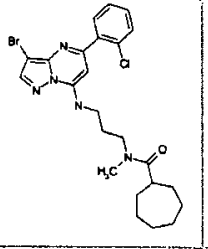
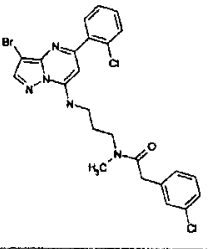
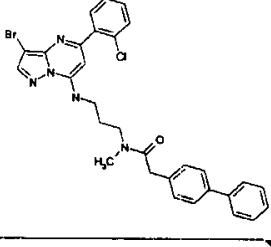
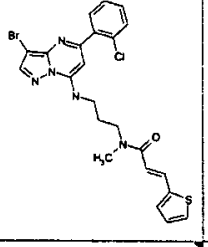
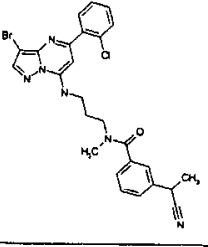
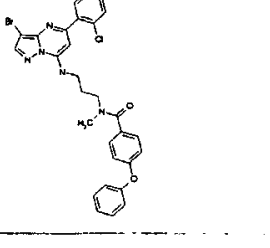
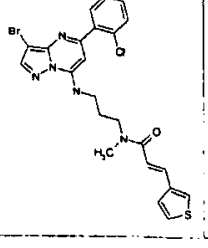
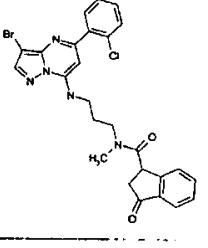
[1391]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5431 2. 543.3		1. 5436 2. 567.3		1. 5441 2. 582.3
	1. 5432 2. 545.3		1. 5437 2. 567.3		1. 5442 2. 589.3
	1. 5433 2. 549.3		1. 5438 2. 567.3		1. 5443 2. 591.3
	1. 5434 2. 553.3		1. 5439 2. 575.3		1. 5444 2. 591.3
	1. 5435 2. 567.3		1. 5440 2. 581.3		1. 5445 2. 529.3

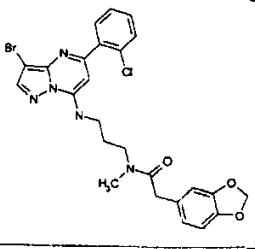
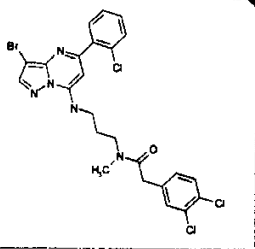
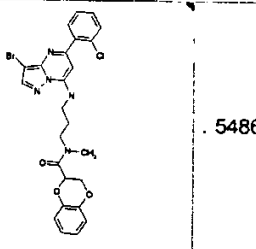
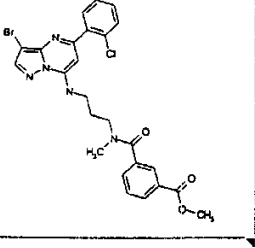
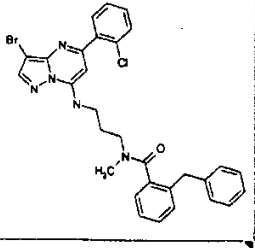
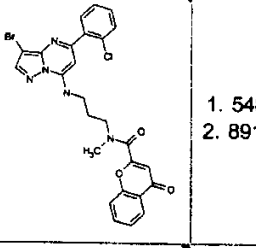
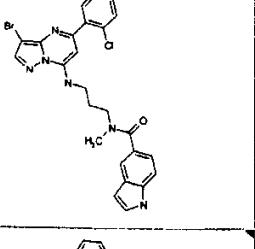
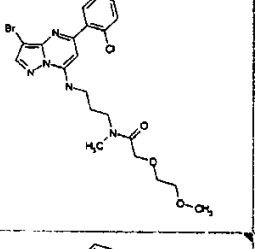
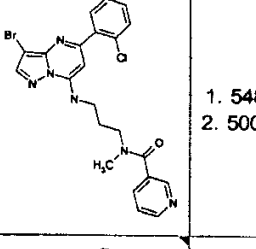
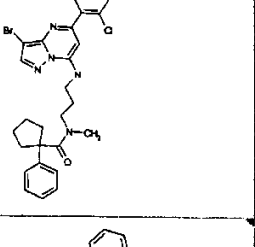
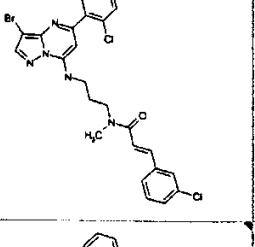
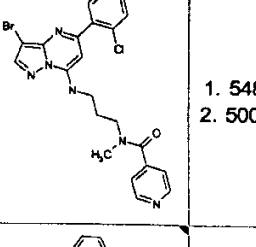
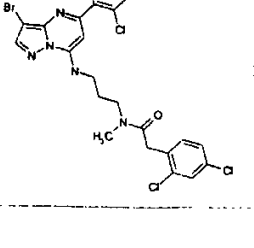
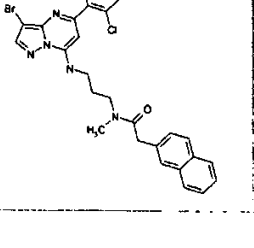
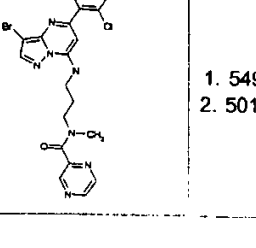
[1392]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5446 2. 500.3		1. 5451 2. 533.3		1. 5456 2. 549.3
	1. 5447 2. 830.5		1. 54525 2. 719.4		1. 5457 2. 555.3
	1. 5448 2. 524.3		1. 5453 2. 543.3		1. 5458 2. 556.3
	1. 5449 2. 524.3		1. 5454 2. 545.3		1.5459 2. 556.3
	1. 5450 2. 529.3		1. 5455 2. 545.3		1. 5460 2. 575.3

[1393]

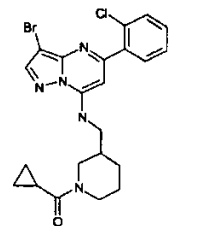
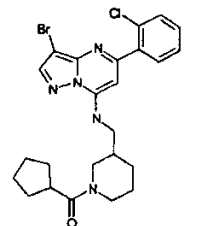
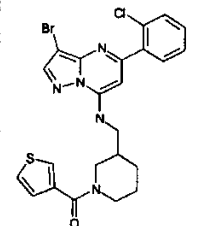
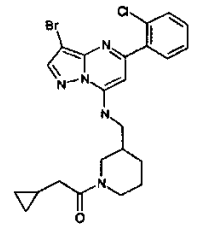
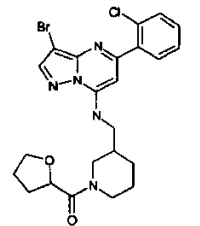
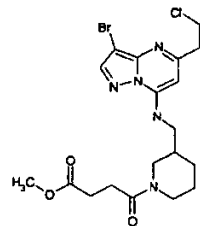
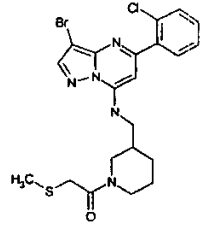
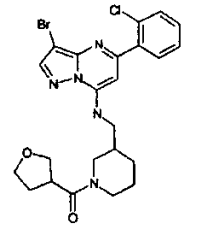
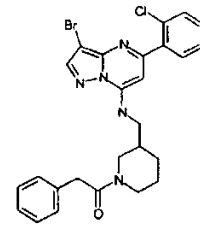
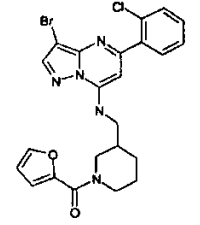
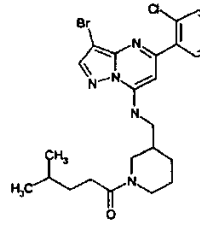
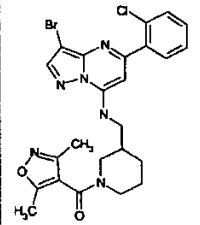
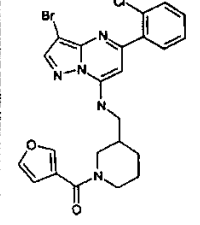
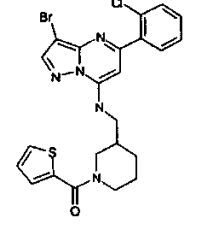
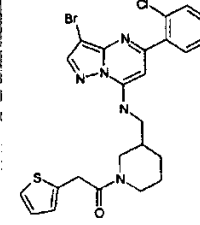
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5461 2. 580.3		1. 5466 2. 502.3		1. 5471 2. 539.3
	1. 5462 2. 580.3		1. 5467 2. 515.3		1. 5472 2. 543.3
	1. 5463 2. 581.3		1. 5468 2. 519.3		1. 5473 2. 547.3
	1. 5464 2. 589.3		1. 5469 2. 531.3		1. 5474 2. 552.3
	1. 5465 2. 591.3		1. 5470 2. 531.3		1. 5475 2. 553.3

[1394]

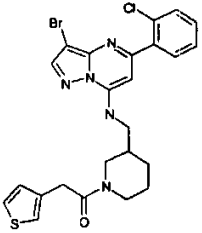
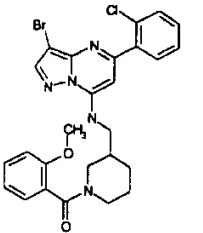
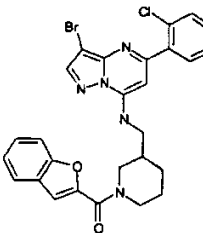
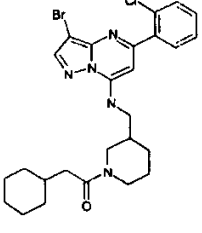
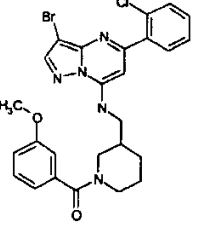
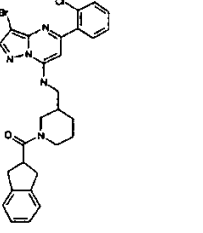
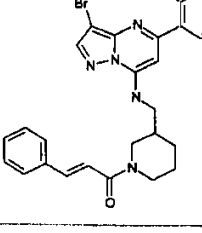
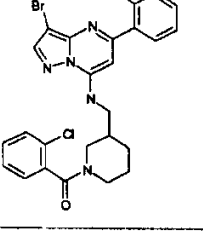
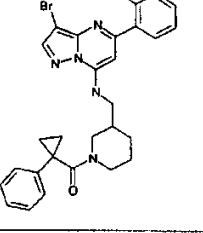
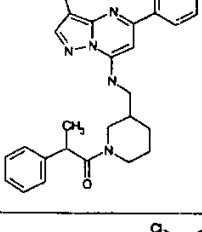
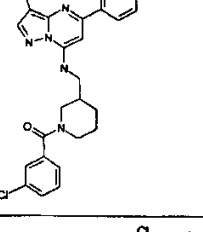
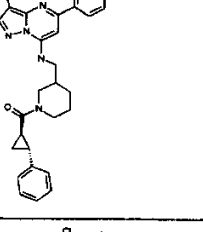
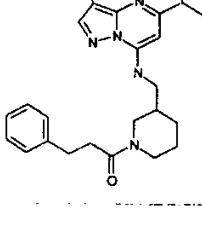
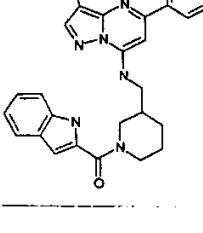
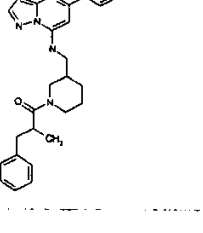
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5476 2. 557.3		1. 5481 2. 581.3		1. 5486 2. 581.3
	1. 5477 2. 557.3		1. 5482 2. 589.3		1. 5487 2. 891.5
	1. 5478 2. 538.3		1. 5483 2. 511.3		1. 5488 2. 500.3
	1. 5479 2. 567.3		1. 5484 2. 559.3		1. 5489 2. 500.3
	1. 5480 2. 581.3		1. 5485 2. 563.3		1. 5490 2. 501.3

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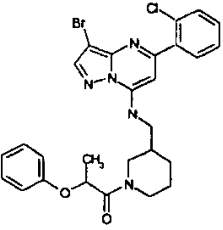
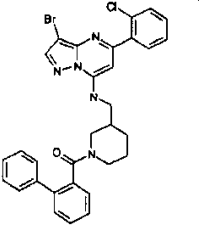
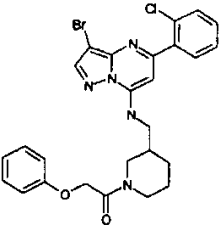
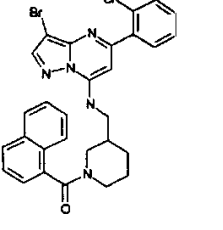
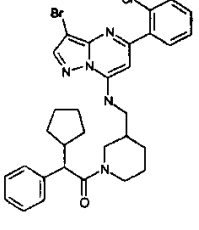
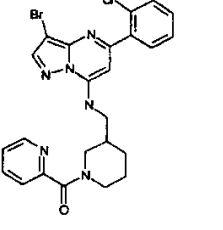
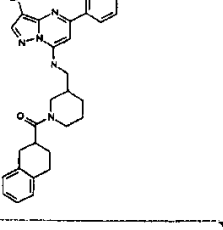
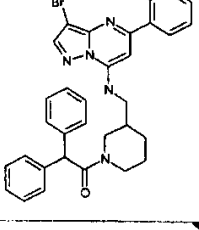
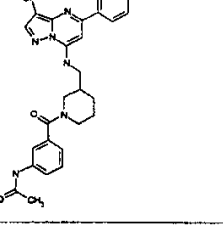
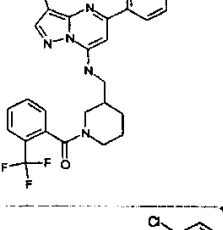
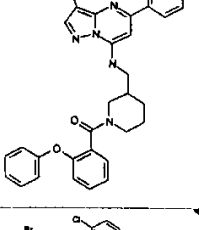
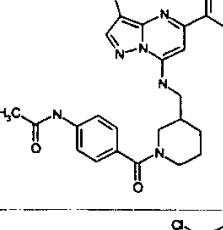
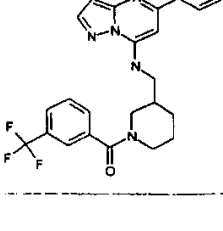
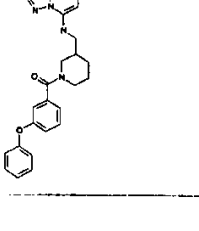
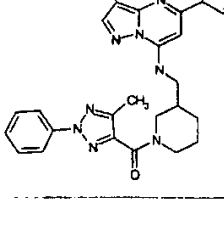
표 55

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5501 2. 488.81		1. 5506 2. 516.87		1. 5511 2. 530.87
	1. 5502 2. 502.84		1. 5507 2. 518.84		1. 5512 2. 534.84
	1. 5503 2. 508.87		1. 5508 2. 518.84		1. 5513 2. 538.87
	1. 5504 2. 514.81		1. 5509 2. 518.88		1. 5514 2. 543.85
	1. 5505 2. 514.81		1. 5510 2. 530.87		1. 5515 2. 544.9

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생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5516 2. 544.9		1. 5521 2. 554.87		1. 5526 2. 564.87
	1. 5517 2. 544.92		1. 5522 2. 554.87		1. 5527 2. 564.91
	1. 5518 2. 550.89		1. 5523 2. 559.29		1. 5528 2. 564.91
	1. 5519 2. 552.9		1. 5524 2. 559.29		1. 5529 2. 564.91
	1. 5520 2. 552.9		1. 5525 2. 563.88		1. 5530 2. 566.93

[1397]

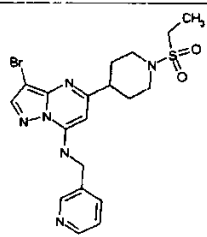
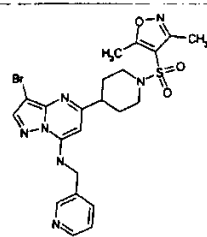
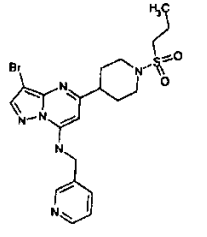
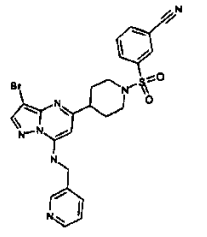
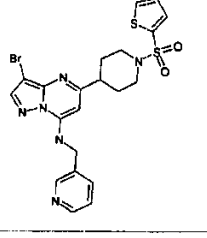
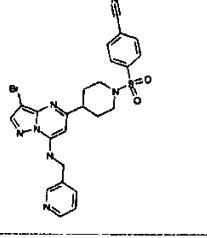
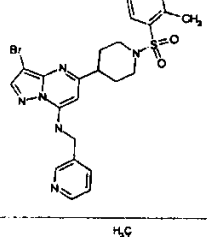
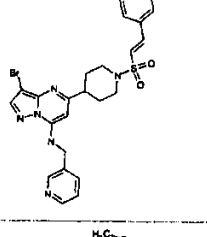
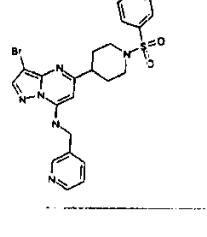
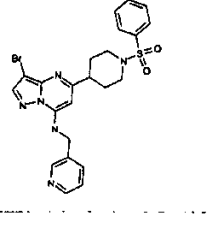
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 5531 2. 568.9		1. 5536 2. 600.95		1. 5541
	1. 5532 2. 574.91		1. 5537 2. 606.99		1. 5542 2. 525.83
	1. 5533 2. 578.94		1. 5538 2. 614.97		1. 5543 2. 581.9
	1. 5534 2. 592.85		1. 5539 2. 616.95		1. 5544 2. 581.9
	1. 5535 2. 592.85		1. 5540 2. 616.95		1. 5545 2. 605.92

[1398]

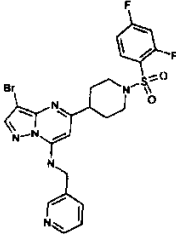
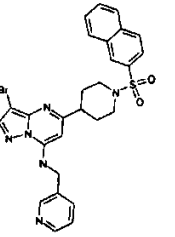
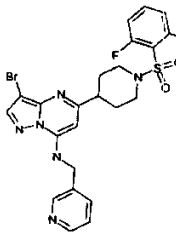
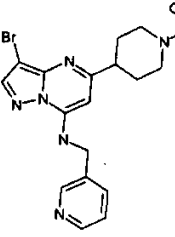
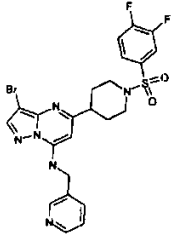
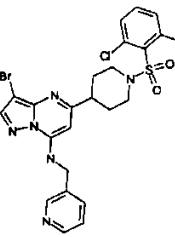
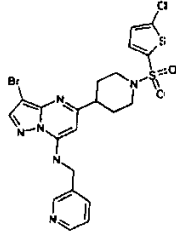
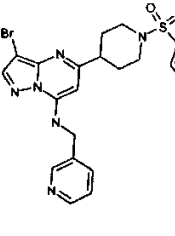
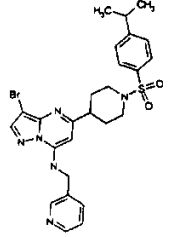
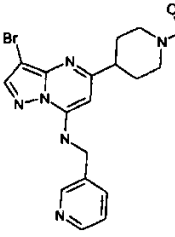
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5546 2. 573.32		1. 5551 2. 525.83
	1. 5547 2. 582.88		1. 5552 2. 526.82
	1. 5548 2. 607.76		1. 5553 2. 573.92
	1. 5549 2. 607.76		
	1. 5550 2. 536.86		

[1399]

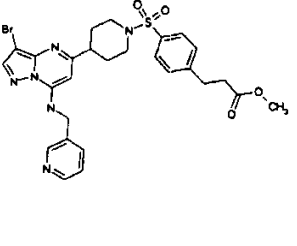
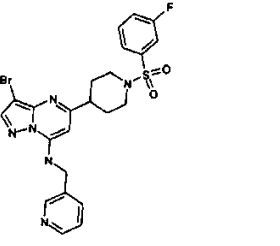
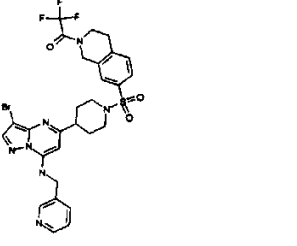
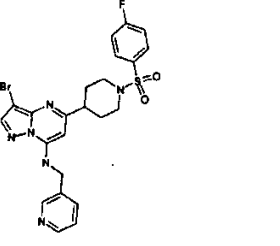
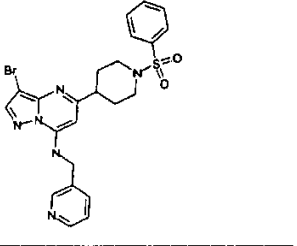
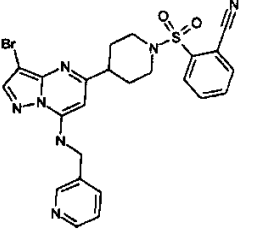
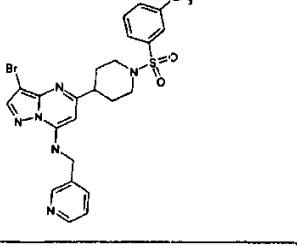
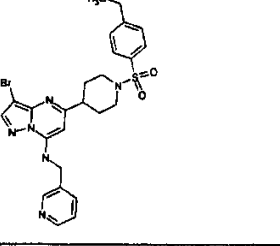
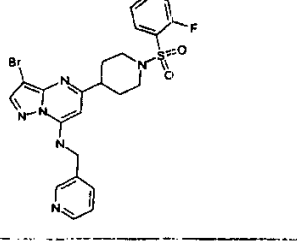
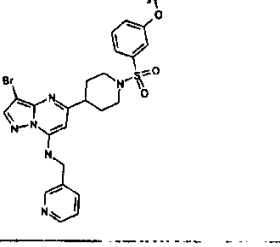
표 56

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5601 2. 481.26		1. 5606 2. 548.3
	1. 5602 2. 495.27		1. 5607 2. 554.3
	1. 5603 2. 535.29		1. 5608 2. 554.3
	1. 5604 2. 543.3		1. 5609 2. 555.31
	1. 5605 2. 543.3		1. 5610 2. 559.31

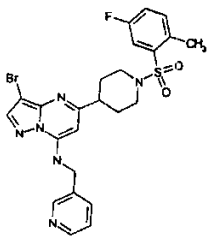
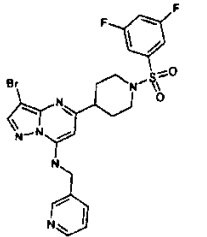
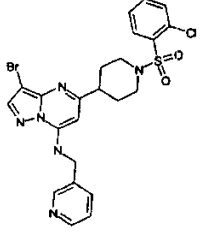
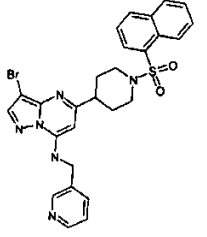
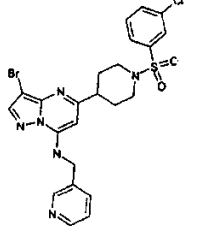
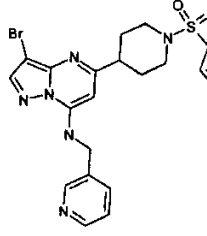
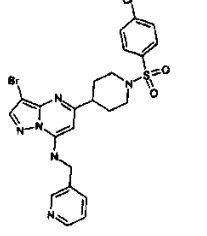
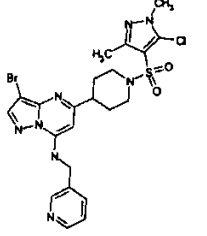
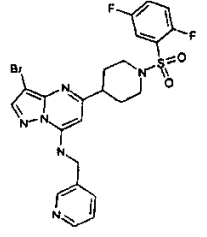
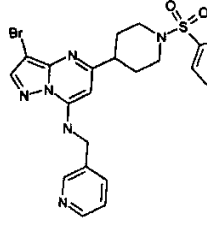
[1400]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	<p>1. 5611 2. 565.31</p>		<p>1. 5616 2. 579.32</p>
	<p>1. 5612 2. 565.31</p>		<p>1. 5617</p>
	<p>1. 5613 2. 565.31</p>		<p>1. 5618</p>
	<p>1. 5614 2. 569.31</p>		<p>1. 5619</p>
	<p>1. 5615 2. 571.31</p>		<p>1. 5620</p>

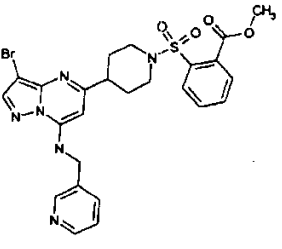
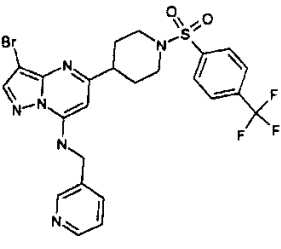
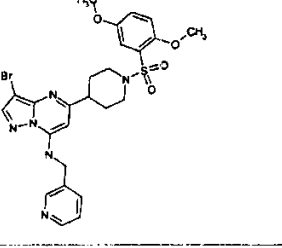
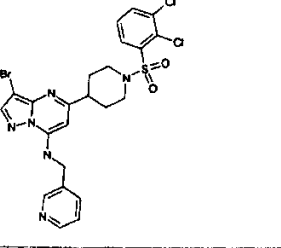
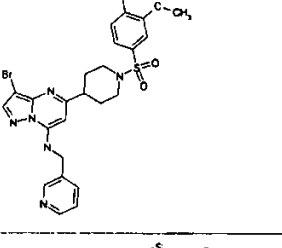
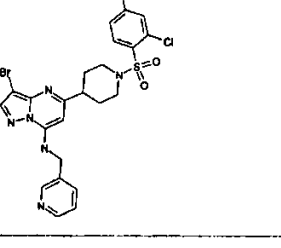
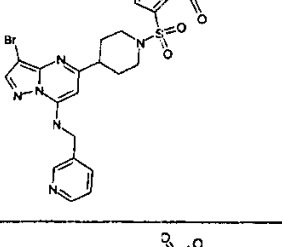
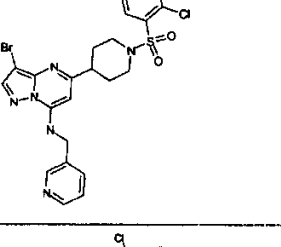
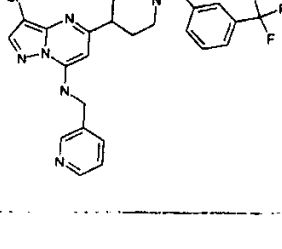
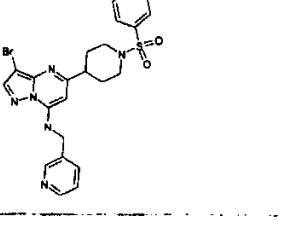
[1401]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	<p>1. 5621 2. 615.34</p>		<p>1. 5626 2. 547.3</p>
	<p>2. 5622 2. 680.37</p>		<p>1. 5627 2. 547.3</p>
	<p>1. 5623 2. 529.29</p>		<p>1. 5628 2. 554.3</p>
	<p>1. 5624 2. 543.3</p>		<p>1. 5629 2. 555.31</p>
	<p>1. 5625 2. 547.3</p>		<p>1. 5630 2. 559.31</p>

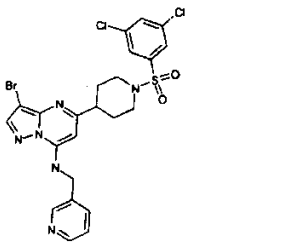
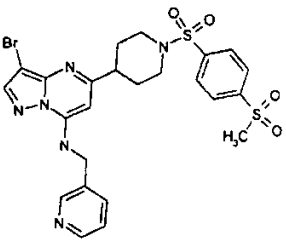
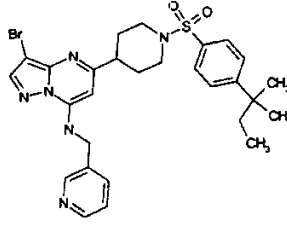
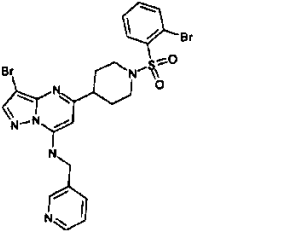
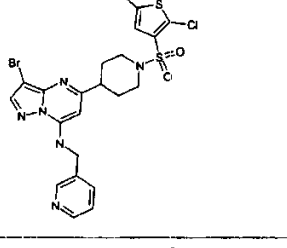
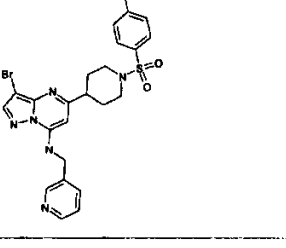
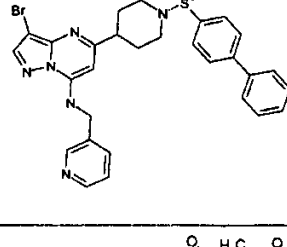
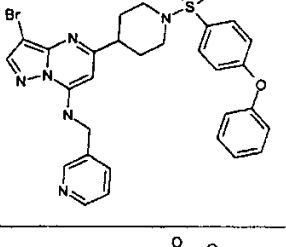
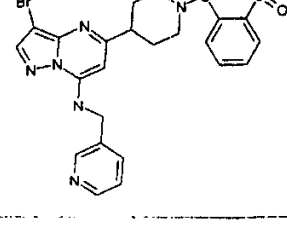
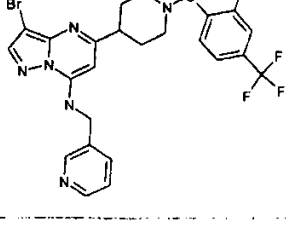
[1402]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5631 2. 561.31		1. 5636 2. 565.31
	1. 5632 2. 563.31		1. 5637 2. 579.32
	1. 5633 2. 563.31		1. 5638 2. 581.32
	1. 5634 2. 563.31		1. 5639 2. 581.32
	1. 5635 2. 563.31		1. 5640 2. 585.32

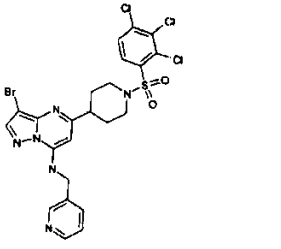
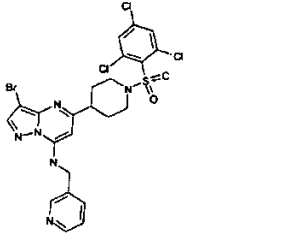
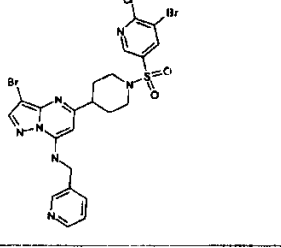
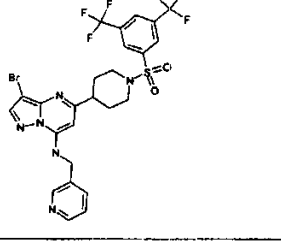
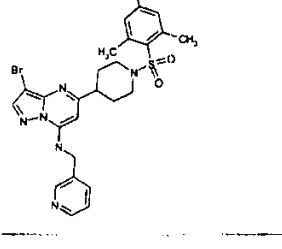
[1403]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5641 2. 587.32		1. 5646
	1. 5642 2. 589.32		1. 5647 2. 597.33
	1. 5643 2. 589.32		1. 5648 2. 597.33
	1. 5644 2. 593.33		1. 5649 2. 597.33
	1. 5645 2. 597.33		1. 5650 2. 597.33

[1404]

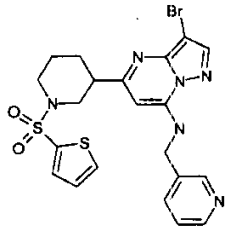
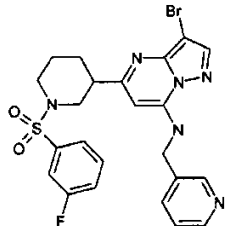
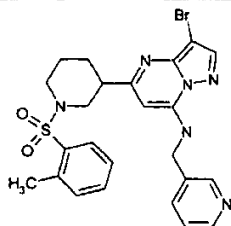
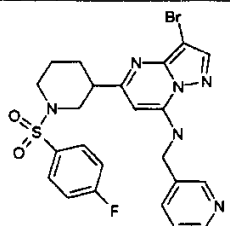
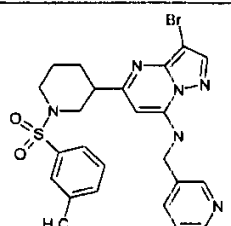
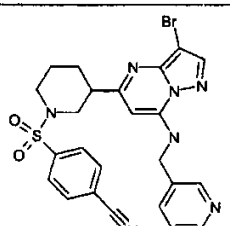
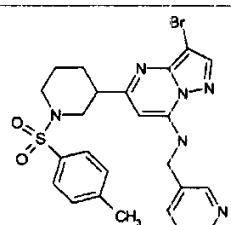
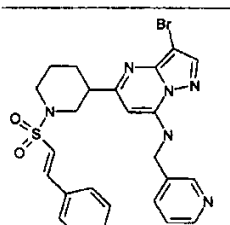
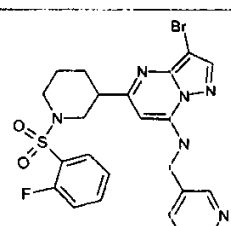
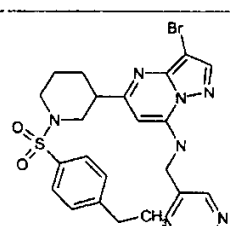
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5651 2. 597.33		1. 5656 2. 607.33
	1. 5652 2. 599.33		1. 5657 2. 607.33
	1. 5653 2. 603.33		1. 5658 2. 607.33
	1. 5654 2. 605.33		1. 5659 2. 621.34
	1. 5655 2. 607.33		1. 5660 2. 631.35

[1405]

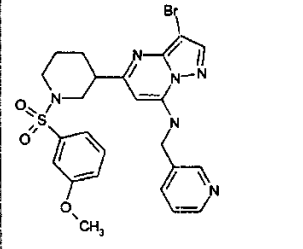
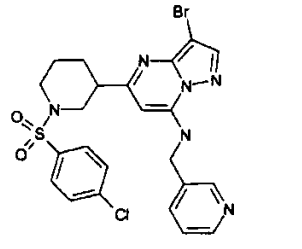
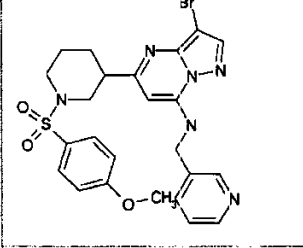
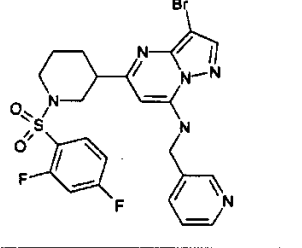
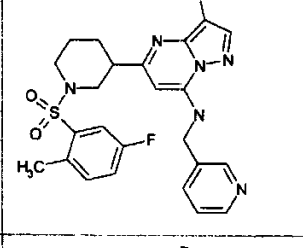
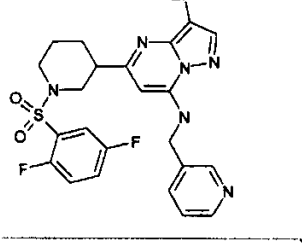
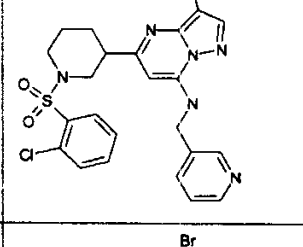
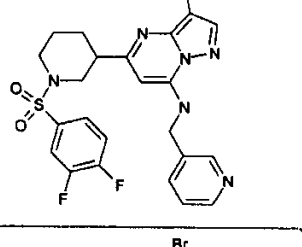
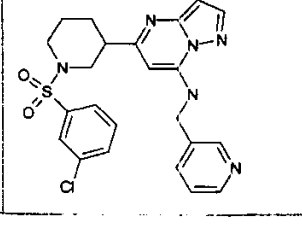
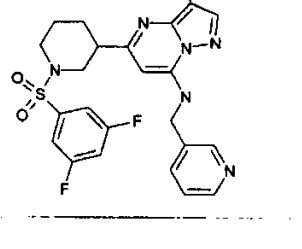
생성물	1. 실시예 2. m/z
	<p>1. 5661 2. 631.35</p>
	<p>1. 5662 2. 631.35</p>
	<p>1. 5663 2. 642.35</p>
	<p>1. 5664 2. 665.37</p>
	<p>1. 5665 2. 571.31</p>

[1406]

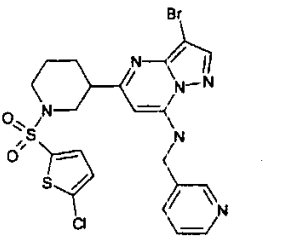
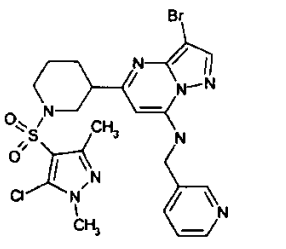
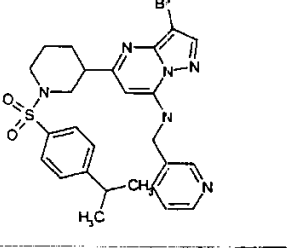
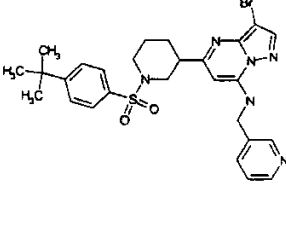
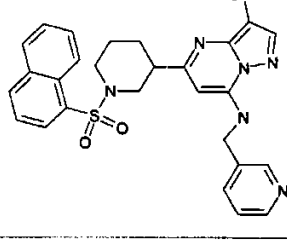
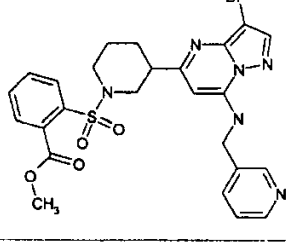
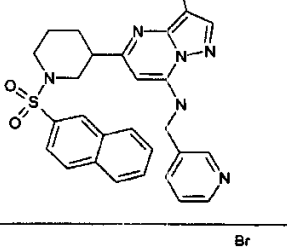
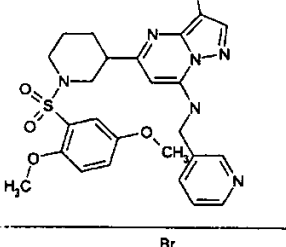
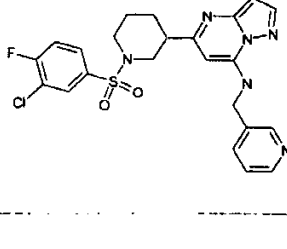
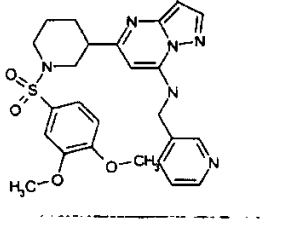
표 57

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5701 2. 535.29		1. 5706 2. 547.3
	1. 5702 2. 540.3		1. 5707 2. 547.3
	1. 5703 2. 543.3		1. 5708 2. 554.3
	1. 5704 2. 543.3		1. 5709 2. 555.31
	1. 5705 2. 547.3		1. 5710 2. 555.31

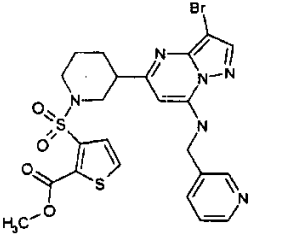
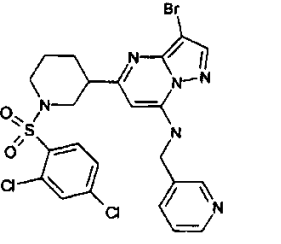
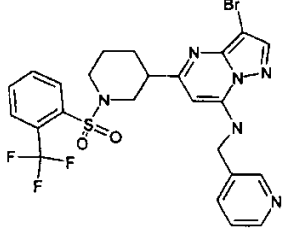
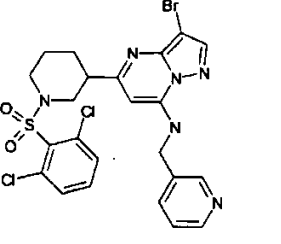
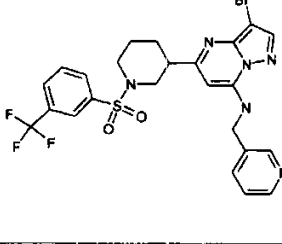
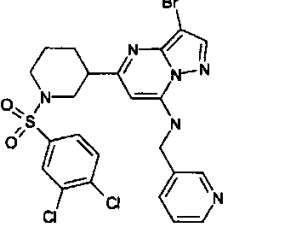
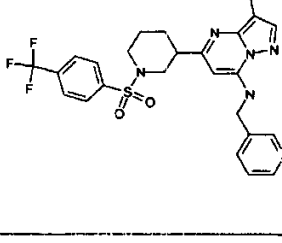
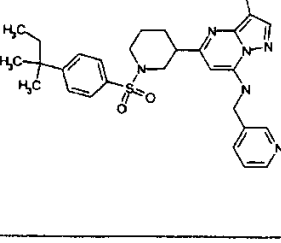
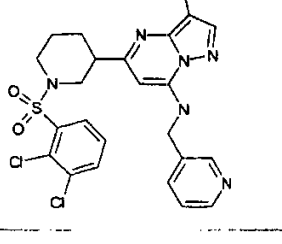
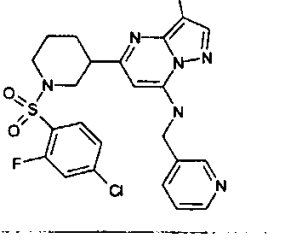
[1407]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5711 2. 559.31		1. 5716 2. 563.31
	1. 5712 2. 559.31		1. 5717 2. 565.31
	1. 5713 2. 561.31		1. 5718 2. 565.31
	1. 5714 2. 562.31		1. 5719 2. 565.31
	1. 5715 2. 563.31		1. 5720 2. 565.31

[1408]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5721 2. 569.31		1. 5726 2. 581.32
	1. 5722 2. 571.31		1. 5727 2. 585.32
	1. 5723 2. 579.32		1. 5728 2. 587.32
	1. 5724 2. 579.32		1. 5729 2. 589.32
	1. 5725 2. 581.32		1. 5730 2. 589.32

[1409]

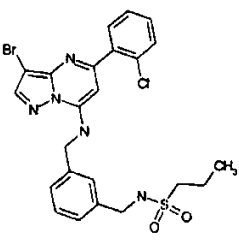
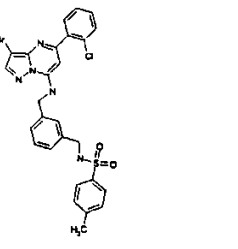
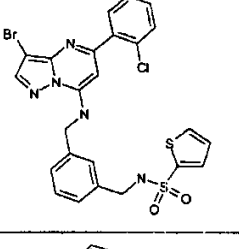
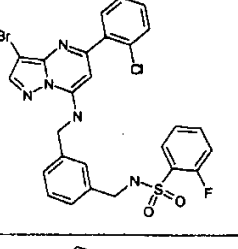
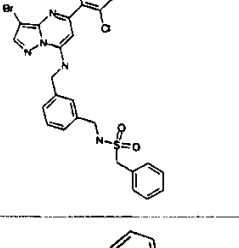
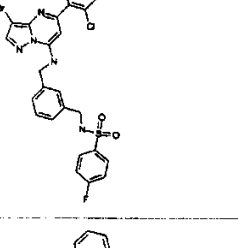
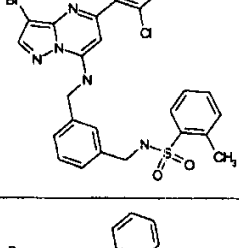
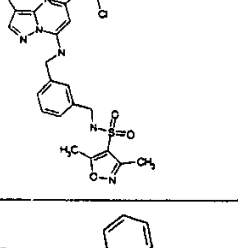
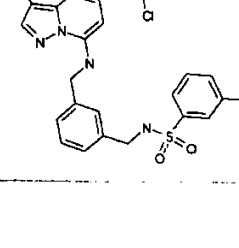
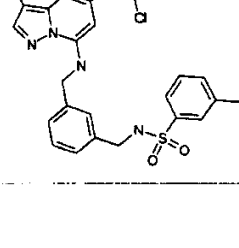
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	<p>1. 5731 2. 591.33</p>		<p>1. 5736 2. 597.33</p>
	<p>1. 5732 2. 597.33</p>		<p>1. 5737 2. 597.33</p>
	<p>1. 5733 2. 595.33</p>		<p>1. 5738 2. 596.33</p>
	<p>1. 5734 2. 597.33</p>		<p>1. 5739 2. 597.33</p>
	<p>1. 5735 2. 597.33</p>		<p>1. 5740 2. 581.32</p>

[1410]

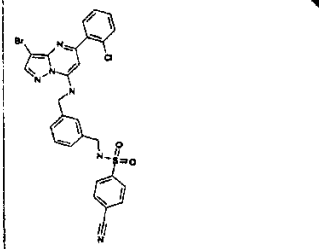
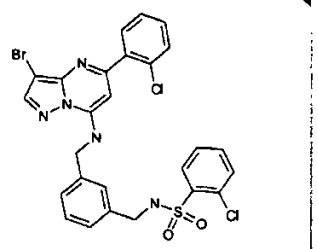
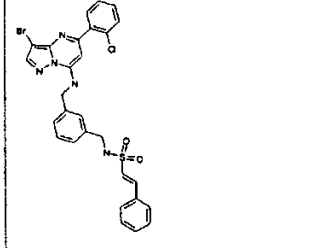
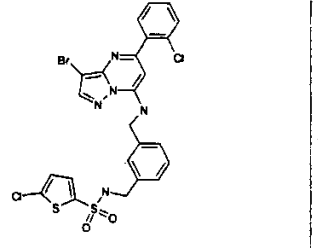
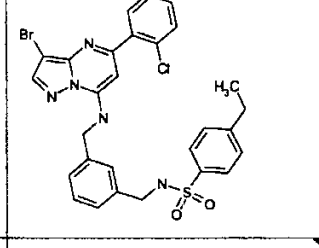
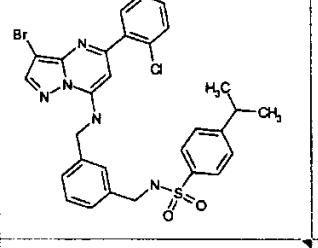
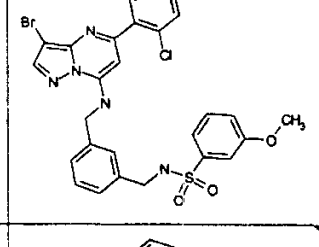
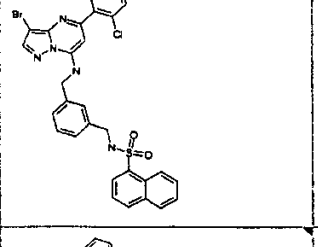
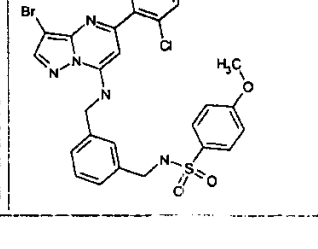
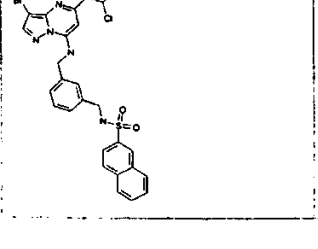
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5741 2. 605.33		1. 5746 2. 613.34
	1. 5742 2. 607.33		1. 5747 2. 615.34
	1. 5743 2. 607.33		1. 5748 2. 621.34
	1. 5744 2. 607.33		1. 5749 2. 631.35
	1. 57454 2. 613.34		1. 5750 2. 680.37

[1411]

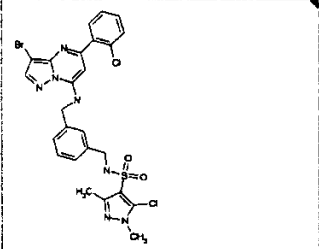
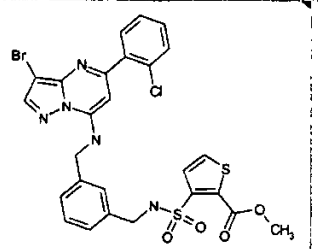
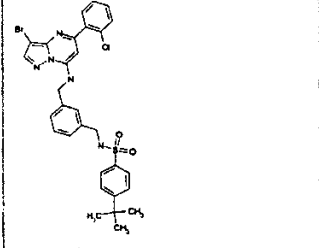
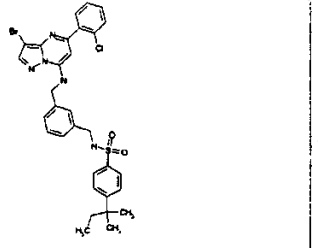
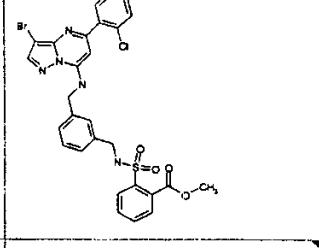
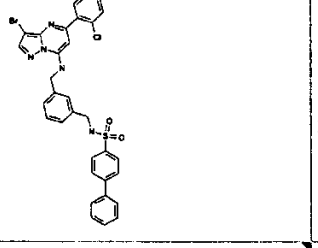
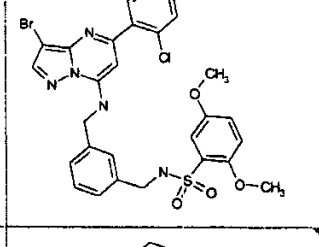
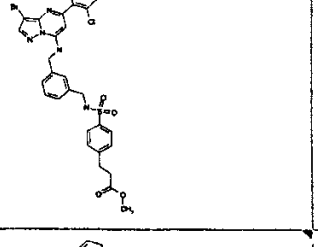
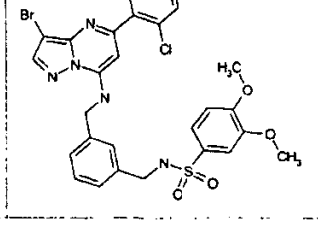
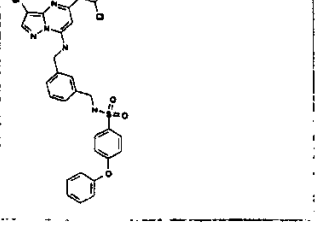
표 58

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5801 2. 550.3		1. 5806 2. 598.33
	1. 5802 2. 590.32		10 5807 2. 602.33
	1. 5803 2. 598.33		1. 5808 2. 602.33
	1. 5804 2. 598.33		1. 5809 2. 603.33
	1. 5805 2. 598.33		1. 5810 2. 609.33

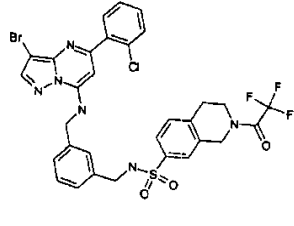
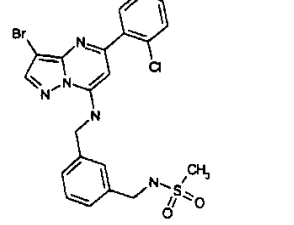
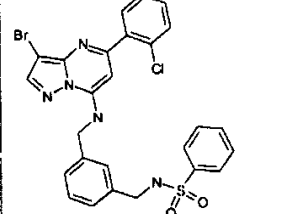
[1412]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5811 2. 609.33		1. 5816 2. 618.34
	1. 5812 2. 610.34		1. 5817 2. 624.34
	1. 5813 2. 612.34		1. 5818 2. 626.34
	1. 5814 2. 614.34		1. 5819 2. 634.35
	1. 5815 2. 614.34		1. 5820 2. 632.35

[1413]

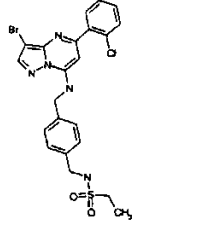
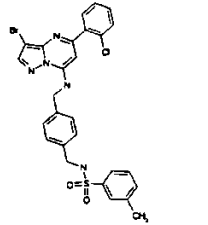
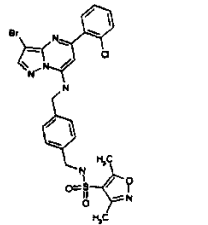
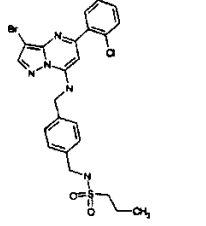
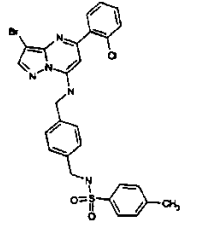
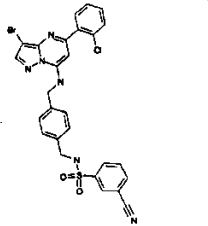
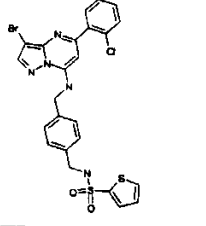
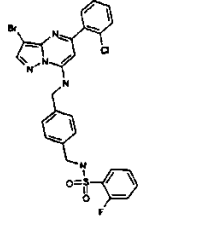
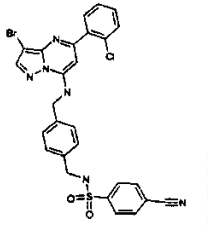
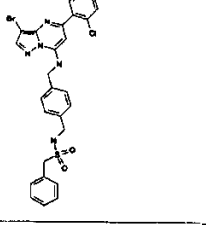
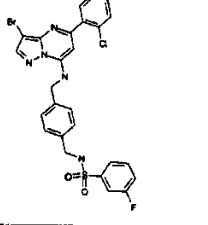
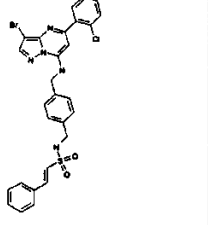
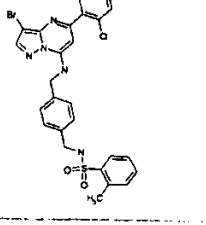
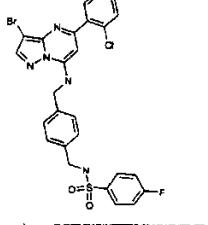
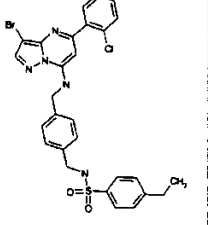
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5821 2. 636.35		1. 5826 2. 648.36
	1. 5822 2. 640.35		1. 5827 2. 654.36
	1. 5823 2. 642.35		1. 5828 2. 660.36
	1. 5824 2. 644.35		1. 5829 2. 670.37
	1. 5825 2. 644.35		1. 5830 2. 676.37

[1414]

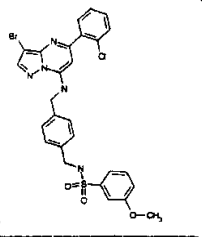
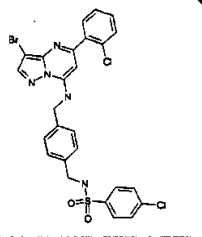
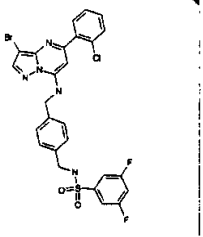
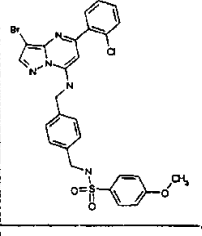
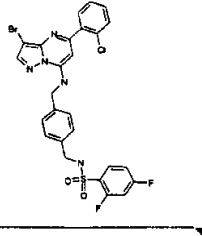
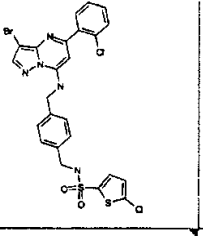
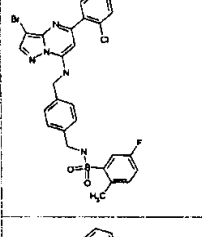
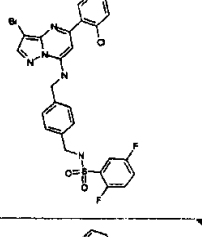
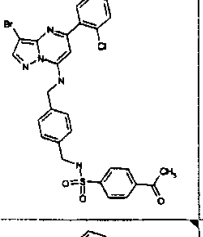
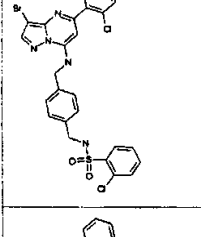
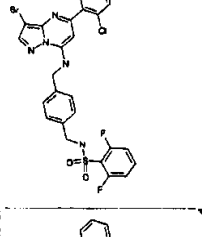
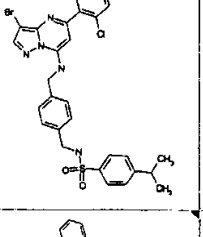
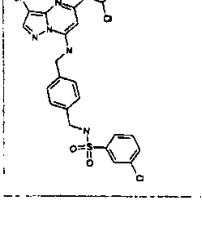
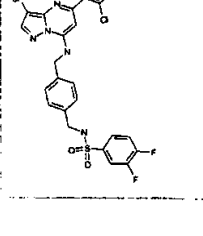
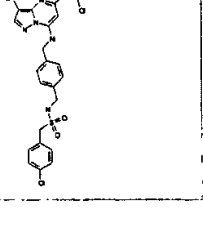
생성물	1. 실시예 2. m/z
	<p>1. 5831 2. 735.4</p>
	<p>1. 5832 2. 522.29</p>
	<p>1. 5833 2. 584.32</p>

[1415]

표 59

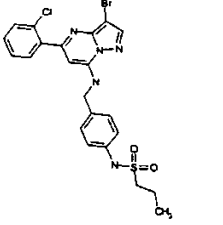
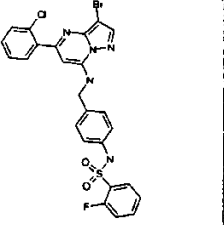
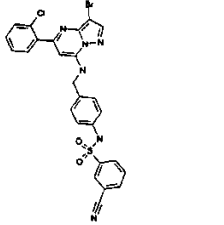
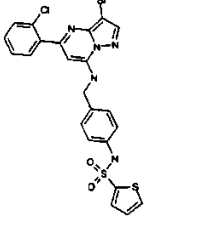
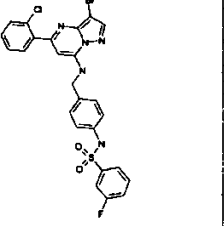
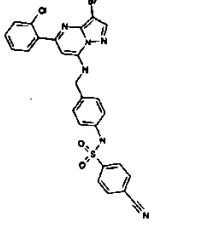
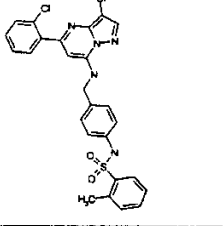
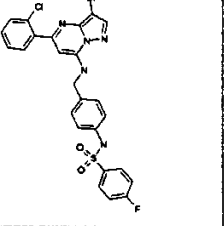
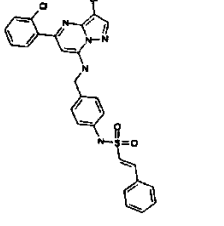
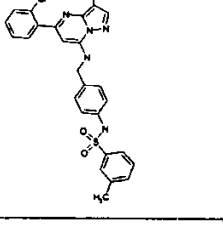
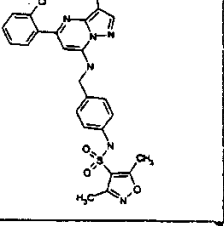
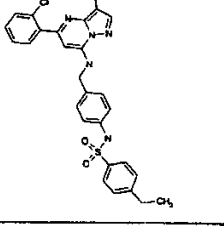
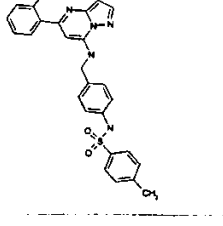
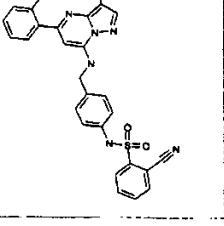
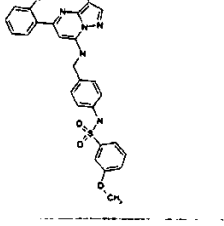
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5901 2. 536.29		1. 5906 2. 598.33		1. 5911 2. 603.33
	1. 5902 2. 550.3		1. 5907 2. 598.33		1. 5912 2. 609.33
	1. 5903 2. 590.32		1. 5908 2. 602.33		1. 5913 2. 609.33
	1. 5904 2. 598.33		1. 5909 2. 602.33		1. 5914 2. 610.34
	1. 5905 2. 598.33		1. 5910 2. 602.33		1. 5915 2. 612.34

[1416]

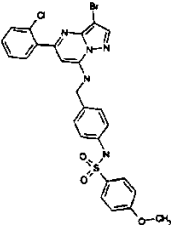
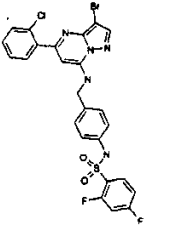
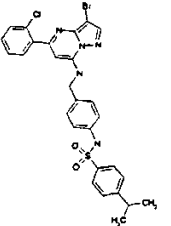
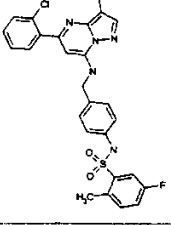
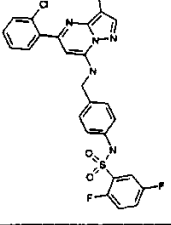
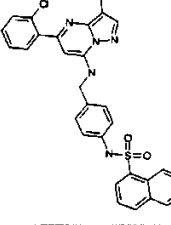
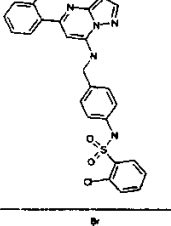
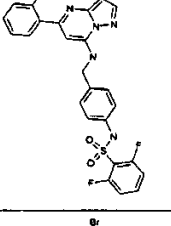
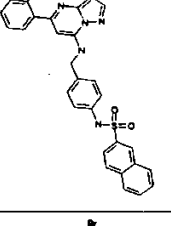
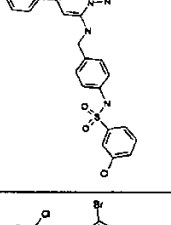
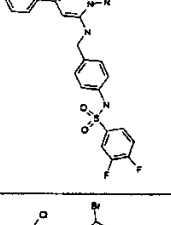
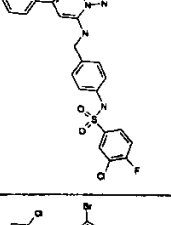
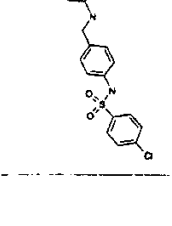
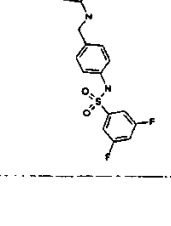
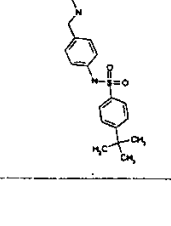
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 5916 2. 614.34		1. 5921 2. 618.34		1. 5926 2. 620.34
	1. 5917 2. 614.34		1. 5922 2. 620.34		1. 5927 2. 624.34
	1. 5918 2. 616.34		1. 5923 2. 620.34		1. 5928 2. 626.34
	1. 5919 2. 618.34		1. 5924 2. 620.34		1. 5929 2. 626.34
	1. 5920 2. 618.34		1. 5925 2. 620.34		1. 5930 2. 632.35

[1417]

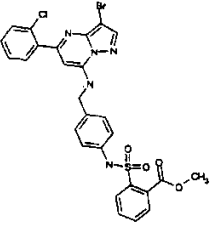
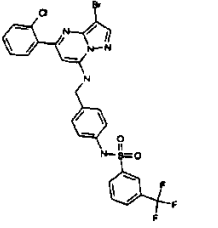
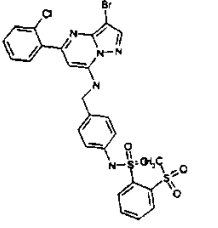
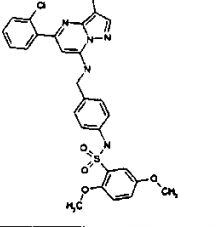
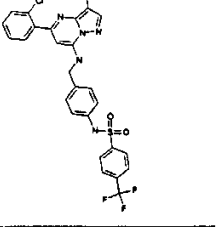
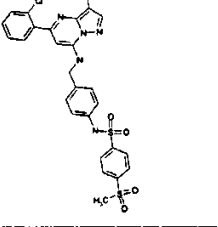
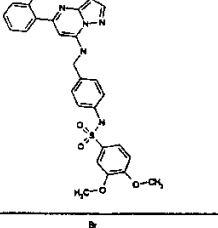
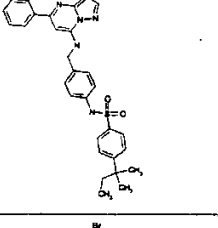
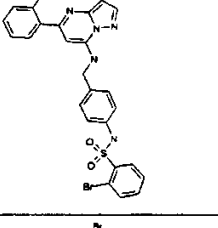
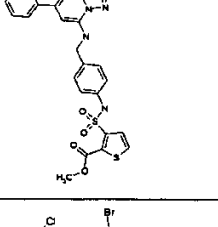
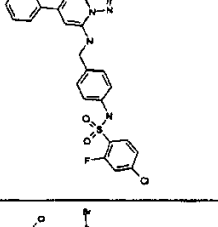
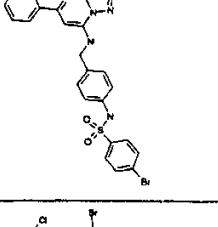
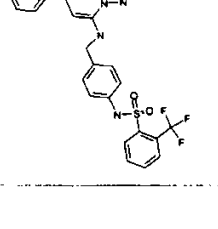
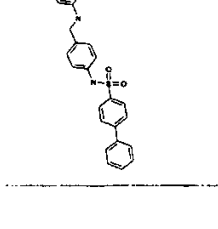
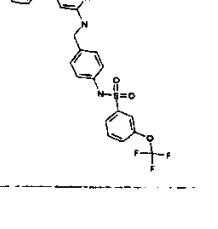
표 60

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 6001 2. 536.29		1. 6006 2. 588.32		1. 6011 2. 595.33
	1. 6002 2. 576.32		1. 6007 2. 588.32		1. 6012 2. 595.33
	1. 6003 2. 584.32		1. 6008 2. 588.32		1. 6013 2. 596.33
	1. 6004 2. 584.32		1. 6009 2. 589.32		1. 6014 2. 598.33
	1. 6005 2. 584.32		1. 6010 2. 595.33		1. 6015 2. 600.33

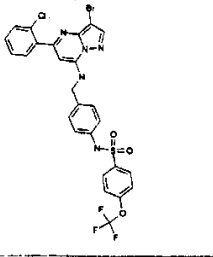
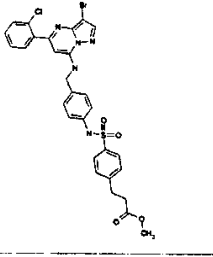
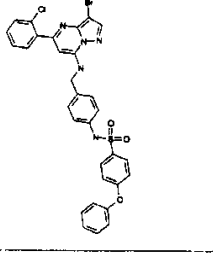
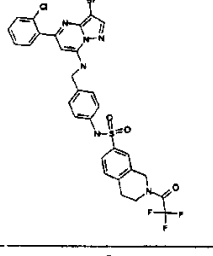
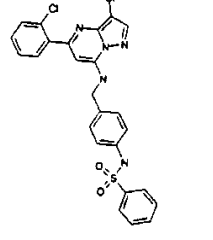
[1418]

생성물	1. 실시예 2. m/z	생성물	1. Ex. 2. m/z	생성물	1. 실시예 2. m/z
	1. 6016 2. 600.33		1. 6021 2. 606.33		1. 6026 2. 612.34
	1. 6017 2. 602.33		1. 6022 2. 606.33		1. 6027 2. 620.34
	1. 6018 2. 604.33		1. 6023 2. 606.33		1. 6028 2. 620.34
	1. 6019 2. 604.33		1. 6024 2. 606.33		1. 6029 2. 622.34
	1. 6020 2. 604.33		1. 6025 2. 606.33		1. 6030 2. 626.34

[1419]

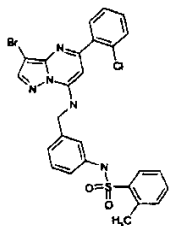
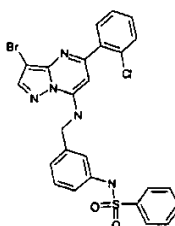
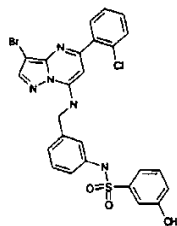
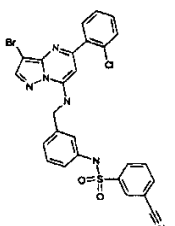
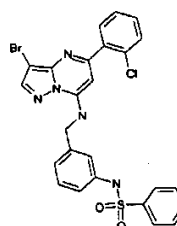
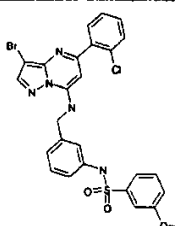
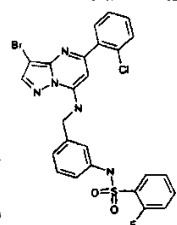
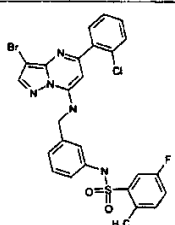
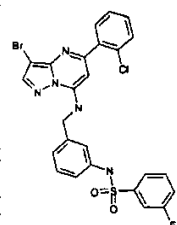
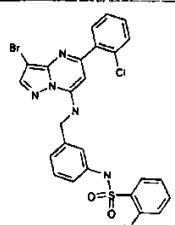
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 6031 2. 628.35		1. 6036 2. 638.35		1. 6041 2. 648.36
	1. 6032 2. 630.35		1. 6037 2. 638.35		1. 60425 2. 648.36
	1. 6033 2. 630.35		1. 6038 2. 638.35		1. 6043 2. 648.36
	1. 6034 2. 634.35		1. 6039 2. 622.34		1. 6044 2. 648.36
	1. 6035 2. 638.35		1. 6040 2. 646.36		1. 6045 2. 654.36

[1420]

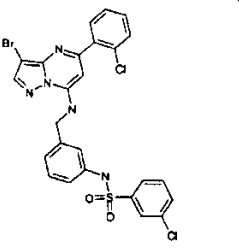
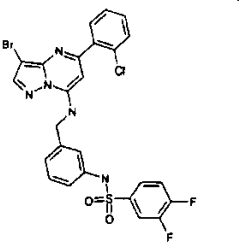
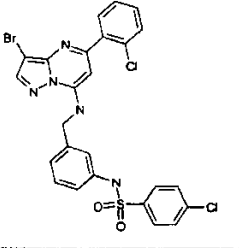
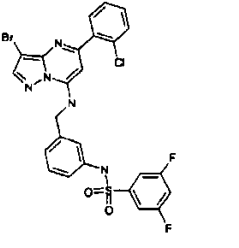
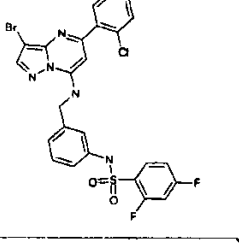
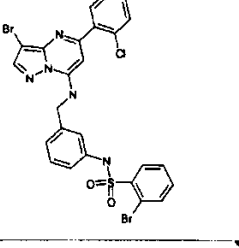
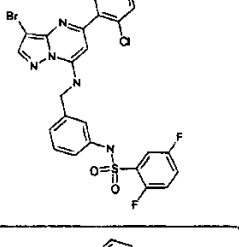
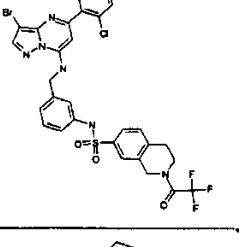
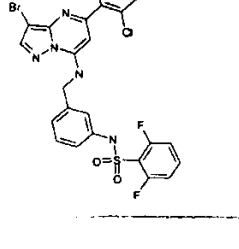
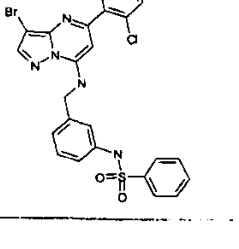
생성물	1. 실시예 2. m/z
	<p>1. 6046 2. 654.36</p>
	<p>1. 6047 2. 656.36</p>
	<p>1. 6048 2. 662.36</p>
	<p>1. 6049 2. 721.4</p>
	<p>1. 6050 2. 570.31</p>

[1421]

표 61

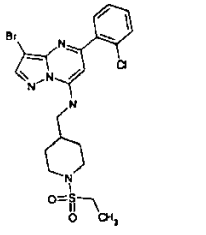
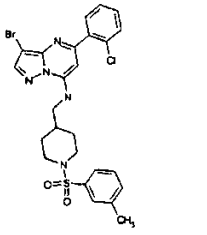
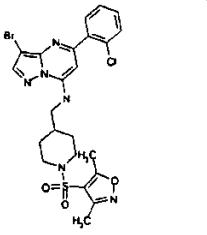
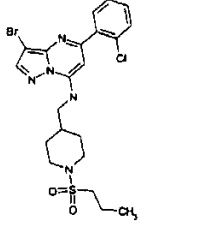
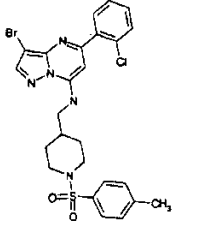
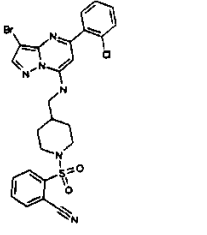
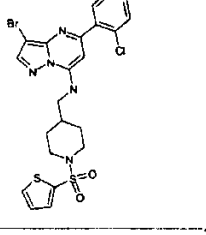
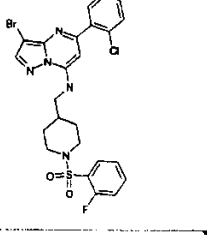
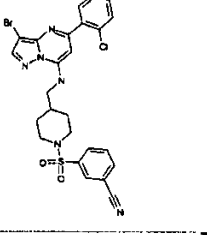
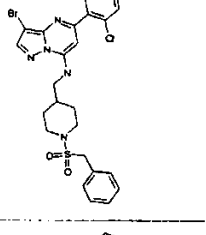
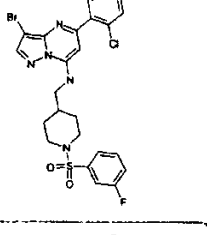
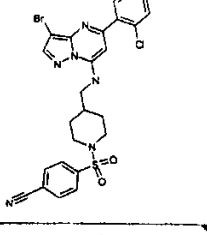
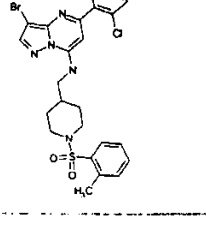
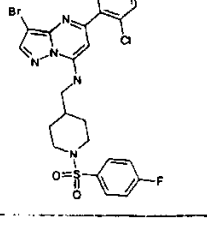
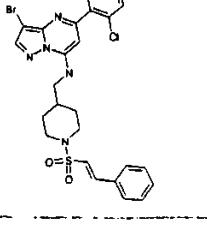
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 6101 2. 584.32		1. 6106 2. 588.32
	1. 6102 2. 584.32		1. 6107 2. 595.33
	1. 6103 2. 584.32		1. 6108 2. 600.33
	1. 6104 2. 588.32		1. 6109 2. 602.33
	1. 6105 2. 588.32		1. 6110 2. 604.33

[1422]

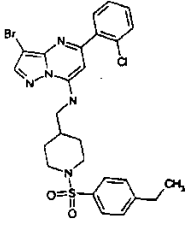
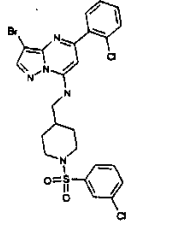
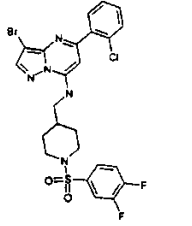
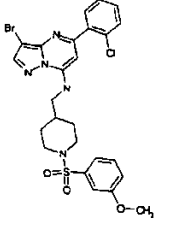
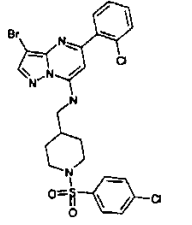
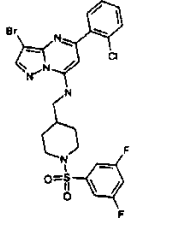
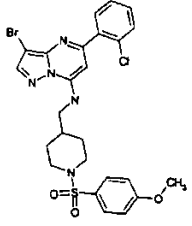
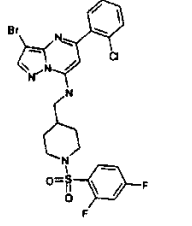
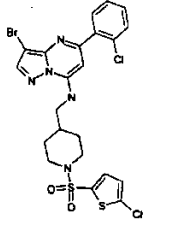
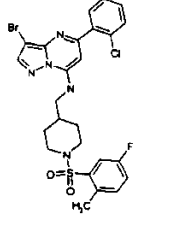
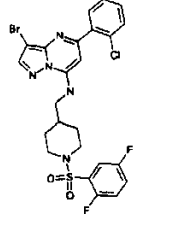
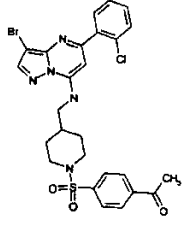
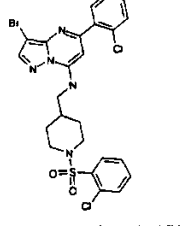
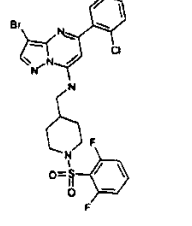
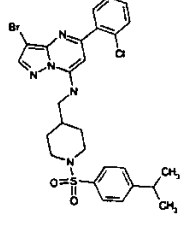
생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 6111 2. 604.33		1. 6116 2. 606.33
	1. 6112 2. 604.33		1. 6117 2. 606.33
	1. 6113 2. 606.33		1. 6118 2. 648.36
	1. 6114 2. 606.33		1. 6119 2. 721.4
	1. 6115 2. 606.33		1. 6120 2. 570.31

[1423]

표 62

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 6201 2. 514.28		1. 6206 2. 576.32		1. 6211 2. 581.32
	1. 6202 2. 528.29		1. 6207 2. 576.32		1. 6212 2. 587.32
	1. 6203 2. 568.31		1. 6208 2. 580.32		1. 6213 2. 587.32
	1. 6204 2. 576.32		1. 6209 2. 580.32		1. 6214 2. 587.32
	1. 6205 2. 576.32		1. 6210 2. 580.32		1. 6215 2. 588.32

[1424]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 6216 2. 590.32		1. 6221 2. 596.33		1. 6226 2. 598.33
	1. 6217 2. 592.33		1. 6222 2. 596.33		1. 6227 2. 596.33
	1. 6218 2. 592.33		1. 6223 2. 598.33		1. 6228 2. 602.33
	1. 6219 2. 592.33		1. 6224 2. 596.33		1. 6229 2. 604.33
	1. 6220 2. 594.33		1. 6225 2. 598.33		1. 6230 2. 604.33

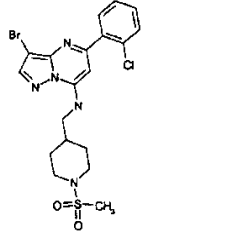
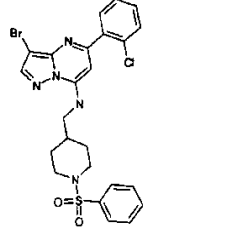
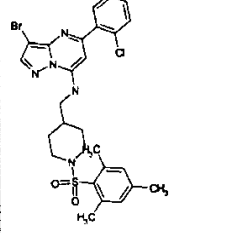
[1425]

생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z	생성물	1. 실시예 2. m/z
	1. 6231 2. 610.34		1. 6236 2. 614.34		1. 6241 2. 630.35
	1. 6232 2. 610.34		1. 6237 2. 618.34		1. 6242 2.
	1. 6233 2. 612.34		1. 6238 2. 622.34		1. 6243 2. 630.35
	1. 6234 2. 612.34		1. 6239 2. 622.34		1. 6244 2. 630.35
	1. 6235 2. 614.34		1. 6240 2. 626.34		1. 6245 2. 630.35

[1426]

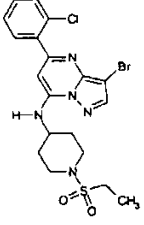
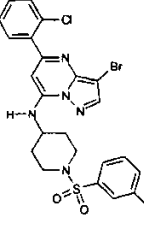
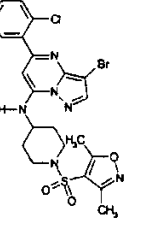
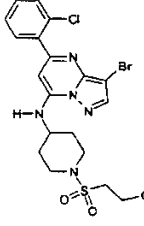
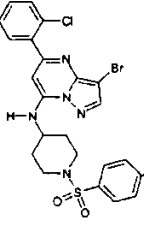
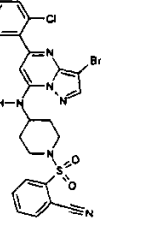
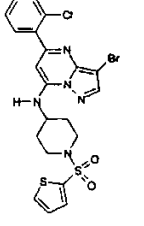
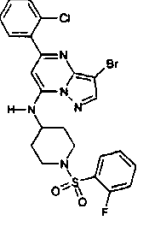
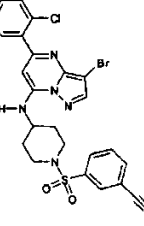
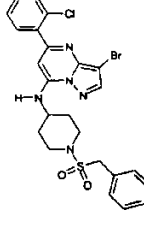
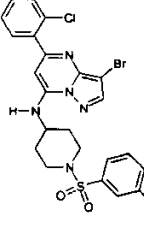
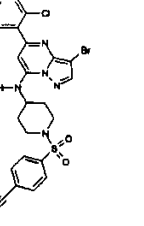
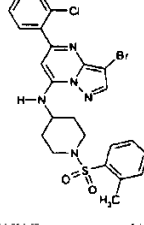
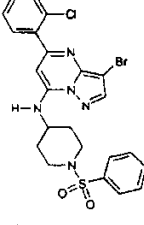
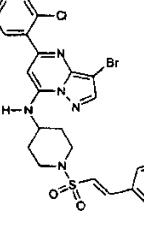
생성물	1.실시에. 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에. 2. m/z
	1. 6246 2. 630.35		1. 6251 2. 636.35		1. 6256 2. 646.36
	1. 6247 2. 630.35		1.0 6252 2. 638.35		1. 6257 2. 646.36
	1. 6248 2. 630.35		1. 6253 2. 640.35		1. 6258 2. 648.36
	1. 6249 2. 630.35		1. 6254 2. 640.35		1. 6259 2. 654.36
	1. 6250 2. 632.35		1. 6255 2. 638.35		1. 6260 2. 713.39

[1427]

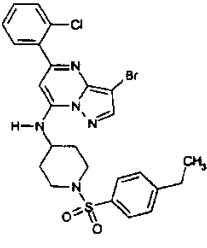
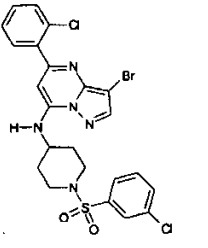
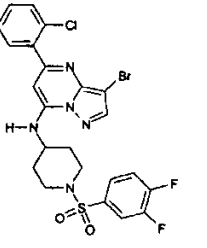
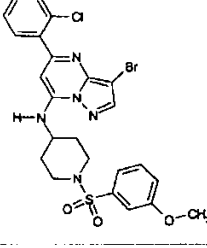
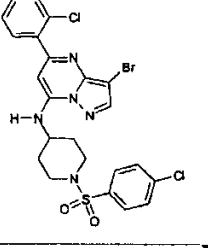
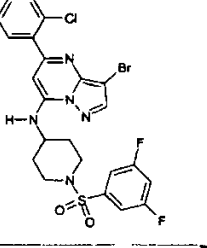
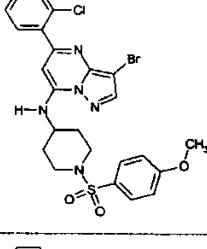
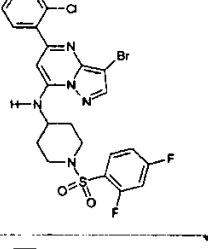
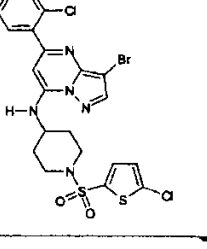
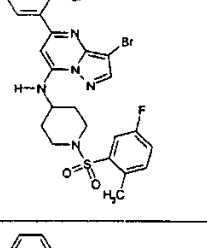
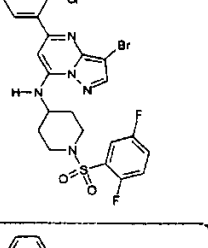
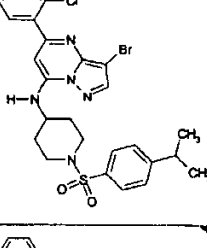
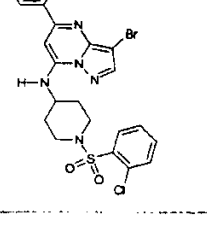
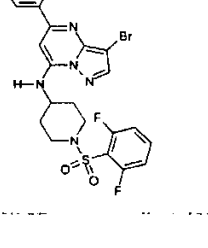
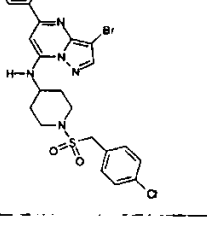
생성물	1. 실시예 2. m/z
	<p>1. 6261 2. 500.27</p>
	<p>1. 6262 2. 562.31</p>
	<p>1. 6263 2. 604.33</p>

[1428]

표 63

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 6301 2. 500.27		1. 6306 2. 562.31		1. 6311 2. 567.31
	1. 6302 2. 514.28		1. 6307 2. 562.31		1. 6312 2. 573.32
	1. 6303 2. 554.3		1. 6308 2. 566.31		1. 6313 2. 573.32
	1. 6304 2. 562.31		1. 6309 2. 566.31		1. 6314 2. 573.32
	1. 6305 2. 562.31		1. 6310 2. 566.31		1. 6315 2. 574.32

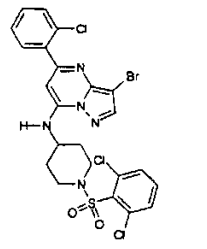
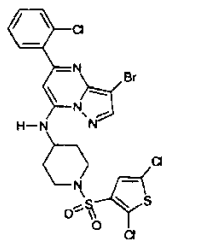
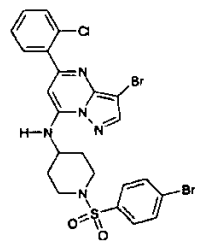
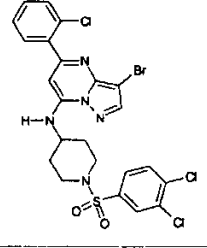
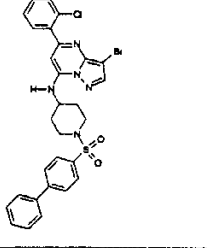
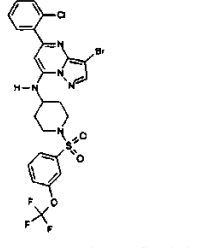
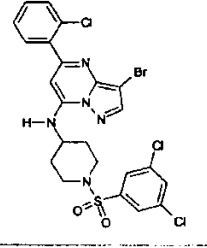
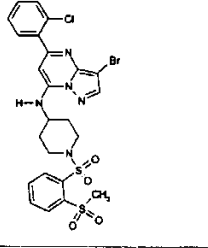
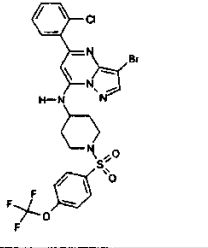
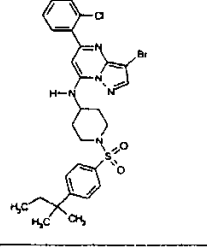
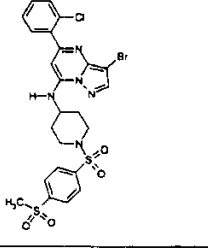
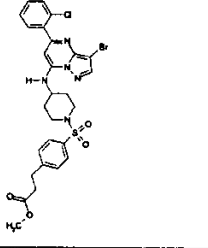
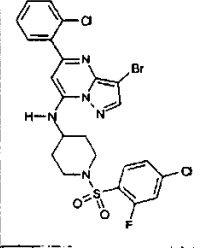
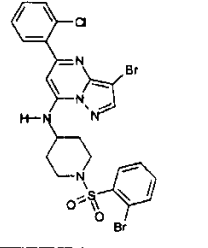
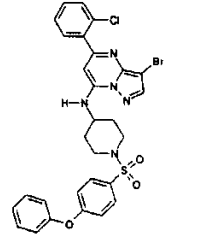
[1429]

생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 6316 2. 576.32		1. 6321 2. 582.32		1. 6326 2. 584.32
	1. 6317 2. 578.32		1. 6322 2. 582.32		1. 6327 2. 584.32
	1. 6318 2. 578.32		1. 6323 2. 584.32		1. 6328 2. 588.32
	1. 6319 2. 580.32		1. 6324 2. 582.32		1. 6329 2. 590.32
	1. 6320 2. 582.32		1. 6325 2. 584.32		1. 6330 2. 596.33

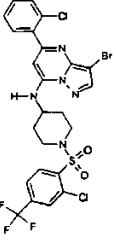
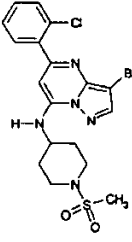
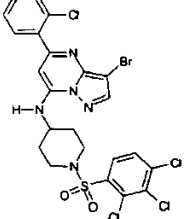
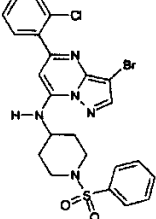
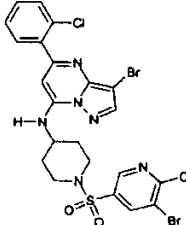
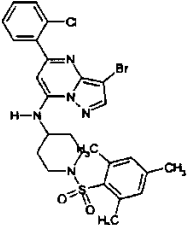
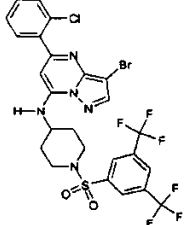
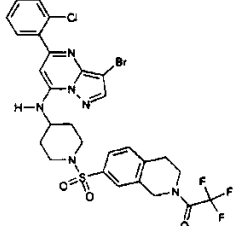
[1430]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 6331 2. 598.33		1. 6336 2. 606.33		1. 6341 2. 616.34
	1. 6332 2. 598.33		1. 6337 2. 608.33		1. 6342 2. 616.34
	1. 6333 2. 600.33		1. 6338 2. 608.33		1. 6343 2. 616.34
	1. 6334 2. 600.33		1. 6339 2. 612.34		1.6344 2. 616.34
	1. 6335 2. 604.33		1. 6340 2. 616.34		1. 6345 2. 616.34

[1431]

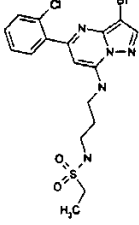
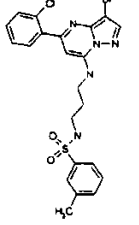
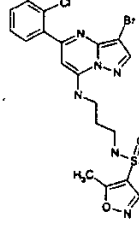
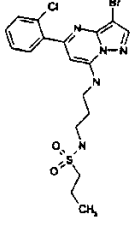
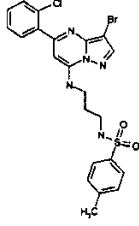
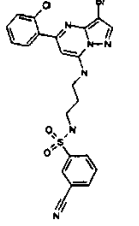
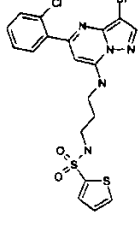
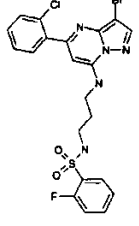
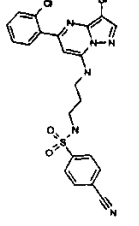
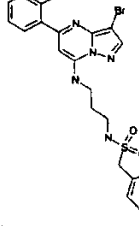
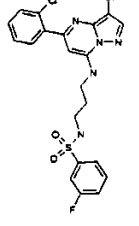
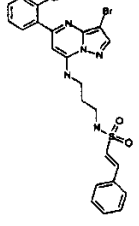
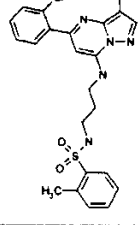
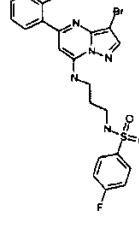
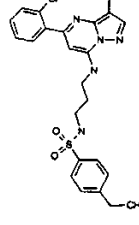
생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 6346 2. 616.34		1. 6351 2. 622.34		1. 6356 2. 626.34
	1. 6347 2. 616.34		1. 6352 2. 624.34		1. 6357 2. 632.35
	1. 6348 2. 616.34		1. 6353 2. 626.34		1. 6358 2. 632.35
	1. 6349 2. 618.34		1. 6354 2. 626.34		1. 6359 2. 634.35
	1. 6350 2. 600.33		1. 6355 2. 626.34		1. 6360 2. 640.35

[1432]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 6361 2. 650.36		1. 6366 2. 486.27
	1. 6362 2. 650.36		1. 6367 2. 548.3
	1. 6363 2. 661.36		1. 6368 2. 590.32
	1. 6364 2. 684.38		
	1. 6365 2. 699.38		

[1433]

표 64

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 6401 2. 474.26		1. 6406 2. 536.29		1. 6411 2. 541.3
	1. 6402 2. 488.27		1. 6407 2. 536.29		1. 6412 2. 547.3
	1. 6403 2. 528.29		1. 6408 2. 540.3		1. 6413 2. 547.3
	1. 6404 2. 536.29		1. 6409 2. 540.3		1. 6414 2. 548.3
	1. 6405 2. 536.29		1. 6410 2. 540.3		1. 6415 2. 550.3

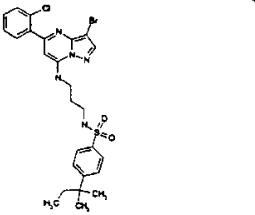
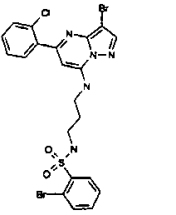
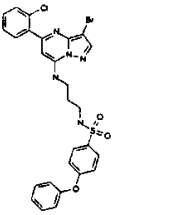
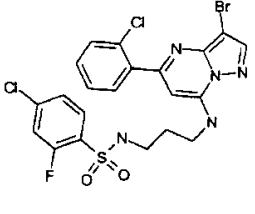
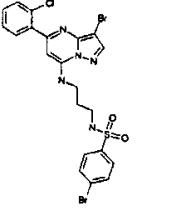
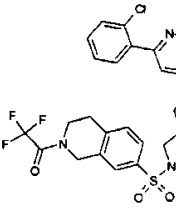
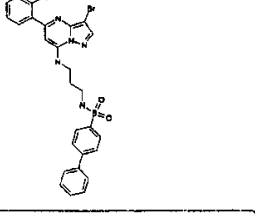
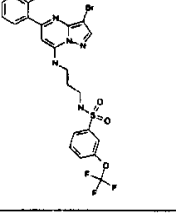
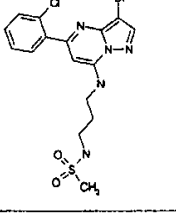
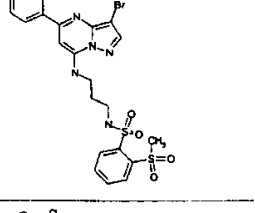
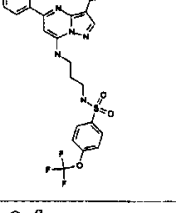
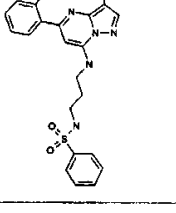
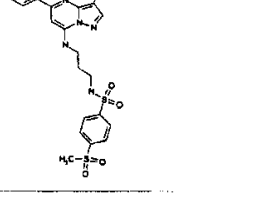
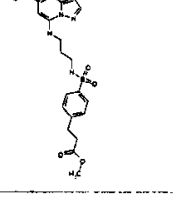
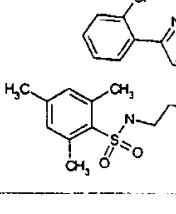
[1434]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 6416 2. 552.3		1. 6421 2. 556.31		1. 6426 2. 558.31
	1. 6417 2. 552.3		1. 6122 2. 558.31		1. 6427 2. 564.31
	1. 6418 2. 554.3		1. 6423 2. 558.31		1. 6428 2. 572.31
	1. 6419 2. 556.31		1. 6424 2. 558.31		1. 6429 2. 572.31
	1. 6420 2. 556.31		1. 6425 2. 558.31		1. 6430 2. 574.32

[1435]

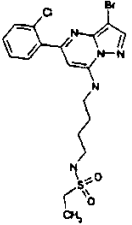
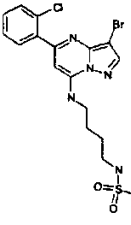
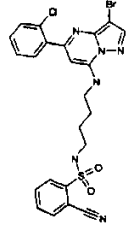
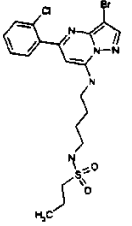
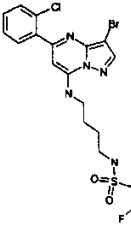
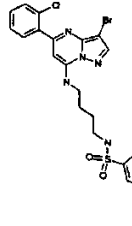
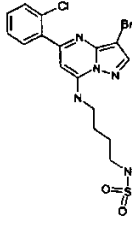
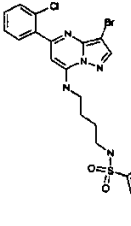
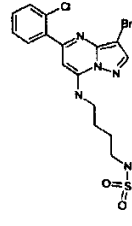
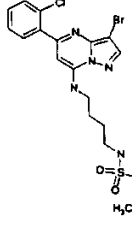
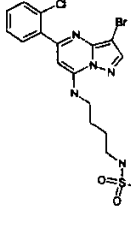
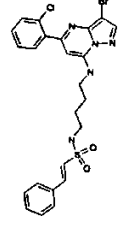
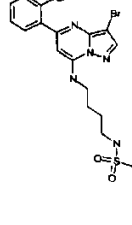
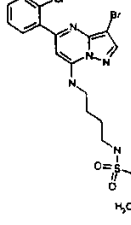
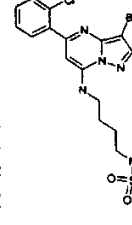
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 6431 2. 574.32		1. 6436 2. 586.32		1. 6441 2. 590.32
	1. 6432 2. 578.32		1. 6437 2. 590.32		1. 6442 2. 590.32
	1. 6433 2. 580.32		1. 6438 2. 590.32		1. 6443 2. 590.32
	1. 6434 2. 582.32		1. 6439 2. 590.32		1. 6444 2. 590.32
	1. 6435 2. 582.32		1. 6440 2. 589.32		1. 6445 2. 590.32

[1436]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 6446 2. 592.33		1. 6451 2. 600.33		1. 6456 2. 614.34
	1. 6447 2. 574.32		1. 6452 2. 600.33		1. 6447 2. 673.37
	1. 6448 2. 598.33		1. 6453 2. 606.33		1. 6458 2. 460.25
	1. 6449 2. 600.33		1. 6454 2. 606.33		6459 2.
	1. 6450 2. 600.33		1. 6455 2. 608.33		1. 6460 2. 564.31

[1437]

표 65

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 6501 2. 488.27		1. 6506 2. 550.3		1. 6511 2. 561.31
	1. 6502 2. 502.28		1. 6507 2. 554.3		1. 6512 2. 561.31
	1. 6503 2. 542.3		1. 6508 2. 554.3		1. 6213 2. 561.31
	1. 6504 2. 550.3		1. 6509 2. 554.3		1. 6514 2. 562.31
	1. 6505 2. 550.3		1. 6510 2. 555.31		1. 6515 2. 564.31

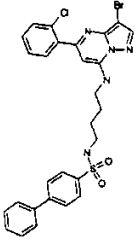
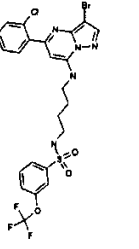
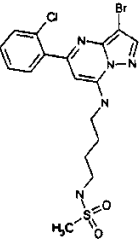
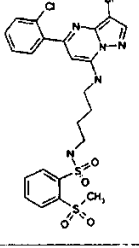
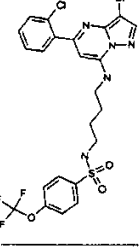
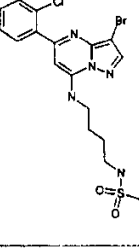
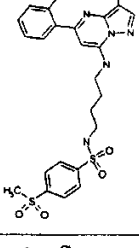
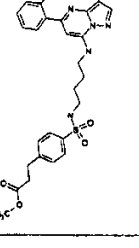
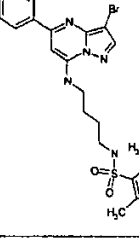
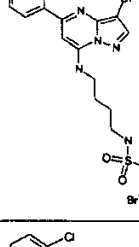
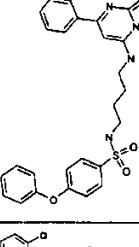
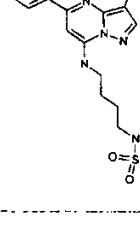
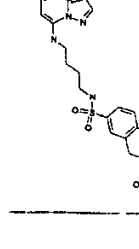
[1438]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 6516 2. 566.31		1. 6521 2. 570.31		1. 6526 2. 576.32
	1. 6517 2. 566.31		1. 6522 2. 572.31		1. 6527 2. 578.32
	1. 6518 2. 568.31		1. 6523 2. 572.31		1. 6528 2. 586.32
	1. 6519 2. 570.31		1. 6524 2. 572.31		1. 6529 2. 586.32
	1. 6520 2. 570.31		1. 6525 2. 572.31		1. 6530 2. 588.32

[1439]

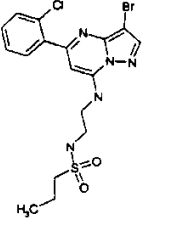
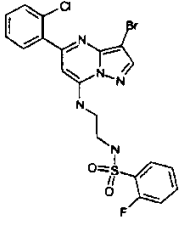
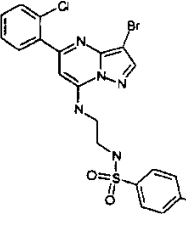
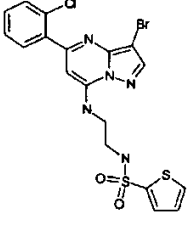
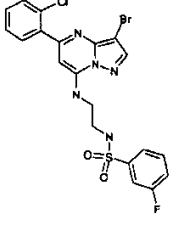
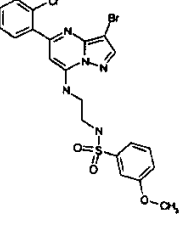
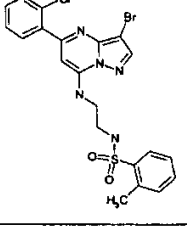
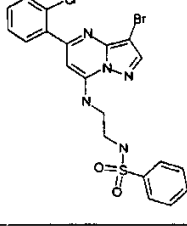
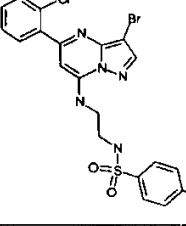
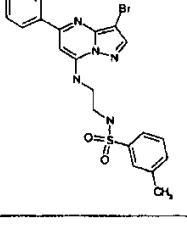
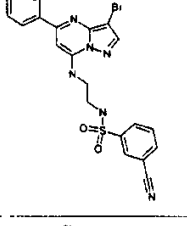
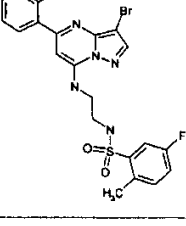
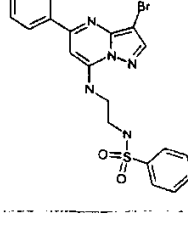
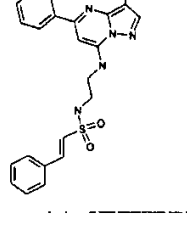
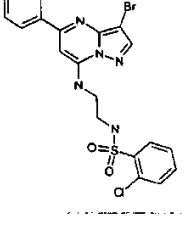
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 6531 2. 588.32		1. 6536 2. 600.33		1. 6541 2. 604.33
	1. 6532 2. 592.33		1. 6537 2. 604.33		1. 6542 2. 604.33
	1. 6533 2. 594.33		1. 6538 2. 604.33		1. 6543 2. 604.33
	1. 6534 2. 596.33		1. 6539 2. 604.33		1. 6544 2. 606.33
	1. 6535 2. 596.33		1. 6540 2. 604.33		1. 6545 2. 588.32

[1440]

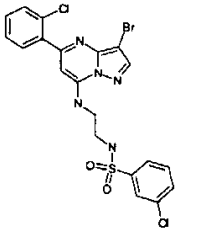
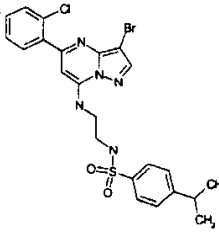
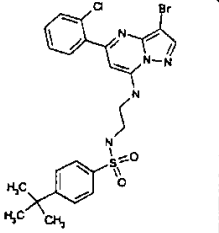
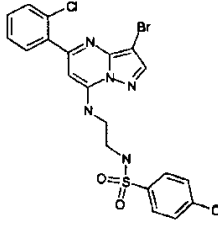
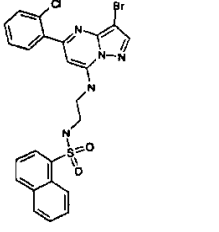
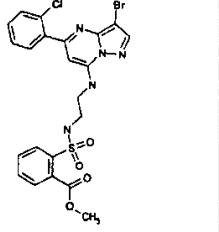
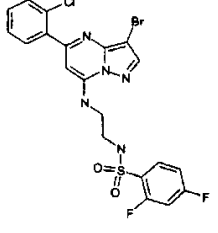
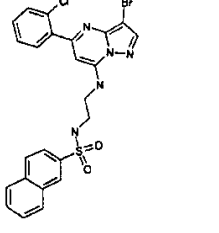
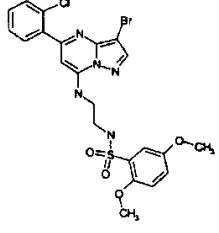
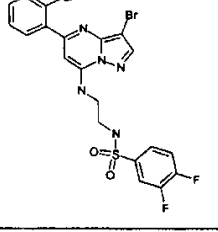
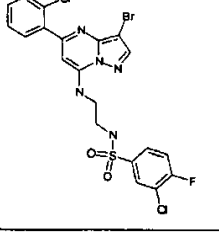
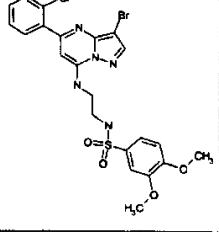
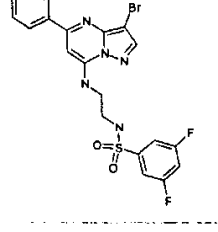
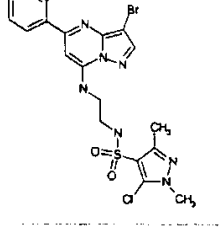
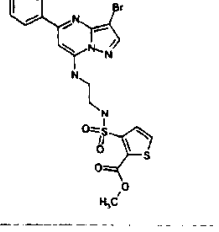
생성물	1.실시예. 2.m/z	생성물	1.실시예. 2.m/z	생성물	1.실시예. 2.m/z
	1. 6546 2. 612.34		1. 6551 2. 620.34		1. 6556 2. 474.26
	1. 6547 2. 614.34		1. 6552 2. 620.34		1. 6557 2. 536.29
	1. 6548 2. 614.34		1. 6553 2. 622.34		1. 6558 2. 578.32
	1. 6549 2. 614.34		1. 6554 2. 628.35		
	1. 6550 2. 614.34		1. 6555 2. 687.38		

[144]

표 67

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 6701 2. 474.26		1. 6706 2. 526.29		1. 6711 2. 536.29
	1. 6702 2. 514.28		1. 6707 2. 526.29		1. 6712 2. 538.3
	1. 6703 2. 522.29		1. 6708 2. 526.29		1. 6713 2. 538.3
	1. 6704 2. 522.29		1. 6709 2. 533.29		1. 6714 2.
	1. 6705 2. 522.29		1. 6710 2. 534.29		1. 6715 2. 542.3

[1442]

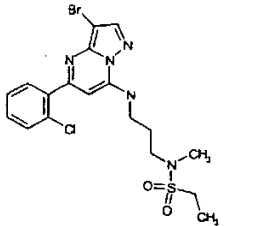
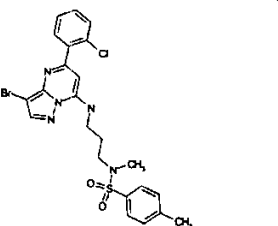
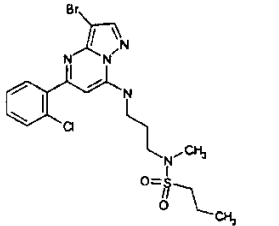
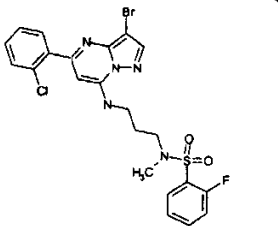
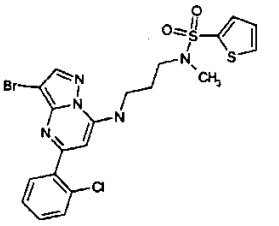
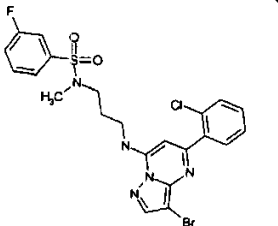
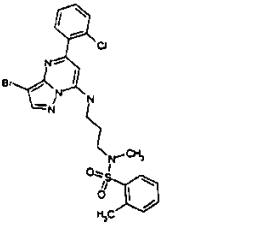
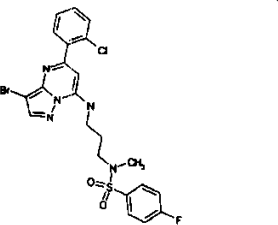
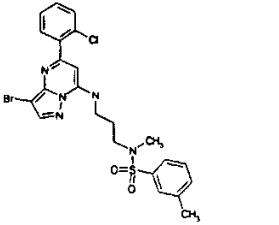
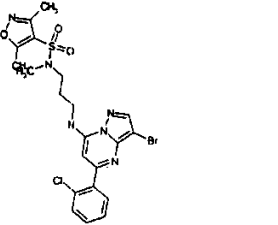
생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 6716 2. 542.3		1. 6721 2. 550.3		1. 6726 2. 564.31
	1. 6717 2. 542.3		1. 6722 2. 558.31		1. 6727 2. 566.31
	1. 6718 2. 544.3		1. 6723 2. 558.31		1. 6728 2. 568.31
	1. 6719 2. 544.3		1. 6724 2. 560.31		1. 6729 2. 568.31
	1. 6720 2. 544.3		1. 6725 2. 560.31		1. 6730 2. 572.31

[1443]

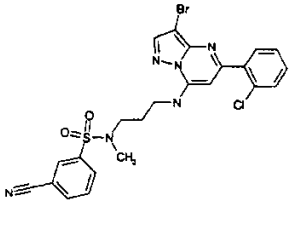
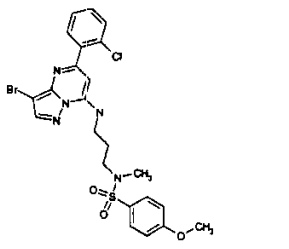
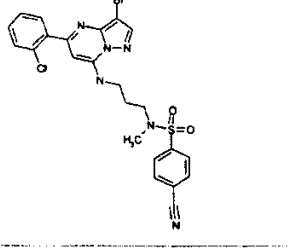
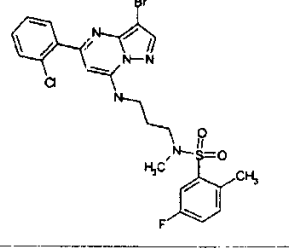
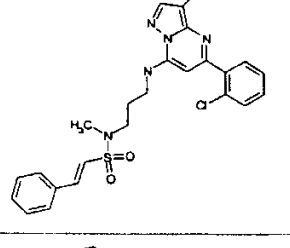
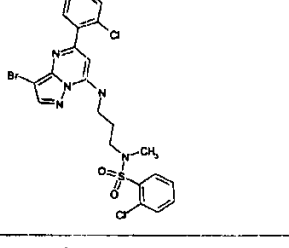
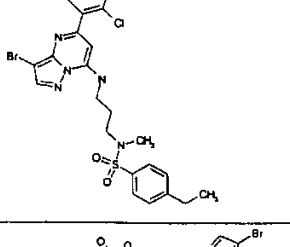
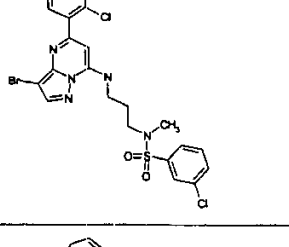
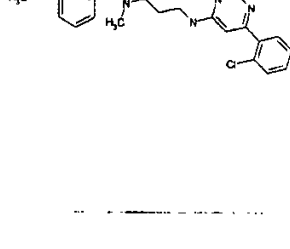
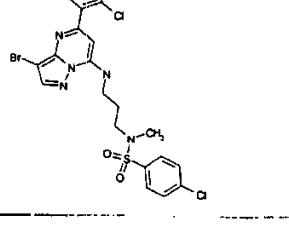
생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 6731 2. 576.32		1. 6736 2. 576.32		1. 6741 2. 586.32
	1. 6732 2. 576.32		1. 6737 2. 576.32		1. 6742 2. 586.32
	1. 6733 2. 576.32		1. 6738 2. 576.32		1. 6743 2. 592.33
	1. 6734 2. 576.32		1. 6739 2. 584.32		1. 6744 2. 592.33
	1. 6735 2. 576.32		1. 6740 2. 586.32		1. 6745 2. 600.33

[1444]

표 68

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 6801 2. 488.27		1. 6806 2. 550.3
	1. 6802 2. 502.28		1. 6807 2. 554.3
	1. 6803 2. 542.3		1. 6808 2. 554.3
	1. 6804 2. 550.3		1. 6809 2. 554.3
	1. 68058 2. 550.3		1. 6810 2. 555.31

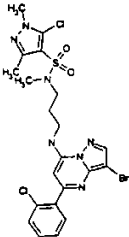
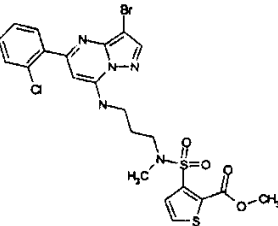
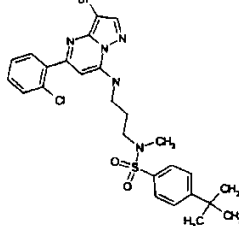
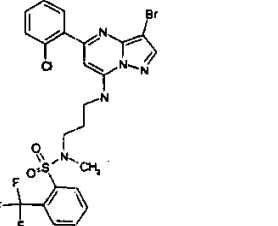
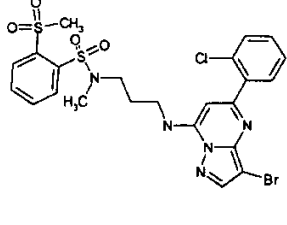
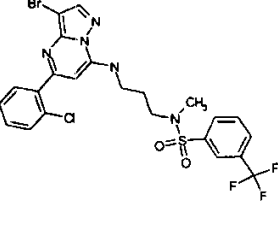
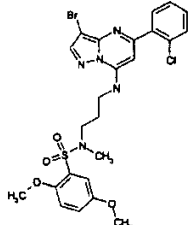
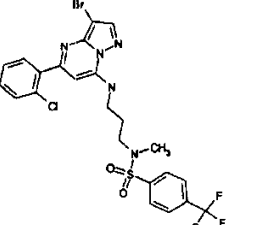
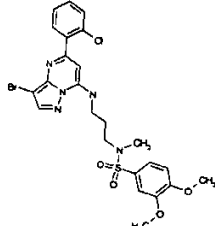
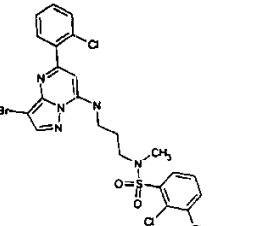
[1445]

생성물	1.실시예 2. m/z	생성물	1.실시예, 2. m/z
	1. 6811 2. 561.31		1. 6816 2. 566.31
	1. 6812 2. 561.31		1. 6817 2. 568.31
	1. 6813 2. 562.31		1. 6818 2. 570.31
	1. 6814 2. 564.31		1. 6819 2. 570.31
	1. 6815 2. 566.31		1. 6820 2. 570.31

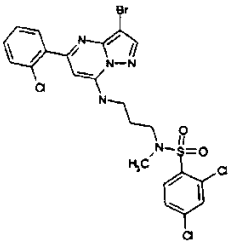
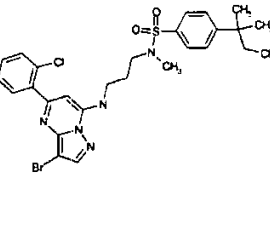
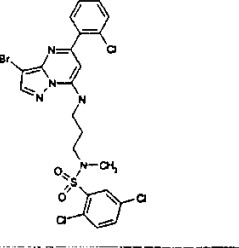
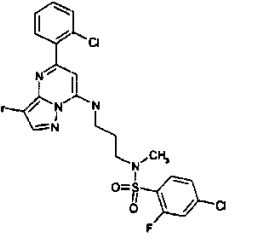
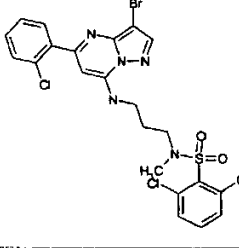
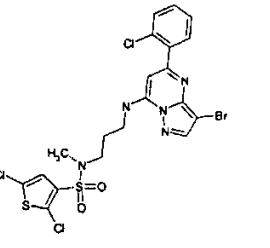
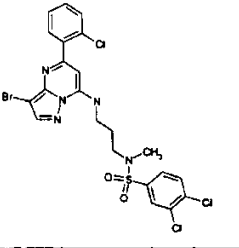
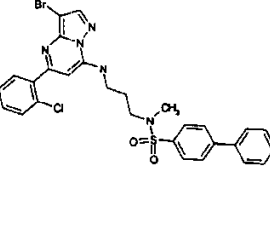
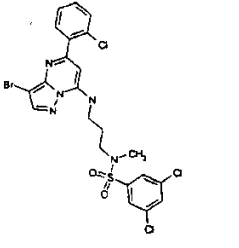
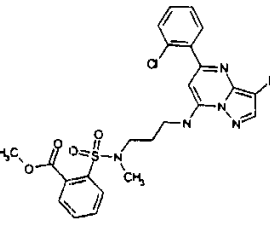
[1446]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 6821 2. 571.31		1. 6826 2. 576.32
	1. 6822 2. 572.31		1. 6827 2. 578.32
	1. 6823 2. 572.31		1. 6828 2. 586.32
	1. 6824 2. 572.31		1. 6829 2. 586.32
	1. 6825 2. 572.31		1. 6830 2. 588.32

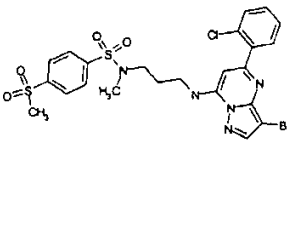
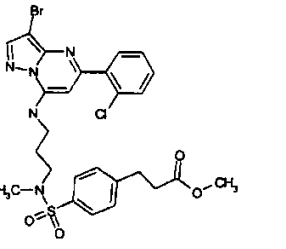
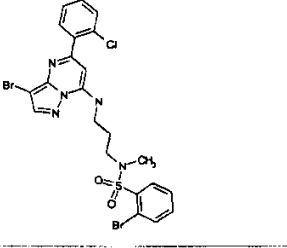
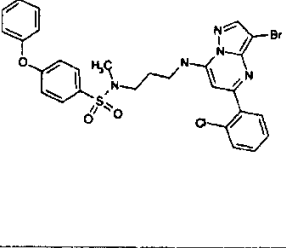
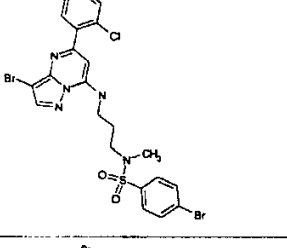
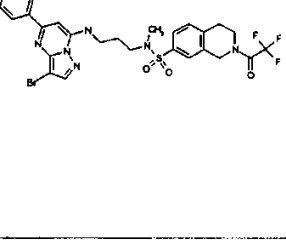
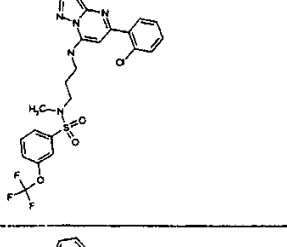
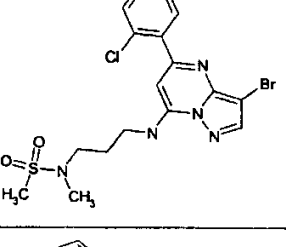
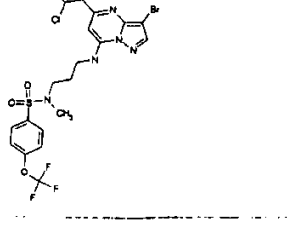
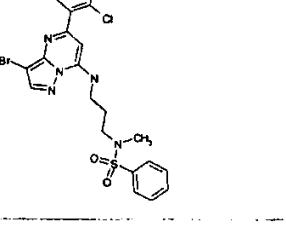
[1447]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	<p>1. 6831 2. 588.32</p>		<p>1. 6836 2. 600.33</p>
	<p>1. 6832 2. 592.33</p>		<p>1. 6837 2. 602.33</p>
	<p>1. 6833 2. 614.34</p>		<p>1. 6838 2. 604.33</p>
	<p>1. 6834 2. 596.33</p>		<p>1. 6839 2. 604.33</p>
	<p>1. 6835 2. 596.33</p>		<p>1. 6840 2. 604.33</p>

[1448]

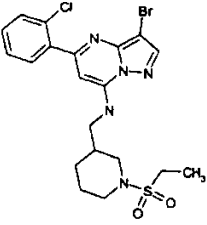
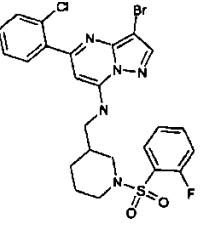
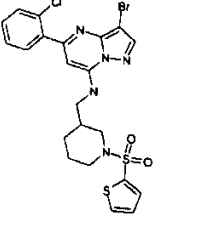
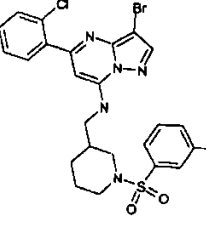
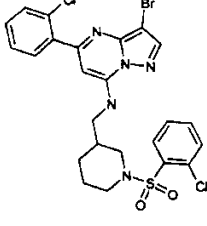
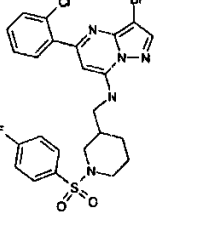
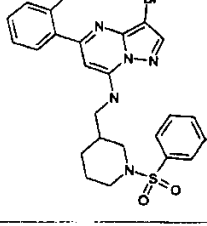
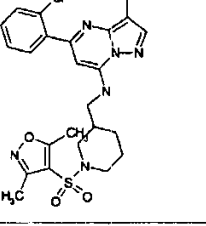
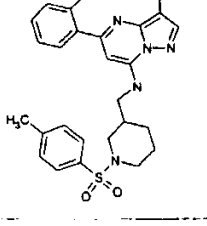
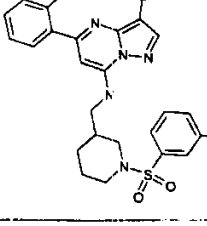
생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	<p>1. 6841 2. 604.33</p>		<p>1. 6846 2. 606.33</p>
	<p>1. 6842 2. 604.33</p>		<p>1. 6847 2. 588.32</p>
	<p>1. 6843 2. 605.33</p>		<p>1. 6848 2. 610.34</p>
	<p>1. 6844 2. 604.33</p>		<p>1. 6849 2. 612.34</p>
	<p>1. 6845 2. 604.33</p>		<p>1. 6850 2. 594.33</p>

[1449]

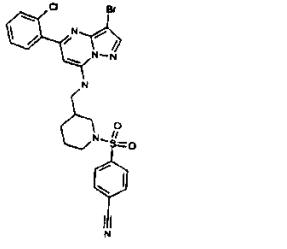
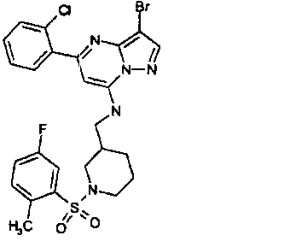
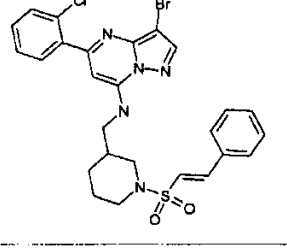
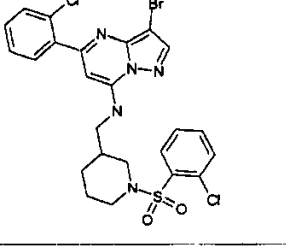
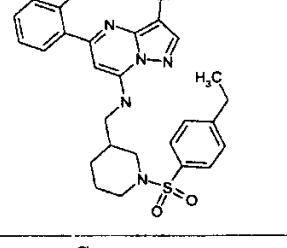
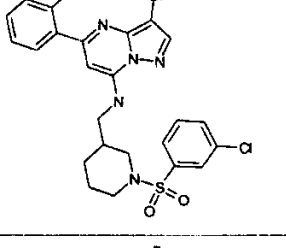
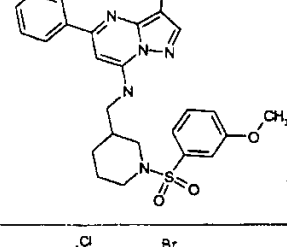
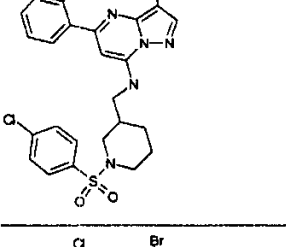
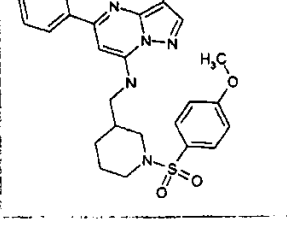
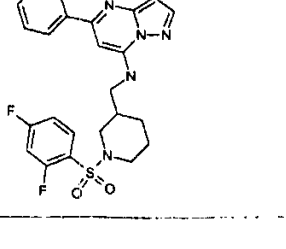
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 6851 2. 614.34		1. 6856 2. 620.34
	1. 6852 2. 614.34		1. 6856 2. 628.35
	1. 6853 2. 614.34		1. 6857 2. 687.38
	1. 6854 2. 620.34		1. 6859 2. 474.26
	1. 6855 2. 620.34		1. 6860 2. 536.29

[1450]

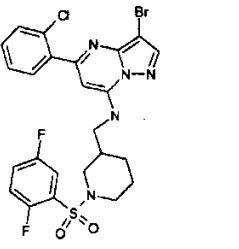
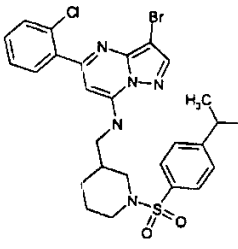
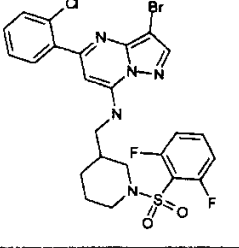
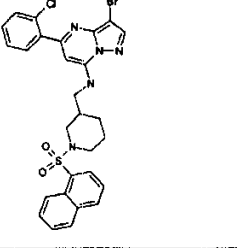
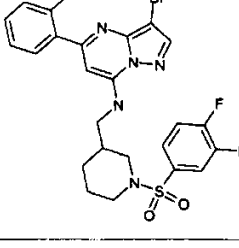
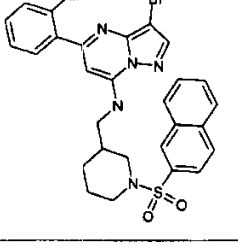
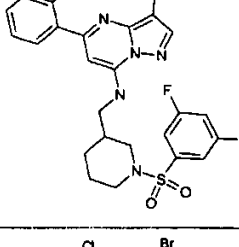
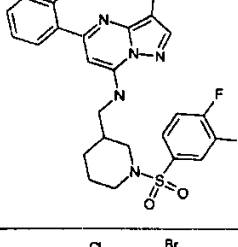
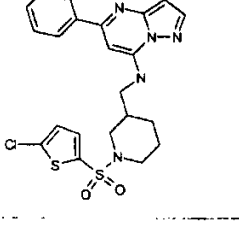
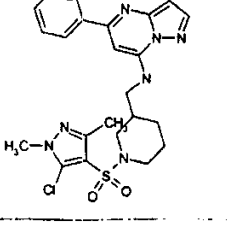
표 69

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 6901 2. 514.28		1. 6906 2. 580.32
	1. 6902 2. 568.31		1. 6907 2. 580.32
	1. 6903 2. 576.32		1. 6908 2. 580.32
	1. 6904 2. 576.32		1. 6909 2. 581.32
	1. 6905 2. 576.32		1. 6910 2. 587.32

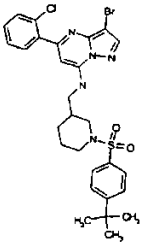
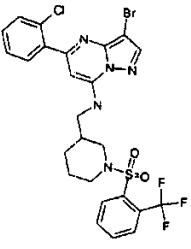
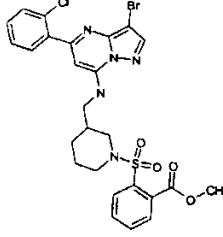
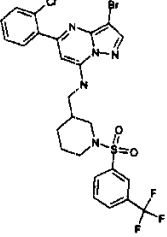
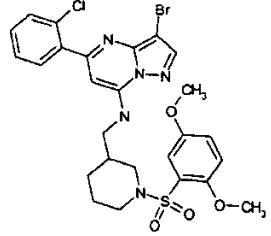
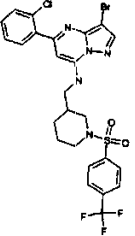
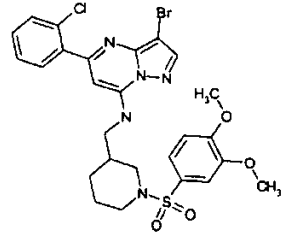
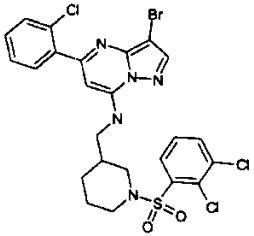
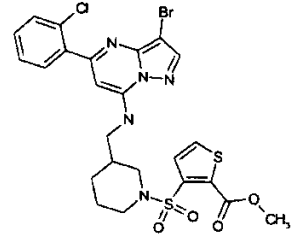
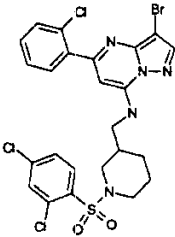
[1451]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 6911 2. 587.32		1. 6916 2. 594.33
	1. 6912 2. 588.32		1. 6917 2. 596.33
	1. 6913 2. 590.32		1. 6918 2. 596.33
	1. 6914 2. 592.33		1. 6919 2. 596.33
	1. 6915 2. 592.33		1. 6920 2. 598.33

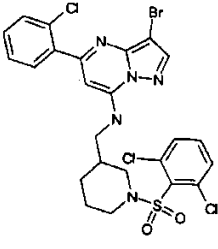
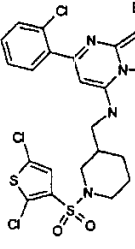
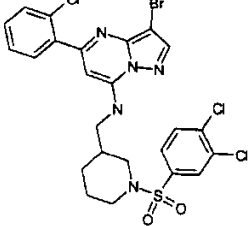
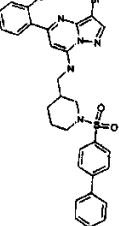
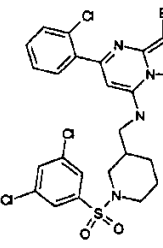
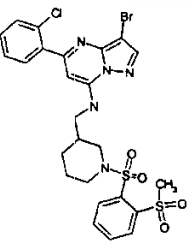
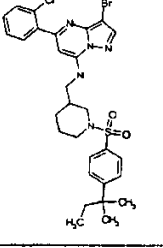
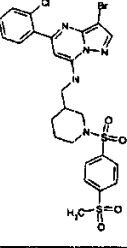
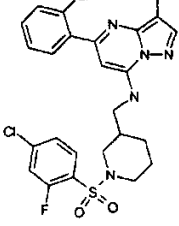
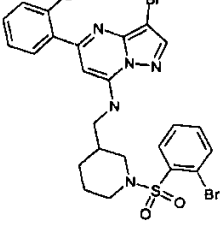
[1452]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 6921 2. 598.33		1. 6926 2. 604.33
	1. 6922 2. 598.33		1. 6927 2. 612.34
	1. 6923 2. 598.33		1. 6928 2. 612.34
	1. 6924 2. 598.33		1. 6929 2. 614.34
	1. 6925 2. 602.33		1. 6930 2. 614.34

[1453]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 6931 2. 618.34		1. 6936 2. 630.35
	1. 6932 2. 620.34		1. 6937 2. 630.35
	1. 6933 2. 622.34		1. 6938 2. 630.35
	1. 6934 2. 622.34		1. 6939 2. 630.35
	1. 6935 2. 626.34		1. 6940 2. 630.35

[1454]

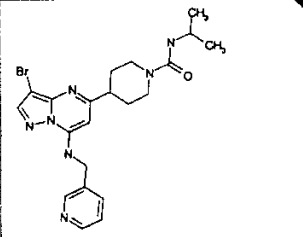
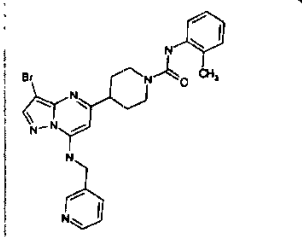
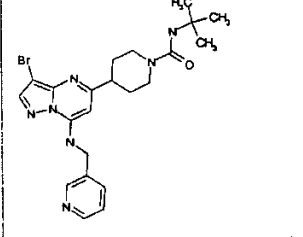
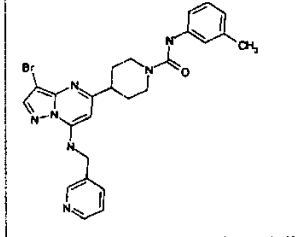
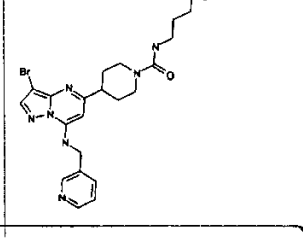
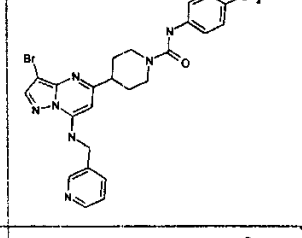
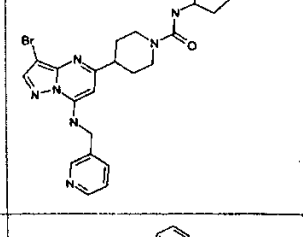
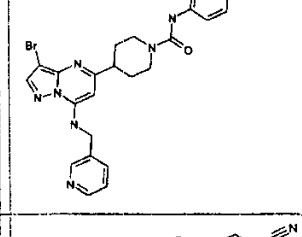
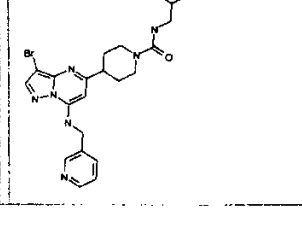
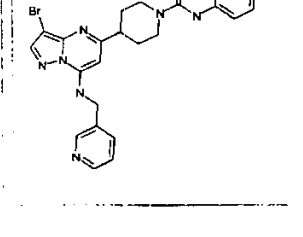
생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 6941 2. 630.35		1. 6946 2. 636.35
	1. 6942 2. 630.35		1. 6947 2. 638.35
	1. 6943 2. 630.35		1. 6948 2. 640.35
	1. 6944 2. 632.35		1. 6949 2. 640.35
	1. 6945 2. 614.34		1. 6950 2. 640.35

[1455]

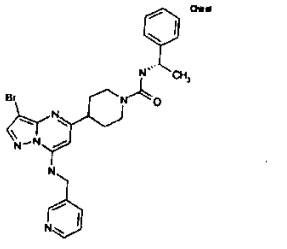
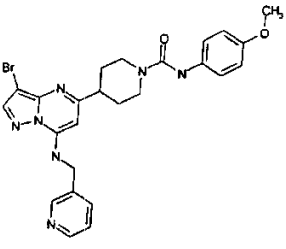
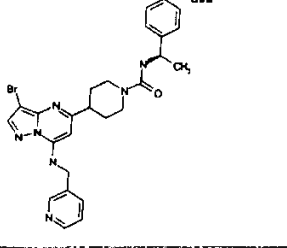
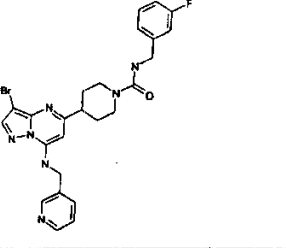
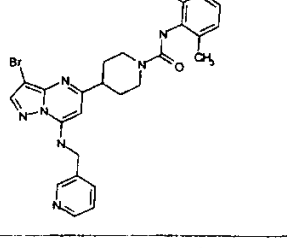
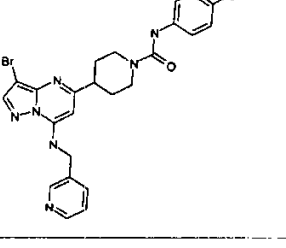
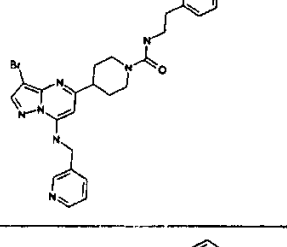
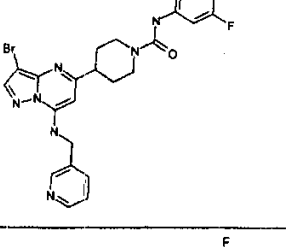
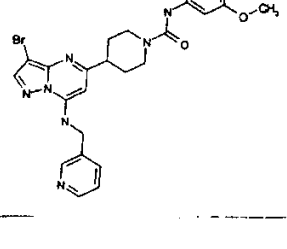
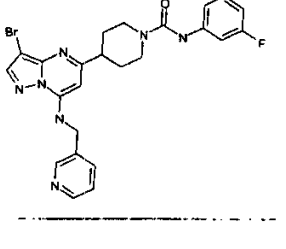
생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 6951 2. 640.35		1. 6956 2. 675.23
	1. 6952 2. 646.36		1. 6957 2. 713.39
	1. 6953 2. 646.36		1. 6958 2. 500.27
	1. 6954 2. 648.36		1. 6959 2. 562.31
	1. 6955 2. 654.36		1. 6960 2. 604.33

[1456]

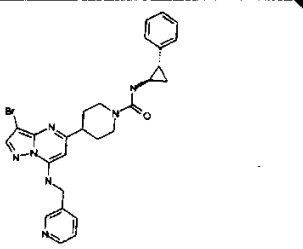
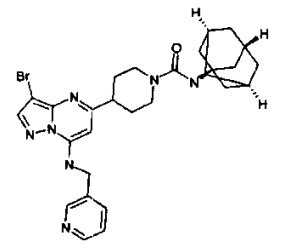
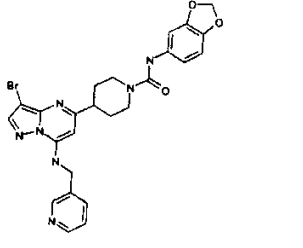
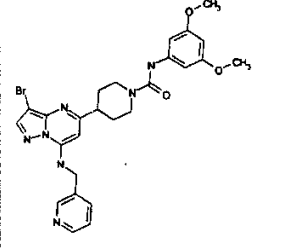
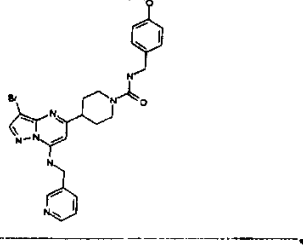
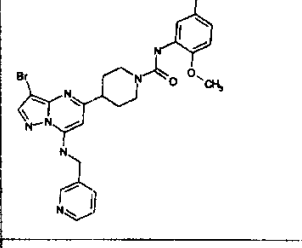
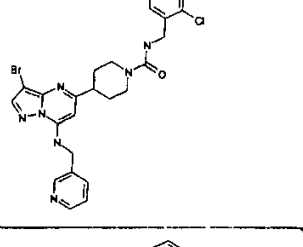
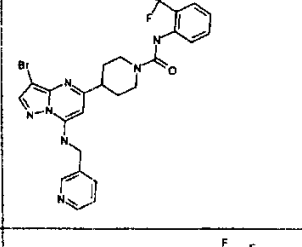
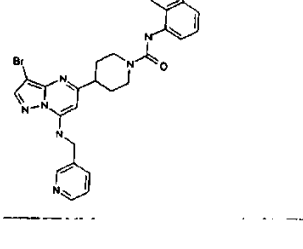
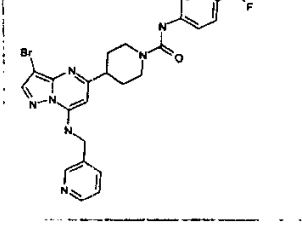
표 70

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 7001 2. 472.26		1. 7006 2. 522.29
	1. 7002 2. 488.27		1. 7007 2. 520.29
	1. 7003 2. 488.27		1. 7008 2. 520.29
	1. 7004 2. 500.27		1. 7009 2. 526.29
	1. 7005 2. 520.29		1. 7010 2. 533.29

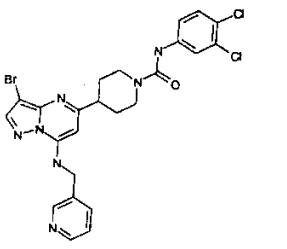
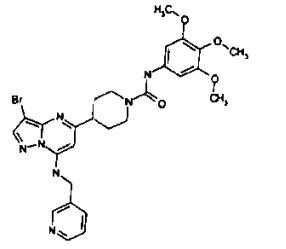
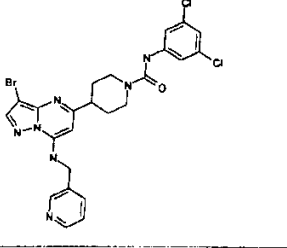
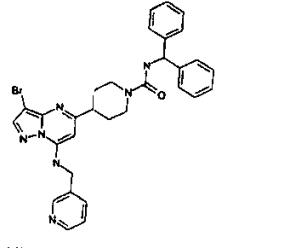
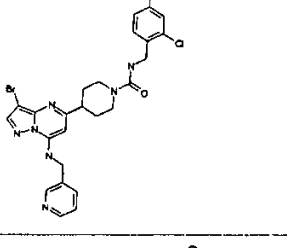
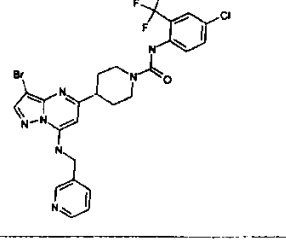
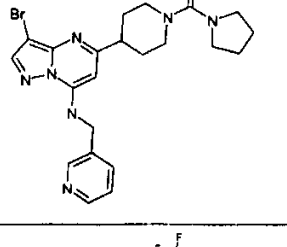
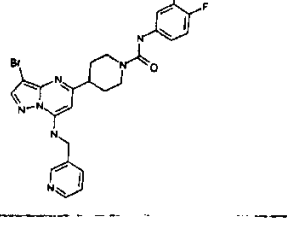
[1457]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7011 2. 536.29		1. 7016 2. 538.3
	1. 7012 2. 536.29		1. 7017 2. 540.3
	1. 7013 2. 536.29		1. 7018 2. 542.3
	1. 7014 2. 536.29		1. 7019 2. 544.3
	1. 7015 2. 536.29		1. 7020 2. 544.3

[1458]

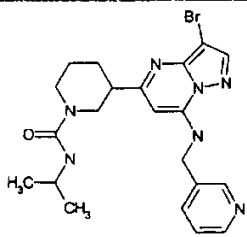
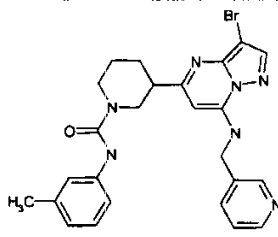
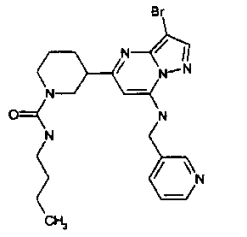
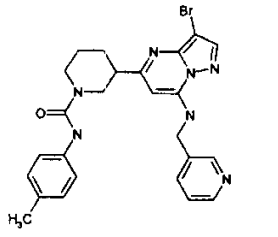
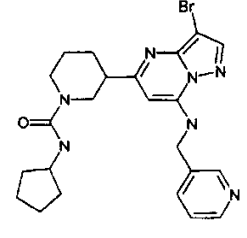
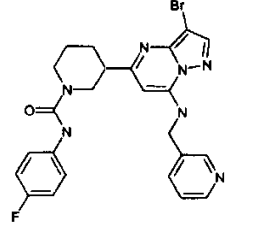
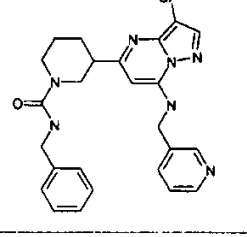
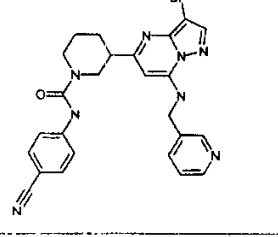
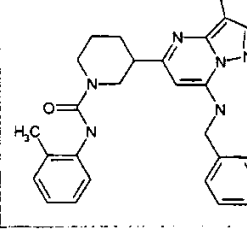
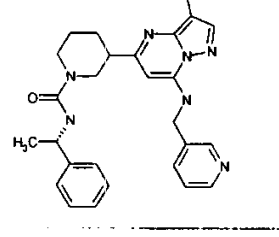
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7021 2. 548.3		1. 7026 2. 566.31
	1. 7022 2. 552.3		1. 7027 2. 568.31
	1. 7023 2. 552.3		1. 7028 2. 572.31
	1. 7024 2. 556.31		1. 7029 2. 576.32
	1. 7025 2. 558.31		1. 7030 2. 576.32

[1459]

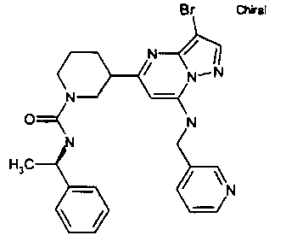
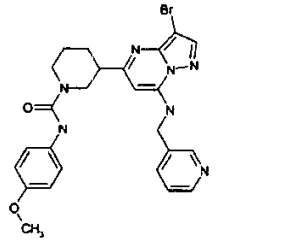
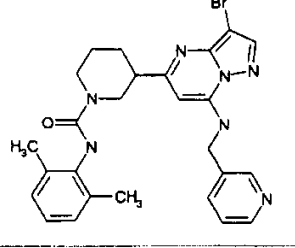
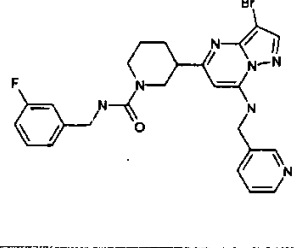
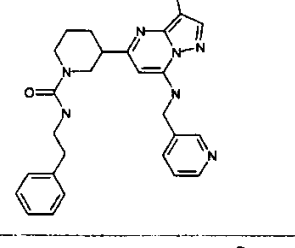
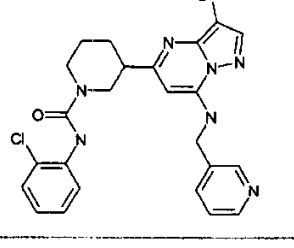
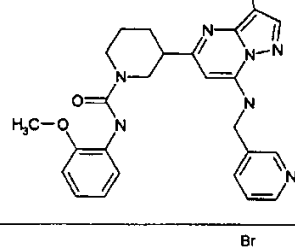
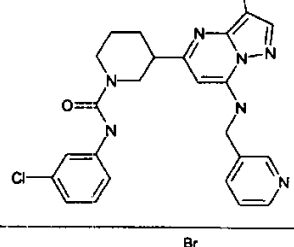
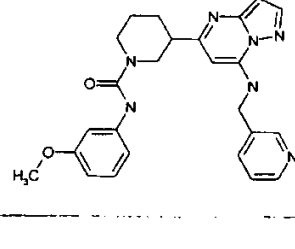
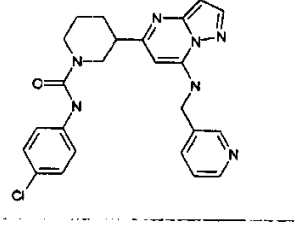
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7031 2. 576.32		1. 7036 2. 598.33
	1. 7032 2. 576.32		1. 7037 2. 598.33
	1. 7033 2. 590.32		1. 7038 2. 610.34
	1. 7034 2. 486.27		
	1. 7035 2. 594.33		

[1460]

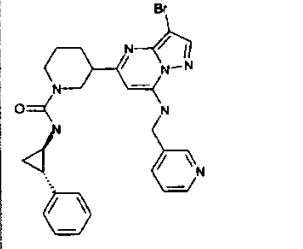
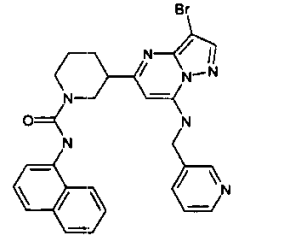
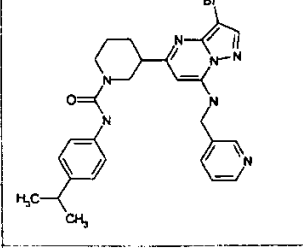
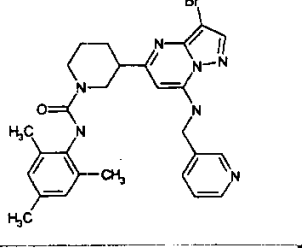
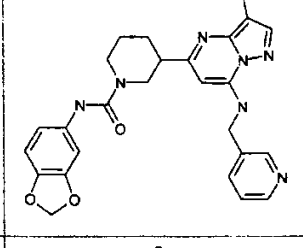
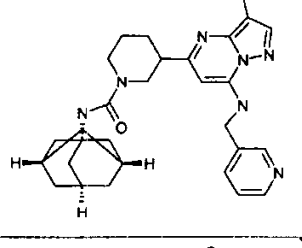
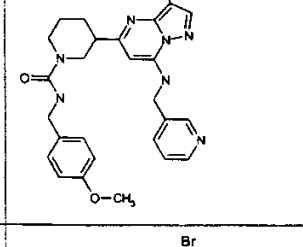
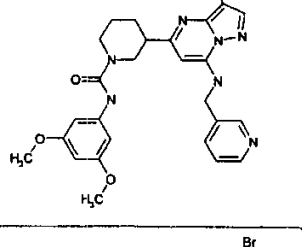
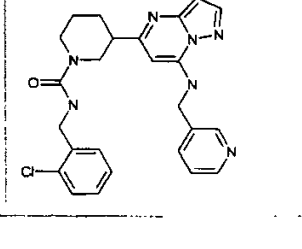
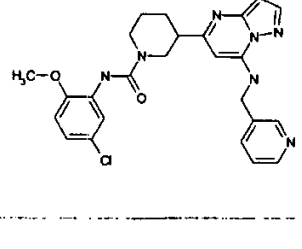
표 71

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7101 2. 474.26		1. 7106 2. 522.29
	1. 7102 2. 488.27		1. 7107 2. 522.29
	1. 7103 2. 500.27		1. 7108 2. 526.3
	1. 7104 2. 522.29		1. 7109 2. 533.29
	1. 7105 2. 522.29		1. 7110 2. 536.29

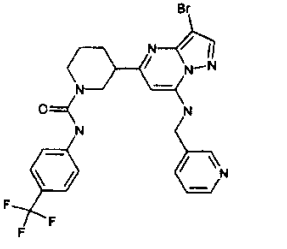
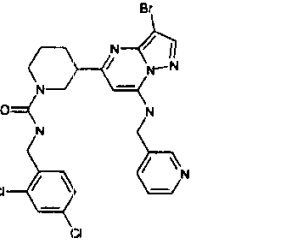
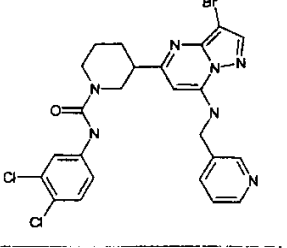
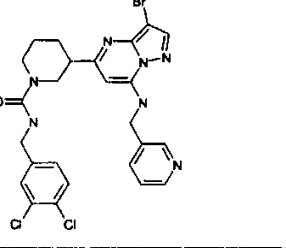
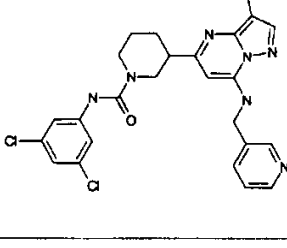
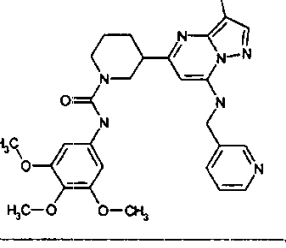
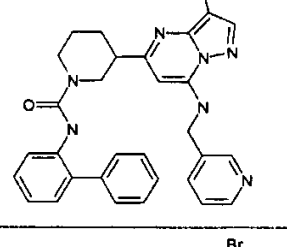
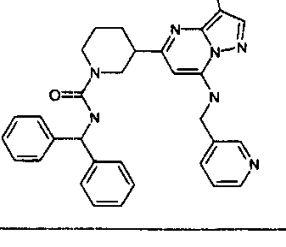
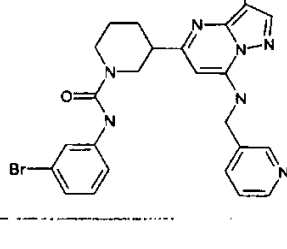
[1461]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 7111 2. 536.29		1. 7116 2. 538.3
	1. 7112 2. 536.29		1. 7117 2. 540.3
	1. 7113 2. 536.29		1. 7118 2. 542.3
	1. 7114 2. 536.29		1. 7119 2. 542.3
	1. 7115 2. 536.3		1. 7120 2. 542.3

[1462]

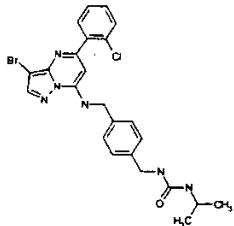
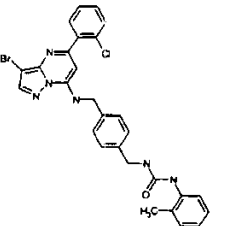
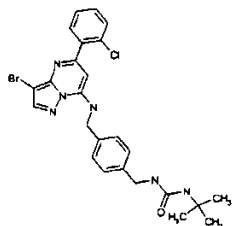
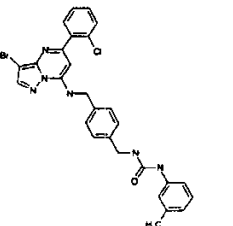
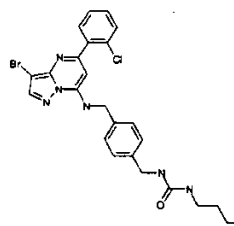
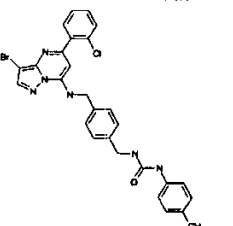
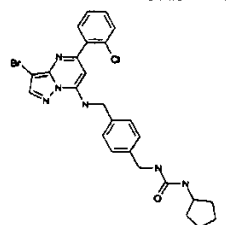
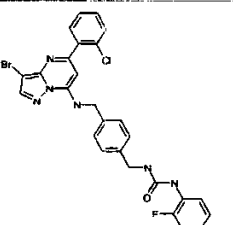
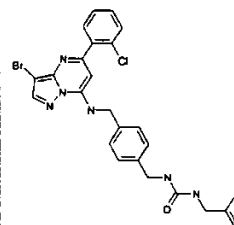
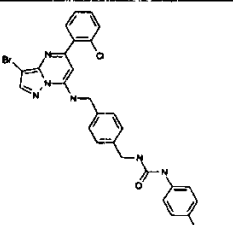
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7121 2. 546.3		1. 7126 2. 558.31
	1. 7122 2. 550.3		1. 7127 2. 550.3
	1. 7123 2. 552.3		1. 7128 2. 566.31
	1. 7124 2. 552.3		1. 7129 2. 565.31
	1. 7125 2. 556.31		1. 7130 2. 572.31

[1463]

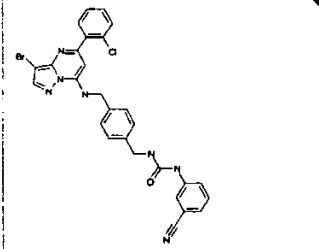
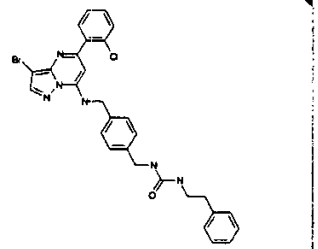
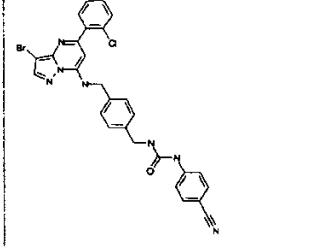
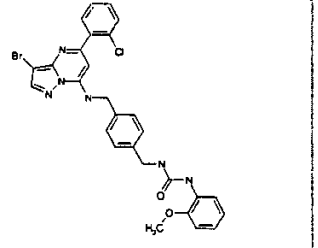
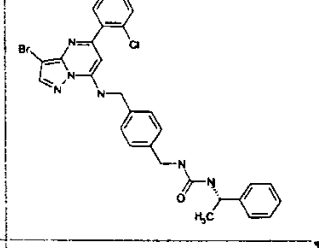
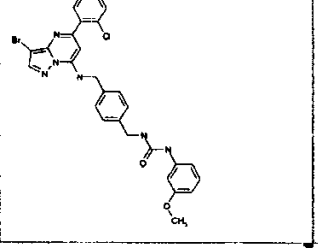
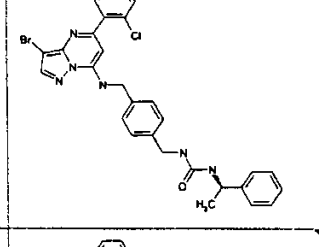
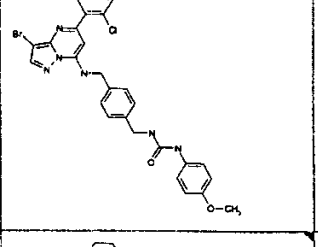
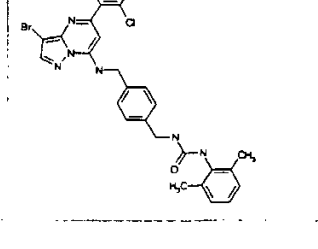
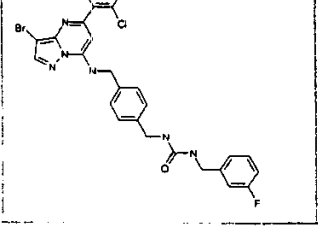
생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 7131 2. 576.32		1. 7136 2. 590.32
	1. 7132 2. 576.32		1. 7137 2. 590.32
	1. 7133 2. 576.32		1. 7138 2. 598.33
	1. 7134 2. 584.32		1. 7139 2. 598.33
	1. 7135 2. 585.3		

[1464]

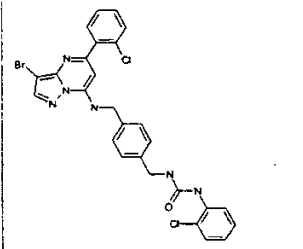
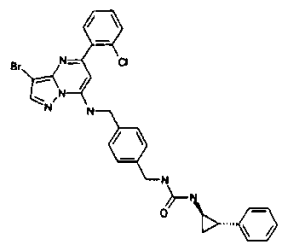
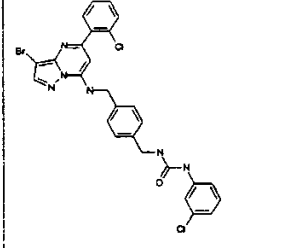
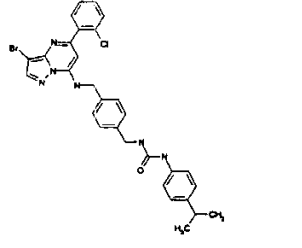
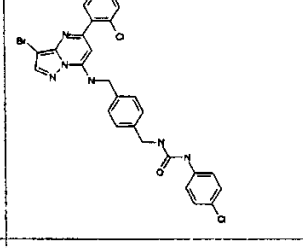
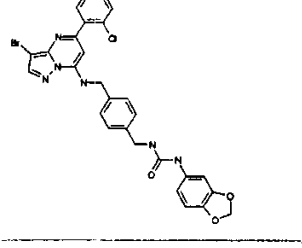
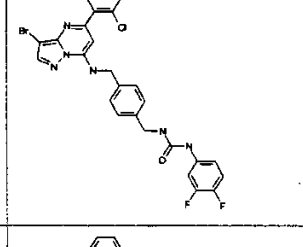
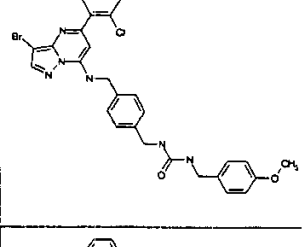
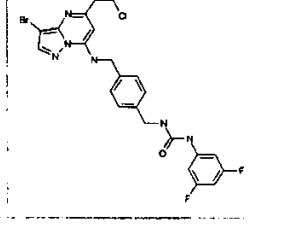
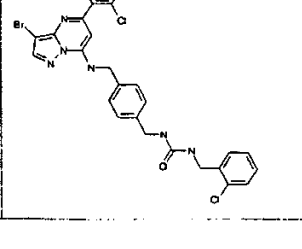
표 72

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7201 2. 529.29		1. 7206 2. 577.32
	1. 7202 2. 543.3		1. 7207 2. 577.32
	1. 7203 2. 543.3		1. 7208 2. 577.32
	1. 7204 2. 555.31		1. 7209 2. 581.32
	1. 7205 2. 577.32		1. 7210 2. 581.32

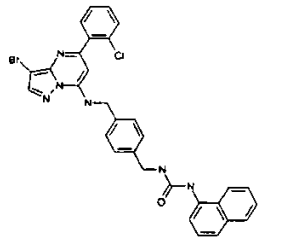
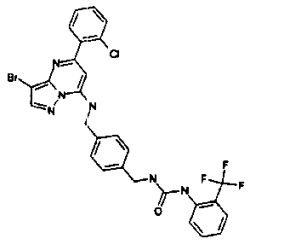
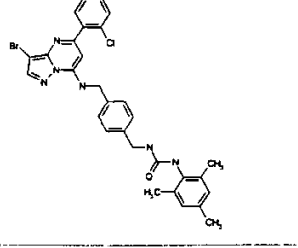
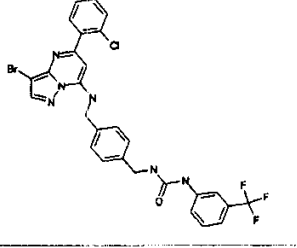
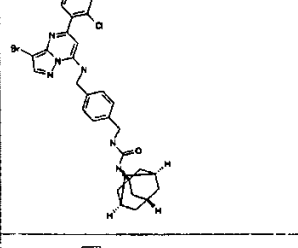
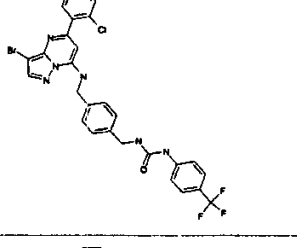
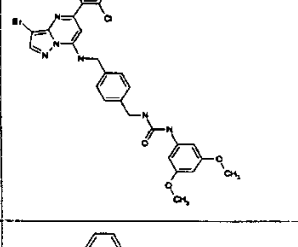
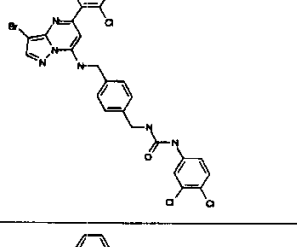
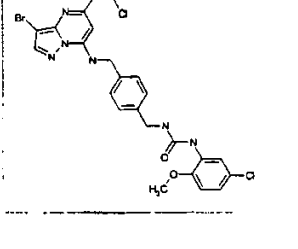
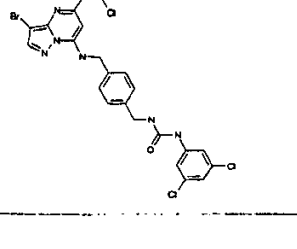
[1465]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7211 2. 588.32		1. 7216 2. 591.33
	1. 7212 2. 588.32		1. 7217 2. 593.33
	1. 7213 2. 591.33		1. 7218 2. 593.33
	1. 7214 2. 591.33		1. 7219 2. 593.33
	1. 7215 2. 591.33		1. 7220 2. 595.33

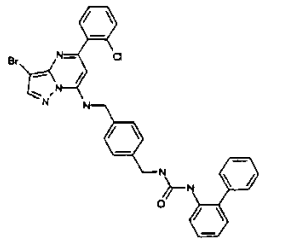
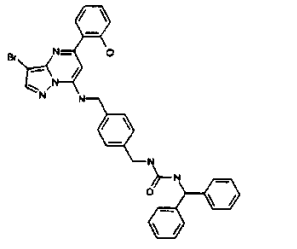
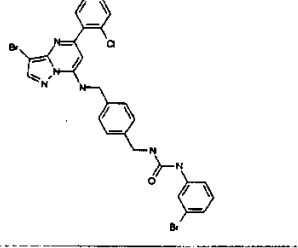
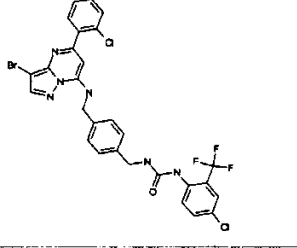
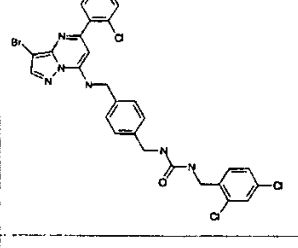
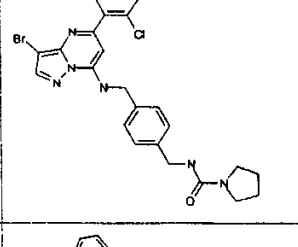
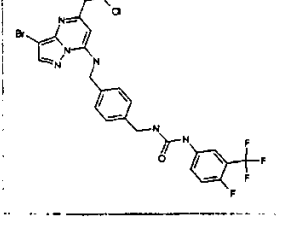
[1466]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7221 2. 597.33		1. 7226 2. 603.33
	1. 7222 2. 597.33		1. 7227 2. 603.33
	1. 7223 2. 597.33		1. 7228 2. 607.33
	1. 7224 2. 599.33		1. 7229 2. 607.14
	1. 7225 2. 599.33		1. 7230 2. 611.34

[1467]

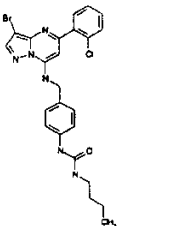
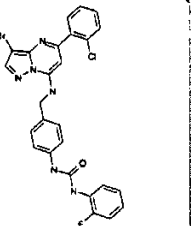
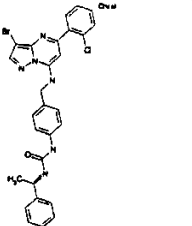
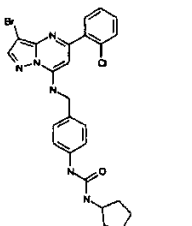
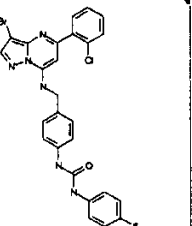
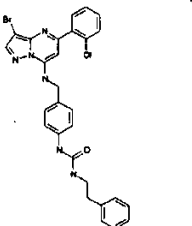
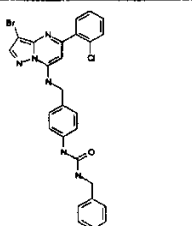
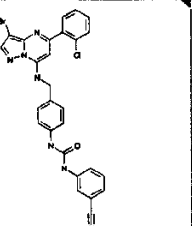
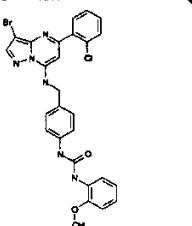
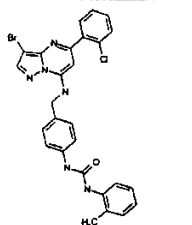
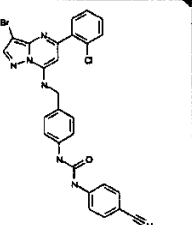
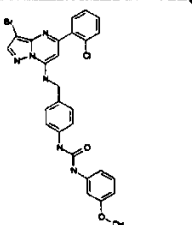
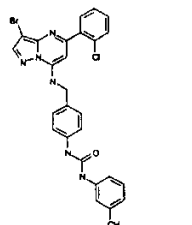
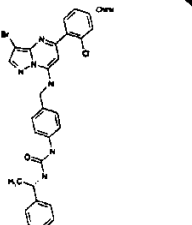
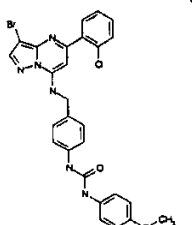
생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 7231 2. 613.34		1. 7236 2. 631.35
	1. 7232 2. 605.33		1. 7237 2. 631.35
	1. 7233 2. 621.34		1. 7238 2. 631.35
	1. 7234 2. 623.34		1. 7239 2. 631.35
	1. 7235 2. 627.34		1. 7240 2. 631.35

[1468]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7241 2. 639.35		1. 7246 2. 653.36
	1. 7242 2. 641.35		1. 7247 2. 665.37
	1. 7243 2. 645.35		
	1. 7244 2. 541.3		
	1. 7245 2. 649.36		

[1469]

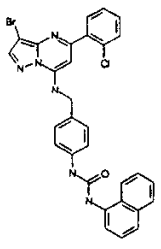
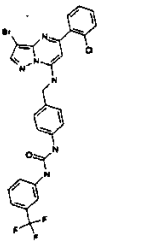
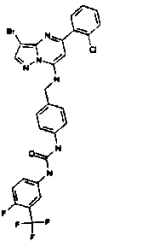
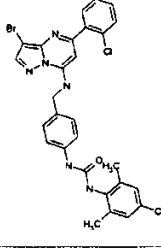
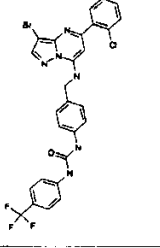
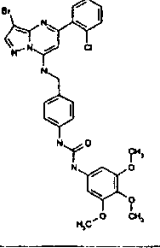
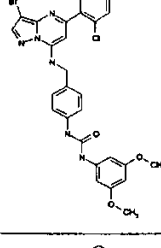
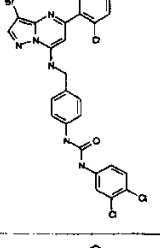
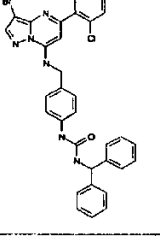
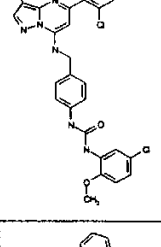
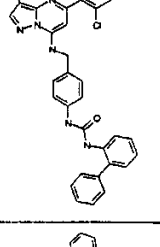
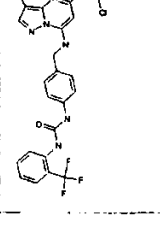
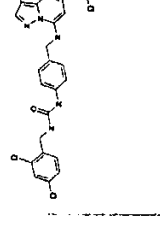
표 73

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7301 2. 529.29		1. 7306 2. 567.31		1. 7311 2. 577.32
	1. 7302 2. 541.3		1. 7307 2. 567.31		1. 7312 2. 577.32
	1. 7303 2. 563.13		1. 7308 2. 574.32		1. 7313 2. 579.32
	1. 7304 2. 563.31		1. 7309 2. 574.32		1. 7314 2. 579.32
	1. 7305 2. 563.31		1. 7310 2. 577.32		1. 7315 2. 579.32

[1470]

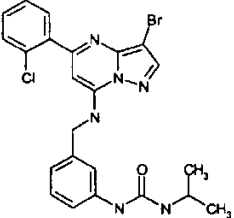
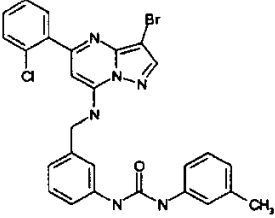
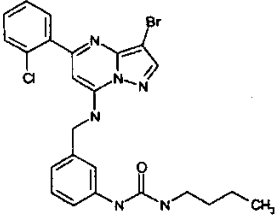
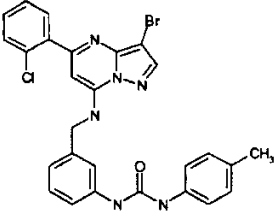
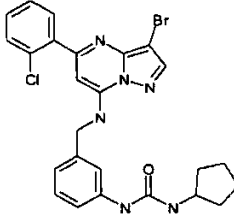
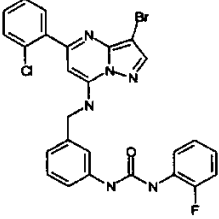
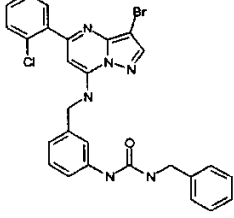
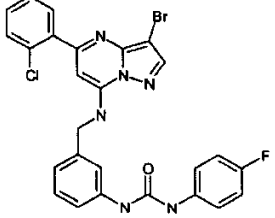
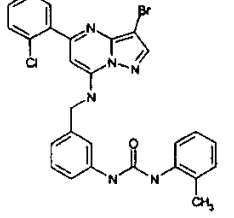
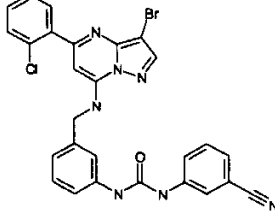
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7316 2. 581.32		1. 7321 2. 585.32		1. 7326 2. 599.33
	1. 7317 2. 583.32		1. 7322 2. 589.32		1. 7327 2. 591.33
	1. 7318 2. 583.32		1. 7323 2. 591.33		1. 7328
	1. 7319 2. 583.32		1. 7324 2. 593.33		1.7329 2. 613.34
	1. 7320 2. 585.32		1. 7325 2. 597.33		1. 7330 2. 617.34

[1471]

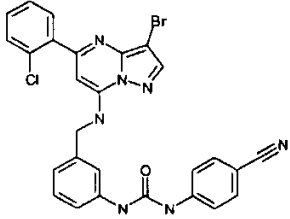
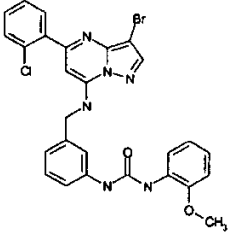
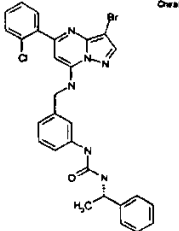
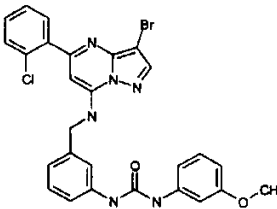
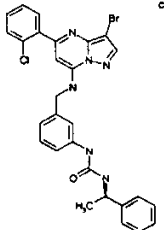
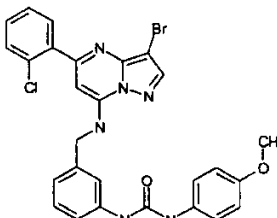
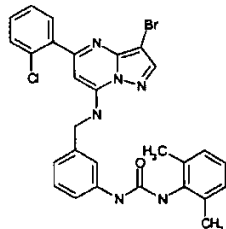
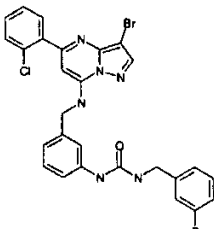
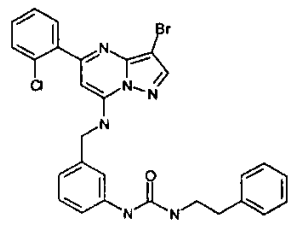
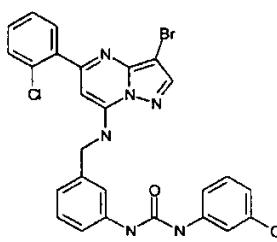
생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 7331 2. 599.33		1. 7336 2. 617.34		1. 73412. 2. 635.35
	1. 7332 2. 591.33		1. 7337 2. 617.34		1. 7342 2. 639.35
	1. 7333 2. 609.33		1. 7338 2. 617.34		1. 7343 2. 639.35
	1. 7334 2. 613.34		1. 7339 2. 625.34		
	1. 7335 2. 617.34		1. 7340 2. 631.35		

[1472]

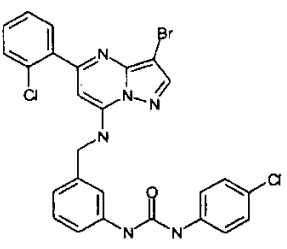
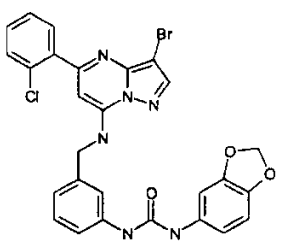
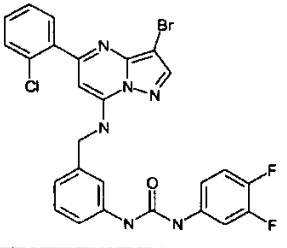
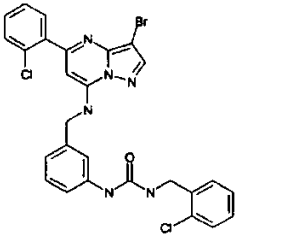
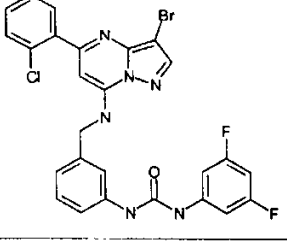
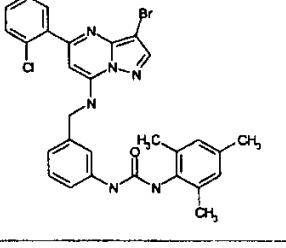
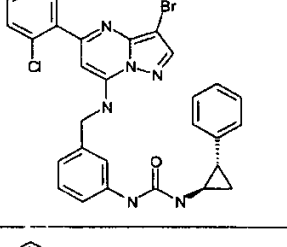
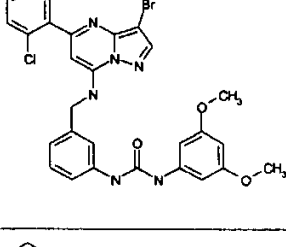
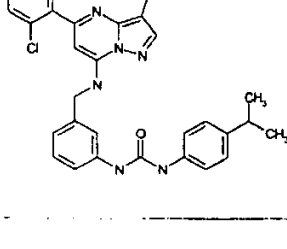
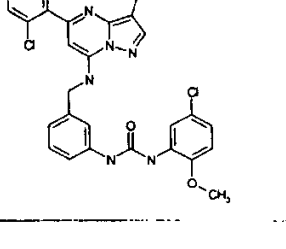
표 74

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7401 2. 515.28		1. 7406 2. 563.31
	1. 7402 2. 529.29		1. 7407 2. 563.31
	1. 7403 2. 541.3		1. 7408 2. 567.31
	1. 7404 2. 563.13		1. 7409 2. 567.31
	1. 7405 2. 563.31		1. 7410 2. 574.32

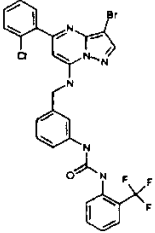
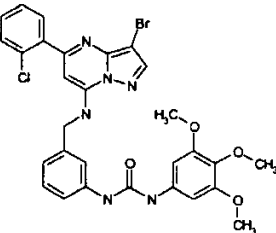
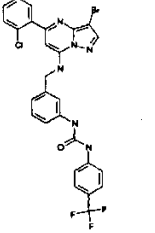
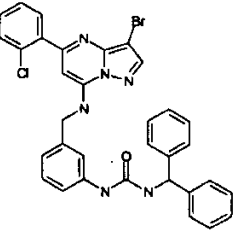
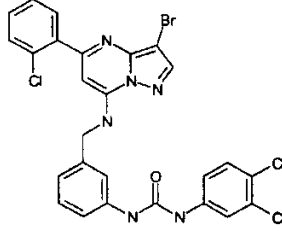
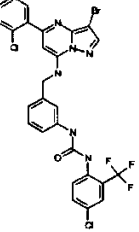
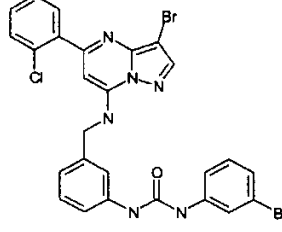
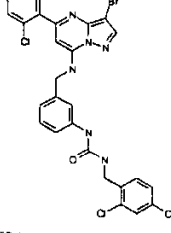
[1473]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 7411 2. 574.32		1. 7416 2. 579.32
	1. 7412 2. 577.14		1. 7417 2. 579.32
	1. 7413 2. 577.32		1. 7418 2. 579.32
	1. 7414 2. 577.32		1. 7419 2. 581.32
	1. 7415 2. 577.32		1. 7420 2. 583.32

[1474]

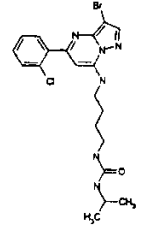
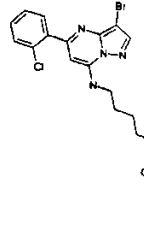
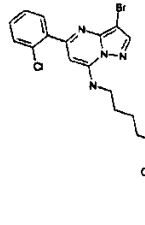
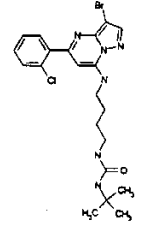
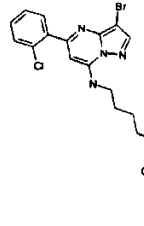
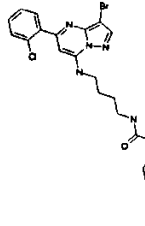
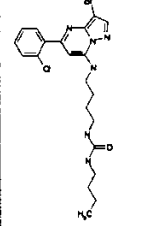
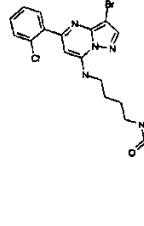
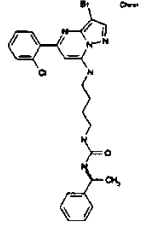
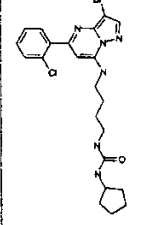
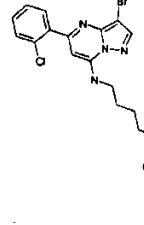
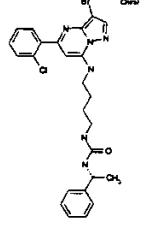
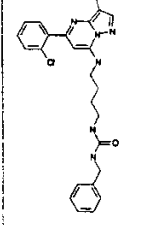
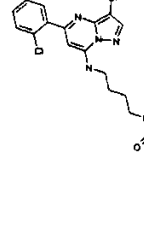
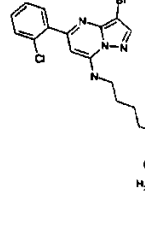
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7421 2. 583.32		1. 7426 2. 593.33
	1. 7422 2. 585.32		1. 7427 2. 597.33
	1. 7423 2. 585.32		1. 7428 2. 591.33
	1. 7424 2. 589.32		1. 7429 2. 609.33
	1. 7425 2. 591.33		1. 7430 2. 613.34

[1475]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	<p>1. 7431 2. 617.34</p>		<p>1. 7436 2. 639.35</p>
	<p>1. 7432 2. 617.34</p>		<p>1. 7437 2. 639.35</p>
	<p>1. 7433 2. 617.34</p>		<p>1. 7438 2. 651.36</p>
	<p>1. 7434 2. 627.34</p>		
	<p>1. 7435 2. 631.35</p>		

[1476]

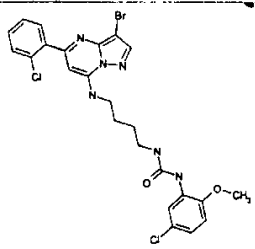
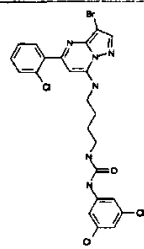
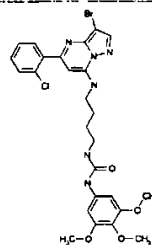
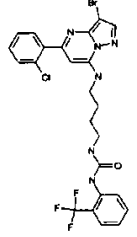
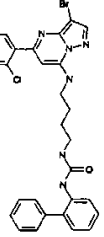
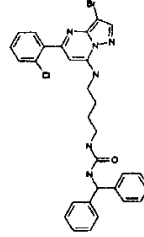
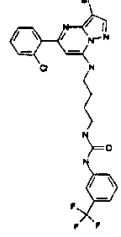
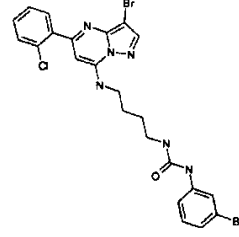
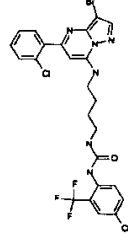
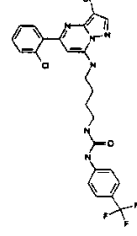
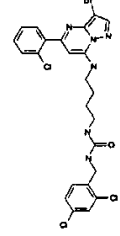
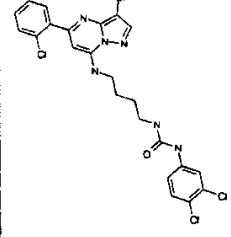
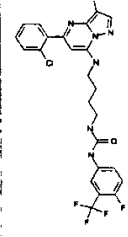
표 75

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7501 2. 481.26		1. 7506 2. 529.29		1. 7511 2. 540.3
	1. 7502 2. 495.27		1. 7507 2. 529.29		1. 7512 2. 540.3
	1. 7503 2. 495.27		1. 7508 2. 529.29		1. 7513 2. 543.3
	1. 7504 2. 507.28		1. 7509 2. 533.29		1. 7514 2. 543.3
	1. 7505 2. 529.29		1. 7510 2. 533.29		1. 7515 2. 543.3

[1477]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 7516 2. 543.3		1. 7521 2. 549.3		1. 7526 2. 555.31
	1. 7517 2. 545.3		1. 7522 2. 549.3		1. 7527 2. 557.31
	1. 7518 2. 545.3		1. 7523 2. 549.3		1. 7528 2. 559.31
	1. 7519 2. 545.3		1. 7524 2. 551.3		1. 7529 2. 560.31
	1. 7520 2. 547.3		1. 7525 2. 551.3		1. 7530 2. 573.32

[1478]

생성물	1.실시예. 2. m/z	생성물	1.실시예. 2. m/z	생성물	1.실시예. 2. m/z
	1. 7531 2. 579.32		1. 7536 2. 583.32		1. 7541 2. 605.33
	1. 7532 2. 583.32		1. 7537 2. 591.33		1. 7542 2. 605.33
	1. 7533 2. 583.32		1. 7538 2. 593.33		1. 7543 2. 614.34
	1. 7534 2. 583.32		1. 7539 2. 597.33		
	1. 7535 2. 583.32		1. 7540 2. 601.33		

[1479]

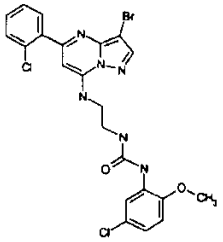
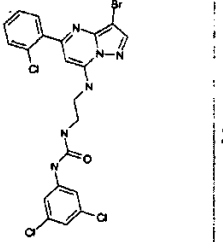
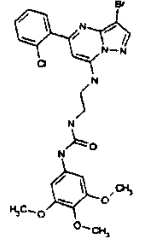
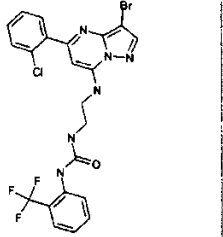
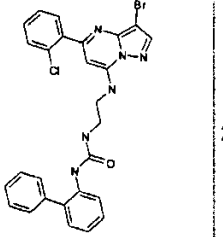
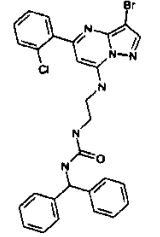
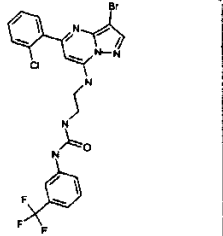
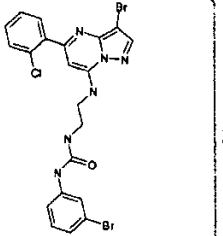
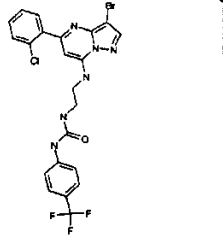
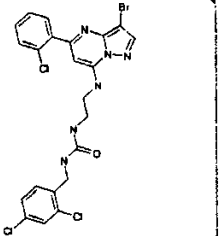
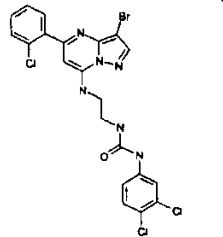
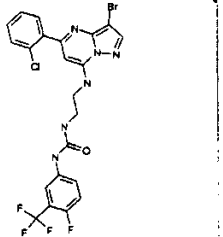
표 76

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7601 2. 453.25		1. 7606 2. 501.28		1. 7611 2. 512.28
	1. 7602 2. 467.26		1. 7607 2. 501.28		1. 7612 2. 512.28
	1. 7603 2. 467.26		1. 7608 2. 501.28		1. 7613 2. 515.28
	1. 7604 2. 479.26		1. 7609 2. 505.28		1. 7614 2. 515.28
	1. 7605 2. 501.28		1. 7610 2. 505.28		1. 7615 2. 515.28

[1480]

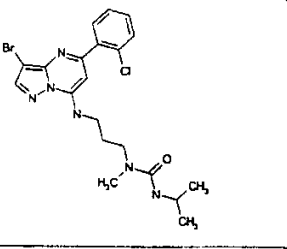
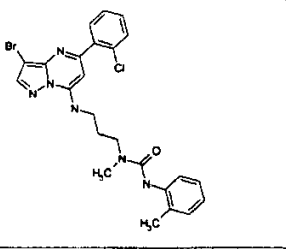
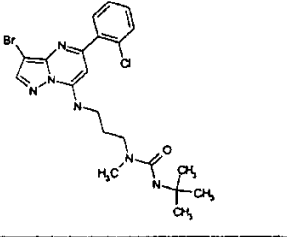
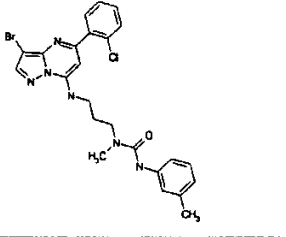
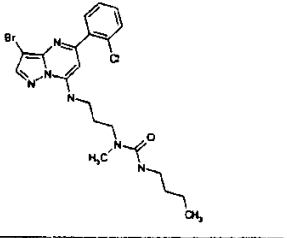
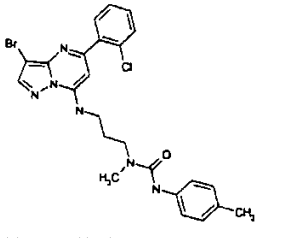
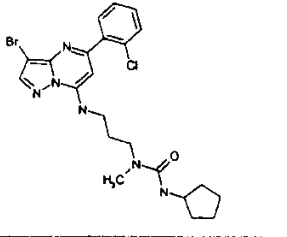
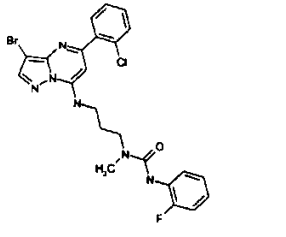
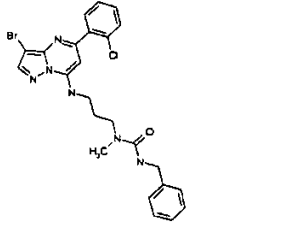
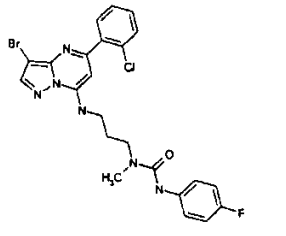
생성물	1.실시예. 2.m/z	생성물	1.실시예. 2.m/z	생성물	1.실시예. 2.m/z
	1. 761.6 2. 515.28		1. 7621 2. 521.29		1. 7626 2. 527.29
	1. 7617 2. 517.28		1. 7622 2. 521.29		1. 7627 2. 529.29
	1. 7618 2. 517.28		1. 7623 2. 521.29		1. 7628 2. 541.3
	1. 7619 2. 517.28		1. 7624 2. 523.29		1. 7629 2. 545.3
	1. 7620 2. 519.29		1. 7625 2. 523.29		1. 7630 2. 547.3

[1481]

생성물	1.실시예. 2.m/z	생성물	1.실시예. 2.m/z	생성물	1.실시예. 2.m/z
	1. 7631 2. 551.3		1. 7636 2. 555.31		1. 7641 2. 577.32
	1. 7632 2. 555.31		1. 7637 2. 563.31		1. 7642 2. 577.32
	1. 7633 2. 555.31		1. 7638 2. 565.31		
	1. 7634 2. 555.31		1. 7639 2. 569.31		
	1. 7635 2. 555.31		1. 7640 2. 573.32		

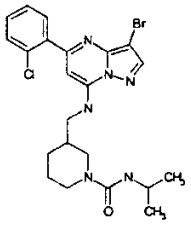
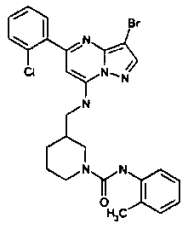
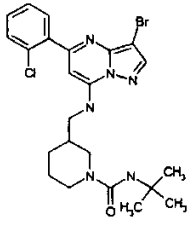
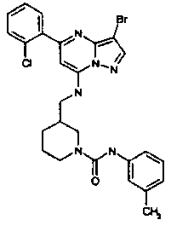
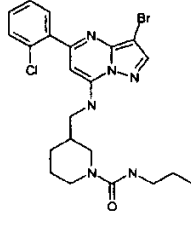
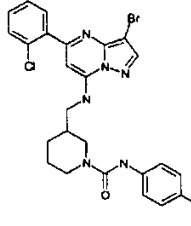
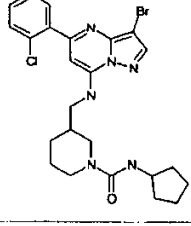
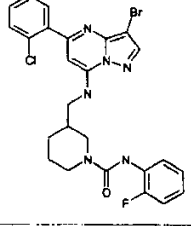
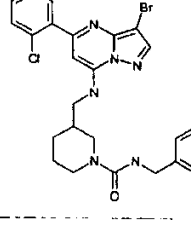
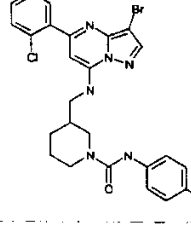
[1482]

표 77

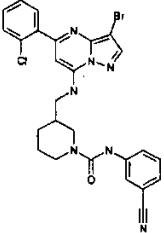
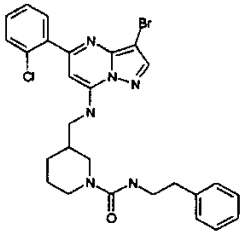
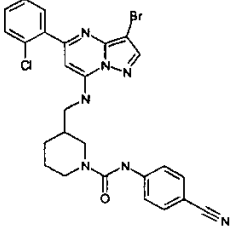
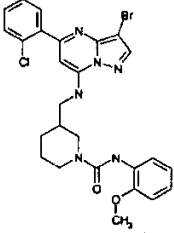
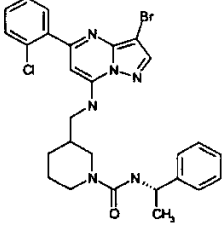
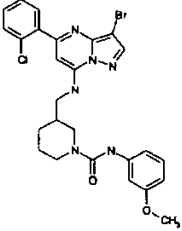
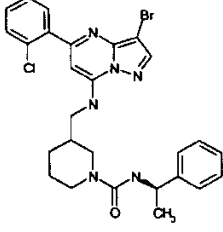
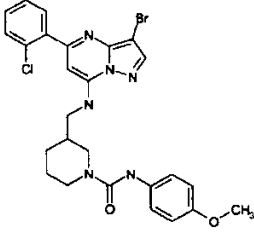
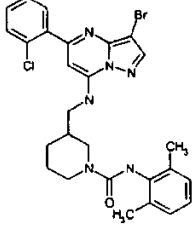
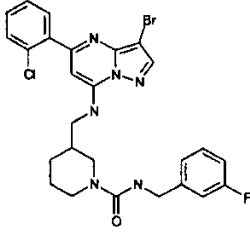
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7701 2. 481.26		1. 7706 2. 529.29
	1. 7702 2. 495.27		1. 7707 2. 529.29
	1. 7703 2. 495.27		1. 7708 2. 529.29
	1. 7704 2. 507.28		1. 7709 2. 533.29
	1. 7705 2. 529.29		1. 7710 2. 533.29

[1483]

표 78

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 7801 2. 507.28		1. 7806 2. 555.31
	1. 7802 2. 521.29		1. 7807 2. 555.31
	1. 7803 2. 521.29		1. 7808 2. 555.31
	1. 7804 2. 533.29		1. 7809 2. 559.31
	1. 7805 2. 555.31		1. 7810 2. 559.31

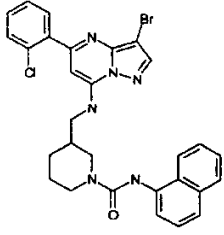
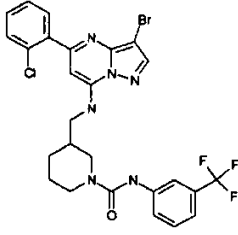
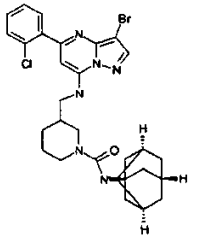
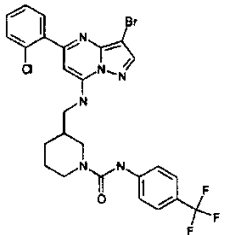
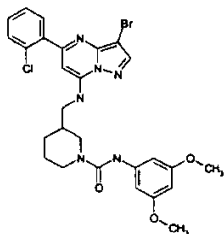
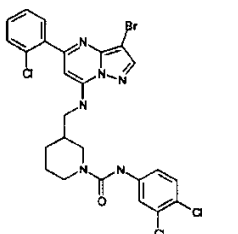
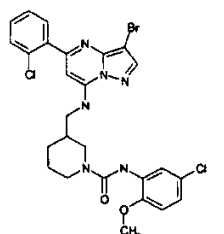
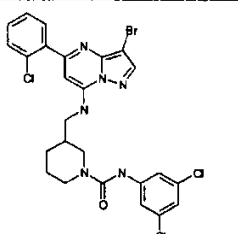
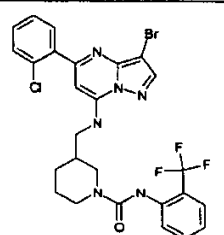
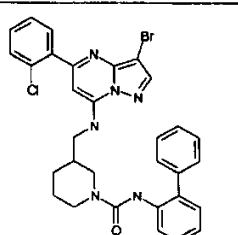
[1484]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7811 2. 566.31		1. 7816 2. 569.31
	1. 7812 2. 566.31		1. 7817 2. 571.31
	1. 7813 2. 569.31		1. 7818 2. 571.31
	1. 7814 2. 569.31		1. 7819 2. 571.31
	1. 7815 2. 569.31		1. 7820 2. 573.31

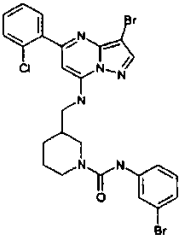
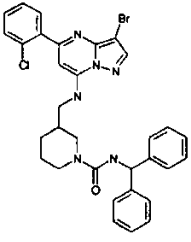
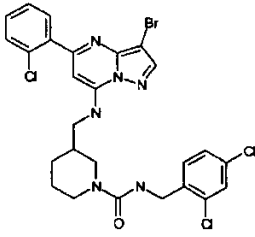
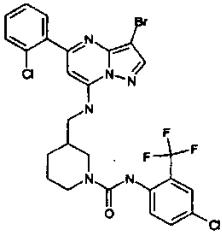
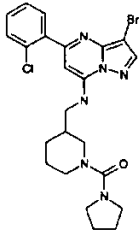
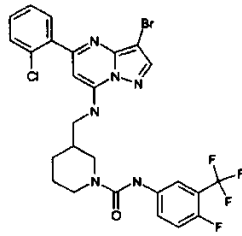
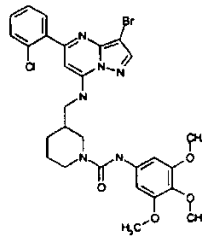
[1485]

생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 7821 2. 575.32		1. 7826 2. 581.32
	1. 7822 2. 575.32		1. 7827 2. 583.32
	1. 7823 2. 575.32		1. 7828 2. 585.32
	1. 7824 2. 577.32		1. 7829 2. 585.32
	1. 7825 2. 577.32		1. 7830 2. 589.32

[1486]

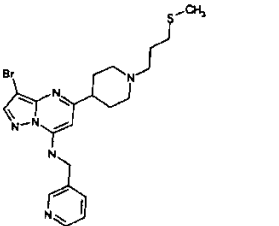
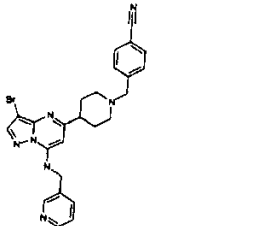
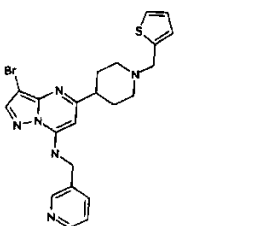
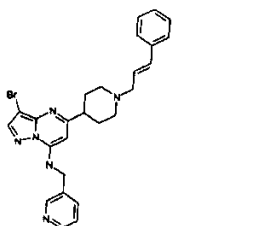
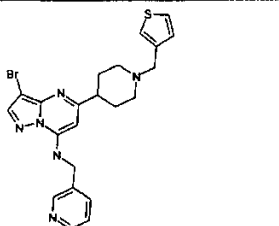
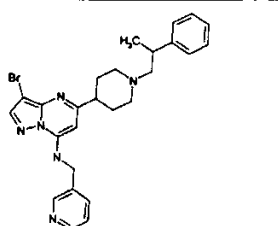
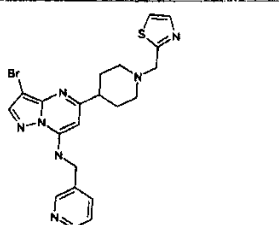
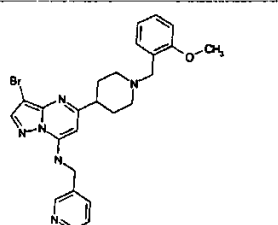
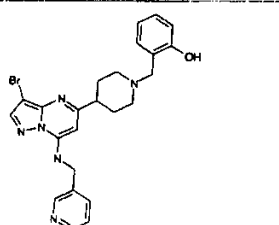
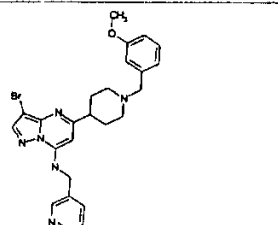
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7831 2. 591.33		1. 7836 2. 609.33
	1. 7832 2. 599.33		1. 7837 2. 609.33
	1. 7833 2. 601.33		1. 7838 2. 609.33
	1. 7834 2. 605.33		1. 7839 2. 609.33
	1. 7835 2. 609.33		1. 7840 2. 617.34

[1487]

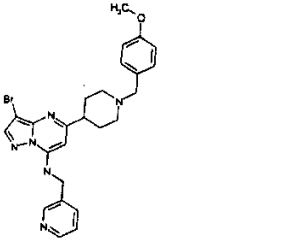
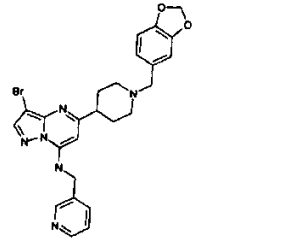
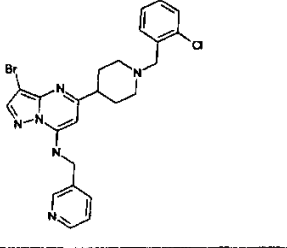
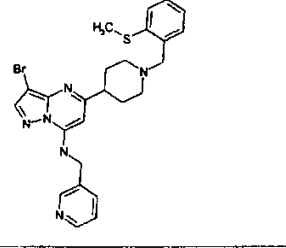
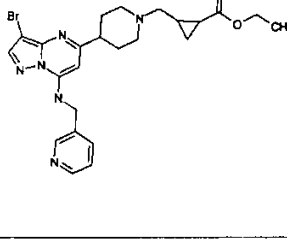
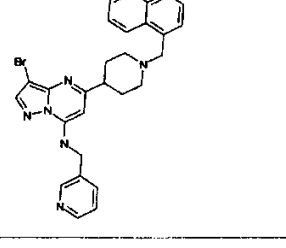
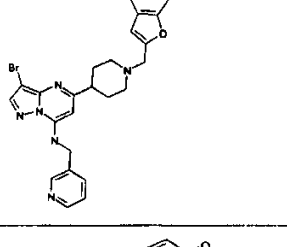
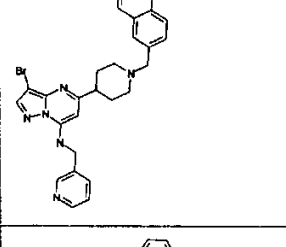
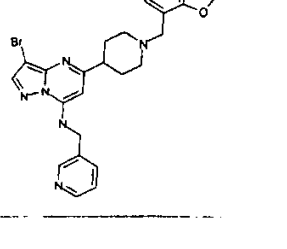
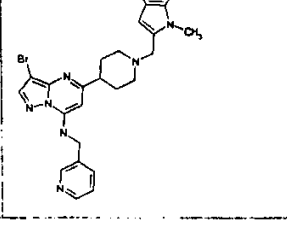
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7841 2. 619.34		1. 7846 2. 631.35
	1. 7842 2. 623.34		1. 7847 2. 643.35
	1. 7843 2. 519.29		
	1. 7844 2. 627.34		
	1. 7845 2. 631.35		

[1488]

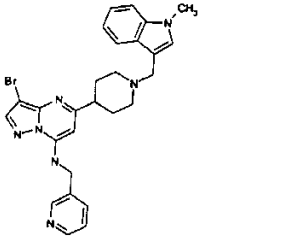
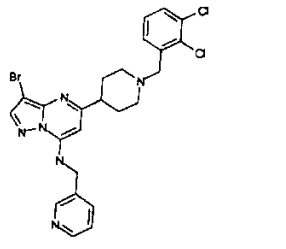
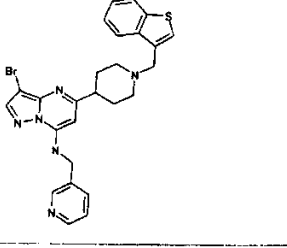
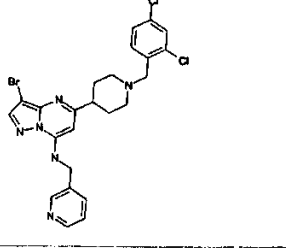
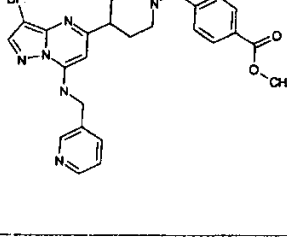
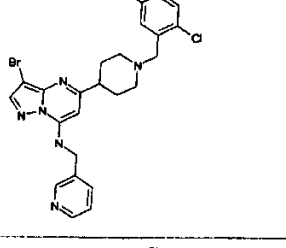
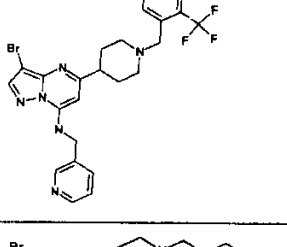
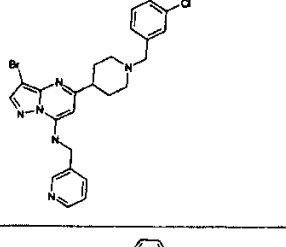
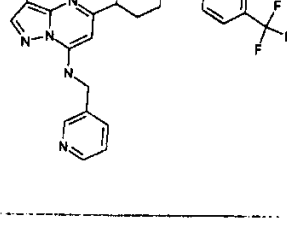
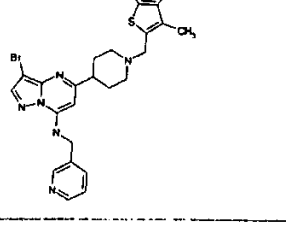
표 79

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7901 2. 477.26		1. 7906 2. 504.28
	1. 7902 2. 485.27		1. 7907 2. 505.28
	1. 7903 2. 485.27		1. 7908 2. 507.28
	1. 7904 2. 486.27		1. 7909 2. 509.28
	1. 7905 2. 495.27		1. 7910 2. 509.28

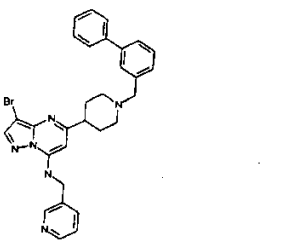
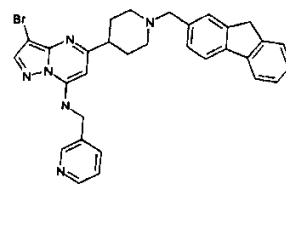
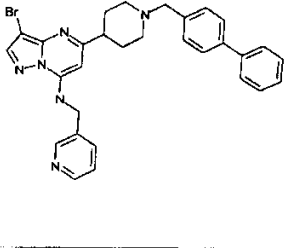
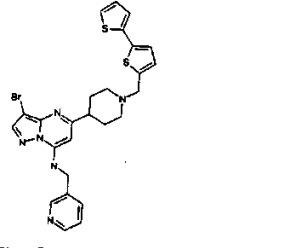
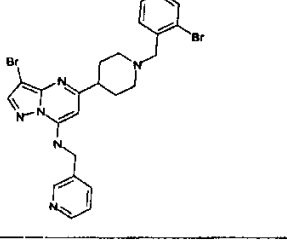
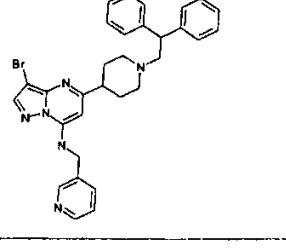
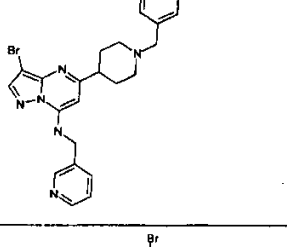
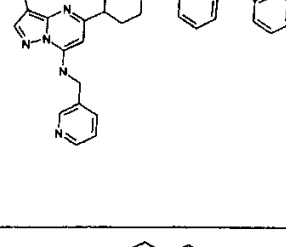
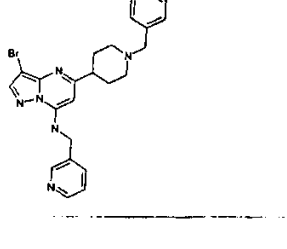
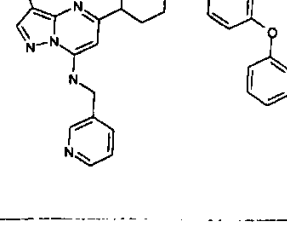
[1489]

생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 7911 2. 509.28		1. 7916 2. 523.29
	1. 7912 2. 513.28		1. 7917 2. 525.29
	1. 7913 2. 515.28		1. 7918 2. 529.29
	1. 7914 2. 519.29		1. 7919 2. 529.29
	1. 7915 2. 523.29		1. 7920 2. 530.29

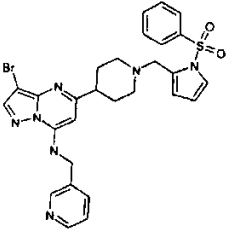
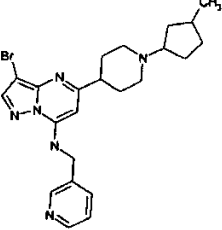
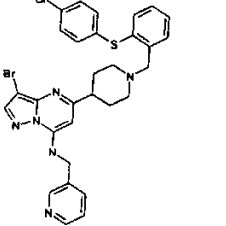
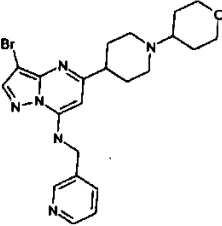
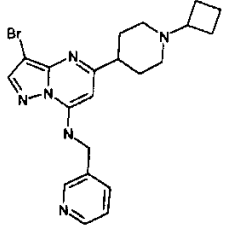
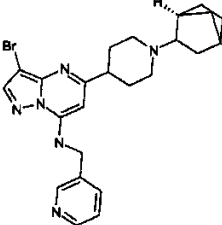
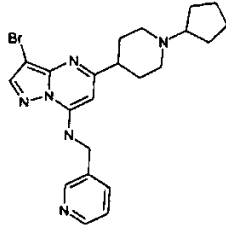
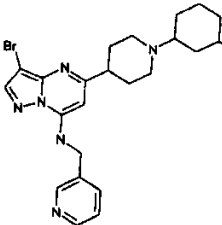
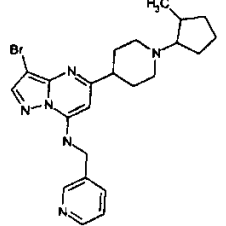
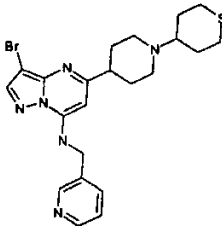
[1490]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 7921 2. 530.29		1. 7926 2. 547.3
	1. 7922 2. 535.29		1. 7927 2. 547.3
	1. 7923 2. 537.3		1. 7928 2. 547.3
	1. 7924 2. 547.3		1. 7929 2. 547.3
	1. 7925 2. 547.3		1. 7930 2. 549.3

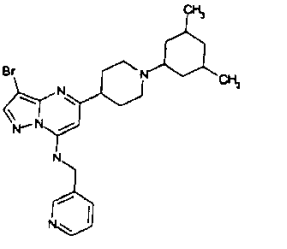
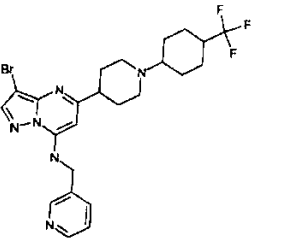
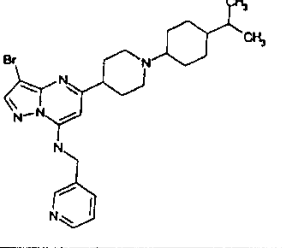
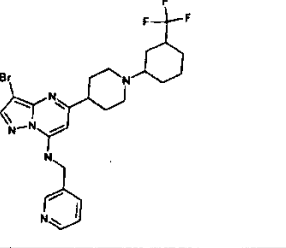
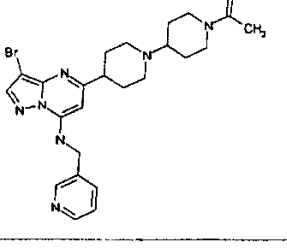
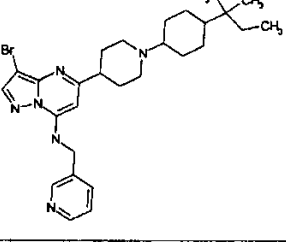
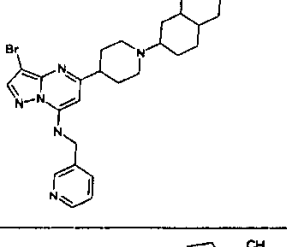
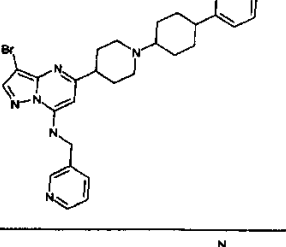
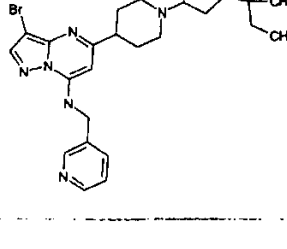
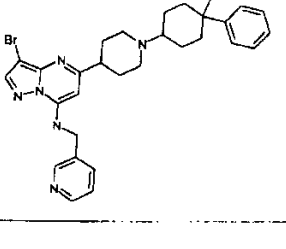
[1491]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 7931 2. 555.31		1. 7936 2. 567.31
	1. 7932 2. 555.31		1. 7937 2. 567.31
	1. 7933 2. 557.31		1. 7938 2. 569.31
	1. 7934 2. 557.31		1. 7939 2. 571.31
	1. 7935 2. 557.31		1. 7940 2. 571.31

[1492]

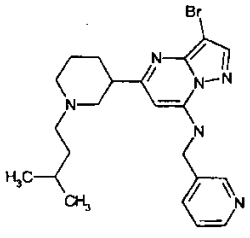
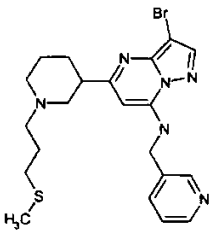
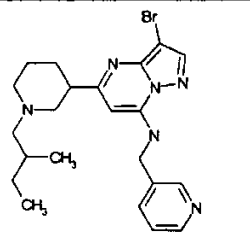
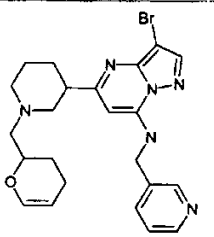
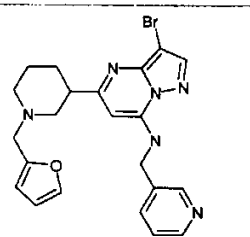
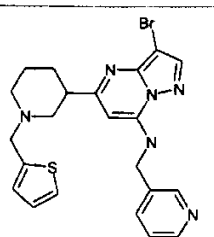
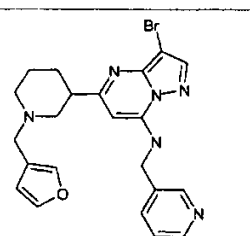
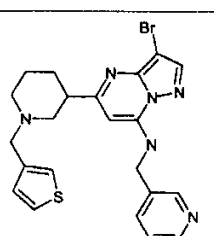
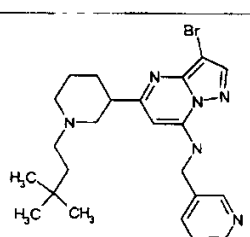
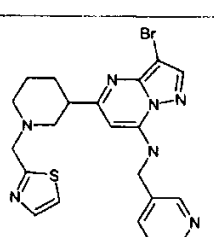
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 7941 2. 608.33		1. 7946 2. 471.26
	1. 7942 2. 621.34		1. 7947 2. 473.26
	1. 7943 2. 443.24		1. 7948 2. 483.27
	1. 7944 2. 457.25		1. 7949 2. 485.27
	1. 7945 2. 471.26		1. 7950 2. 489.27

[1493]

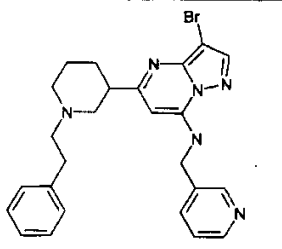
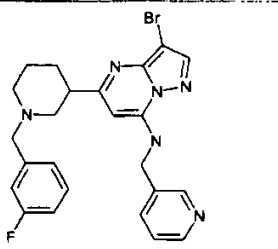
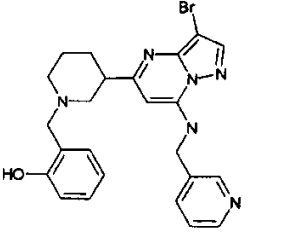
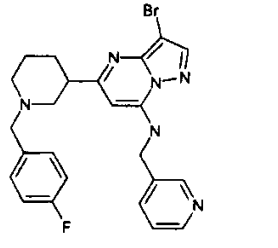
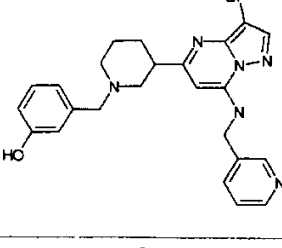
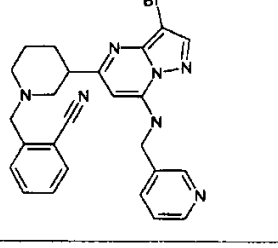
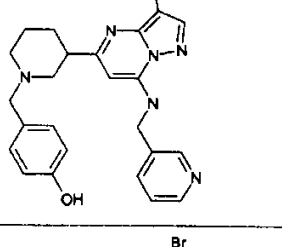
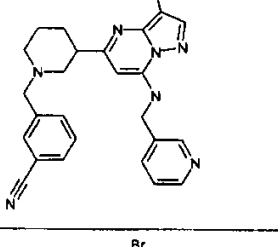
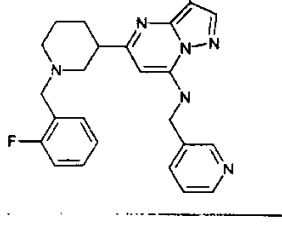
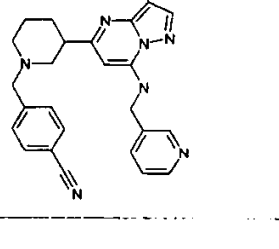
생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 7951 2. 499.27		1. 7956 2. 536.29
	1. 7952 2. 513.28		1. 7957 2. 539.3
	1. 7953 2. 514.28		1. 7958 2. 541.3
	1. 7954 2. 525.29		1. 7959 2. 547.3
	1. 7955 2. 525.29		1. 7960 2. 572.31

[1494]

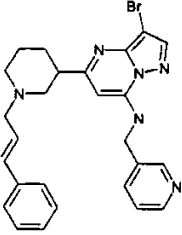
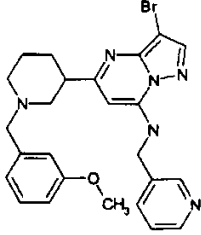
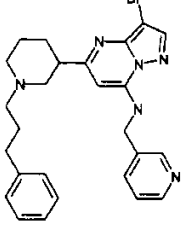
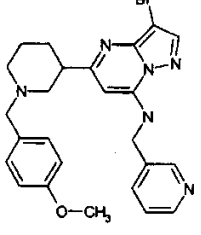
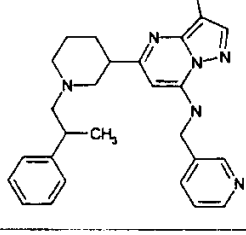
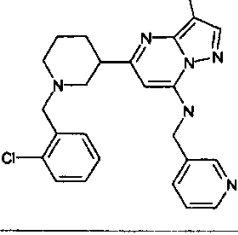
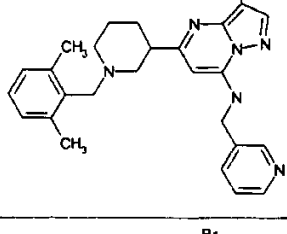
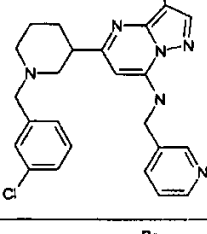
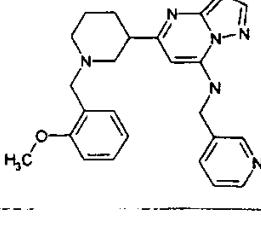
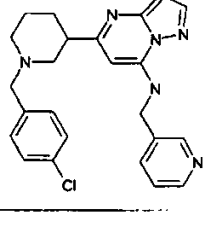
표 80

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8001 2. 459.25		1. 8006 2. 477.26
	1.8002 2. 459.25		1. 8007 2 485.27
	1. 8003 2. 469.26		1. 8008 2. 485.27
	1. 8004 2. 469.26		1. 8009 2. 485.27
	1. 8005 2. 473.26		1. 8010 2. 486.27

[1495]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8011 2. 493.27		1. 8016 2. 495.27
	1. 8012 2. 495.27		1. 8017 2. 495.27
	1. 8013 2. 495.27		1. 8018 2. 502.28
	1. 8014 2. 495.27		1. 8019 2. 502.28
	1. 8015 2. 495.27		1. 8020 2. 502.28

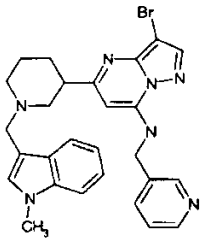
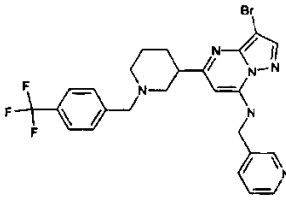
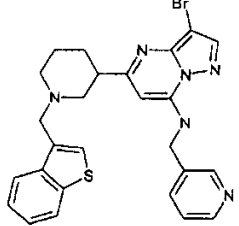
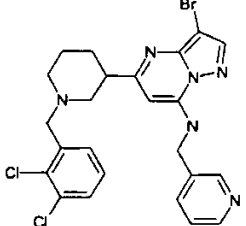
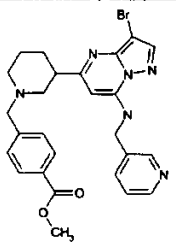
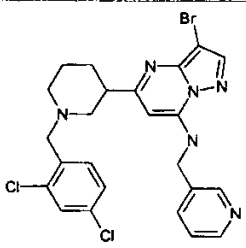
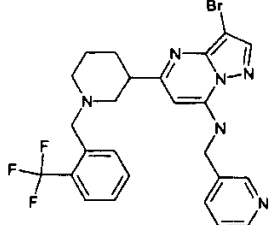
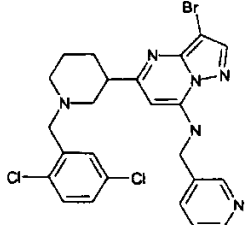
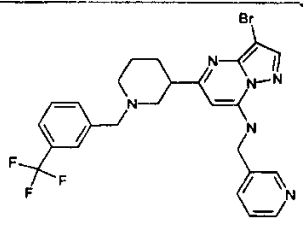
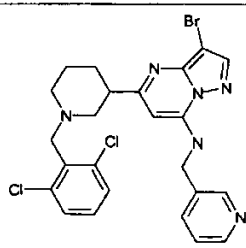
[1496]

생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 8021 2. 505.28		1. 8026 2. 509.28
	1. 8022 2. 505.28		1. 8027 2. 509.28
	1. 8023 2. 507.28		1. 8028 2. 513.28
	1. 8024 2. 507.28		1. 8029 2. 513.28
	1. 8025 2. 507.28		1. 8030 2. 513.28

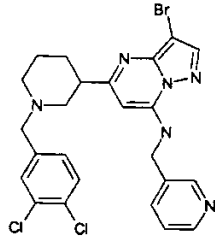
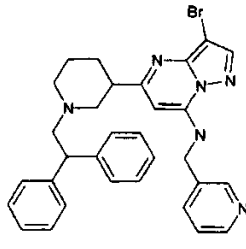
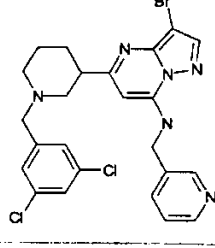
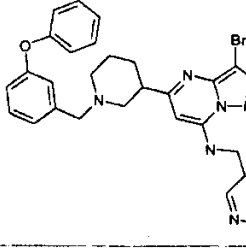
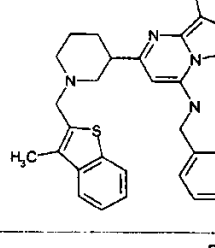
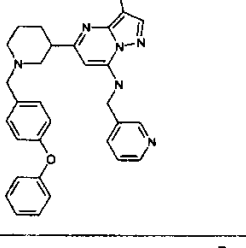
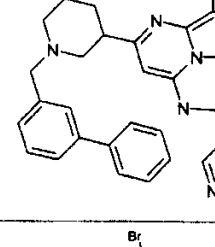
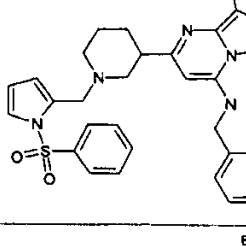
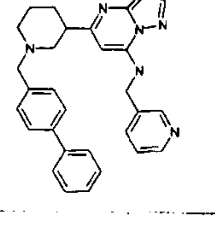
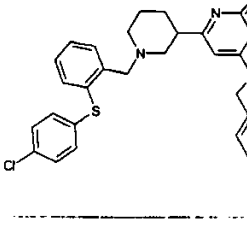
[1497]

생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 8031 2. 515.28		1. 8036 2. 523.29
	1. 8032 2. 519.29		1. 8037 2. 525.29
	1. 8033 2. 521.29		1. 8038 2. 529.29
	1. 8034 2. 523.29		1. 8039 2. 529.29
	1. 8035 2. 523.29		1. 8040 2. 530.29

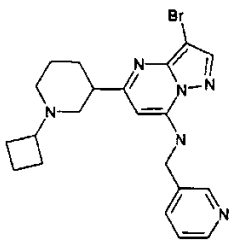
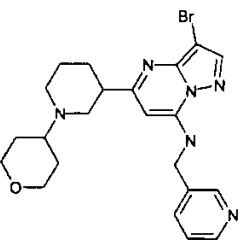
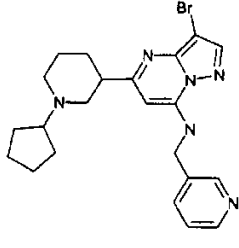
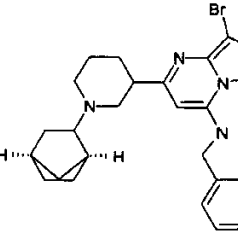
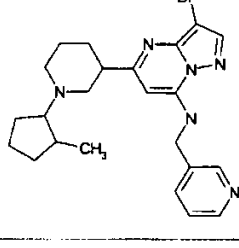
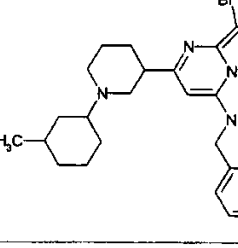
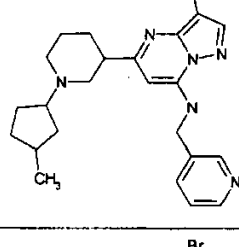
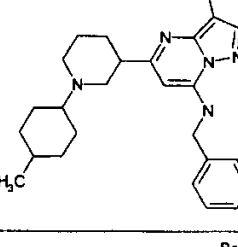
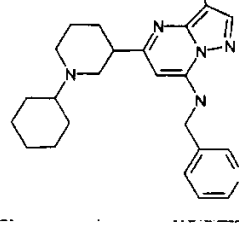
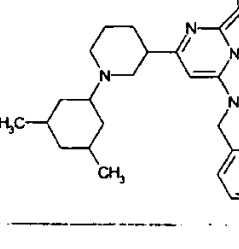
[1498]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 8041 2. 530.29		1. 8046 2. 547.3
	1. 8042 2. 535.29		1. 8047 2. 544.3
	1. 8043 2. 537.3		1. 8048 2. 547.3
	1. 8044 2. 547.3		1. 8049 2. 547.3
	1. 8045 2. 547.3		1. 8050 2. 547.3

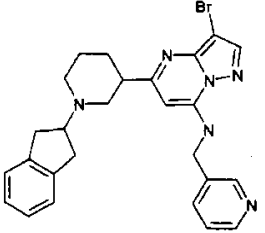
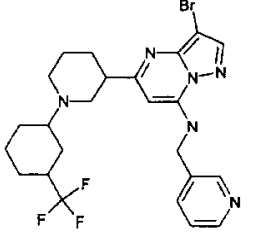
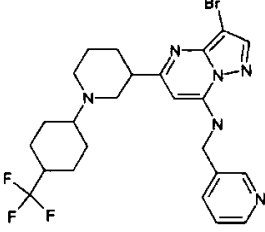
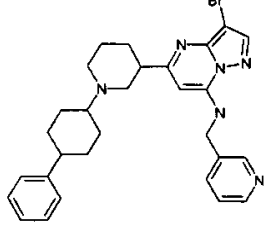
[1499]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8051 2. 548.3		1. 8056 2. 569.31
	1. 8052 2. 548.3		1. 8057 2. 569.31
	1. 8053 2. 547.3		1. 8058 2. 571.31
	1. 8054 2. 555.31		1. 8059 2. 608.33
	1. 8055 2. 553.3		1. 8060 2. 621.34

[1500]

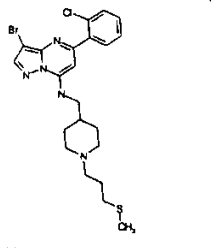
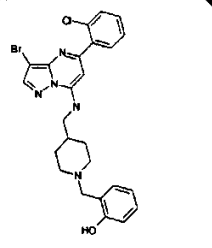
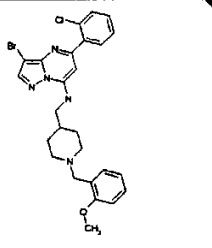
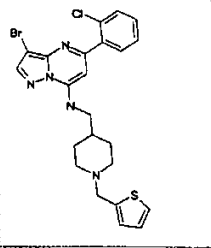
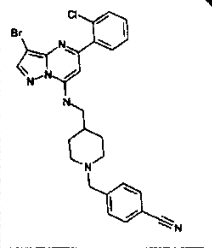
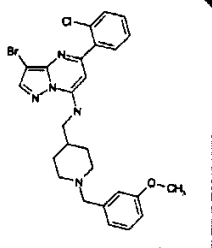
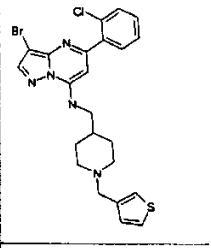
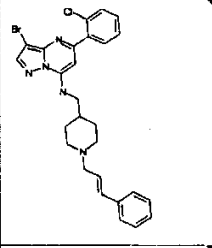
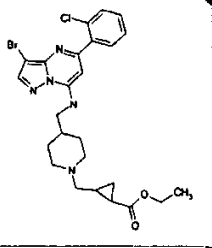
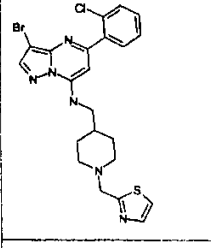
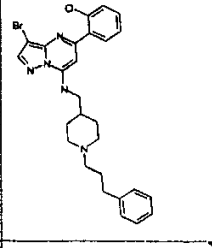
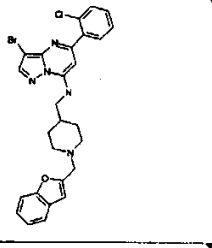
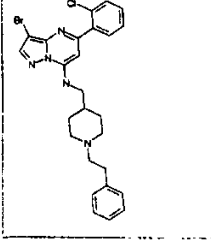
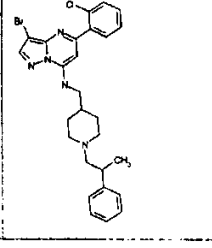
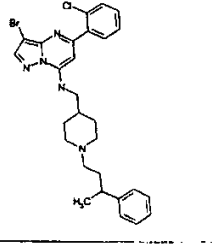
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8061 2. 443.24		1. 8066 2. 473.26
	1. 8062 2. 457.25		1. 8067 2. 483.27
	1. 8063 2. 471.26		1. 8068 2. 485.27
	1. 8064 2. 471.26		1. 8069 2. 483.27
	1. 8065 2. 469.26		1. 8070 2. 499.27

[1501]

생성물	1.실시예 2. m/z
	1. 8071 2. 505.2 8
	1. 8072 2. 537.3
	1. 8073 2. 537.3
	1. 8074 2. 547.3

[1502]

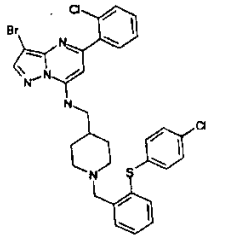
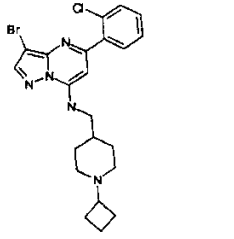
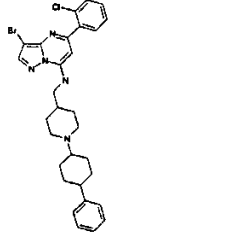
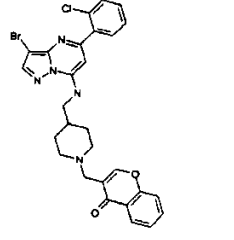
표 81

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8101 2. 510.28		1. 8106 2. 528.29		1. 8111 2. 542.3
	1. 8102 2. 518.28		1. 8107 2. 537.3		1. 8112 2. 542.3
	1. 8103 2. 518.28		1. 8108 2. 538.3		1. 8113 2. 548.3
	1. 8104 2. 519.29		1. 8109 2. 540.3		1. 8114 2. 552.3
	1. 8105 2. 526.29		1. 8110 2. 540.3		1. 8115 2. 554.3

[1503]

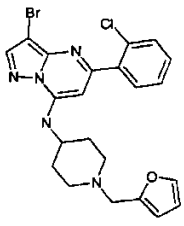
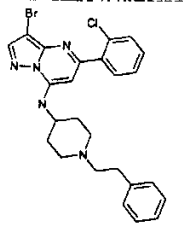
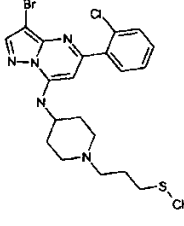
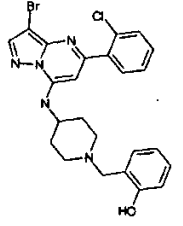
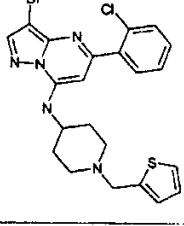
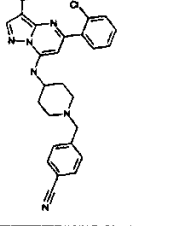
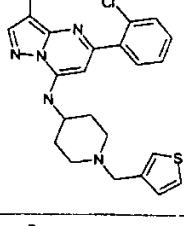
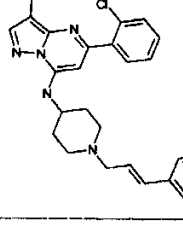
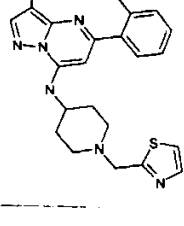
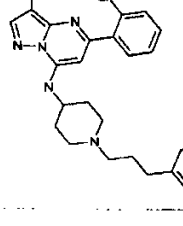
생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8116 2. 556.31		1. 8121 2. 580.32		1. 8126 2. 588.32
	1. 8117 2. 558.31		1. 8122 2. 580.32		1. 8127 2. 590.32
	1. 8118 2. 562.31		1. 8123 2. 580.32		1. 8128 2. 590.32
	1. 8119 2. 580.32		1. 8125 2. 580.32		1. 8129 2. 604.33
	1. 8120 2. 580.32		1. 8126 2. 588.32		1. 8130 2. 612.34

[1504]

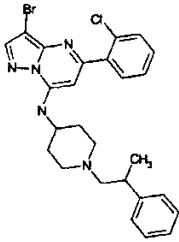
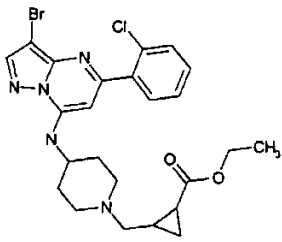
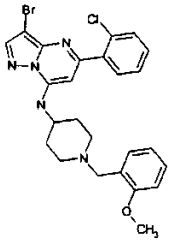
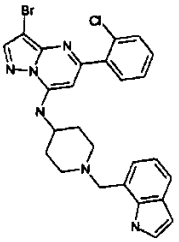
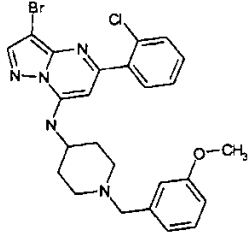
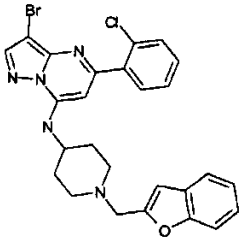
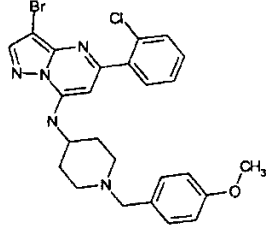
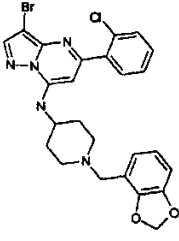
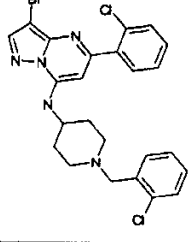
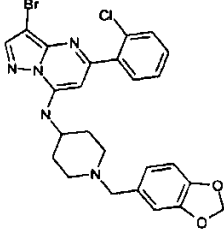
생성물	1.실시예 2.m/z
	<p>1. 8131 2. 654.36</p>
	<p>1. 8132 2. 476.26</p>
	<p>1. 8133 2. 580.32</p>
	<p>1. 8134 2. 580.32</p>

[1505]

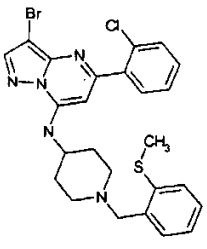
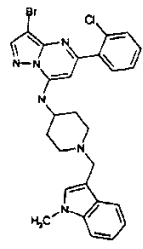
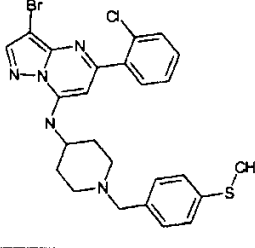
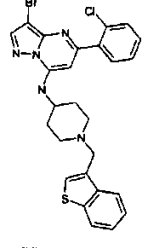
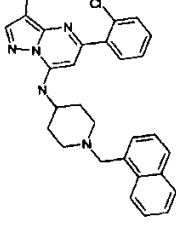
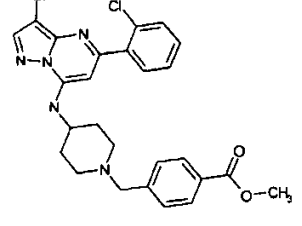
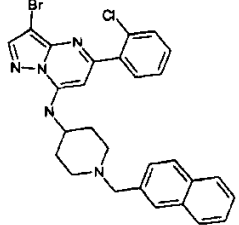
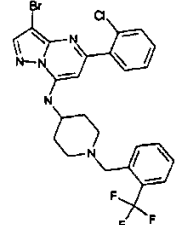
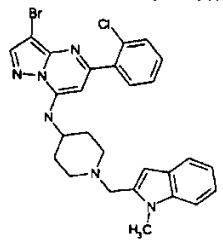
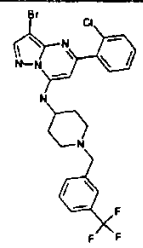
표 82

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8201 2. 488.27		1. 8206 2. 512.28
	1. 8202 2. 496.27		1. 8207 2. 514.28
	1. 8203 2. 504.28		1. 8208 2. 523.29
	1. 8204 2. 504.28		1. 8209 2. 524.29
	1. 8205 2. 505.28		1. 8210 2. 526.29

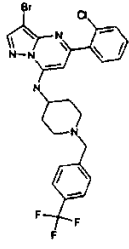
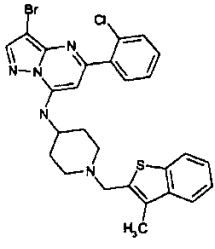
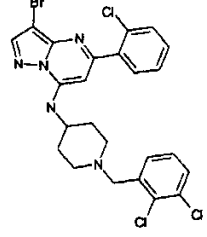
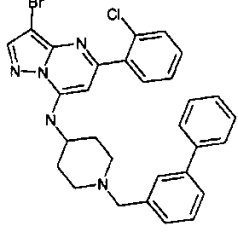
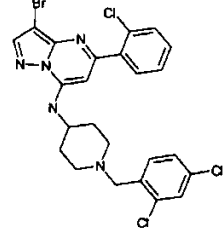
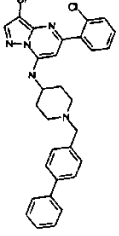
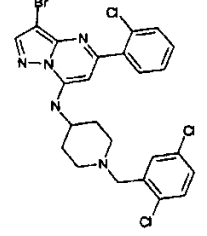
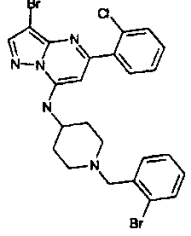
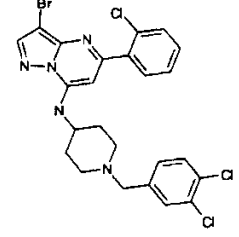
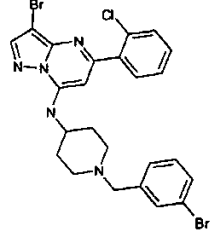
[1506]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8211 2. 526.29		1. 8216 2. 534.29
	1. 8212 2. 528.29		1. 8217 2. 537.3
	1. 8213 2. 528.29		1. 8218 2. 538.3
	1. 8214 2. 528.29		1. 8219 2. 542.3
	1. 8215 2. 532.29		1. 8220 2. 542.3

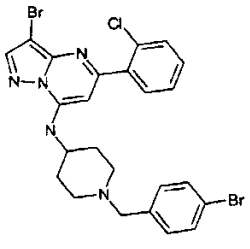
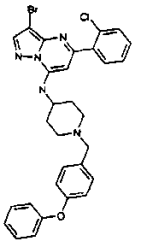
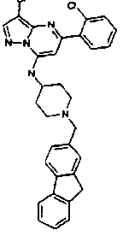
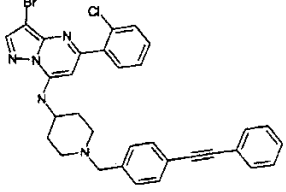
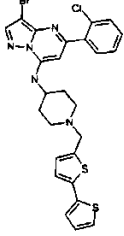
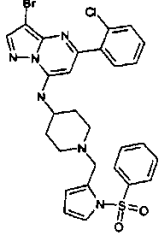
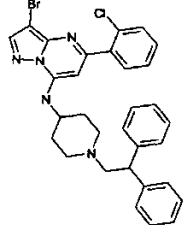
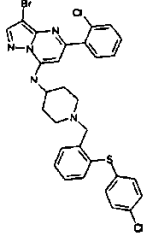
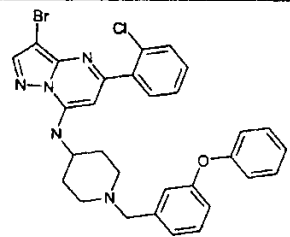
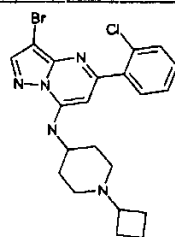
[1507]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8221 2. 544.3		1. 8226 2. 551.3
	1. 8222 2. 544.3		1. 8227 2. 554.3
	1. 8223 2. 548.3		1. 8228 2. 556.31
	1. 8224 2. 548.3		1. 8229 2. 566.31
	1. 8225 2. 551.3		1. 8230 2. 566.31

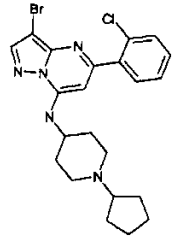
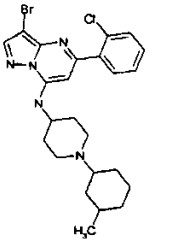
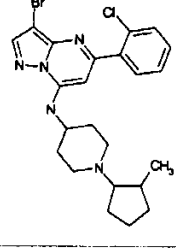
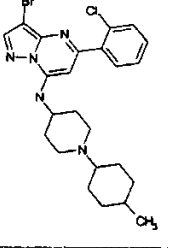
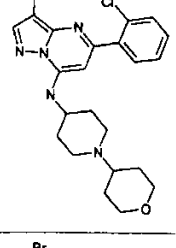
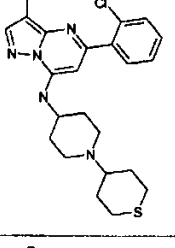
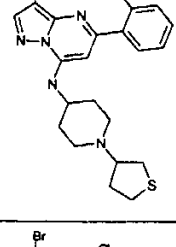
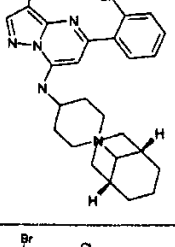
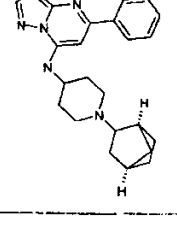
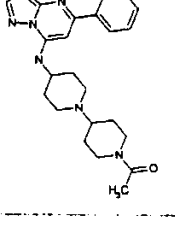
[1508]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8231 2. 566.31		1. 8236 2. 568.31
	1. 8232 2. 566.31		1. 8237 2. 574.32
	1. 8233 2. 566.31		1. 8238 2. 574.32
	1. 8243 2. 566.31		1. 8239 2. 576.32
	1. 8235 2. 566.31		1. 8240 2. 576.32

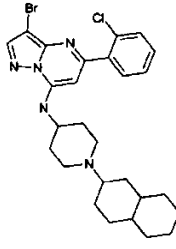
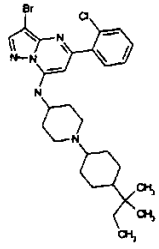
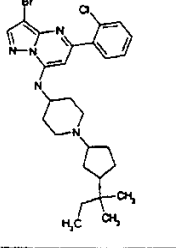
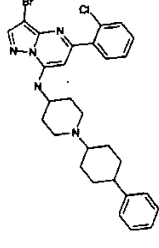
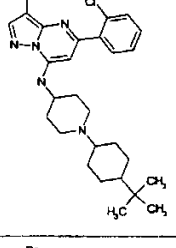
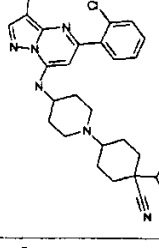
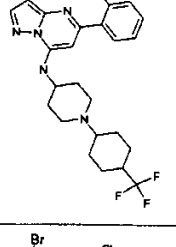
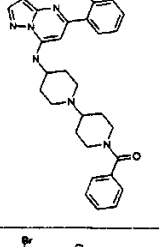
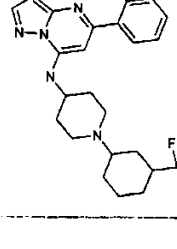
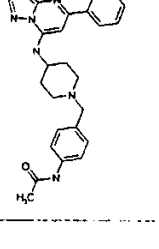
[1509]

생성물	1.실시예 2.m/z	생성물	1.실시예 2.m/z
	1. 8241 2. 576.32		1. 8246 2. 590.32
	1. 8242 2. 586.32		1. 8247 2. 598.33
	1. 8243 2. 586.32		1. 8248 2. 627.34
	1. 8244 2. 588.32		1. 8249 2. 640.35
	1. 8245 2. 590.32		1. 8250 2. 462.25

[1510]

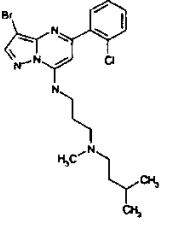
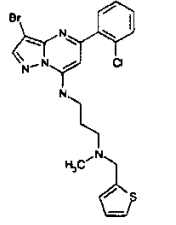
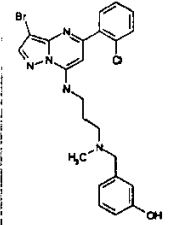
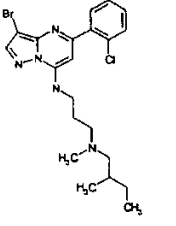
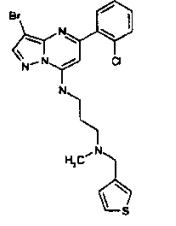
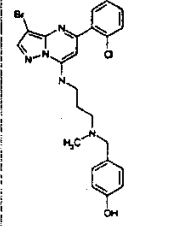
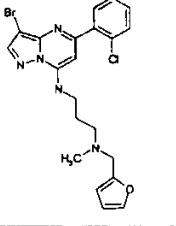
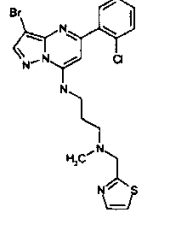
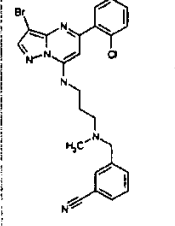
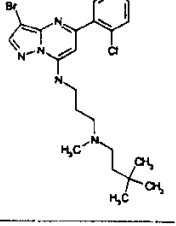
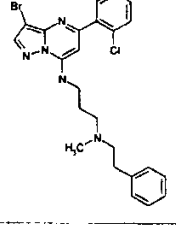
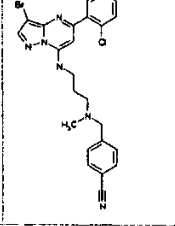
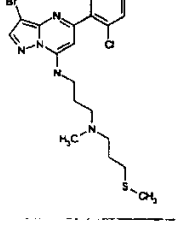
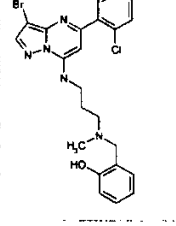
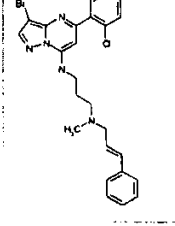
생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 8251 2. 476.26		1. 8256 2. 504.28
	1. 8252 2. 490.27		1. 8257 2. 504.28
	1. 8253 2. 492.27		1. 8258 2. 508.28
	1. 8254 2. 492.27		1. 8259 2. 530.29
	1. 8255 2. 502.28		1. 8260 2. 533.29

[1511]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8261 2. 544.3		1. 8266 2. 560.31
	1. 8262 2. 546.3		1. 8267 2. 566.31
	1. 8263 2. 546.3		1. 8268 2. 591.33
	1. 8264 2. 558.31		1. 8269 2. 595.33
	1. 8265 2. 558.31		1. 8270 2. 555.31

[1512]

표 83

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8301 2. 465.882		1. 8306 2. 491.79		1. 8311 2. 501.825
	1. 8302 2. 465.885		1. 8307 2. 491.792		1. 8312 2. 501.833
	1. 8303 2. 475.827		1. 8308 2. 492.787		1. 8313 2. 510.822
	1. 8304 2. 479.89		1. 8309 2. 499.846		1. 8314 2. 510.821
	1. 8305 2. 483.829		1. 8310 2. 501.826		1. 8315 2. 511.841

[1513]

생성물	1.실시예. 2. m/z	생성물	1.실시예. 2. m/z	생성물	1.실시예 2. m/z
	1. 8316 2. 513.855		1. 8321 2. 519.783		1. 8326 2. 531.804
	1. 8317 2. 515.832		1. 8322 2. 519.781		1. 8327 2. 531.812
	1. 8318 2. 515.832		1. 8323 2. 525.813		1. 8328 2. 535.83
	1. 8319 2. 515.837		1. 8324 2. 529.806		1. 8329 2. 535.831
	1. 8320 2. 519.782		1. 8325 2. 529.81		1. 8330 2. 541.788

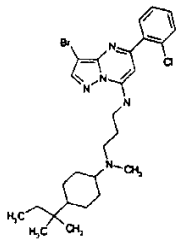
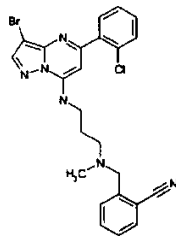
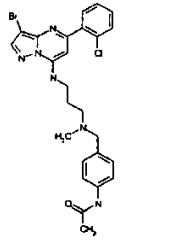
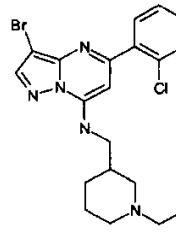
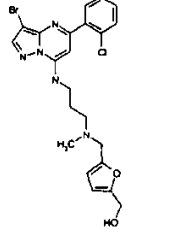
[1514]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8331 2. 543.821		1. 8336 2. 554.727		1. 8341 2. 561.838
	1. 8332 2. 553.797		1. 8337 2. 554.738		1. 8342 2. 564.714
	1. 8333 2. 553.796		1. 8338 2. 554.738		1. 8343 2. 564.704
	1. 8334 2. 553.795		1. 8339 2. 554.727		1. 8344 2. 564.72
	1. 8335 2. 554.73		1. 8340 2. 561.836		1. 8345 2. 573.823

[1515]

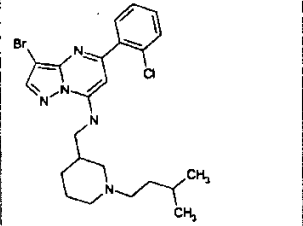
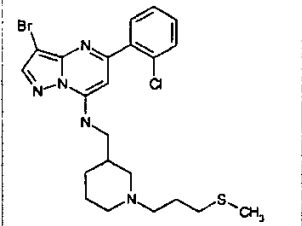
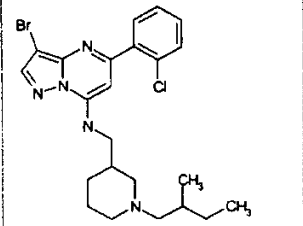
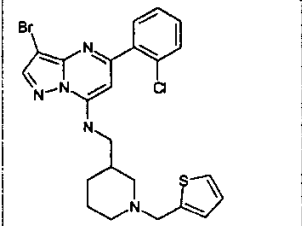
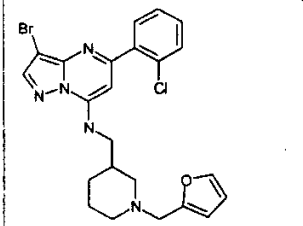
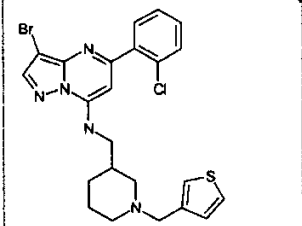
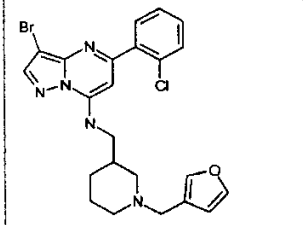
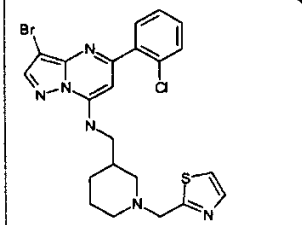
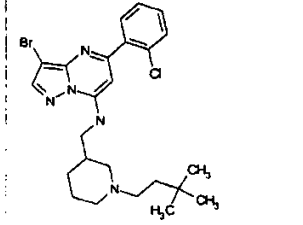
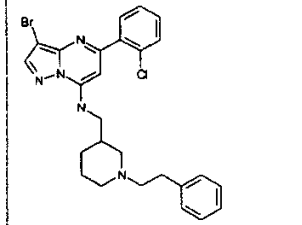
생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8346 2. 573.735		1. 8351 2. 529.808		1. 8356 2. 479.856
	1. 8347 2. 575.839		1. 8352 2. 614.763		1. 8357 2. 511.842
	1. 8348 2. 577.818		1. 8353 2. 628.727		1. 8358 2. 520.859
	1. 8349 2. 577.814		1. 8354 2. 449.857		1. 8359 2. 533.903
	1. 9350 2. 585.818		1. 8355 2. 463.867		1. 8360 2. 545.823

[1516]

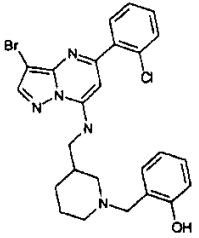
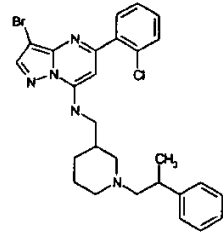
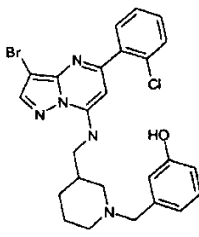
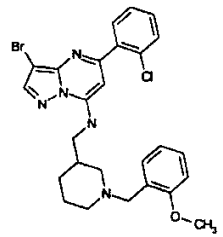
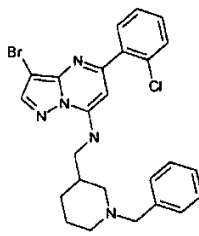
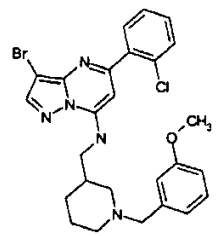
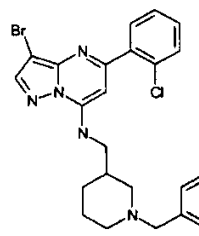
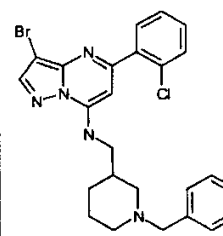
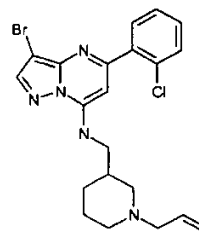
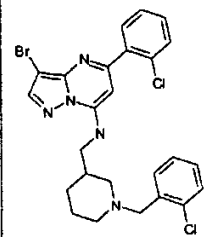
생성물	1.실시에 2. m/z
	<p>1. 8361 2. 547.909</p>
	<p>1. 8362 2. 510.817</p>
	<p>1. 8363 2. 542.833</p>
	<p>1. 8364 2. 573.815</p>
	<p>1. 8365 2. 547.798</p>

[1517]

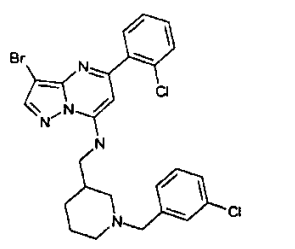
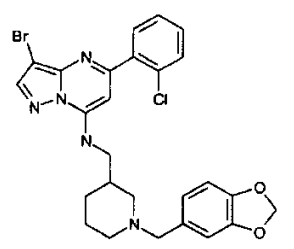
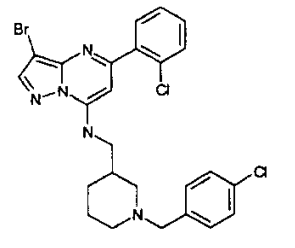
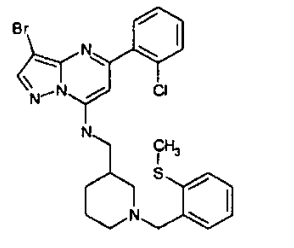
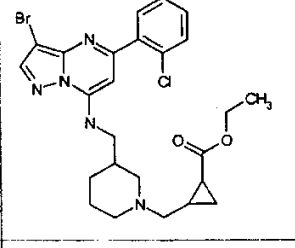
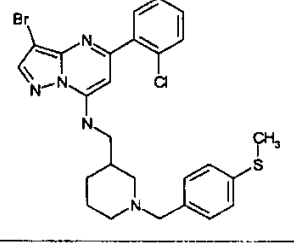
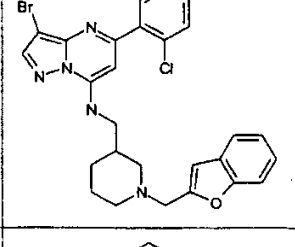
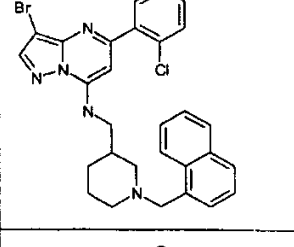
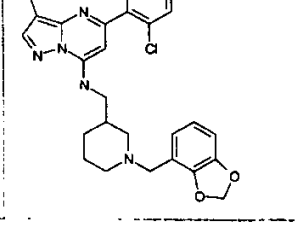
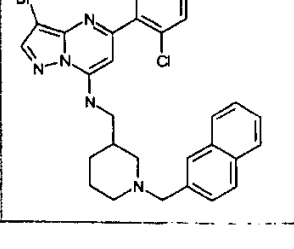
표 84

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8401 2. 491.883		1. 8406 2. 509.829
	1. 8402 2. 491.883		1. 8407 2. 517.795
	1. 8403 2. 501.823		1. 8408 2. 517.799
	1. 8404 2. 501.827		1. 8409 2. 518.796
	1. 8405 2. 505.89		1. 8410 2. 525.851

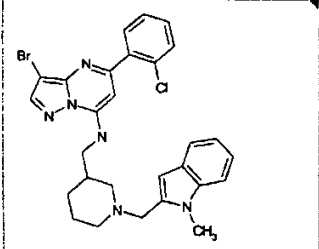
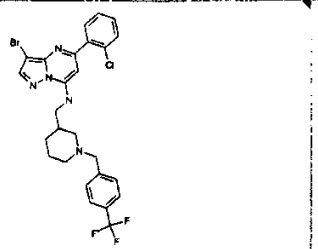
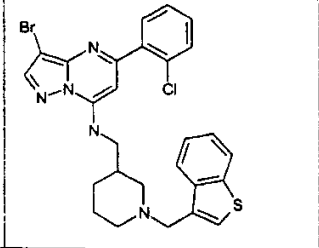
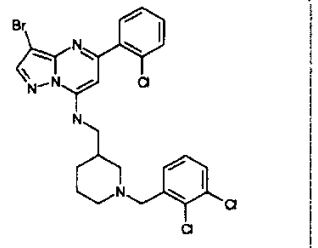
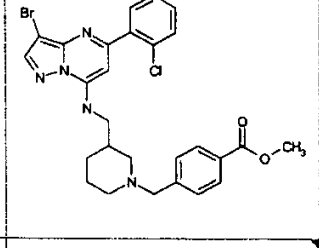
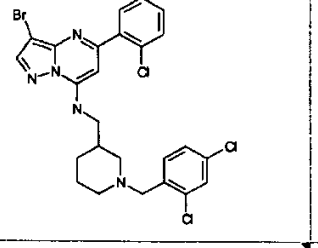
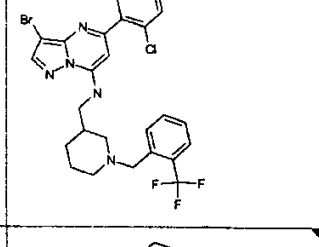
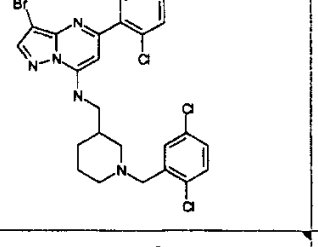
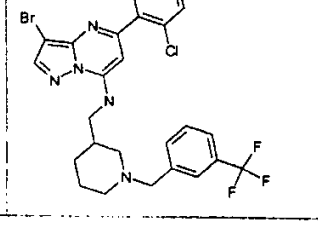
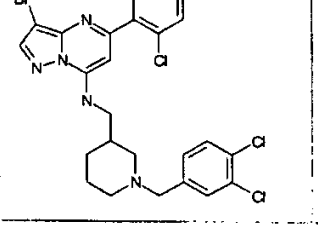
[1518]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8411 2. 527.831		1. 8416 2. 539.859
	1. 8412 2. 527.833		1. 8417 2. 541.84
	1. 8413 2. 536.833		1. 8418 2. 541.843
	1. 8414 2. 536.829		1. 8419 2. 541.843
	1. 8415 2. 537.845		1. 8420 2. 546.786

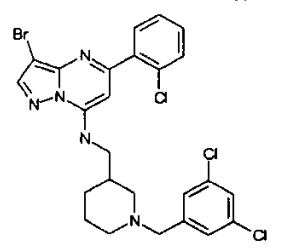
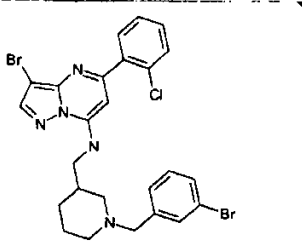
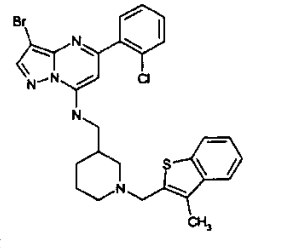
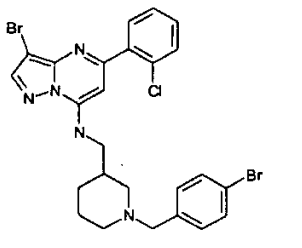
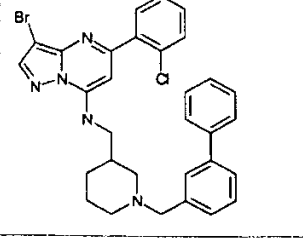
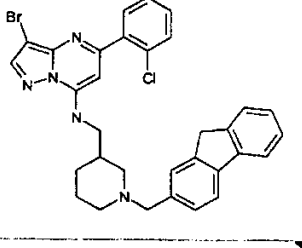
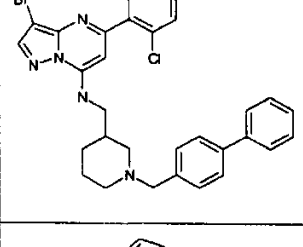
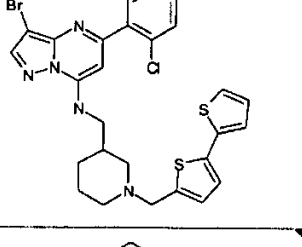
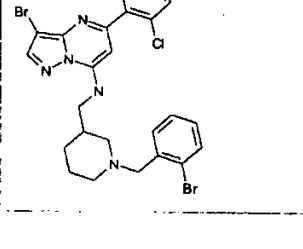
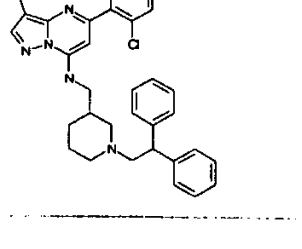
[1519]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8421 2. 546.792		1. 8426 2. 555.817
	1. 8422 2. 546.79		1. 8427 2. 557.81
	1. 8423 2. 547.854		1. 8428 2. 557.813
	1. 8424 2. 551.826		1. 8429 2. 561.839
	1. 8425 2. 555.819		1. 8430 2. 561.833

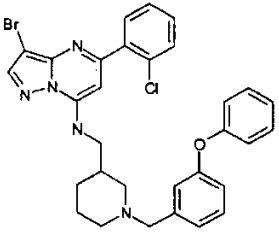
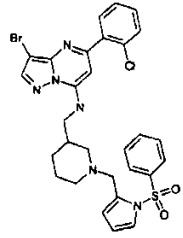
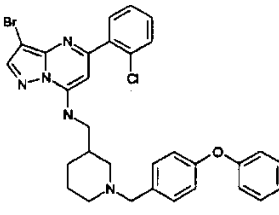
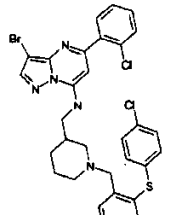
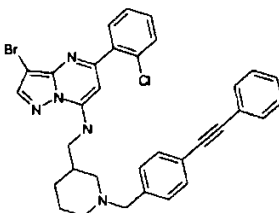
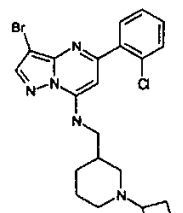
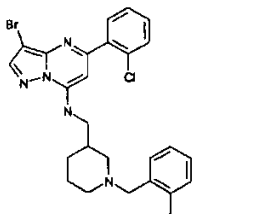
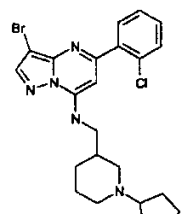
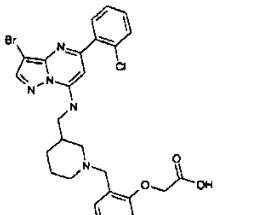
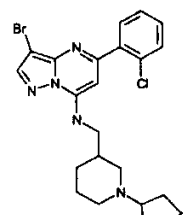
[1520]

생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 8431 2. 564.841		1. 8436 2. 579.794
	1. 8432 2. 567.795		1. 8437 2. 580.738
	1. 8433 2. 569.823		1. 8438 2. 580.732
	1. 8434 2. 579.797		1. 8439 2. 580.733
	1. 8435 2. 579.796		1. 8440 2. 580.734

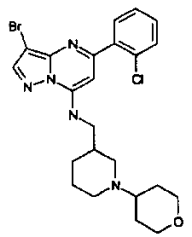
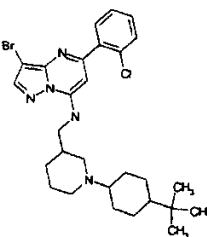
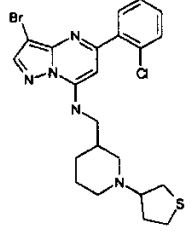
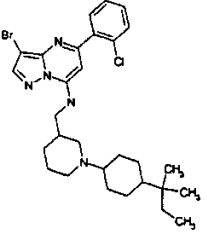
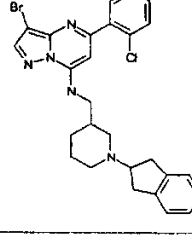
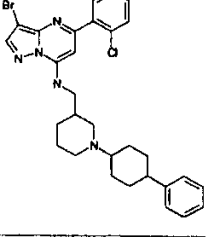
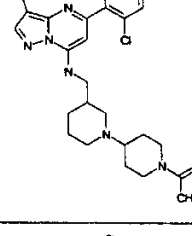
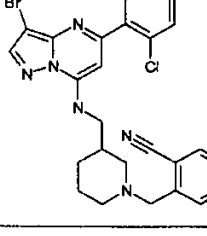
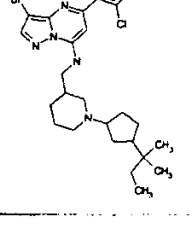
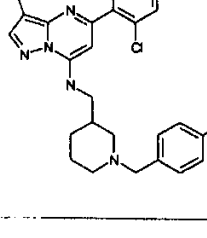
[1521]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8441 2. 580.726		1. 8446 2. 590.726
	1. 8442 2. 581.805		1. 8447 2. 590.724
	1. 8443 2. 587.844		1. 8448 2. 599.834
	1. 8444 2. 587.835		1. 8449 2. 599.749
	1. 8445 2. 590.723		1. 8450 2. 601.854

[1522]

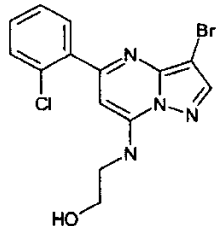
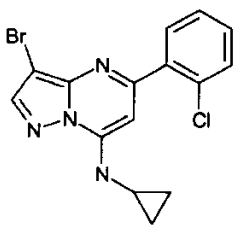
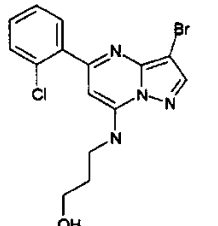
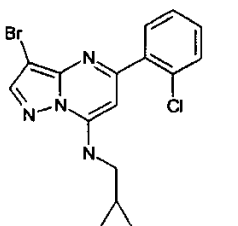
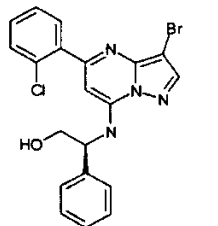
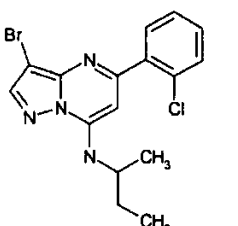
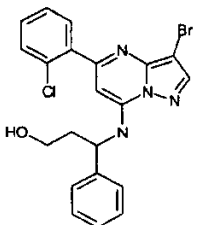
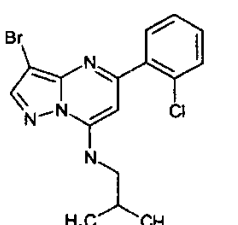
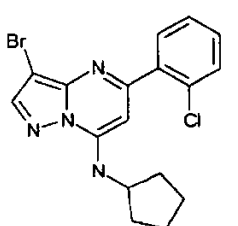
생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 8451 2. 603.831		1. 8456 2. 640.779
	1. 8452 2. 603.83		1. 8457 2. 654.746
	1. 8453 2. 611.83		1. 8458 2. 475.871
	1. 8454 2. 555.824		1. 8459 2. 489.879
	1. 8455 2. 585.817		1. 8460 2. 503.885

[1523]

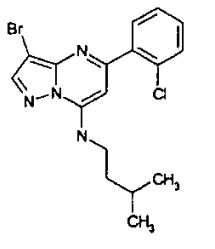
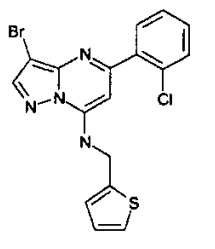
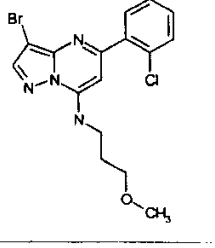
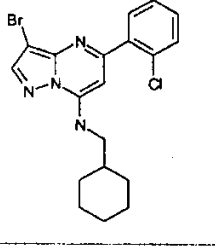
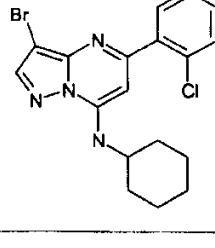
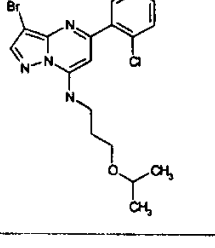
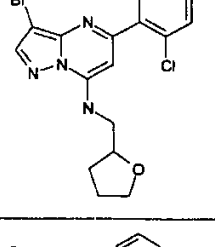
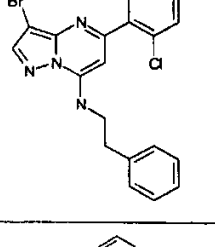
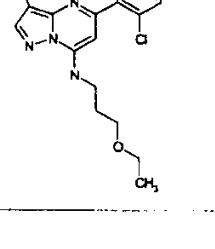
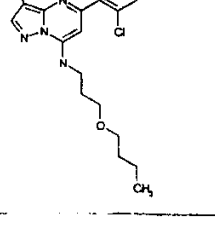
생성물	1.실시에 2.m/z	생성물	1.실시에 2.m/z
	1. 8461 2. 505.866		1. 8466 2. 559.919
	1. 8462 2. 507.828		1. 8467 2. 573.925
	1. 8463 2. 537.859		1. 8468 2. 579.876
	1. 8464 2. 546.877		1. 8469 2. 536.831
	1. 8465 2. 559.921		1. 8470 2. 568.843

[1524]

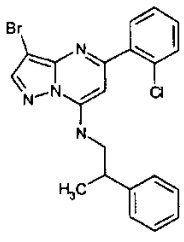
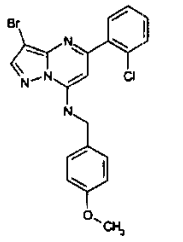
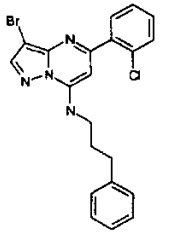
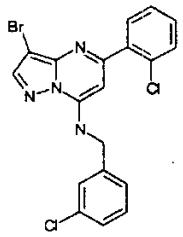
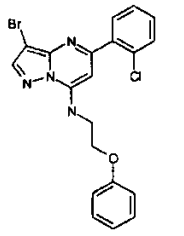
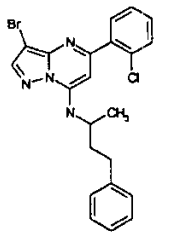
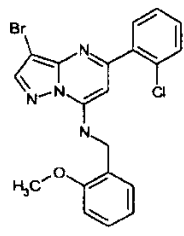
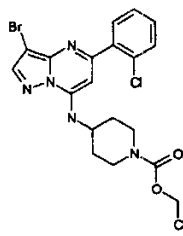
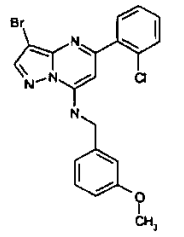
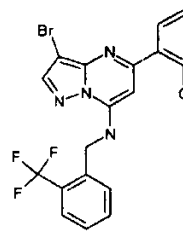
표 85

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8501 2. 367.2		1. 8506 2. 443.1
	1. 8502 2. 381.2		1. 8507 2. 323.1
	1. 8503 2. 443.2		1. 8508 2. 365.2
	1. 8504 2. 457.3		1. 8509 2. 379.21
			1. 8510 2. 381.21

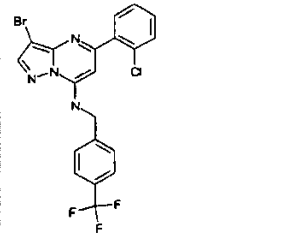
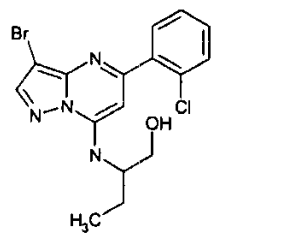
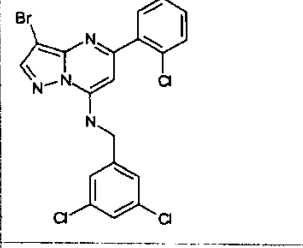
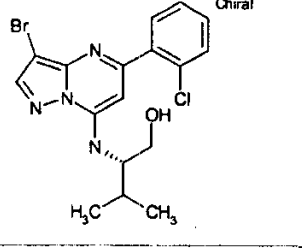
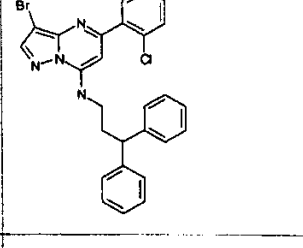
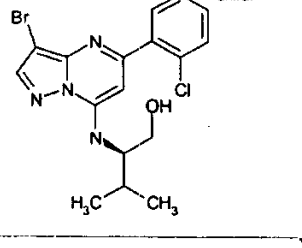
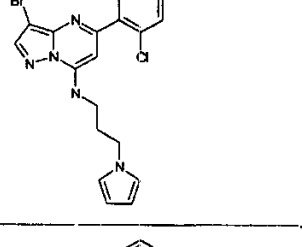
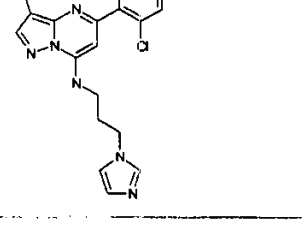
[1525]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8511 2. 381.21		1. 8516 2. 409.22
	1. 8512 2. 393.22		1. 8517 2. 411.23
	1. 8513 2. 395.22		1. 8518 2. 421.23
	1. 8514 2. 397.22		1. 8519 2. 421.23
	1. 8515 2. 407.22		1. 8520 2. 425.23

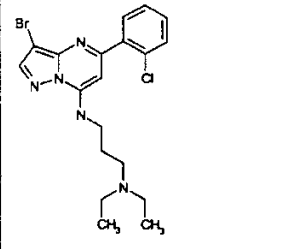
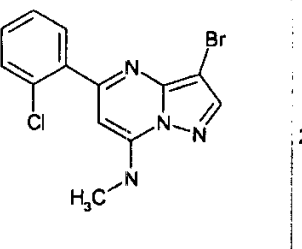
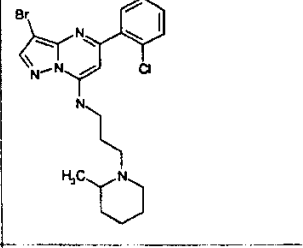
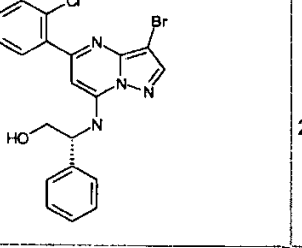
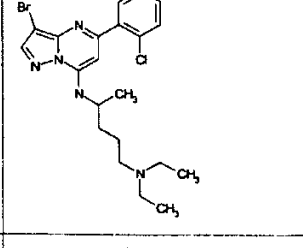
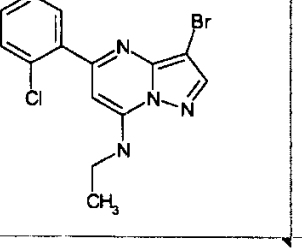
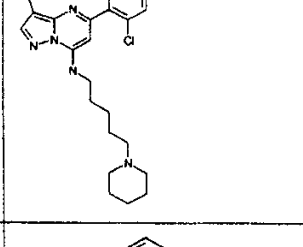
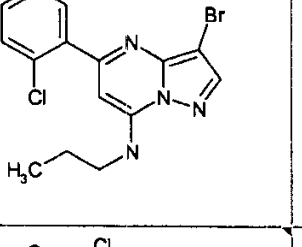
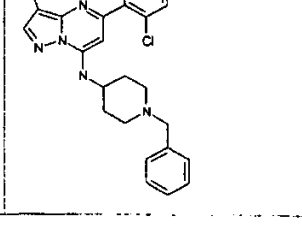
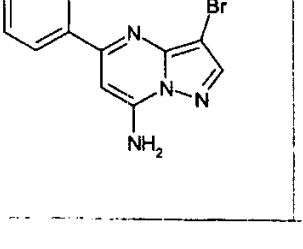
[1526]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8521 2. 429.24		1. 8526 2. 445.24
	1. 8522 2. 439.24		1. 8527 2 .444.24
	1. 8523 2. 443.24		1. 8528 2. 444.24
	1. 8524 2. 443.24		1. 8529 2. 446.25
	1. 8525 2. 445.24		1. 8530 2. 457.25

[1527]

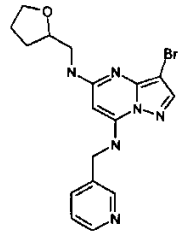
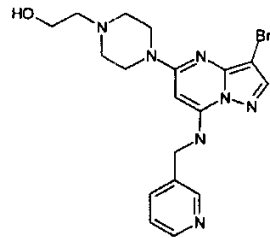
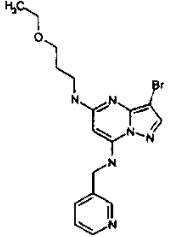
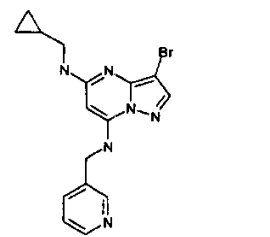
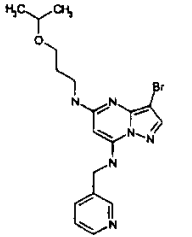
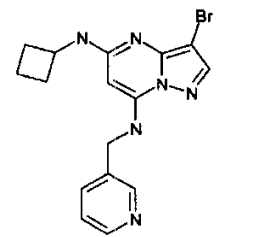
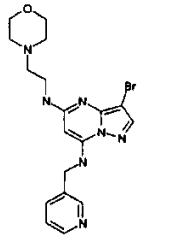
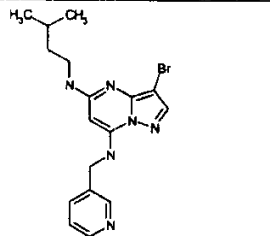
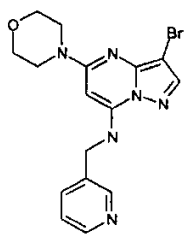
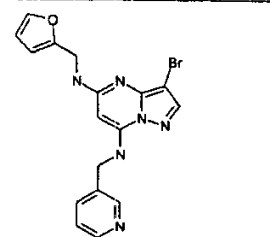
생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8531 2. 480.26		1. 8536 2. 431.24
	1. 8532 2. 483.27		1. 8537 2. 429.24
	1. 8533 2. 483.27		1. 8538 2. 397.22
			1. 8539 2. 411.23
			1. 8540 2. 411.23

[1528]

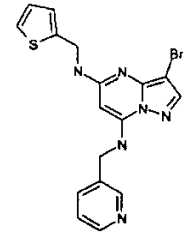
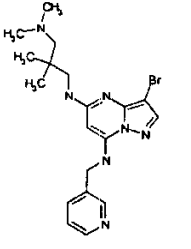
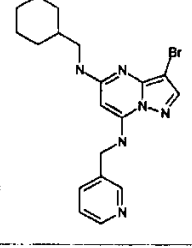
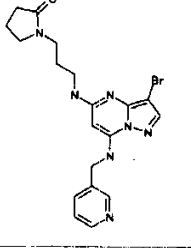
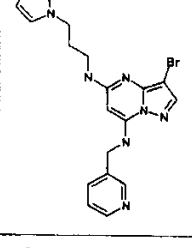
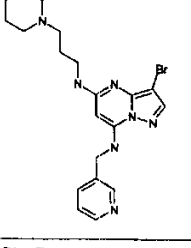
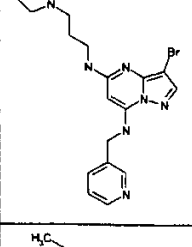
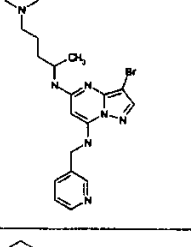
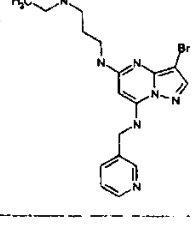
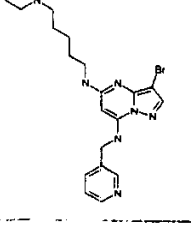
생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8541 2. 432.24		1. 8547 2. 478.26
	1. 8542 2. 433.24		1. 8548 2. 498.27
	1. 8543 2. 438.24		1. 8549 2. 365.1
	1. 8545 2. 464.26		1. 8549 2. 337.1
	1. 8546 2. 466.26		1. 8550 2. 351.1

[1529]

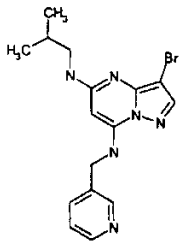
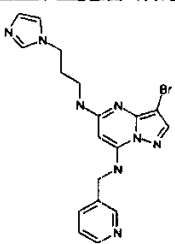
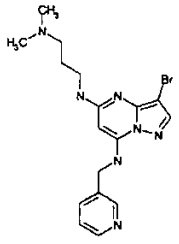
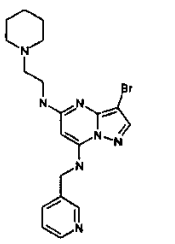
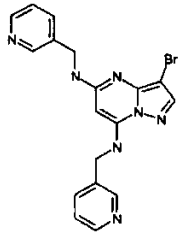
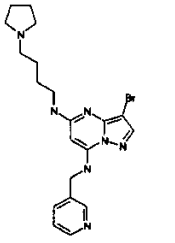
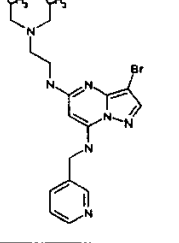
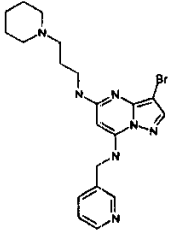
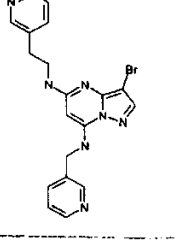
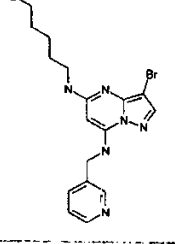
표 86

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8601 2. 403.22		1. 8606 2. 434.24
	1. 8602 2. 407.22		1. 8607 2. 375.21
	1. 8603 2. 421.23		1. 8608 2. 375.21
	1. 8604 2. 434.24		1. 8609 2. 391.22
	1. 8605 2. 391.22		1. 8610 2. 399.22

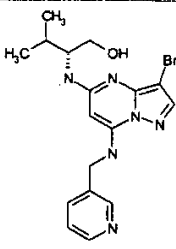
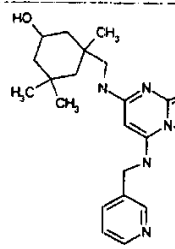
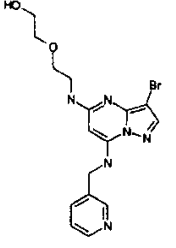
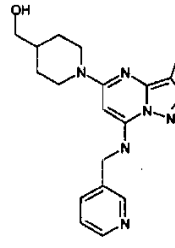
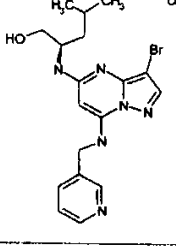
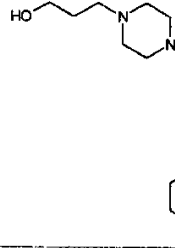
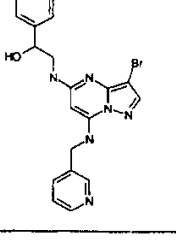
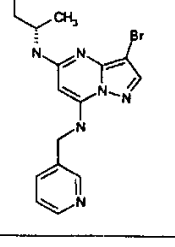
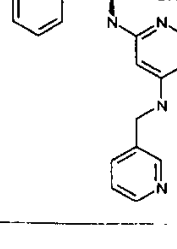
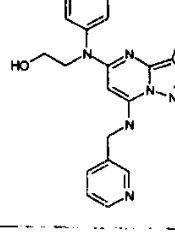
[1530]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8611 2. 417.23		1. 8616 2. 434.24
	1. 8612 2. 415.23		1. 8617 2. 446.25
	1. 8613 2. 428.24		1. 8618 2. 460.25
	1. 8614 2. 430.24		1. 8619 2. 459.25
	1. 8615 2. 434.24		1. 8620 2. 474.26

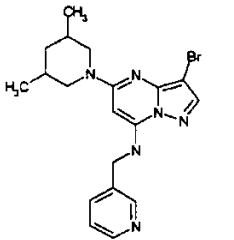
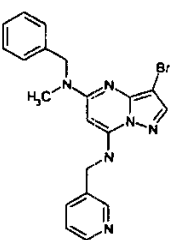
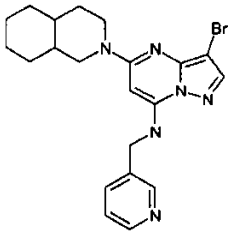
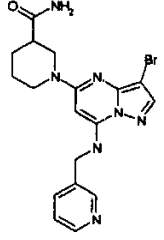
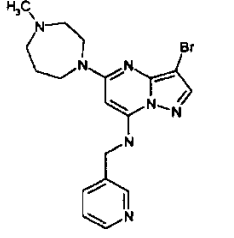
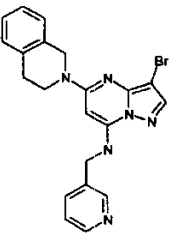
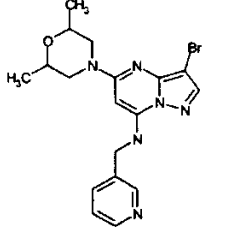
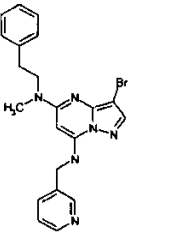
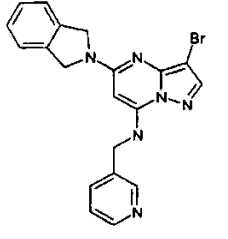
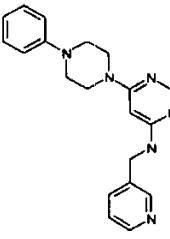
[1531]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8621 2. 377.21		1. 8626 2. 427.23
	1. 8622 2. 406.22		1. 8627 2. 431.24
	1. 8623 2. 412.23		1. 8628 2. 446.25
	1. 8624 2. 420.23		1. 8629 2. 446.25
	1. 8625 2. 426.23		1. 8630 2. 407.2

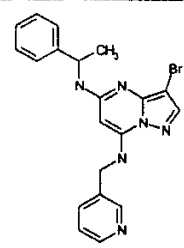
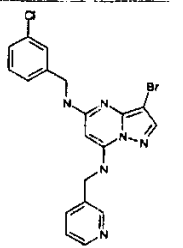
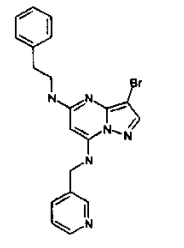
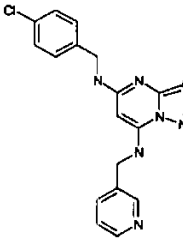
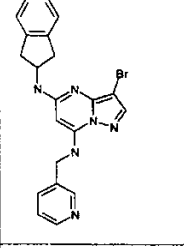
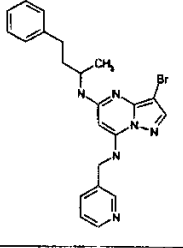
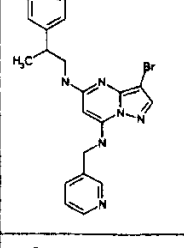
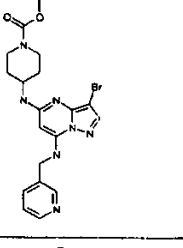
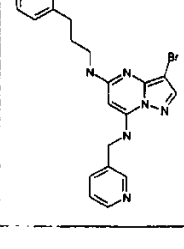
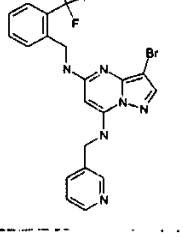
[1532]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
 <p>Chiral</p>	1. 8631 2. 407.2	 <p>Chiral</p>	1. 8636 2. 475.3
	1. 8632 2. 409.2		1. 8637 2. 419.2
 <p>Chiral</p>	1. 8633 2. 421.2		1. 8638 2. 448.2
	1. 8634 2. 439.2	 <p>Chiral</p>	1. 8639 2. 379.2
	1. 8635 2. 455.3		1. 8640 2. 437.2

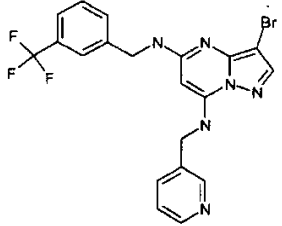
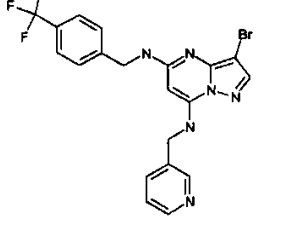
[1533]

생성물	1.실시에 2. m/z	생성물	1.실시에 2. m/z
	1. 8641 2. 415.23		1. 8646 2. 423.23
	1. 8642 2. 443.24		1. 8647 2. 430.24
	1. 8643 2. 416.23		1. 8648 2. 437.24
	1. 8644 2. 417.23		1. 8649 2. 439.24
	1. 8645 2. 423.23		1. 8650 2. 466.26

[1534]

생성물	1.실시예 2. m/z	생성물	1.실시예 2. m/z
	1. 8651 2. 423.23		1. 8656 2. 445.24
	1. 8652 2. 425.23		1. 8657 2. 445.24
	1. 8653 2. 437.24		1. 8658 2. 451.25
	1. 8654 2. 437.24		1. 8659 2. 476.26
	1. 8655 2. 437.24		1. 8660 2. 479.26

[1535]

생성물	1.실시예 2. m/z		
	<p>1. 8661 2. 477.26</p>		
	<p>1. 8662 2. 479.26</p>		

[1536]