

【명세서】**【발명의 명칭】**

폴리유비퀴틴화에 의한 표적 단백질 또는 폴리펩티드의 분해용 신규 화합물

5 【기술분야】

【0001】 본 발명은 유비퀴틴을 이용하여 표적 단백질 또는 폴리펩티드를 분해할 수 있는 신규한 화합물에 관한 것으로, 더욱 상세하게는 표적 단백질과 결합하는 리간드가 포함된 TBM(targeted protein binding moiety) 구조와 공유결합으로 연결이 가능한 동시에, 유비퀴틴이
10 직접적으로 결합될 수 있는 UBM(ubiquitin binding moiety) 구조를 갖는 화합물에 관한 것이다.

【배경기술】

【0002】 유비퀴틴(ubiquitin)은 분해가 필요한 단백질 말단에 공유결합하는 분자 식별 표지로, 이 과정에서 체내 존재하는 E1 (유비퀴틴
15 활성화 효소), E2 (유비퀴틴 운반체 단백질), E3 효소(유비퀴틴-단백질 연결 효소, E3 ligase)가 관여한다. 유비퀴틴이 결합하는 것을 단백질의 유비퀴틴화(ubiquitination)라고 하며 생체 내에서 여러 개의 유비퀴틴이 결합하는 폴리유비퀴틴화(polyubiquitylation)가 일어나는 경우 프로테아좀(proteasome) 또는 라이소좀(lysosome)을 포함하는 세포 내
20 단백 분해 기전을 통해 분해된다. 이렇게 분해된 단백질 잔해는 세포 내에서

- 재사용되기도 한다. 세포 내 엔도솜(endosome) 혹은 오토파고솜(autophagosome)에 의해 인지되어 라이소솜과 결합하고 엔도/오토 라이소솜(endo/auto lysosome)을 통해 분해되는 과정을 엔도/오토라이소조말 분해(endo/lysosomal degradation)라고 한다. 또한,
- 5 프로테오솜에 표적이 되어 분해되는 과정을 유비퀴틴-프로테아솜 시스템(ubiquitin-proteasome system, UPS)이라고 한다. 표적 단백질 또는 폴리펩티드 분해에 있어서, 특히 인산화 효소인 키나아제 또는 특정 수용체가 표적인 경우, 유비퀴틴화 분해 경로를 이용하는 것은 매우 유용하다.
- 10 【0003】 한편, 유비퀴틴-프로테아솜 시스템을 이용하기 위하여, ‘표적 단백질 또는 폴리펩티드에 결합하는 모이어티’와 ‘E3 효소와 결합하는 모이어티’가 ‘링커’로 연결된 이작용성 화합물이 사용되고 있으며, 이와 같이 표적 단백질의 라이신 잔기를 유비퀴틴화 시킴으로써 표적 단백질의 분해를 유도하는 기술을 PROTAC(proteolysis-targeting chimera)이라고 한다.
- 15 이는 기존 저분자 화합물 및 항체, 의약품으로 조절이 어려운 질병 관련 단백질, 예컨대, 전사인자, 스캐폴드 단백질, 타우(tau) 단백질 등을 분해할 수 있고, 표적에 대한 선택성이 높으며, 재사용이 가능하므로 저용량 투여가 가능하다는 장점이 있다. 또한, 리간드-수용체 결합에 의해 야기되는 질환에서 리간드를 차단하거나 길항제(antagonist)를 사용함으로써 과도한
- 20 리간드의 작용을 중화시키는 것은 환자들에게 내성이 발달할 가능성이 높고,

선택성이 매우 낮은 치료법이므로 리간드와 결합하는 수용체 단백질 자체를 분해하는 접근법이 보다 효과적이다.

【0004】 다만 PROTAC 화합물은 결합하는 E3 효소의 종류에 따라 표적 단백질 분해 효과의 차이가 크게 발생한다. 600여개 이상의 E3 효소 중 현재 PROTAC 기술에 활용되는 것은 5종 정도이며 주로 사용되는 것은 CRBN, VHL, IAP 등이다. 또한, 표적 단백질 결합 모이어티와 E3 효소 결합 모이어티가 모두 펩타이드로 이루어져 있는 PROTAC 화합물의 경우 세포투과성(cell permeability)이 낮은 단점이 있고, 이를 개선하기 위해 E3 효소 결합 리간드로 펩타이드가 아닌 저분자를 이용하거나 WO 2020/251971의 일부 실시예에서 라이신(lysine)을 모방하는 부분이 유비퀴틴화되어 유비퀴틴-프로테아좀 경로(UPP)를 통한 분해가 가능함이 보고되고 있으나, 아직 상용화된 제품은 없어, 이에 대한 기술의 연구·개발이 필요한 실정이다.

【발명의 상세한 설명】

15 【기술적 과제】

【0005】 본 발명의 일 목적은 유비퀴틴이 직접적으로 결합될 수 있는 UBM(ubiquitin binding moiety) 구조를 갖는 화합물을 제공하는 것을 목적으로 한다.

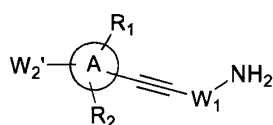
【0006】 본 발명의 다른 목적은 상기 UBM 구조를 갖는 20 화합물과 TBM(targeted protein/polypeptide binding moiety) 구조를 갖는

화합물이 서로 연결된 화합물을 제공하는 것을 목적으로 한다.

【기술적 해결방법】

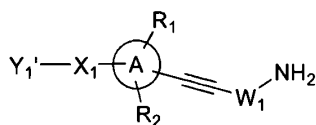
- 【0007】 상기의 목적을 달성하기 위하여, 본 발명의 일 측면은
하기 화학식 I 내지 화학식 IV로 표시되는 화합물 또는 이의 약학적으로
5 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭을 제공한다.

【0008】 [화학식 I]



【0009】

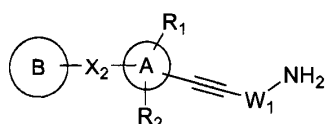
【0010】 [화학식 II]



【0011】

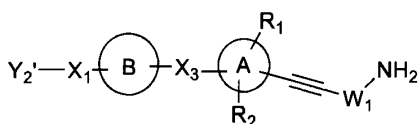
10

【0012】 [화학식 III]



【0013】

【0014】 [화학식 IV]

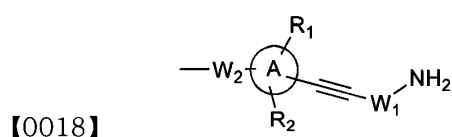


【0015】

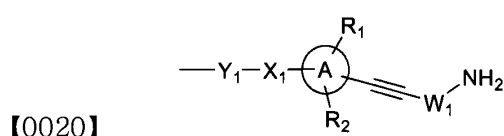
- 【0016】 또한, 상기 목적을 달성하기 위하여, 본 발명의 또
15 다른 측면은 TBM-UBM의 화학 구조를 가지고, 상기 TBM은 표적 단백질

또는 폴리펩티드에 결합하는 부분(moiety)이고, 상기 UBM은 하기 화학식 V 내지 화학식 VIII로 표시되는 화학 구조인 것인, 화합물 또는 그의 약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭을 제공한다.

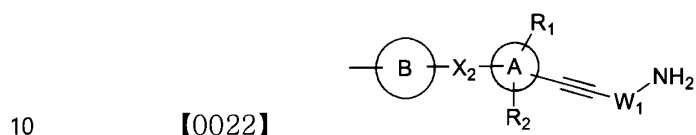
5 【0017】 [화학식 V]



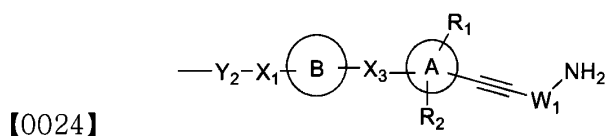
【0019】 [화학식 VI]



【0021】 [화학식 VII]



【0023】 [화학식 VIII]



【발명의 효과】

【0025】 본 발명에 따른 화합물들은 표적 단백질 또는
15 폴리펩티드의 폴리유비퀴틴화를 유도할 수 있는 UBM 구조를 포함하여

프로테아좀 또는 라이소좀에 의해 표적 단백질 또는 폴리펩티드를
 선택적으로 분해할 수 있는 분해자(degrader)가 될 수 있다. 즉, UBM에
 의해 유비퀴틴화가 유도된 표적 단백질 또는 폴리펩티드는 기존 PROTAC과
 같이 UPS를 이용한 표적 단백질 분해뿐만 아니라 엔도/오토라이소좀
 5 분해를 이용할 수 있기 때문에 본 발명의 TBM-UBM 화합물은 단백질
 복합체(protein complex) 및 단백질 집합체(protein aggregate)를
 선택적으로 표적하여 분해할 수 있는 장점이 있다.

【0026】 다만, 본 발명의 효과는 상기에서 언급한 효과로
 제한되지 아니하며, 언급되지 않은 또 다른 효과들은 하기의 기재로부터
 10 당업자에게 명확히 이해될 수 있을 것이다.

【도면의 간단한 설명】

【0027】 도 1은 본 발명의 TBM-UBM 화합물들이 표적
 단백질 또는 폴리펩티드와 결합하여 형성된 단백질 분해자가 작동하는
 원리를 나타낸 모식도이다.

15 【0028】 도 2는 UBM 화합물들이 유비퀴틴과 직접적으로
 결합하는 수용체임을 확인하기 위해 실시한 Pulldown assay 결과이다.

【0029】 도 3은 BRD4 분해자가 유비퀴틴과 직접 결합하는
 것을 확인하기 위해 실시한 원형 단백질 분석법을 통한 질량 분석 값을
 나타낸 것이다.

20 【발명의 실시를 위한 형태】

【0030】 먼저, 본 발명에서 이용된 용어를 정의한다.

【0031】 본 발명에서의 하기 용어는 달리 지시되지 않으면 하기 의미를 가진다. 정의되지 않은 임의의 용어는 당해 분야에서 이해되는 의미를 가진다.

5 【0032】 명세서 전체에서 어떤 구성요소를 "포함"한다는 것은 특별히 반대되는 기재가 없는 한 다른 구성요소를 제외하는 것이 아니라 다른 구성요소를 더 포함할 수 있다는 것을 의미한다.

【0033】 본 명세서의 구조식에서, 원자 및/또는 기(group)를 결합하는 기호 "-"는 단일 결합, 기호 "="는 이중 결합을 의미할 수 있다.

10 상기 기호는 생략될 수 있으며, 결합 원자 또는 결합 위치를 특정하는 경우 등 필요한 경우 표시될 수도 있다.

【0034】 본 발명에서 일컫는 '할로겐'은 플루오르(F), 염소(Cl), 브롬(Br), 요오드(I)를 의미한다.

【0035】 본 발명에서 일컫는 '알킬'은 이중결합 또는
15 삼중결합을 포함하지 않는 고리형 또는 비고리형의 지방족 탄화수소기로서,
달리 나타내지 않는 한 상기 비고리형의 알킬은 탄소수 1 내지 20, 1 내지
19, 1 내지 18, 1 내지 17, 1 내지 16, 1 내지 15, 1 내지 14, 1 내지 13, 1
내지 12, 1 내지 11, 1 내지 10, 예컨대 탄소수 1 내지 6, 특히 탄소수 1
내지 4인 것일 수 있고, 직쇄 또는 분지쇄일 수 있다. 상기 알킬기의
20 구체적인 예로는 메틸기, 에틸기, 프로필기, n-프로필기, 이소프로필기,

부틸기, n-부틸기, 이소부틸기, tert-부틸기, sec-부틸기, 1-메틸부틸기, 1-에틸부틸기, 펜틸기, n-펜틸기, 이소펜틸기, 네오펜틸기, tert-펜틸기, 헥실기, n-헥실기, 1-메틸펜틸기, 2-메틸펜틸기, 4-메틸-2-펜틸기, 3,3-디메틸부틸기, 2-에틸부틸기, 헵틸기, n-헵틸기, 1-메틸헥실기, 옥틸기, n-옥틸기, tert-옥틸기, 1-메틸헵틸기, 2-에틸헥실기, 2-프로필펜틸기, n-노닐기, 2,2-디메틸헵틸기, 1-에틸프로필기, 1,1-디메틸프로필기, 이소헥실기, 4-메틸헥실기, 5-메틸헥실기, 벤질기 등이 있으나, 이에 한정되는 것은 아니다.

또한, 상기 고리형의 알킬은 본 발명에서 특별히 "시클로알킬"라고 칭하며, 상기 '시클로알킬'은 이중결합 또는 삼중결합을 포함하지 않는 고리형의 지방족 탄화수소기로서, 달리 나타내지 않는 한 탄소수 3 내지 30, 3 내지 28, 3 내지 26, 3 내지 24, 3 내지 22, 3 내지 20, 3 내지 18, 3 내지 16, 3 내지 14, 3 내지 12, 3 내지 10, 예컨대 탄소수 3 내지 8, 특히 탄소수 3 내지 6인 것일 수 있고, 단환 또는 다환일 수 있다. 상기 다환은 시클로알킬기가 다른 고리기와 직접 연결되거나 축합된 기를 의미하고,

여기서 다른 고리기는 시클로알킬기일 수도 있으나, 다른 종류의 고리기, 예컨대 헤테로시클로알킬기, 아릴기, 헤테로아릴기 등일 수도 있다. 상기 시클로알킬기의 구체적인 예로는 시클로프로필기, 시클로부틸기, 시클로펜틸기, 3-메틸시클로펜틸기, 2,3-디메틸시클로펜틸기, 시클로헥실기, 3-메틸시클로헥실기, 4-메틸시클로헥실기, 2,3-디메틸시클로헥실기, 3,4,5-트리메틸시클로헥실기, 4-tert-부틸시클로헥실기, 시클로헵틸기,

시클로옥틸기, 시클로노닐기, 시클로데실기, 시클로운데실기,
 시클로도데실기, 바이시클로[2.2.1]헵틸기, 바이시클로[2.2.2]옥틸기,
 바이시클로[3.2.2]노닐기; 바이시클로[4.4.0]데실기;
 바이시클로[4.1.0]헵틸기 등이 있으나, 이에 한정되는 것은 아니다.

- 5 【0036】 본 발명에서 일컫는 ‘알케닐’은 적어도 하나의
 이중결합을 포함하는 고리형 또는 비고리형의 지방족 탄화수소기로서, 달리
 나타내지 않는 한 상기 비고리형의 알케닐은 탄소수 2 내지 20, 2 내지 19,
 2 내지 18, 2 내지 17, 2 내지 16, 2 내지 15, 2 내지 14, 2 내지 13, 2 내지
 12, 2 내지 11, 2 내지 10, 예컨대 탄소수 2 내지 6, 특히 탄소수 2 내지
 10 4인 것일 수 있고, 직쇄 또는 분지쇄일 수 있다. 상기 알케닐기의 구체적인
 예로는 비닐기, 1-프로페닐기, 이소프로페닐기, 1-부테닐기, 2-부테닐기, 3-
 부테닐기, 1-펜테닐기, 2-펜테닐기, 3-펜테닐기, 3-메틸-1-부테닐기, 1,3-
 부타디에닐기, 알릴기, 1-페닐비닐-1-일기, 2-페닐비닐-1-일기, 2,2-
 디페닐비닐-1-일기, 2-페닐-2-(나프틸-1-일)비닐-1-일기, 2,2-
 15 비스(디페닐-1-일)비닐-1-일기, 스티베닐기, 스티레닐기 등이 있으나, 이에
 한정되는 것은 아니다. 또한, 상기 고리형의 알케닐은 본 발명에서 특별히
 “시클로알케닐”이라고 칭하며, 상기 ‘시클로알케닐’은 적어도 하나의
 이중결합을 포함하는 고리형의 지방족 탄화수소기로서, 달리 나타내지 않는
 한 탄소수 3 내지 30, 3 내지 28, 3 내지 26, 3 내지 24, 3 내지 22, 3 내지
 20 20, 3 내지 18, 3 내지 16, 3 내지 14, 3 내지 12, 3 내지 10, 예컨대 탄소수

3 내지 8, 특히 탄소수 3 내지 6인 것일 수 있고, 단환 또는 다환일 수 있다. 상기 다환은 시클로알케닐기가 다른 고리기와 직접 연결되거나 축합된 기를 의미하고, 여기서 다른 고리기는 시클로알킬기일 수도 있으나, 다른 종류의 고리기, 예컨대 헤테로시클로알킬기, 아릴기, 헤테로아릴기 등일 수도
 5 있다. 상기 시클로알케닐기의 구체적인 예로는 시클로펜테닐기, 시클로헥세닐기, 시클로펜타-1,3-디에닐기, 시클로헵테닐기, 시클로옥테닐기, 시클로옥타-1,4-디에닐기 등이 있으나, 이에 한정되는 것은 아니다.

【0037】 본 발명에서 일컫는 ‘알킬’은 적어도 하나의 삼중결합을 포함하는 지방족 탄화수소기로서, 달리 나타내지 않는 한 탄소수
 10 2 내지 20, 2 내지 19, 2 내지 18, 2 내지 17, 2 내지 16, 2 내지 15, 2 내지 14, 2 내지 13, 2 내지 12, 2 내지 11, 2 내지 10, 예컨대 탄소수 2 내지 6, 특히 탄소수 2 내지 4인 것일 수 있고, 직쇄 또는 분지쇄일 수 있다. 상기 알킬기의 구체적인 예로는 에틸닐기, 프로피닐기, 부티닐기, 펜티닐기, 헥시닐기 등이 있으나, 이에 한정되는 것은 아니다.

15 【0038】 본 발명에서 일컫는 ‘아릴’은 방향족 탄화수소기로서, 달리 나타내지 않는 한 탄소수 6 내지 30, 6 내지 28, 6 내지 26, 6 내지 24, 6 내지 22, 6 내지 20, 6 내지 18, 6 내지 16, 6 내지 14, 예컨대 탄소수 6 내지 12인 것일 수 있고, 단환 또는 다환일 수 있다. 상기 다환이란 아릴기가 다른 고리기와 직접 연결되거나 축합된 기를 의미하고, 여기서
 20 다른 고리기로 아릴기일 수도 있으나, 다른 종류의 고리기, 예컨대

시클로알킬기, 헤테로시클로알킬기, 헤테로아릴기 등일 수도 있다. 또한 상기 아릴기는 스피로기를 포함한다. 상기 아릴기의 구체적인 예로는 페닐기, 바이페닐기, 트리페닐기, 나프틸기, 안트릴기, 크라이세닐기, 페난트레닐기, 페릴레닐기, 플루오란테닐기, 트리페닐레닐기, 페날레닐기, 파이레닐기, 테트라세닐기, 펜타세닐기, 플루오레닐기, 인데닐기, 아세나프틸레닐기, 벤조플루오레닐기, 스피로비플루오레닐기, 2,3-디히드로-1H-인데닐기, 이들의 축합고리기 등을 들 수 있으나, 이에 한정되는 것은 아니다.

【0039】 본 발명에서 일컫는 ‘헤테로시클로알킬’, ‘헤테로시클로알케닐’ 및 ‘헤테로아릴’은, 각각 상기 설명한 시클로알킬, 시클로알케닐 및 아릴의 고리를 구성하는 적어도 하나의 원자가 O, S, Se, N, Si 등과 같은 헤테로 원자로 치환된 것을 의미한다.

【0040】 본 발명에서 일컫는 ‘약학적으로 허용가능’이란 통상의 의약적 복용량(medicinal dosage)으로 이용할 때 상당한 독성 효과를 피함으로써, 동물, 더 구체적으로는 인간에게 사용할 수 있다는 연방 또는 주 정부의 규제 기구의 승인을 받을 수 있거나 또는 바람직하게는 승인받거나, 또는 미국 약전에 열거되거나, 또는 기타 일반적인 약전으로 인지되는 것을 의미한다.

【0041】 본 발명에서 일컫는 ‘약학적으로 허용가능한 염’이란 약제학적으로 허용가능하고 모 화합물(parent compound)의 바람직한 생물학적 또는 약리학적 활성을 갖는 본 발명의 화합물의 염을 의미한다.

그러한 염의 예는 이에 한정되지 않지만, 무기산(inorganic acid)[예를 들어, 염산(hydrochloric acid), 브롬화수소산(hydrobromic acid), 황산(sulfuric acid), 인산(phosphoric acid), 질산(nitric acid) 등]으로 형성되는 산 부가 염, 및 아세트산(acetic acid), 옥살산(oxalic acid), 타르타르산(tartari acid), 호박산(succinic acid), 말산(malic acid), 푸마르산(fumaric acid), 말레산(maleic acid), 아스코르브산(ascorbic acid), 트리플루오로아세트산(trifluoroacetic acid), 벤조산(benzoic acid), 타닌산(tannic acid), 파모산(pamoic acid), 알긴산(alginic acid), 폴리글루타민산(polyglutamic acid), 나프탈렌 술폰산(naphthalene sulfonic acid), 나프탈렌 디술폰산(naphthalene disulfonic acid), 및 폴리-갈락투론산(poly-galacturonic acid)과 같은 유기산(organic acid)으로 형성된 염을 포함한다. 상기 화합물은 또한 당업자에게 알려진 약학적으로 허용가능한 사차 염으로 투여될 수 있는데, 특히, 클로라이드, 브로마이드, 요오다이드, -O-알킬, 톨루엔술포네이트, 메틸술포네이트, 술포네이트, 포스페이트, 또는 카르복실레이트(예를 들어, 벤조에이트, 숙시네이트, 아세테이트, 글리코레이트, 말리에이트(maleate), 말레이트(malate), 푸마레이트, 시트레이트, 타르트레이트, 아스코르베이트, 시나모에이트, 만델로에이트 및 디페닐아세테이트)를 포함한다. 본 발명의 화학식의 화합물은 약학적으로 허용 가능한 염뿐만 아니라, 통상의 방법에 의해 제조될 수 있는 모든 염, 수화물 및 용매화물을 모두 포함할 수 있다.

【0042】 본 발명에서 일컫는 ‘수화물(hydrate)’은 비공유적 분자간력(non-covalent intermolecular force)에 의해 결합된 화학양론적(stoichiometric) 또는 비화학양론적(non-stoichiometric) 양의 물을 포함하고 있는 본 발명의 화합물 또는 그것의 염을 의미한다.

5 【0043】 본 발명에서 일컫는 ‘용매화물(solvate)’은 비공유적 분자간력에 의해 결합된 화학양론적 또는 비화학양론적 양의 용매를 포함하고 있는 본 발명의 화합물 또는 그것의 염을 의미한다. 그에 관한 바람직한 용매들로는 휘발성, 비독성 및 /또는 인간에게 투여되기에 적합한 용매들이 있다.

10 【0044】 본 발명에서 일컫는 ‘프로드럭(prodrug)’은 생체내에서 모 약제(parent drug)로 변형되는 물질을 의미한다. 이는 활성 화합물, 특히 본 발명의 화합물을 공급하기 위해 가수분해되고, 산화되고, 생물학 조건(생체 외 또는 생체 내)하에 다른 반응을 할 수 있는 본 발명의 화합물을 의미한다. 프로드럭의 예들은, 생가수분해될 수
15 있는(biohydrolyzable) 아미드, 생가수분해될 수 있는 에스테르, 생가수분해될 수 있는 카르바메이트(carbamates), 생가수분해될 수 있는 탄산염, 생가수분해될 수 있는 우레이드(ureides), 그리고 생가수분해될 수 있는 인산염 유사체들 같은 생가수분해될 수 있는 부분을 포함하는, 생가수분해되어 본 발명의 화합물을 생성하는 화합물들을 포함하나, 이러한
20 구체적 태양에 한정되는 것은 아니다. 이러한 프로드럭은 공지된 다양한

문헌을 기초로 용이하게 제조된 화합물들을 포함한다.

【0045】 본 발명에서 일컫는 ‘이성질체(isomer)’는 동일한 화학식 또는 분자식을 가지지만 구조적 또는 입체적으로 다른 본 발명의 화합물 또는 그것의 염을 의미한다. 이러한 이성질체에는 호변이성질체(tautomer) 등의 구조 이성질체와, 비대칭 탄소 중심을 가지는 R 또는 S 이성체, 기하이성질체(트랜스, 시스) 등의 입체 이성질체, 광학 이성질체(enantiomer)가 모두 포함된다. 또한, 이들 모든 이성체 및 그것의 혼합물들 역시 본 발명의 범위에 포함된다.

【0046】 본 발명에서 일컫는 ‘약제학적으로 허용가능한 담체’는 본 발명의 화합물과 투여되는 희석제, 보조약, 첨가제 또는 담체를 말한다.

【0047】 본 발명에서 일컫는 ‘예방’은 질병 또는 장애를 얻을 위험의 감소(즉, 질병의 하나 이상의 임상 증상이 상기 질병에 노출되거나 또는 발병하기 쉽지만 아직 상기 질병이 발병하지 않았거나 상기 질병의 증상이 보이지 않는 개체에게서 진행되지 않도록 하는 것)를 말한다.

【0048】 본 발명에서 일컫는 ‘치료’는 질병 또는 장애를 개선시키는 것(즉, 질병의 진행 또는 상기 질병의 하나 이상의 임상 증상을 저지 또는 감소시키는 것), 또는 개체가 인식할 수 없는 하나 이상의 물리적 지표(physical parameter)를 개선시키는 것, 또는 질병 또는 장애를 물리적이거나(예, 인식하지 못하는 증상의 안정화), 정신적으로(예, 물리적 지표의 안정화), 또는 양쪽 방향으로 조절하는 것을 의미한다.

【0049】

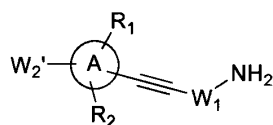
【0050】 이하, 본 발명을 상세히 설명한다.

【0051】

【0052】 1. UBM (ubiquitin binding moiety) 화합물

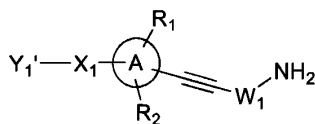
5 【0053】 본 발명의 일 측면은 하기 화학식 I 내지 IV로 표시되는 화합물 또는 이의 약학적으로 허용가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭을 제공한다.

【0054】 [화학식 I]



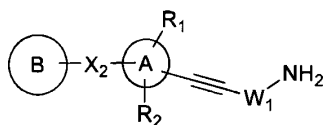
【0055】

10 【0056】 [화학식 II]



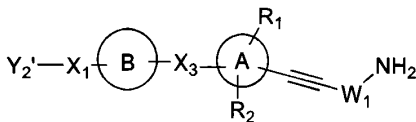
【0057】

【0058】 [화학식 III]



【0059】

【0060】 [화학식 IV]



15 【0061】

【0062】 상기 화학식 I 내지 화학식 IV에서, 치환기 W_1 , A, R_1 , R_2 , X_1 , X_2 , X_3 , B, W_2' , Y_1' 및 Y_2' 은 각각 독립적으로 하기와 같이 정의될 수 있다.

【0063】 상기 W_1 은 -알킬렌-, -알킬렌-O-, -알킬렌-OSO₂- 및
5 -알킬렌-N(R')SO₂-로 구성되는 군에서 선택되는 어느 하나일 수 있다.

【0064】 상기 W_1 은 중수소, 알킬, C(O)OR', C(O)N(R')(R''),
알킬렌-C(O)OR', 알킬렌-C(O)N(R')(R''), 알킬렌-OR', 알킬렌-SR', 알킬렌-
N(R')(R''), 알킬렌-OP(O)(OR')(OR''), 알킬렌-P(O)(OR')(OR'') 및 알킬렌-
OP(O)(R')(R'')으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는
10 비치환될 수 있다. 예컨대, 상기 W_1 은 C(O)OR', C(O)N(R')(R''), 알킬렌-
OR', 알킬렌-SR' 및 알킬렌-OP(O)(OR')(OR'')으로 구성되는 군에서
선택되는 적어도 하나로 치환 또는 비치환될 수 있다. 구체적으로 상기
 W_1 은 알킬렌-OR' 및 알킬렌-OP(O)(OR')(OR'')으로 구성되는 군에서
선택되는 적어도 하나로 치환 또는 비치환될 수 있다.

15 【0065】 상기 A는 아릴, 헤테로아릴, 시클로알킬,
헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느
하나일 수 있다. 예컨대, 상기 A는 아릴, N, O 및 S로 구성되는 군에서
선택되는 적어도 하나를 포함하는 5원 내지 10원의 헤테로아릴, 3원 내지
10원의 시클로알킬, N, O 및 S로 구성되는 군에서 선택되는 적어도 하나를
20 포함하는 3원 내지 10원의 헤테로시클로알킬 및 N, O 및 S로 구성되는

군에서 선택되는 적어도 하나를 포함하는 3원 내지 10원의
 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나일 수 있다.
 구체적으로, 상기 A는 벤젠, 퓨란, 벤조퓨란, 피리딘, 티오펜, 이미다졸 및
 옥사졸로 구성되는 군에서 선택되는 어느 하나일 수 있다.

- 5 【0066】 상기 R_1 및 R_2 는, 각각 독립적으로, 수소, 알킬,
 알케닐, 알키닐, 할로젠, 옥소, CN, NO₂, OR', SR', N(R')(R''), O-(알킬렌)-
 OR', -N(R')-(알킬렌)-OR', C(O)R', C(NH)R', C(S)R', C(O)OR',
 C(O)N(R')(R''), P(O)(R')(R''), P(O)(OR')(OR''), C(NH)N(R')(R''), C(S)OR',
 C(S)N(R')(R''), C(O)O-(알킬렌)-OC(O)R', C(O)O-(알킬렌)-
 10 메타크릴로일옥시, (알킬렌)-OR', (알킬렌)-SR', (알킬렌)-N(R')(R''),
 (알키닐렌)-N(R')(R''), (알킬렌)-P(O)(R')(R''), (알킬렌)-P(O)(OR')(OR''),
 (알킬렌)-OP(O)(R')(R''), (알킬렌)-OP(O)(OR')(OR''), (알킬렌)-
 OP(O)(벤질옥시)₂, (알킬렌)-OP(O)(페녹시)₂, (알킬렌)-OP(O)(페녹시)(NH-
 CH(R')C(O)OR''), (알킬렌)-C(O)OR', (알케닐렌)-C(O)OR', (알키닐렌)-
 15 C(O)OR', (알킬렌)-C(O)N(R')(R''), (알케닐렌)-C(NH)N(R')(R''), (알키닐렌)-
 C(S)N(R')(R''), (알킬렌)-C(O)R', (알킬렌)-C(NH)R', (알킬렌)-C(S)R', 아릴,
 헤테로아릴, 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서
 선택되는 어느 하나일 수 있다. 예컨대, R_1 및 R_2 는, 각각 독립적으로, 수소,
 알킬, 알케닐, 할로젠, OR', N(R')(R''), O-(알킬렌)-OR', C(O)R', C(O)OR',
 20 C(O)N(R')(R''), C(NH)N(R')(R''), C(O)O-(알킬렌)-OC(O)R', C(O)O-

(알킬렌)-메타크릴로일옥시, (알킬렌)-OR', (알킬렌)-SR', (알킬렌)-N(R')(R''),
 (알키닐렌)-N(R')(R''), (알킬렌)-OP(O)(OR')(OR''), (알킬렌)-
 OP(O)(벤질옥시)₂, (알킬렌)-OP(O)(페녹시)₂, (알킬렌)-OP(O)(페녹시)(NH-
 CH(R')C(O)OR''), (알킬렌)-C(O)OR', 아릴, 헤테로아릴, 헤테로시클로알킬
 5 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나일 수 있다.
 구체적으로, 상기 R₁ 및 R₂는, 각각 독립적으로, 수소, 알킬, OR', C(O)R',
 C(O)OR', C(O)N(R')(R''), (알킬렌)-OR', (알킬렌)-SR', (알킬렌)-
 OP(O)(OR')(OR''), 헤테로아릴 및 헤테로시클로알킬로 구성되는 군에서
 선택되는 어느 하나일 수 있다.

10 【0067】 또한, 상기 R₁ 및 R₂는, 각각 독립적으로, 1개 이상의
 할로젠으로 치환될 수 있으며, 각각 독립적으로 상기 R₁ 및 R₂가 아릴,
 헤테로아릴, 헤테로시클로알킬 또는 헤테로시클로알케닐인 경우에는 1개
 이상의 위치에서 1개 이상의 할로젠으로 치환 또는 비치환된 알킬 또는
 N(R')(R'')로 치환될 수 있다.

15 【0068】 상기 X₁은 직접 결합이거나, 또는 -N(R')-, -O-, -S-,
 -C(O)-, -SO-, SO₂-, =N-O- 및 -O-N=로 구성되는 X1a 군, -OC(O)-, -
 C(O)O-, -N(R')C(O)-, -C(O)N(R')-, -N(R')SO-, -SON(R')-, -N(R')SO₂- 및
 -SO₂N(R')-로 구성되는 X1b 군 및 -알킬렌-, -알케닐렌- 및 -알키닐렌-
 으로 구성되는 X1c 군으로부터 선택되는 어느 하나이거나, 또는 둘 이상이
 20 서로 연결된 것일 수 있다. 예컨대, 상기 X₁은 직접 결합이거나, 상기 X1a

군 및 상기 X1b 군으로부터 선택되는 어느 하나이거나, 또는 상기 X1a 군
 및 상기 X1b 군으로부터 선택되는 어느 하나와 상기 X1c 군으로부터
 선택되는 어느 하나가 X1a-X1c 또는 X1b-X1c의 형태로 연결된 것일 수
 있다. 구체적으로, 상기 X₁은 직접 결합이거나, 또는 상기 X₁을 구성하는
 5 상기 X1a 군이 -N(R')- 및 -O-로 구성되거나, 상기 X1b 군이 -C(O)O-, -
 N(R')C(O)- 및 -C(O)N(R')-로 구성되거나, 또는 상기 X1c 군이 -알킬렌-
 및 -알키닐렌-으로 구성되는 것일 수 있다.

【0069】 상기 X₂는 직접 결합이거나, 또는 -N(R')-, -O-, -S-,
 -C(O)-, -SO-, SO₂-, =N-O- 및 -O-N=로 구성되는 X2a 군, -OC(O)-, -
 10 N(R')C(O)-, -N(R')C(O)O-, -N(R')SO₂-O- 및 -N(R')C(S)O-로 구성되는
 X2b 군, -C(O)O-, -C(O)N(R')-, -O-SO₂-N(R')-, -O-C(S)N(R')- 및 -O-
 C(O)N(R')-로 구성되는 X2c 군 및 -알킬렌-, -알케닐렌- 및 -알키닐렌-
 으로 구성되는 X2d 군으로부터 선택되는 어느 하나이거나, 또는 둘 이상이
 서로 연결된 것일 수 있다. 예컨대, 상기 X₂는 직접 결합이거나, 상기 X2a
 15 군, 상기 X2b 군 및 상기 X2c 군으로부터 선택되는 어느 하나이거나, 또는
 둘 이상이 서로 연결된 것이거나, 또는 상기 X2b 군, 상기 X2c 군 및 상기
 X2d 군에서 선택되는 어느 하나 또는 둘 이상이 X2b-X2d-X2b, X2b-X2d-
 X2c, X2c-X2d-X2b 또는 X2c-X2d-X2c의 형태로 연결된 것일 수 있다.
 구체적으로, 상기 X₂는 직접 결합이거나, 또는 상기 X₂를 구성하는 상기
 20 X2a 군이 -N(R')-, -O-, -C(O)- 및 =N-O-로 구성되거나, 상기 X2b 군이

-N(R')C(O)-로 구성되거나, 상기 X2c 군은 -C(O)N(R')-로 구성되거나,
또는 상기 X2d 군이 알킬렌-, 알케닐렌- 및 -알키닐렌-으로 구성되는 것일
수 있다.

【0070】 상기 X3은 직접 결합이거나, 또는 -알킬렌-, -O-, -S-,
5 -C(O)-, -N(R')-, -SO-, -SO2- 및 이들의 조합으로 구성되는 군으로부터
선택되는 어느 하나일 수 있다. 예컨대, 상기 X3은 직접 결합이거나, 또는 -
C(O)-, -N(R')- 및 이들의 조합으로 구성되는 군으로부터 선택되는 어느
하나일 수 있다.

【0071】 상기 B는 히드록시, 알콕시 및 옥소로 구성되는
10 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 아릴, 헤테로아릴,
시클로알킬, 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서
선택되는 어느 하나이거나, 또는 히드록시, 알콕시 및 옥소로 구성되는
군에서 선택되는 적어도 하나로 치환 또는 비치환된, 아릴, 헤테로아릴,
시클로알킬, 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서
15 선택되는 둘 이상이 직접 연결, -알킬렌-, -O-, -S-, -C(O)-, -N(R')-, -
SO-, -SO2- 또는 이들의 조합으로 연결된 것일 수 있다. 예컨대, 상기 B는
히드록시, 알콕시 및 옥소로 구성되는 군에서 선택되는 적어도 하나로 치환
또는 비치환된, 아릴, 5원 내지 10원의 헤테로아릴, 3원 내지 10원의
헤테로시클로알킬 및 3원 내지 10원의 헤테로시클로알케닐로 구성되는
20 군에서 선택되는 어느 하나이거나, 또는 히드록시 및 옥소로 구성되는

- 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 아릴, 5원 내지 10원의
 헤테로아릴, 3원 내지 10원의 헤테로시클로알킬 및 3원 내지 10원의
 헤테로시클로알케닐로 구성되는 군에서 선택되는 둘 이상이 직접, -알킬렌-,
 -C(O)-, -N(R')-, 또는 이들의 조합으로 연결된 것일 수 있다. 구체적으로,
- 5 상기 B는 히드록시 및 옥소로 구성되는 군에서 선택되는 적어도 하나로
 치환 또는 비치환된, 5원 내지 10원의 헤테로아릴, 3원 내지 10원의
 헤테로시클로알킬 및 3원 내지 10원의 헤테로시클로알케닐로 구성되는
 군에서 선택되는 어느 하나이거나, 또는 비치환된, 5원 내지 10원의
 헤테로아릴, 3원 내지 10원의 헤테로시클로알킬 및 3원 내지 10원의
- 10 헤테로시클로알케닐로 구성되는 군에서 선택되는 둘 이상이 직접, -알킬렌-,
 -C(O)-, -N(R')- 또는 이들의 조합으로 연결된 것일 수 있다.

- 【0072】 상기 W₂'은 수소, 알킬, 알케닐 및 알키닐로 구성되는
 군에서 선택되는 어느 하나일 수 있다. 예컨대, 상기 W₂'은 수소, 알케닐 및
 알키닐로 구성되는 군에서 선택되는 어느 하나일 수 있다. 구체적으로, 상기
- 15 W₂'은 수소 및 알키닐로 구성되는 군에서 선택되는 어느 하나일 수 있다.

- 【0073】 또한, 상기 W₂'은 중수소, 할로젠, 알킬, -알킬렌-
 C(O)OR', 알킬렌-C(O)N(R')(R''), 알킬렌-OR', 알킬렌-SR', 알킬렌-
 N(R')(R''), 알킬렌-OP(O)(OR')(OR''), 알킬렌-P(O)(OR')(OR''), 알킬렌-
 OP(O)(R')(R''), -N(R')(R''), -OR', -SR', -C(O)R', -SOR', -SO₂R', =N-OR', -
- 20 C(O)OR', -C(O)N(R')(R''), -OC(O)OR', -OC(O)N(R')(R''), -N(R')C(O)O(R''),

-N(R')SO(R'), -SON(R')(R''), -N(R')SO₂(R'') 및 -SO₂N(R')(R'')으로
 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환될 수 있다.
 예컨대, 상기 W₂'은 할로젠, 알킬렌-OR', 알킬렌-OP(O)(OR')(OR''), -
 N(R')(R''), -OR' 및 -C(O)OR'으로 구성되는 군에서 선택되는 적어도 하나로
 5 치환 또는 비치환될 수 있다.

【0074】 상기 Y₁'은 알킬, 알케닐, 알키닐, (CH₃CH₂O)-(CH₂CH₂O)_{n-1}CH₂- 및 (CH₃CH₂O)-(CH₂CH₂O)_{n-1}CH₂CH₂-로 구성되는
 군에서 선택되는 어느 하나이고, 상기 n은 1~4일 수 있다. 예컨대, 상기
 Y₁'은 알킬, 알케닐, 알키닐, (CH₃CH₂O)-(CH₂CH₂O)_{n-1}CH₂- 및 (CH₃CH₂O)-
 10 (CH₂CH₂O)_{n-1}CH₂CH₂-로 구성되는 군에서 선택되는 어느 하나이고, 상기
 n은 1~2일 수 있다. 구체적으로, 상기 Y₁'은 알킬, 알케닐 및 알키닐로
 구성되는 군에서 선택되는 어느 하나일 수 있다.

【0075】 또한, 상기 Y₁'은 할로젠, -N(R')(R''), -OR', -SR', -
 C(O)R', -SOR', SO₂R', =N-OR', -C(O)OR', -C(O)N(R')(R''), -OC(O)OR', -
 15 OC(O)N(R')(R''), -N(R')C(O)O(R''), -N(R')SO(R'), -SON(R')(R''), -
 N(R')SO₂(R'') 및 -SO₂N(R')(R'')으로 구성되는 군에서 선택되는 적어도
 하나로 치환 또는 비치환될 수 있다. 구체적으로, 상기 Y₁'은 할로젠, -
 N(R')(R''), -OR' 및 -C(O)OR'으로 구성되는 군에서 선택되는 적어도 하나로
 치환 또는 비치환될 수 있다.

20 【0076】 상기 Y₂'은 알킬, 알케닐, 알키닐, 헤테로시클로알킬 및

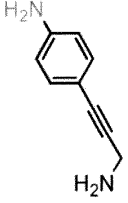
헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나일 수 있다. 예컨대, 상기 Y_2' 은 알킬, 알케닐, 알키닐 및 헤테로시클로알킬로 구성되는 군에서 선택되는 어느 하나일 수 있다. 구체적으로 상기 Y_2' 은 알킬 및 헤테로시클로알킬로 구성되는 군에서 선택되는 어느 하나일 수 있다.

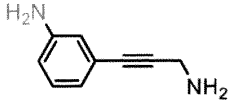
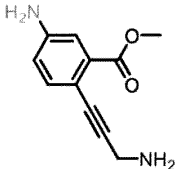
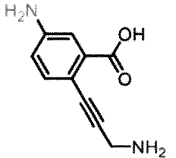
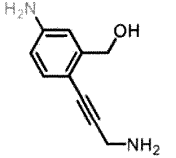
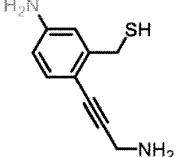
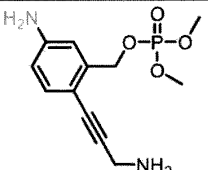
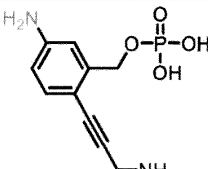
- 5 【0077】 또한, 상기 Y_2' 은 할로젠, $-N(R')(R'')$, $-OR'$, $-SR'$, $-C(O)R'$, $-SOR'$, SO_2R' , $=N-OR'$, $-C(O)OR'$, $-C(O)N(R')(R'')$, $-OC(O)OR'$, $-OC(O)N(R')(R'')$, $-N(R')C(O)O(R'')$, $-N(R')SO(R')$, $-SON(R')(R'')$, $-N(R')SO_2(R'')$ 및 $-SO_2N(R')(R'')$ 으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환될 수 있다. 예컨대, 상기 Y_2' 은 할로젠, $-N(R')(R'')$,
10 $-OR'$ 및 $-C(O)OR'$ 으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환될 수 있다.

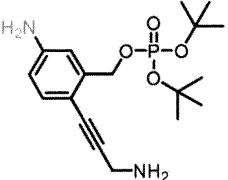
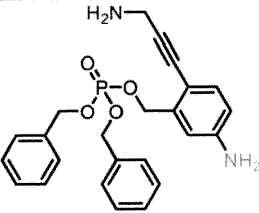
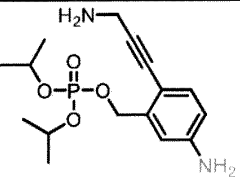
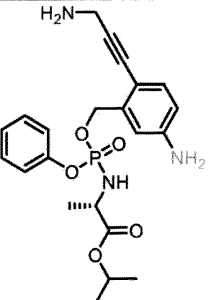
 【0078】 한편, 상기 치환기들을 구성하는 작용기들에서 R' 및 R'' 은 각각 독립적으로 수소 또는 알킬일 수 있다.

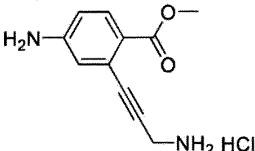
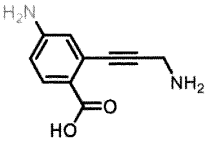
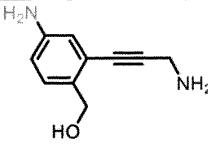
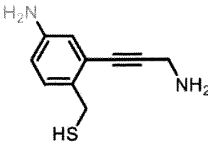
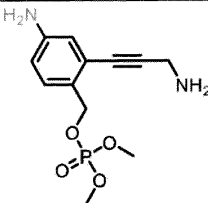
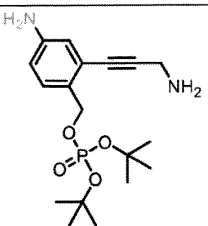
- 【0079】 특히, 상기 화학식 I으로 표시되는 화합물의 구체적인
15 예들은 하기 표 1에 제시된 것일 수 있으나, 이에 한정되지 아니한다.

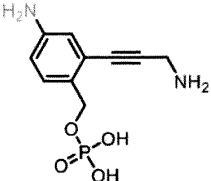
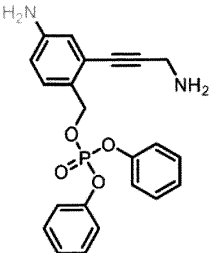
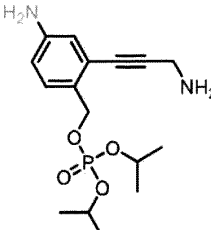
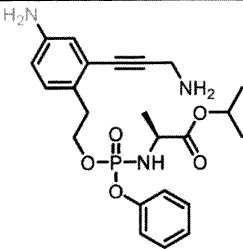
【표 1】

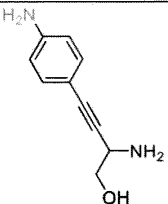
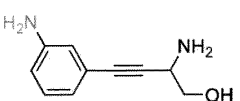
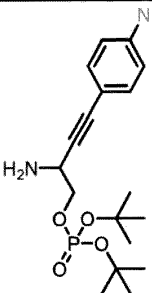
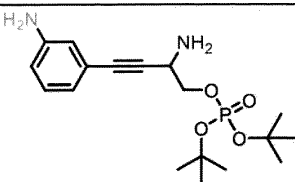
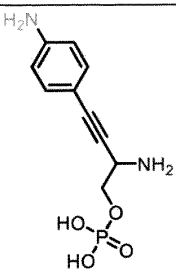
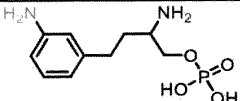
번호	화합물
1-1	4-(3-aminoprop-1-yn-1-yl)aniline hydrochloride 

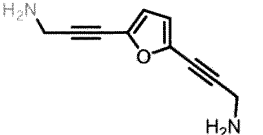
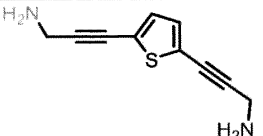
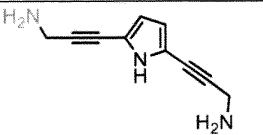
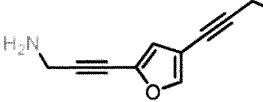
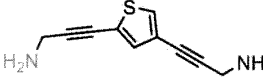
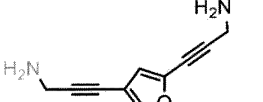
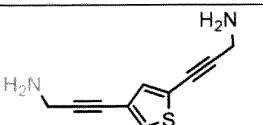
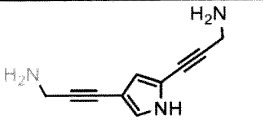
1-3	3-(3-aminoprop-1-yn-1-yl)aniline hydrochloride 
3-1	 methyl 5-amino-2-(3-aminoprop-1-yn-1-yl)benzoate
3-2	 5-amino-2-(3-aminoprop-1-yn-1-yl)benzoic acid
3-3	 (5-amino-2-(3-aminoprop-1-yn-1-yl)phenyl)methanol
3-6	 (5-amino-2-(3-aminoprop-1-yn-1-yl)phenyl)methanethiol
3-7	 5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl dimethyl phosphate
3-8	

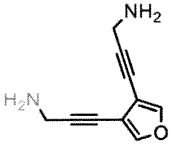
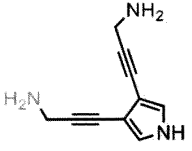
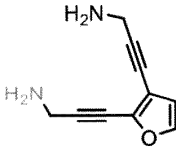
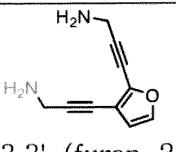
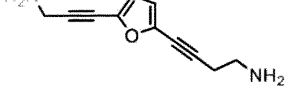
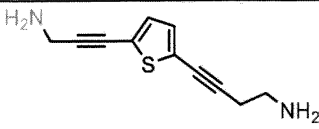
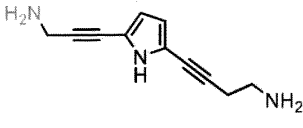
	5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl dihydrogen phosphate
3-9	 5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl di-tert-butyl phosphate
3-10	 5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl dibenzyl phosphate
3-11	 5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl diisopropyl phosphate
3-12	 isopropyl (((5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl)oxy)(phenoxy)phosphoryl)-L-alaninate

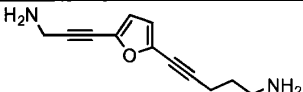
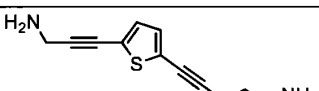
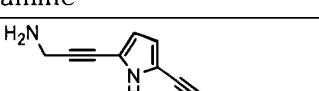
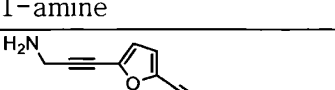
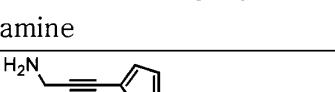
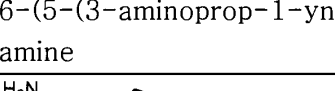
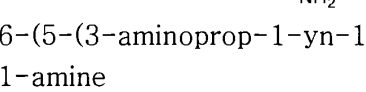
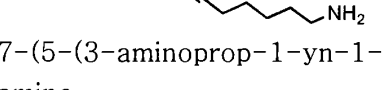
3-25	 methyl 4-amino-2-(3-aminoprop-1-yn-1-yl)benzoate hydrochloride
3-26	 4-amino-2-(3-aminoprop-1-yn-1-yl)benzoic acid
3-27	 (4-amino-2-(3-aminoprop-1-yn-1-yl)phenyl)methanol
3-28	 (4-amino-2-(3-aminoprop-1-yn-1-yl)phenyl)methanethiol
3-30	 4-amino-2-(3-aminoprop-1-yn-1-yl)benzyl dimethyl phosphate
3-31	 4-amino-2-(3-aminoprop-1-yn-1-yl)benzyl di-tert-butyl phosphate

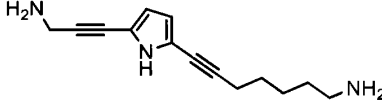
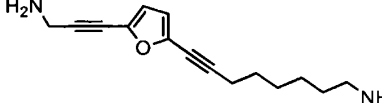
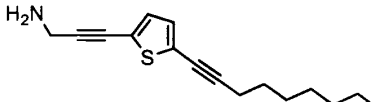
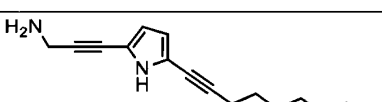
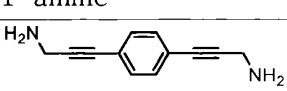
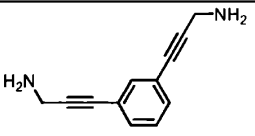
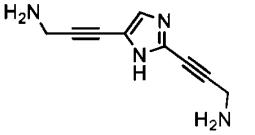
3-32	 4-amino-2-(3-aminoprop-1-yn-1-yl)benzyl dihydrogen phosphate
3-33	 4-amino-2-(3-aminoprop-1-yn-1-yl)benzyl diphenyl phosphate
3-34	 4-amino-2-(3-aminoprop-1-yn-1-yl)benzyl diisopropyl phosphate
3-35	 isopropyl ((4-amino-2-(3-aminoprop-1-yn-1-yl)phenethoxy)(phenoxy)phosphoryl)-L-alaninate
3-49	2-amino-4-(4-aminophenyl)but-3-yn-1-ol hydrochloride

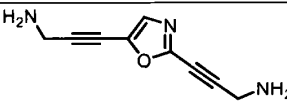
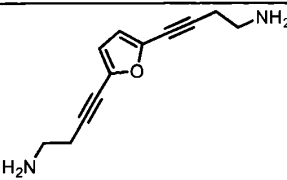
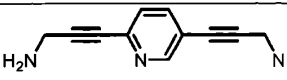
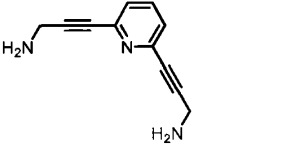
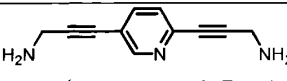
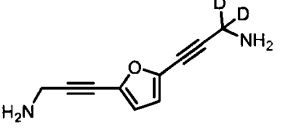
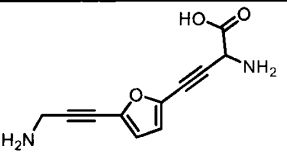
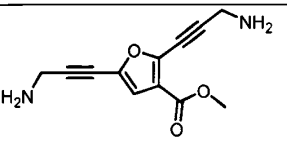
	
3-51	2-amino-4-(3-aminophenyl)but-3-yn-1-ol 
3-53	 2-amino-4-(4-aminophenyl)but-3-yn-1-yl di-tert-butyl phosphate
3-55	 2-amino-4-(3-aminophenyl)but-3-yn-1-yl di-tert-butyl phosphate
3-57	 2-amino-4-(4-aminophenyl)but-3-yn-1-yl dihydrogen phosphate
3-60	

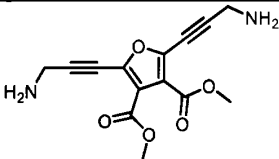
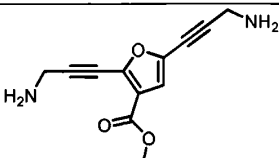
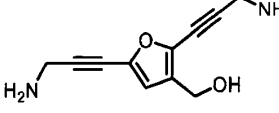
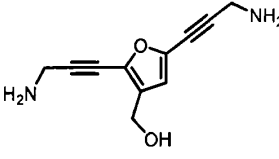
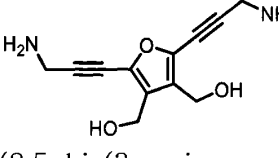
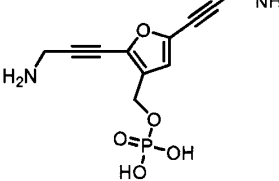
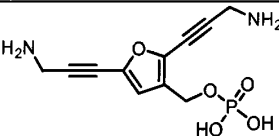
	2-amino-4-(3-aminophenyl)butyl dihydrogen phosphate
4-1	 3,3'-(furan-2,5-diyl)bis(prop-2-yn-1-amine)
4-10	 3,3'-(thiophene-2,5-diyl)bis(prop-2-yn-1-amine)
4-13	 3,3'-(1H-pyrrole-2,5-diyl)bis(prop-2-yn-1-amine)
4-16	 3,3'-(furan-2,4-diyl)bis(prop-2-yn-1-amine)
4-19	 3,3'-(thiophene-2,4-diyl)bis(prop-2-yn-1-amine)
4-25	 3,3'-(furan-2,4-diyl)bis(prop-2-yn-1-amine)
4-28	 3,3'-(thiophene-2,4-diyl)bis(prop-2-yn-1-amine)
4-31	 3,3'-(1H-pyrrole-2,4-diyl)bis(prop-2-yn-1-amine)

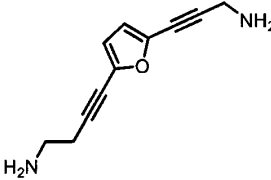
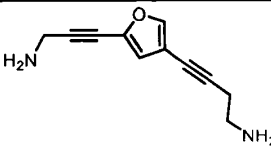
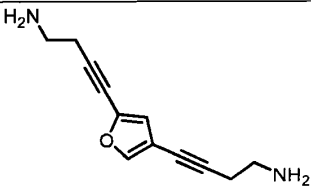
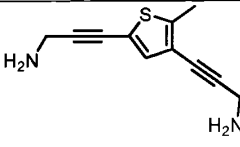
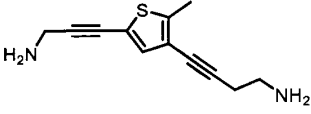
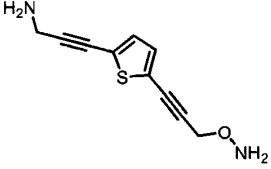
4-34	 3,3'-(furan-3,4-diyl)bis(prop-2-yn-1-amine)
4-40	 3,3'-(1H-pyrrole-3,4-diyl)bis(prop-2-yn-1-amine)
4-43	 3,3'-(furan-2,3-diyl)bis(prop-2-yn-1-amine)
4-52	 3,3'-(furan-2,3-diyl)bis(prop-2-yn-1-amine)
4-61	 4-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)but-3-yn-1-amine
4-62	 4-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)but-3-yn-1-amine
4-63	 4-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)but-3-yn-1-amine

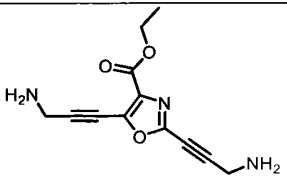
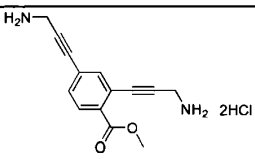
4-64	 5-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)pent-4-yn-1-amine
4-65	 5-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)pent-4-yn-1-amine
4-66	 5-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)pent-4-yn-1-amine
4-67	 6-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)hex-5-yn-1-amine
4-68	 6-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)hex-5-yn-1-amine
4-69	 6-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)hex-5-yn-1-amine
4-70	 7-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)hept-6-yn-1-amine
4-71	

	7-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)hept-6-yn-1-amine
4-72	 7-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)hept-6-yn-1-amine
4-73	 8-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)oct-7-yn-1-amine
4-74	 8-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)oct-7-yn-1-amine
4-75	 8-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)oct-7-yn-1-amine
4-128	 3,3'-(1,4-phenylene)bis(prop-2-yn-1-amine)
4-129	 3,3'-(1,3-phenylene)bis(prop-2-yn-1-amine)
4-130	 3,3'-(1H-imidazole-2,5-diyl)bis(prop-2-yn-1-amine)

4-131	 3,3'-(oxazole-2,5-diyl)bis(prop-2-yn-1-amine)
4-147	 4,4'-(furan-2,5-diyl)bis(but-3-yn-1-amine)
4-177	 3,3'-(pyridine-2,5-diyl)bis(prop-2-yn-1-amine)
4-178	 3,3'-(pyridine-2,6-diyl)bis(prop-2-yn-1-amine)
4-179	 3,3'-(pyridine-2,5-diyl)bis(prop-2-yn-1-amine)
4-180	 3-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1,1-d2-1-amine
4-181	 2-amino-4-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)but-3-ynoic acid
4-182	 methyl 2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-carboxylate

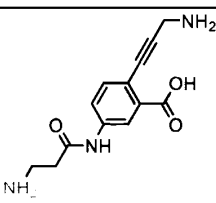
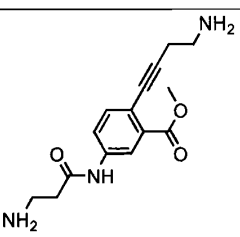
4-183	 dimethyl 2,5-bis(3-aminoprop-1-yn-1-yl)furan-3,4-dicarboxylate
4-184	 methyl 2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-carboxylate
4-185	 (2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-yl)methanol
4-186	 (2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-yl)methanol
4-187	 (2,5-bis(3-aminoprop-1-yn-1-yl)furan-3,4-diyl)dimethanol
4-188	 (2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-yl)methyl dihydrogen phosphate
4-189	

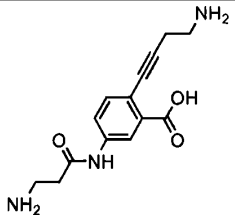
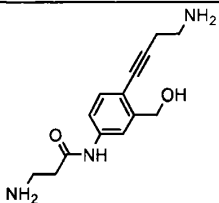
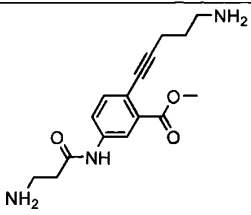
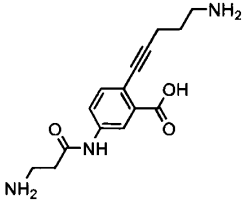
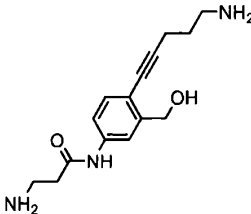
	(2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-yl)methyl dihydrogen phosphate
4-200	 4-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)but-3-yn-1-amine
4-201	 4-(5-(3-aminoprop-1-yn-1-yl)furan-3-yl)but-3-yn-1-amine
4-202	 4,4'-(furan-2,4-diyl)bis(but-3-yn-1-amine)
4-218	 3,3'-(5-methylthiophene-2,4-diyl)bis(prop-2-yn-1-amine)
4-219	 4-(5-(3-aminoprop-1-yn-1-yl)-2-methylthiophen-3-yl)but-3-yn-1-amine
4-223	 3-(5-(3-(aminooxy)prop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-amine

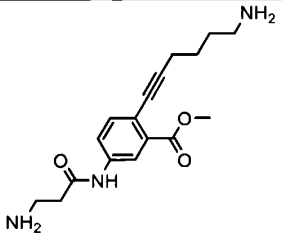
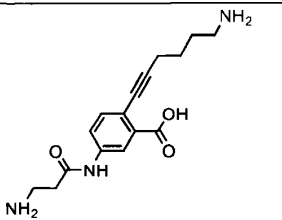
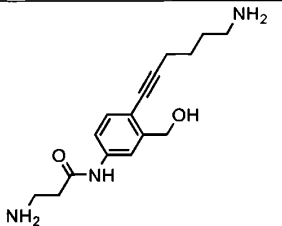
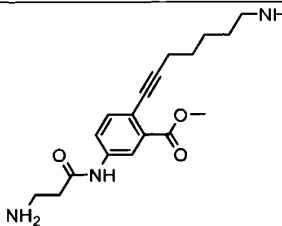
5-52	 ethyl 2,5-bis(3-aminoprop-1-yn-1-yl)oxazole-4-carboxylate
5-116	 methyl 2,4-bis(3-aminoprop-1-yn-1-yl)benzoate dihydrochloride

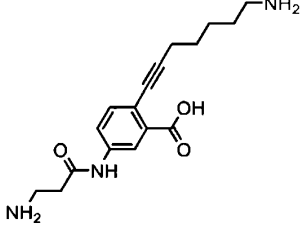
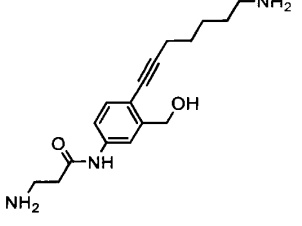
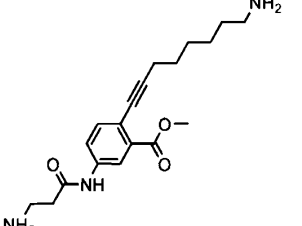
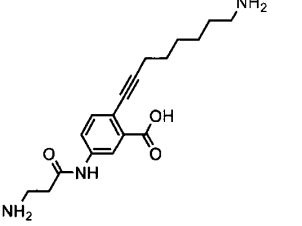
【0080】 특히, 상기 화학식 II 로 표시되는 화합물의 구체적인 예들은 하기 표 2에 제시된 것일 수 있으나, 이에 한정되지 아니한다.

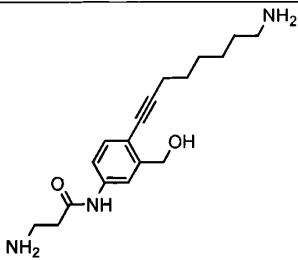
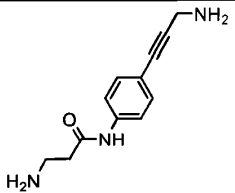
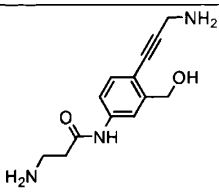
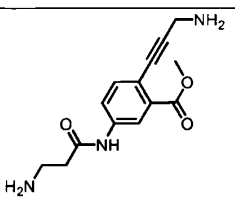
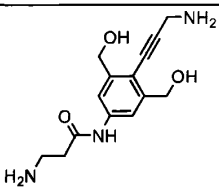
【표 2】

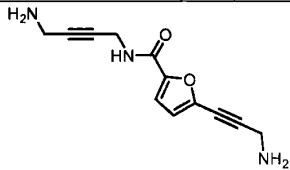
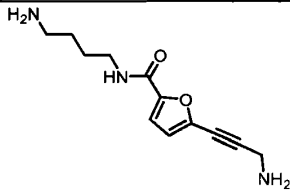
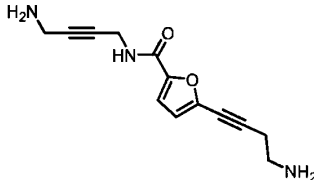
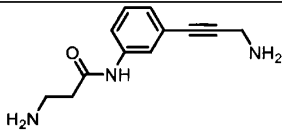
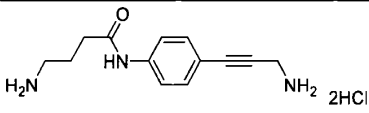
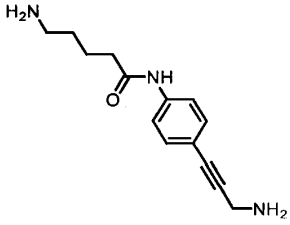
번호	화합물
4-6	 2-(3-aminoprop-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-109	 methyl 2-(4-aminobut-1-yn-1-yl)-5-(3-aminopropanamido)benzoate

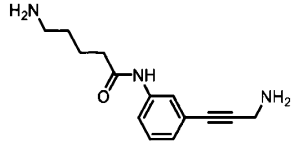
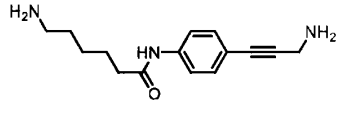
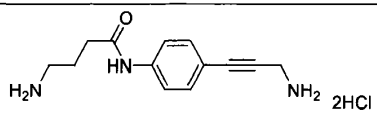
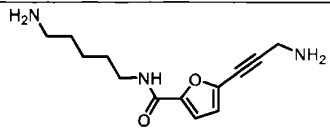
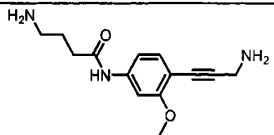
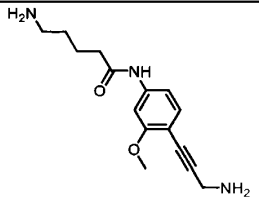
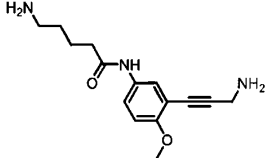
4-110	 2-(4-aminobut-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-111	 3-amino-N-(4-(4-aminobut-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-112	 methyl 2-(5-aminopent-1-yn-1-yl)-5-(3-aminopropanamido)benzoate
4-113	 2-(5-aminopent-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-114	 3-amino-N-(4-(5-aminopent-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide

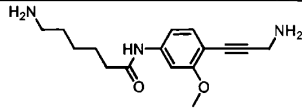
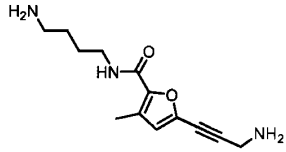
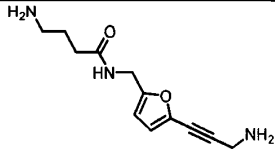
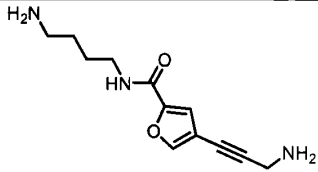
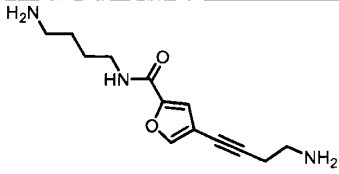
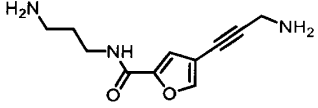
	(hydroxymethyl)phenyl)propanamide
4-115	 methyl 2-(6-aminohex-1-yn-1-yl)-5-(3-aminopropanamido)benzoate
4-116	 2-(6-aminohex-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-117	 3-amino-N-(4-(6-aminohex-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-118	 methyl 2-(7-aminohept-1-yn-1-yl)-5-(3-aminopropanamido)benzoate

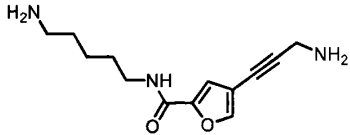
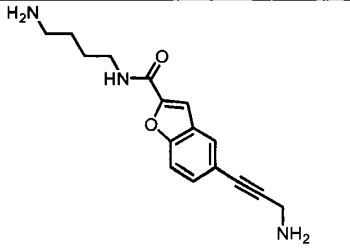
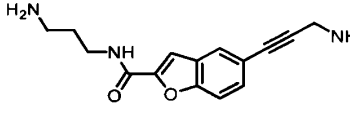
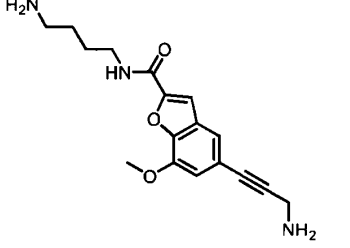
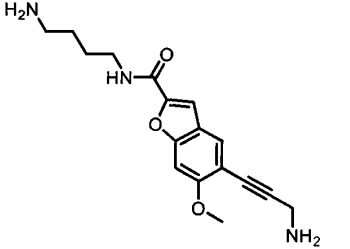
4-119	 2-(7-aminohept-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-120	 3-amino-N-(4-(7-aminohept-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-121	 methyl 2-(8-amino-oct-1-yn-1-yl)-5-(3-aminopropanamido)benzoate
4-122	 2-(8-amino-oct-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid

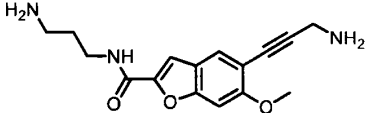
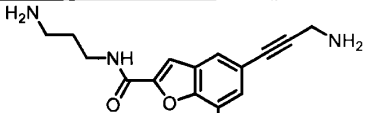
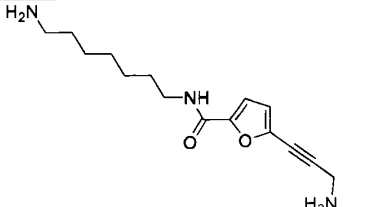
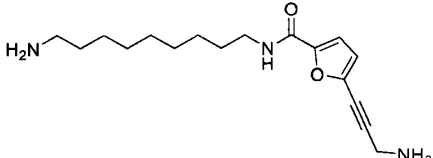
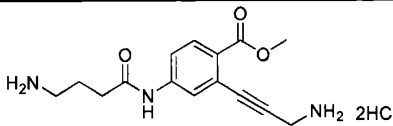
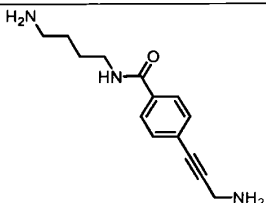
4-123	 3-amino-N-(4-(8-aminooct-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-124	 3-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)propanamide
4-125	 3-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-126	 methyl 2-(3-aminoprop-1-yn-1-yl)-5-(3-aminopropanamido)benzoate
4-127	 3-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3,5-bis(hydroxymethyl)phenyl)propanamide

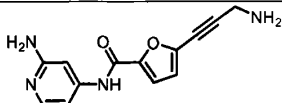
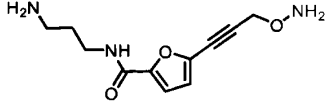
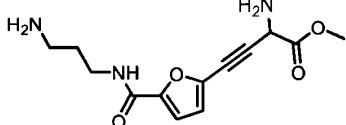
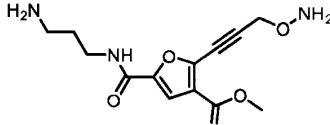
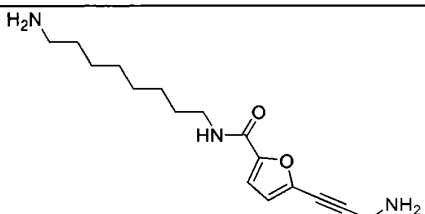
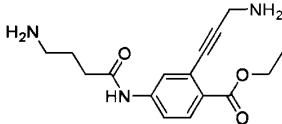
4-148	 N-(4-aminobut-2-yn-1-yl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-149	 N-(4-aminobutyl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-150	 5-(4-aminobut-1-yn-1-yl)-N-(4-aminobut-2-yn-1-yl)furan-2-carboxamide
4-161	 3-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)propanamide
4-162	 4-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)butanamide dihydrochloride
4-163	 5-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)pentanamide

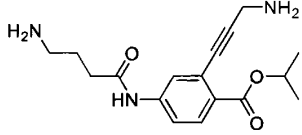
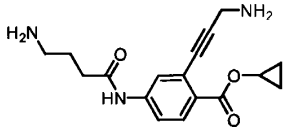
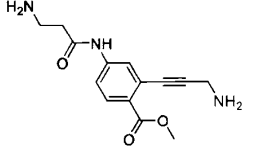
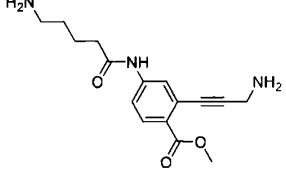
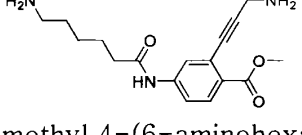
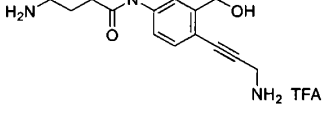
4-164	 5-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)pentanamide
4-165	 6-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)hexanamide
4-166	 5-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)furan-2-carboxamide dihydrochloride
4-167	 N-(5-aminopentyl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-168	 4-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)butanamide
4-169	 5-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)pentanamide
4-170	 5-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-methoxyphenyl)pentanamide

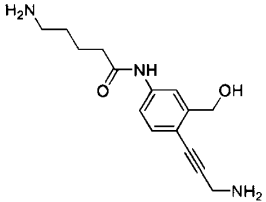
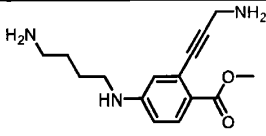
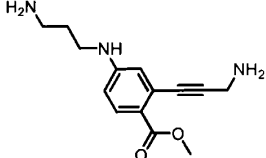
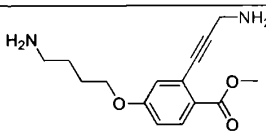
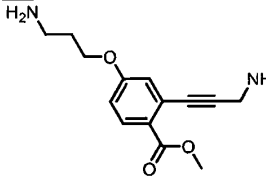
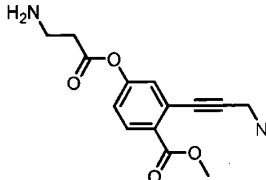
	methoxyphenyl)pentanamide
4-171	 6-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)hexanamide
4-192	 N-(4-aminobutyl)-5-(3-aminoprop-1-yn-1-yl)-3-methylfuran-2-carboxamide
4-199	 4-amino-N-((5-(3-aminoprop-1-yn-1-yl)furan-2-yl)methyl)butanamide
4-203	 N-(4-aminobutyl)-4-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-204	 4-(4-aminobut-1-yn-1-yl)-N-(4-aminobutyl)furan-2-carboxamide
4-205	 4-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)furan-2-carboxamide

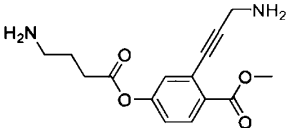
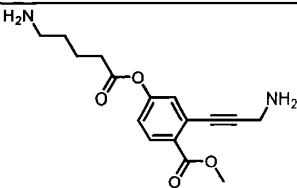
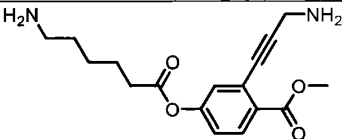
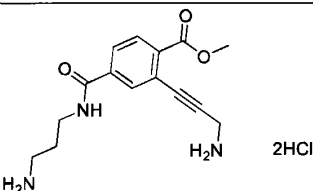
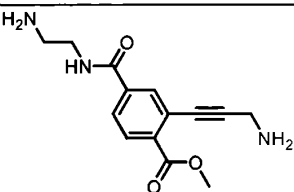
4-206	 N-(5-aminopentyl)-4-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-209	 N-(4-aminobutyl)-5-(3-aminoprop-1-yn-1-yl)benzofuran-2-carboxamide
4-210	 5-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)benzofuran-2-carboxamide
4-214	 N-(4-aminobutyl)-5-(3-aminoprop-1-yn-1-yl)-7-methoxybenzofuran-2-carboxamide
4-215	 N-(4-aminobutyl)-5-(3-aminoprop-1-yn-1-yl)-6-methoxybenzofuran-2-carboxamide

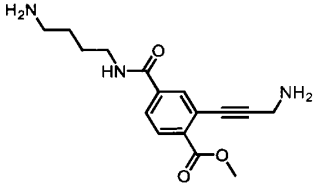
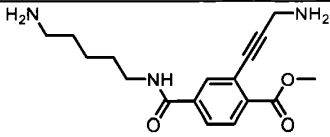
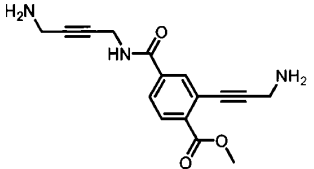
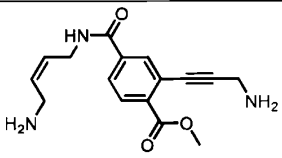
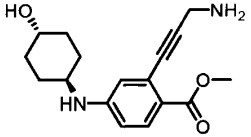
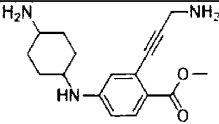
4-216	 5-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)-6-methoxybenzofuran-2-carboxamide
4-217	 5-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)-7-methoxybenzofuran-2-carboxamide
4-224	 N-(7-aminoheptyl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-225	 N-(9-aminononyl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-228	 methyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate dihydrochloride
4-229	 N-(4-aminobutyl)-4-(3-aminoprop-1-yn-1-yl)benzamide

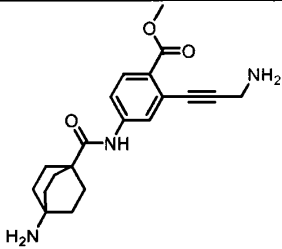
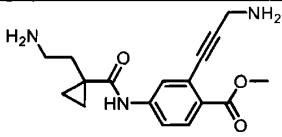
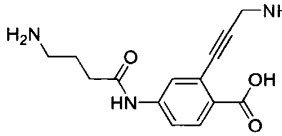
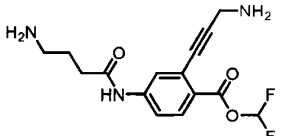
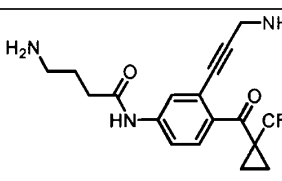
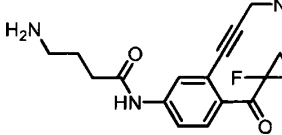
4-231	 5-(3-aminoprop-1-yn-1-yl)-N-(2-aminopyridin-4-yl)furan-2-carboxamide
4-232	 5-(3-(aminooxy)prop-1-yn-1-yl)-N-(3-aminopropyl)furan-2-carboxamide
4-233	 methyl 2-amino-4-(5-((3-aminopropyl)carbamoyl)furan-2-yl)but-3-ynoate
4-234	 methyl 2-(3-(aminooxy)prop-1-yn-1-yl)-5-((3-aminopropyl)carbamoyl)furan-3-carboxylate
4-235	 N-(8-aminooctyl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
5-1	 ethyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate

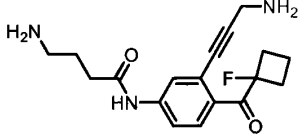
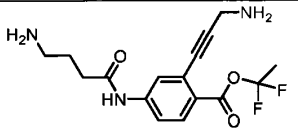
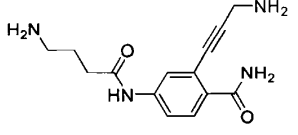
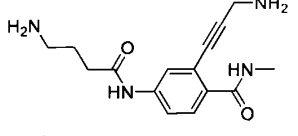
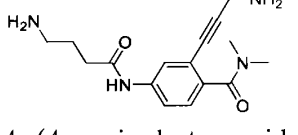
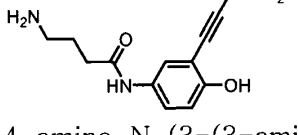
5-2	 isopropyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-3	 cyclopropyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-4	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-aminopropanamido)benzoate
5-5	 methyl 4-(5-aminopentanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-6	 methyl 4-(6-aminohexanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-8	 4-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)butanamide trifluoroacetic acid

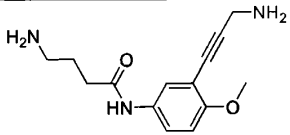
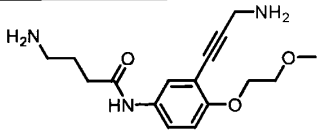
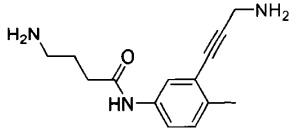
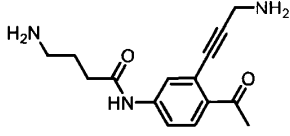
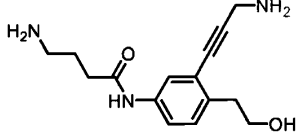
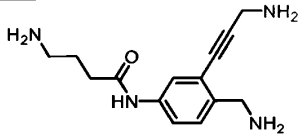
5-9	 5-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)pentanamide
5-10	 methyl 4-((4-aminobutyl)amino)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-11	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-aminopropyl)amino)benzoate
5-12	 methyl 4-(4-aminobutoxy)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-13	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-aminopropoxy)benzoate
5-14	 methyl 4-(3-aminoprop-1-yn-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate

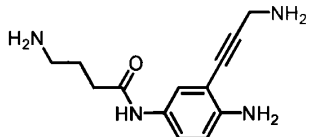
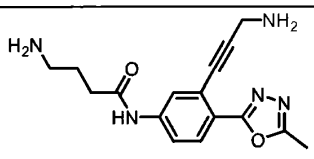
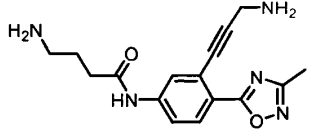
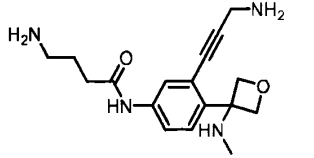
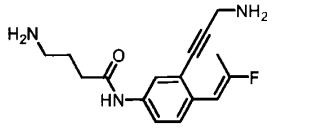
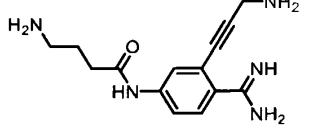
	methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-aminopropanoyl)oxy)benzoate
5-15	 methyl 4-((4-aminobutanoyl)oxy)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-16	 methyl 4-((5-aminopentanoyl)oxy)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-17	 methyl 4-((6-aminohexanoyl)oxy)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-18	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-aminopropyl)carbamoyl)benzoate dihydrochloride
5-19	 methyl 4-((2-aminoethyl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate

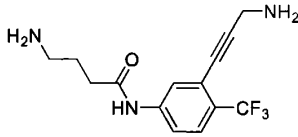
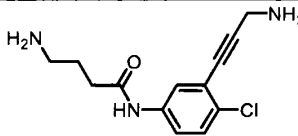
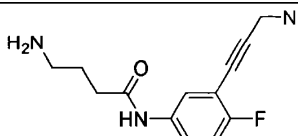
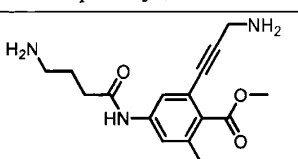
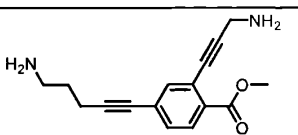
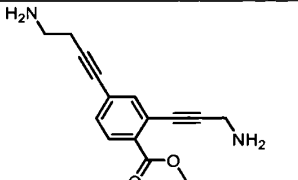
5-20	 methyl 4-((4-aminobutyl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-21	 methyl 4-((5-aminopentyl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-30	 methyl 4-((4-aminobut-2-yn-1-yl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-31	 methyl (Z)-4-((4-aminobut-2-en-1-yl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-34	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(((1r,4r)-4-hydroxycyclohexyl)amino)benzoate
5-35	 methyl 4-((4-aminocyclohexyl)amino)-2-(3-aminoprop-1-yn-1-yl)benzoate

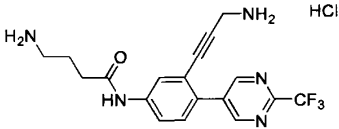
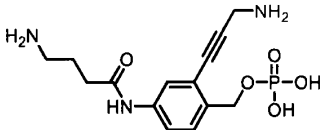
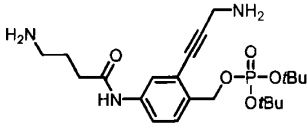
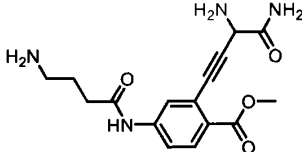
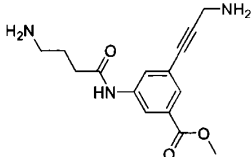
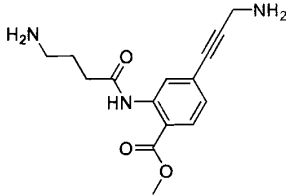
5-49	 methyl 4-(4-aminobicyclo[2.2.2]octane-1-carboxamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-50	 methyl 4-(1-(2-aminoethyl)cyclopropane-1-carboxamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-53	 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoic acid
5-54	 difluoromethyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-55	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-(trifluoromethyl)cyclopropane-1-carbonyl)phenyl)butanamide
5-56	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-(fluoromethyl)cyclopropane-1-carbonyl)phenyl)butanamide

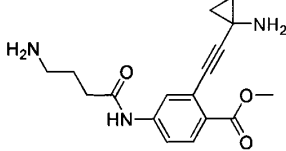
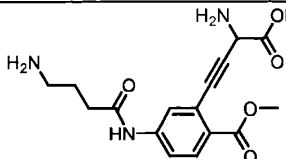
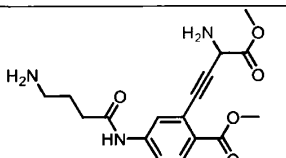
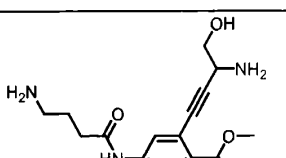
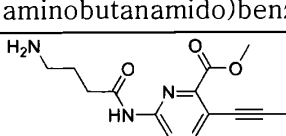
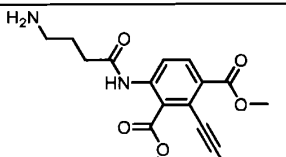
	fluorocyclopropane-1-carbonyl)phenyl)butanamide
5-57	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-fluorocyclobutane-1-carbonyl)phenyl)butanamide
5-58	 1,1-difluoroethyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-59	 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzamide
5-60	 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)-N-methylbenzamide
5-61	 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)-N,N-dimethylbenzamide
5-62	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-hydroxyphenyl)butanamide

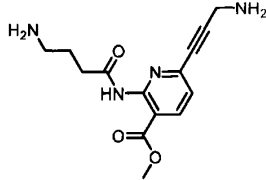
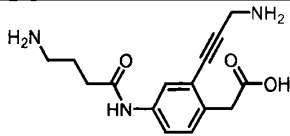
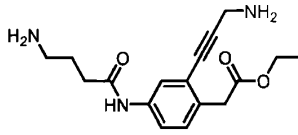
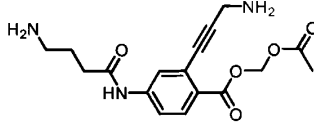
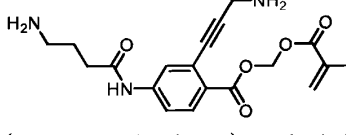
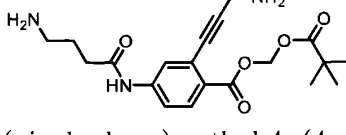
5-63	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-methoxyphenyl)butanamide
5-64	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-methoxyethoxy)phenyl)butanamide
5-65	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-methylphenyl)butanamide
5-66	 N-(4-acetyl-3-(3-aminoprop-1-yn-1-yl)phenyl)-4-aminobutanamide
5-67	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-hydroxyethyl)phenyl)butanamide
5-68	 4-amino-N-(4-(aminomethyl)-3-(3-aminoprop-1-yn-1-yl)phenyl)butanamide

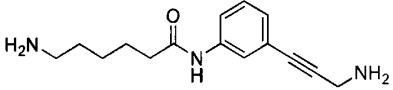
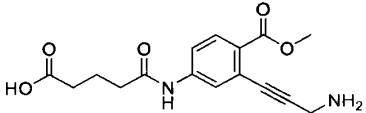
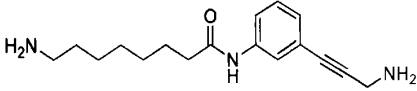
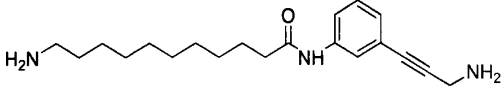
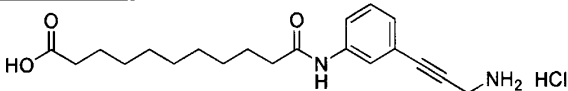
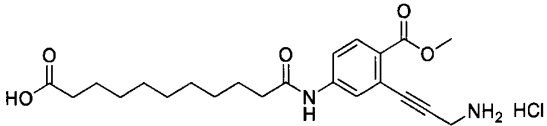
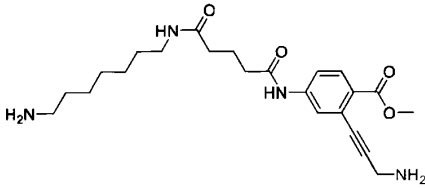
5-69	 4-amino-N-(4-amino-3-(3-aminoprop-1-yn-1-yl)phenyl)butanamide
5-70	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)butanamide
5-71	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)butanamide
5-72	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(3-(methylamino)oxetan-3-yl)phenyl)butanamide
5-73	 (E)-4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-fluoroprop-1-en-1-yl)phenyl)butanamide
5-74	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-carbamimidoylphenyl)butanamide

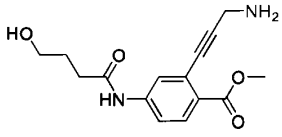
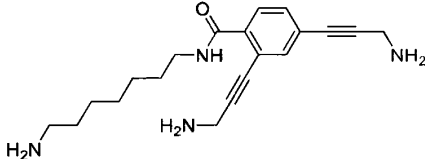
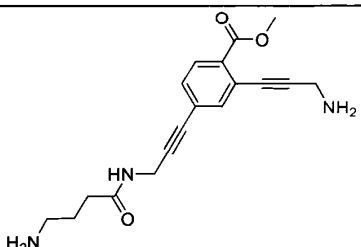
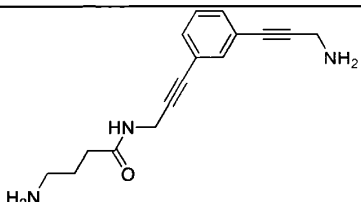
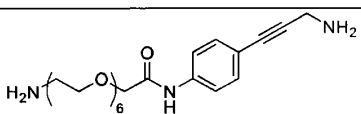
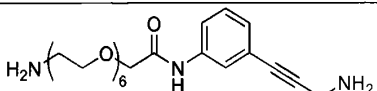
5-75	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(trifluoromethyl)phenyl)butanamide
5-76	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-chlorophenyl)butanamide
5-77	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-fluorophenyl)butanamide
5-78	 methyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)-6-methylbenzoate
5-79	 methyl 4-(5-aminopent-1-yn-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-80	 methyl 4-(4-aminobut-1-yn-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate

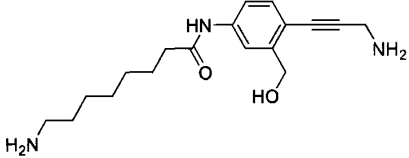
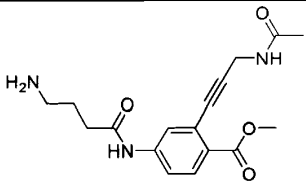
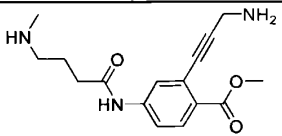
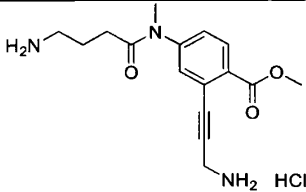
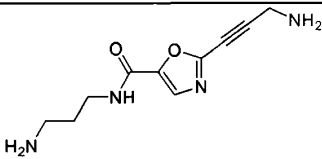
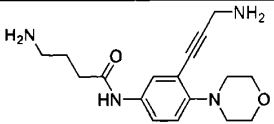
5-81	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)butanamide dihydrochloride
5-82	 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzyl dihydrogen phosphate
5-83	 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzyl di-tert-butyl phosphate
5-87	 methyl 4-(4-aminobutanamido)-2-(3,4-diamino-4-oxobut-1-yn-1-yl)benzoate
5-89	 methyl 3-(4-aminobutanamido)-5-(3-aminoprop-1-yn-1-yl)benzoate
5-90	 methyl 2-(4-aminobutanamido)-4-(3-aminoprop-1-yn-1-yl)benzoate

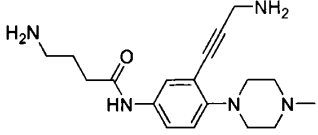
	yl)benzoate
5-92	 methyl 4-(4-aminobutanamido)-2-((1-aminocyclopropyl)ethynyl)benzoate
5-93	 2-amino-4-(5-(4-aminobutanamido)-2-(methoxycarbonyl)phenyl)but-3-ynoic acid
5-94	 methyl 2-(3-amino-4-methoxy-4-oxobut-1-yn-1-yl)-4-(4-aminobutanamido)benzoate
5-95	 methyl 2-(3-amino-4-hydroxybut-1-yn-1-yl)-4-(4-aminobutanamido)benzoate
5-96	 methyl 6-(4-aminobutanamido)-3-(3-aminoprop-1-yn-1-yl)picolinate
5-97	 dimethyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)-6-(methoxycarbonyl)benzoate

	yl)isophthalate
5-98	 methyl 2-(4-(4-aminobutanamido)-6-(3-aminoprop-1-yn-1-yl)nicotinate
5-99	 2-(4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)phenyl)acetic acid
5-100	 ethyl 2-(4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)phenyl)acetate
5-101	 acetoxymethyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-102	 (methacryloyloxy)methyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-103	 (pivaloyloxy)methyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate

5-104	 6-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)hexanamide
5-106	 5-((3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)phenyl)amino)-5-oxopentanoic acid
5-107	 8-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)octanamide
5-108	 11-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)undecanamide
5-109	 11-((3-(3-aminoprop-1-yn-1-yl)phenyl)amino)-11-oxoundecanoic acid hydrochloride
5-110	 11-((3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)phenyl)amino)-11-oxoundecanoic acid hydrochloride
5-113	 methyl 4-(5-((7-aminoheptyl)amino)-5-oxopentanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate

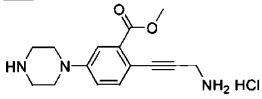
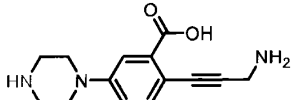
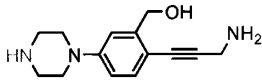
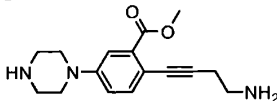
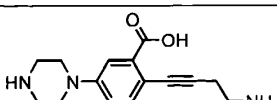
5-115	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-hydroxybutanamido)benzoate
5-121	 N-(7-aminoheptyl)-2,4-bis(3-aminoprop-1-yn-1-yl)benzamide
5-122	 methyl 4-(3-(4-aminobutanamido)prop-1-yn-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-123	 4-amino-N-(3-(3-(3-aminoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl)butanamide
5-126	 20-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-3,6,9,12,15,18-hexaoxaicosanamide
5-127	 20-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-3,6,9,12,15,18-hexaoxaicosanamide

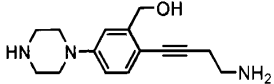
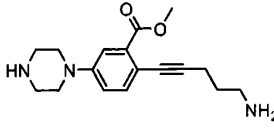
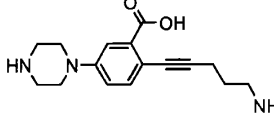
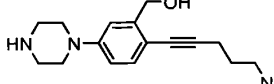
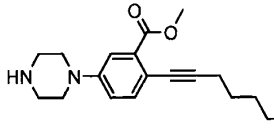
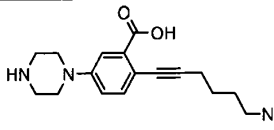
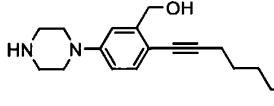
	3,6,9,12,15,18-hexaoxaicosanamide
5-135	 8-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)octanamide
5-148	 methyl 2-(3-acetamidoprop-1-yn-1-yl)-4-(4-aminobutanamido)benzoate
5-149	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(methylamino)butanamido)benzoate
5-150	 methyl 4-(4-amino-N-methylbutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate hydrochloride
5-169	 2-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)oxazole-5-carboxamide
5-170	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(4-aminobutanamido)phenyl)octanamide

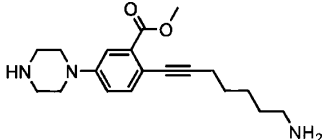
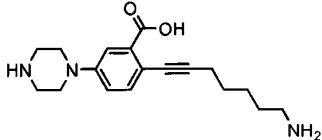
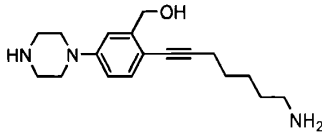
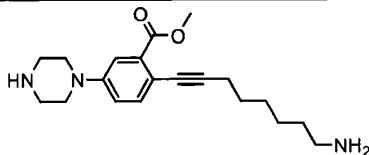
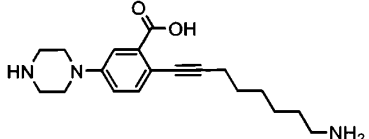
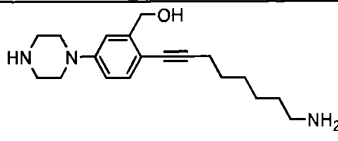
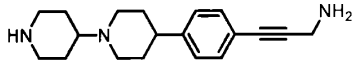
	morpholinophenyl)butanamide
5-171	 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(4-methylpiperazin-1-yl)phenyl)butanamide

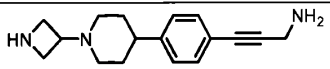
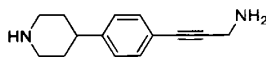
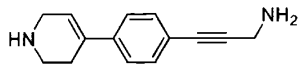
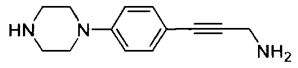
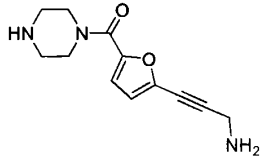
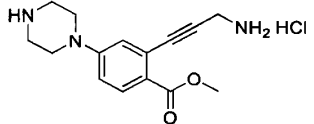
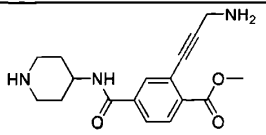
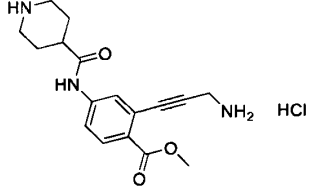
【0081】 특히, 상기 화학식 III으로 표시되는 화합물의 구체적인 예들은 하기 표 3에 제시된 것일 수 있으나, 이에 한정되지 아니한다.

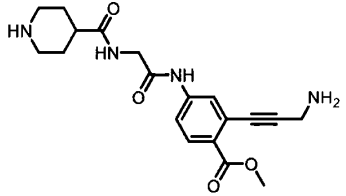
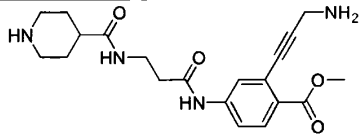
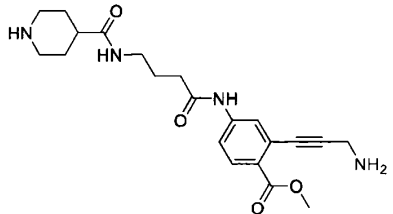
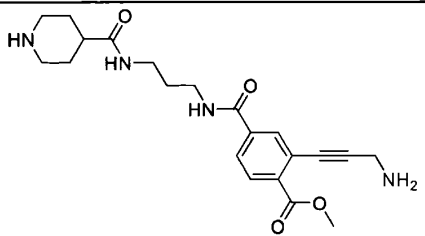
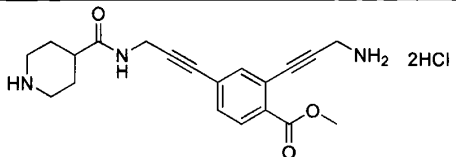
【표 3】

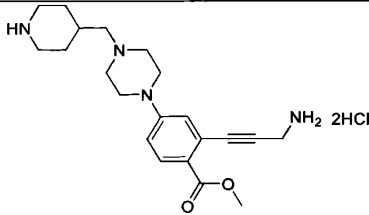
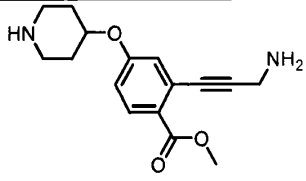
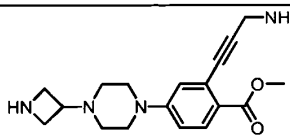
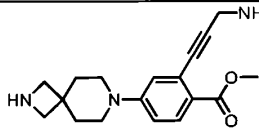
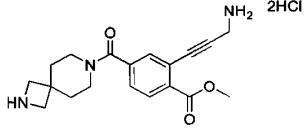
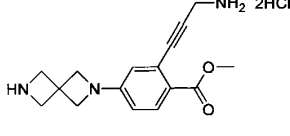
번호	화합물
4-2	 methyl 2-(3-aminoprop-1-yn-1-yl)-5-(piperazin-1-yl)benzoate hydrochloride
4-3	 2-(3-aminoprop-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-4	 (2-(3-aminoprop-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol
4-94	 methyl 2-(4-aminobut-1-yn-1-yl)-5-(piperazin-1-yl)benzoate
4-95	 2-(4-aminobut-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid

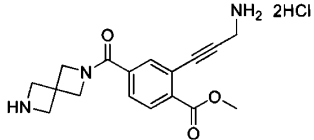
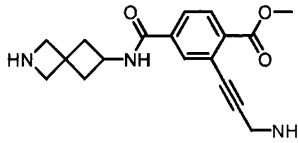
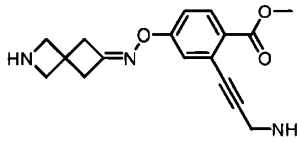
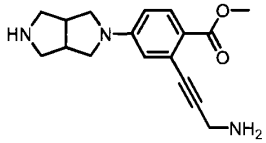
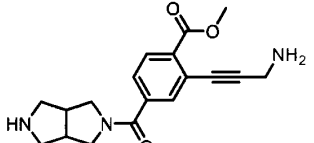
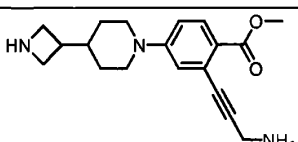
4-96	 (2-(4-aminobut-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol
4-97	 methyl 2-(5-aminopent-1-yn-1-yl)-5-(piperazin-1-yl)benzoate
4-98	 2-(5-aminopent-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-99	 (2-(5-aminopent-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol
4-100	 methyl 2-(6-aminohex-1-yn-1-yl)-5-(piperazin-1-yl)benzoate
4-101	 2-(6-aminohex-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-102	 (2-(6-aminohex-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol

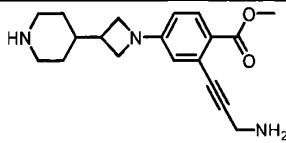
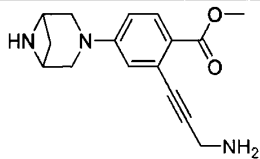
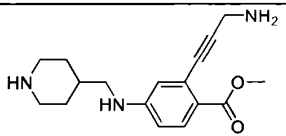
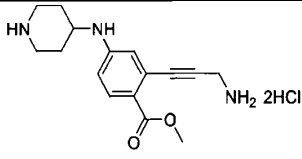
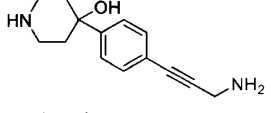
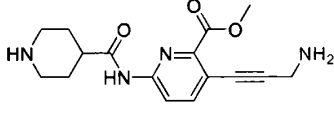
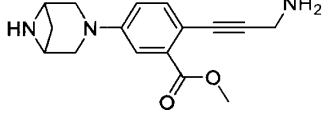
4-103	 methyl 2-(7-aminohept-1-yn-1-yl)-5-(piperazin-1-yl)benzoate
4-104	 2-(7-aminohept-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-105	 (2-(7-aminohept-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol
4-106	 methyl 2-(8-aminooct-1-yn-1-yl)-5-(piperazin-1-yl)benzoate
4-107	 2-(8-aminooct-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-108	 (2-(8-aminooct-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol
4-134	 3-(4-([1,4'-bipiperidin]-4-yl)phenyl)prop-2-yn-1-amine

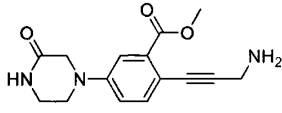
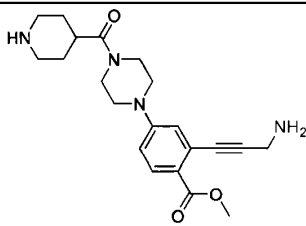
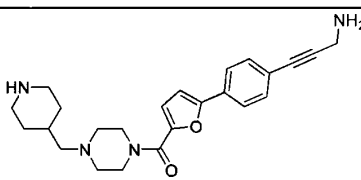
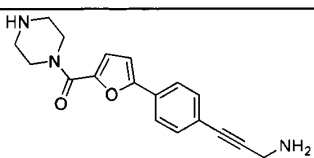
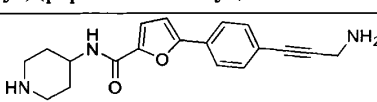
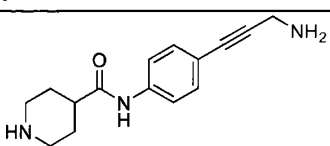
4-135	 3-(4-(1-(azetidin-3-yl)piperidin-4-yl)phenyl)prop-2-yn-1-amine
4-136	 3-(4-(piperidin-4-yl)phenyl)prop-2-yn-1-amine
4-146	 3-(4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)prop-2-yn-1-amine
4-226	 3-(4-(piperazin-1-yl)phenyl)prop-2-yn-1-amine
4-227	 (5-(3-aminoprop-1-yn-1-yl)furan-2-yl)(piperazin-1-yl)methanone
5-7	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperazin-1-yl)benzoate hydrochloride
5-22	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidin-4-ylcarbamoyl)benzoate
5-23	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidine-4-carboxamido)benzoate hydrochloride

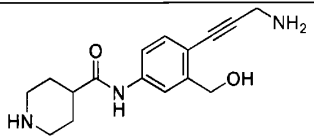
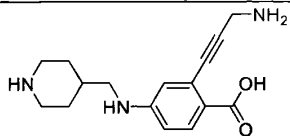
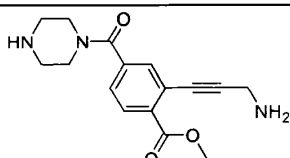
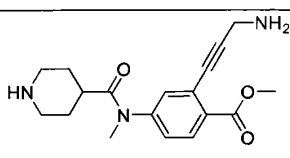
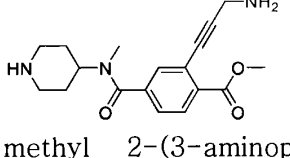
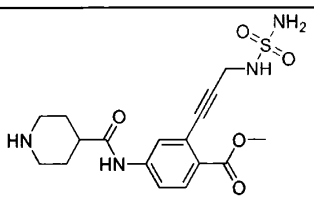
5-24	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2-(piperidine-4-carboxamido)acetamido)benzoate
5-25	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(piperidine-4-carboxamido)propanamido)benzoate
5-26	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(piperidine-4-carboxamido)butanamido)benzoate
5-27	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-(piperidine-4-carboxamido)propyl)carbamoyl)benzoate
5-28	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(piperidine-4-carboxamido)prop-1-yn-1-yl)benzoate dihydrochloride

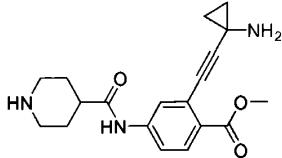
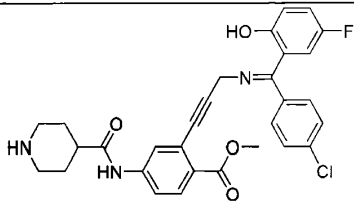
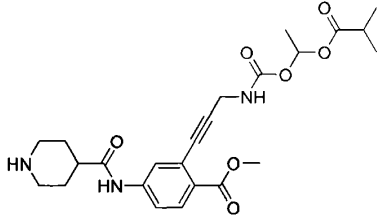
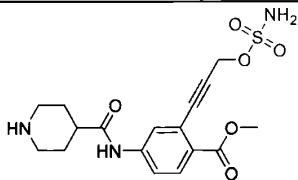
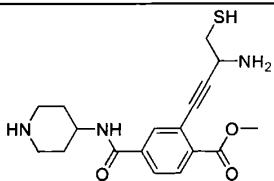
5-29	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(piperidin-4-ylmethyl)piperazin-1-yl)benzoate dihydrochloride
5-36	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidin-4-yloxy)benzoate
5-37	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(azetidin-3-yl)piperazin-1-yl)benzoate
5-38	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,7-diazaspiro[3.5]nonan-7-yl)benzoate
5-39	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,7-diazaspiro[3.5]nonane-7-carbonyl)benzoate dihydrochloride
5-40	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptan-2-yl)benzoate dihydrochloride

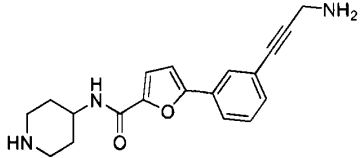
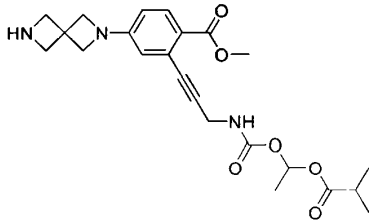
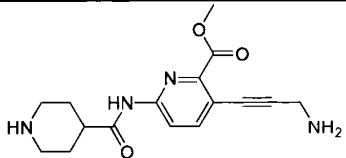
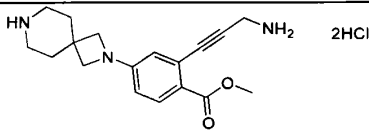
5-41	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptan-2-carbonyl)benzoate dihydrochloride
5-42	 methyl 4-(((2-azaspiro[3.3]heptan-6-yl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-43	 methyl 4-(((2-azaspiro[3.3]heptan-6-ylidene)amino)oxy)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-44	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)benzoate
5-45	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzoate
5-46	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(azetidin-3-yl)piperidin-1-yl)benzoate

5-47	
	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(piperidin-4-yl)azetidin-1-yl)benzoate
5-48	
	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3,6-diazabicyclo[3.1.1]heptan-3-yl)benzoate
5-85	
	methyl 2-(3-aminoprop-1-yn-1-yl)-4-((piperidin-4-ylmethyl)amino)benzoate
5-86	
	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidin-4-ylamino)benzoate dihydrochloride
5-88	
	4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperidin-4-ol
5-112	
	methyl 3-(3-aminoprop-1-yn-1-yl)-6-(piperidine-4-carboxamido)picolinate
5-118	
	methyl 2-(3-aminoprop-1-yn-1-yl)-5-(3,6-diazabicyclo[3.1.1]heptan-3-yl)benzoate

	diazabicyclo[3.1.1]heptan-3-yl)benzoate
5-119	 methyl 2-(3-aminoprop-1-yn-1-yl)-5-(3-oxopiperazin-1-yl)benzoate
5-120	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(piperidine-4-carbonyl)piperazin-1-yl)benzoate
5-124	 (5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-yl)(4-(piperidin-4-ylmethyl)piperazin-1-yl)methanone
5-125	 (5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-yl)(piperazin-1-yl)methanone
5-129	 5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(piperidin-4-yl)furan-2-carboxamide
5-131	 N-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperidine-4-carboxamide

5-134	 N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperidine-4-carboxamide
5-139	 2-(3-aminoprop-1-yn-1-yl)-4-((piperidin-4-ylmethyl)amino)benzoic acid
5-140	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperazine-1-carbonyl)benzoate
5-152	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(N-methylpiperidine-4-carboxamido)benzoate
5-153	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(methyl(piperidin-4-yl)carbamoyl)benzoate
5-154	 methyl 4-(piperidine-4-carboxamido)-2-(3-(sulfamoylamino)prop-1-yn-1-yl)benzoate

5-155	 methyl 2-(((1-aminocyclopropyl)ethynyl)-4-(piperidine-4-carboxamido)benzoate
5-156	 methyl 2-(3-(((4-chlorophenyl)(5-fluoro-2-hydroxyphenyl)methylene)amino)prop-1-yn-1-yl)-4-(piperidine-4-carboxamido)benzoate
5-157	 methyl 2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)-4-(piperidine-4-carboxamido)benzoate
5-158	 methyl 4-(piperidine-4-carboxamido)-2-(3-(sulfamoyloxy)prop-1-yn-1-yl)benzoate
5-159	 methyl 2-(3-amino-4-mercaptobut-1-yn-1-yl)-4-(piperidine-4-ylcarbamoyl)benzoate

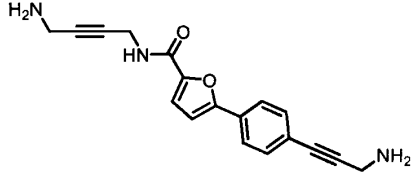
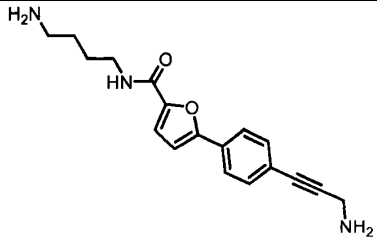
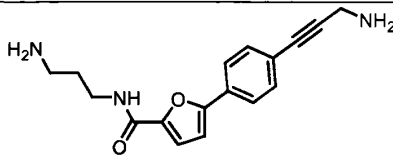
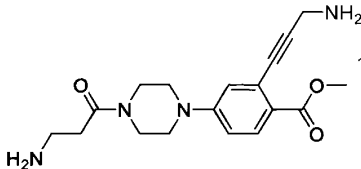
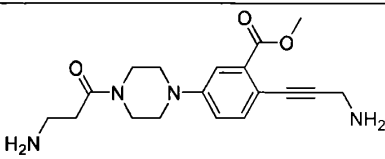
5-160	 5-(3-(3-aminoprop-1-yn-1-yl)phenyl)-N-(piperidin-4-yl)furan-2-carboxamide
5-162	 methyl 2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptan-2-yl)benzoate
5-167	 methyl 3-(3-aminoprop-1-yn-1-yl)-6-(piperidine-4-carboxamido)picolinate
5-168	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,7-diazaspiro[3.5]nonan-2-yl)benzoate dihydrochloride

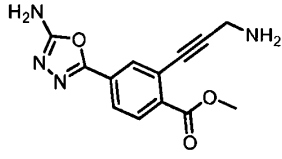
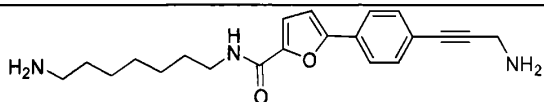
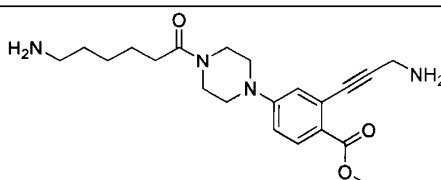
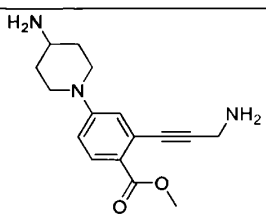
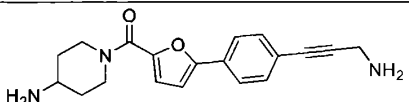
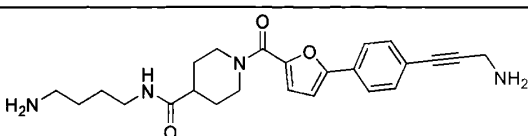
【0082】 특히, 상기 화학식 IV로 표시되는 화합물의 구체적인

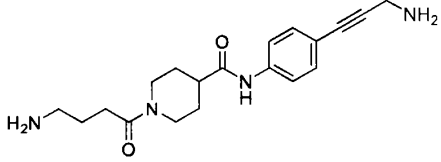
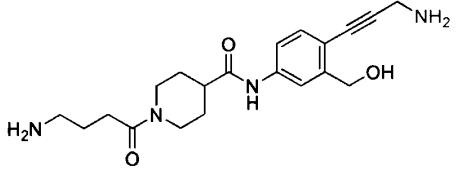
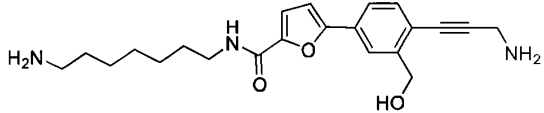
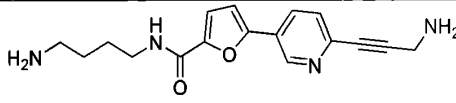
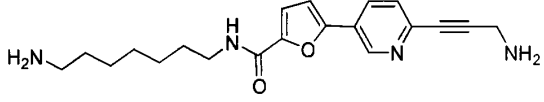
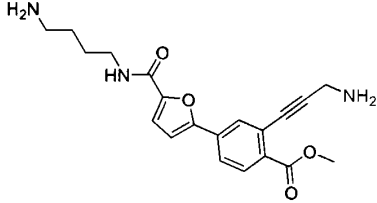
예들은 하기 표 4에 제시된 것일 수 있으나, 이에 한정되지 아니한다.

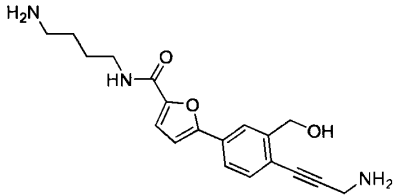
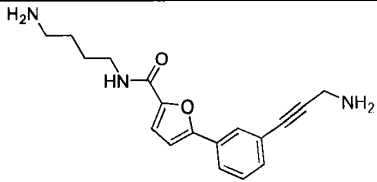
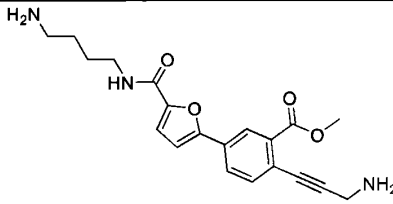
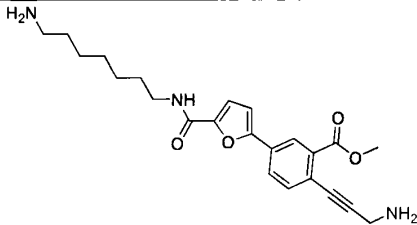
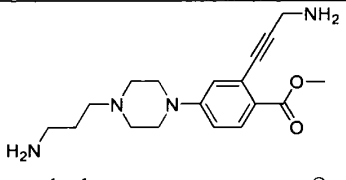
【표 4】

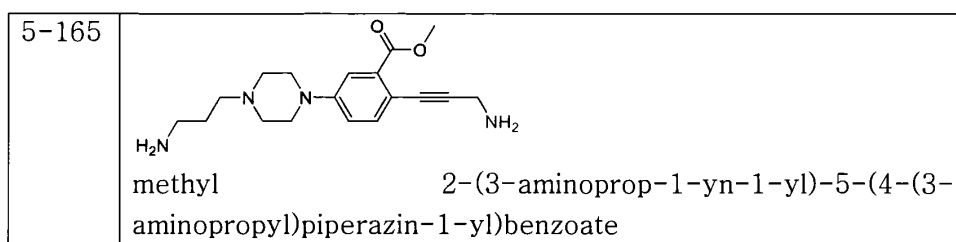
번호	화합물
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4-207	 N-(4-aminobut-2-yn-1-yl)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carboxamide
4-208	 N-(4-aminobutyl)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carboxamide
4-211	 5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(3-aminopropyl)furan-2-carboxamide
5-32	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-aminopropanoyl)piperazin-1-yl)benzoate
5-33	 methyl 2-(3-aminoprop-1-yn-1-yl)-5-(4-(3-aminopropanoyl)piperazin-1-yl)benzoate

5-51	 methyl 4-(5-amino-1,3,4-oxadiazol-2-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-111	 N-(7-aminoheptyl)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carboxamide
5-114	 methyl 4-(4-(6-aminohexanoyl)piperazin-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-117	 methyl 4-(4-aminopiperidin-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-128	 (4-aminopiperidin-1-yl)(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-yl)methanone
5-130	 N-(4-aminobutyl)-1-(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carbonyl)piperidine-4-carboxamide

5-132	 1-(4-aminobutanoyl)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperidine-4-carboxamide
5-133	 1-(4-aminobutanoyl)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperidine-4-carboxamide
5-136	 N-(7-aminoheptyl)-5-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)furan-2-carboxamide
5-137	 N-(4-aminobutyl)-5-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)furan-2-carboxamide
5-138	 N-(7-aminoheptyl)-5-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)furan-2-carboxamide
5-141	 methyl 4-(5-((4-aminobutyl)carbamoyl)furan-2-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate

5-142	 N-(4-aminobutyl)-5-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)furan-2-carboxamide
5-143	 N-(4-aminobutyl)-5-(3-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carboxamide
5-144	 methyl 5-(5-((4-aminobutyl)carbamoyl)furan-2-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-145	 methyl 5-(5-((7-aminoheptyl)carbamoyl)furan-2-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-164	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-aminopropyl)piperazin-1-yl)benzoate



【0083】 특히, 상기 화학식 I 내지 IV로 표시되는 화합물들에서, W₁을 포함한 프로파질기(propargyl)에 존재하는 아민기(-NH₂)는 유비퀴틴이 결합하는 자리이다. 따라서, 상기 화학식 I 내지 IV로 표시되는 화합물들은 그 자체로, 또는 다른 표적 단백질 또는 폴리펩티드에

5 특이적으로 결합하는 리간드와 결합하여 상기 표적 단백질 또는 폴리펩티드의 분해자(degrader)가 될 수 있다. 상술한 바와 같이, 상기 화학식 I 내지 IV로 표시되는 화합물들에서 W₁을 포함한 프로파질기(propargyl)에 존재하는 아민기(-NH₂)는 유비퀴틴이 결합하는 자리이므로, 상기 화학식 I 내지 IV로 표시되는 화합물들이 상기 다른

10 표적 단백질 또는 폴리펩티드에 대한 리간드와 연결되는 경우에는, 상기 W₁을 포함한 프로파질기(propargyl)에 존재하는 아민기(-NH₂)는 제외한 자리에서 연결되는 것이 바람직하다.

【0084】

【0085】 2. 표적 단백질/폴리펩티드 분해자(target protein/polypeptide degrader)

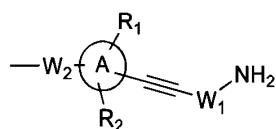
15

【0086】 본 발명의 다른 측면은 TBM-UBM의 화학 구조를 가지는 화합물 또는 이의 약학적으로 허용 가능한 염, 이성질체, 용매화물,

수화물 또는 프로드럭을 제공한다.

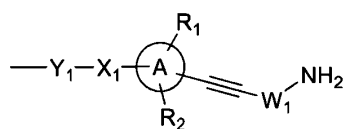
【0087】 상기 UBM은 하기 화학식 V 내지 VIII로 표시되는 화학 구조일 수 있다.

【0088】 [화학식 V]



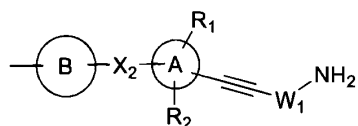
5 【0089】

【0090】 [화학식 VI]



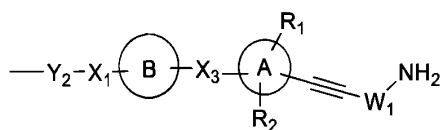
【0091】

【0092】 [화학식 VII]



【0093】

10 【0094】 [화학식 VIII]



【0095】

【0096】 상기 화학식 V 내지 화학식 VIII에서, 치환기 W₁, A, R₁, R₂, X₁, X₂, X₃ 및 B는 각각 독립적으로, 상기 화학식 I 내지 화학식 IV로 표시되는 화합물과 관련하여 설명한 바와 동일하다.

15 【0097】 한편, 상기 화학식 V 내지 화학식 VIII에서, 치환기

W_2 , Y_1 및 Y_2 는 각각 독립적으로 하기와 같이 정의될 수 있다.

【0098】 상기 W_2 는 직접 결합이거나, 또는 -알킬렌-, -알케닐렌- 및 -알키닐렌-으로 구성되는 군에서 선택되는 어느 하나일 수 있다. 예컨대, 상기 W_2 는 직접 결합이거나, 또는 -알케닐렌- 및 -알키닐렌-
5 으로 구성되는 군에서 선택되는 어느 하나일 수 있다. 구체적으로, 상기 W_2 는 직접 결합이거나, 또는 -알키닐렌-일 수 있다.

【0099】 또한, 상기 W_2 는 중수소, 알킬, $C(O)OR'$, $C(O)N(R')(R'')$, 알킬렌- $C(O)OR'$, 알킬렌- $C(O)N(R')(R'')$, 알킬렌- OR' , 알킬렌- SR' , 알킬렌- $N(R')(R'')$, 알킬렌- $OP(O)(OR')(OR'')$, 알킬렌-
10 $P(O)(OR')(OR'')$ 및 알킬렌- $OP(O)(R')(R'')$ 으로 구성된 군에서 선택되는 적어도 하나로 치환 또는 비치환될 수 있다. 예컨대, 상기 W_2 는 알킬렌- OR' , 알킬렌- SR' 및 알킬렌- $OP(O)(OR')(OR'')$ 으로 구성된 군에서 선택되는 적어도 하나로 치환 또는 비치환될 수 있다. 구체적으로, 상기 W_2 는 알킬렌- OR' 및 알킬렌- $OP(O)(OR')(OR'')$ 으로 구성된 군에서 선택되는
15 적어도 하나로 치환 또는 비치환될 수 있다.

【0100】 상기 Y_1 은 직접 결합이거나, 알킬렌, 알케닐렌, 알키닐렌, $-(CH_2CH_2O)_nCH_2-$ 및 $-(CH_2CH_2O)_nCH_2CH_2-$ 로 구성되는 군에서 선택되는 어느 하나이고, 상기 n 은 1~4일 수 있다. 예컨대, 상기 Y_1 은 직접 결합이거나, 알킬렌, 알케닐렌, 알키닐렌, $-(CH_2CH_2O)_nCH_2-$ 및 -
20 $(CH_2CH_2O)_nCH_2CH_2-$ 로 구성되는 군에서 선택되는 어느 하나이고, 상기 n 은

1~2일 수 있다. 구체적으로, 상기 Y_1 은 직접 결합, 알킬렌, 알케닐렌 및 알키닐렌으로 구성되는 군에서 선택되는 어느 하나일 수 있다.

【0101】 상기 Y_2 는 직접 결합, 알킬렌, 알케닐렌, 알키닐렌, 헤테로시클로알킬렌 및 헤테로시클로알케닐렌으로 구성되는 군에서 선택되는
5 어느 하나일 수 있다. 예컨대, 상기 Y_2 는 직접 결합, 알킬렌, 알케닐렌, 알키닐렌 및 헤테로시클로알킬렌으로 구성되는 군에서 선택되는 어느 하나일 수 있다. 구체적으로, 상기 Y_2 는 직접 결합, 알킬렌 및 헤테로시클로알킬렌으로 구성되는 군에서 선택되는 어느 하나일 수 있다.

【0102】 또한, 상기 치환기들을 구성하는 작용기들에서 R' 및
10 R'' 은 각각 독립적으로 수소 또는 알킬일 수 있다.

【0103】 상기 TBM은 표적 단백질 또는 폴리펩티드에 결합하는 부분(moiety)일 수 있다.

【0104】 상기 표적 단백질 또는 폴리펩티드는 본 발명에 따른 화합물이 결합하여 분해할 대상, 즉 표적이 되는 단백질 또는 폴리펩티드를
15 의미한다. 상기 표적 단백질 또는 폴리펩티드는 임의의 단백질 또는 폴리펩티드뿐만 아니라, 이의 단편, 이의 유사체 및/또는 이의 동족체를 포함한다. 상기 표적 단백질 또는 폴리펩티드는 구조, 조절, 호르몬, 효소, 유전자, 면역학, 수축, 저장, 운송, 그리고 신호전달을 비롯한 임의의 생물학적 기능 또는 활성을 갖는 단백질 또는 폴리펩티드일 수 있다. 일
20 예로, 상기 표적 단백질 또는 폴리펩티드는 구조 단백질, 수용체, 효소, 세포

표면 단백질, 촉매 활성, 아로마타아제 활성, 운동 활성, 헬리카아제 활성, 물질대사 과정(동화 및 분해대사), 항산화 활성, 단백질분해, 생합성, 키나아제 활성을 갖는 단백질, 산화환원 효소 활성, 전달효소 활성, 가수분해효소 활성, 리아제 활성, 이성화효소 활성, 리가아제 활성, 효소조절인자 활성, 신호 변환기 활성, 구조적 분자 활성, 결합 활성(단백질, 지질 탄수화물), 수용체 활성, 세포운동성, 막 융합, 세포 통신, 생물학적 과정의 조절, 발달, 세포 분화, 자극에 대한 반응에 관련된 단백질을 비롯하여, 세포의 통합된 기능에 관련된 단백질, 행동 단백질, 세포 부착 단백질, 세포 사멸에 관련된 단백질, 수송(단백질 전달체 활성, 핵 수송, 이온 전달체 활성, 통로 전달체 활성, 담체 활성, 투과효소 활성, 분비활성, 전자 전달체 활성, 병인, 샤프론 조절인자 활성, 핵산 결합 활성, 전사 조절인자 활성, 세포의 조직화 및 생물발생 활성, 번역 조절인자 활성 포함)에 관련된 단백질일 수 있다. 다른 예로, 상기 표적 단백질 또는 폴리펩티드는 약물 요법을 위한 표적으로서 다양한 다른 것들 중에서 인간, 미생물, 바이러스, 균류 및 기생충을 비롯한 미생물, 바이러스, 균류 및 기생충, 가축을 비롯한 다른 동물, 항생제에 대한 표적의 결정을 위한 미생물 및 다른 길항미생물과 식물, 그리고 심지어 바이러스를 비롯하여, 진핵생물이나 원핵생물로부터 유래한 단백질 또는 폴리펩티드일 수 있다.

【0105】 보다 구체적으로, 상기 표적 단백질 또는 폴리펩티드는 인간을 대상으로 하는 치료제로 이용되는 다수 약물의 표적일 수 있다.

예컨대, 상기 표적 단백질 또는 폴리펩티드는 B7.1 및 B7, TNFR1m, TNFR2, NADPH 옥시다아제, Bcl2Bax를 포함하는 세포사멸 기전에 연관된 단백질들, Ras, Raf. 를 포함하는 MAP/ERK 신호 경로 관련 단백질, NF-
 kB신호 경로에 연관된 단백질들, mTOR 신호 경로에 연관된 단백질들, wnt
 5 신호 경로에 연관된 단백질들, AKT 신호 경로에 연관된 단백질들, JAK-STAT 신호 경로에 연관된 단백질들, NOX 복합체들과 그에 신호 경로에 연관된 단백질들. 혈관 내피 성장 인자 및 수용체와 그에 신호 경로에 연관된 단백질들, TLR 수용체 및 그에 신호 경로에 연관된 단백질들, G 단백질 연결 수용체들과 그 신호 경로에 연관된 단백질들, TCR-MHC
 10 복합체 연관 수용체들과 신호 경로에 연관된 단백질들, 세포주기 검문 지점 단백질들과 그 신호 경로에 연관된 단백질들, 유전자 전사 및 번역을 조절하는 인자를 포함하는 단백질, 유전자 복제에 연관된 단백질 및 그 조절 인자 단백질들. 유전자 발현을 위한 히스톤 단백질 조절 인자를 포함하는 단백질, 후성 유전을 조절하는 인자 및 관련 단백질들. 세포 고격을
 15 구성하고 그를 조절하는 단백질들, 세포내 수송을 조절 하는 단백질과 그를 조절하는 단백질들, C5a 수용체, 도파민 수용체들, 5HT 수용체들, 케모킨 수용체들, 히스타민 수용체들, CD40/CD40L, CD23, CD124, CD4, CD5, VCAM, VLA-4 인테그린, 셀렉틴, ICOS, ICAM1, IL-2 수용체, IL-1 수용체, TNF-알파 수용체, 및 그 밖의 사이토카인 수용체들 및 케모카인 수요체,
 20 옥시토신 수용체, 글리신 수용체, 노르아드레날린 재흡수 수용체, 엔도텔린

수용체, 에스트로겐 수용체, 안드로겐 수용체, 아데노신 수용체, NGF에 대한 TrkA 수용체, 비트로넥틴 수용체, 인테그린 수용체, 뉴로키닌 및 수용체, 상피세포 성장인자 수용체들, 푸린성 수용체(P2Y1, P2Y2, P2Y4, P2Y6, P2X1-7), EGF 수용체, HMG-CoA 환원효소, PDE V 포스포디에스테라아제

5 유형, PDE IV 포스포디에스테라아제 유형 4, PDE I, PDEII, PDEIII, 스쿠알렌 시클라아제 저해제, 산화질소(NO) 신타아제, 시클로옥시게나아제 1, 시클로옥시게나아제 2, 5-리폭시게나아제, 트립신분해효소 세린 프로테아제, 티미딜산염 신타아제, 퓨린 뉴클레오시드 인산화효소, GAPDH

트라이파노소마성, 글리코겐 인산화효소, 탄산 탈수효소, 이의 유사체, P-

10 당단백질 및 MRP, 티로신 키나아제, 티로신 키나아제 p56 lck, Cat+ 통로, 이노신 일인산염 탈수소효소, 인터류킨-1 전환 효소, 카스파제글리신아미드 리보뉴클레오티드 포르밀 전달효소, 폴리(ADP-리보오스) 중합효소, 아세틸콜린 에스테라제, 사이클린 의존성 키나아제, 마이크로솜 전달 단백질

저해제, 담즙산 수송 저해제, 5 알파 환원효소 저해제, 안지오텐신 11,

15 아데노신 수용체, 아데노신 키나아제 및 AMP 탈아미노효소, 파르네실전달효소, 게라닐게라닐 전달효소, 베타-아밀로이드, 티로신 키나아제 Her-21 neu, 텔로머라아제 저해, 세포질 포스포리파아제A2, 그리고 티로신 키나아제, 아세틸-CoA 카르복실라아제, 아데닐로숙신산염 합성효소, 프로토포피리노겐 옥시다아제 및 에놀피루빌쉬키 메이트-인산염

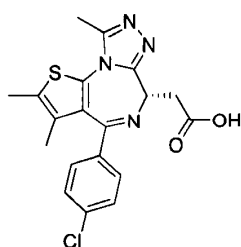
20 신타아제, 엑디손 20-모노산소첨가효소, GABA 게이팅된 염화물 통로의

이온 통로, 전압-민감성 나트륨 통로 단백질, 나트륨 통로, 칼슘 방출 통로 단백질들, 염화물 통로 단백질들과 이 단백질로부터 유도된 폴리펩타이드, , HCV NS3 프로테아제, HCV NS3 RNA 헬리카아제, 리노바이러스 3C 프로테아제, 단순 헤르페스 바이러스-1(HSV-I) 프로테아제, 5 시토메갈로바이러스(CMV) 프로테아제, 다중 약제 내성(MDR) 단백질들, HIV 1 프로테아제, HIV 1 인테그라아제, 인플루엔자, 뉴라미니다아제, B형 간염 역전사효소와 같은 세균 혹은 바이러스 단백질들과 그로부터 유도된 폴리펩타이드들, 혈관작용성 장펩티드, 프리온, 신경펩티드 Y 및 수용체들과 같은 단백질들과 폴리 펩타이드들을 포함한다. 특히, 상기 표적 단백질 또는 10 폴리펩티드는 브로모도메인-내포 단백질, Aurora 키나제 A 또는 p38 MAPK(mitogen activated protein kinase)일 수 있다.

【0106】 상술한 바와 같이, 상기 TBM은 상기 표적 단백질 또는 폴리펩티드에 결합하는 부분(moiety)이므로, 상기 표적 단백질 또는 폴리펩티드에 결합하는 것으로 알려진 다양한 화합물들이 무제한적으로 15 상기 TBM으로 이용될 수 있다. 예컨대, 상기 TBM으로는 브로모도메인-내포 단백질을 표적으로 하는 화합물, Aurora 키나제 A를 표적으로 하는 화합물, p38 MAPK를 표적으로 하는 화합물 등을 들 수 있으나, 이에 한정되는 것은 아니다. 특히, 상기 브로모도메인-내포 단백질을 표적으로 하는 화합물은 BRD4 저해제일 수 있고, 상기 BRD4 저해제는 하기 화학식 20 1의 화학 구조를 가지는 것일 수 있다. 또한, 상기 Aurora 키나제 A를

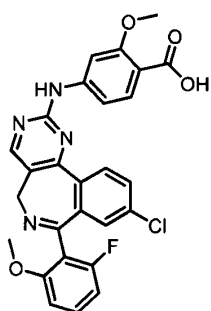
표적으로 하는 화합물은 Aurora A 저해제일 수 있고, 상기 Aurora A 저해제는 하기 화학식 2의 화학 구조를 가지는 것일 수 있다. 또한, 상기 p38 MAPK를 표적으로 하는 화합물은 p38 저해제일 수 있고, 상기 p38 저해제는 하기 화학식 3의 화학 구조를 가지는 것일 수 있다.

5 【0107】 [화학식 1]



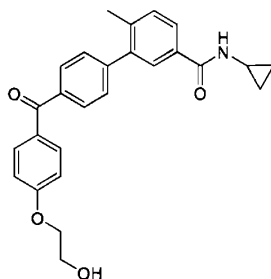
【0108】

【0109】 [화학식 2]



【0110】

【0111】 [화학식 3]



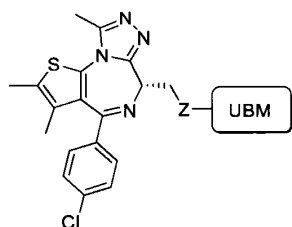
10

【0112】

【0113】 한편, 상기 TBM과 UBM은 공유 결합으로 연결되며,
 상기 공유 결합 부위가 직접 결합이거나, 또는 $-N(R')-$, $-O-$, $-C(R')(R'')$ -
 $O-$, $-S-$, $-C(O)-$, $-SO-$, SO_2- , $=N-O-$, $-O-N=$, $-OC(O)-$, $-C(O)O-$, $-$
 $N(R')C(O)-$, $-C(O)N(R')-$, $-OC(O)O-$, $-OC(O)N(R')-$, $-N(R')C(O)O-$, $-$
 5 $N(R')SO-$, $-SON(R')-$, $-N(R')SO_2-$ 및 $-SO_2N(R')-$ 로 구성되는 군에서
 선택되는 어느 하나를 형성하도록 TBM과 UBM은 각각 변형될 수 있다.
 예컨대, 상기 TBM과 UBM이 연결되는 공유 결합 부위가 직접 결합이거나,
 또는 $-N(R')-$, $-O-$, $-C(R')(R'')$ - $O-$, $-OC(O)-$, $-OC(O)N(R')-$ 및 $-$
 $C(O)N(R')-$ 로 구성되는 군에서 선택되는 어느 하나를 형성하도록 TBM과
 10 UBM은 각각 변형될 수 있다. 구체적으로는, 상기 TBM과 UBM이 연결되는
 공유 결합 부위가 직접 결합이거나, 또는 $-O-$, $-C(R')(R'')$ - $O-$, $-OC(O)-$,
 $-OC(O)N(R')-$ 및 $-C(O)N(R')-$ 로 구성되는 군에서 선택되는 어느 하나를
 형성하도록 TBM과 UBM은 각각 변형될 수 있다. 따라서, 예를 들어, 상기
 TBM이 상기 화학식 1의 화학 구조를 가지는 화합물인 경우에는 상기
 15 UBM과 결합하여 하기 화학식 4의 화학 구조를 가지는 화합물이 될 수
 있고, 상기 TBM이 상기 화학식 2의 화학 구조를 가지는 화합물인 경우에는
 상기 UBM과 결합하여 하기 화학식 5의 화학 구조를 가지는 화합물이 될
 수 있고, 상기 TBM이 상기 화학식 3의 화학 구조를 가지는 화합물인
 경우에는 상기 UBM과 결합하여 하기 화학식 6의 화학 구조를 가지는
 20 화합물이 될 수 있으며, 하기 화학식 4 내지 화학식 6에서 각각 독립적으로

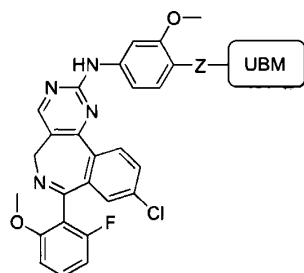
Z는 직접 결합이거나, 또는 -N(R')-, -O-, -C(R')(R'')-O-, -S-, -C(O)-, -SO-, SO₂-, =N-O-, -O-N=, -OC(O)-, -C(O)O-, -N(R')C(O)-, -C(O)N(R')-, -OC(O)O-, -OC(O)N(R')-, -N(R')C(O)O-, -N(R')SO-, -SON(R')-, -N(R')SO₂- 및 -SO₂N(R')-로 구성되는 군에서 선택되는 어느
 5 하나일 수 있는 것이고, 상기 R' 및 R''은 각각 독립적으로 수소 또는 알킬이다.

【0114】 [화학식 4]



【0115】

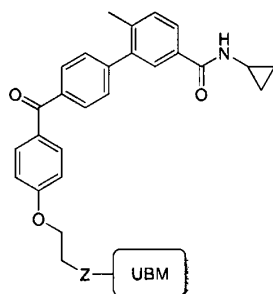
【0116】 [화학식 5]



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【0117】

【0118】 [화학식 6]

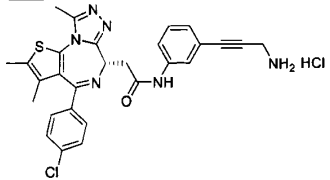
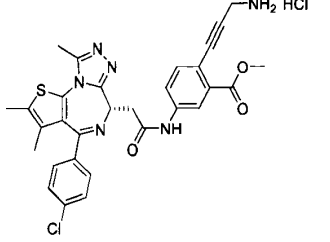
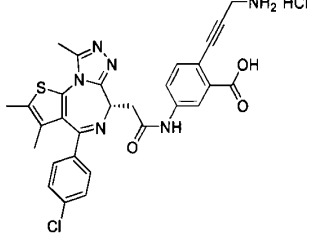
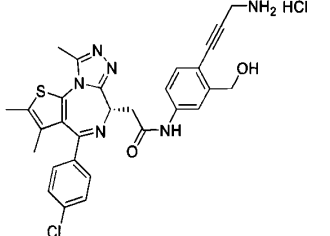


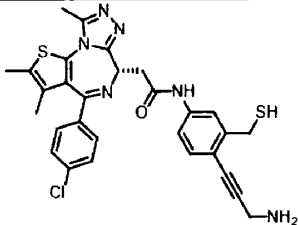
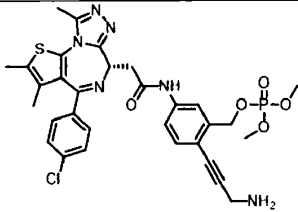
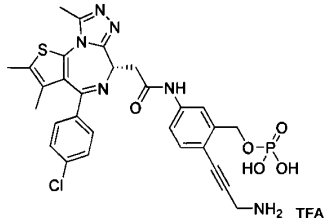
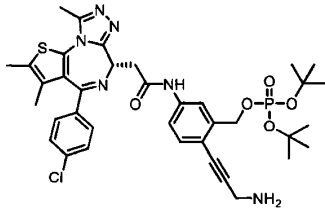
【0119】

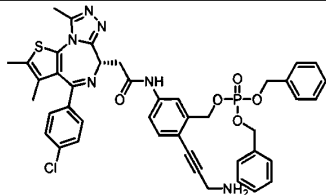
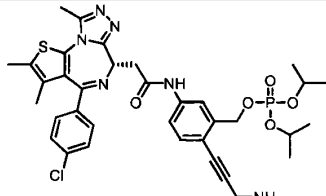
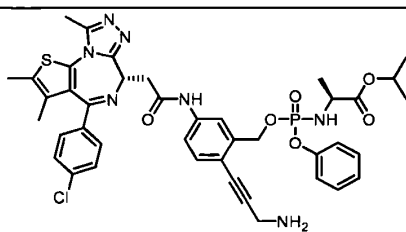
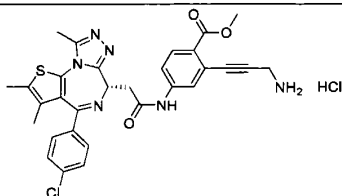
【0120】 보다 구체적으로, 상기 화학식 V으로 표시되는 화합물에서, 상기 TBM으로 상기 화학식 1의 화합물이 결합된 경우의 구체적인 예들은 하기 표 5에, 상기 TBM으로 상기 화학식 2의 화합물이 결합된 경우의 구체적인 예들은 하기 표 6에, 상기 TBM으로 상기 화학식 3의 화합물이 결합된 경우의 구체적인 예들은 하기 표 7에 각각 제시된 것일 수 있으나, 이에 한정되지 아니한다.

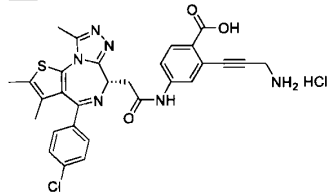
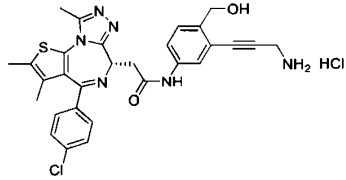
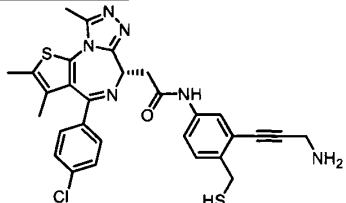
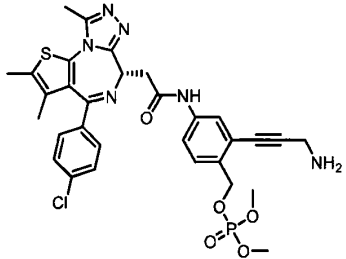
【표 5】

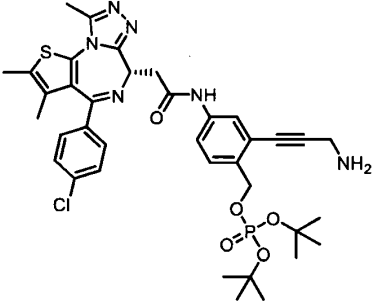
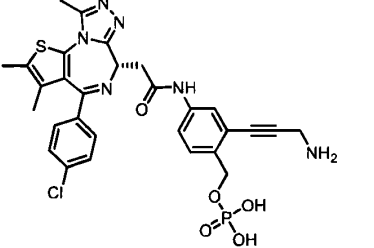
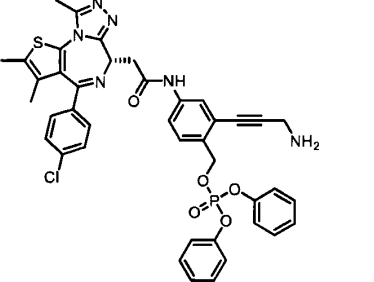
번호	화합물
1-1'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

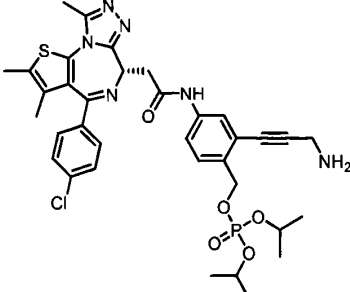
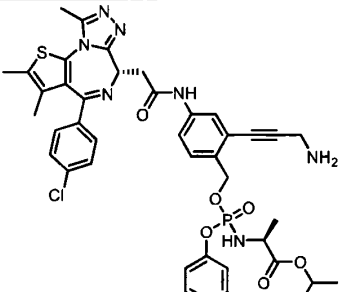
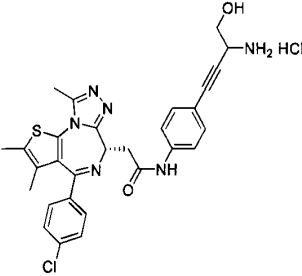
1-3'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
3-1'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoate hydrochloride
3-2'	 (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoic acid hydrochloride
3-3'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

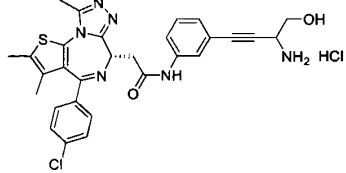
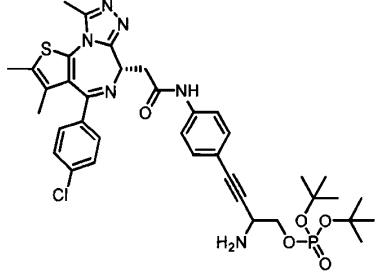
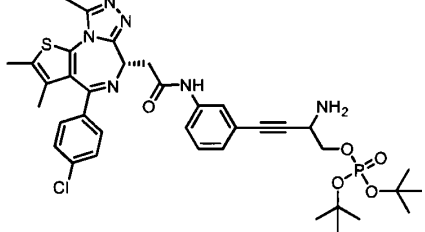
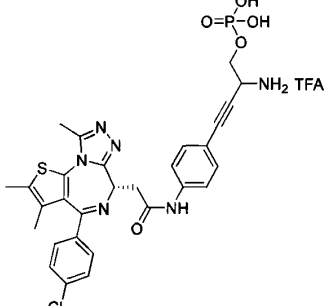
	trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
3-6'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(mercaptomethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
3-7'	 (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl dimethyl phosphate
3-8'	 (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl dihydrogen phosphate trifluoroacetic acid
3-9'	 (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl dihydrogen phosphate

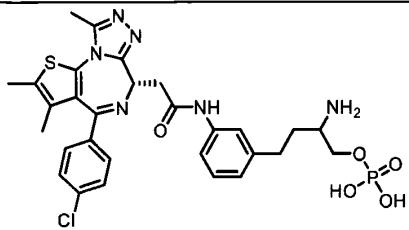
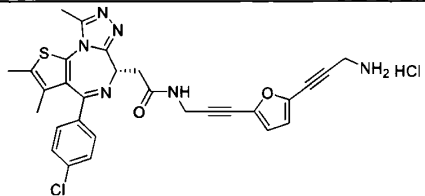
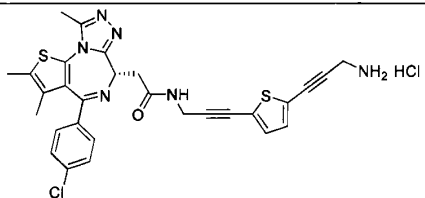
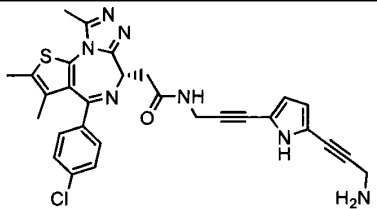
	2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl di-tert-butyl phosphate
3-10'	 (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl dibenzyl phosphate
3-11'	 (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl diisopropyl phosphate
3-12'	 isopropyl (((2-(3-aminoprop-1-yn-1-yl)-5-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl)oxy)(phenoxy)phosphoryl)-L-alaninate
3-25'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl)oxy)(phenoxy)phosphoryl)-L-alaninate

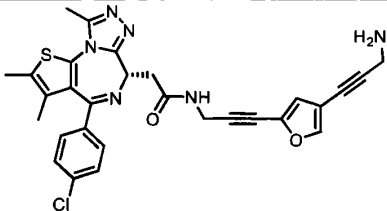
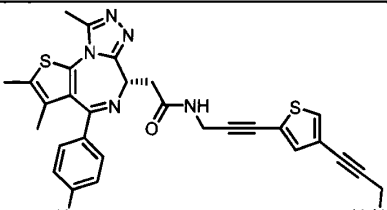
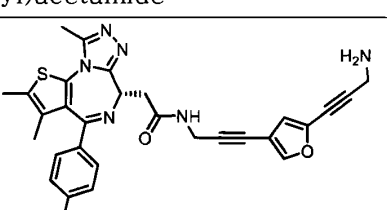
	f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoate hydrochloride
3-26'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoic acid hydrochloride
3-27'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(hydroxymethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
3-28'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(mercaptomethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
3-30'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-

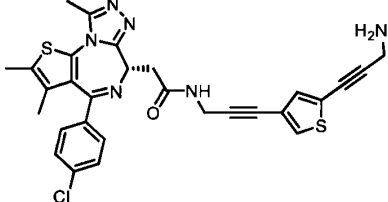
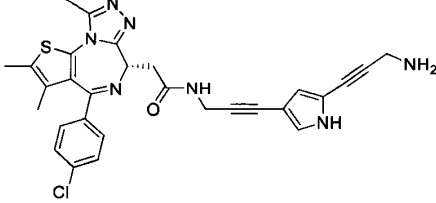
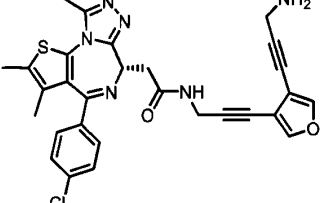
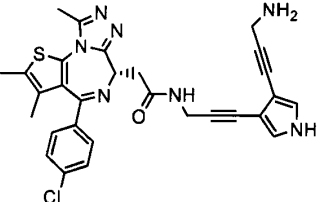
	a)[[1,4]diazepin-6-yl)acetamido)benzyl dimethyl phosphate
3-31'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl di-tert-butyl phosphate
3-32'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl dihydrogen phosphate
3-33'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl diphenyl phosphate

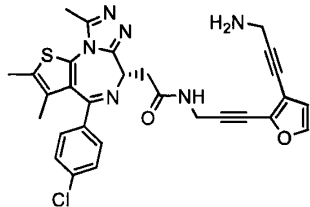
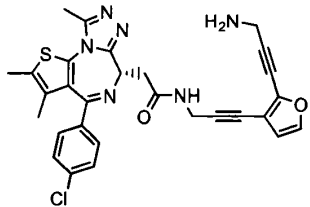
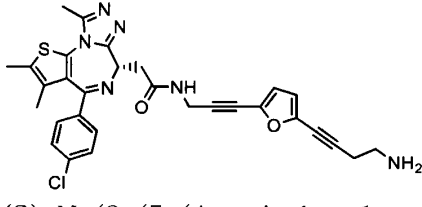
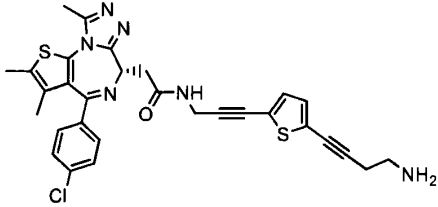
3-34'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl diisopropyl phosphate
3-35'	 isopropyl (((2-(3-aminoprop-1-yn-1-yl)-4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl)oxy)(phenoxy)phosphoryl)-L-alaninate
3-49'	 N-(4-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)-2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

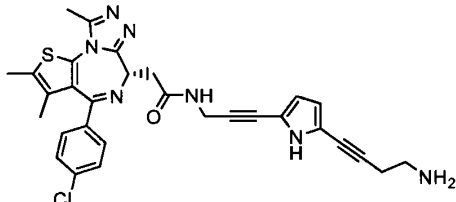
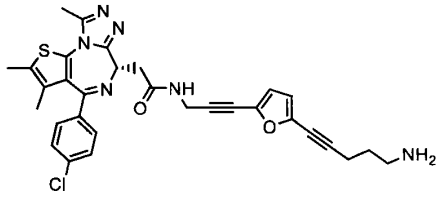
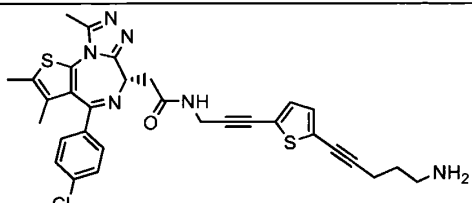
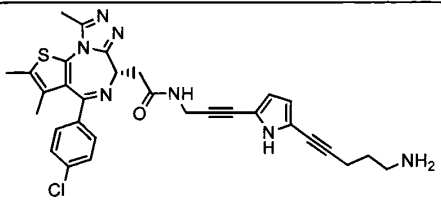
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3-53'	 2-amino-4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)but-3-yn-1-yl di-tert-butyl phosphate
3-55'	 2-amino-4-(3-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)but-3-yn-1-yl di-tert-butyl phosphate
3-57'	 2-amino-4-(3-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)but-3-yn-1-yl di-tert-butyl phosphate

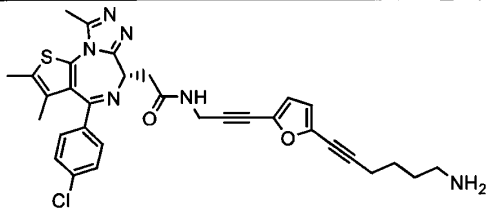
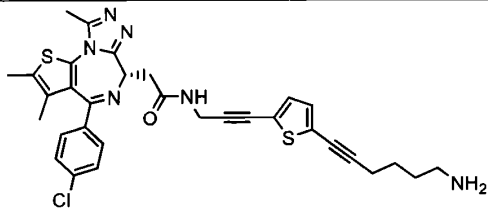
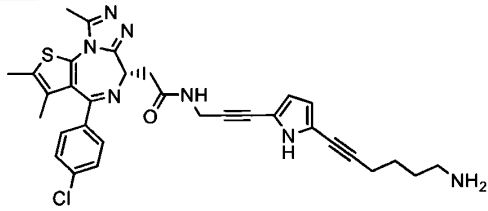
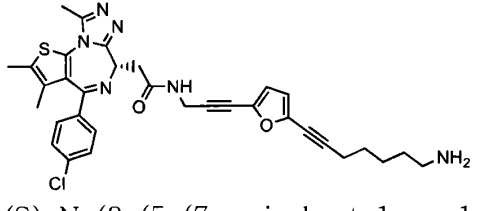
	2-amino-4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)but-3-yn-1-yl dihydrogen phosphate trifluoroacetic acid
3-60'	 2-amino-4-(3-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)butyl dihydrogen phosphate
4-1'	 (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-10'	 (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-13'	

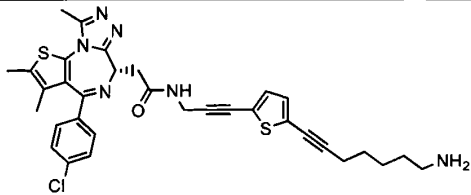
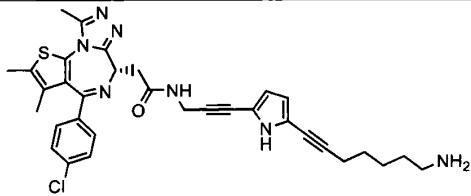
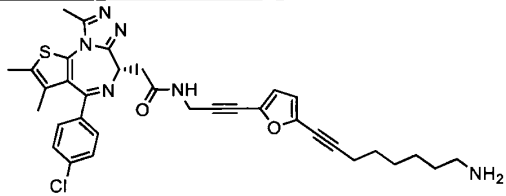
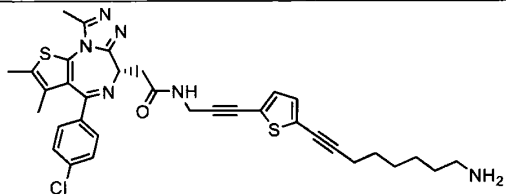
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4-16'	 (S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-19'	 (S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-25'	 (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)furan-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

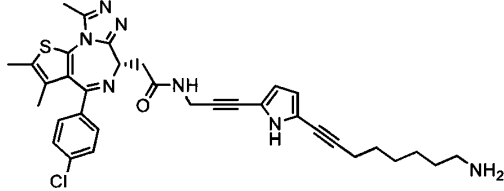
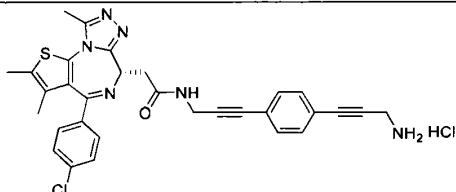
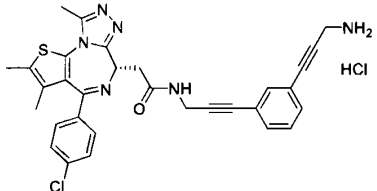
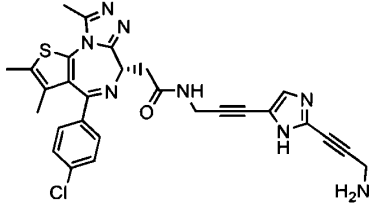
4-28'	 (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)thiophen-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-31'	 (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-34'	 (S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)furan-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-40'	 (S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

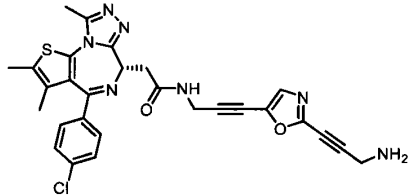
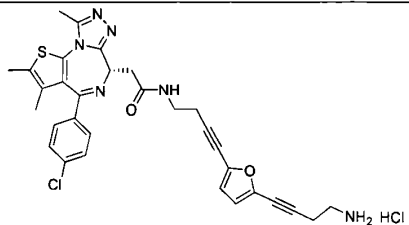
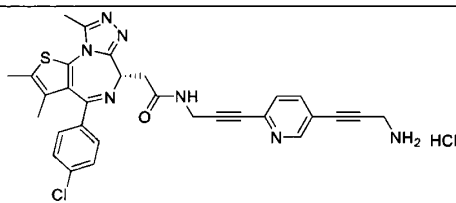
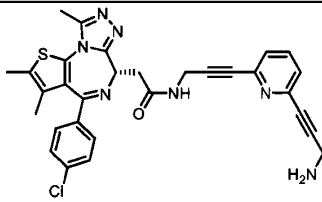
	6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-43'	 (S)-N-(3-(3-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-52'	 (S)-N-(3-(2-(3-aminoprop-1-yn-1-yl)furan-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-61'	 (S)-N-(3-(5-(4-aminobut-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-62'	 (S)-N-(3-(5-(4-aminobut-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

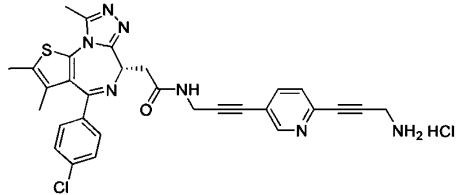
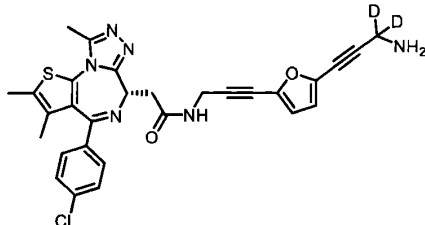
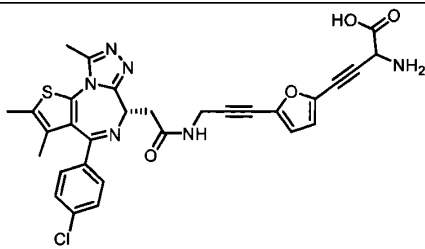
	thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-63'	 (S)-N-(3-(5-(4-aminobut-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-64'	 (S)-N-(3-(5-(5-aminopent-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-65'	 (S)-N-(3-(5-(5-aminopent-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-66'	 (S)-N-(3-(5-(5-aminopent-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

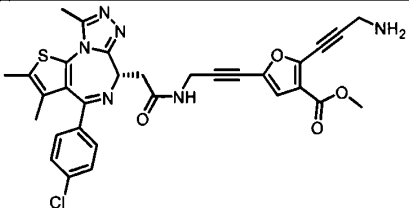
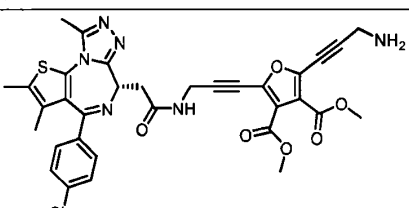
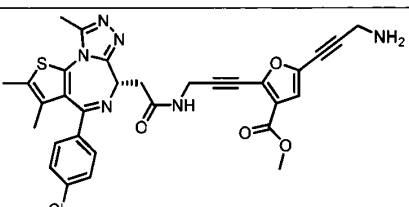
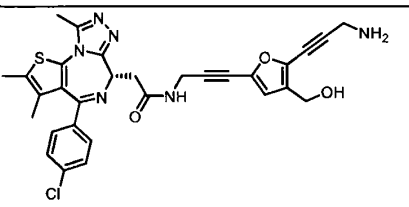
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4-67'	 (S)-N-(3-(5-(6-aminohex-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-68'	 (S)-N-(3-(5-(6-aminohex-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-69'	 (S)-N-(3-(5-(6-aminohex-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-70'	 (S)-N-(3-(5-(7-aminohept-1-yn-1-yl)furan-2-yl)prop-2-

	yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-71'	 (S)-N-(3-(5-(7-aminohept-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-72'	 (S)-N-(3-(5-(7-aminohept-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-73'	 (S)-N-(3-(5-(8-aminooct-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-74'	 (S)-N-(3-(5-(8-aminooct-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-

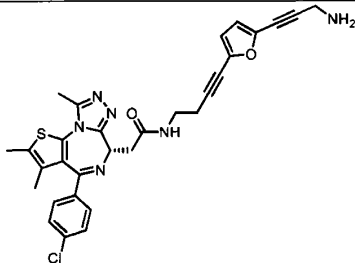
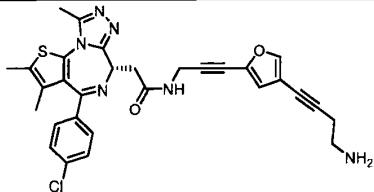
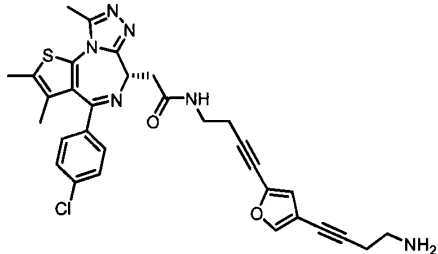
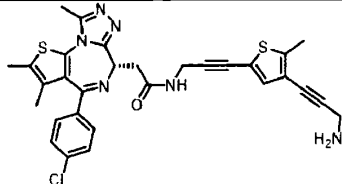
	thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-75'	 (S)-N-(3-(5-(8-amino-oct-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-128'	 ((S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-129'	 (S)-N-(3-(3-(3-aminoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-130'	 (S)-N-(3-(2-(3-aminoprop-1-yn-1-yl)-1H-imidazol-5-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-

	6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4- 131'	 (S)-N-(3-(2-(3-aminoprop-1-yn-1-yl)oxazol-5-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4- 147'	 (S)-N-(4-(5-(4-aminobut-1-yn-1-yl)furan-2-yl)but-3-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4- 177'	 (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)pyridin-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4- 178'	 (S)-N-(3-(6-(3-aminoprop-1-yn-1-yl)pyridin-2-yl)prop-2-

	yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-179'	 (S)-N-(3-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-180'	 (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl-3,3-d2)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-181'	 2-amino-4-(5-(3-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-2-yl)but-3-ynoic acid

4- 182'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-3-carboxylate
4- 183'	 dimethyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-3,4-dicarboxylate
4- 184'	 methyl (S)-5-(3-aminoprop-1-yn-1-yl)-2-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-3-carboxylate
4- 185'	 (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)-4-(hydroxymethyl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

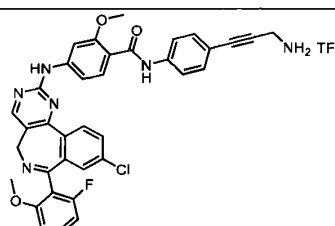
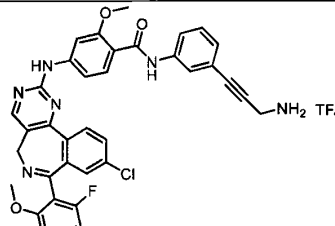
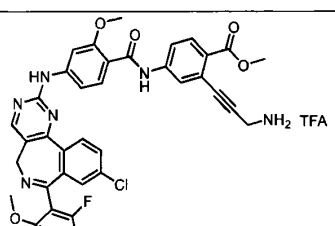
	f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4- 186'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4- 187'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)-3,4-bis(hydroxymethyl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4- 188'	(S)-(5-(3-aminoprop-1-yn-1-yl)-2-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-3-yl)methyl dihydrogen phosphate
4- 189'	(S)-(2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

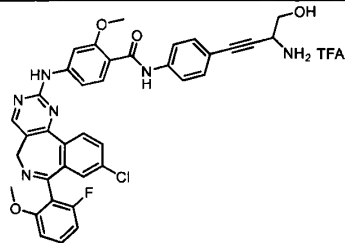
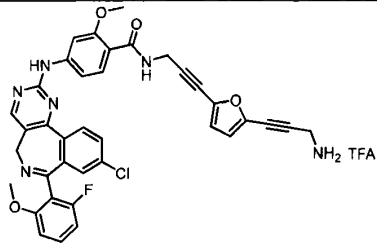
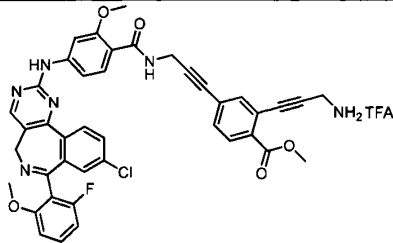
	f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-3-yl)methyl dihydrogen phosphate
4-200'	 (S)-N-(4-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)but-3-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-201'	 (S)-N-(3-(4-(4-aminobut-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-202'	 (S)-N-(4-(4-(4-aminobut-1-yn-1-yl)furan-2-yl)but-3-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-218'	 (S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)-5-methylthiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

	trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4- 219'	(S)-N-(3-(4-(4-aminobut-1-yn-1-yl)-5-methylthiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4- 223'	(S)-N-(3-(5-(3-(aminooxy)prop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
5-52'	ethyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)oxazole-4-carboxylate
5- 116'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(2-(4-(4-

	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)benzoate hydrochloride
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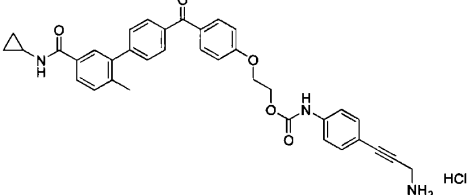
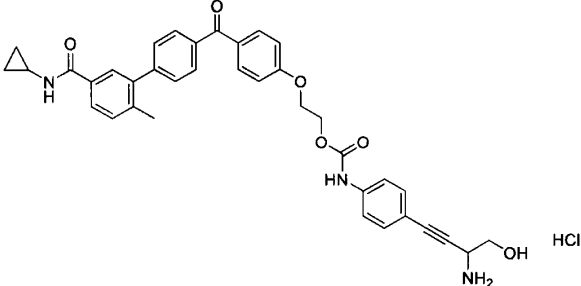
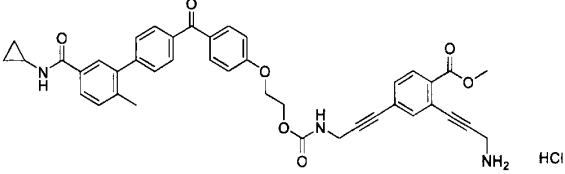
【표 6】

번호	화합물
1-1''	 N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
1-3''	 N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
3-25''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)benzoate

	trifluoroacetic acid
3-49''	 N-(4-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
4-1''	 N-(3-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
5-116''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)prop-1-yn-1-yl)benzoate trifluoroacetic acid

【표 7】

번호	화합물
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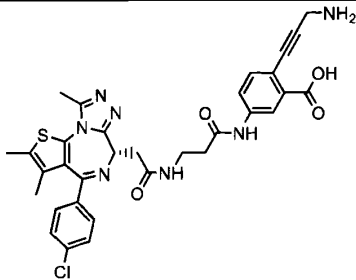
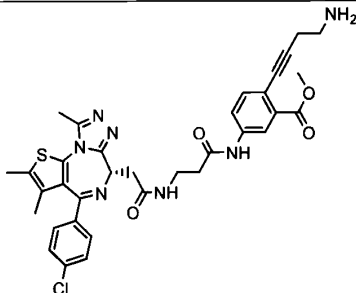
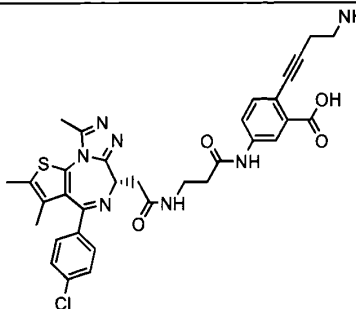
1-1'''	 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl 4-(3-aminoprop-1-yn-1-yl)phenyl carbamate hydrochloride
3-49'''	 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl 4-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl carbamate hydrochloride
5-116'''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(((2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate hydrochloride

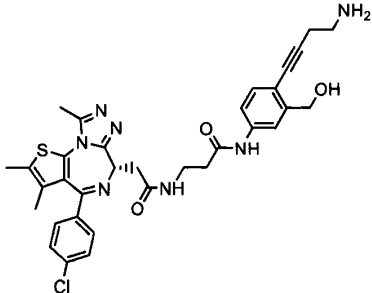
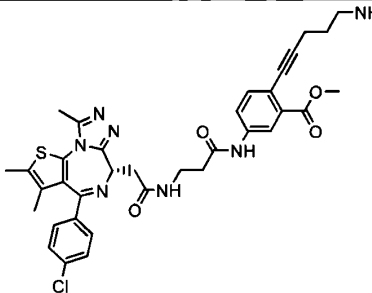
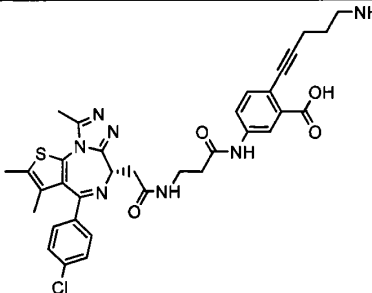
【0121】 보다 구체적으로, 상기 화학식 VI으로 표시되는 화합물에서, 상기 TBM으로 상기 화학식 1의 화합물이 결합된 경우의 구체적인 예들은 하기 표 8에, 상기 TBM으로 상기 화학식 2의 화합물이 결합된 경우의 구체적인 예들은 하기 표 9에, 그리고 상기 TBM으로 상기

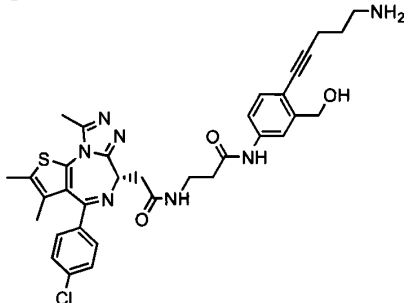
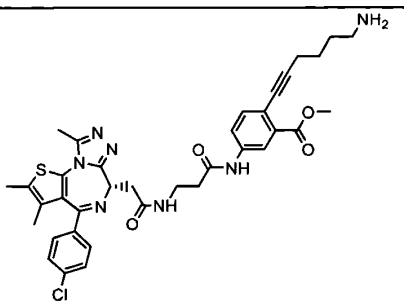
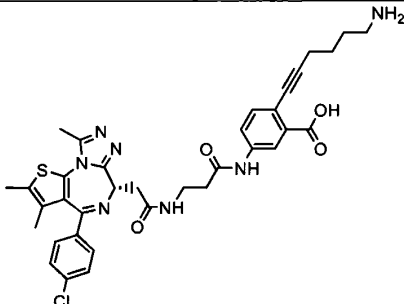
5 화학식 3의 화합물이 결합된 경우의 구체적인 예들은 하기 표 10에 각각

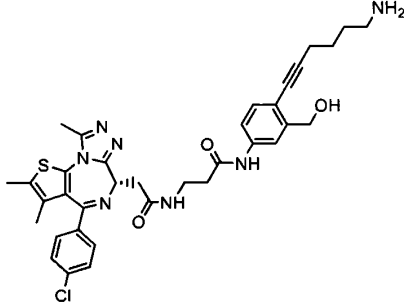
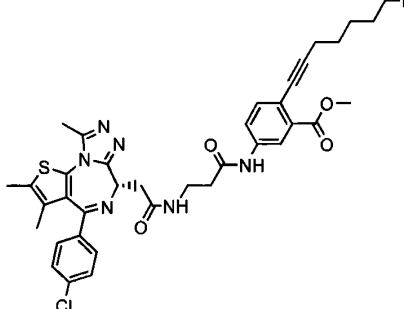
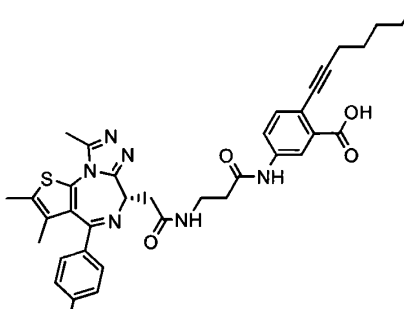
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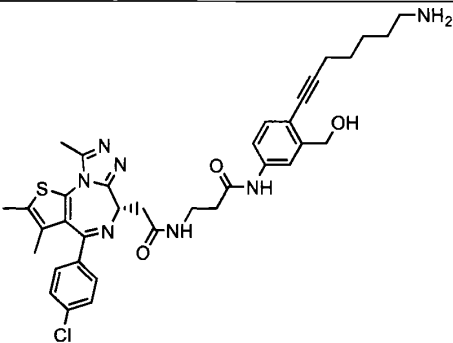
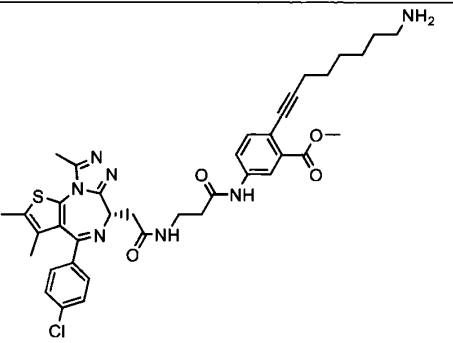
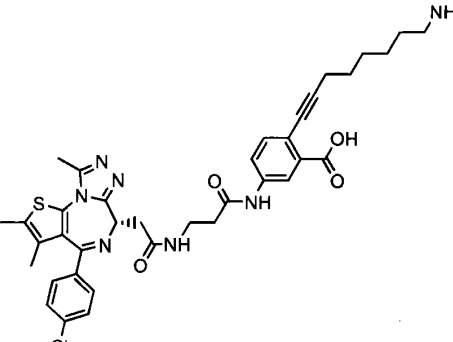
【표 8】

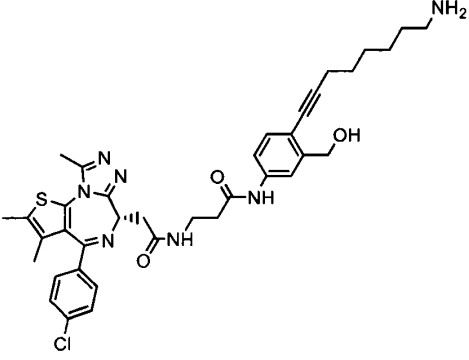
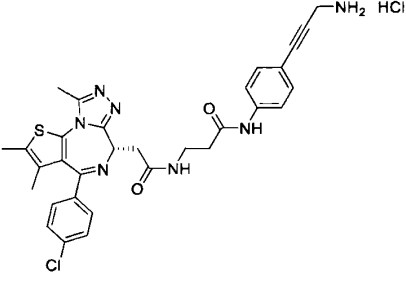
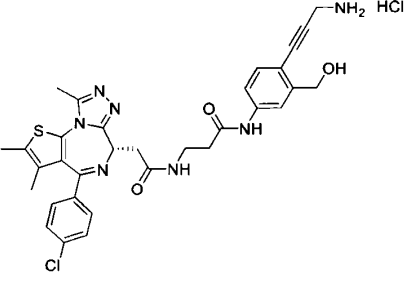
번호	화합물
4-6'	 (S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid
4-109'	 methyl (S)-2-(4-aminobut-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate
4-110'	 (S)-2-(4-aminobut-1-yn-1-yl)-5-(3-(2-(4-(4-

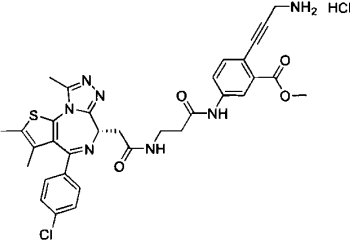
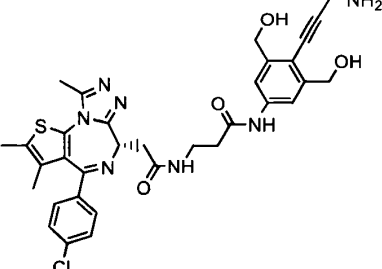
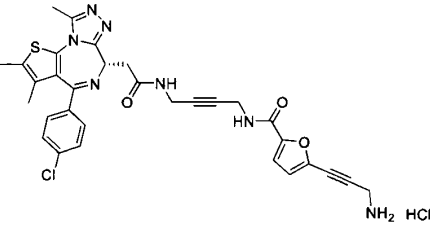
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid
4-111'	 (S)-N-(4-(4-aminobut-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-112'	 methyl (S)-2-(5-aminopent-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate
4-113'	 (S)-2-(5-aminopent-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid

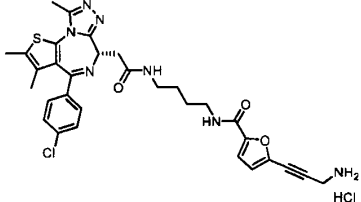
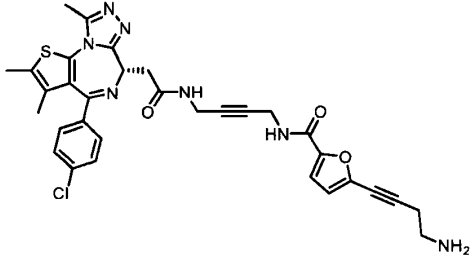
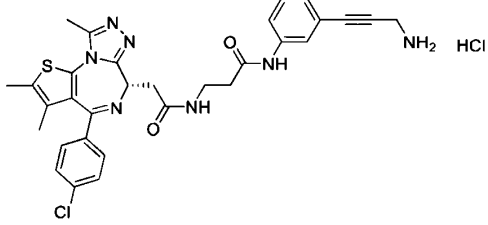
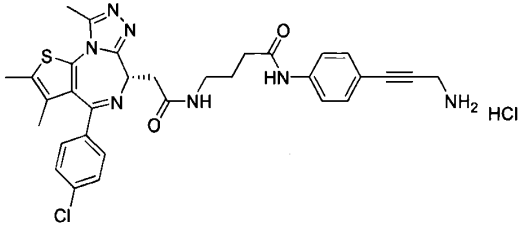
	yl)acetamido)propanamido)benzoic acid
4-114'	 (S)-N-(4-(5-aminopent-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-115'	 methyl (S)-2-(6-aminohex-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate
4-116'	 (S)-2-(6-aminohex-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid

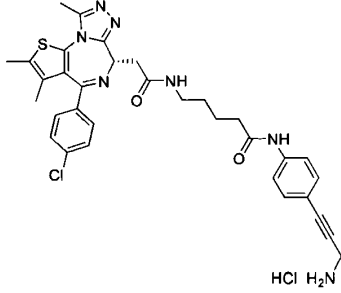
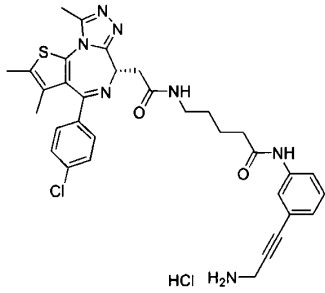
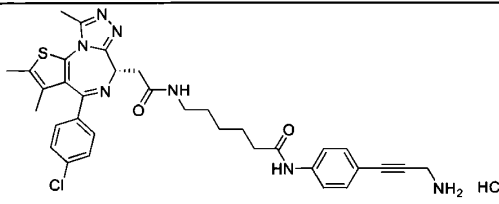
4-117'	 (S)-N-(4-(6-aminohept-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-118'	 methyl (S)-2-(7-aminohept-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate
4-119'	 (S)-2-(7-aminohept-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid

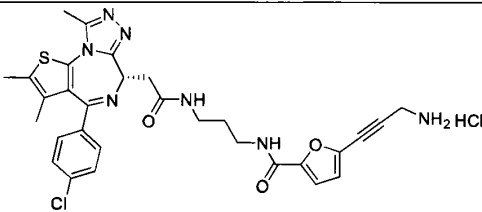
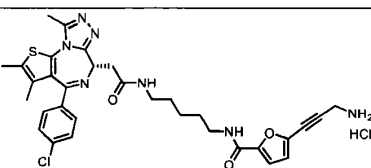
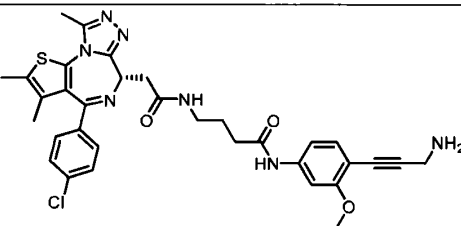
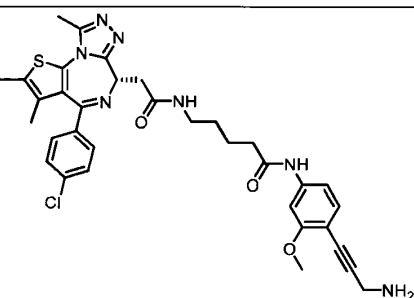
4-120'	 (S)-N-(4-(7-aminohept-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-121'	 methyl (S)-2-(8-aminooct-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate
4-122'	 (S)-2-(8-aminooct-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid

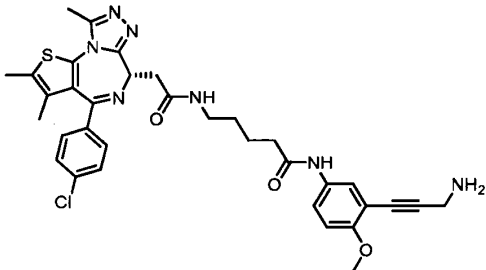
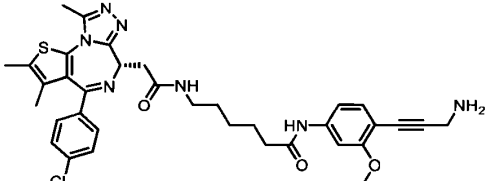
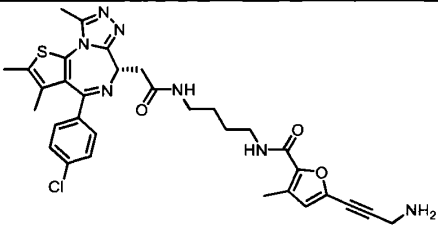
	f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid
4-123'	 (S)-N-(4-(8-aminooct-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-124'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide hydrochloride
4-125'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide hydrochloride

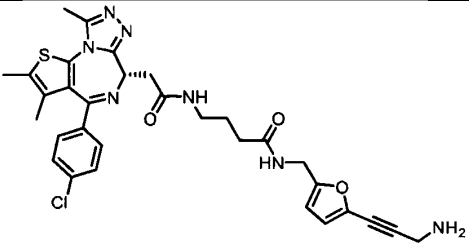
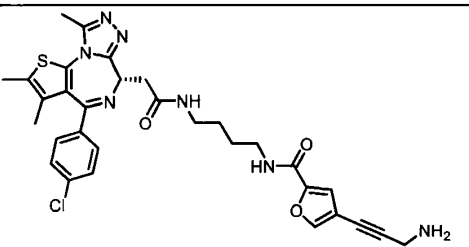
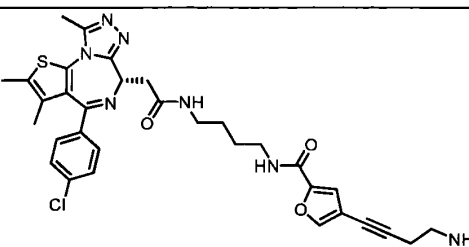
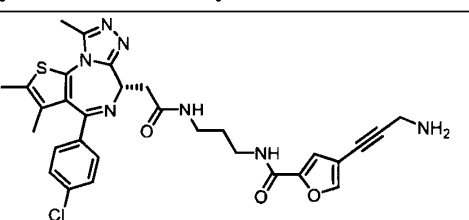
	a)[1,4]diazepin-6-yl)acetamido)propanamide hydrochloride
4-126'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate hydrochloride
4-127'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3,5-bis(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-148'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-yn-1-yl)furan-2-carboxamide hydrochloride

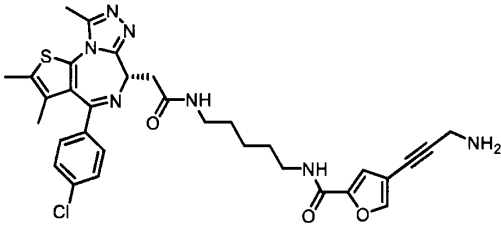
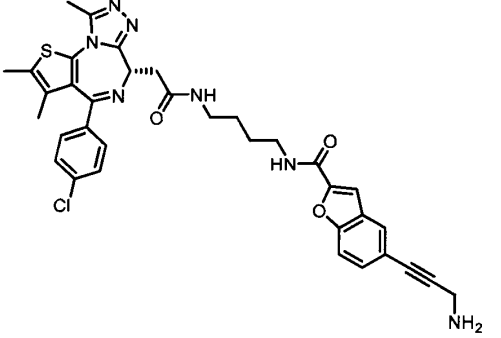
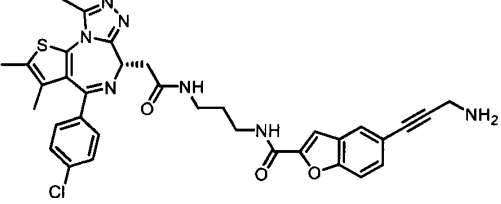
4-149'	 ((S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide hydrochloride
4-150'	 (S)-5-(4-aminobut-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-yn-1-yl)furan-2-carboxamide
4-161'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide hydrochloride
4-162'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride

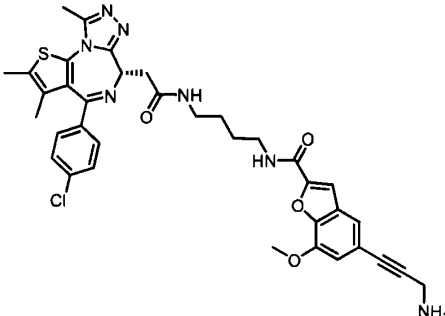
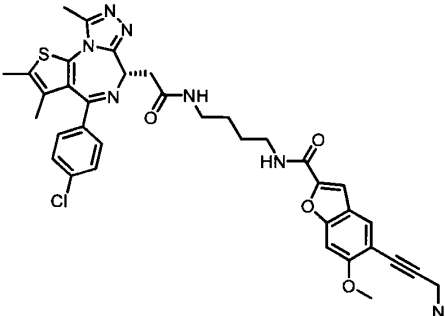
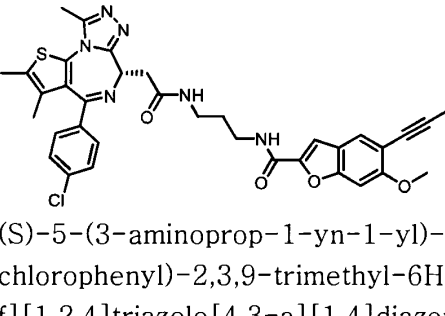
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride
4-163'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide hydrochloride
4-164'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide hydrochloride
4-165'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamide hydrochloride

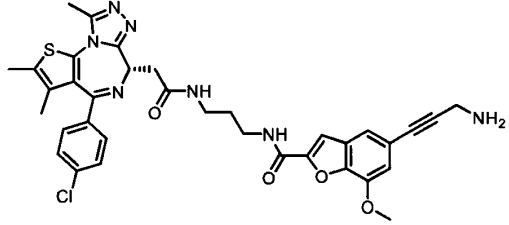
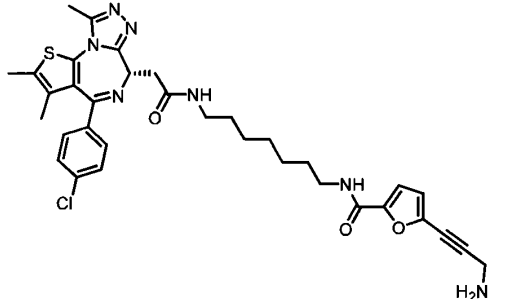
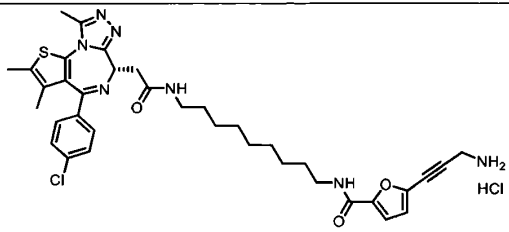
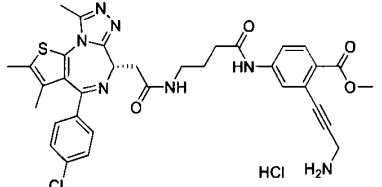
4-166'	 ((S)-5-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)furan-2-carboxamide hydrochloride
4-167'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentyl)furan-2-carboxamide hydrochloride
4-168'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
4-169'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentyl)furan-2-carboxamide

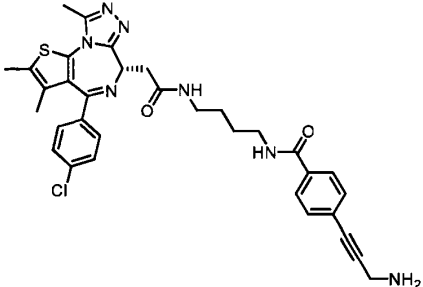
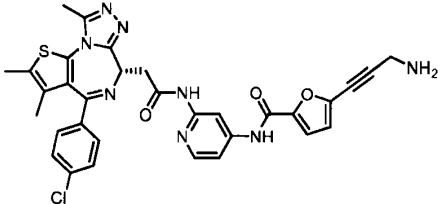
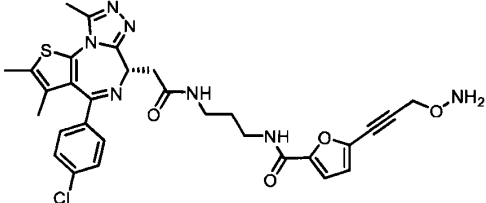
	(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide
4-170'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-methoxyphenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide
4-171'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)-6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamide
4-192'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)-3-methylfuran-2-carboxamide

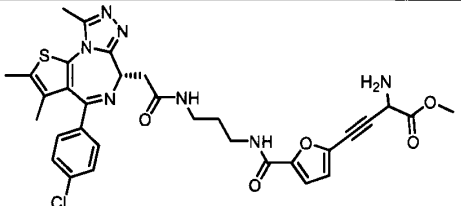
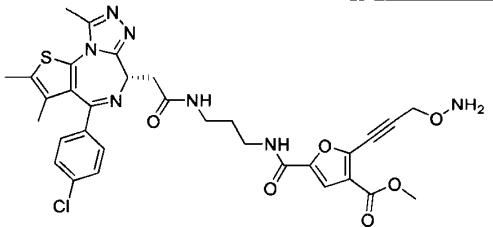
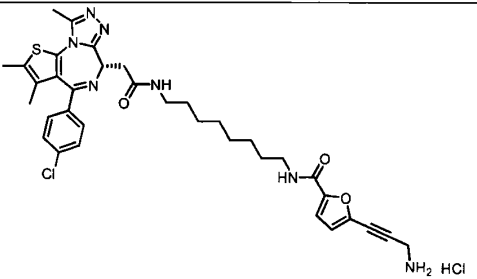
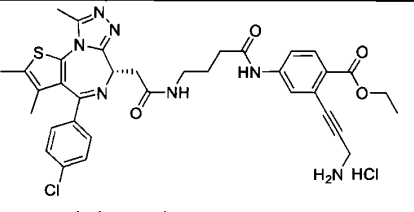
4-199'	 (S)-N-((5-(3-aminoprop-1-yn-1-yl)furan-2-yl)methyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
4-203'	 (S)-4-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
4-204'	 (S)-4-(4-aminobut-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
4-205'	 (S)-4-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide

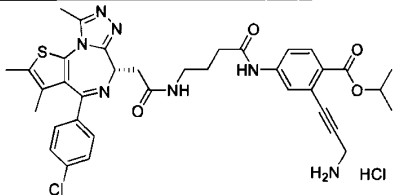
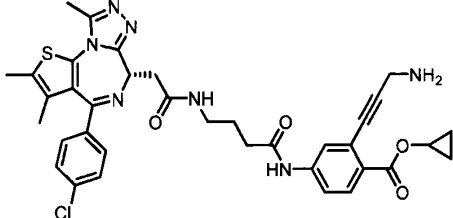
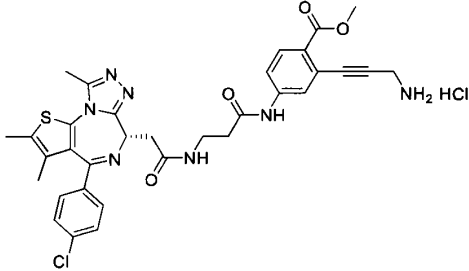
	(S)-4-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)furan-2-carboxamide
4-206'	 (S)-4-(3-aminoprop-1-yn-1-yl)-N-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentyl)furan-2-carboxamide
4-209'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)benzofuran-2-carboxamide
4-210'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)benzofuran-2-carboxamide

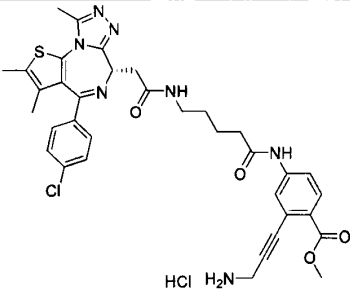
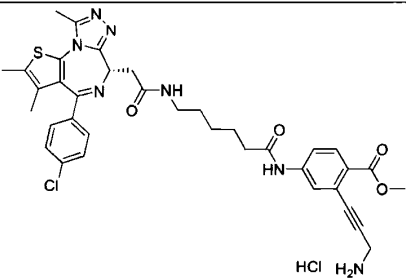
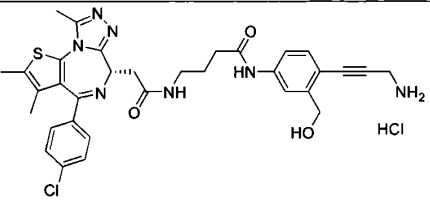
4-214'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)-7-methoxybenzofuran-2-carboxamide
4-215'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)-6-methoxybenzofuran-2-carboxamide
4-216'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)-6-methoxybenzofuran-2-carboxamide

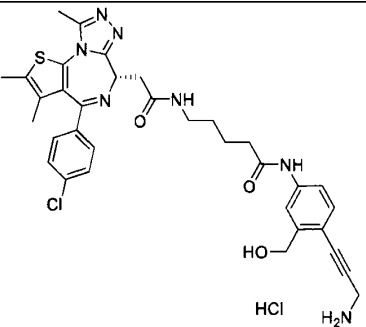
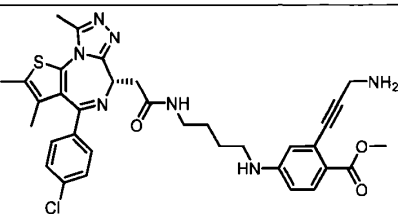
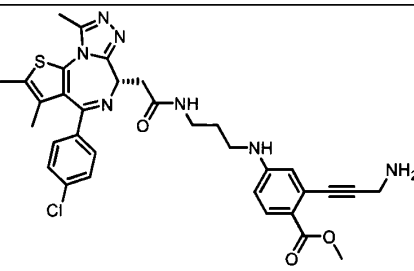
4-217'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)-7-methoxybenzofuran-2-carboxamide
4-224'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide
4-225'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(9-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)nonyl)furan-2-carboxamide hydrochloride
4-228'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)-7-methoxybenzofuran-2-carboxamide

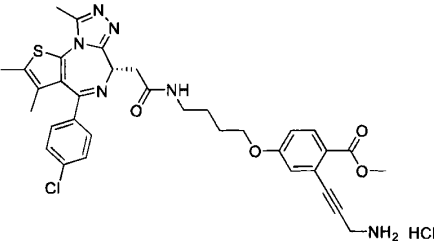
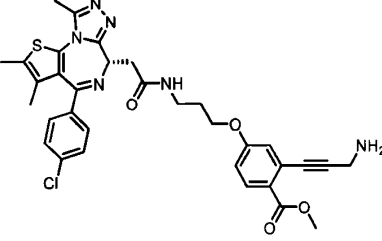
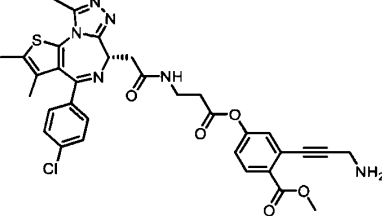
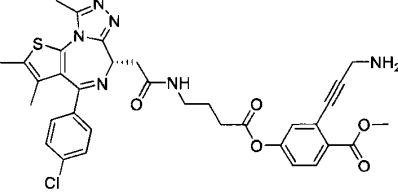
	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride
4-229'	 (S)-4-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)benzamide
4-231'	 (S)-5-(3-aminoprop-1-yn-1-yl)-N-(2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pyridin-4-yl)furan-2-carboxamide
4-232'	 (S)-5-(3-(aminooxy)prop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)furan-2-carboxamide

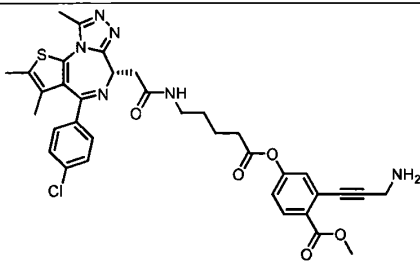
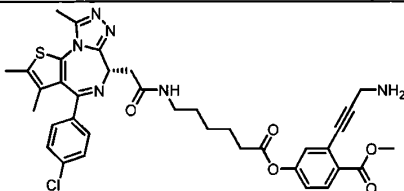
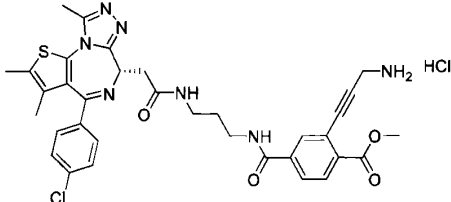
4-233'	 methyl 2-amino-4-((3-((2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)carbamoyl)furan-2-yl)but-3-ynoate
4-234'	 methyl (S)-2-(3-(aminooxy)prop-1-yn-1-yl)-5-((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)carbamoyl)furan-3-carboxylate
4-235'	 ((S)-5-(3-aminoprop-1-yn-1-yl)-N-(8-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)octyl)furan-2-carboxamide hydrochloride
5-1'	 ethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-3-yn-1-yl)furan-3-carboxylate hydrochloride

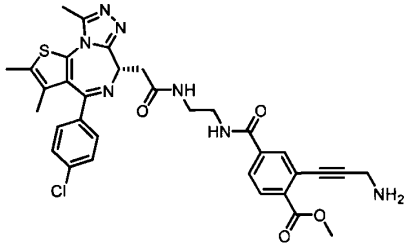
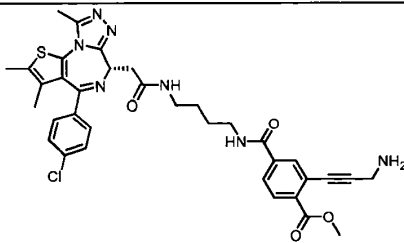
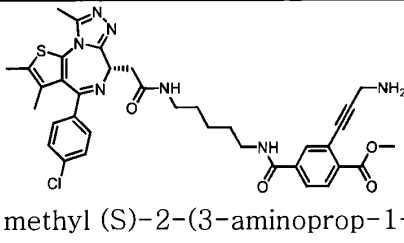
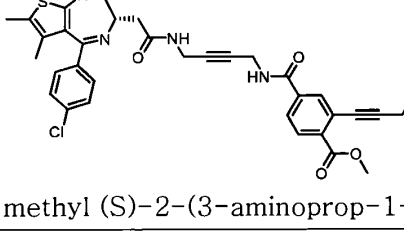
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride
5-2'	 isopropyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride
5-3'	 cyclopropyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-4'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate hydrochloride

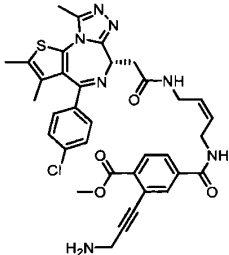
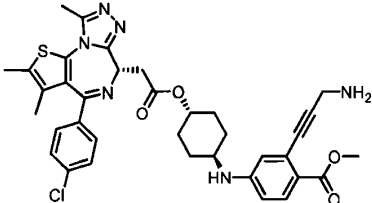
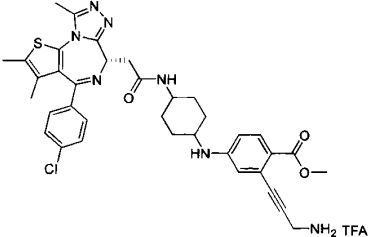
5-5'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamido)benzoate hydrochloride
5-6'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamido)benzoate hydrochloride
5-8'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride

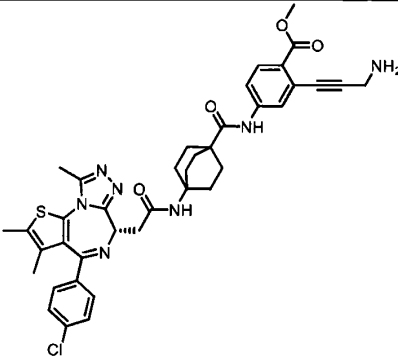
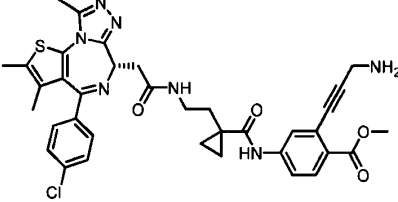
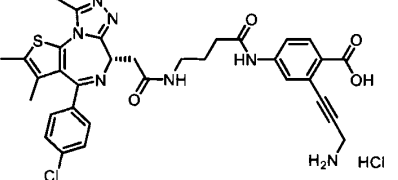
5-9'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide hydrochloride
5-10'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)amino)benzoate
5-11'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)amino)benzoate

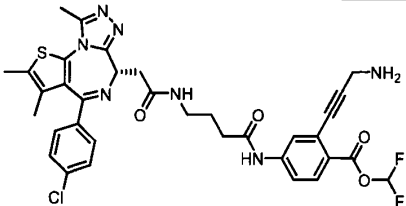
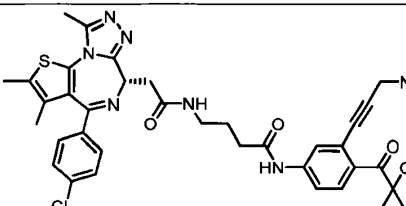
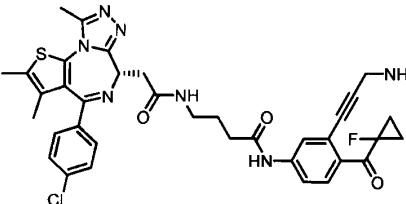
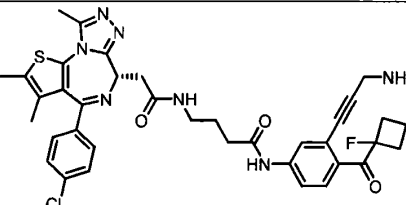
5-12'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butoxy)benzoate hydrochloride
5-13'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propoxy)benzoate
5-14'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanoyl)oxy)benzoate
5-15'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyryl)oxy)benzoate

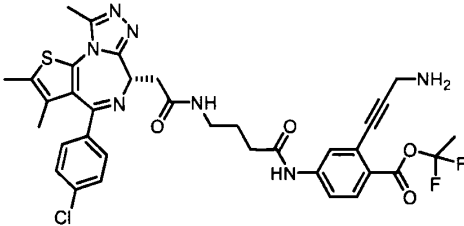
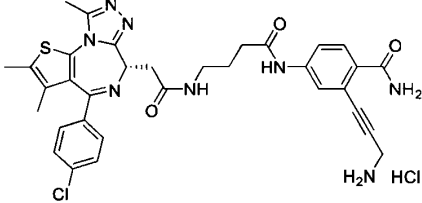
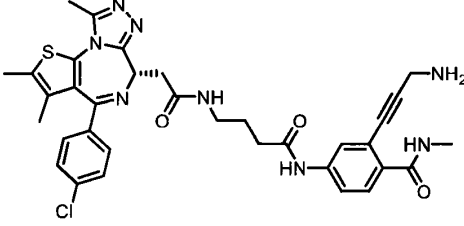
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanoyl)oxy)benzoate
5-16'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanoyl)oxy)benzoate
5-17'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanoyl)oxy)benzoate
5-18'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)carbamoyl)benzoate hydrochloride

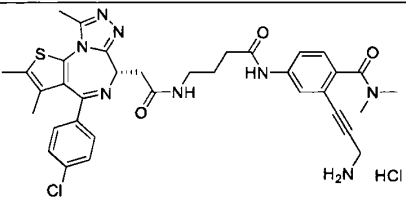
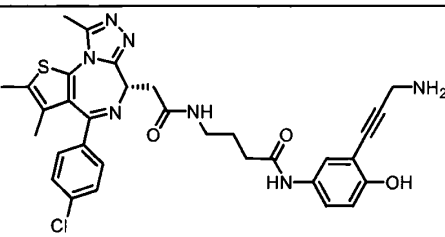
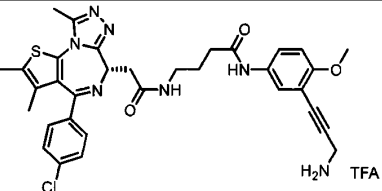
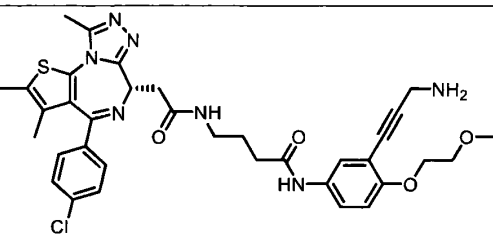
5-19'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)ethyl)carbamoyl)benzoate
5-20'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)carbamoyl)benzoate
5-21'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentyl)carbamoyl)benzoate
5-30'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)carbamoyl)benzoate

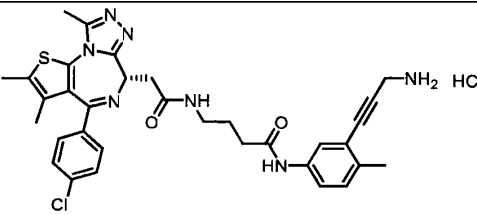
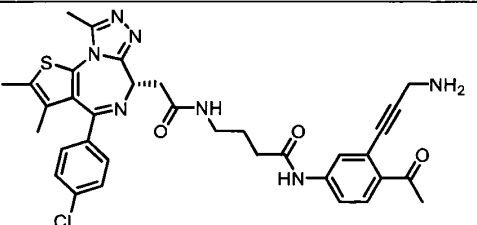
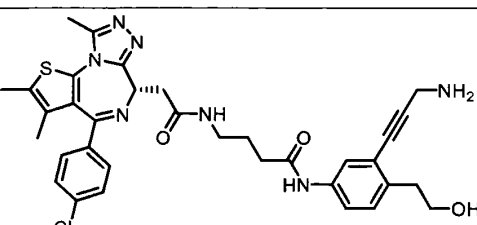
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-yn-1-yl)carbamoyl)benzoate
5-31'	 methyl (S,Z)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-en-1-yl)carbamoyl)benzoate
5-34'	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(((1S,4r)-4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetoxycyclohexyl)amino)benzoate
5-35'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)cyclohexyl)amino)benzoate trifluoroacetic acid

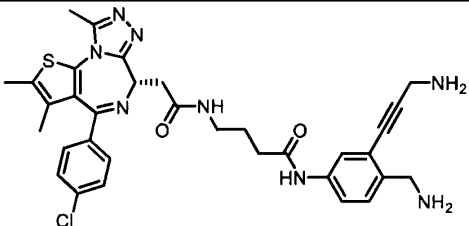
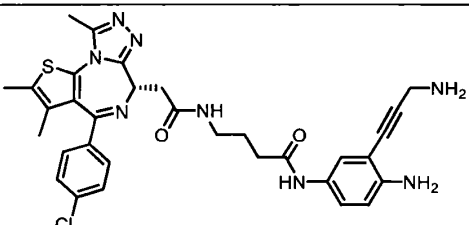
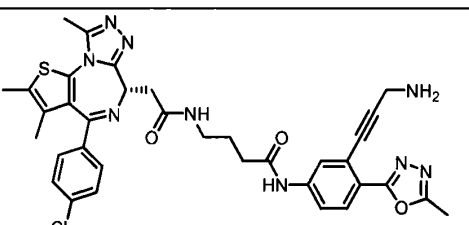
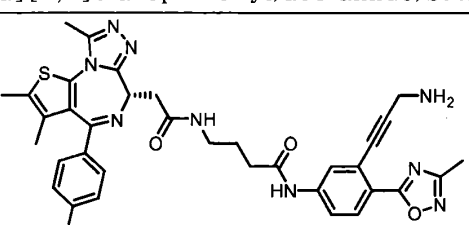
5-49'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)bicyclo[2.2.2]octane-1-carboxamido)benzoate
5-50'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(1-(2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)ethyl)cyclopropane-1-carboxamido)benzoate
5-53'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoic acid hydrochloride

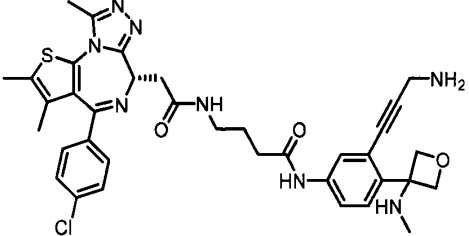
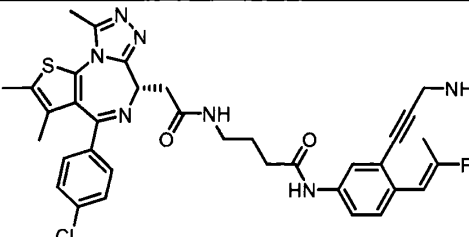
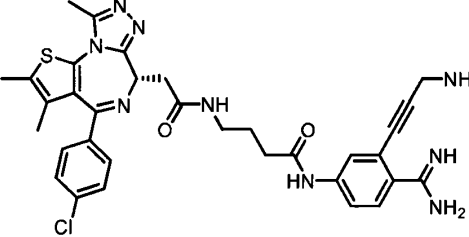
5-54'	 difluoromethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-55'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-(trifluoromethyl)cyclopropane-1-carbonyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-56'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-fluorocyclopropane-1-carbonyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-57'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-

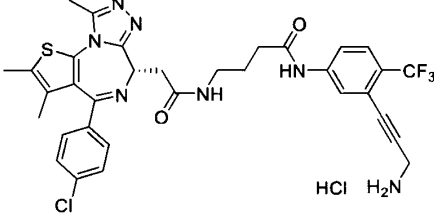
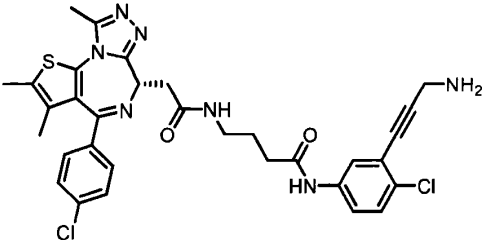
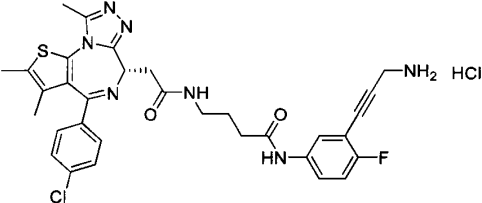
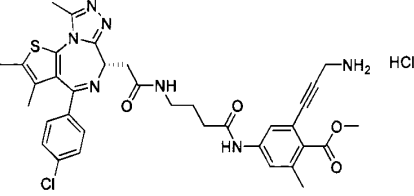
	fluorocyclobutane-1-carbonyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-58'	 1,1-difluoroethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-59'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzamide hydrochloride
5-60'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-N-methylbenzamide

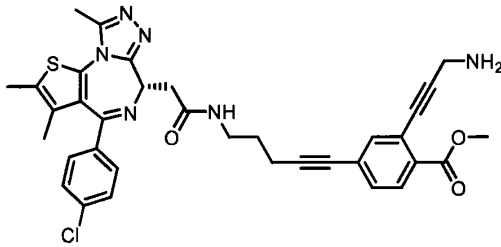
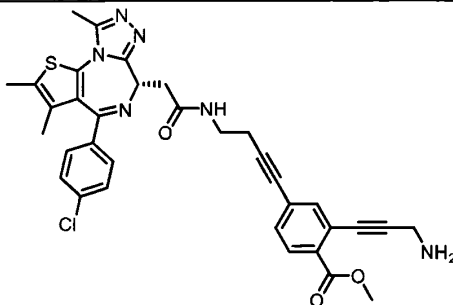
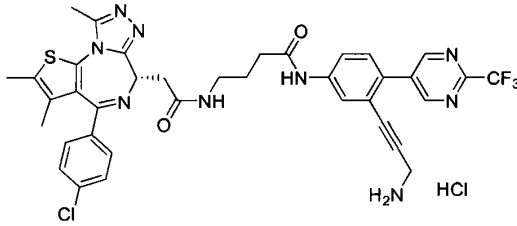
5-61'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-N,N-dimethylbenzamide hydrochloride
5-62'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-hydroxyphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-63'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-methoxyphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide trifluoroacetic acid
5-64'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-

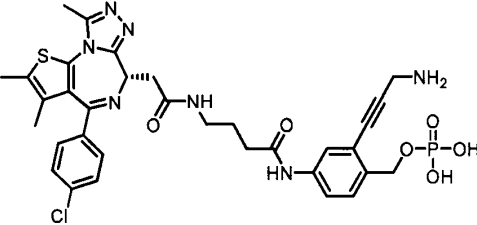
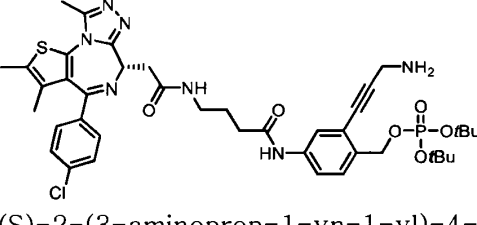
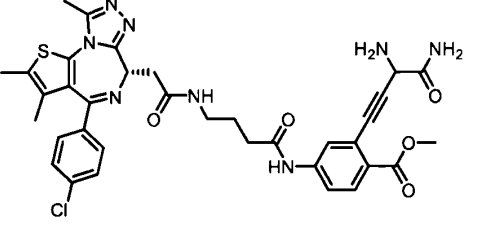
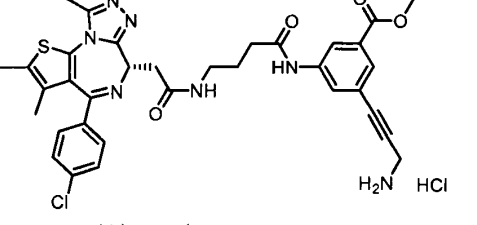
	methoxyethoxy)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-65'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-methylphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride
5-66'	 (S)-N-(4-acetyl-3-(3-aminoprop-1-yn-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-67'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-hydroxyethyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide

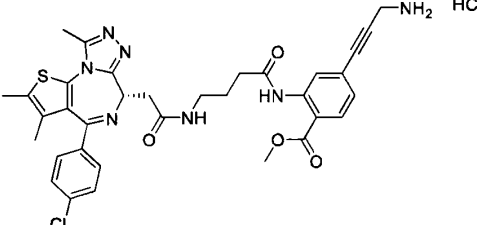
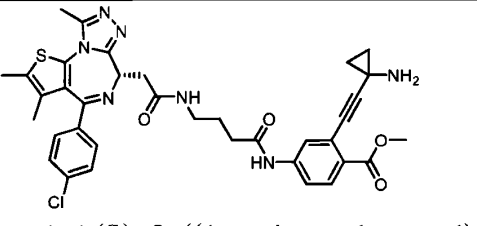
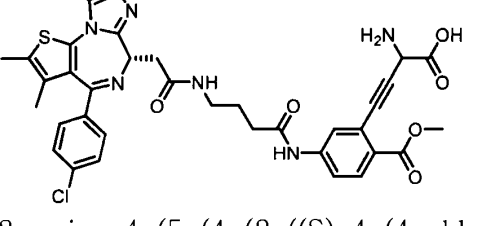
5-68'	 (S)-N-(4-(aminomethyl)-3-(3-aminoprop-1-yn-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-69'	 (S)-N-(4-amino-3-(3-aminoprop-1-yn-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-70'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-71'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide

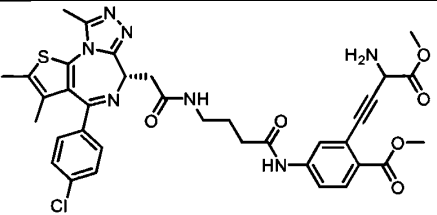
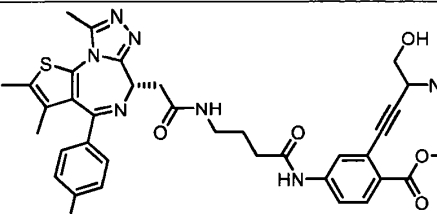
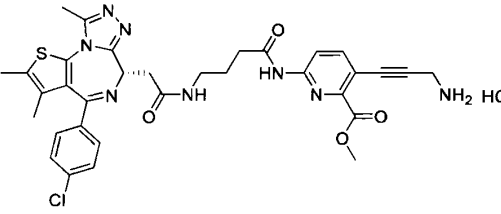
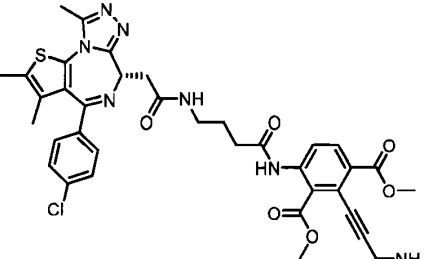
	oxadiazol-5-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-72'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(3-(methylamino)oxetan-3-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-73'	 (S,E)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-fluoroprop-1-en-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-74'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-carbamimidoylphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide

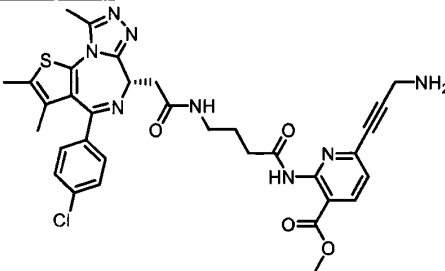
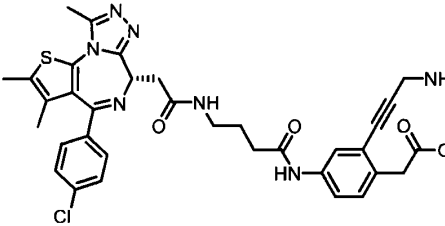
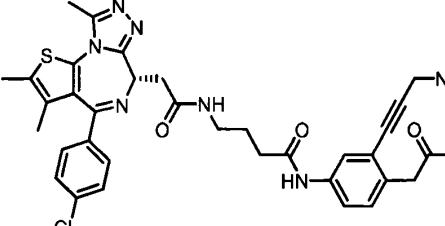
5-75'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(trifluoromethyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride
5-76'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-chlorophenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-77'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-fluorophenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride
5-78'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide

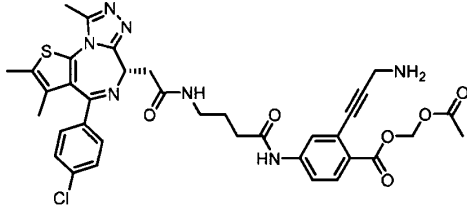
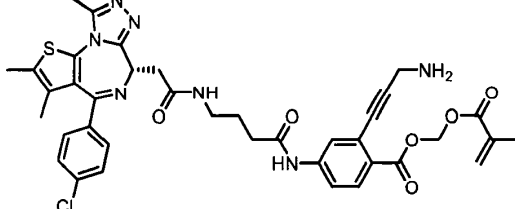
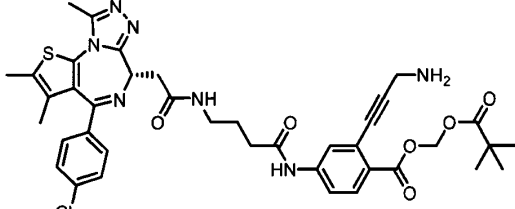
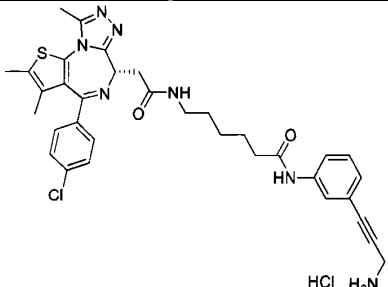
	f)[1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-6-methylbenzoate hydrochloride
5-79'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pent-1-yn-1-yl)benzoate
5-80'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-1-yn-1-yl)benzoate
5-81'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride

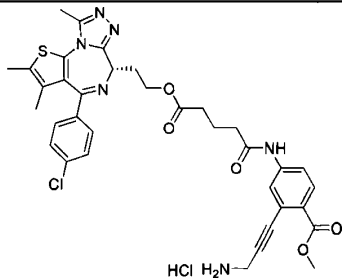
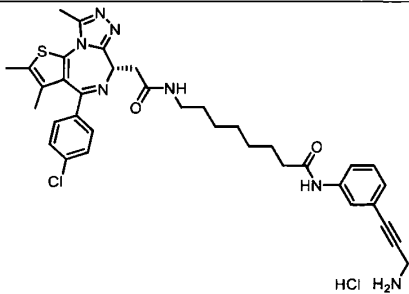
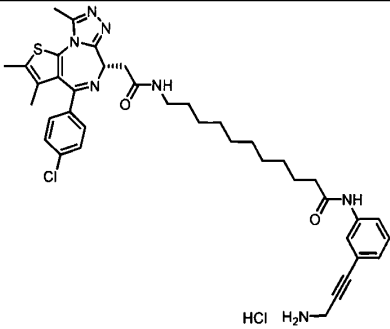
5-82'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzyl dihydrogen phosphate
5-83'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzyl di-tert-butyl phosphate
5-87'	 methyl 4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-2-(3,4-diamino-4-oxobut-1-yn-1-yl)benzoate
5-89'	 methyl (S)-3-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride

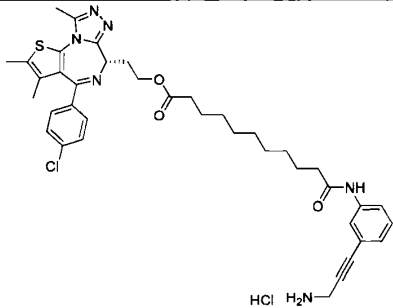
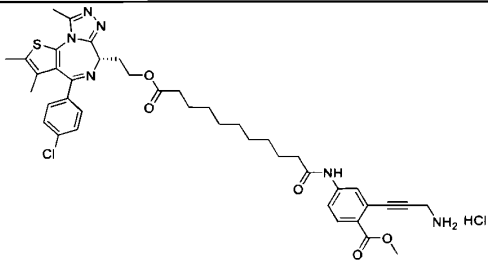
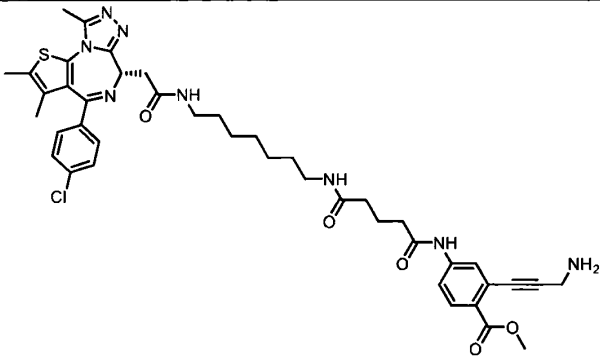
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride
5-90'	 methyl (S)-4-(3-aminoprop-1-yn-1-yl)-2-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride
5-92'	 methyl (S)-2-((1-aminocyclopropyl)ethynyl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-93'	 2-amino-4-(5-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-2-(methoxycarbonyl)phenyl)but-3-ynoic acid

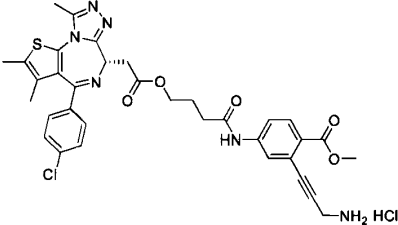
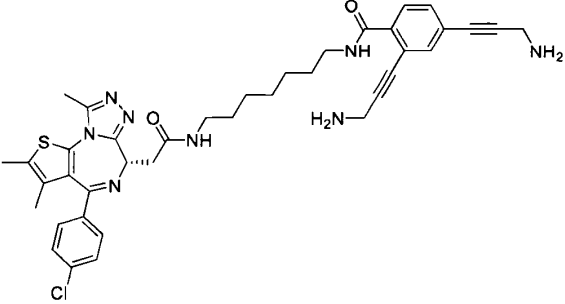
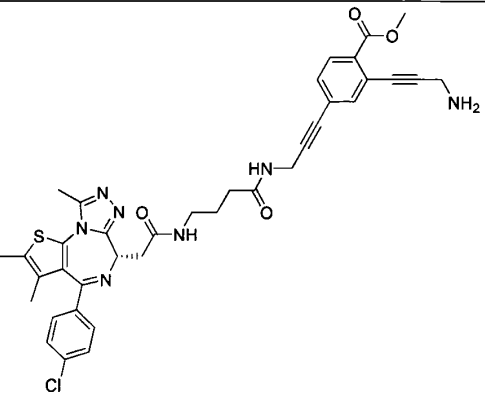
5-94'	 methyl 2-(3-amino-4-methoxy-4-oxobut-1-yn-1-yl)-4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-95'	 methyl 2-(3-amino-4-hydroxybut-1-yn-1-yl)-4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-96'	 methyl (S)-3-(3-aminoprop-1-yn-1-yl)-6-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)picolinate hydrochloride
5-97'	 dimethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate

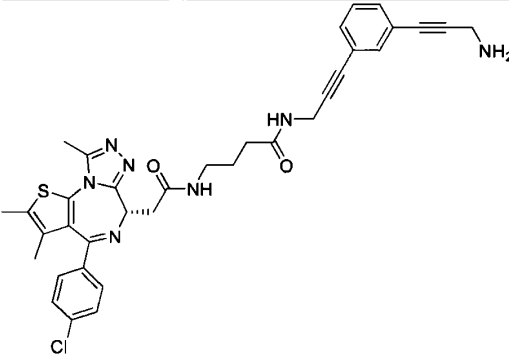
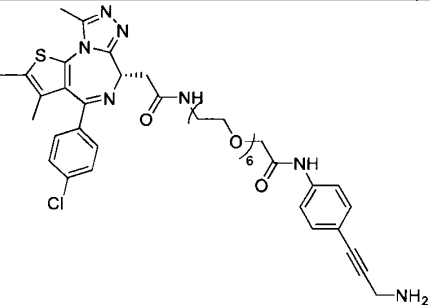
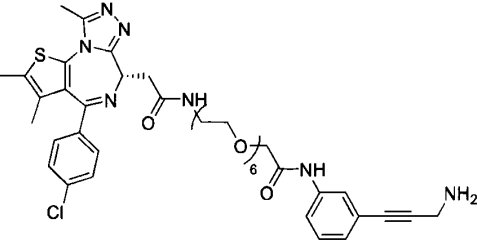
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)isophthalate
5-98'	 methyl (S)-6-(3-aminoprop-1-yn-1-yl)-2-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)nicotinate
5-99'	 (S)-2-(2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)phenyl)acetic acid
5-100'	 ethyl (S)-2-(2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)phenyl)acetate

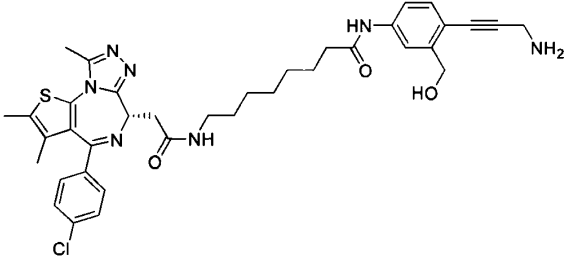
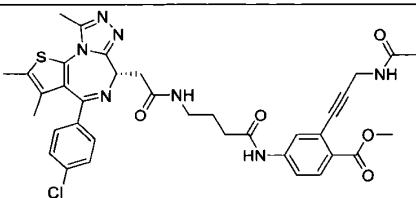
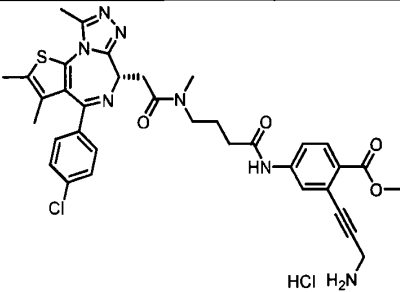
5-101'	 acetoxymethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-102'	 (methacryloyloxy)methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-103'	 (pivaloyloxy)methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-104'	 HCl H₂N

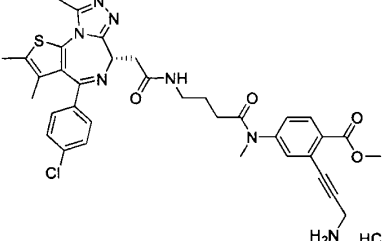
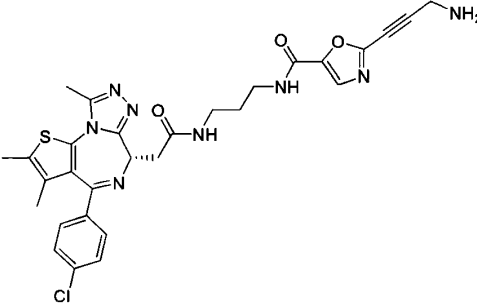
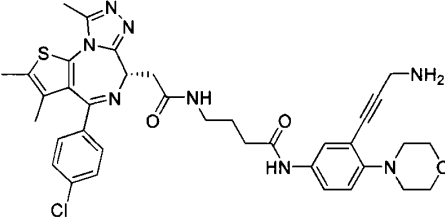
	(S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamide hydrochloride
5-106'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethoxy)-5-oxopentanamido)benzoate hydrochloride
5-107'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-8-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)octanamide hydrochloride
5-108'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-11-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)undecanamide hydrochloride

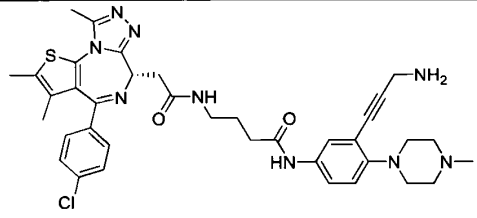
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)undecanamide hydrochloride
5-109'	 (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethyl 11-((3-(3-aminoprop-1-yn-1-yl)phenyl)amino)-11-oxoundecanoate hydrochloride
5-110'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(11-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethoxy)-11-oxoundecanamido)benzoate hydrochloride
5-113'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-((7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethoxy)-11-oxoundecanamido)benzoate hydrochloride

	f)[1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)amino)-5-oxopentanamido)benzoate
5-115'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetoxymethyl)butanamido)benzoate hydrochloride
5-121'	 (S)-2,4-bis(3-aminoprop-1-yn-1-yl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)benzamide
5-122'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

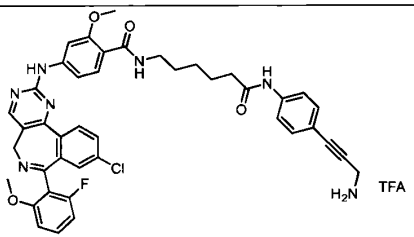
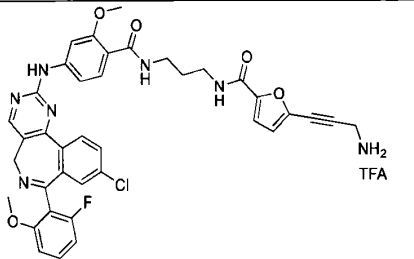
	yl)acetamido)butanamido)prop-1-yn-1-yl)benzoate
5-123'	 (S)-N-(3-(3-(3-aminoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-126'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-20-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-3,6,9,12,15,18-hexaoxaicosanamide
5-127'	 (S)-N-(3-(3-(3-aminoprop-1-yn-1-yl)phenyl)-20-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-3,6,9,12,15,18-hexaoxaicosanamide

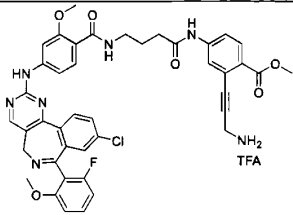
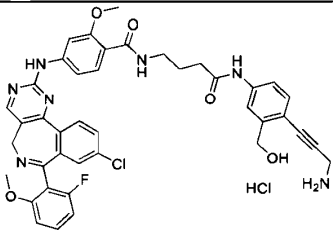
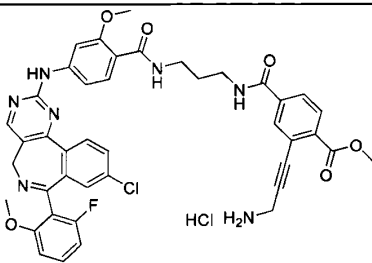
5-135'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-8-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)octanamide
5-148'	 methyl (S)-2-(3-acetamidoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-149'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-methylacetamido)butanamido)benzoate hydrochloride

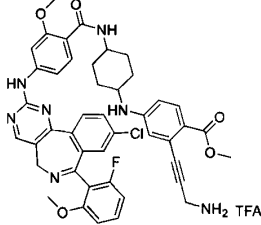
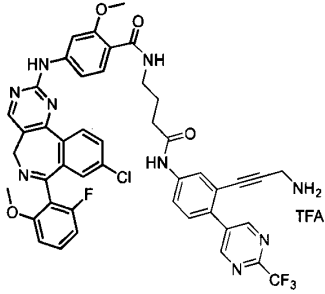
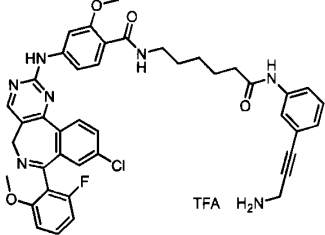
5-150'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-N-methylbutanamido)benzoate hydrochloride
5-169'	 (S)-2-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)oxazole-5-carboxamide
5-170'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-morpholinophenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide

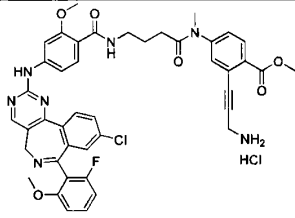
5-171'	 (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(4-methylpiperazin-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
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【표 9】

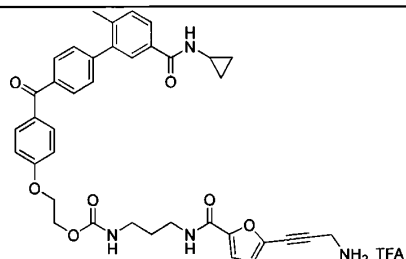
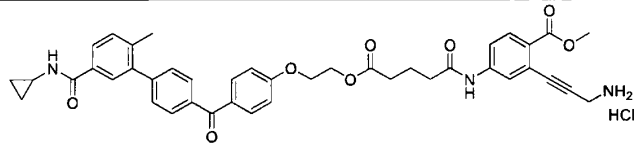
번호	화합물
4-165''	 N-(6-((4-(3-aminoprop-1-yn-1-yl)phenyl)amino)-6-oxohexyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
4-166''	 5-(3-aminoprop-1-yn-1-yl)-N-(3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propyl)furan-2-carboxamide trifluoroacetic acid

4- 228''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)butanamido)benzoate trifluoroacetic acid
5-8''	 N-(4-((4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)amino)-4-oxobutyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
5-18''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propyl)carbamoyl)benzoate hydrochloride

5-35''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-((4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)cyclohexyl)amino)benzoate trifluoroacetic acid
5-81''	 N-(4-((3-(3-aminoprop-1-yn-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)amino)-4-oxobutyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
5-104''	 N-(6-((3-(3-aminoprop-1-yn-1-yl)phenyl)amino)-6-oxohexyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid

5-150''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)-N-methylbutanamido)benzoate trifluoroacetic acid
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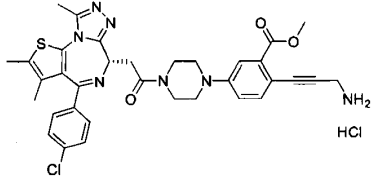
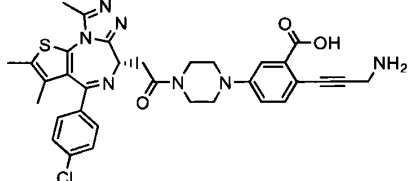
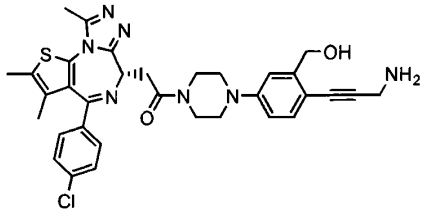
【표 10】

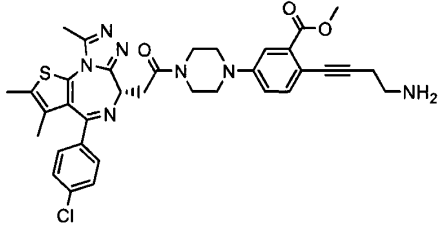
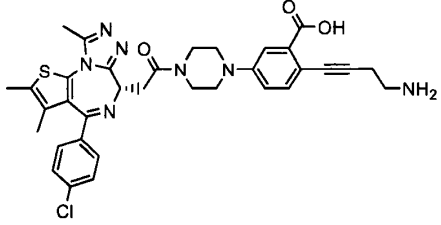
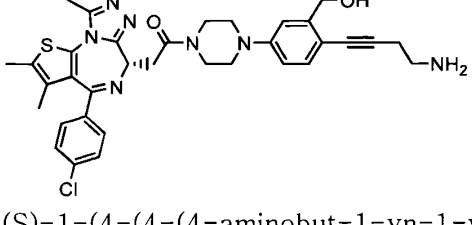
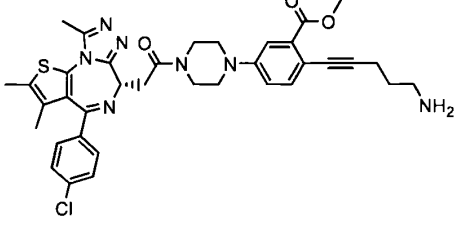
번호	화합물
4-166'''	 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (3-(5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamido)propyl)carbamate trifluoroacetic acid
5-106'''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethoxy)-5-oxopentanamido)benzoate hydrochloride

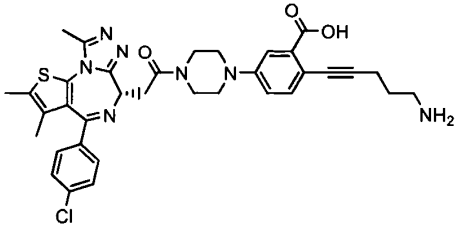
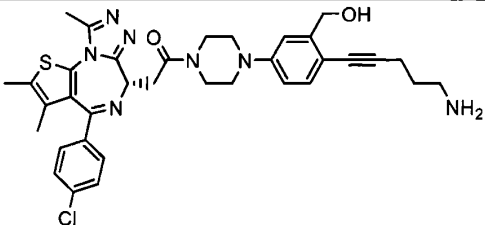
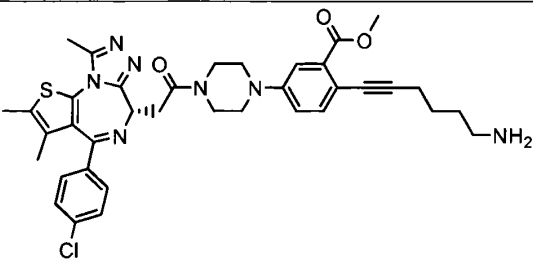
【0122】 보다 구체적으로, 상기 화학식 VII으로 표시되는 화합물에서, 상기 TBM으로 상기 화학식 1의 화합물이 결합된 경우의 구체적인 예들은 하기 표 11에, 상기 TBM으로 상기 화학식 2의 화합물이

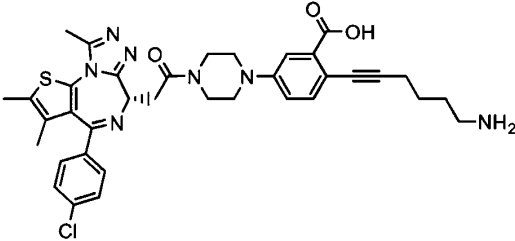
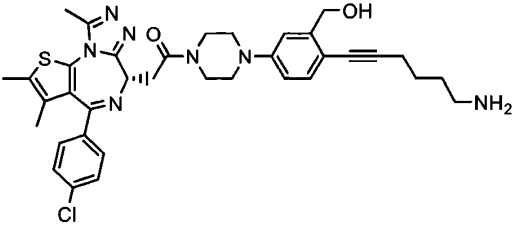
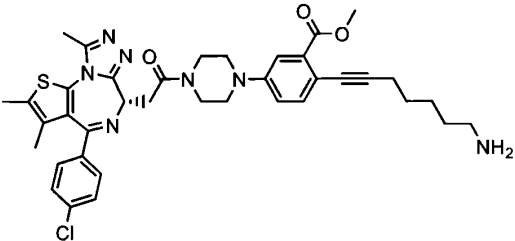
결합된 경우의 구체적인 예들은 하기 표 12에, 그리고 상기 TBM으로 상기 화학식 3의 화합물이 결합된 경우의 구체적인 예들은 하기 표 13에 각각 제시된 것일 수 있으나, 이에 한정되지 아니한다.

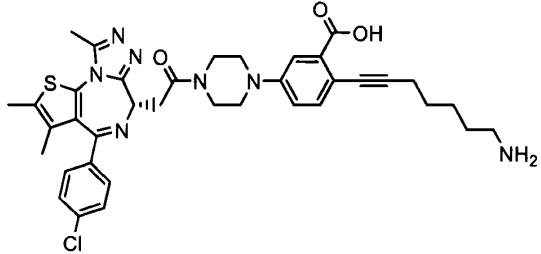
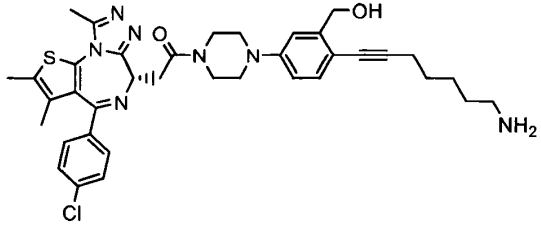
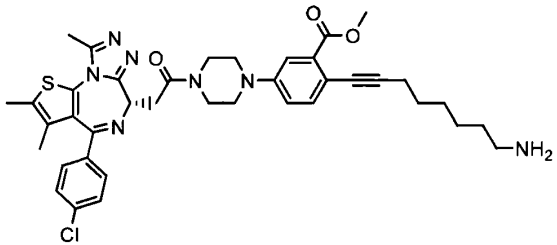
【표 11】

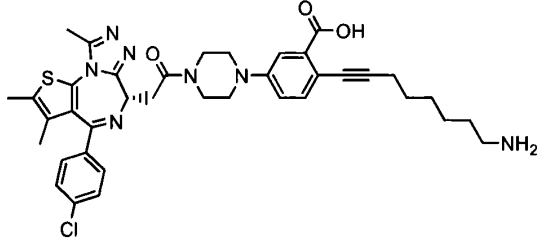
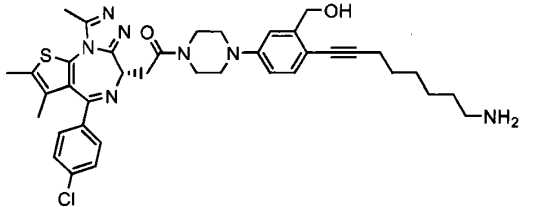
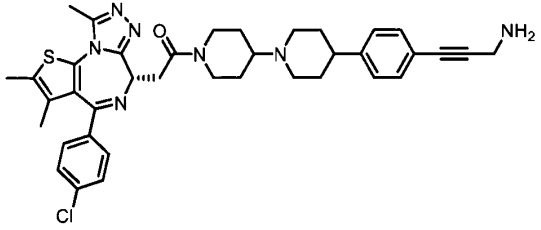
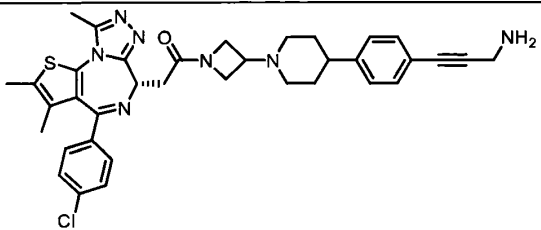
번호	화합물
4-2'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate hydrochloride
4-3'	 (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoic acid
4-4'	 (S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one

4-94'	 methyl (S)-2-(4-aminobut-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate
4-95'	 (S)-2-(4-aminobut-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoic acid
4-96'	 (S)-1-(4-(4-(4-aminobut-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-97'	 methyl (S)-2-(5-aminopent-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate

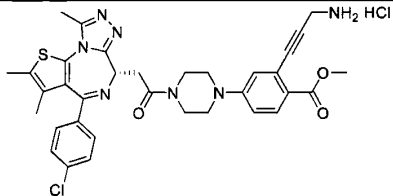
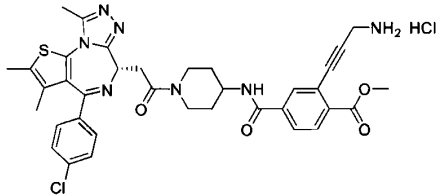
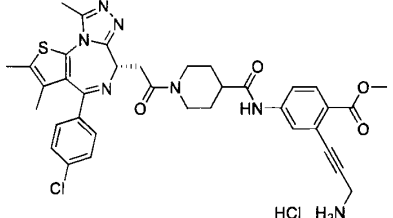
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate
4-98'	 (S)-2-(5-aminopent-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoic acid
4-99'	 (S)-1-(4-(4-(5-aminopent-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-100'	 methyl (S)-2-(6-aminohex-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate

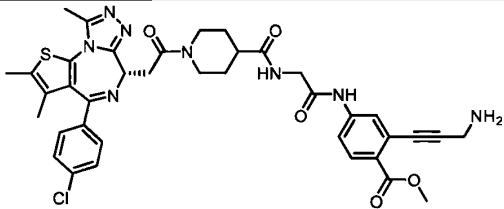
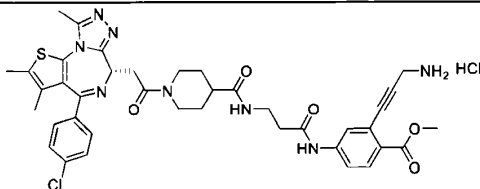
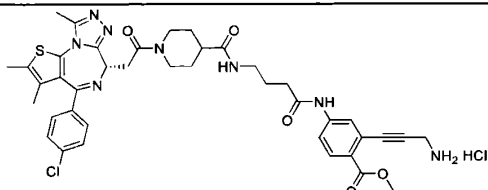
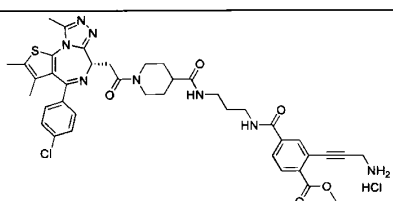
4- 101'	 (S)-2-(6-aminohept-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoic acid
4- 102'	 (S)-1-(4-(4-(6-aminohept-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4- 103'	 methyl (S)-2-(7-aminohept-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate

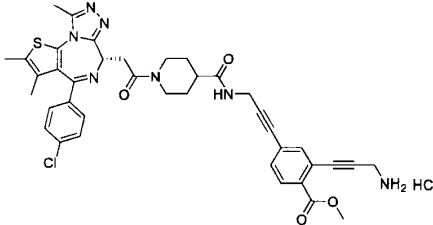
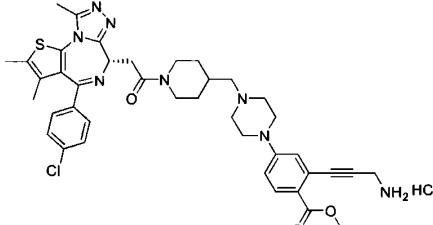
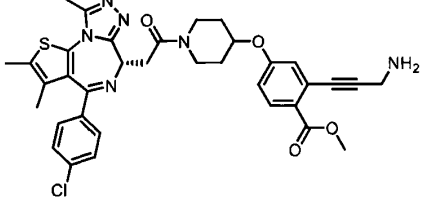
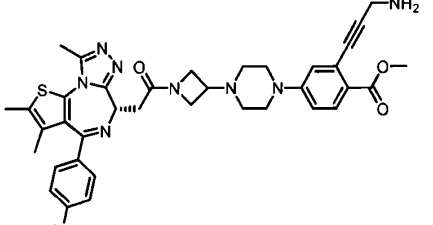
4- 104'	 (S)-2-(7-aminohept-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoic acid
4- 105'	 (S)-1-(4-(4-(7-aminohept-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4- 106'	 methyl (S)-2-(8-aminooct-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate

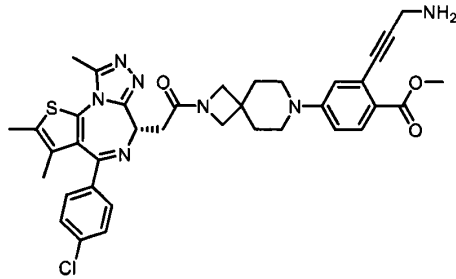
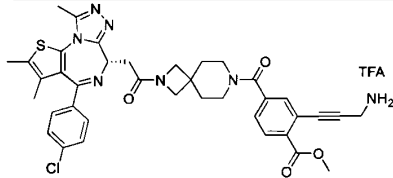
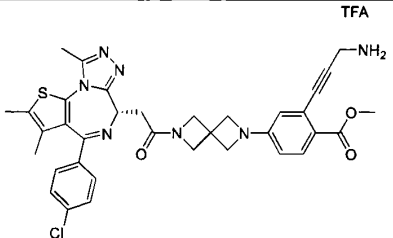
4- 107'	 (S)-2-(8-aminooct-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoic acid
4- 108'	 (S)-1-(4-(4-(8-aminooct-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4- 134'	 (S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)-[1,4'-bipiperidin]-1'-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4- 135'	 (S)-1-(3-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperidin-1-

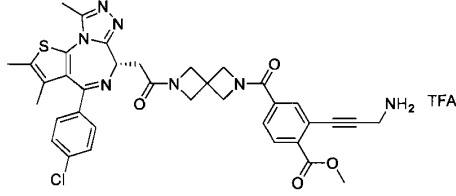
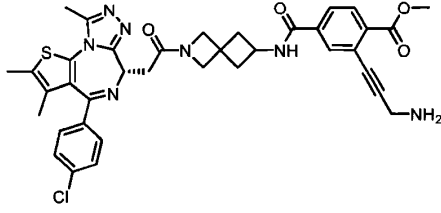
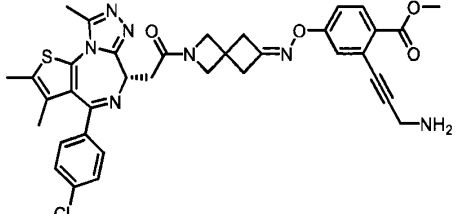
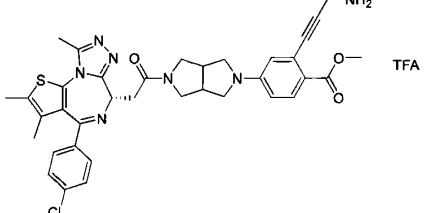
	yl)azetidin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-136'	(S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperidin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-146'	(S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-226'	(S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one hydrochloride
4-227'	(S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one hydrochloride

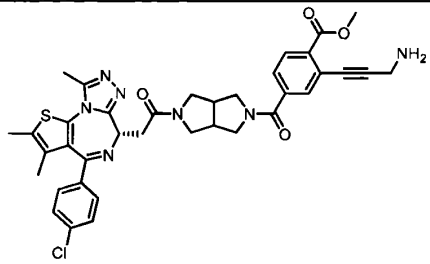
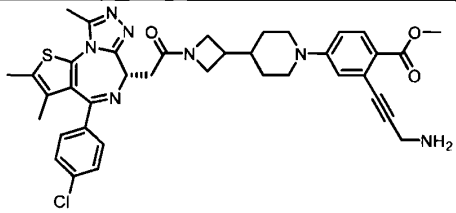
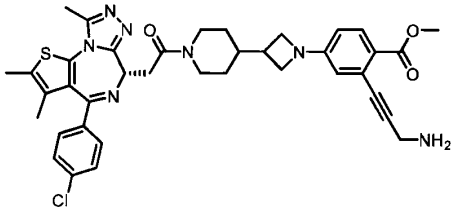
	(S)-1-(4-(5-(3-aminoprop-1-yn-1-yl)furan-2-carbonyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one hydrochloride
5-7'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate hydrochloride
5-22'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)carbamoyl)benzoate hydrochloride
5-23'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)benzoate hydrochloride

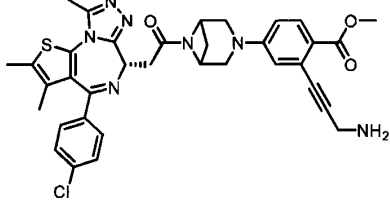
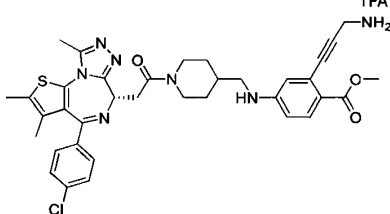
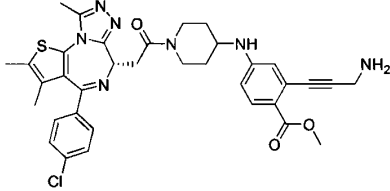
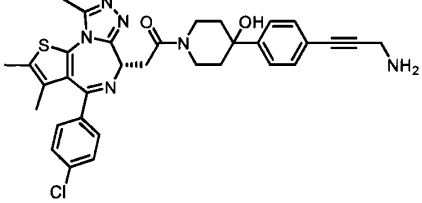
5-24'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)acetamido)benzoate
5-25'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)propanamido)benzoate hydrochloride
5-26'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)butanamido)benzoate hydrochloride
5-27'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)propyl)carbamoyl)benzoate hydrochloride

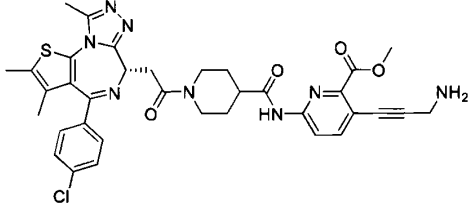
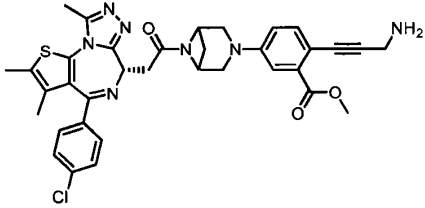
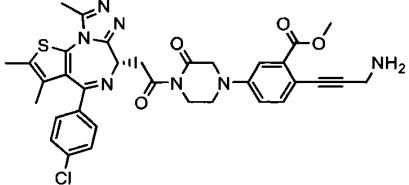
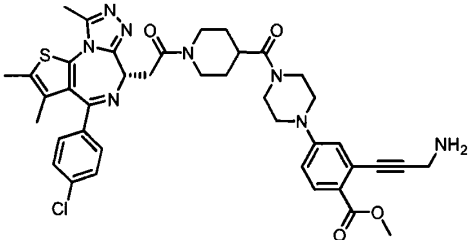
5-28'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)prop-1-yn-1-yl)benzoate hydrochloride
5-29'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)piperazin-1-yl)benzoate hydrochloride
5-36'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)oxy)benzoate
5-37'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)piperazin-1-yl)benzoate

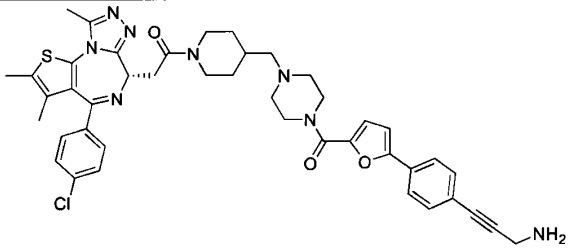
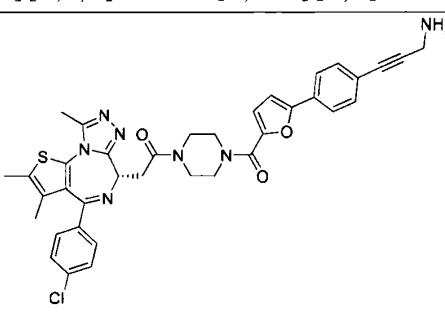
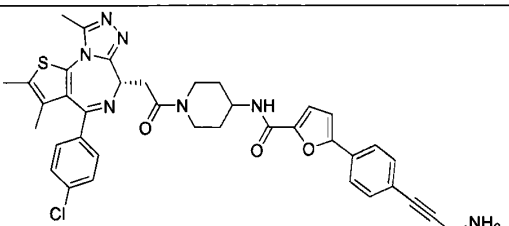
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)azetidin-3-yl)piperazin-1-yl)benzoate
5-38'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,7-diazaspiro[3.5]nonan-7-yl)benzoate
5-39'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,7-diazaspiro[3.5]nonane-7-carbonyl)benzoate trifluoroacetic acid
5-40'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,6-diazaspiro[3.3]heptan-2-yl)benzoate trifluoroacetic acid

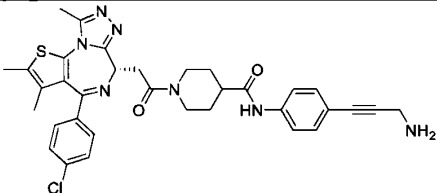
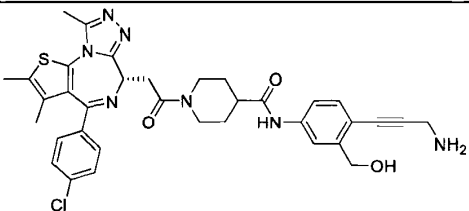
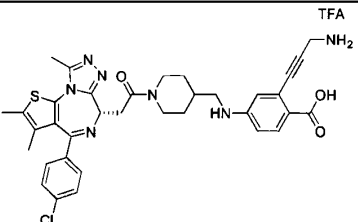
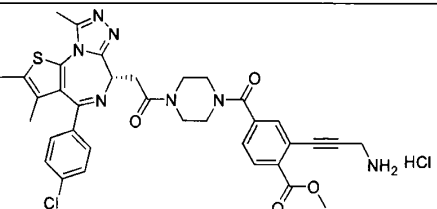
5-41'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,6-diazaspiro[3.3]heptane-2-carbonyl)benzoate trifluoroacetic acid
5-42'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2-azaspiro[3.3]heptan-6-yl)carbamoyl)benzoate
5-43'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2-azaspiro[3.3]heptan-6-ylidene)amino)oxy)benzoate
5-44'	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-((S)-4-(4-

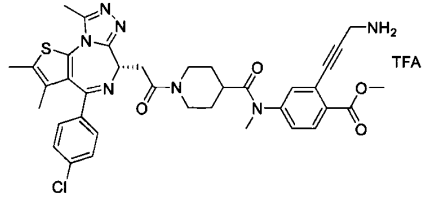
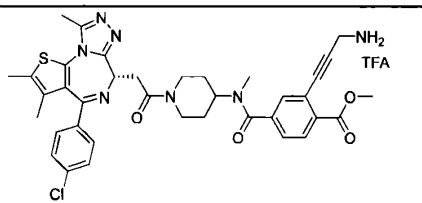
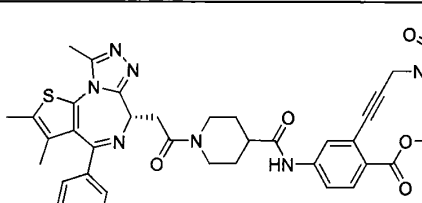
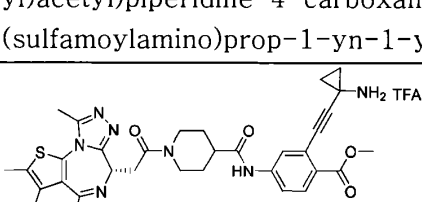
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)benzoate trifluoroacetic acid
5-45'	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzoate
5-46'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)azetidin-3-yl)piperidin-1-yl)benzoate
5-47'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)azetidin-1-yl)benzoate

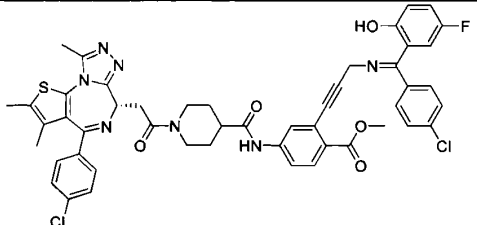
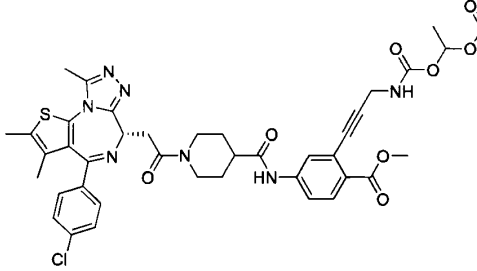
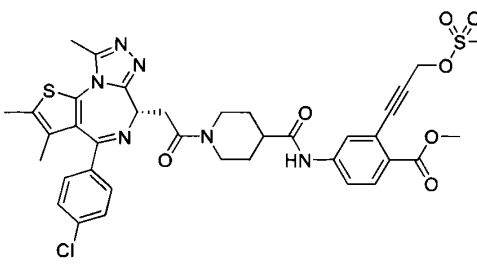
5-48'	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(6-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)benzoate
5-85'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)amino)benzoate trifluoroacetic acid
5-86'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)amino)benzoate
5-88'	 (S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)-4-hydroxypiperidin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl

	a)[1,4]diazepin-6-yl)ethan-1-one
5- 112'	 methyl (S)-3-(3-aminoprop-1-yn-1-yl)-6-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)picolinate
5- 118'	 methyl 2-(3-aminoprop-1-yn-1-yl)-5-(6-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)benzoate
5- 119'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-3-oxopiperazin-1-yl)benzoate
5- 120'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)picolinate

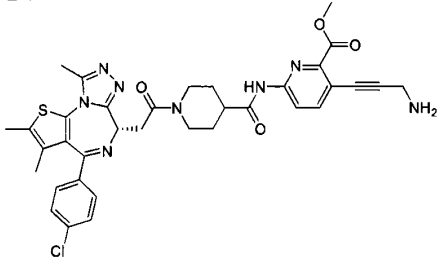
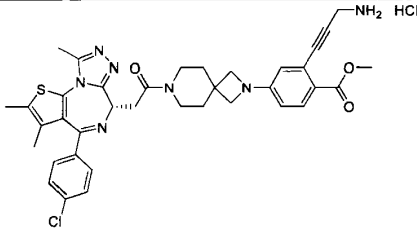
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carbonyl)piperazin-1-yl)benzoate
5-124'	 (S)-1-(4-((4-(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carbonyl)piperazin-1-yl)methyl)piperidin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
5-125'	 (S)-1-(4-(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carbonyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
5-129'	 (S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)furan-2-carboxamide

5- 131'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamide
5- 134'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamide
5- 139'	 (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)amino)benzoic acid trifluoroacetic acid
5- 140'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazine-4-yl)methyl)amino)benzoate hydrochloride

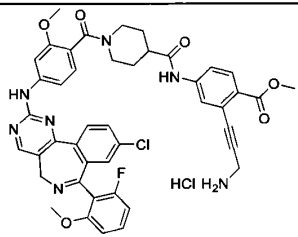
	1-carbonyl)benzoate hydrochloride
5- 152'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-N-methylpiperidine-4-carboxamido)benzoate trifluoroacetic acid
5- 153'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)(methyl)carbamoyl)benzoate trifluoroacetic acid
5- 154'	 methyl (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-(sulfamoylamino)prop-1-yn-1-yl)benzoate trifluoroacetic acid
5- 155'	 methyl (S)-2-((1-aminocyclopropyl)ethynyl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-N-methylpiperidine-4-carboxamido)benzoate trifluoroacetic acid

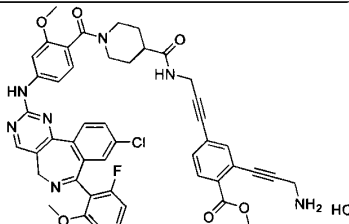
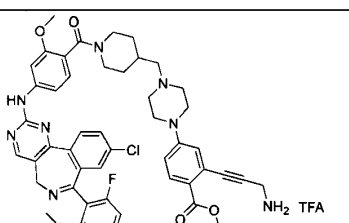
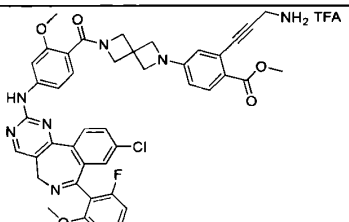
	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)benzoate
5-156'	 methyl (S)-2-(3-(((4-chlorophenyl)(5-fluoro-2-hydroxyphenyl)methylene)amino)prop-1-yn-1-yl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)benzoate
5-157'	 methyl 4-(1-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate
5-158'	 methyl (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-

	(sulfamoyloxy)prop-1-yn-1-yl)benzoate trifluoroacetic acid
5- 159'	Chemical structure of compound 5-159': A thienotriazole core substituted with a 4-chlorophenyl group, a methyl group, and a (S)-5-(3-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)carbamoyl)benzoate group. The benzoate part is further substituted with a (1-((2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)carbamoyl)benzoate) group. methyl 2-(3-amino-4-mercaptobut-1-yn-1-yl)-4-((1-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)carbamoyl)benzoate
5- 160'	Chemical structure of compound 5-160': A thienotriazole core substituted with a 4-chlorophenyl group, a methyl group, and a (S)-5-(3-(3-aminoprop-1-yn-1-yl)phenyl)-N-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)furan-2-carboxamide group. (S)-5-(3-(3-aminoprop-1-yn-1-yl)phenyl)-N-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)furan-2-carboxamide
5- 162'	Chemical structure of compound 5-162': A thienotriazole core substituted with a 4-chlorophenyl group, a methyl group, and a (S)-5-(3-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate group. methyl 4-(6-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate

5-167'	 methyl (S)-3-(3-aminoprop-1-yn-1-yl)-6-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)picolinate
5-168'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,7-diazaspiro[3.5]nonan-2-yl)benzoate hydrochloride

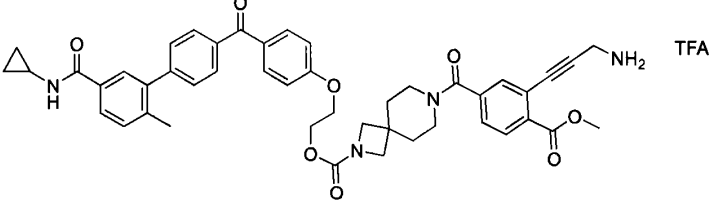
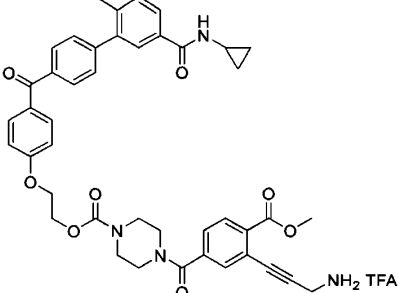
【표 12】

번호	화합물
5-23''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(1-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)piperidine-4-carboxamido)benzoate hydrochloride

5-28''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)piperidine-4-carboxamido)prop-1-yn-1-yl)benzoate trifluoroacetic acid
5-29''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-((1-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)benzoate trifluoroacetic acid
5-40''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(6-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)-2,6-diazaspiro[3.3]heptan-2-yl)benzoate trifluoroacetic acid

【표 13】

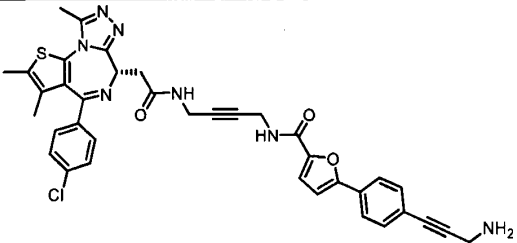
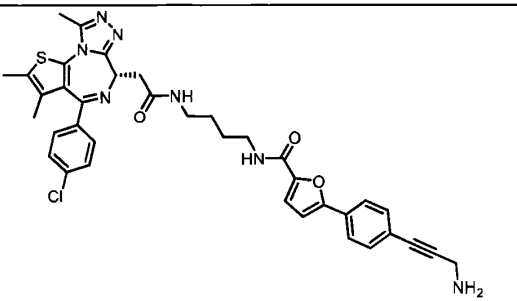
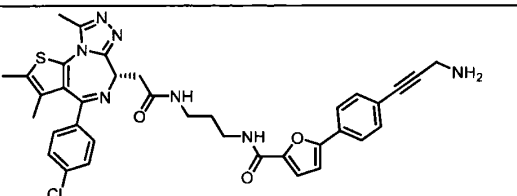
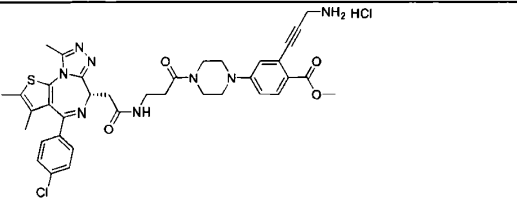
번호	화합물
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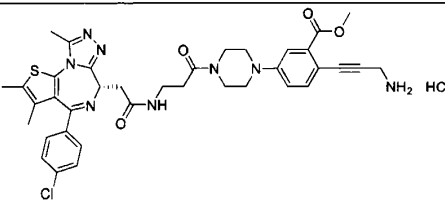
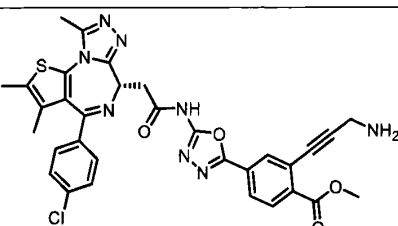
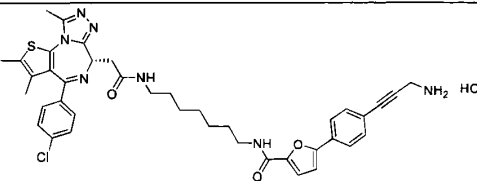
5-39'''	 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl 7-(3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)benzoyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate trifluoroacetic acid
5-140'''	 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl 4-(3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)benzoyl)piperazine-1-carboxylate trifluoroacetic acid

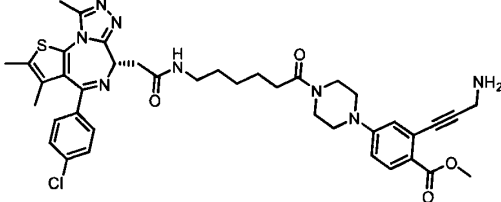
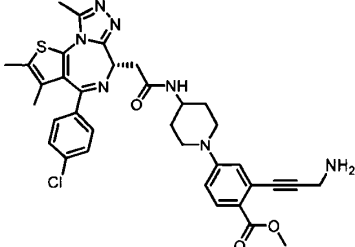
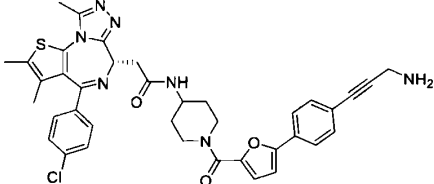
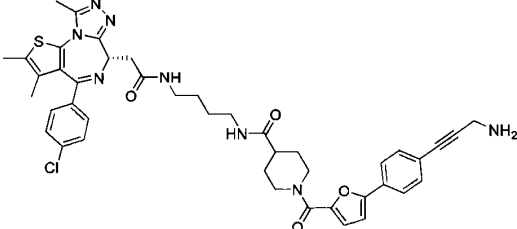
【0123】 보다 구체적으로, 상기 화학식 VIII으로 표시되는 화합물에서, 상기 TBM으로 상기 화학식 1의 화합물이 결합된 경우의 구체적인 예들은 하기 표 14에, 상기 TBM으로 상기 화학식 2의 화합물이 결합된 경우의 구체적인 예들은 하기 표 15에 각각 제시된 것일 수 있으나, 5 이에 한정되지 아니한다.

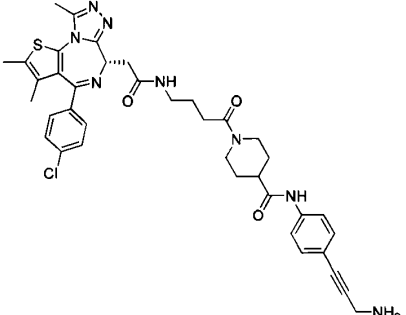
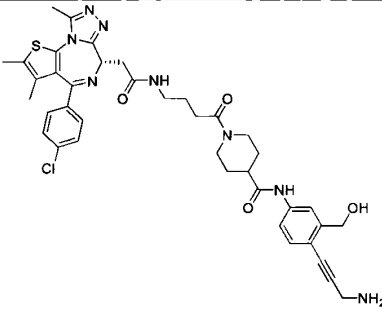
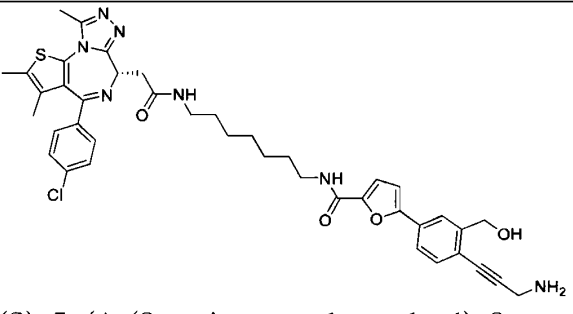
【표 14】

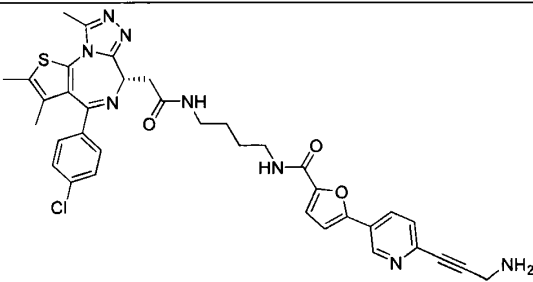
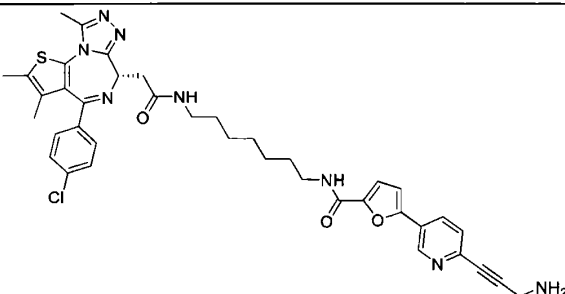
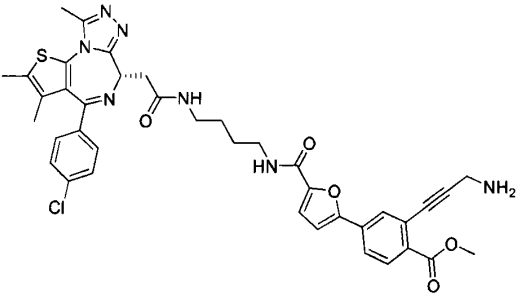
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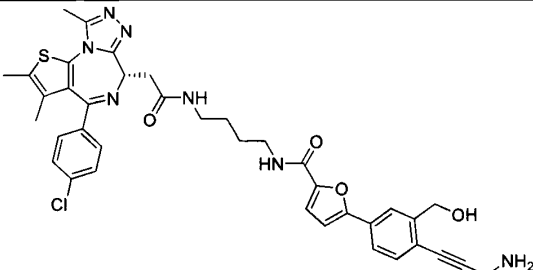
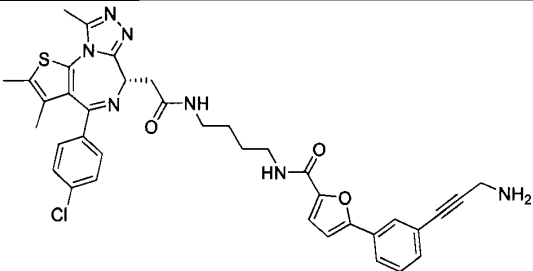
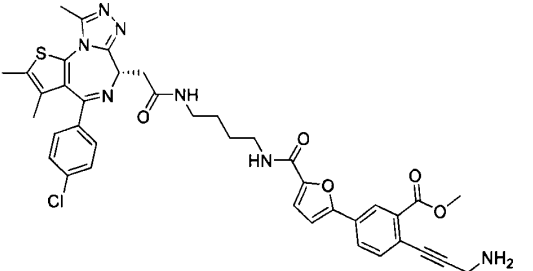
4-207'	 (S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-yn-1-yl)furan-2-carboxamide
4-208'	 (S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
4-211'	 (S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)furan-2-carboxamide
5-32'	 (S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)furan-2-carboxamide

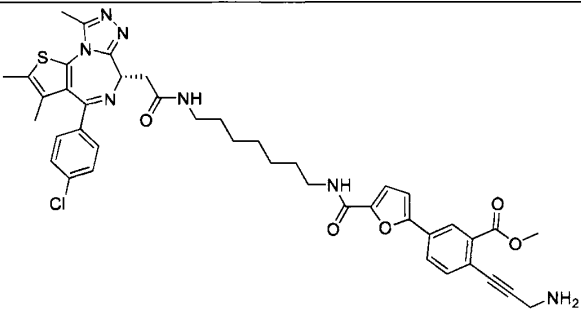
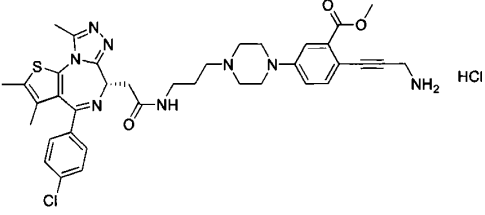
	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanoyl)piperazin-1-yl)benzoate hydrochloride
5-33'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanoyl)piperazin-1-yl)benzoate hydrochloride
5-51'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-1,3,4-oxadiazol-2-yl)benzoate
5-111'	 (S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide hydrochloride

5-114'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanoyl)piperazin-1-yl)benzoate
5-117'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)piperidin-1-yl)benzoate
5-128'	 (S)-N-(1-(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carbonyl)piperidin-4-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
5-130'	 (S)-1-(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carbonyl)piperidin-4-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

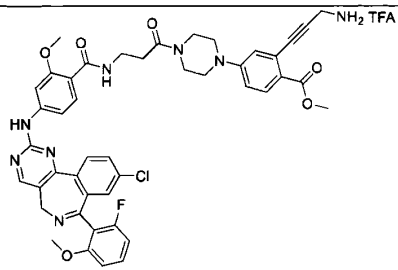
	carbonyl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)piperidine-4-carboxamide
5-132'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-1-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanoyl)piperidine-4-carboxamide
5-133'	 (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-1-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanoyl)piperidine-4-carboxamide
5-136'	 (S)-5-(4-(3-aminoprop-1-yn-1-yl)-3-

	(hydroxymethyl)phenyl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide
5-137'	 (S)-5-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
5-138'	 (S)-5-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide
5-141'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

	yl)acetamido)butyl)carbamoyl)furan-2-yl)benzoate
5-142'	 (S)-5-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
5-143'	 (S)-5-(3-(3-aminoprop-1-yn-1-yl)phenyl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
5-144'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(5-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)carbamoyl)furan-2-yl)benzoate

5-145'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(5-((7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)carbamoyl)furan-2-yl)benzoate
5-164'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)piperazin-1-yl)benzoate hydrochloride
5-165'	 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)piperazin-1-yl)benzoate hydrochloride

【표 15】

번호	화합물
5-32''	 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-(4-((9-chloro-

	7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propanoyl)piperazin-1-yl)benzoate trifluoroacetic acid
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【0124】 상기와 같이 TBM-UBM의 화학 구조를 가지는 본 발명의 화합물은 표적 단백질 또는 폴리펩티드를 분해할 수 있다. 구체적으로, 도 1에 도시된 바와 같이, 본 발명의 화합물의 TBM이 표적 단백질 또는 폴리펩티드에 결합한 다음, 본 발명의 화합물의 UBM에 유비퀴틴이 결합하면((폴리)유비퀴틴화 되면), 상기 표적 단백질 또는 폴리펩티드는 프로테아좀 또는 라이소좀에 의해 분해될 수 있다.

【0125】

【0126】 3. 약학적 조성물

【0127】 본 발명의 다른 측면은 상기 화학식 I 내지 VIII로 표시되는 화합물, 또는 이의 약학적으로 허용가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭을 유효성분으로 포함하는 약학적 조성물을 제공한다.

【0128】 상술한 바와 같이 상기 화학식 I 내지 IV로 표시되는 화합물이나 상기 화학식 V 내지 VIII로 표시되는 화합물은 표적 단백질 또는 폴리펩티드의 분해자(degrader)로서의 활성을 가지는 바, 본 발명의 상기 약학적 조성물은 상기와 같은 표적 단백질 또는 폴리펩티드에 의해 유발되는 질환의 예방 또는 치료를 위해 이용될 수 있다.

【0129】 특히, 본 발명의 상기 약학적 조성물은 상기 화학식 V

내지 VIII로 표시되는 화합물, 또는 이의 약학적으로 허용가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭을 유효성분으로 포함할 수 있고, 이때 상기 약학적 조성물의 구체적인 용도는 TBM이 결합하는 표적 단백질 또는 폴리펩티드의 종류에 따라서 달라질 수 있다.

5 **【0130】** 예컨대, 상기 TBM이 결합하는 표적 단백질 또는 폴리펩티드가 BRD2, BRD3, BRD4, BRDT 등과 같은 브로모도메인-내포 단백질이거나 상기 TBM이 BRD4 저해제 등과 같이 브로모도메인-내포 단백질을 표적으로 하는 화합물인 경우, 상기 약학적 조성물은 브로모도메인-내포 단백질 관련 질환의 예방 또는 치료를 위해 이용될 수
10 있다.

【0131】 상기 브로모도메인-내포 단백질 관련 질환은, 예를 들어 BRD2, BRD3, BRD4, BRDT 등과 같은 브로모도메인-내포 단백질이 과발현 또는 과활성화되어 발병, 진행, 악화되는 질환 또는 병태일 수 있고, 구체적으로, 급성 또는 만성 자가면역 및 염증 질환일 수 있다.

15 **【0132】** 본 발명의 또 다른 구체예에서, 상기 브로모도메인-내포 단백질 관련 질환 또는 병태는, 선천적, 혹은 후천적으로 발생하는 과염증 반응과 지속적인 염증으로 발생하는 질환 예를 들어 후천성혈우병 A, 원형 탈모증, 강직성척추염, Anti-NMDA 수용체 뇌염, 항인지질 항체 증후군(CAPS), 애디슨병, 자가면역자율신경병증(AAG), autoimmune
20 gastrointestinal dysmotility(AGID), 자가면역뇌염,

급성파종뇌척수염(ADEM), 자가면역성 위염, 자가면역성용혈성빈혈(AIHA),
 자가면역 간염(AIH), 자가면역 고지혈증, 임파구성 뇌하수체염, 자가면역성
 내이질환(AIED), 자가면역 림프증식성 증후군(ALPS), 자가면역 골수섬유증,
 자가면역 심근염, 자가면역 난소염, 자가면역 췌장염(AIP), 1, 2, 3형
 5 자가면역(기존용어사전-자가면역질환)성 다선 증후군(APS type 1, APS type
 2, APS type 3, APECED), 자가면역 프로게스테론 피부염, 자가면역
 망막병증(AIR), 자가면역 감각신경성 난청(SNHL), 발로병, 베체트병,
 산탄맥락망막병증(BSCR), 물집유사천포창, 캐슬만병, 복강병, 샤가스병, 만성
 염증성 수초탈락성 다발성 신경병증(CIDP), 만성 두드러기(CU), 호산구성
 10 육아종 다발혈관염(EGPA), 코간증후군, 한랭응집소병, 크레스트 증후군,
 크론 증후군(CD), 크론카이트-카나다 증후군(CSS), 특발성 기질화
 폐렴(COP), 피부근염, 시신경척수염(NMO), 1형 당뇨병, 드레슬러증후군,
 아토피염, 자궁내막증, 호산구 식도염, 호산구성 근막염, 결절성 홍반,
 원발성 혼합 한랭-글로불린증, 에반스 증후군, 섬유소(성)폐렴,
 15 거세포성동맥염, 사구체신염, 굿파스치증후군, 다발혈관염 동반
 육아종증(GPA), 그레이브스병, 기안 바레 증후군(GBS), 만성 림프구성
 갑상선염, 헤노흐 쉰라인 자반증, 화농성 한선염, 저감마글로불린혈증,
 면역글로불린 A 신병증, 면역-매개 괴사성 근육병증(IMNM), 면역성
 혈소판감소증(ITP), 봉입체 근염, IgG4-연관 다발성 경화증(ISD), 간질성
 20 방광염, 소아특발관절염, 소아다발성 근염, 소아 피부근염, 가와사키병,

- 람베르트-이튼 근무력 증후군(LEMS), 백혈구과피혈관염, 편평태선, 경화성태선, 결막염, 선IgA물집피부병(LAD), 선IgA물집피부병(LABD), 루푸스 신염, 림프구성 대장염, 메니에르병, 미세다발 혈관염(MPA), 혼합 결합 조직병(MCTD), 무렌각막궤양, 급성태선모양잔비늘증,
- 5 다초점운동신경병증, 다발성경화증(MS), 근육통성뇌수막염(ME), 중증근무력증(MG), 눈 홍터 유사천포창, 안구간대경련-근간대경련증후군(OMS), 재발성류마티즘, 신생물탈립소뇌변성, 종양 연관성 천포창, 진행 반얼굴 위축증(HFA), 발작성야간혈색소뇨증, 정맥주위염, 파르소니지 터너증후군, 임신성 유천포창, 낙엽천포창, 보통 천포창,
- 10 악성빈혈, POEMS 증후군, 결절다발동맥염(PAN), 류마티스성 다발근통, 다발성 근염, 체위성 기립성 빈맥 증후군(POT), 원발성 담즙성 간경변증(PBC), 건선, 손발바닥 농포증, 건선 관절염, 특발성 폐섬유증(IPF), 순적혈구무형성증(PRCA), 괴저 화농 피부염, 레이노병, 반응성관절염, 복합부위 통증 증후군(RSD), 재발성 다발연골염, 하지불안증후군(RLS),
- 15 류마티스 열, 류마티스 관절염, 유육종증, 2형 자가면역성 다선 증후군, 공막염, 피부경화증, 뱀모양 맥락막염, 세그렌 증후군, 강직인간증후군(SPS), 소섬유신경병증, 전신성 홍반성 루푸스(SLE), 스삭증후군, 시대남 무도병, 교감신경섬유, 타카야수 동맥염, 고환염, 톨로사 헛트 증후군, 횡단성 척수염(TM), 간질성 신염 포도막염 증후군(TINU), 궤양성 대장염(UC),
- 20 미분화 결합조직질환, 포도막염, 혈관염, 백반증, 보그트 고양이나기 하라다병

질환 또는 병태들을 포함하지만, 이에 국한되는 것은 아니고 상기 질환에 의해 발생하는 동맹경화증에도 적용이 되며, 피험체에서 발생하는 염증성 질환에 포괄적으로 적용이 가능하다.

【0133】 본 발명의 또 다른 구체예에서, 상기 브로모도메인-

5 내포 단백질 관련 질환 또는 병태는 세포 증식성 장애일 수 있다. 상기 세포 증식성 장애는 암성 과증식 장애(예를 들어, 뇌, 폐, 편평상피세포, 방광, 위, 췌장, 유방, 두부, 경부, 신장, 간, 신장, 난소, 전립선, 결장직장, 결장, 표피, 식도, 고환, 부인과 또는 갑상선암, 급성 골수성백혈병, 다발성 골수종, 중피종, 비소세포 폐 암종(NSCLC), 소세포 폐암(SCLC), 신경아세포종 및

10 급성 림프구성백혈병(ALL)); 비암성 과증식 장애(예를 들어, 피부의 양성 비대증(예를 들어, 건선), 재협착증 및 양성 전립선비대증(BPH)); 및 혈관 생성 또는 신생혈관생성과 관련된 질병(예를 들어, 종양 신생혈관생성, 혈관종, 신경교종, 흑색종, 카포시 육종 및 난소, 유방, 폐, 췌장, 전립선, 결장 및 표피암)을 포함하지만, 이들로 제한되는 것은 아니다. 세포 증식성

15 장애는 원발성 및 전이성 암을 추가로 포함한다. 특히, 화합물은 가성점액종, 간내, 담도암, 간모세포종, 간암, 결장암, 고환암, 골수이형성증후군, 교모세포종, 구강암, 구순암, 구인두-편도암(HPV관련), 구인두-하인두암(HPV비관련), 균상식육종, 기저세포암, 난소상피암, 난소생식세포종양, 남성유방암, 뇌종양, 뇌하수체선종, 담낭·담도암, 담낭암,

20 담도암, 대장암, 만성골수성백혈병, 만성림프구백혈병, 망막모세포종,

맥락막흑색종, 미만성거대B세포림프종, 바터팽대부암, 방광암, 복막암, 부갑상선암, 부신암, 비부비동암, 비호지킨림프종, 설암, 성상세포종, 소아청소년뇌종양, 소아청소년림프종, 소아청소년백혈병, 소장암, 수막종, 식도암, 신경모세포종, 신우암, 신장암, 심장암, 십이지장암, 5 악성연부조직종양, 악성골종양, 악성림프종, 악성중피종, 악성흑색종, 안종양, 외음부암, 요관암, 요도암, 원발부위불명암, 위림프종, 위암, 위유암종, 위장관기질종양, 율름스종양, 유방암, 육종, 음경암, 임신용모질환, 자궁경부암, 자궁내막암, 자궁육종, 전립선암, 전이성 골종양, 전이성 뇌종양, 종격동암, 직장, 신경내분비종양, 직장암, 질암, 척수종양, 청신경초종, 10 췌장암, 침샘암, 파제트병, 편평상피세포암, 폐선암, 폐암, 폐편평상피세포암, 피부암, 항문암, 횡문근육종, 후두암, 흉선암을 포함하지만, 단지 이 암세포 종에 국한 하지 않고, 이 질병의 전이로 인한 질병, 또한, 재발로 발생하는 돌연변이를 포함하는 변이종을 포함하지만, 이들로 제한되는 것은 아닌, 피험체에서의 암의 치료에서 유용하다.

15 【0134】 예컨대, 상기 TBM이 결합하는 표적 단백질 또는 폴리펩티드가 Aurora 키나제 A이거나, 상기 TBM이 Aurora A 저해제 등과 같이 Aurora 키나제 A를 표적으로 하는 화합물인 경우, 상기 약학적 조성물은 세포 증식성 장애의 예방 또는 치료를 위해 이용될 수 있다. 상기 세포 증식성 장애는 상술한 바와 같다.

20 【0135】 예컨대, 상기 TBM이 결합하는 표적 단백질 또는

폴리펩티드가 상기 p38 MAPK이거나, 상기 TBM이 p38 저해제 등과 같이 p38 MAPK를 표적으로 하는 화합물인 경우, 상기 약학적 조성물은 염증 및 염증 관련 질환의 예방 또는 치료를 위해 이용될 수 있다.

- 【0136】 상기 염증 또는 염증 관련 질환은 선천적, 혹은
- 5 후천적으로 발생하는 과염증 반응과 지속적인 염증으로 발생하는 질환 예를 들어 후천성혈우병 A, 원형 탈모증, 강직성척추염, Anti-NMDA 수용체 뇌염, 항인지질 항체 증후군(CAPS), 에디슨병, 자가면역자율신경병증(AAG), autoimmune gastrointestinal dysmotility(AGID), 자가면역뇌염, 급성파종뇌척수염(ADEM), 자가면역성 위염, 자가면역성용혈성빈혈(AIHA),
- 10 자가면역 간염(AIH), 자가면역 고지혈증, 임파구성 뇌하수체염, 자가면역성 내이질환(AIED), 자가면역 림프종식성 증후군(ALPS), 자가면역 골수섬유증, 자가면역 심근염, 자가면역 난소염, 자가면역 췌장염(AIP), 1, 2, 3형 자가면역(기존용어사전-자가면역질환)성 다선 증후군(APS type 1, APS type 2, APS type 3, APECED), 자가 면역 프로게스테론 피부염, 자가면역
- 15 망막병증(AIR), 자가면역 감각신경성 난청(SNHL), 발로병, 베체트병, 산탄매락망막병증(BSCR), 물집유사천포창, 캐슬만병, 복강병, 샤가스병, 만성 염증성 수초탈락성 다발성 신경병증(CIDP), 만성 두드러기(CU), 호산구성 육아종 다발혈관염(EGPA), 코간증후군, 한랭응집소병, 크레스트 증후군, 크론 증후군(CD), 크론카이트-캐나다 증후군(CSS), 특발성 기질화
- 20 폐렴(COP), 피부근염, 시신경척수염(NMO), 1형 당뇨병, 드레슬러증후군,

- 아토피염, 자궁내막증, 호산구 식도염, 호산구성 근육염, 결절성 홍반,
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 거세포성동맥염, 사구체신염, 콧파스처증후군, 다발혈관염 동반
 육아종증(GPA), 그레이브스병, 기안 바레 증후군(GBS), 만성 림프구성
 5 갑상선염, 헤노흐 쉐라인 자반증, 화농성 한선염, 저감마글로불린혈증,
 면역글로불린 A 신병증, 면역-매개 피사성 근육병증(IMNM), 면역성
 혈소판감소증(ITP), 봉입체 근염, IgG4-연관 다발성 경화증(ISD), 간질성
 방광염, 소아특발관절염, 소아다발성 근염, 소아 피부근염, 가와사키병,
 람베르트-이튼 근무력 증후군(LEMS), 백혈구과괴혈관염, 편평태선,
 10 경화성태선, 결막염, 선IgA물집피부병(LAD), 선IgA물집피부병(LABD),
 루푸스 신염, 림프구성 대장염, 메니에르병, 미세다발 혈관염(MPA), 혼합
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 다초점운동신경병증, 다발성경화증(MS), 근육통성뇌수막염(ME),
 중증근무력증(MG), 눈 홍터 유사천포창, 안구간대경련-
 15 근간대경련증후군(OMS), 재발성류마티즘, 신생물탈립소뇌변성, 중앙 연관성
 천포창, 진행 반얼굴 위축증(HFA), 발작성야간혈색소뇨증, 정맥주위염,
 파르소니지 터너증후군, 임신성 유천포창, 낙엽천포창, 보통 천포창,
 악성빈혈, POEMS 증후군, 결절다발동맥염(PAN), 류마티스성 다발근통,
 다발성 근염, 체위성 기립성 빈맥 증후군(POT), 원발성 담즙성
 20 간경변증(PBC), 건선, 손발바닥 농포증, 건선 관절염, 특발성 폐섬유증(IPF),

순적혈구무형성증(PRCA), 피저 화농 피부염, 레이노병, 반응성관절염,
 복합부위 통증 증후군(RSD), 재발성 다발연골염, 하지불안증후군(RLS),
 류마티스 열, 류마티스 관절염, 유육종증, 2형 자가면역성 다선 증후군,
 공막염, 피부경화증, 뱀모양 맥락막염, 세그렌 증후군, 강직인간증후군(UPS),
 5 소섬유신경병증, 전신성 홍반성 루푸스(SLE), 스삭증후군, 시데남 무도병,
 교감신경섬유, 타카야수 동맥염, 고환염, 톨로사 헌트 증후군, 횡단성
 척수염(TM), 간질성 신염 포도막염 증후군(TINU), 궤양성 대장염(UC),
 미분화 결합조직질환, 포도막염, 혈관염, 백반증, 보그트 고야나기 하라다병
 질환 또는 병태들을 포함하지만, 이에 국한되는 것은 아니고 상기 질환에
 10 의해 발생하는 동맹경화증에도 적용이 된다. P38의 염증반응에 관련된
 기전은 상기 명시된 선천적 또는 후천적 면역에 의한 질병 뿐만 아니라,
 감염체 의한 급성 염증, 즉 에볼라바이러스병, 마버그열, 라싸열,
 크리미안콩고 출혈열, 남아메리카 출혈열, 리프트밸리열, COIVD19 포함하는
 신종 감염병증후군, 중금급성 호흡기 증후군(SARS), 중동호흡기
 15 증후군(MERS), 동물 인플루엔자 인체 감염증, 신종 인플루엔자, 수두, 홍역,
 장티푸스, 라티푸스, 장출혈성 대장균 감염증, A형 감염, 백일해,
 유행성이하선염, 풍진, 수막구균 감염증, b형 헤모필루스 인플루엔자 감염증,
 폐렴구균 감염증, 선히열, 반코마이신 내성 황색 포도알균(VRSA) 감염증,
 카바페넴내성 장내세균속 균종(CRE) 감염증, E형 감염, 파상풍, 일본뇌염,
 20 레지오넬라증, 비브리오패혈증, 발진티푸스, 발진열, 찰라사증,

렙스피라증, 브루셀라증, 공수병, 신증후군출혈열, 황열, 뎅기열, 큐열, 웨스트나일열, 라임병, 진드기매개뇌염, 치쿤구니아열, 중증열성혈소판 감소증후군(SFTS), 반코마이신내성장알균(VRE) 감염증, 메티실린내성 황색포도알균(MRSA) 감염증, 다제내성 녹농균(MRPA) 감염증, 다제내성아시네토박터바우마니균(MRAB) 감염증, 장관 감염증, 급성 호흡기 감염증, 엔테로바이러스 감염증, 사람유두종 바이러스 감염증을 포함하되 이에 국한되는 것은 아니며, 피험체에서 발생하는 감염성, 선천성, 또는 후천성 면역성 질환에 포괄적으로 적용이 가능하다.

【0137】 본 발명의 상기 약학적 조성물은 약학적으로 허용가능한 담체(carrier) 또는 첨가제를 더 포함할 수 있다.

【0138】 본 발명의 상기 유효성분은 단독으로 또는 어떤 편리한 담체 등과 함께 혼합하여 투여될 수 있고, 그러한 투여 제형은 단회 투여 또는 반복 투여 제형일 수 있다. 상기 약학적 조성물은 고형 제제 또는 액상 제제일 수 있다. 고형 제제는 산제, 과립제, 정제, 캡슐제, 좌제 등이 있으나, 이에 한정되는 것은 아니다. 고형 제제에는 담체, 착향제, 결합제, 방부제, 붕해제, 활택제, 충전제 등이 포함될 수 있으나 이에 한정되는 것은 아니다. 액상 제제로는 물, 프로필렌 글리콜 용액 같은 용액제, 현탁액제, 유제 등이 있으나, 이에 한정되는 것은 아니며, 적당한 착색제, 착향제, 안정화제, 점성화제 등을 첨가하여 제조할 수 있다. 예를 들어, 산제는 본 발명의 유효 성분과 유당, 전분, 미결정셀룰로오스 등 약제학적으로

허용가능한 적당한 담체를 단순 혼합함으로써 제조될 수 있다. 과립제는 본 발명의 상기 유효성분, 약학적으로 허용가능한 적당한 담체 및 폴리비닐피롤리돈, 하이드록시프로필셀룰로오스 등의 약학적으로 허용가능한 적당한 결합제를 혼합한 후, 물, 에탄올, 이소프로판올 등의 용매를 이용한 습식과립법 또는 압축력을 이용한 건식과립법을 이용하여 제조될 수 있다.

또한 정제는 상기 과립제를 마그네슘스테아레이트 등의 약학적으로 허용가능한 적당한 활택제와 혼합한 후, 타정기를 이용하여 타정함으로써 제조될 수 있다.

【0139】 본 발명의 상기 약학적 조성물은 치료해야 할 질환 및 개체의 상태에 따라 경구제, 주사제(예를 들어, 근육주사, 복강주사, 정맥주사, 주입(infusion), 피하주사, 임플란트), 흡입제, 비강투여제, 질제, 직장투여제, 설하제, 트랜스더말제, 토피칼제 등으로 투여될 수 있으나, 이에 한정되는 것은 아니다. 투여 경로에 따라 통상적으로 사용되고 비독성인, 약학적으로 허용가능한 운반체, 첨가제, 비히클을 포함하는 적당한 투여 유닛 제형으로 제제화될 수 있다.

【0140】 본 발명의 약학적 조성물은 매일 약 0.0001 mg/kg 내지 약 10 g/kg이 투여될 수 있으며, 약 0.001 mg/kg 내지 약 1 g/kg의 1일 투여 용량으로 투여될 수 있다. 그러나 상기 투여량은 상기 혼합물의 정제 정도, 환자의 상태(연령, 성별, 체중 등), 치료하고 있는 상태의 심각성 등에 따라 다양할 수 있다. 필요에 따라 편리성을 위하여 1일 총 투여량을

하루 동안 여러 번 나누어 투여될 수 있다.

【0141】

【0142】 이하, 본 발명을 실시예에 의하여 상세히 설명한다.

【0143】 단, 하기 실시예는 본 발명을 구체적으로 예시하는
5 것이며, 본 발명의 내용이 하기 실시예에 의해 한정되지 아니한다.

【0144】

【0145】 **【제조예】**

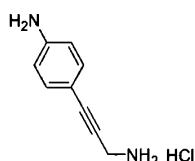
【0146】 먼저, 본 발명의 상기 화학식 I 내지 화학식 IV로
표시되는 화합물들을 설계하고 아래와 같이 합성하였다. 합성 과정에서
10 이용된 시료들의 일부는 아래와 같이 약어로 표현한다: ACN: acetonitrile,
DCM: dichloromethane, HCl: hydrochloride, EtOAc: ethyl acetate, MeOH:
methanol, EtOH: ethanol, DCE: dichloroethane, DMSO: dimethyl sulfoxide,
DMF: N, N-dimethylformamide, THF: tetrahydrofuran, TBSCl: tert-
butyldimethylsilyl chloride, TBAI: tetrabutylammonium iodide, DEA;
15 diethylamine, TEA: triethylamine, DIPEA: N, N-diisopropylethylamine,
NIS: N-iodosuccinimide, PTSA: p-toluenesulfonic acid, TFA:
trifluoroacetic acid, BINAP: (2,2'-bis(diphenylphosphino)-1,1'-
binaphthyl), NBS: N-bromosuccinimide, EDC: 1-ethyl-3-(3-
dimethylaminopropyl)carbodiimide, HATU: 1-
20 [bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-

oxid hexafluorophosphate, HOBT: 1-hydroxybenzotriazole hydrate, DCC: N,N'-dicyclohexylcarbodiimide, DMAP: 4-dimethylaminopyridine 및 mCPBA: meta-chloroperoxybenzoic acid.

【0147】 [제조예 I]

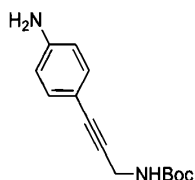
- 5 **【0148】** 본 발명의 화학식 I에 해당하는 화합물들을 아래와 같이 합성하였다.

【0149】 [제조예 1-1] 4-(3-aminoprop-1-yn-1-yl)aniline hydrochloride



【0150】

- 10 **【0151】** 단계 1: tert-butyl (3-(4-aminophenyl)prop-2-yn-1-yl)carbamate(중간체 1-1a)



【0152】

- 【0153】** 4-Iodoaniline (1.0 mmol, 1.0 eq), n-boc propargylamine (1.5 eq), Pd(PPh₃)₄ (0.01 eq), CuI (0.03 eq), DEA (1.5 eq),
15 Et₂O 3.0 mL를 혼합한 뒤 반응 용기 내 기체를 Ar 기체로 치환한 후 실온에서 밤새 교반하였다. 반응물은 EtOAc, H₂O로 추출 후 유기층을

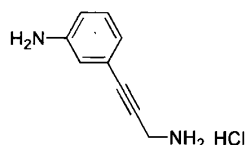
Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 1-1a을 합성하였다.

【0154】 단계 2: 4-(3-aminoprop-1-yn-1-yl)aniline hydrochloride

5 **【0155】** 단계 1에서 합성한 중간체 1-1a (0.5 mmol, 1.0 eq)를 DCM 3.0 mL에 녹인 후 HCl solution (4.0 M in dioxane, 2.0 eq)를 적가하였다. 1 시간 뒤 생성된 고체를 여과 후 건조하여 별도의 정제과정 없이 실시예 1-1을 합성하였다.

【0156】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.41 (s, 3H), 7.24 (d, 10 *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.1 Hz, 2H), 3.89 (q, *J* = 5.6 Hz, 2H)

【0157】 **【제조예 1-3】** 3-(3-aminoprop-1-yn-1-yl)aniline hydrochloride

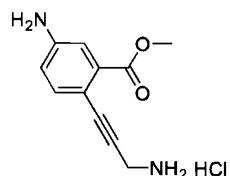


【0158】

【0159】 3-Iodoaniline으로부터 제조예 1-1과 동일한 방법으로 15 중간체 1-3a (tert-butyl (3-(3-aminophenyl)prop-2-yn-1-yl)carbamate)를 합성한 후 실시예 1-3을 합성하였다.

【0160】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.57 (s, 3H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.29 (dd, *J* = 24.4, 14.7 Hz, 3H), 3.99 (t, *J* = 5.5 Hz, 2H)

【0161】 **【제조예 3-1】** methyl 5-amino-2-(3-aminoprop-1-

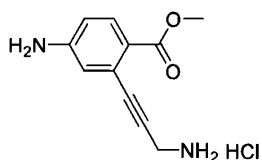
yn-1-yl)benzoate hydrochloride

【0162】

【0163】 Methyl 5-amino-2-iodobenzoate로부터 제조예 1-1과 동일한 방법으로 중간체 3-1a (methyl 5-amino-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate)를 합성한 후 실시예 3-1을 합성하였다.

【0164】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.42 (s, 3H), 7.26 (d, $J = 8.4$ Hz, 1H), 7.13 (d, $J = 2.4$ Hz, 1H), 6.82 (dd, $J = 8.4, 2.4$ Hz, 1H), 3.90 (q, $J = 5.7$ Hz, 2H), 3.79 (s, 3H)

10 【0165】 [제조예 3-25] methyl 4-amino-2-(3-aminoprop-1-yn-1-yl)benzoate hydrochloride

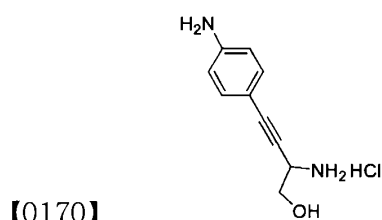


【0166】

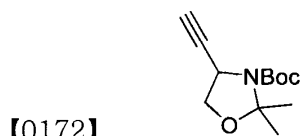
【0167】 Methyl 4-amino-2-iodobenzoate로부터 제조예 1-1과 동일한 방법으로 중간체 3-25a (methyl 4-amino-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate)를 합성한 후 실시예 3-25을 합성하였다.

【0168】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.47 (s, 3H), 7.67 (d, $J = 8.7$ Hz, 1H), 6.72 (dd, $J = 4.9, 2.3$ Hz, 1H), 6.62 (ddd, $J = 8.7, 4.3, 2.2$ Hz, 1H), 3.99 (dd, $J = 5.8, 3.0$ Hz, 2H), 3.74 (s, 3H)

【0169】 [제조예 3-49] 2-amino-4-(4-aminophenyl)but-3-yn-1-ol hydrochloride



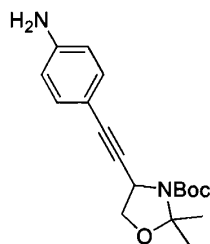
【0171】 단계 1: tert-butyl 4-ethynyl-2,2-dimethyloxazolidine-3-carboxylate (중간체 3-49a)



10 【0173】 tert-Butyl 4-formyl-2,2-dimethyloxazolidine-3-carboxylate (8.7 mmol, 1.0 eq), dimethyl-1-diazo-2-oxopropyl phosphonate (1.5 eq)를 MeOH에 녹인 후 0 °C에서 K_2CO_3 (2.0 eq)를 첨가하고, 혼합물을 0 °C에서 1 시간 교반한 뒤 실온에서 밤새 교반하였다. 반응물은 n-hexane, H_2O 로 추출 후 유기층을 Na_2SO_4 로 건조하였다.

15 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 화합물을 합성하였다.

【0174】 단계 2: tert-butyl 4-((4-aminophenyl)ethynyl)-2,2-dimethyloxazolidine-3-carboxylate (중간체 3-49b)



【0175】

【0176】 단계 1에서 합성한 중간체 3-49a (4.4 mmol, 1.0 eq),
5 4-iodoaniline (1.0 eq), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.1 eq), CuI (0.1 eq)를 DEA 40.0 mL에 녹인 후 실온에서 밤새 교반하였다. 반응물을 감압증류한 뒤 flash column을 통해 정제해 화합물을 합성하였다.

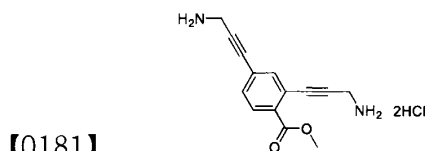
【0177】 단계 3: 2-amino-4-(4-aminophenyl)but-3-yn-1-ol hydrochloride

10 【0178】 단계 3에서 합성한 중간체 3-49b로부터 제조예 1-1의 단계 2와 동일한 방법으로 실시예 3-49를 합성하였다.

【0179】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.98 (s, 3H), 7.38 (d, $J = 8.4$ Hz, 2H), 6.63 – 6.61 (m, 2H), 3.60 – 3.57 (m, 2H), 3.51 (d, $J = 4.9$ Hz, 1H)

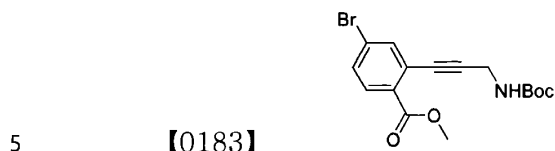
15 【0180】 [제조예 5-116] methyl 2,4-bis(3-aminoprop-1-yn-

1-yl)benzoate dihydrochloride



【0181】

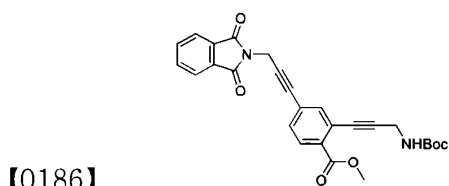
【0182】 단계 1: methyl 4-bromo-2-(3-((tert-carbonyl)amino)prop-1-yn-1-yl)benzoate (중간체 5-116a)



【0183】

【0184】 Methyl 4-bromo-2-iodobenzoate로부터 제조예 1-1의 단계 1과 동일한 방법으로 중간체 5-116a를 합성하였다.

【0185】 단계 2: methyl 2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)benzoate (중간체 5-116b)



【0186】

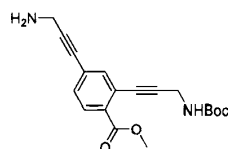
【0187】 중간체 5-116a (0.3 mmol, 1.0 eq), n-propargylphthalimide (1.5 eq), Pd(PPh₃)₄ (0.1 eq), CuI (0.3 eq), TBAI (3.0 eq), DMF 3.0 mL, TEA 1.0 mL를 혼합한 뒤 반응 용기 내 기체를 Ar 기체로
15 치환한 후 M.W. 하에 110 °C, 20 분간 가열하였다. 반응물은 EtOAc, H₂O로

추출 후 유기층을 Na_2SO_4 로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 화합물을 합성하였다.

【0188】 단계 3: methyl 4-(3-aminoprop-1-yn-1-yl)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate (중간체 5-116c)

5

【0189】

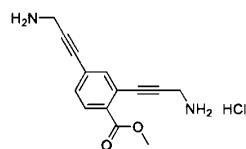


【0190】 중간체 5-116b (0.17 mmol, 1.0 eq), hydrazine monohydrate (3.0 eq), MeOH 0.8 mL, H_2O 0.2 mL를 혼합한 후 50 °C에서 2 시간 교반하였다. 반응물은 EtOAc, H_2O 로 추출 후 유기층을 Na_2SO_4 로 건조한 뒤 감압증류하여 별도의 정제 과정없이 화합물을 합성하였다.

10

【0191】 단계 4: methyl 2,4-bis(3-aminoprop-1-yn-1-yl)benzoate dihydrochloride

【0192】



【0193】 중간체 5-116c로부터 제조예 1-1의 단계 2와 동일한 방법으로 실시예 5-116을 합성하였다.

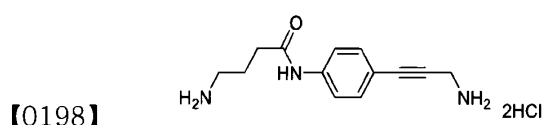
15

【0194】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.61 (d, J = 14.6 Hz, 6H), 7.93 – 7.88 (m, 1H), 7.61 (d, J = 1.7 Hz, 1H), 7.57 (dd, J = 8.2, 1.7 Hz, 1H), 3.98 (dd, J = 5.9, 3.0 Hz, 4H), 3.84 (s, 3H).

【0195】 [제조예 II]

【0196】 본 발명의 화학식 II에 해당하는 화합물들을 아래와 같이 합성하였다.

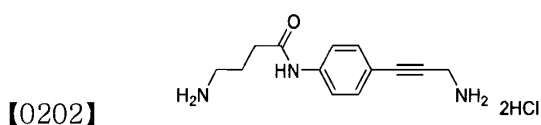
【0197】 [제조예 4-162] 4-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)butanamide dihydrochloride



【0199】 4-((tert-Butoxycarbonyl)amino)butanoic acid와 중간체 1-1a로부터 제조예 1-1'과 동일한 방법으로 실시예 4-162을 합성하였다.

10 【0200】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.46 (s, 1H), 8.45 (s, 3H), 7.99 (s, 3H), 7.68 – 7.62 (m, 2H), 7.38 – 7.32 (m, 2H), 3.92 (q, J = 5.6 Hz, 2H), 2.78 (h, J = 6.2 Hz, 2H), 2.43 (d, J = 7.2 Hz, 2H), 1.83 (p, J = 7.3 Hz, 2H).

15 【0201】 [제조예 4-166] 5-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)furan-2-carboxamide dihydrochloride

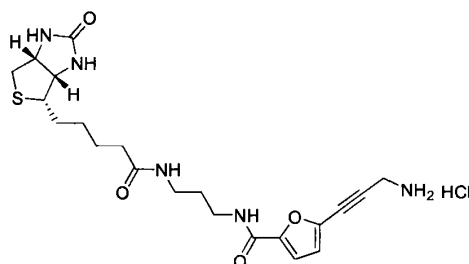


【0203】 tert-Butyl (3-aminopropyl)carbamate와 중간체 4-227b로부터 제조예 1-1'과 동일한 방법으로 실시예 4-166를 합성하였다.

【0204】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.79 (t, $J = 5.9$ Hz, 1H), 8.67 (s, 3H), 8.00 (s, 3H), 7.21 (d, $J = 3.6$ Hz, 1H), 6.96 (d, $J = 3.6$ Hz, 1H), 4.02 (q, $J = 5.6$ Hz, 2H), 3.24 (q, $J = 6.5$ Hz, 2H), 2.75 (dq, $J = 11.9$, 6.2 Hz, 2H), 1.78 – 1.71 (m, 2H).

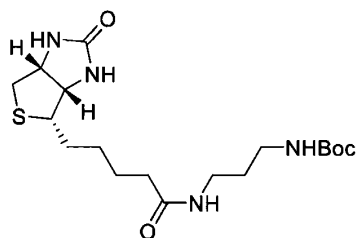
5 【0205】 추가로 비오틴을 이용한 pulldown assay에 이용하고자 비오틴이 결합된 화합물 4-166을 다음과 같이 제조하였다.

【0206】 5-(3-aminoprop-1-yn-1-yl)-N-(3-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)propyl)furan-2-carboxamide hydrochloride



10 【0207】

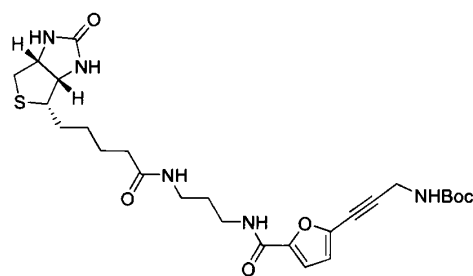
【0208】 단계 1: tert-butyl (3-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)propyl)carbamate



【0209】

【0210】 Biotin, tert-butyl (3-aminopropyl)carbamate로부터 제조예 1-1'의 단계 1과 동일한 방법으로 중간체 tert-butyl (3-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)propyl)carbamate를 합성하였다.

5 【0211】 단계 2: tert-butyl (3-(5-((3-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)propyl)carbamoyl)furan-2-yl)prop-2-yn-1-yl)carbamate



【0212】

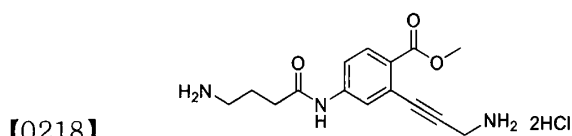
10 【0213】 단계 1의 중간체로부터 제조예 1-22'의 단계 2와 동일한 방법으로 반응하고, 추가 정제 없이 감압농축한 반응물에 중간체 4-227b를 첨가하고 제조예 1-1'의 단계 1과 동일한 방법으로 중간체 tert-butyl (3-(5-((3-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)propyl)carbamoyl)furan-2-yl)prop-2-yn-1-yl)carbamate를 합성하였다.

15 【0214】 단계 3: 5-(3-aminoprop-1-yn-1-yl)-N-(3-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)propyl)furan-2-carboxamide hydrochloride

【0215】 상기 단계 2의 중간체로부터 제조예 1-1의 단계 2와 동일한 방법으로 비오틴이 결합한 4-166화합물을 합성하였다.

【0216】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.61 – 8.48 (m, 4H), 7.86 (t, J = 5.7 Hz, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.00 (d, J = 3.6 Hz, 1H), 6.44 (s, 1H), 4.30 (dd, J = 7.7, 4.6 Hz, 1H), 4.14 – 4.10 (m, 1H), 4.08 (q, J = 5.6 Hz, 2H), 3.20 (q, J = 6.2 Hz, 2H), 3.12 – 3.03 (m, 3H), 2.81 (dd, J = 12.4, 5.1 Hz, 1H), 2.57 (d, J = 12.4 Hz, 1H), 2.06 (t, J = 7.4 Hz, 2H), 1.63 – 1.56 (m, 3H), 1.54 – 1.43 (m, 3H), 1.33 – 1.25 (m, 2H), MS m/z $[\text{M} + \text{H}]^+$ 448.43.

【0217】 [제조예 4-228] methyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate dihydrochloride



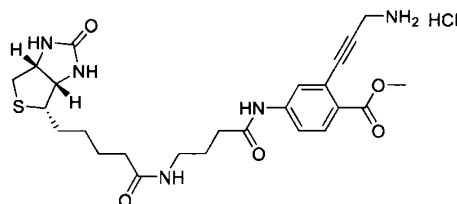
【0219】 4-((tert-Butoxycarbonyl)amino)butanoic acid와 중간체 3-25a로부터 제조예 1-1'과 동일한 방법으로 중간체 4-228a (methyl 4-(4-aminobutanamido)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate)를 거쳐 실시예 4-228을 합성하였다.

【0220】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.92 (s, 1H), 8.60 (s, 3H), 8.13 (s, 3H), 8.08 (d, J = 2.2 Hz, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.71

(dd, $J = 8.7, 2.2$ Hz, 1H), 4.07 – 3.99 (m, 2H), 3.83 (s, 3H), 2.96 (dt, $J = 9.2, 4.6$ Hz, 2H), 2.82 (q, $J = 6.7$ Hz, 2H), 2.53 (t, $J = 7.3$ Hz, 2H).

【0221】 추가로 비오틴을 이용한 pulldown assay에 이용하고자 비오틴이 결합된 4-228 화합물을 다음과 같이 제조하였다.

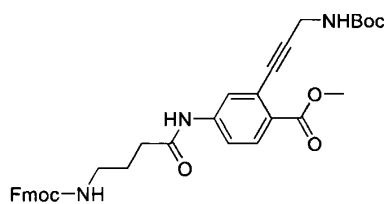
5 【0222】 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)butanamido)benzoate hydrochloride



【0223】

【0224】 단계 1: methyl 4-(4-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)butanamido)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate

10

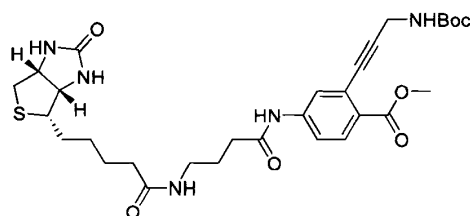


【0225】

【0226】 중간체 3-25a (0.2 mmol, 1.0 eq), 4-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)butanoic acid (1.0 eq), HATU (1.1 eq)를 dry DMF (0.7 mL)에 녹인 후 반응 용기 내 기체를 Ar 기체로 치환하였다. TEA (2.0 eq)를 적가한 후 실온에서 6 시간 교반하였다. 반응물은 flash

column을 통해 정제해 중간체 methyl 4-(4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)butanamido)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate를 합성하였다.

【0227】 단계 2: methyl 2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(4-(5-(((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)butanamido)benzoate



【0228】

【0229】 단계 1에서 제조한 중간체 (0.06 mmol, 1.0 eq)를 piperidine/DMF (1:4) 0.3 mL에 녹인 후 상온에서 1 시간 교반하였다. 반응물을 감압농축한 뒤, biotin (1.0 eq)을 첨가하고 위의 단계 1과 동일한 방법으로 중간체 methyl 2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(4-(5-(((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)butanamido)benzoate를 합성하였다.

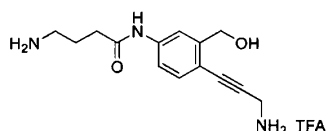
【0230】 단계 3: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(5-(((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)butanamido)benzoate hydrochloride

【0231】 단계 2에서 제조한 중간체로부터 제조예 1-1의 단계

2와 동일한 방법으로 비오틴이 결합된 4-228 화합물을 합성하였다.

【0232】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.43 (s, 1H), 8.36 (s, 3H), 8.13 (d, $J = 2.2$ Hz, 1H), 7.89 (d, $J = 8.7$ Hz, 1H), 7.85 (t, $J = 5.5$ Hz, 1H), 7.55 (dd, $J = 8.7, 2.2$ Hz, 1H), 6.43 (s, 1H), 6.38 (s, 1H), 4.29 (dd, $J = 7.6, 4.7$ Hz, 1H), 4.14 - 4.08 (m, 1H), 4.06 (q, $J = 5.6$ Hz, 2H), 3.83 (s, 3H), 3.10 - 3.05 (m, 3H), 2.80 (dd, $J = 12.4, 5.1$ Hz, 1H), 2.56 (d, $J = 12.6$ Hz, 1H), 2.38 - 2.32 (m, 3H), 2.05 (t, $J = 7.4$ Hz, 2H), 1.73 - 1.67 (m, 2H), 1.62 - 1.56 (m, 1H), 1.53 - 1.46 (m, 2H), 1.31 - 1.26 (m, 2H), MS m/z $[\text{M} + \text{H}]^+$ 516.47.

10 【0233】 【제조예 5-8】 4-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)butanamide trifluoroacetic acid



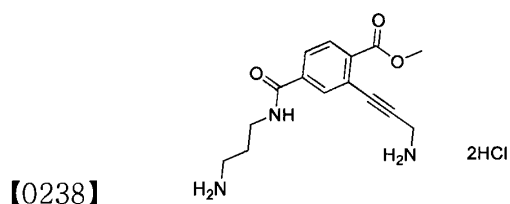
【0234】

【0235】 4-((tert-Butoxycarbonyl)amino)butanoic acid 와
중간체 3-27c로부터 순차적으로 제조예 3-3'의 단계, 제조예 1-1의 단계
15 2와 동일한 방법을 적용하여 합성한 뒤 prep HPLC 로 추가 정제하여
실시예 5-8을 합성하였다.

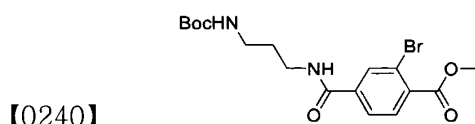
【0236】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.62 (d, $J = 2.2$ Hz, 1H), 7.44 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 1H), 4.58 (s, 2H), 3.91 (s, 2H), 2.84 (t, $J = 7.7$ Hz, 2H), 2.40 (d, $J = 7.3$ Hz, 2H), 1.86 - 1.82

(m, 2H); MS m/z $[M+Na]^+$ 284.30.

【0237】 [제조예 5-18] methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-aminopropyl)carbamoyl)benzoate dihydrochloride



5 **【0239】** 단계 1: methyl 2-bromo-4-((3-((tert-butoxycarbonyl)amino)propyl)carbamoyl)benzoate (5-18a)



【0241】 tert-Butyl (3-aminopropyl)carbamate와 3-bromo-4-(methoxycarbonyl)benzoic acid로부터 제조예 4-1'의 단계 5와 동일한
10 방법으로 중간체 5-18a를 합성하였다.

【0242】 단계 2: methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-aminopropyl)carbamoyl)benzoate dihydrochloride

【0243】 중간체 5-18a로부터 제조예 1-1과 동일한 방법으로 실시예 5-18을 합성하였다.

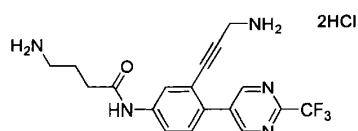
15 **【0244】** ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.01 (s, 1H), 8.52 (s, 3H), 8.09 – 8.08 (m, 1H), 8.01 – 7.99 (m, 2H), 7.95 (s, 3H), 4.08 – 4.03 (m, 2H), 3.90 (s, 3H), 3.35 – 3.29 (m, 2H), 2.86 – 2.80 (m, 2H), 1.82 (p, $J = 6.9$

Hz, 2H).

【0245】 [제조예 5-81] 4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)butanamide dihydrochloride

5

【0246】



【0247】 4-((tert-Butoxycarbonyl)amino)butanoic acid와

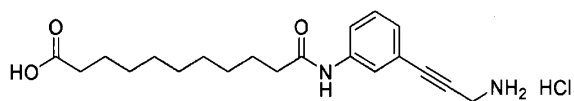
중간체 5-81c로부터 제조예 1-1'과 동일한 방법으로 실시예 5-81을 합성하였다.

【0248】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.69 (s, 1H), 9.30 (s, 2H), 8.38 (s, 3H), 8.16 (d, J = 2.2 Hz, 1H), 7.97 (s, 3H), 7.77 (dd, J = 8.6, 2.2 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 3.94 (s, 2H), 2.85 (s, 2H), 2.53 (s, 2H), 1.90 - 1.87 (m, 2H).

【0249】 [제조예 5-109] 11-((3-(3-aminoprop-1-yn-1-yl)phenyl)amino)-11-oxoundecanoic acid hydrochloride

15

【0250】

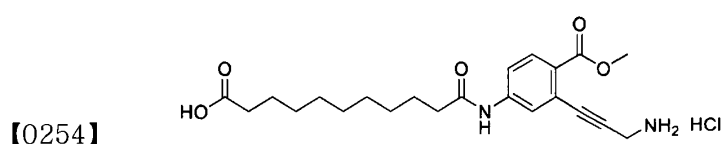


【0251】 Undecanedioic acid, 중간체 1-3a로부터 제조예 5-77'의 단계 2와 동일한 방법으로 실시예 5-109를 합성하였다.

【0252】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.15 (s, 1H), 8.45

(s, 3H), 7.96 – 7.91 (m, 1H), 7.53 – 7.49 (m, 1H), 7.33 (t, $J = 7.9$ Hz, 1H), 7.11 (dt, $J = 7.7, 1.2$ Hz, 1H), 3.99 (s, 2H), 2.34 – 2.24 (m, 4H), 1.61 – 1.44 (m, 4H), 1.30 – 1.19 (m, 10H).

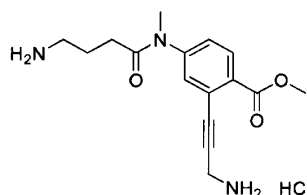
【0253】 [제조예 5-110] 11-((3-(3-aminoprop-1-yn-1-yl)-
5 4-(methoxycarbonyl)phenyl)amino)-11-oxoundecanoic acid hydrochloride



【0255】 Undecanedioic acid, 중간체 3-25a로부터 제조예 5-77'의 단계 2와 동일한 방법으로 실시예 5-110를 합성하였다.

【0256】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.43 (s, 1H), 8.85
10 (s, 1H), 8.41 (s, 3H), 8.13 (d, $J = 2.2$ Hz, 1H), 7.89 (d, $J = 8.7$ Hz, 1H), 7.56
(dd, $J = 8.7, 2.2$ Hz, 1H), 4.04 (s, 2H), 3.83 (s, 3H), 2.34 (t, $J = 7.4$ Hz, 2H),
2.25 (d, $J = 7.4$ Hz, 2H), 1.57 (t, $J = 7.0$ Hz, 2H), 1.54 – 1.42 (m, 12H).

【0257】 [제조예 5-150] methyl 4-(4-amino-N-methylbutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate hydrochloride



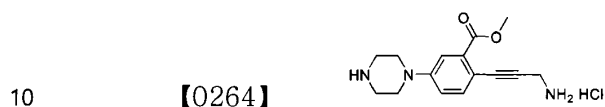
【0259】 4-Aminobutanoic acid와 중간체 5-150a로부터
제조예 5-77'의 단계 2와 동일한 방법으로 실시예 5-150을 합성하였다.

【0260】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.55 (s, 3H), 7.95 – 7.93 (m, 1H), 7.90 (s, 3H), 7.63 – 7.59 (m, 1H), 7.54 – 7.51 (m, 1H), 4.06 – 4.00 (m, 2H), 3.88 (s, 3H), 3.23 (s, 3H), 2.95 – 2.84 (m, 2H), 2.81 – 2.72 (m, 2H), 1.81 – 1.73 (m, 2H).

5 **【0261】** **【제조예 III】**

【0262】 본 발명의 화학식 III에 해당하는 화합물들을 아래와 같이 합성하였다.

【0263】 **【제조예 4-2】 methyl 2-(3-aminoprop-1-yn-1-yl)-5-(piperazin-1-yl)benzoate hydrochloride**

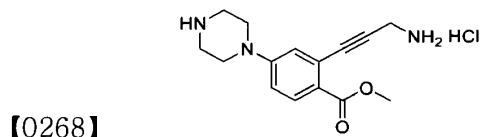


【0265】 Methyl 2-bromo-5-fluorobenzoate로부터 제조예 5-7과 동일한 방법으로 실시예 4-2를 합성하였다.

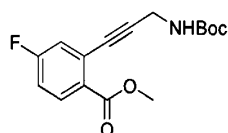
【0266】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.40 (s, 2H), 8.46 (s, 3H), 7.42 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 2.7 Hz, 1H), 7.18 (dd, J = 8.8, 2.8 Hz, 1H), 3.93 (q, J = 5.7 Hz, 2H), 3.82 (s, 3H), 3.47 (s, 4H), 3.15 (s, 4H)

15

【0267】 **【제조예 5-7】 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperazin-1-yl)benzoate hydrochloride**



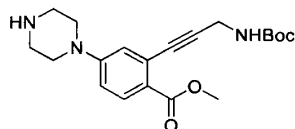
【0269】 단계 1: methyl 2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-fluorobenzoate (중간체 5-7a)



【0270】

【0271】 Methyl 2-bromo-4-fluorobenzoate로부터 제조예 4-179'의 단계 2와 동일한 방법으로 중간체 5-7a를 합성하였다.

【0272】 단계 2: methyl 2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(piperazin-1-yl)benzoate(중간체 5-7b)



【0273】

【0274】 중간체 5-7a (0.6 mmol, 1.0 eq), piperazine (3.0 eq), K_2CO_3 (1.5 eq), DMSO 2.0 mL를 혼합한 뒤 반응 용기 내 기체를 Ar 기체로 치환하였다. 외부 빛을 차단한 뒤 95 °C에서 18 시간 교반하였다. 반응물은 EtOAc, H_2O 로 추출 후 유기층을 Na_2SO_4 로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 5-7b를 합성하였다.

【0275】 단계 3: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperazin-1-yl)benzoate hydrochloride

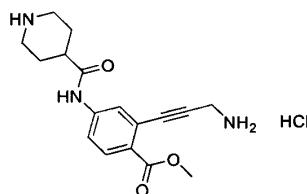
【0276】 중간체 5-7b로부터 제조예 1-1의 단계 2와 동일한

방법으로 실시예 5-7을 합성하였다.

【0277】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.35 (s, 2H), 8.50 (s, 3H), 7.79 (d, $J = 8.9$ Hz, 1H), 7.10 (d, $J = 2.7$ Hz, 1H), 7.06 (dd, $J = 8.9, 2.7$ Hz, 1H), 3.97 (q, $J = 5.6$ Hz, 2H), 3.77 (s, 3H), 3.53 (t, $J = 5.3$ Hz, 4H), 3.14

5 (d, $J = 13.1$ Hz, 4H).

【0278】 [제조예 5-23] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidine-4-carboxamido)benzoate hydrochloride



【0279】

【0280】 1-(tert-Butoxycarbonyl)piperidine-4-carboxylic

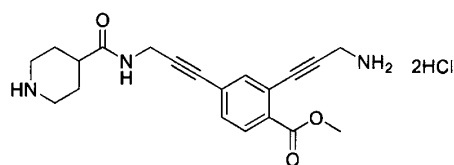
10 acid와 중간체 3-25a로부터 제조예 1-1'과 동일한 방법으로 실시예 5-23을 합성하였다.

【0281】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.85 (s, 1H), 9.04 (d, $J = 11.2$ Hz, 1H), 8.78 (d, $J = 11.0$ Hz, 1H), 8.47 (s, 3H), 8.06 (d, $J = 2.2$ Hz, 1H), 7.86 (d, $J = 8.7$ Hz, 1H), 7.64 (dd, $J = 8.7, 2.2$ Hz, 1H), 4.00 (q, $J = 5.6$ Hz, 2H), 3.80 (s, 3H), 3.31 - 3.23 (m, 2H), 2.86 (q, $J = 11.7$ Hz, 2H), 2.72 (tt, $J = 11.1, 3.8$ Hz, 1H), 1.94 (d, $J = 13.4$ Hz, 2H), 1.83 - 1.74 (m, 2H).

15

【0282】 [제조예 5-28] methyl 2-(3-aminoprop-1-yn-1-yl)-

**4-(3-(piperidine-4-carboxamido)prop-1-yn-1-yl)benzoate
dihydrochloride**



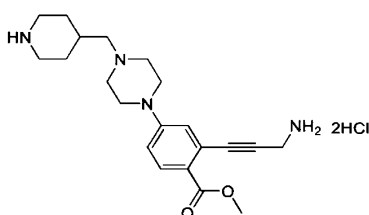
【0283】

【0284】 1-(tert-Butoxycarbonyl)piperidine-4-carboxylic

5 acid와 중간체 5-116c로부터 제조예 1-1'과 동일한 방법으로 실시예 5-28을 합성하였다.

【0285】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.56 (dd, $J = 12.3$, 6.8 Hz, 4H), 7.88 – 7.84 (m, 1H), 7.57 (d, $J = 1.8$ Hz, 1H), 7.51 (dd, $J = 8.2$, 1.7 Hz, 1H), 4.11 (d, $J = 5.4$ Hz, 2H), 3.98 (q, $J = 5.6$ Hz, 2H), 3.83 (s, 3H),
10 3.21 (d, $J = 12.5$ Hz, 2H), 2.89 – 2.77 (m, 2H), 2.42 (dt, $J = 11.0$, 3.9 Hz, 1H), 1.85 – 1.80 (m, 2H), 1.75 – 1.68 (m, 2H).

【0286】 [제조예 5-29] methyl 2-(3-aminoprop-1-yn-1-yl)-
4-(4-(piperidin-4-ylmethyl)piperazin-1-yl)benzoate dihydrochloride



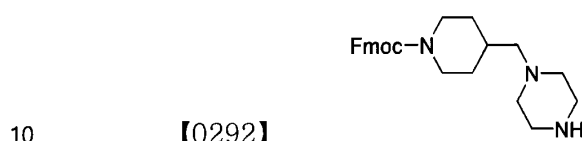
【0287】

15 【0288】 단계 1: (9H-fluoren-9-yl)methyl 4-(bromomethyl)piperidine-1-carboxylate (중간체 5-29a)



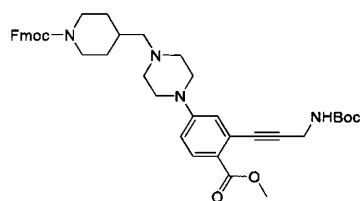
【0290】 4-(Bromomethyl)piperidine hydrochloride (1.0 eq), (9H-fluoren-9-yl)methyl carbonochloridate (1.2 eq), pyridine (1.5 eq), dry DCM을 혼합한 뒤 실온에서 2 시간 교반하였다. 반응물은 EtOAc, H₂O를 이용하여 유기층으로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column으로 정제해 중간체 5-29a를 합성하였다.

【0291】 단계 2: (9H-fluoren-9-yl)methyl 4-(piperazin-1-ylmethyl)piperidine-1-carboxylate (중간체 5-29b)



【0293】 중간체 5-29a (1.0 eq), piperazine (9.0 eq), dry ACN을 혼합한 뒤 80 °C에서 밤새 교반하였다. 반응물은 EtOAc, H₂O를 이용하여 유기층으로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column으로 정제해 중간체 5-29b를 합성하였다.

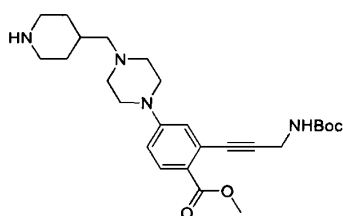
15 【0294】 단계 3: (9H-fluoren-9-yl)methyl 4-((4-(3-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(methoxycarbonyl)phenyl)piperazin-1-yl)methyl)piperidine-1-carboxylate (중간체 5-29c)



【0295】

【0296】 중간체 5-29b (1.0 eq), 중간체 5-116a (1.0 eq), RuPhos Pd G₃ (0.1 eq), CS₂CO₃ (3.0 eq), dioxane 1.5 mL를 혼합한 뒤 100 °C에서 밤새 교반하였다. 반응물은 EtOAc, H₂O를 이용하여 유기층으로
5 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column으로 정제하여 중간체 5-29c를 합성하였다.

【0297】 단계 4: methyl 2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(4-(piperidin-4-ylmethyl)piperazin-1-yl)benzoate (중간체 5-29d)



10 【0298】

【0299】 중간체 5-29c (1.0 eq), DEA 1.0 mL, THF 1.0 mL를 혼합한 뒤 실온에서 1 시간 교반하였다. 반응물은 감압증류한 뒤 flash column을 통해 정제해 중간체 5-29d을 합성하였다.

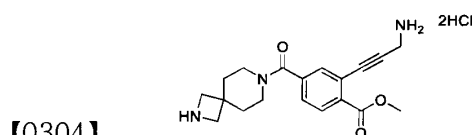
【0300】 단계 5: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(piperidin-4-ylmethyl)piperazin-1-yl)benzoate hydrochloride
15

【0301】 중간체 5-29d로부터 제조예 1-1의 단계 2와 동일한

방법으로 실시예 5-29을 합성하였다.

【0302】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.12 – 8.84 (m, 2H), 8.60 (s, 3H), 7.83 (d, J = 8.9 Hz, 1H), 7.20 (d, J = 2.7 Hz, 1H), 7.13 (dd, J = 9.0, 2.7 Hz, 1H), 3.99 (s, 2H), 3.81 (s, 3H), 3.54 – 3.45 (m, 6H), 3.26 (d, J = 12.6 Hz, 2H), 3.08 (s, 4H), 2.85 (q, J = 11.8 Hz, 2H), 2.18 (s, 1H), 2.07 – 2.00 (m, 2H), 1.45 (d, J = 12.3 Hz, 2H).

【0303】 [제조예 5-39] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,7-diazaspiro[3.5]nonane-7-carbonyl)benzoate dihydrochloride



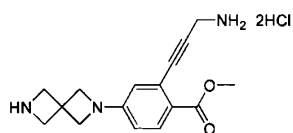
10 【0305】 tert-Butyl 2,7-diazaspiro[3.5]nonane-2-carboxylate을 이용하여 제조예 5-41과 동일한 방법으로 실시예 5-39를 합성하였다.

【0306】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.49 (s, 3H), 7.92 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 1.7 Hz, 1H), 4.00 (s, 2H), 3.85 (s, 3H), 3.68 (s, 8H), 3.53 (s, 4H).

【0307】 [제조예 5-40] methyl 2-(3-aminoprop-1-yn-1-yl)-

4-(2,6-diazaspiro[3.3]heptan-2-yl)benzoate dihydrochloride

【0308】

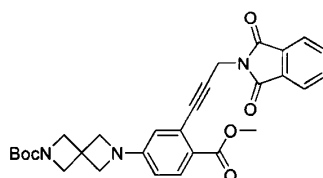


【0309】

단계 1: tert-butyl 6-(3-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-(methoxycarbonyl)phenyl)-2,6-

5 diazaspiro[3.3]heptane-2-carboxylate (중간체 5-40a)

【0310】



【0311】

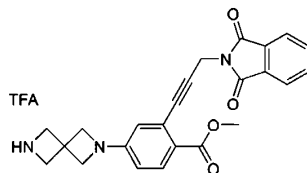
중간체 5-35a (0.5 mmol, 1.0 eq), tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate (1.0 eq), SPhos Pd G3 (0.1 eq), CS₂CO₃ (3.0 eq), dioxane 1.5 mL를 혼합한 뒤 100 °C에서 밤새 교반하였다. 반응물은 EtOAc, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 5-40a를 합성하였다.

【0312】

단계 2: methyl 2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptan-2-yl)benzoate

15 trifluoroacetic acid (중간체 5-40b)

【0313】



【0314】 중간체 5-40a로부터 제조예 4-1'의 단계 4과 동일한 방법으로 실시예 5-40b을 합성하였다.

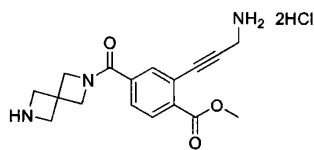
【0315】 단계 3: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptan-2-yl)benzoate dihydrochloride

【0316】 중간체 5-40b로부터 제조예 5-116의 단계 3 및 제조예 1-1의 단계 2와 동일한 방법을 순차적으로 적용하여 실시예 5-40을 합성하였다.

【0317】 ^1H NMR (500 MHz, DMSO- d_6) δ 9.65 (s, 2H), 8.71 (s, 3H), 7.31 (d, J = 8.7 Hz, 1H), 6.72 (d, J = 2.3 Hz, 1H), 6.67 (d, J = 9.6 Hz, 1H), 3.98 (s, 2H), 3.96 (s, 3H), 3.65 – 3.62 (m, 4H), 3.56 (s, 4H).

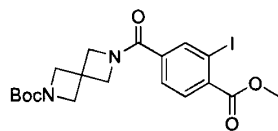
【0318】 [제조예 5-41] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptane-2-carbonyl)benzoate dihydrochloride

【0319】



【0320】 단계 1: tert-butyl 6-(3-iodo-4-(methoxycarbonyl)benzoyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (중간체 5-41a)

【0321】



【0322】

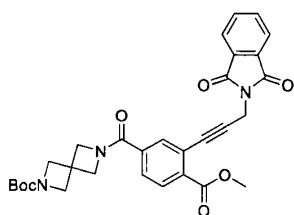
3-Iodo-4-(methoxycarbonyl)benzoic acid와 tert-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate로부터 제조예 4-1'의 단계 1과 동일한 방법으로 중간체 5-41a를 합성하였다.

5

【0323】

단계 2: tert-butyl 6-(3-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-(methoxycarbonyl)benzoyl)-2,6-diazaspiro[3.3]heptane-2-carboxylate (중간체 5-41b)

【0324】



【0325】

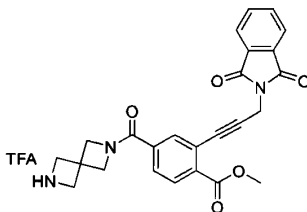
중간체 5-41a로부터 제조예 5-85'의 단계 2과 동일한 방법으로 중간체 5-41b를 합성하였다.

10

【0326】

단계 3: methyl 2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptane-2-carbonyl)benzoate trifluoroacetic acid (중간체 5-41c)

【0327】



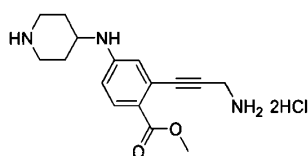
【0328】 중간체 5-41b로부터 제조예 4-1'의 단계 4와 동일한 방법으로 중간체 5-41c를 합성하였다.

【0329】 단계 4: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptane-2-carbonyl)benzoate

5 【0330】 중간체 5-41c로부터 제조예 5-116의 단계 3 및 제조예 1-1의 단계 2과 동일한 방법을 순차적으로 적용하여 실시예 5-41을 합성하였다.

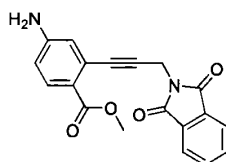
【0331】 ^1H NMR (500 MHz, DMSO- d_6) δ 9.27 (s, 3H), 7.53 (s, 1H), 7.46 – 7.41 (m, 2H), 7.39 – 7.35 (m, 2H), 4.06 – 3.99 (m, 2H), 3.94 (s, 10 3H), 3.91 (s, 8H).

【0332】 [제조예 5-86] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidin-4-ylamino)benzoate dihydrochloride



【0333】

【0334】 단계 1: methyl 4-amino-2-(3-(1,3-dioxoisindolin-15 2-yl)prop-1-yn-1-yl)benzoate (중간체 5-86a)

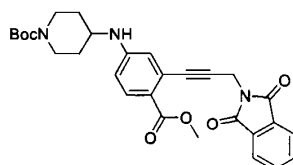


【0335】

【0336】 Methyl 4-amino-2-iodobenzoate로부터 제조예 5-

116'의 단계 2와 동일한 방법으로 중간체 5-86a를 합성하였다.

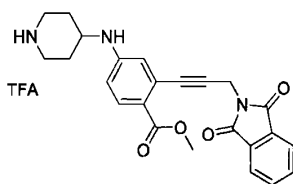
【0337】 단계 2: tert-butyl 4-((3-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-(methoxycarbonyl)phenyl)amino)piperidine-1-carboxylate (중간체 5-86b)



5 【0338】

【0339】 중간체 5-86a로부터 tert-butyl 4-oxopiperidine-1-carboxylate을 사용하여 제조예 5-85c의 단계 1과 동일한 방법으로 중간체 5-86b를 합성하였다.

【0340】 단계 3: methyl 2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-(piperidin-4-ylamino)benzoate trifluoroacetic acid (중간체 5-86c)



【0341】

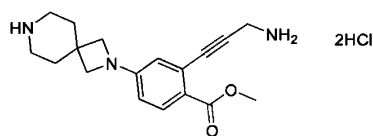
【0342】 중간체 5-86b로부터 제조예 4-1'의 단계 4과 동일한 방법으로 중간체 5-86c를 합성하였다.

15 【0343】 단계 4: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidin-4-ylamino)benzoate hydrochloride

【0344】 중간체 5-86c로부터 제조예 5-116의 단계 3 및 제조예 1-1의 단계 2과 동일한 방법을 순차적으로 적용하여 실시예 5-86을 합성하였다.

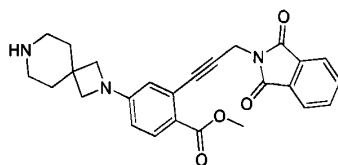
【0345】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.60 (s, 3H), 8.53 (s, 2H), 7.86 (d, J = 13.7 Hz, 1H), 6.79 (d, J = 50.9 Hz, 1H), 6.67 (dd, J = 24.5, 2.4 Hz, 1H), 4.02 (d, J = 7.1 Hz, 2H), 3.75 (s, 3H), 3.62 (dt, J = 10.9, 4.7 Hz, 2H), 3.31 – 3.26 (m, 2H), 3.21 (dt, J = 10.4, 6.5 Hz, 2H), 3.05 – 2.93 (m, 2H), 2.91 – 2.84 (m, 1H).

【0346】 [제조예 5-168] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,7-diazaspiro[3.5]nonan-2-yl)benzoate dihydrochloride



【0347】

【0348】 단계 1: tert-butyl 2-(3-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-(methoxycarbonyl)phenyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate (중간체 5-168a)



【0349】

【0350】 중간체 5-35a (0.5 mmol, 1.0 eq), tert-butyl 2,7-diazaspiro[3.5]nonane-7-carboxylate (1.0 eq), RuPhos Pd G3 (0.1 eq),

CS₂CO₃ (3.0 eq), toluene 1.5 mL를 혼합한 뒤 80 °C에서 밤새 교반하였다. 반응물은 EtOAc, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 5-168a를 합성하였다.

5 **【0351】** 단계 2: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,7-diazaspiro[3.5]nonan-2-yl)benzoate dihydrochloride

【0352】 중간체 5-168a로부터 제조예 1-1의 단계 2, 제조예 5-116의 단계 3과 동일한 방법을 순차적으로 적용하여 중간체 5-168b(methyl 2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-(2,7-diazaspiro[3.5]nonan-2-yl)benzoate)를 거쳐 실시예 5-168을 합성하였다.

【0353】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.03 (d, *J* = 61.5 Hz, 3H), 8.54 (s, 3H), 7.67 (d, *J* = 8.9 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.76 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.97 – 3.94 (m, 2H), 3.81 (s, 2H), 3.73 (s, 1H), 3.72 (s, 3H), 3.69 (s, 1H), 3.07 – 2.99 (m, 4H), 1.81 – 1.67 (m, 4H).

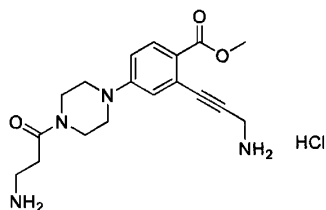
15 **【0354】** **【제조예 IV】**

【0355】 본 발명의 화학식 IV에 해당하는 화합물들을 아래와 같이 합성하였다.

【0356】 **【제조예 5-32】** methyl 2-(3-aminoprop-1-yn-1-yl)-

4-(4-(3-aminopropanoyl)piperazin-1-yl)benzoate hydrochloride

【0357】

【0358】 β -Alanine 과 중간체 5-7b로부터 제조예 1-1'과

동일한 방법으로 실시예 5-32를 합성하였다.

5 【0359】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.80 (s, 3H), 8.59 (s, 3H), 7.93 (d, J = 7.5 Hz, 1H), 7.12 - 7.02 (m, 2H), 3.99 (t, J = 5.7 Hz, 2H), 3.79 (s, 3H), 3.62 (t, J = 5.3 Hz, 6H), 3.43 - 3.35 (m, 4H), 3.00 (q, J = 6.0 Hz, 2H).

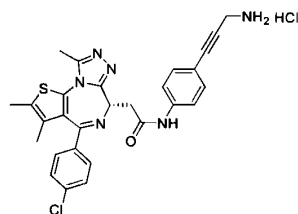
【0360】 [제조예 1']

10 【0361】 BRD4(Bromodomain-containing protein 4)

억제제로서의 활성을 나타내는 화합물(JQ1)이 본 발명의 화학식 I에 해당하는 화합물들과 연결된 TBM-UBM 화합물을 아래와 같이 합성하였다.

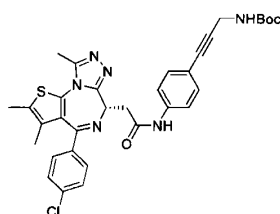
【0362】 [제조예 1-1'] (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride



【0363】

【0364】 단계 1: tert-butyl (S)-(3-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)prop-2-yn-1-yl)carbamate
(중간체 1-1'a)



【0365】

【0366】 상업적으로 구입가능한 JQ1 carboxylic acid ((S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid) (1.0 mmol, 1.2 eq),
중간체 1-1a (1.0 eq), HOBt (1.5 eq), DIPEA (2.0 eq), EDC (1.5 eq), dry DCM 3 mL를 혼합 후 실온에서 16 시간 교반하였다. 반응물은 EtOAc, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 1-1'a를 합성하였다.

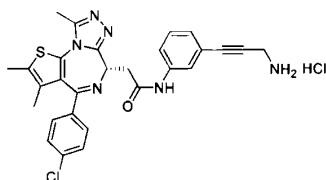
【0367】 단계 2: (S)-N-(4-(3-aminoprop-1-yn-1-

yl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

【0368】 중간체 1-1'로부터 제조예 1-1의 단계 2와 동일한 방법으로 실시예 1-1'을 합성하였다.

5 【0369】 ^1H NMR (500 MHz, Methanol- d_4) δ 8.41 – 8.34 (m, 2H), 8.24 – 8.12 (m, 6H), 5.51 – 5.48 (m, 1H), 4.45 – 4.35 (m, 4H), 3.49 (s, 3H), 3.23 (d, $J = 0.9$ Hz, 3H), 2.48 (d, $J = 0.8$ Hz, 3H); MS m/z $[\text{M} + \text{H}]^+$ 531.35.

10 【0370】 [제조예 1-3'] (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride



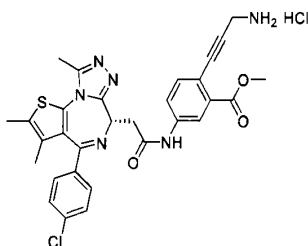
【0371】

15 【0372】 중간체 1-3a로부터 제조예 1-1'과 동일한 방법으로 중간체 1-3'a(tert-butyl (S)-(3-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)prop-2-yn-1-yl)carbamate)를 합성한 후 실시예 1-3'을 합성하였다.

【0373】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.53 (s, 1H), 8.39

(s, 3H), 7.89 (t, $J = 1.9$ Hz, 1H), 7.55 (ddd, $J = 8.3, 2.2, 1.1$ Hz, 1H), 7.47 – 7.44 (m, 2H), 7.41 – 7.36 (m, 2H), 7.34 (t, $J = 7.9$ Hz, 1H), 7.11 (dt, $J = 7.9, 1.2$ Hz, 1H), 4.57 (dd, $J = 7.6, 6.7$ Hz, 1H), 3.95 (td, $J = 6.2, 5.7, 3.6$ Hz, 2H), 3.49 (dd, $J = 7.3, 3.1$ Hz, 2H), 2.58 (s, 3H), 2.39 (d, $J = 0.9$ Hz, 3H), 1.59 (d, $J = 0.8$ Hz, 3H); MS m/z $[M+H]^+$ 531.35.

【0374】 **【제조예 3-1'】** methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoate hydrochloride



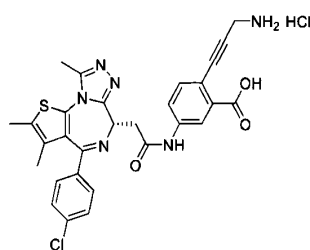
10 **【0375】**

【0376】 중간체 3-1a로부터 제조예 1-1'과 동일한 방법으로 중간체 3-1'a (methyl (S)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoate)을 합성한 후 실시예 3-1'을 합성하였다.

【0377】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.79 (s, 1H), 8.44 (s, 3H), 8.26 (d, $J = 2.2$ Hz, 1H), 7.86 (dd, $J = 8.6, 2.3$ Hz, 1H), 7.55 (d, $J =$

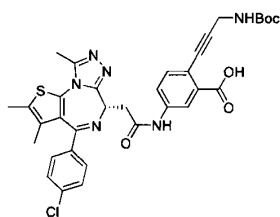
8.4 Hz, 1H), 7.50 – 7.47(m, 2H), 7.45 – 7.41 (m, 2H), 4.64 (d, J = 7.8 Hz, 1H), 3.99 (d, J = 5.8 Hz, 2H), 3.56 (s, 3H), 2.63 (s, 3H), 2.43 (s Hz, 3H), 1.63 (s, 3H); MS m/z $[M+H]^+$ 587.35.

【0378】 [제조예 3-2'] (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoic acid hydrochloride



【0379】

【0380】 단계 1: (S)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoic acid (중간체 3-2'a)



【0381】

【0382】 중간체 3-1'a (0.1 mmol, 1.0 eq), LiOH·H₂O (3.0 eq), THF 0.1 mL, H₂O 0.1 mL, MeOH 0.1 mL를 혼합한 후 혼합 후 실온에서 5

시간 교반하였다. 반응물은 H₂O로 추출 후 수층을 2N HCl 수용액을 적가하여 pH를 5 이하로 맞춘 뒤 chloroform/IPA 혼합용매로 추출한다. 유기층을 Na₂SO₄로 건조하고 혼합물을 감압여과 후 증류한 뒤 별도의 정제 과정 없이 중간체 3-2'a를 합성하였다.

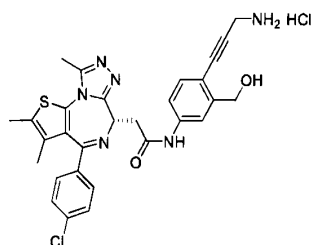
5 **【0383】** 단계 2: (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoic acid hydrochloride

【0384】 중간체 3-2'a로부터 제조예 1-1의 단계 2와 동일한 방법으로 실시예 3-2'을 합성하였다.

10 **【0385】** ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.77 (s, 1H), 8.35 (s, 3H), 8.28 (d, *J* = 2.1 Hz, 1H), 7.87 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.45 – 7.41 (m, 2H), 4.62 (d, *J* = 7.6 Hz, 1H), 4.03 (d, *J* = 5.3 Hz, 2H), 2.63 (s, 3H), 2.43 (s, 3H), 1.64 (s, 3H); MS *m/z* [M+ H]⁺ 573.35.

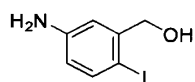
15 **【0386】** **[제조예 3-3']** (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

hydrochloride



【0387】

【0388】 단계 1: (5-amino-2-iodophenyl)methanol (중간체 3-3a)



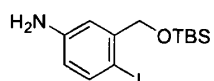
5

【0389】

【0390】 Methyl 5-amino-2-iodobenzoate (0.4 mmol, 1.0 eq)를 dry THF에 녹인 후 lithium aluminium hydride solution (2.0 M in THF, 2.0 eq)를 천천히 적가한 뒤 50 °C에서 2 시간 가열하였다. 반응물에 2 N HCl 수용액을 넣어 pH 6~7로 맞춘 뒤 EtOAc로 화합물을 추출하였다. 유기층을 Na₂SO₄로 건조한 뒤 감압여과 하였다. 혼합물을 감압증류한 뒤 flash column을 통해 정제해 중간체 3-3a을 합성하였다.

10

【0391】 단계 2: 3-(((tert-butyldimethylsilyl)oxy)methyl)-4-iodoaniline (중간체 3-3b)



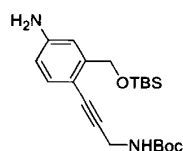
【0392】

15

【0393】 단계 1에서 합성한 중간체 3-3a (1.1 mmol, 1.0 eq), imidazole (2.2 eq)를 dry DCM에 녹인 후 TBSCl (1.1 eq)를 첨가한 뒤

반응용기 내 기체를 Ar으로 치환한 후 실온에서 30 분 교반하였다.
혼합물을 감압증류한 뒤 flash column으로 정제해 중간체 3-3b를
합성하였다.

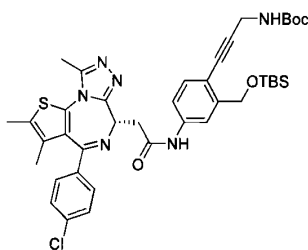
【0394】 단계 3: tert-butyl (3-(4-amino-2-(((tert-
5 butyldimethylsilyl)oxy)methyl)phenyl)prop-2-yn-1-yl)carbamate (중간체
3-3c)



【0395】

【0396】 단계 2에서 합성한 중간체 3-3b로부터 제조예 1-1의
단계 1과 동일한 방법으로 중간체 3-3c를 합성하였다.

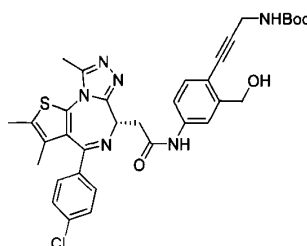
10 【0397】 단계 4: tert-butyl (S)-(3-(2-(((tert-
butyldimethylsilyl)oxy)methyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-
trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
yl)acetamido)phenyl)prop-2-yn-1-yl)carbamate (중간체 3-3'a)



【0398】

15 【0399】 중간체 3-3c로부터 제조예 1-1'의 단계 1과 동일한
방법으로 중간체 3-3'a를 합성하였다.

【0400】 단계 5: tert-butyl (S)-(3-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-2-(hydroxymethyl)phenyl)prop-2-yn-1-yl)carbamate (중간체 3-3'b)



5 【0401】

【0402】 중간체 3-3'a (0.2 mmol, 1.0 eq)를 THF 1.5 mL에 녹인 후 0 °C에서 TBAF (1.0 M in THF, 1.5 eq)를 적가하였다. 3 시간 뒤 용매를 감압 증류한 후 flash column로 정제해 중간체 3-3'b을 합성하였다.

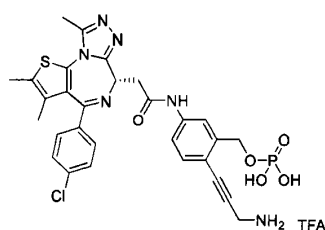
【0403】 단계 6: (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

【0404】 중간체 3-3'b를 이용하여 제조예 1-1의 단계 2와 동일한 방법으로 실시예 3-3'을 합성하였다.

15 【0405】 ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.54 (s, 1H), 8.37 (s, 3H), 7.83 (s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.48 (s, 2H), 7.44 (s, 2H), 7.36 (s, 1H), 4.64 (s, 3H), 4.00 (s, 2H), 3.54 (s, 2H), 2.61 (s, 3H), 2.43 (s,

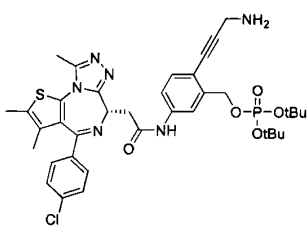
3H), 1.64 (s, 3H); MS m/z [M+H]⁺ 559.35.

- 【0406】 [제조예 3-8'] (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl dihydrogen phosphate trifluoroacetic acid



【0407】

- 【0408】 단계 1: tert-butyl (S)-3-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-2-(((di-tert-butoxyphosphoryl)oxy)methyl)phenyl)prop-2-yn-1-yl)carbamate (중간체 3-8'a)



【0409】

- 【0410】 중간체 3-3'b (0.1 mmol, 1.0 eq), tetrazole (10.0 eq)를 dry DMF 1.7 mL에 녹인 후 반응 용기 내 기체를 Ar 기체로 치환하였다.
- 15 Di-tert-butyl N,N-diisopropylphosphoramidite (5.0 eq)를 첨가한 뒤

실온에서 3 시간 교반하였다. $-20\text{ }^{\circ}\text{C}$ 에서 H_2O_2 (excess)를 적가한 뒤 10분 후 NaHSO_3 로 반응을 종결하였다. 반응물은 EtOAc , H_2O 로 추출 후 유기층을 Na_2SO_4 로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 3-8'a를 합성하였다.

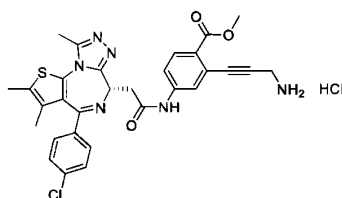
5 **【0411】** 단계 2: (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl dihydrogen phosphate
trifluoroacetic acid

【0412】 중간체 3-8'a로부터 제조예 4-1'의 단계 4와 동일한
10 방법으로 실시예 3-8'을 합성하였다.

【0413】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.56 (s, 1H), 8.56 (s, 3H), 7.72 (d, $J = 2.2$ Hz, 1H), 7.65 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.47 – 7.42 (m, 2H), 7.40 – 7.34 (m, 3H), 4.90 (d, $J = 5.5$ Hz, 2H), 4.56 (t, $J = 7.2$ Hz, 1H), 3.93 (s, 2H), 3.53 – 3.45 (m, 2H), 2.56 (s, 3H), 2.38 (d, $J = 0.9$ Hz, 3H), 1.59 (d, $J = 0.9$ Hz, 3H). ^{31}P NMR (202 MHz, $\text{DMSO}-d_6$) δ -0.47; MS
15 m/z $[\text{M} + \text{H}]^+$ 639.26.

【0414】 [제조예 3-25'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoate

hydrochloride



【0415】

【0416】 중간체 3-25a로부터 제조예 1-1'과 동일한 방법으로

중간체 3-25'a(methyl (S)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-

5 1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoate)를 합성한

후 실시예 3-25'을 합성하였다.

【0417】 ^1H NMR (400 MHz, DMSO- d_6) δ 10.89 (s, 1H), 8.46

(s, 3H), 8.10 (d, J = 2.2 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.67 (dd, J = 8.7,

10 2.2 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 4.62 (t, J =

7.2 Hz, 1H), 4.03 (t, J = 5.6 Hz, 2H), 3.85 (s, 3H), 3.58 (d, J = 7.2 Hz, 2H),

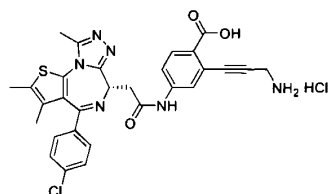
2.63 (s, 3H), 2.43 (s, 3H), 1.64 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 587.25.

【0418】 [제조예 3-26'] (S)-2-(3-aminoprop-1-yn-1-yl)-4-

(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

15 f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoic acid

hydrochloride



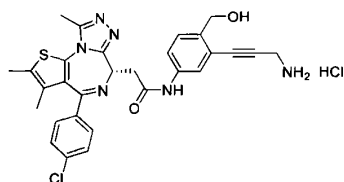
【0419】

【0420】 중간체 3-25'a로부터 제조예 3-2'과 동일한 방법으로 실시예 3-26'을 합성하였다.

5 【0421】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.80 (s, 1H), 8.38 (s, 2H), 8.06 (d, $J = 2.2$ Hz, 1H), 7.88 (d, $J = 8.7$ Hz, 1H), 7.59 (dd, $J = 8.7$, 2.2 Hz, 1H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.39 (d, $J = 8.5$ Hz, 2H), 4.66 – 4.47 (m, 1H), 4.05 – 3.89 (m, 2H), 3.62 – 3.45 (m, 2H), 2.59 (d, $J = 1.1$ Hz, 3H), 2.39 (d, $J = 1.0$ Hz, 3H), 1.65 – 1.52 (m, 3H); MS m/z $[\text{M} + \text{H}]^+$ 573.35.

10 【0422】 [제조예 3-27'] (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(hydroxymethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

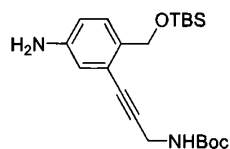
hydrochloride



【0423】

15 【0424】 단계 1: tert-butyl (3-(5-amino-2-(((tert-butyl)dimethylsilyl)oxy)methyl)phenyl)prop-2-yn-1-yl)carbamate (중간체

3-27c)



【0425】

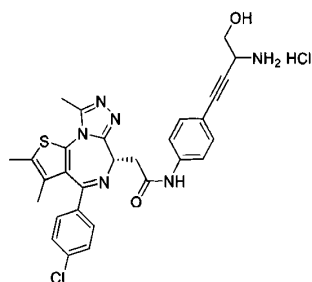
【0426】 Methyl 4-amino-2-iodobenzoate로부터 제조예 3-3'의 단계 1 내지 3과 동일한 방법으로 중간체 3-27c를 합성하였다.

5 【0427】 단계 2: (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(hydroxymethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

10 【0428】 중간체 3-27c로부터 제조예 3-3'과 동일한 방법으로
중간체 3-27'a (tert-butyl (S)-(3-(2-(((tert-butyl-
dimethylsilyl)oxy)methyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-
trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
yl)acetamido)phenyl)prop-2-yn-1-yl)carbamate)를 합성한 후 실시예 3-
27'을 합성하였다.

15 【0429】 ^1H NMR (400 MHz, DMSO- d_6) δ 10.54 (s, 1H), 8.53 (s, 3H), 7.87 (s, 1H), 7.69 - 7.55 (m, 1H), 7.53 - 7.47 (m, 3H), 7.43 (d, J = 8.3 Hz, 2H), 4.88 (s, 1H), 4.62 (d, J = 14.8 Hz, 2H), 4.09 - 3.96 (m, 2H), 3.54 (td, J = 7.3, 6.8, 3.5 Hz, 2H), 2.65 (s, 3H), 2.43 (s, 3H), 1.64 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 559.25.

【0430】 【제조예 3-49'】 N-(4-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)-2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

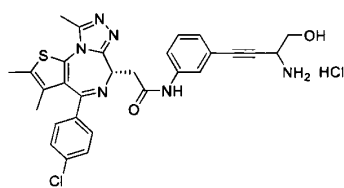


【0431】

5 【0432】 중간체 3-49b로부터 제조예 1-1'과 동일한 방법으로 실시예 3-49'를 합성하였다.

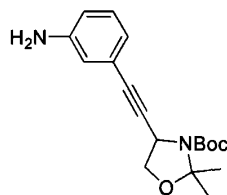
【0433】 MS m/z $[M+H]^+$ 559.35.

10 【0434】 【제조예 3-51'】 N-(3-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)-2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride



【0435】

【0436】 단계 1: tert-butyl 4-((3-aminophenyl)ethynyl)-2,2-dimethyloxazolidine-3-carboxylate (중간체 3-51a)



【0437】

【0438】 출발물질 3-Iodoaniline과 중간체 3-49a로부터 제조예 3-49의 단계 2와 동일한 방법으로 중간체 3-51a를 합성하였다.

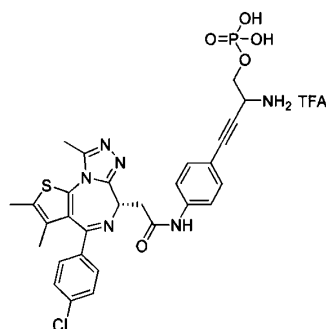
【0439】 단계 2: N-(3-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)-2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

【0440】 중간체 3-51a로부터 제조예 1-1'과 동일한 방법으로 실시예 3-51'을 합성하였다.

【0441】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.57 (s, 1H), 8.43 (bs, 3H), 7.93 (t, $J = 1.8$ Hz, 1H), 7.59 (ddd, $J = 8.3, 2.2, 1.1$ Hz, 1H), 7.53 – 7.46 (m, 2H), 7.45 – 7.34 (m, 3H), 7.15 (dt, $J = 7.8, 1.3$ Hz, 1H), 4.61 (dd, $J = 7.6, 6.8$ Hz, 1H), 4.03 – 3.96 (m, 2H), 3.55 – 3.50 (m, 2H), 2.62 (s, 3H), 2.43 (s, 3H), 1.63 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 559.35.

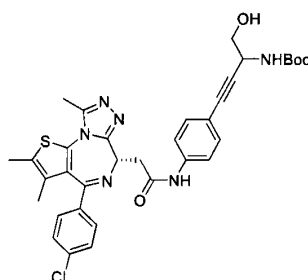
【0442】 [제조예 3-57'] 2-amino-4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)but-3-yn-1-yl dihydrogen

phosphate trifluoroacetic acid



【0443】

【0444】 단계 1: tert-butyl (4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)-1-hydroxybut-3-yn-2-yl)carbamate (중간체 3-57'a)



【0445】

【0446】 실시예 3-49' (0.1 mmol, 1.0 eq)을 MeOH 3 mL에 녹인 후 0 °C에서 TEA (excess), Boc₂O (excess)를 천천히 적가해 6 시간 교반하였다. 반응물은 DCM, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 3-57'a를 합성하였다.

【0447】 단계 2: 2-amino-4-(4-(2-((S)-4-(4-chlorophenyl)-

2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)but-3-yn-1-yl dihydrogen phosphate trifluoroacetic acid

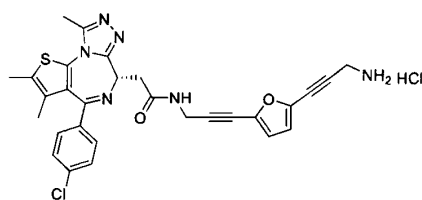
【0448】 중간체 3-57'a를 이용하여 제조예 3-8'과 동일한 방법으로 실시예 3-57'을 합성하였다.

【0449】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.53 (s, 1H), 7.70 – 7.63 (m, 2H), 7.49 – 7.42 (m, 2H), 7.42 – 7.36 (m, 4H), 4.54 (dd, J = 4.1, 2.4 Hz, 1H), 4.11 – 3.97 (m, 2H), 3.49 (d, J = 7.2 Hz, 2H), 2.56 (s, 3H), 2.38 (d, J = 1.0 Hz, 3H), 1.59 (d, J = 1.0 Hz, 3H). ^{31}P NMR (202 MHz, $\text{DMSO}-d_6$) δ -0.60; MS m/z $[\text{M} + \text{H}]^+$ 639.36.

【0450】 [제조예 4-1'] (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

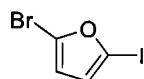
15

【0451】



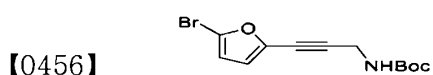
【0452】 단계 1: 2-bromo-5-iodofuran (중간체 4-1a)

【0453】



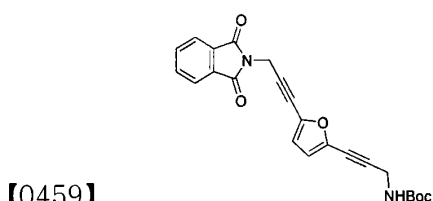
【0454】 2-bromofuran (2.0 mmol, 1.0 eq), NIS (1.1 eq), PTSA (0.1 eq)를 EtOH 4.0 mL에 녹인 후 50 °C에서 10 분간 교반하였다. Na₂S₂O₃를 사용하여 반응을 종결하였다. 반응물은 EtOAc, H₂O로 추출 후 유기층을 Na₂SO₄로 건조한 뒤 감압증류하여 별도의 정제과정 없이 화합물을 합성하였다.

【0455】 단계 2: tert-butyl (3-(5-bromofuran-2-yl)prop-2-yn-1-yl)carbamate (중간체 4-1b)



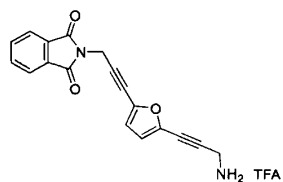
【0457】 중간체 4-1a로부터 제조예 1-1의 단계 1과 동일한 방법으로 중간체 4-1b를 합성하였다.

【0458】 단계 3: tert-butyl (3-(5-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)carbamate (중간체 4-1c)



【0460】 중간체 4-1b로부터 제조예 5-116의 단계 2와 동일한 방법으로 중간체 4-1c를 합성하였다.

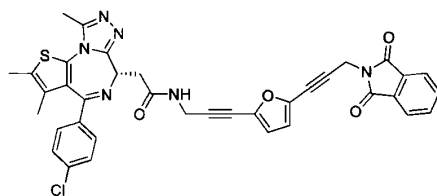
【0461】 단계 4: 2-(3-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)isoindoline-1,3-dione trifluoroacetic acid (중간체 4-1d)



【0462】

【0463】 중간체 4-1c (0.18 mmol, 1.0 eq)를 DCM 3.0 mL에 녹인 후 TFA (excess)를 적가하여 실온에서 1 시간 교반하였다. 반응물을 감압증류하여 별도의 정제과정없이 중간체 4-1d를 합성하였다.

5 【0464】 단계 5: (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-(5-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)acetamide (중간체 4-1'a)



【0465】

10 【0466】 JQ1 carboxylic acid (0.2 mmol, 1.0 eq), 중간체 4-1d (1.2 eq), HATU (1.5 eq)를 dry DCM에 녹인 후 반응 용기 내 기체를 Ar기체로 치환하였다. DIPEA (3.0 eq)를 적가한 후 실온에서 16시간 교반하였다. 반응물은 EtOAc, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해

15 중간체 4-1'a를 합성하였다.

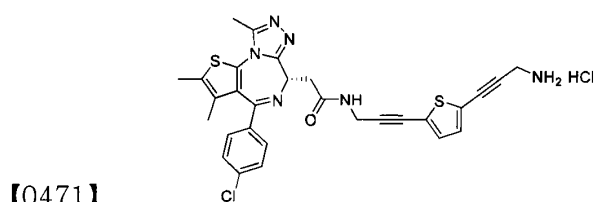
【0467】 단계 6: (S)-N-(3-(5-(3-aminoprop-1-yn-1-

yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-
6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
hydrochloride

【0468】 중간체 4-1'a로부터 순차적으로 제조예 5-116의
5 단계 3, 제조예 1-1의 단계 2와 동일한 방법을 적용하여 실시예 4-1'을
합성하였다.

【0469】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.83 (t, J = 5.6 Hz,
1H), 8.45 (s, 3H), 7.43 - 7.25 (m, 4H), 6.92 (d, J = 3.6 Hz, 1H), 6.86 (d, J
= 3.6 Hz, 1H), 4.50 (dd, J = 8.5, 5.9 Hz, 1H), 4.27 - 4.13 (m, 2H), 4.03 (q,
10 J = 5.6 Hz, 2H), 3.33 - 3.15 (m, 2H), 2.57 (s, 3H), 2.38 (d, J = 0.9 Hz, 3H),
1.56 (d, J = 0.9 Hz, 3H); MS m/z $[\text{M} + \text{H}]^+$ 557.28.

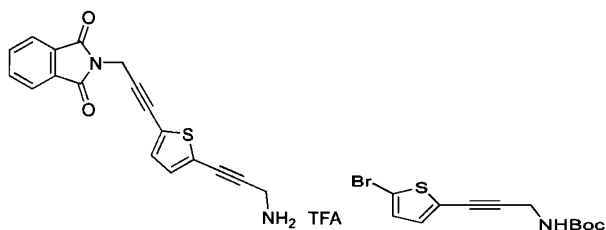
【0470】 [제조예 4-10'] (S)-N-(3-(5-(3-aminoprop-1-yn-1-
yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-
trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
15 yl)acetamide hydrochloride



【0472】 단계 1: 2-(3-(5-(3-aminoprop-1-yn-1-
yl)thiophen-2-yl)prop-2-yn-1-yl)isoindoline-1,3-dione trifluoroacetic

acid (중간체 4-10d)

【0473】



【0474】

2-Bromothiophene으로부터 제조예 4-1'의 단계 1 내지 4와 동일한 방법으로 중간체 4-10b(tert-butyl (3-(5-bromothiophen-2-yl)prop-2-yn-1-yl)carbamate)를 거쳐 중간체 4-10d를 합성하였다.

【0475】

단계 2: (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

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【0476】

중간체 4-10d로부터 제조예 4-1'의 단계 6과 동일한 방법으로 실시예 4-10'을 합성하였다.

【0477】

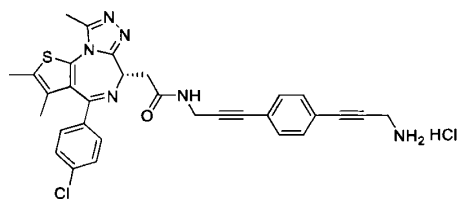
¹H NMR (500 MHz, DMSO-*d*₆) δ 8.85 (s, 1H), 8.47 (s, 2H), 7.52 - 7.35 (m, 4H), 7.34 (d, *J* = 3.9 Hz, 1H), 7.31 (d, *J* = 3.8 Hz, 1H), 4.60 - 4.49 (m, 1H), 4.23 (qd, *J* = 18.0, 5.6 Hz, 2H), 4.10 - 4.02 (m, 2H), 3.41 - 3.28 (m, 1H), 3.27 - 3.17 (m, 1H), 2.62 (d, *J* = 2.9 Hz, 3H), 2.42 (d, *J* = 2.9 Hz, 3H), 1.61 (d, *J* = 5.5 Hz, 3H); MS *m/z* [M+H]⁺ 573.21.

15

【0478】

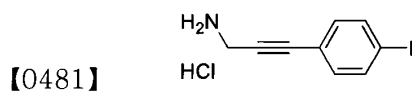
[제조예 4-128'] ((S)-N-(3-(4-(3-aminoprop-1-yn-

1-yl)phenyl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-
6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
hydrochloride



【0479】

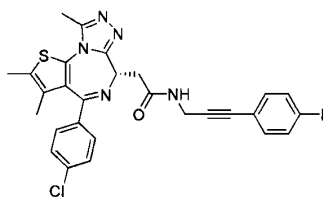
5 【0480】 단계 1: 3-(4-iodophenyl)prop-2-yn-1-amine
hydrochloride (중간체 4-128a)



【0481】

 【0482】 1,4-Diiodobenzene로부터 제조예 1-1과 동일한
방법으로 중간체 4-128a를 합성하였다.

10 【0483】 단계 2: (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-
6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-(4-
iodophenyl)prop-2-yn-1-yl)acetamide (중간체 4-128'a)



【0484】

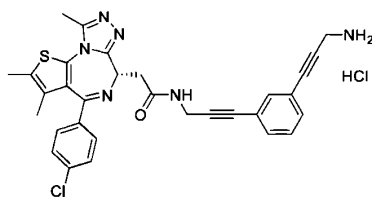
 【0485】 중간체 4-128a로부터 제조예 4-1'의 단계 5과 동일한
15 방법으로 중간체 4-128'a를 합성하였다.

【0486】 단계 3: ((S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

5 【0487】 중간체 4-128'a로부터 제조예 1-1과 동일한 방법으로 실시예 4-128'을 합성하였다.

【0488】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.82 (t, $J = 5.5$ Hz, 1H), 8.35 (bs, 3H), 7.51 – 7.32 (m, 8H), 4.53 (dd, $J = 8.4, 5.9$ Hz, 1H), 4.21 (qd, $J = 17.8, 5.5$ Hz, 2H), 4.03 (q, $J = 5.5$ Hz, 2H), 3.35 – 3.20 (m, 2H),
10 2.60 (s, 3H), 2.41 (s, 3H), 1.60 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 567.25.

【0489】 [제조예 4-129'] (S)-N-(3-(3-(3-aminoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride



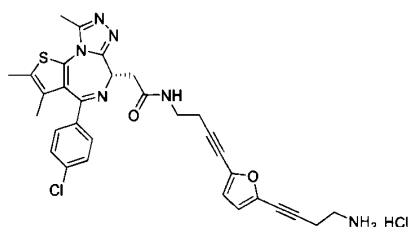
15 【0490】

【0491】 1,3-Diiodobenzene으로부터 제조예 4-128'과 동일한 방법으로 실시예 4-129'를 합성하였다.

【0492】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.82 (t, $J = 5.5$ Hz,

1H), 8.39 (bs, 3H), 7.54 – 7.32 (m, 8H), 4.53 (dd, $J = 8.4, 5.9$ Hz, 1H), 4.20 (qd, $J = 17.7, 5.4$ Hz, 2H), 4.01 (q, $J = 5.6$ Hz, 2H), 3.36 – 3.20 (m, 2H), 2.60 (s, 3H), 2.41 (s, 3H), 1.60 (s, 3H); MS m/z $[M+H]^+$ 567.25.

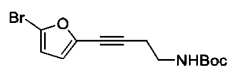
【0493】 【제조예 4-147'】 (S)-N-(4-(5-(4-aminobut-1-yn-1-yl)furan-2-yl)but-3-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride



【0494】

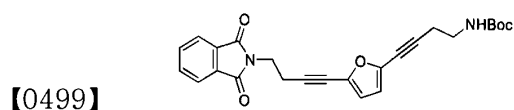
【0495】 단계 1: tert-butyl (4-(5-bromofuran-2-yl)but-3-yn-1-yl)carbamate (중간체 4-147a)

【0496】



【0497】 중간체 4-1a, tert-butyl but-3-yn-1-ylcarbamate를 이용하여 제조예 1-1의 단계 1과 동일한 방법으로 중간체 4-147a를 합성하였다.

【0498】 단계 2: tert-butyl (4-(5-(4-(1,3-dioxoisindolin-2-yl)but-1-yn-1-yl)furan-2-yl)but-3-yn-1-yl)carbamate (중간체 4-147b)



【0500】 중간체 4-147a, 2-(but-3-yn-1-yl)isoindoline-1,3-dione을 이용하여 제조예 5-116의 단계 2와 동일한 방법으로 중간체 4-147b를 합성하였다.

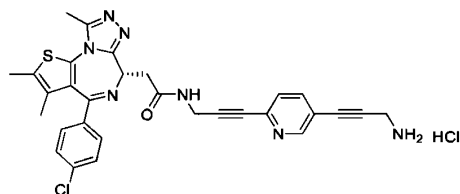
5 【0501】 단계 3: (S)-N-(4-(5-(4-aminobut-1-yn-1-yl)furan-2-yl)but-3-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

10 【0502】 중간체 4-147b로부터 제조예 4-1'의 단계 4 내지 6과 동일한 방법으로 실시예 4-147'을 합성하였다.

15 【0503】 ^1H NMR (500 MHz, Methanol- d_4) δ 7.53 – 7.47 (m, 2H), 7.43 (dd, J = 8.7, 3.0 Hz, 2H), 6.56 (d, J = 3.5 Hz, 1H), 6.50 (d, J = 3.5 Hz, 1H), 4.98 (s, 1H), 3.51 – 3.44 (m, 2H), 3.44 – 3.40 (m, 2H), 3.17 – 3.12 (m, 2H), 2.86 – 2.83 (m, 5H), 2.70 (td, J = 6.6, 3.5 Hz, 2H), 2.50 – 2.44 (m, 2H), 1.73 – 1.66 (m, 2H); MS m/z $[\text{M} + \text{H}]^+$ 585.21.

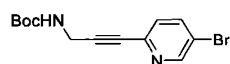
 【0504】 [제조예 4-177'] (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)pyridin-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamide hydrochloride



【0505】

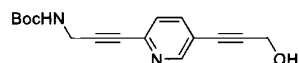
【0506】 단계 1: tert-butyl (3-(5-bromopyridin-2-yl)prop-2-yn-1-yl)carbamate (중간체 4-177a)



5 【0507】

【0508】 5-Bromo-2-iodopyridine를 출발물질로 하여 제조예 1-1의 단계 1과 동일한 방법으로 중간체 4-177a를 합성하였다.

【0509】 단계 2: tert-butyl (3-(5-(3-hydroxyprop-1-yn-1-yl)pyridin-2-yl)prop-2-yn-1-yl)carbamate (중간체 4-177b)

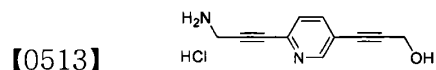


10 【0510】

【0511】 중간체 4-177a (0.7 mmol, 1.0 eq), propargyl alcohol (2.0 eq), Pd(PPh₃)₄ (0.1 eq), CuI (0.3 eq), TBAI (3.0 eq), TEA 0.6 mL, dry THF 2.4 mL를 혼합한 뒤 반응 용기 내 기체를 Ar 기체로 치환한 후 M.W.로 100°C, 50 분간 반응하였다, 반응물은 EtOAc, H₂O로 추출 후
15 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 4-177b를 합성하였다.

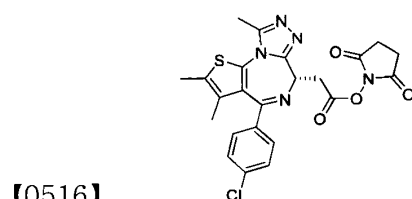
【0512】 단계 3: 3-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-

yl)prop-2-yn-1-ol hydrochloride(중간체 4-177c)



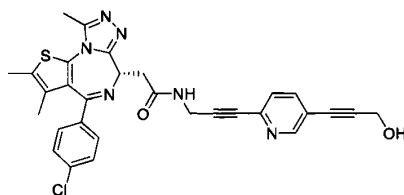
【0514】 중간체 4-177b로부터 제조예 1-1의 단계 2와 동일한 방법으로 중간체 4-177c를 합성하였다.

5 【0515】 단계 4: 2,5-dioxopyrrolidin-1-yl (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (JQ1 NHS ester)



10 【0517】 JQ1 carboxylic acid (1.0 mmol, 1.2 eq), *N*-hydroxysuccinimide (2.0 eq), EDC (2.0 eq), DCM 15 mL를 혼합하여 반응 용기 내 기체를 Ar 기체로 치환 후 상온조건에서 밤새 교반하였다. 반응물은 감압증류한 뒤 flash column을 통해 정제해 중간체 JQ1 NHS ester를 합성하였다.

15 【0518】 단계 5: (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-(5-(3-hydroxyprop-1-yn-1-yl)pyridin-2-yl)prop-2-yn-1-yl)acetamide (중간체 4-177'a)

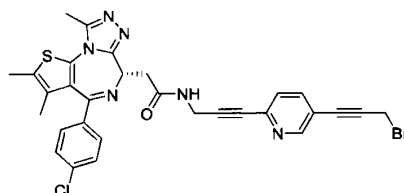


【0519】

【0520】 JQ1 NHS ester (0.3 mmol, 1.0 eq), 중간체 4-177c (1.0 eq)을 dry DCM에 녹인 후 반응 용기 내 기체를 Ar 기체로 치환하였다. DIPEA (2.4 eq)를 적가한 후 실온에서 밤새 교반하였다. 반응물은

5 감압증류한 뒤 flash column을 통해 정제해 중간체 4-177'a을 합성하였다.

【0521】 단계 6: (S)-N-(3-(5-(3-bromoprop-1-yn-1-yl)pyridin-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide (중간체 4-177'b)



10

【0522】

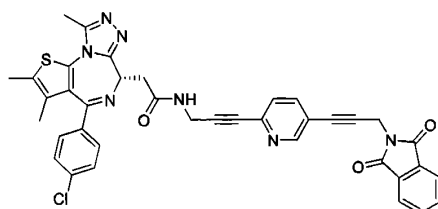
【0523】 중간체 4-177'a (0.05 mmol, 1.0 eq), CBr₄ (2.0 eq)를 dry DCM에 녹인 후 반응 용기 내 기체를 Ar 기체로 치환하였다. PPh₃ (2.0 eq)를 천천히 첨가한 뒤 실온에서 6 시간 교반하였다. 반응물은 감압증류한 뒤 flash column을 통해 정제해 중간체 4-177'b을 합성하였다.

15

【0524】 단계 7: (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-(5-(3-

(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)pyridin-2-yl)prop-2-yn-1-yl)acetamide (중간체 4-177'c)

【0525】



【0526】 중간체 4-177'b (0.02 mmol, 1.0 eq), phthalimide (1.3

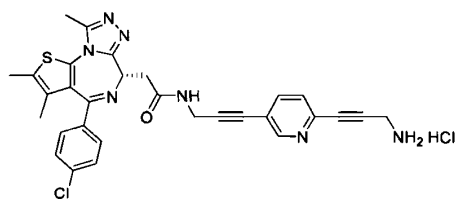
5 eq), CS₂CO₃ (2.0 eq)를 ACN 0.6 mL, THF 0.2 mL에 녹인 후 실온에서 밤새 교반하였다. 반응물은 감압증류한 뒤 flash column을 통해 정제해 중간체 4-177c'를 합성하였다.

【0527】 단계 8: (S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)pyridin-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

【0528】 중간체 4-177'c로부터 제조예 4-1'의 단계 6와 동일한 방법으로 실시예 4-177'을 합성하였다.

【0529】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.41 (s, 3H), 7.94 (s, 1H), 7.64 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 4.56 (t, *J* = 6.7 Hz, 1H), 4.06 - 4.00 (m, 1H), 3.86 (s, 2H), 3.75 (s, 4H), 3.53 (s, 5H), 2.57 (s, 3H), 2.38 (s, 3H), 1.59 (s, 3H); MS *m/z* [M+H]⁺ 568.23.

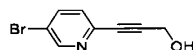
【0530】 [제조예 4-179'] (S)-N-(3-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride



5 【0531】

【0532】 단계 1: 3-(5-bromopyridin-2-yl)prop-2-yn-1-ol
(중간체 4-179a)

【0533】

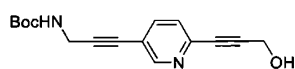


【0534】 5-Bromo-2-iodopyridine (1.0 mmol, 1.0 eq),

10 propargylalcohol (1.1 eq), PdCl₂(PPh₃)₂ (0.05 eq), CuI (0.1 eq), TEA 1.0 mL, dry THF 4.0 mL를 혼합한 뒤 반응 용기 내 기체를 Ar 기체로 치환 후 M.W.하에 100°C, 30 분간 가열하였다, 반응물은 EtOAc, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 4-179a를 합성하였다.

15 【0535】 단계 2: tert-butyl (3-(6-(3-hydroxyprop-1-yn-1-yl)pyridin-3-yl)prop-2-yn-1-yl)carbamate (중간체 4-179b)

【0536】

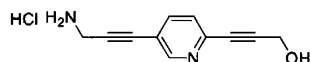


【0537】 중간체 4-179a, n-boc propargylamine로부터 제조예 4-177'의 단계 2와 동일한 방법으로 중간체 4-179b를 합성하였다.

【0538】 단계 3: 3-(5-(3-aminoprop-1-yn-1-yl)pyridin-2-yl)prop-2-yn-1-ol hydrochloride (중간체 4-179c)

5

【0539】



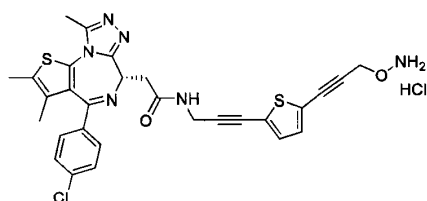
【0540】 중간체 4-179b로부터 제조예 1-1의 단계 2와 동일한 방법으로 중간체 4-179c를 합성하였다.

【0541】 단계 4: (S)-N-(3-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride

【0542】 중간체 4-179c로부터 제조예 4-177'의 단계 5 내지 8과 동일한 방법으로 실시예 4-179'를 합성하였다.

【0543】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.48 (t, J = 5.8 Hz, 1H), 8.14 (t, J = 5.7 Hz, 1H), 7.87 - 7.83 (m, 2H), 7.46 - 7.41 (m, 5H), 7.39 - 7.36 (m, 2H), 7.09 (q, J = 3.5 Hz, 2H), 4.46 (dd, J = 8.1, 6.1 Hz, 1H), 3.49 (s, 2H), 3.19 (d, J = 5.8 Hz, 3H), 3.14 - 3.09 (m, 2H), 3.05 (dq, J = 12.9, 6.2 Hz, 2H), 2.54 (d, J = 2.0 Hz, 3H), 2.35 (d, J = 3.1 Hz, 3H), 1.57 (s, 3H), 1.52 (d, J = 8.1 Hz, 2H), 1.48 (d, J = 7.6 Hz, 2H), 1.40 (s, 2H), 1.19 (s, 4H); MS m/z $[\text{M} + \text{H}]^+$ 568.23.

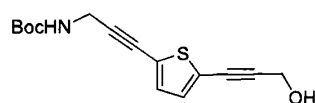
【0544】 [제조예 4-223'] (S)-N-(3-(5-(3-(aminooxy)prop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride



5

【0545】

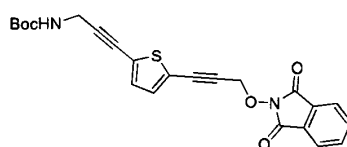
【0546】 단계 1: tert-butyl (3-(5-(3-hydroxyprop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)carbamate (중간체 4-223a)



【0547】

【0548】 중간체 4-10b로부터 제조예 4-177'의 단계 2와
10 동일한 방법으로 중간체 4-223a를 합성하였다.

【0549】 단계 2: tert-butyl (3-(5-(3-((1,3-dioxoisindolin-2-yl)oxy)prop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)carbamate
(중간체 4-223b)

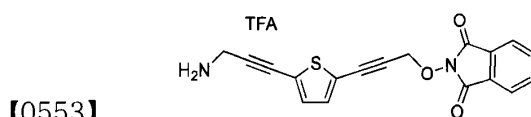


【0550】

【0551】 PPh₃ (1.2 eq)를 dry THF에 녹인 후 Ar 치환하고,
15 0 °C에서 diisopropyl azodicarboxylate (1.0 eq), 중간체 4-223a (0.2 mmol,

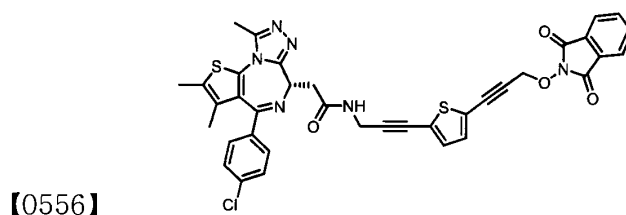
1.0 eq)를 첨가한 뒤 5 분 교반하고 N-hydroxyphthalimide (1.0 eq)을 첨가한 뒤 실온에서 5 시간 교반하였다. 반응물은 감압증류한 뒤 flash column을 통해 정제해 중간체 4-223b를 합성하였다.

【0552】 단계 3: 2-((3-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)oxy)isoindoline-1,3-dione trifluoroacetic acid (중간체 4-223c)



【0554】 중간체 4-223b로부터 제조예 4-1'의 단계 4와 동일한 방법으로 중간체 4-223c를 합성하였다.

10 【0555】 단계 4: (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(3-(5-((1,3-dioxoisindolin-2-yl)oxy)prop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)acetamide (중간체 4-223'a)



15 【0557】 중간체 4-223c로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 4-223'a를 합성하였다.

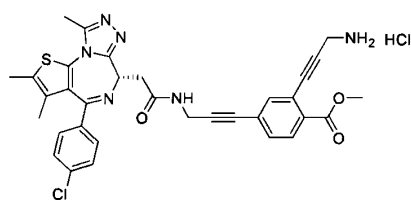
【0558】 단계 5: (S)-N-(3-(5-(3-(aminooxy)prop-1-yn-1-

yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

【0559】 중간체 4-223'a로부터 제조예 5-116의 단계 3 및
5 제조예 1-1의 단계 2와 동일한 방법을 순차적으로 적용하여 실시예 4-223'을 합성하였다.

【0560】 ^1H NMR (500 MHz, Methanol- d_4) δ 7.50 – 7.43 (m, 2H), 7.33 – 7.26 (m, 2H), 7.22 (d, J = 3.8 Hz, 1H), 7.19 (d, J = 3.9 Hz, 1H), 4.80 – 4.74 (m, 1H), 4.49 – 4.37 (m, 2H), 4.22 (d, J = 17.8 Hz, 1H), 3.51
10 (dd, J = 15.1, 9.6 Hz, 1H), 3.43 – 3.32 (m, 2H), 2.79 (s, 3H), 2.47 (s, 3H), 1.70 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 589.21.

【0561】 [제조예 5-116'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)benzoate hydrochloride
15



【0562】

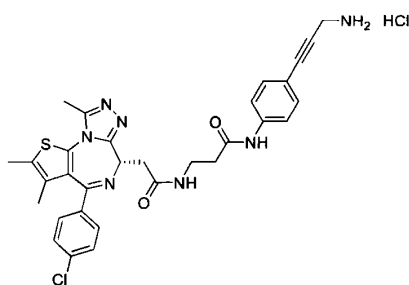
【0563】 중간체 5-116c로부터 제조예 1-1'과 동일한 방법으로 실시예 5-116'를 합성하였다.

【0564】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.81 (t, $J = 5.4$ Hz, 1H), 8.38 (s, 3H), 7.88 (d, $J = 8.2$ Hz, 1H), 7.59 (d, $J = 1.7$ Hz, 1H), 7.55 (dd, $J = 8.2, 1.7$ Hz, 1H), 7.40 – 7.36 (m, 2H), 7.32 (d, $J = 8.9$ Hz, 2H), 4.50 (dd, $J = 8.3, 6.2$ Hz, 1H), 4.19 (t, $J = 5.5$ Hz, 2H), 4.00 (q, $J = 5.7$ Hz, 2H), 3.84 (s, 3H), 3.37 – 3.17 (m, 2H), 2.56 (s, 3H), 2.37 (d, $J = 0.9$ Hz, 3H), 1.56 (d, $J = 0.9$ Hz, 3H); MS m/z $[\text{M} + \text{H}]^+$ 625.37.

【0565】 [제조예 II']

【0566】 BRD4(Bromodomain-containing protein 4) 억제제로서의 활성을 나타내는 화합물(JQ1)이 본 발명의 화학식 II에 해당하는 화합물들과 연결된 TBM-UBM 화합물을 아래와 같이 합성하였다.

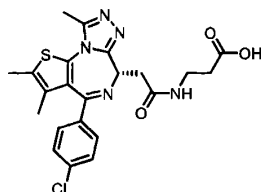
【0567】 [제조예 4-124'] (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide hydrochloride



15 【0568】

【0569】 단계 1: (S)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)propanoic acid (중간체 4-124'a)



【0570】

【0571】 β -Alanine 로부터 제조예 4-177'의 단계 5과 동일한 방법으로 중간체 4-124'a를 합성하였다.

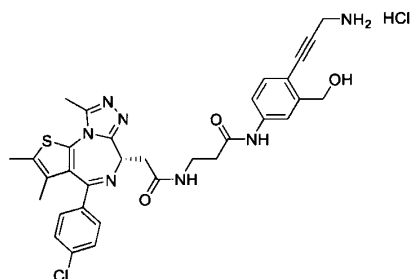
5 【0572】 단계 2: (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide hydrochloride

 【0573】 중간체 4-124'a와 중간체 1-1a로부터 제조예 1-1' 와
10 동일한 방법으로 실시예 4-124'를 합성하였다.

 【0574】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.29 (s, 1H), 8.38 (s, 3H), 7.73 - 7.60 (m, 2H), 7.52 (d, J = 8.6 Hz, 1H), 7.38 (tt, J = 8.7, 4.2 Hz, 5H), 4.51 (d, J = 6.9 Hz, 1H), 3.92 (d, J = 5.8 Hz, 2H), 3.40 - 3.22 (m, 4H), 3.30 - 3.00 (m, 2H), 2.63 - 2.57 (m, 3H), 2.56 - 2.50 (m, 2H), 2.38
15 (s, 3H), 1.60 - 1.54 (m, 3H); MS m/z $[\text{M} + \text{H}]^+$ 600.32.

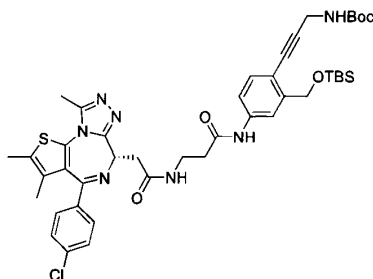
 【0575】 [제조예 4-125'] (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)propanamide hydrochloride



【0576】

【0577】 단계 1: tert-butyl (S)-(3-(2-(((tert-butyl)dimethylsilyl)oxy)methyl)-4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)phenyl)prop-2-yn-1-yl)carbamate(중간체 4-125'a)

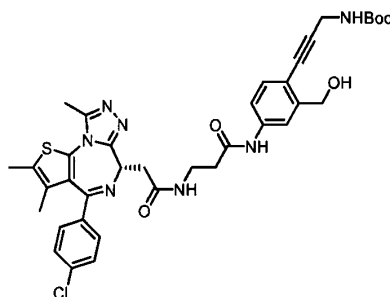


【0578】

【0579】 중간체 4-124'a 와 중간체 3-3c로부터 제조예 1-1'의 단계 1과 동일한 방법으로 중간체 4-125'a를 합성하였다.

【0580】 단계 2: (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)propanamide hydrochloride



【0581】

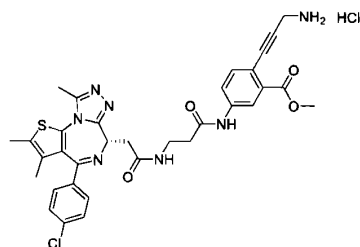
【0582】 중간체 4-125'a로부터 제조예 3-3'의 단계 5 내지

6과 동일한 방법으로 실시예 4-125를 합성하였다.

5 【0583】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.24 (d, $J = 11.4$ Hz, 1H), 8.41 (d, $J = 35.7$ Hz, 3H), 7.76 (s, 1H), 7.63 – 7.57 (m, 1H), 7.42 – 7.35 (m, 4H), 7.29 (d, $J = 8.3$ Hz, 1H), 4.58 (s, 1H), 4.56 – 4.42 (m, 2H), 3.94 (d, $J = 6.3$ Hz, 2H), 3.42 – 3.30 (m, 2H), 3.29 – 3.10 (m, 2H), 2.59 (q, $J = 4.9, 4.2$ Hz, 3H), 2.53 (t, $J = 7.0$ Hz, 2H), 2.38 (s, 3H), 1.61 – 1.55 (m, 3H); MS m/z $[\text{M} + \text{H}]^+$ 630.46.

10 【0584】 [제조예 4-126'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)propanamido)benzoate hydrochloride

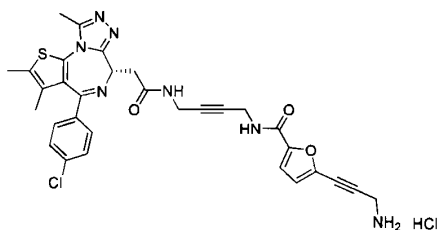


【0585】

【0586】 중간체 4-124'a와 중간체 3-1a로부터 제조예 1-1' 과 동일한 방법으로 실시예 4-126'를 합성하였다.

5 【0587】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.49 (d, $J = 13.2$ Hz, 1H), 8.39 (d, $J = 25.3$ Hz, 3H), 8.24 (d, $J = 2.1$ Hz, 1H), 7.83 (dd, $J = 8.5, 2.3$ Hz, 1H), 7.50 (d, $J = 8.5$ Hz, 1H), 7.43 – 7.33 (m, 4H), 4.50 (d, $J = 5.6$ Hz, 1H), 4.01 – 3.91 (m, 2H), 3.83 (s, 3H), 3.43 – 3.30 (m, 2H), 3.27 – 3.10 (m, 2H), 2.58 (dd, $J = 3.9, 1.6$ Hz, 3H), 2.54 (d, $J = 6.8$ Hz, 2H), 2.41 – 2.34 (m, 3H), 1.58 – 1.53 (m, 3H); MS m/z $[\text{M} + \text{H}]^+$ 658.47.

10 【0588】 [제조예 4-148'] (S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-yn-1-yl)furan-2-carboxamide hydrochloride

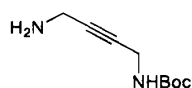


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【0589】

【0590】 단계 1: tert-butyl (4-aminobut-2-yn-1-yl)carbamate (중간체 4-148a)

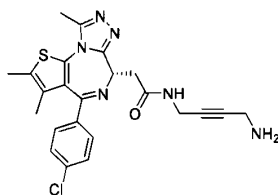
【0591】



【0592】 But-2-yne-1,4-diamine로부터 제조예 3-57'의 단계 1과 동일한 방법으로 중간체 4-148a를 합성하였다.

【0593】 단계 2: (S)-N-(4-aminobut-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride (중간체 4-148'a)

【0594】



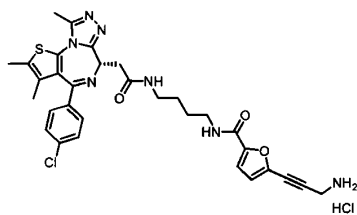
【0595】 JQ1 carboxylic acid와 중간체 4-148a로부터 제조예 1-1'과 동일한 방법으로 중간체 4-148'a를 합성하였다.

【0596】 단계 3: (S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-yn-1-yl)furan-2-carboxamide hydrochloride

【0597】 중간체 4-148'a와 중간체 4-227b로부터 제조예 1-1'과 동일한 방법으로 실시예 4-148'을 합성하였다.

【0598】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.96 (t, $J = 5.7$ Hz, 1H), 8.61 (t, $J = 5.5$ Hz, 1H), 8.41 (s, 3H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.41 – 7.35 (m, 2H), 7.21 (d, $J = 3.6$ Hz, 1H), 6.97 (d, $J = 3.6$ Hz, 1H), 4.47 (dd, $J = 8.2, 6.0$ Hz, 1H), 4.08 – 3.97 (m, 3H), 3.28 – 3.12 (m, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 1.58 (s, 3H). MS m/z $[\text{M} + \text{H}]^+$ 614.25.

【0599】 [제조예 4-149'] ((S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide hydrochloride

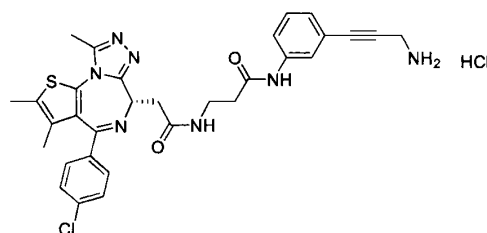


10 【0600】

【0601】 tert-butyl (4-aminobutyl)carbamate로부터 제조예 4-148'의 단계 2 내지 3과 동일한 방법으로 실시예 4-149'를 합성하였다.

【0602】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.57 (t, $J = 5.8$ Hz, 1H), 8.50 (s, 3H), 8.24 (t, $J = 5.6$ Hz, 1H), 7.49 (d, $J = 8.8$ Hz, 2H), 7.41 (d, $J = 8.7$ Hz, 2H), 7.18 (d, $J = 3.6$ Hz, 1H), 6.99 (d, $J = 3.6$ Hz, 1H), 4.52 (dd, $J = 8.3, 6.0$ Hz, 1H), 4.08 (s, 2H), 3.26 – 3.18 (m, 4H), 3.17 – 3.08 (m, 2H), 2.61 (s, 3H), 2.41 (d, $J = 0.9$ Hz, 3H), 1.61 (d, $J = 0.9$ Hz, 3H), 1.52 (d, $J = 7.0$ Hz, 2H), 1.47 (d, $J = 7.1$ Hz, 2H); MS m/z $[\text{M} + \text{H}]^+$ 618.16.

【0603】 【제조예 4-161'】 (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide hydrochloride

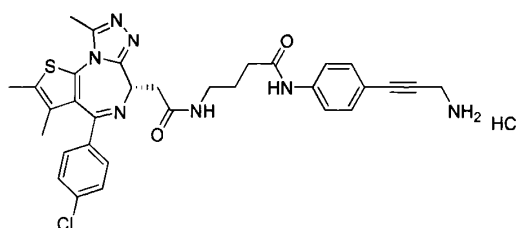


5 【0604】

【0605】 중간체 4-124'a와 중간체 1-3a로부터 제조예 1-1'와 동일한 방법으로 실시예 4-161'을 합성하였다.

【0606】 MS m/z [M+H]⁺ 600.36.

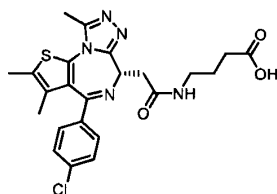
【0607】 【제조예 4-162'】 (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride



【0608】

【0609】 단계 1: (S)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)butanoic acid (중간체 4-162'a)



【0610】

【0611】 4-Aminobutanoic acid로부터 제조예 4-177'의 단계 5와 동일한 방법으로 중간체 4-162'a를 합성하였다.

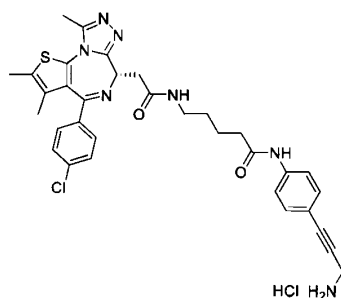
5 【0612】 단계 2: (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride

10 【0613】 중간체 4-162'a 와 중간체 1-1a로부터 제조예 1-1'과 동일한 방법으로 실시예 4-162'을 합성하였다.

15 【0614】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.19 (s, 1H), 8.33 (s, 3H), 8.25 (d, $J = 5.7$ Hz, 1H), 7.66 – 7.60 (m, 2H), 7.42 (d, $J = 8.9$ Hz, 2H), 7.39 – 7.32 (m, 4H), 4.48 (dd, $J = 8.2, 6.1$ Hz, 1H), 3.93 (q, $J = 5.6$ Hz, 2H), 3.27 – 3.05 (m, 4H), 2.57 (s, 3H), 2.39 – 2.36 (m, 3H), 2.36 – 2.30 (m, 2H), 1.74 (q, $J = 7.3$ Hz, 2H), 1.59 – 1.54 (m, 3H); MS m/z $[\text{M} + \text{H}]^+$ 614.36.

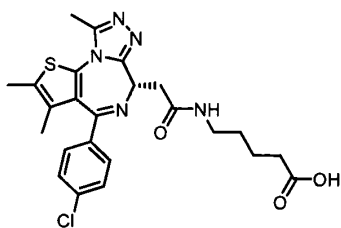
【0615】 [제조예 4-163'] (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide
hydrochloride



【0616】

【0617】 단계 1: (S)-5-(2-(4-(4-chlorophenyl)-2,3,9-
5 trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
yl)acetamido)pentanoic acid (중간체 4-163'a)



【0618】

【0619】 5-Aminopentanoic acid로부터 제조예 4-177'의 단계
5와 동일한 방법으로 중간체 4-163'a를 합성하였다.

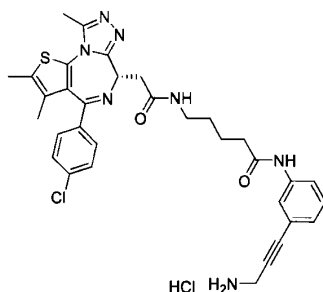
10 【0620】 단계 2: (S)-N-(4-(3-aminoprop-1-yn-1-
yl)phenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide
hydrochloride

【0621】 중간체 4-163'a 와 중간체 1-1a로부터 제조예 1-1'과

동일한 방법으로 실시예 4-163'을 합성하였다.

【0622】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.24 (d, $J = 2.3$ Hz, 1H), 8.42 (s, 3H), 8.24 (t, $J = 5.8$ Hz, 1H), 7.64 (d, $J = 8.3$ Hz, 2H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.39 – 7.29 (m, 4H), 4.51 (d, $J = 6.7$ Hz, 1H), 3.95 – 3.86 (m, 2H), 3.27 – 3.01 (m, 4H), 2.63 – 2.54 (m, 3H), 2.41 – 2.36 (m, 3H), 2.33 (t, $J = 7.4$ Hz, 2H), 1.60 (dd, $J = 7.3, 3.1$ Hz, 2H), 1.57 – 1.52 (m, 3H), 1.44 (p, $J = 7.1$ Hz, 2H); MS m/z $[\text{M} + \text{H}]^+$ 628.46.

【0623】 [제조예 4-164'] (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide hydrochloride



【0624】

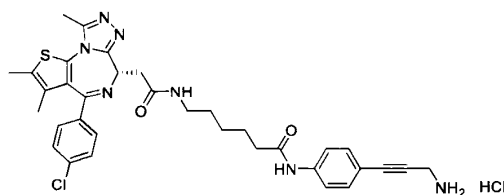
【0625】 중간체 4-163'a 와 중간체 1-3a로부터 제조예 1-1'과 동일한 방법으로 실시예 4-164'를 합성하였다.

【0626】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.16 (d, $J = 3.5$ Hz, 1H), 8.40 (s, 3H), 8.24 (t, $J = 5.8$ Hz, 1H), 7.90 (d, $J = 1.9$ Hz, 1H), 7.49 (dd, $J = 8.3, 1.9$ Hz, 1H), 7.46 – 7.41 (m, 2H), 7.40 – 7.34 (m, 2H), 7.28 (t,

$J = 7.9$ Hz, 1H), 7.07 (dt, $J = 7.7, 1.3$ Hz, 1H), 4.49 (dd, $J = 8.3, 5.7$ Hz, 1H), 3.97 – 3.85 (m, 2H), 3.26 – 2.98 (m, 4H), 2.58 (d, $J = 1.1$ Hz, 3H), 2.37 (d, $J = 0.9$ Hz, 3H), 2.31 (q, $J = 8.5, 7.9$ Hz, 2H), 1.58 (s, 2H), 1.56 (d, $J = 0.9$ Hz, 3H), 1.44 (p, $J = 7.1$ Hz, 2H); MS m/z $[M+H]^+$ 628.46.

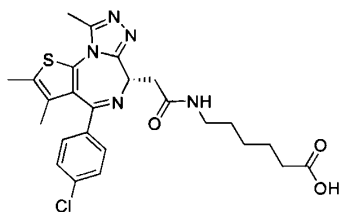
- 5 **【0627】** **【제조예 4-165'】** (S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamide hydrochloride

【0628】



- 10 **【0629】** 단계 1: (S)-6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanoic acid (중간체 4-165'a)

【0630】



【0631】 6-Aminohexanoic acid로부터 제조예 4-177'의 단계

- 15 5와 동일한 방법으로 중간체 4-165'a를 합성하였다.

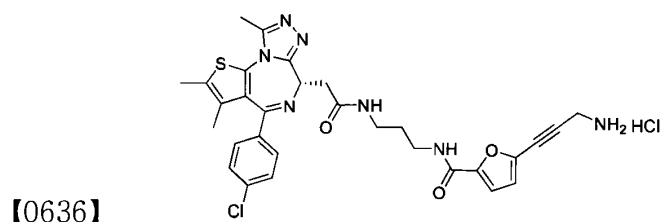
【0632】 단계 2: (S)-N-(4-(3-aminoprop-1-yn-1-

yl)phenyl)-6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamide hydrochloride

【0633】 중간체 4-165'a 와 중간체 1-1a로부터 제조예 1-1'과
5 동일한 방법으로 실시예 4-165'을 합성하였다.

【0634】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.10 (s, 1H), 8.25 (s, 3H), 8.17 (s, 1H), 7.66 – 7.58 (m, 2H), 7.50 – 7.42 (m, 2H), 7.40 – 7.29 (m, 4H), 4.49 – 4.42 (m, 1H), 3.94 (d, $J = 5.7$ Hz, 2H), 3.24 – 3.02 (m, 4H), 2.55 (d, $J = 3.2$ Hz, 3H), 2.37 (s, 3H), 2.34 – 2.25 (m, 2H), 1.57 (s, 3H),
10 1.56 (d, $J = 10.1$ Hz, 2H), 1.48 – 1.37 (m, 2H), 1.35 – 1.26 (m, 2H); MS m/z $[\text{M} + \text{H}]^+$ 642.46.

【0635】 [제조예 4-166'] ((S)-5-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)furan-2-
15 carboxamide hydrochloride

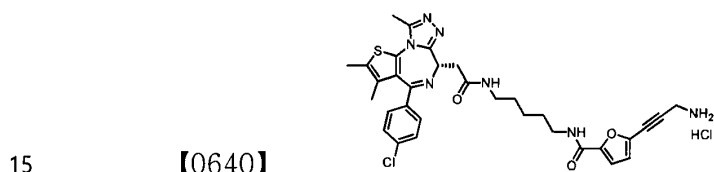


【0637】 tert-Butyl (3-aminopropyl)carbamate로부터 제조예 4-1의 단계 5, 제조예 1-1의 단계 2를 순차적으로 적용하여 중간체 4-

166'a((S)-N-(3-aminopropyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride)를 한 뒤, 이로부터 제조예 1-1'과 동일한 방법으로 실시예 4-166'를 합성하였다.

- 5 **【0638】** ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.57 (t, *J* = 5.8 Hz, 1H), 8.52 (s, 3H), 8.31 (t, *J* = 5.7 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 3.6 Hz, 1H), 7.00 (d, *J* = 3.6 Hz, 1H), 4.53 (dd, *J* = 8.2, 6.1 Hz, 1H), 4.08 (t, *J* = 5.7 Hz, 2H), 3.29 – 3.20 (m, 4H), 3.19 – 3.11 (m, 2H), 2.61 (s, 3H), 2.41 (d, *J* = 0.9 Hz, 3H), 1.68 (t, *J* = 7.0 Hz, 2H),
10 1.63 – 1.60 (m, 3H); MS *m/z* [M+ H]⁺ 604.16.

【0639】 **【제조예 4-167'】** (S)-5-(3-aminoprop-1-yn-1-yl)-N-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentyl)furan-2-carboxamide hydrochloride

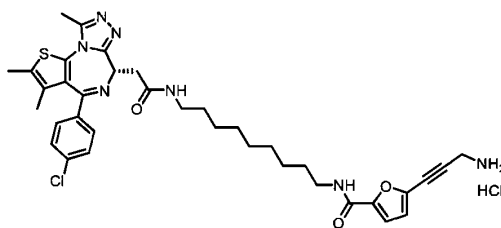


【0641】 실시예 137'로부터 제조예 4-166'와 동일한 방법으로 실시예 4-167'를 합성하였다.

【0642】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.53 (dd, *J* = 10.3,

4.4 Hz, 4H), 8.24 (t, $J = 5.5$ Hz, 1H), 7.50 (d, $J = 8.8$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.18 (d, $J = 3.6$ Hz, 1H), 6.98 (d, $J = 3.6$ Hz, 1H), 4.54 (dd, $J = 8.2, 6.0$ Hz, 2H), 4.07 (d, $J = 5.6$ Hz, 2H), 3.25 - 3.17 (m, 4H), 3.11 (dt, $J = 30.0, 6.9$ Hz, 2H), 2.61 (s, 3H), 2.41 (d, $J = 1.0$ Hz, 3H), 1.63 - 1.60 (m, 4H), 1.52 (q, $J = 7.3$ Hz, 2H), 1.46 (q, $J = 7.4$ Hz, 2H), 1.32 (q, $J = 8.6, 8.1$ Hz, 2H); MS m/z $[M+H]^+$ 632.27.

【0643】 **【제조예 4-225'】** (S)-5-(3-aminoprop-1-yn-1-yl)-N-(9-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)nonyl)furan-2-carboxamide hydrochloride



【0644】

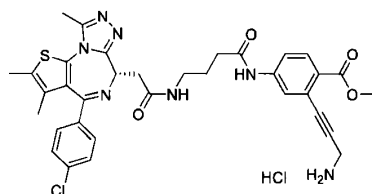
【0645】 실시예 1-33'으로부터 제조예 4-166'과 동일한 방법으로 실시예 4-225'를 합성하였다.

【0646】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.53 - 8.44 (m, 3H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.40 - 7.37 (m, 2H), 7.36 (d, $J = 8.7$ Hz, 1H), 7.13 (d, $J = 3.6$ Hz, 1H), 7.10 (d, $J = 3.1$ Hz, 1H), 6.94 (d, $J = 3.6$ Hz, 1H), 4.49 (d, $J = 2.4$ Hz, 1H), 4.04 (p, $J = 5.9$ Hz, 2H), 3.34 - 3.30 (m, 2H), 3.17 (t, J

= 9.3 Hz, 6=4H), 2.57 (s, 3H), 2.37 (d, J = 0.9 Hz, 3H), 1.58 (d, J = 1.0 Hz, 3H), 1.40 (dt, J = 15.1, 6.9 Hz, 4H), 1.20 (d, J = 9.9 Hz, 10H); MS m/z [M+ H]⁺ 688.42.

【0647】 [제조예 4-228'] (methyl (S)-2-(3-aminoprop-1-yn-
5 1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
yl)acetamido)butanamido)benzoate hydrochloride

【0648】

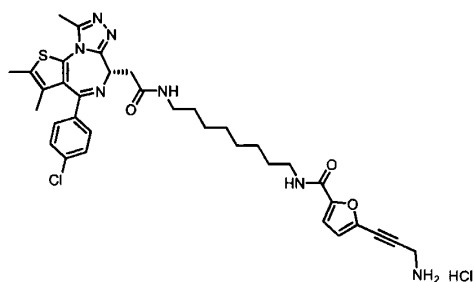


【0649】 중간체 3-25a로부터 제조예 5-77'의 단계 2와 동일한
10 방법으로 실시예 4-228'을 합성하였다.

【0650】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.50 (s, 1H), 8.40
(s, 3H), 8.29 (t, J = 5.6 Hz, 1H), 8.09 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 8.7
Hz, 1H), 7.55 (dd, J = 8.7, 2.2 Hz, 1H), 7.43 – 7.36 (m, 4H), 4.49 (dd, J =
7.9, 6.4 Hz, 1H), 4.01 (q, J = 5.6 Hz, 2H), 3.79 (s, 3H), 3.53 (d, J = 4.6 Hz,
15 1H), 3.34 (q, J = 7.0 Hz, 1H), 3.27 – 3.06 (m, 5H), 2.57 (s, 3H), 2.37 (s,
3H), 1.73 (p, J = 7.1 Hz, 2H), 1.57 (s, 3H); MS m/z [M+ H]⁺ 672.34.

【0651】 [제조예 4-235'] ((S)-5-(3-aminoprop-1-yn-1-yl)-
N-(8-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)octyl)furan-2-carboxamide hydrochloride



【0652】

【0653】 실시예 1-38'로부터 제조예 4-166'과 동일한

5 방법으로 실시예 4-235'를 합성하였다.

【0654】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.53 – 8.44 (m, 4H),

8.16 (t, $J = 5.7$ Hz, 1H), 7.47 – 7.43 (m, 2H), 7.41 – 7.36 (m, 2H), 7.13 (d, $J = 3.6$ Hz, 1H), 6.94 (d, $J = 3.6$ Hz, 1H), 4.48 (dd, $J = 8.2, 6.0$ Hz, 1H), 4.04

(q, $J = 5.7$ Hz, 2H), 3.37 – 3.17 (m, 2H), 3.17 – 2.99 (m, 4H), 2.57 (d, $J =$

10 1.1 Hz, 3H), 2.40 – 2.36 (m, 3H), 1.59 – 1.56 (m, 3H), 1.40 (dd, $J = 15.3, 8.4$ Hz, 4H), 1.28 – 1.16 (m, 8H); MS m/z $[\text{M} + \text{H}]^+$ 674.42.

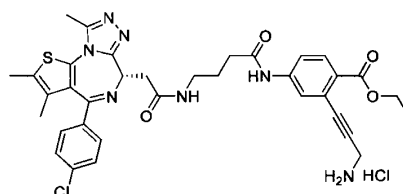
【0655】 [제조예 5-1'] ethyl (S)-2-(3-aminoprop-1-yn-1-

yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

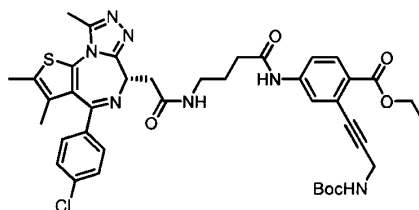
yl)acetamido)butanamido)benzoate hydrochloride

【0656】



【0657】 단계 1: ethyl (S)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate (중간체 5-1'a)

【0658】



【0659】 중간체 5-53'a (0.02 mmol, 1.0 eq), K₂CO₃ (3.0 eq), dry DMF 0.5 mL에 녹인 후 반응 용기 내 기체를 Ar 기체로 치환하였다.

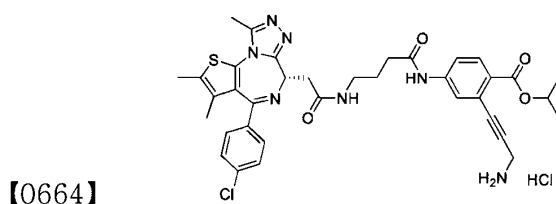
10 반응물을 실온에서 30 분 교반한 뒤 iodoethane (3.0 eq)를 적가한 후 실온에서 밤새 교반하였다. 반응물을 flash column으로 정제하여 중간체 5-1'a를 합성하였다.

【0660】 단계 2: ethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride

【0661】 중간체 5-1'a로부터 제조예 1-1의 단계 2와 동일한 방법으로 실시예 5-1'을 합성하였다.

【0662】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.44 (s, 1H), 8.37 (s, 3H), 8.30 (t, $J = 5.7$ Hz, 1H), 8.17 (d, $J = 2.1$ Hz, 1H), 7.89 (d, $J = 8.7$ Hz, 1H), 7.53 (dd, $J = 8.7, 2.3$ Hz, 1H), 7.45 (d, $J = 8.9$ Hz, 2H), 7.40 (d, $J = 8.7$ Hz, 2H), 4.50 (dd, $J = 7.9, 6.3$ Hz, 1H), 4.29 (q, $J = 7.1$ Hz, 2H), 4.04 (q, $J = 5.6$ Hz, 2H), 3.23 – 3.13 (m, 4H), 2.59 (s, 3H), 2.43 (dd, $J = 7.7, 2.3$ Hz, 2H), 2.41 (s, 3H), 1.78 (q, $J = 7.3$ Hz, 2H), 1.61 (s, 3H), 1.32 (d, $J = 7.2$ Hz, 3H); MS m/z $[\text{M} + \text{H}]^+$ 686.48.

10 【0663】 [제조예 5-2'] isopropyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride

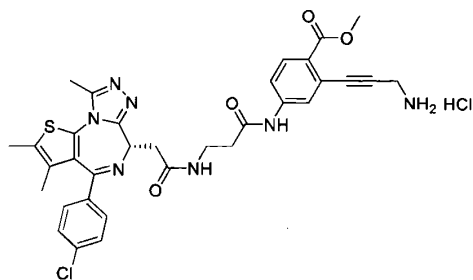


15 【0665】 중간체 5-53'a과 2-iodopropane로부터 실시예 5-1'과 동일한 방법으로 실시예 5-2'를 합성하였다.

【0666】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.44 (d, $J = 2.3$ Hz, 1H), 8.37 (s, 3H), 8.30 (s, 1H), 8.17 (t, $J = 2.3$ Hz, 1H), 7.86 (dd, $J = 8.7,$

2.3 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.44 (dd, J = 8.8, 2.3 Hz, 2H), 7.40 (dd, J = 8.6, 2.3 Hz, 2H), 5.09 (ddd, J = 12.6, 6.3, 2.4 Hz, 1H), 4.54 - 4.43 (m, 1H), 4.06 - 4.01 (m, 2H), 3.24 - 3.15 (m, 4H), 2.59 (d, J = 2.3 Hz, 3H), 2.42 (s, 2H), 2.41 (d, J = 2.3 Hz, 3H), 1.79 - 1.74 (m, 2H), 1.61 (d, J = 2.3 Hz, 3H), 1.31 (dd, J = 6.3, 2.3 Hz, 6H); MS m/z $[M+H]^+$ 700.39.

【0667】 **【제조예 5-4'】** methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate hydrochloride



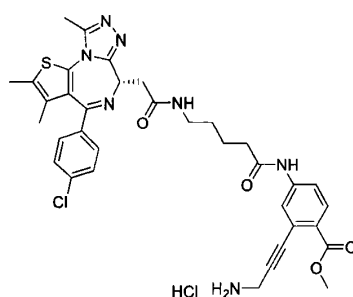
10 **【0668】**

【0669】 중간체 4-124'a와 중간체 3-25a로부터 제조예 1-1'과 동일한 방법으로 실시예 5-4'를 합성하였다.

【0670】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.62 (s, 1H), 8.54 - 8.35 (m, 4H), 8.14 (d, J = 2.2 Hz, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.63 (dd, J = 8.7, 2.2 Hz, 1H), 7.47 - 7.37 (m, 4H), 4.53 (dd, J = 8.1, 6.0 Hz, 1H), 4.05 (q, J = 5.6 Hz, 2H), 3.84 (s, 3H), 3.41 (dd, J = 10.0, 6.1 Hz, 2H), 3.29 - 3.16 (m, 2H), 2.61 (s, 5H), 2.42 (d, J = 0.9 Hz, 3H), 1.61 (s, 3H); MS m/z

$[M+H]^+$ 658.38.

- 【0671】 【제조예 5-5'】 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamido)benzoate hydrochloride



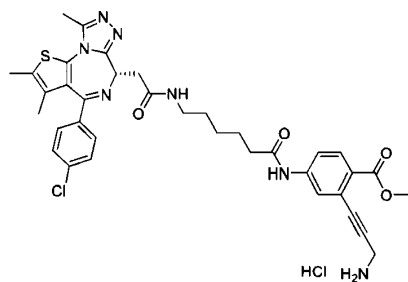
【0672】

- 【0673】 중간체 3-25a로부터 제조예 5-77'의 단계 2와 동일한 방법으로 실시예 5-5'를 합성하였다.

- 【0674】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.39 (s, 1H), 8.33 (s, 3H), 8.25 (t, $J = 5.6$ Hz, 1H), 8.15 (d, $J = 2.2$ Hz, 1H), 7.89 (d, $J = 8.7$ Hz, 1H), 7.53 (dd, $J = 8.7, 2.2$ Hz, 1H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.40 (d, $J = 8.6$ Hz, 2H), 4.50 (dd, $J = 8.4, 5.9$ Hz, 1H), 4.06 (q, $J = 5.7$ Hz, 2H), 3.83 (s, 3H), 3.26 (dd, $J = 15.0, 8.4$ Hz, 2H), 3.17 (dd, $J = 10.5, 4.4$ Hz, 2H), 2.59 (d, $J = 2.8$ Hz, 3H), 2.41 - 2.40 (m, 3H), 2.39 - 2.36 (m, 2H), 1.63 (d, $J = 8.2$ Hz, 2H), 1.60 (d, $J = 0.8$ Hz, 3H), 1.51 - 1.47 (m, 2H); MS m/z $[M+H]^+$ 686.47.

- 【0675】 【제조예 5-6'】 methyl (S)-2-(3-aminoprop-1-yn-1-

yl)-4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamido)benzoate hydrochloride



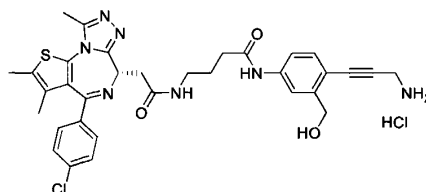
【0676】

5 【0677】 중간체 4-165'a 와 중간체 3-25a로부터 제조예 5-77'의 단계 2와 동일한 방법으로 실시예 5-6'를 합성하였다.

 【0678】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.36 (s, 1H), 8.32 (s, 3H), 8.21 (t, *J* = 5.7 Hz, 1H), 8.16 (d, *J* = 2.2 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.52 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 4.50 (dd, *J* = 8.1, 6.1 Hz, 1H), 4.05 (dd, *J* = 11.2, 5.6 Hz, 2H), 3.83 (s, 3H), 3.25 – 3.18 (m, 2H), 2.67 – 2.62 (m, 2H), 2.59 (s, 3H), 2.41 (s, 3H), 2.38 – 2.33 (m, 4H), 1.62 (s, 3H), 1.46 (q, *J* = 7.4 Hz, 2H), 1.35 (d, *J* = 7.1 Hz, 2H); MS *m/z* [M+ H]⁺ 700.47.

 【0679】 [제조예 5-8'] (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)butanamide hydrochloride



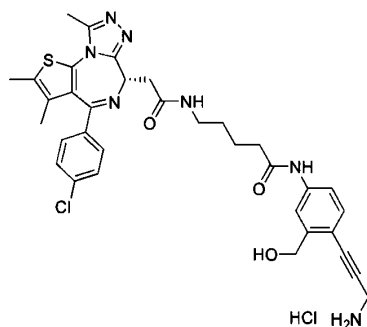
【0680】

【0681】 중간체 3-3c를 이용하여 제조예 4-125'와 동일한 방법으로 실시예 5-8'을 합성하였다.

5 【0682】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.15 (s, 1H), 8.30 (d, $J = 5.3$ Hz, 4H), 7.76 (d, $J = 2.2$ Hz, 1H), 7.63 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.51 – 7.42 (m, 2H), 7.41 (d, $J = 8.7$ Hz, 2H), 7.33 (d, $J = 8.4$ Hz, 1H), 4.77 (s, 1H), 4.62 (s, 2H), 4.51 (dd, $J = 8.1, 6.2$ Hz, 1H), 4.01 (q, $J = 5.6$ Hz, 2H), 3.20 – 3.08 (m, 2H), 2.60 (s, 3H), 2.41 (d, $J = 0.9$ Hz, 3H), 2.39 (s, 2H),
10 2.02 – 1.94 (m, 2H), 1.81 – 1.72 (m, 2H), 1.61 (d, $J = 1.0$ Hz, 3H); MS m/z $[\text{M} + \text{H}]^+$ 644.45.

【0683】 [제조예 5-9'] (S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)pentanamide hydrochloride



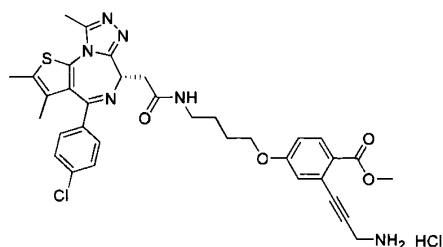
【0684】

【0685】 중간체 4-163'a 와 중간체 3-3c로부터 제조예 4-125'와 동일한 방법으로 실시예 5-9'를 합성하였다.

5 【0686】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.10 (s, 1H), 8.29 (s, 3H), 8.21 (t, $J = 5.6$ Hz, 1H), 7.70 (d, $J = 2.2$ Hz, 1H), 7.60 (dd, $J = 8.4$, 2.2 Hz, 1H), 7.43 (d, $J = 8.8$ Hz, 2H), 7.37 (d, $J = 8.5$ Hz, 2H), 7.28 (d, $J = 8.4$ Hz, 1H), 4.73 (s, 1H), 4.57 (s, 2H), 4.47 (dd, $J = 8.4$, 5.8 Hz, 1H), 3.96 (q, $J = 5.7$ Hz, 2H), 3.22 (dd, $J = 15.0$, 8.5 Hz, 2H), 3.13 (dd, $J = 10.5$, 4.5
10 Hz, 2H), 2.55 (s, 3H), 2.38 – 2.35 (m, 3H), 2.34 – 2.29 (m, 2H), 1.56 (d, $J = 0.9$ Hz, 3H), 1.48 – 1.39 (m, 4H); MS m/z $[\text{M} + \text{H}]^+$ 658.34.

【0687】 [제조예 5-12'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butoxy)benzoate

hydrochloride

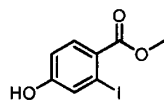


【0688】

【0689】 단계 1: methyl 4-hydroxy-2-iodobenzoate (중간체 5-12a)

5

【0690】



【0691】

Methyl 4-amino-2-iodobenzoate (1.0 mmol, 1.0 eq),
H₂SO₄ 0.3 mL, H₂O 3.0 mL의 혼합물을 0 °C 하에 교반하면서 소량의
H₂O로 녹인 Na₂NO₃ (1.0 eq)를 적가하였다. 30 분 뒤 반응물을 여과 후
여액을 30 분간 환류조건에서 교반하였다. 이후 반응온도를 실온으로 내린
10 뒤 18 시간 교반하였다. 반응물을 Et₂O로 추출 후 유기층을 MgSO₄로
건조한 뒤 감압여과 후 감압증류하여 추가정제 없이 중간체 5-12a를
합성하였다.

【0692】

단계

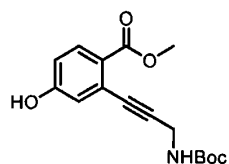
2:

methyl

2-(3-((tert-

butoxycarbonyl)amino)prop-1-yn-1-yl)-4-hydroxybenzoate (중간체 5-

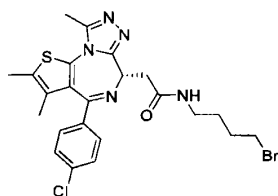
15 12b)



【0693】

【0694】 중간체 5-12a로부터 제조예 1-1의 단계 1과 동일한 방법으로 중간체 5-12b를 합성하였다.

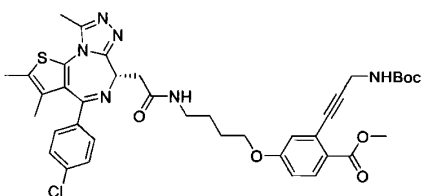
【0695】 단계 3: (S)-N-(4-bromobutyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide (중간체 5-12'a)



【0696】

【0697】 4-Bromobutan-1-amine hydrochloride로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-12'a를 합성하였다.

【0698】 단계 4: methyl (S)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butoxy)benzoate (중간체 5-12'b)



【0699】

【0700】 중간체 5-12'a (0.03 mmol, 1.0 eq), 중간체 5-12b (4.8 eq), K₂CO₃ (4.8 eq), TBAI (0.1 eq)에 dry DMF를 적가한 뒤 반응 용기 내 기체를 Ar 기체로 치환 후 100 °C에서 반응을 진행하였다. 2시간 뒤 반응물에 H₂O를 넣어 반응을 종결한 뒤 DCM을 이용하여 유기층으로
5 화합물을 추출한 후 유기층을 MgSO₄로 건조하였다. 감압여과 및 증류 후 flash column으로 정제하여 중간체 5-12'b를 합성하였다.

【0701】 단계 5: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butoxy)benzoate
10 hydrochloride

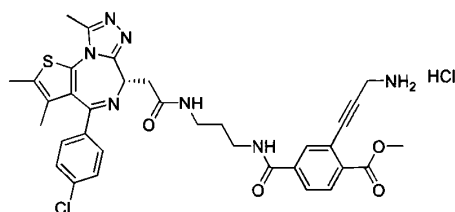
【0702】 중간체 5-12'b로부터 제조예 1-1의 단계 2 과 동일한 방법으로 실시예 5-12'을 합성하였다.

【0703】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.35 (s, 3H), 8.27 (t, *J* = 5.8 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.43 (q, *J* = 8.8 Hz, 4H), 7.11 - 7.06 (m, 2H), 4.50 (dd, *J* = 8.3, 6.0 Hz, 1H), 4.11 - 4.00 (m, 4H), 3.82 (s, 3H), 3.28 - 3.14 (m, 4H), 2.59 (s, 3H), 2.41 (s, 3H), 2.03 - 1.95 (m, 2H), 1.78 (q, *J* = 7.3 Hz, 2H), 1.63 - 1.56 (m, 3H); MS *m/z* [M+ H]⁺ 659.54.
15

【0704】 [제조예 5-18'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
20

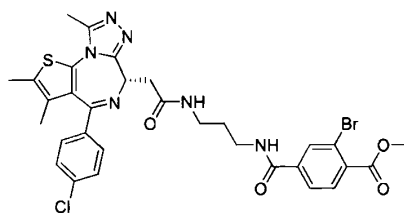
yl)acetamido)propyl)carbamoyl)benzoate hydrochloride

【0705】



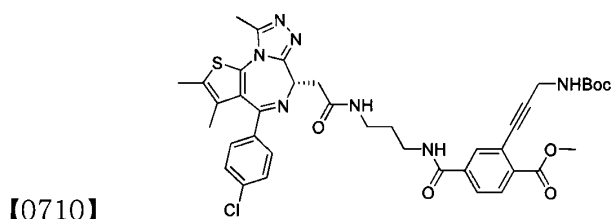
【0706】 단계 1: methyl (S)-2-bromo-4-(((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)carbamoyl)benzoate (중간체 5-18'a)

【0707】



【0708】 중간체 4-166'a와 3-bromo-4-(methoxycarbonyl)benzoic acid로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-18'a를 합성하였다.

【0709】 단계 2: methyl (S)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)carbamoyl)benzoate (중간체 5-18'b)



【0711】 중간체 5-18'a로부터 제조예 4-179'의 단계 2와 동일한 방법으로 중간체 5-18'b를 합성하였다.

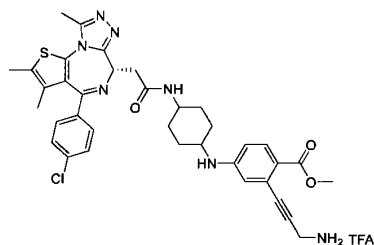
【0712】 단계 3: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-
5 ((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
yl)acetamido)propyl)carbamoyl)benzoate hydrochloride

【0713】 중간체 5-18'b로부터 제조예 1-1의 단계 2와 동일한 방법으로 실시예 5-18'을 합성하였다.

10 【0714】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.80 (t, $J = 5.6$ Hz, 1H), 8.42 (s, 3H), 8.30 (t, $J = 5.7$ Hz, 1H), 8.07 (t, $J = 1.2$ Hz, 1H), 7.99 – 7.97 (m, 2H), 7.49 – 7.39 (m, 4H), 4.51 (dd, $J = 8.1, 6.1$ Hz, 1H), 4.06 (q, $J = 5.7$ Hz, 2H), 3.89 (s, 3H), 3.38 – 3.10 (m, 6H), 2.60 (s, 3H), 2.41 (s, 3H), 1.72 (p, $J = 6.9$ Hz, 2H), 1.60 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 672.42.

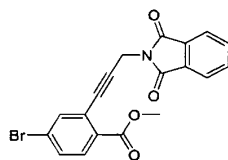
15 【0715】 [제조예 5-35'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)cyclohexyl)amino)benzoate trifluoroacetic acid



【0716】

【0717】 단계 1: methyl 4-bromo-2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)benzoate (중간체 5-35a)

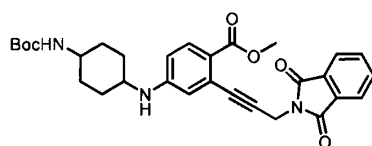


5

【0718】

【0719】 Methyl 4-bromo-2-iodobenzoate(2.0 mmol, 1.0 eq), n-propargylphthalimide (1.1 eq), Pd(PPh₃)₄ (0.01 eq), CuI (0.05 eq) 와 ACN 7.0 mL를 혼합한 후 반응용기 내 기체를 Ar 기체로 치환하였다. 반응물을 3 시간동안 실온에서 교반한 후 celite를 통해 감압여과 한 뒤
10 감압증류하였다. 혼합물은 flash column으로 정제하여 중간체 5-35a를 합성하였다.

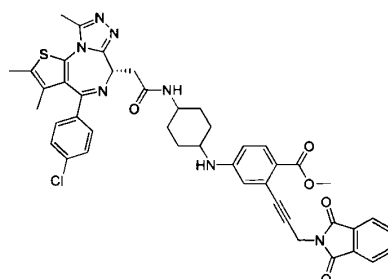
【0720】 단계 2: methyl 4-((4-((tert-butoxycarbonyl)amino)cyclohexyl)amino)-2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)benzoate (중간체 5-35b)



【0721】

【0722】 중간체 5-35a와 tert-butyl(4-aminocyclohexyl)carbamate로부터 제조예 5-40의 단계 1와 동일한 방법으로 중간체 5-35b를 합성하였다.

5 【0723】 단계 3: methyl (S)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)cyclohexyl)amino)-2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)benzoate (중간체 5-35'a)



【0724】

10 【0725】 중간체 5-35b로부터 제조예 4-1'의 단계 4 내지 5와 동일한 방법으로 중간체 5-35'a를 합성하였다.

【0726】 단계 4: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)cyclohexyl)amino)benzoate trifluoroacetic acid

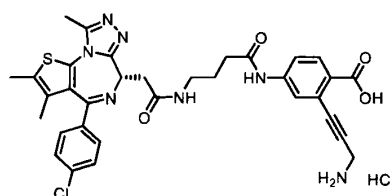
15

【0727】 중간체 5-35'a로부터 제조예 5-85'의 단계 5과 동일한 방법으로 실시예 5-35'을 합성하였다.

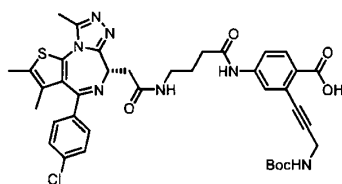
【0728】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.26 (s, 3H), 8.13 (t, $J = 7.2$ Hz, 1H), 7.67 (dd, $J = 8.8, 4.8$ Hz, 1H), 7.53 – 7.32 (m, 4H), 6.77 – 6.53 (m, 2H), 4.46 (dd, $J = 8.4, 5.9$ Hz, 1H), 3.99 (q, $J = 5.7$ Hz, 2H), 3.71 (s, 2H), 3.16 – 3.09 (m, 5H) 2.55 (s, 3H), 2.37 (s, 3H), 1.65 (d, $J = 23.1$ Hz, 8H), 1.98 – 1.84 (m, 2H), 1.57 (d, $J = 4.7$ Hz, 3H); MS m/z $[\text{M} + \text{H}]^+$ 684.61.

【0729】 [제조예 5-53'] (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoic acid hydrochloride

【0730】



【0731】 단계 1: (S)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoic acid (중간체 5-53'a)



【0732】

【0733】 중간체 4-228'a로부터 제조예 3-2'의 단계 1과 동일한 방법으로 중간체 5-53'a를 합성하였다.

【0734】 단계 2: (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-
5 (4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
yl)acetamido)butanamido)benzoic acid hydrochloride

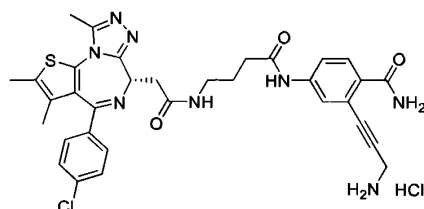
【0735】 중간체 5-53'a로부터 제조예 1-1의 단계 2와 동일한 방법으로 실시예 5-53'을 합성하였다.

10 【0736】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.39 (s, 1H), 8.34 (s, 4H), 8.15 (d, $J = 2.3$ Hz, 1H), 7.88 (d, $J = 8.6$ Hz, 1H), 7.46 – 7.41 (m, 5H), 4.51 (dd, $J = 8.0, 6.4$ Hz, 1H), 4.04 (q, $J = 5.7$ Hz, 2H), 3.67 (dd, $J = 4.8, 1.4$ Hz, 2H), 3.26 – 3.23 (m, 2H), 3.21 – 3.17 (m, 2H), 2.60 (s, 3H), 2.41 (s, 3H), 1.78 (d, $J = 7.5$ Hz, 2H), 1.61 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 658.37.

15 【0737】 [제조예 5-59'] (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)butanamido)benzamide hydrochloride

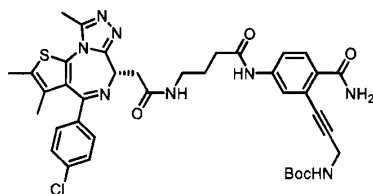
【0738】



【0739】

단계 1: tert-butyl (S)-3-(2-carbamoyl-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)phenyl)prop-2-yn-1-yl)carbamate (중간체 5-59'a)

【0740】



【0741】

중간체 5-53'a (0.04 mmol, 1.0 eq)를 DCM 1.0 mL에 녹인 후 SOCl_2 를 소량 적가한 다음, 환류 조건에서 1 시간 교반하였다. 반응 온도를 0 °C로 내린 뒤 암모니아수 2.0 mL를 천천히 적가한 후 실온에서 18 시간 교반하였다. 반응물을 Na_2SO_4 로 건조한 뒤 감압여과하였다. 혼합물을 감압증발한 뒤 flash column으로 정제하여 중간체 5-59'a를 합성하였다.

15

【0742】

단계 2: (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzamide hydrochloride

【0743】 중간체 5-59'a로부터 제조예 1-1의 단계 2 와 동일한 방법으로 실시예 5-59'을 합성하였다.

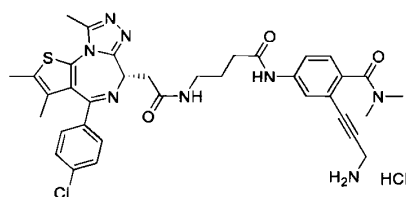
5 【0744】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.27 (s, 1H), 8.31 (dd, J = 11.8, 6.3 Hz, 4H), 8.06 (d, J = 2.2 Hz, 1H), 7.65 (s, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.49 – 7.45 (m, 3H), 7.43 – 7.41 (m, 3H), 4.51 (dd, J = 7.9, 6.4 Hz, 1H), 4.02 (t, J = 5.6 Hz, 2H), 3.50 – 3.48 (m, 2H), 3.21 (ddd, J = 27.8, 11.7, 7.6 Hz, 4H), 2.60 (s, 3H), 2.42 – 2.41 (m, 3H), 1.78 (d, J = 7.4

10 Hz, 2H), 1.62 – 1.61 (m, 3H); MS m/z $[\text{M} + \text{H}]^+$ 657.44.

【0745】 [제조예 5-61'] (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-N,N-dimethylbenzamide hydrochloride

15

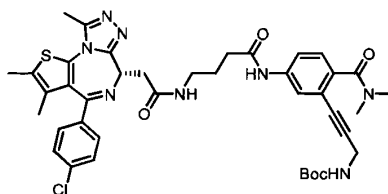
【0746】



【0747】 단계 1: tert-butyl (S)-3-(5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-2-

(dimethylcarbamoyl)phenyl)prop-2-yn-1-yl)carbamate (중간체 5-61'a)

【0748】



【0749】 중간체 5-53'a (0.03 mmol, 1.0 eq)를 dry DCE 0.8

mL에 녹인 후 반응 용기 내 기체를 Ar 기체로 치환하였다. DEA (2.0 M in

5 THF) 0.01 mL를 적가한 뒤 실온에서 5 분 교반하였다. DCC (1.5 eq), HOBT

(1.5 eq)를 추가로 혼합한 뒤 70 °C에서 3 시간 반응하였다. 반응물을

감압증류한 후 flash column으로 정제하여 중간체 5-61'a를 합성하였다.

【0750】 단계 2: (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-

(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

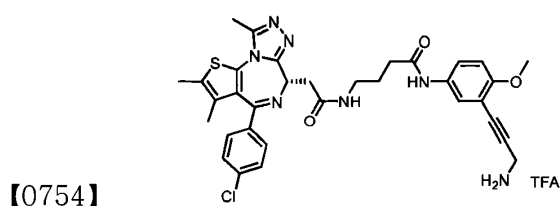
10 f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-N,N-
dimethylbenzamide hydrochloride

【0751】 중간체 5-61'a로부터 제조예 1-1의 단계 2와 동일한
방법으로 실시예 5-61'을 합성하였다.

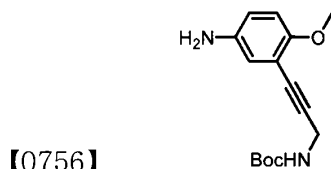
【0752】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.27 (s, 1H), 8.36
15 (s, 3H), 8.33 – 8.30 (m, 1H), 8.03 (d, *J* = 2.1 Hz, 1H), 7.51 (dd, *J* = 8.4, 2.2
Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.4
Hz, 1H), 4.54 – 4.51 (m, 1H), 4.01 (d, *J* = 5.7 Hz, 2H), 3.71 – 3.67 (m, 2H),
3.27 – 3.16 (m, 4H), 3.01 (s, 3H), 2.81 (s, 3H), 2.60 (s, 3H), 2.41 (s, 3H),

1.80 – 1.76 (m, 2H), 1.61 (s, 3H); MS m/z [M+H]⁺ 685.61.

【0753】 [제조예 5-63'] (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-methoxyphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide trifluoroacetic acid



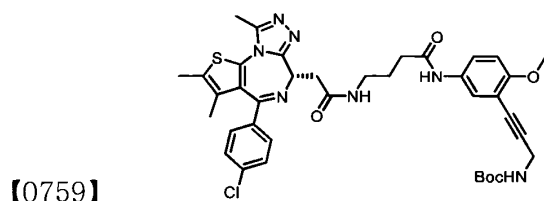
【0755】 단계 1: tert-butyl (3-(5-amino-2-methoxyphenyl)prop-2-yn-1-yl)carbamate (중간체 5-63a)



10 **【0757】** 3-Iodo-4-methoxyaniline로부터 제조예 1-1의 단계 1과 동일한 방법으로 중간체 5-63a를 합성하였다.

【0758】 단계 2: tert-butyl (S)-(3-(5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-2-methoxyphenyl)prop-2-yn-1-yl)carbamate(중간체 5-63'a)

15



【0760】 중간체 4-162'a와 5-63a로부터 제조예 4-1'의 단계

5와 동일한 방법으로 중간체 5-63'b를 합성하였다.

【0761】 단계 3: (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-methoxyphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide trifluoroacetic acid

【0762】 중간체 5-63'a로부터 제조예 4-1'의 단계 4와 동일한 방법으로 실시예 5-63'을 합성하였다.

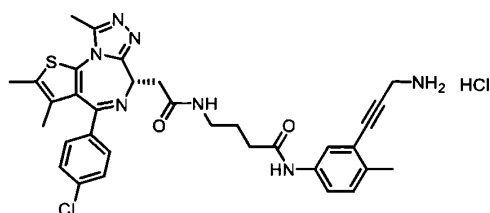
10 【0763】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.89 (s, 1H), 8.27 (d, $J = 6.5$ Hz, 3H), 7.89 (d, $J = 2.7$ Hz, 1H), 7.47 – 7.39 (m, 6H), 7.04 (d, $J = 9.1$ Hz, 1H), 4.50 (dd, $J = 8.2, 6.2$ Hz, 1H), 4.03 (d, $J = 5.6$ Hz, 2H), 3.78 (s, 3H), 3.20 (ddt, $J = 37.0, 23.1, 6.8$ Hz, 6H), 2.60 (s, 3H), 2.41 (d, $J = 0.9$ Hz, 4H), 2.34 (t, $J = 7.5$ Hz, 2H), 1.79 – 1.73 (m, 2H), 1.62 – 1.61 (m, 3H); MS

15 m/z $[\text{M} + \text{H}]^+$ 644.45.

【0764】 [제조예 5-65'] (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-methylphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)butanamide hydrochloride

【0765】



【0766】 3-Iodo-4-methylaniline로부터 제조예 5-77'과

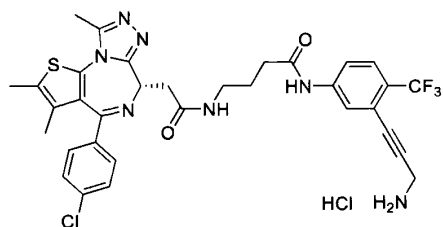
동일한 방법으로 실시예 5-65'를 합성하였다.

5 【0767】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.162 (s, 1H), 8.531 (brs, 3H), 8.351(t, $J = 1.3\text{Hz}$, 1H), 7.878(d, $J = 0.2\text{ Hz}$), 7.481 – 7.411 (m, 5H), 7.203(d, 1.1 Hz, 1H), 4.572 (t, $J = 1.6\text{ Hz}$, 1H), 4.016 (d, $J = 0.2\text{ Hz}$, 2H), 3.282 – 3.163 (m, 4H), 2.644 (s, 3H), 2.416 (s, 3H), 2.396 – 2.357 (m, 2H), 2.338 (s, 3H), 1.798 – 1.743 (m, 2H), 1.612 (s, 3H); MS m/z

10 $[\text{M} + \text{H}]^+$ 628.4.

【0768】 [제조예 5-75'] (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(trifluoromethyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride

【0769】

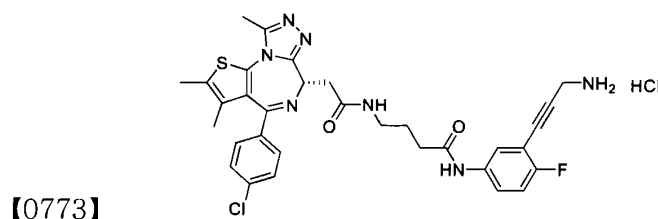


15

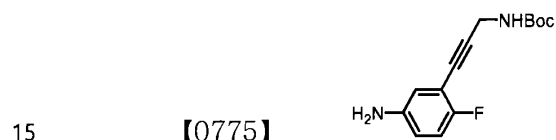
【0770】 3-Iodo-4-(trifluoromethyl)aniline로부터 제조예 5-77'과 동일한 방법으로 실시예 5-75'를 합성하였다.

【0771】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.18 (s, 1H), 9.03 (s, 1H), 8.75 (s, 1H), 8.62 (s, 1H), 8.34 (s, 3H), 8.20 (s, 1H), 7.95 (s, 2H), 7.94 (s, 1H), 7.71 (s, 1H), 7.57 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.5$ Hz, 1H), 7.10 (s, 1H), 7.08 (s, 1H), 4.55 (s, 2H), 3.92 (s, 2H), 3.80 (s, 3H), 3.13 (s, 2H), 2.38 (s, 2H), 1.85 (s, 2H); MS m/z $[\text{M} + \text{H}]^+$ 682.41.

【0772】 [제조예 5-77'] (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-fluorophenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride



【0774】 단계 1: tert-butyl (3-(5-amino-2-fluorophenyl)prop-2-yn-1-yl)carbamate (중간체 5-77a)



【0776】 4-Fluoro-3-iodoaniline (1.0 mmol, 1.0 eq), n-boc

propargylamine (1.5 eq), Pd(PPh₃)₄ (0.1 eq), CuI (0.2 eq)에 TEA 3.0 mL를 적가하였다. 반응 용기 내 기체를 Ar 기체로 치환한 뒤 70 °C에서 밤새 교반하였다. Celite를 이용하여 감압여과 후 증발하였다. 혼합물을 flash column으로 정제하여 중간체 5-77a를 합성하였다.

5 **【0777】** 단계 2: (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-fluorophenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride

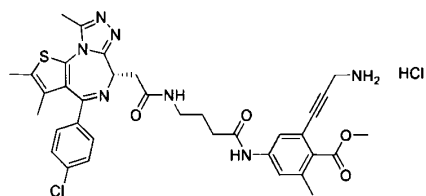
【0778】 중간체 4-162'a와 5-77a로부터 제조예 4-1'의 단계
10 5, 제조예 1-1의 단계 2와 동일한 방법을 순차적으로 적용하여 제조예 5-77'를 합성하였다.

【0779】 ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.368 (s, 1H), 8.530 (brs, 3H), 8.354 – 8.341 (m, 1H), 7.994 – 7.972 (m, 1H), 7.574 (s, 1H), 7.475 – 7.407 (m, 4H), 7.288 – 7.242 (m, 1H), 4.573 – 4.538 (m, 1H), 4.044 – 4.031 (m, 2H), 3.275 – 3.132 (m, 4H), 2.632 (s, 3H), 2.414 (s, 15 3H), 2.390 – 2.371 (m, 2H), 1.779 – 1.747 (m, 2H), 1.611 (s, 3H); ¹⁹F NMR (400 MHz, DMSO-*d*₆) -117.332; MS m/z [M+ H]⁺ 632.10.

【0780】 [제조예 5-78'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
20 f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-6-

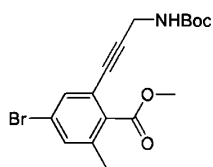
methylbenzoate hydrochloride

【0781】



【0782】 단계 1: methyl 4-bromo-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-6-methylbenzoate (중간체 5-78a)

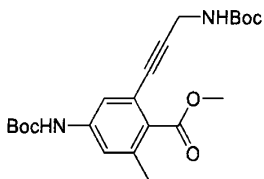
【0783】



【0784】 Methyl 4-bromo-2-iodo-6-methylbenzoate로부터
제조예 1-1의 단계 1과 동일한 방법으로 중간체 5-78a을 합성하였다.

【0785】 단계 2: methyl 4-((tert-butoxycarbonyl)amino)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-6-methylbenzoate
(중간체 5-78b)

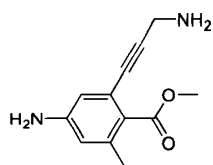
【0786】



【0787】 중간체 5-78a (0.5 mmol, 1.0 eq), tert-butyl carbamate (3.0 eq), BrettPhos Pd G3 (0.1 eq), CS₂CO₃ (3.0 eq), dioxane

1.5 mL를 혼합한 뒤 100 °C에서 밤새 교반하였다. 반응물은 EtOAc, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 5-78b를 합성하였다.

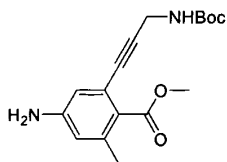
【0788】 단계 3: methyl 4-amino-2-(3-aminoprop-1-yn-1-yl)-6-methylbenzoate (중간체 5-78c)



【0789】

【0790】 중간체 5-78b로부터 제조예 1-1의 단계 2와 동일한 방법으로 중간체 5-78c를 합성하였다.

【0791】 단계 4: methyl 4-amino-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-6-methylbenzoate (중간체 5-78d)



【0792】

【0793】 중간체 5-78c (0.1 mmol, 1.0 eq)을 DCM 3.0 mL에 녹인 후 0 °C에서 TEA (3.0 eq), Boc₂O (1.0 eq)를 천천히 적가해 2 시간 교반하였다. 반응물은 DCM, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 5-78d를 합성하였다.

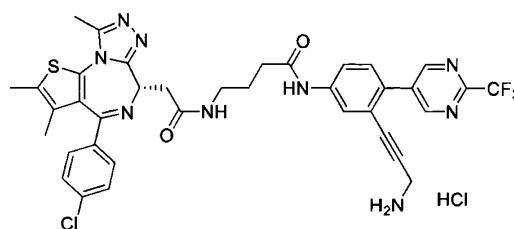
【0794】 단계 5: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-6-methylbenzoate hydrochloride

5 【0795】 중간체 5-78d로부터 제조예 5-77'의 단계 2 내지 3과 동일한 방법으로 실시예 5-78'을 합성하였다.

【0796】 ^1H NMR (400 MHz, DMSO- d_6) δ 10.38 (s, 1H), 8.50 (s, 3H), 8.34 (t, $J = 14$ Hz, 1H), 7.86 (s, 1H), 7.48 – 7.41 (m, 5H), 4.56 – 4.53 (m, 1H), 4.00 – 3.98 (m, 2H), 3.86 (s, 3H), 3.27 – 3.15 (m, 2H), 2.62 (s, 3H), 2.41 (s, 5H), 2.25 (s, 3H), 1.80 – 1.76 (m, 2H), 1.61 (s, 3H); MS m/z [M+H] $^+$ 686.4.

【0797】 [제조예 5-81'] (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride

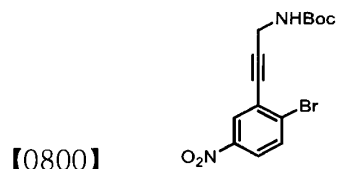
【0798】



【0799】

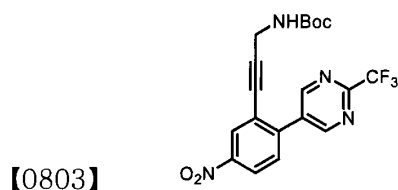
단계 1: tert-butyl (3-(2-bromo-5-nitrophenyl)prop-

2-yn-1-yl)carbamate (5-81a)



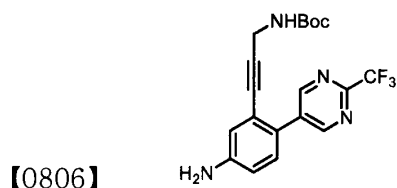
【0801】 Bromo-2-iodo-4-nitrobenzene로부터 제조예 5-89'의 단계 1과 동일한 방법으로 중간체 5-81a을 합성하였다.

5 【0802】 단계 2: tert-butyl (3-(5-nitro-2-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)prop-2-yn-1-yl)carbamate (중간체 5-81b)



【0804】 중간체 5-81a (3.0 mmol, 1.0 eq), (2-(trifluoromethyl)pyrimidin-5-yl)boronic acid (1.1 eq), Pd(dppf)Cl₂ (0.1 eq), K₂CO₃ (2.0 eq), dioxane/H₂O 10.0 mL를 혼합한 뒤 50 °C에서 12 시간 교반하였다. 반응물은 flash column으로 정제하여 중간체 화합물 5-81b를 합성하였다.

【0805】 단계 3: tert-butyl (3-(5-amino-2-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)prop-2-yn-1-yl)carbamate (중간체 5-81c)



【0807】 중간체 5-81b (1.5 mmol, 1.0 eq), Fe (3.0 eq), NH₄Cl (5.0 eq), EtOH/H₂O를 80 °C에서 2 시간 교반하였다. 반응물은 flash column으로 정제하여 중간체 5-81c를 합성하였다.

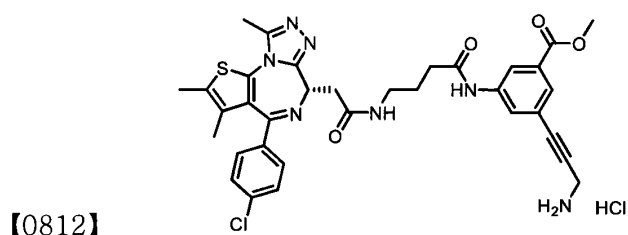
5 【0808】 단계 4: (S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride

10 【0809】 중간체 5-81c로부터 제조예 5-77'의 단계 2 내지 3과 동일한 방법으로 실시예 5-81'을 합성하였다.

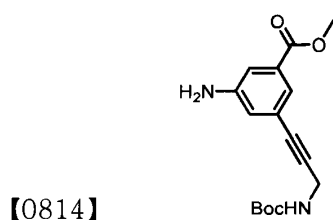
15 【0810】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.36 (s, 1H), 9.25 (s, 2H), 8.28 (dd, *J* = 13.5, 7.6 Hz, 4H), 8.18 (t, *J* = 1.3 Hz, 1H), 7.62 (d, *J* = 1.8 Hz, 2H), 7.42 (d, *J* = 8.9 Hz, 2H), 7.40 – 7.35 (m, 2H), 4.48 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.91 (q, *J* = 5.6 Hz, 2H), 3.51 (s, 1H), 3.27 – 3.07 (m, 4H), 2.56 (s, 3H), 2.43 – 2.34 (m, 5H), 1.76 (q, *J* = 7.3 Hz, 2H), 1.58 (d, *J* = 0.9 Hz, 3H); MS *m/z* [M+ H]⁺ 760.44.

 【0811】 [제조예 5-89'] methyl (S)-3-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
yl)acetamido)butanamido)benzoate hydrochloride



【0813】 단계 1: methyl 3-amino-5-(3-((tert-
5 butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate (중간체 5-89a)



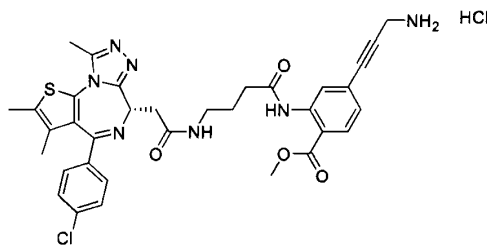
【0815】 Methyl 3-amino-5-bromobenzoate (4.0 mmol, 1.0
eq), n-boc propargylamine (2.0 eq), Xphos Pd G₄ (0.03 eq), CuI (0.1 eq),
Cs₂CO₃ (3.0 eq), dry toluene 10.0 mL을 혼합한 뒤 100 °C에서 12 시간
10 교반하였다. 반응물을 celite를 통해 감압여과하였다. 혼합물을 감압증발 후
flash column으로 정제하여 중간체 5-89a를 합성하였다.

【0816】 단계 2: methyl (S)-3-(3-(3-aminoprop-1-yn-1-yl)-5-
(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
15 yl)acetamido)butanamido)benzoate hydrochloride

【0817】 중간체 5-89a로부터 제조예 5-77'의 단계 2 내지 3과 동일한 방법으로 실시예 5-89'를 합성하였다.

【0818】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.26 (s, 1H), 8.26 (t, $J = 5.8$ Hz, 1H), 8.13 (s, 1H), 7.96 (s, 1H), 7.54 (s, 1H), 7.44 – 7.35 (m, 6H), 4.46 (dd, $J = 8.3, 6.0$ Hz, 1H), 3.81 (s, 3H), 3.57 (s, 3H), 3.17 (d, $J = 6.4$ Hz, 2H), 3.11 – 3.08 (m, 2H), 2.55 (s, 3H), 2.36 (s, 3H), 1.74 (q, $J = 7.2$ Hz, 3H), 1.57 (s, 4H); MS m/z $[\text{M} + \text{H}]^+$ 672.52.

【0819】 [제조예 5-90'] methyl (S)-4-(3-aminoprop-1-yn-1-yl)-2-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride



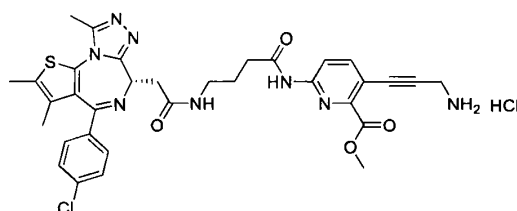
【0820】

【0821】 Methyl 2-amino-4-iodobenzoate로부터 실시예 5-77'과 동일한 방법으로 실시예 5-90'을 합성하였다.

【0822】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.61 (s, 1H), 8.36 (d, $J = 1.7$ Hz, 1H), 8.29 (t, $J = 5.7$ Hz, 1H), 7.87 (d, $J = 8.2$ Hz, 1H), 7.49 – 7.38 (m, 6H), 7.16 (dd, $J = 8.2, 1.7$ Hz, 1H), 4.49 (dd, $J = 8.3, 5.9$ Hz, 1H),

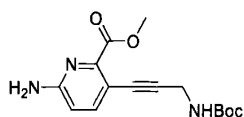
3.81 (s, 3H), 3.52 (s, 2H), 3.26 – 3.22 (m, 2H), 3.14 (ddd, $J = 16.9, 7.9, 5.6$ Hz, 2H), 2.58 (d, $J = 2.6$ Hz, 3H), 2.40 (d, $J = 0.9$ Hz, 4H), 1.80 (dd, $J = 13.9, 6.7$ Hz, 3H), 1.61 (t, $J = 1.2$ Hz, 4H); MS m/z $[M+H]^+$ 672.52.

【0823】 [제조예 5-96'] methyl (S)-3-(3-aminoprop-1-yn-1-yl)-6-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)picolinate hydrochloride



【0824】

【0825】 단계 1: methyl 6-amino-3-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)picolinate (중간체 5-96a)



【0826】

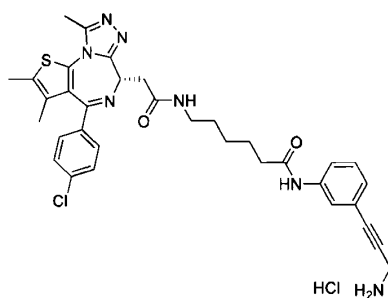
【0827】 Methyl 6-amino-3-bromopicolinate을 이용하여 제조예 5-89'의 단계 1과 동일한 방법으로 중간체 5-96a를 합성하였다.

【0828】 단계 2: methyl (S)-3-(3-aminoprop-1-yn-1-yl)-6-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)picolinate hydrochloride

【0829】 중간체 5-96a로부터 제조예 5-77'의 단계 2 내지 3과 동일한 방법으로 실시예 5-96'를 합성하였다.

【0830】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.99 (s, 1H), 8.30 (d, $J = 8.8$ Hz, 1H), 8.26 (s, 4H), 8.22 (t, $J = 5.7$ Hz, 1H), 7.97 (d, $J = 8.7$ Hz, 1H), 7.45 – 7.39 (m, 2H), 7.39 – 7.33 (m, 2H), 4.46 (dd, $J = 8.3, 6.0$ Hz, 1H), 4.02 (q, $J = 5.6$ Hz, 2H), 3.85 (s, 3H), 3.26 – 3.04 (m, 4H), 2.55 (s, 5H), 2.37 (d, $J = 0.8$ Hz, 3H), 1.72 (p, $J = 7.2$ Hz, 2H), 1.57 (d, $J = 0.8$ Hz, 3H); MS m/z $[\text{M} + \text{H}]^+$ 673.42.

【0831】 【제조예 5-104'】 (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamide hydrochloride



【0832】

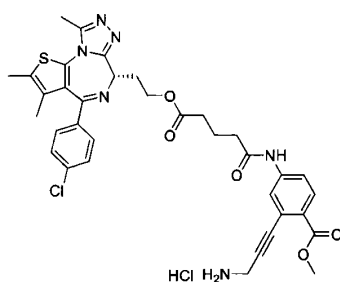
【0833】 중간체 4-165'a 와 중간체 1-3a로부터 제조예 5-77'의 단계 2 내지 3과 동일한 방법으로 실시예 5-104'을 합성하였다.

【0834】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.09 (s, 1H), 8.35 (s, 3H), 8.19 (s, 1H), 7.92 (s, 1H), 7.46 (d, $J = 8.8$ Hz, 4H), 7.38 (d, $J = 8.5$

Hz, 2H), 7.29 (t, $J = 7.9$ Hz, 1H), 7.07 (d, $J = 10.1$ Hz, 1H), 4.50 – 4.46 (m, 1H), 3.96 (t, $J = 5.6$ Hz, 2H), 3.24 – 3.12 (m, 2H), 3.10 – 3.03 (m, 2H), 2.57 (s, 3H), 2.37 (s, 3H), 2.28 (t, $J = 7.5$ Hz, 2H), 1.57 (d, $J = 7.2$ Hz, 6H), 1.47 – 1.40 (m, 2H), 1.34 – 1.27 (m, 2H); MS m/z $[M+H]^+$ 642.45.

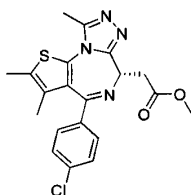
- 5 **【0835】** **[제조예 5-106'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethoxy)-5-oxopentanamido)benzoate hydrochloride**

【0836】



- 10 **【0837】** 단계 1: methyl (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetate (중간체 5-106'a)

【0838】

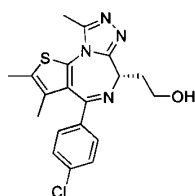


- 【0839】** JQ1 carboxylic acid (1.5 mmol, 1.0 eq)를 MeOH 8.0

- 15 mL에 녹인 후 SOCl_2 (3.0 eq)를 적가하였다. 실온에서 3 시간 교반 후 감압

하에 용매를 제거한 다음 DCM을 적가 후 재감압을 통해 잔여 용매를 제거하였다. EtOAc 소량으로 화합물을 녹인 뒤 n-hexane을 이용한 재결정으로 생성된 고체를 여과하여 추가적 정제과정 없이 중간체 5-106'a를 합성하였다.

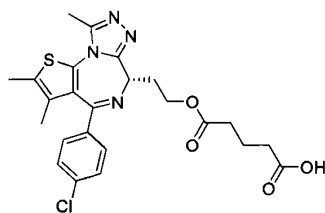
- 5 【0840】 단계 2: (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-ol
(중간체 5-106'b)



【0841】

- 【0842】 중간체 5-106'a (0.3 mmol, 1.0 eq)를 dry THF 3.0
10 mL에 녹인 뒤 0 °C에서 교반한다. 1.0 M lithium aluminium hydride solution
in THF (1.5 eq)를 10 분간 천천히 적가 하였다. 5 분 뒤 얼음물을 가해
반응을 종결하였다. 혼합물에 2N HCl 수용액을 적가하여 pH 3까지
산성화하였다. EtOAc와 H₂O로 추출 후 유기층을 NaHCO₃와 NaCl
수용액으로 씻어주었다. 유기층을 Na₂SO₄로 건조한 뒤 감압여과 후
15 증발시켜 추가적 정제과정 없이 중간체 5-106'b를 합성하였다.

 【0843】 단계 3: (S)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethoxy)-5-oxopentanoic acid (중간체 5-106'c)



【0844】

【0845】 중간체 5-106'b (0.1 mmol, 1.0 eq), glutaric acid (2.0 eq)를 dry DCM에 녹인 뒤 실온에서 교반하였다. DCC (1.1 eq), DMAP (1.1 eq)를 적가한 뒤 18 시간 교반하였다. 반응 후 생긴 침전물을 여과한 후
5 여액을 flash column으로 정제하여 중간체 5-106'c를 합성하였다.

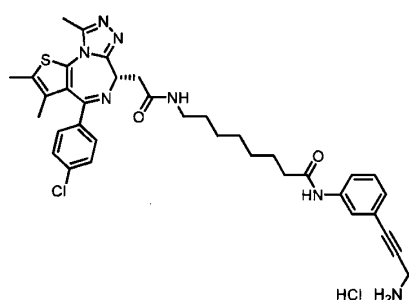
【0846】 단계 4: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethoxy)-5-oxopentanamido)benzoate hydrochloride

10 【0847】 중간체 5-106'c와 중간체 3-25a로부터 제조예 5-77'의 단계 2 내지 3과 동일한 방법으로 실시예 5-106'을 합성하였다.

【0848】 ^1H NMR (500 MHz, DMSO- d_6) δ 7.89 – 7.82 (m, 1H), 7.50 – 7.45 (m, 7H), 7.21 (s, 1H), 6.67 (s, 1H), 4.44 – 4.39 (m, 2H), 4.18 – 4.15 (m, 1H), 4.05 (s, 2H), 3.79 (s, 3H), 2.65 – 2.63 (m, 2H), 2.59 (s, 3H), 2.36 (s, 3H), 2.18 (t, J = 7.3 Hz, 2H), 2.02 (s, 2H), 1.60 (s, 3H); MS
15 m/z $[\text{M} + \text{H}]^+$ 687.31.

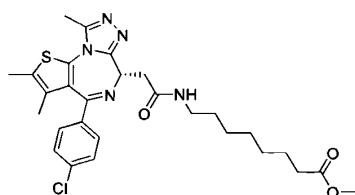
【0849】 [제조예 5-107'] (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-8-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)octanamide
hydrochloride



【0850】

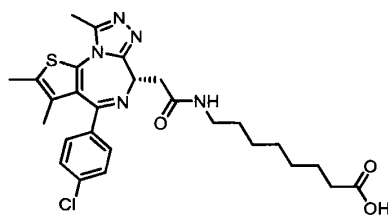
【0851】 단계 1: methyl (S)-8-(2-(4-(4-chlorophenyl)-2,3,9-
5 trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
yl)acetamido)octanoate(중간체 5-107'a)



【0852】

【0853】 Methyl 8-aminooctanoate로부터 제조예 4-1'의 단계
5와 동일한 방법으로 중간체 5-107'a를 합성하였다.

10 【0854】 단계 2: (S)-8-(2-(4-(4-chlorophenyl)-2,3,9-
trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
yl)acetamido)octanoic acid (중간체 5-107'b)



【0855】

【0856】 중간체 5-107'a로부터 3-2'의 단계 1과 동일한 방법으로 중간체 5-107'b를 합성하였다.

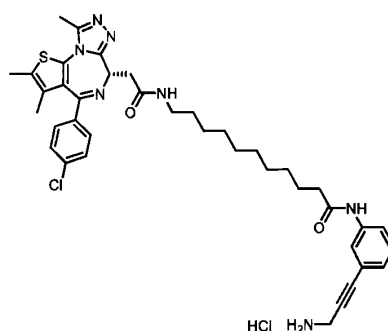
【0857】 단계 3: (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-8-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)octanamide hydrochloride

【0858】 중간체 5-107'b와 중간체 1-3a로부터 제조예 5-77'의 단계 2 내지 3과 동일한 방법으로 실시예 5-107'을 합성하였다.

10 【0859】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.12 (s, 1H), 8.42 (s, 3H), 8.17 (t, J = 5.6 Hz, 1H), 7.90 (t, J = 1.9 Hz, 1H), 7.50 - 7.43 (m, 3H), 7.41 - 7.36 (m, 2H), 7.28 (t, J = 7.9 Hz, 1H), 7.07 (dt, J = 7.7, 1.3 Hz, 1H), 4.49 (dd, J = 8.0, 6.1 Hz, 1H), 3.95 (q, J = 5.7 Hz, 2H), 3.24 - 3.12 (m, 2H), 3.06 (dq, J = 22.0, 6.4 Hz, 2H), 2.58 (s, 3H), 2.37 (d, J = 1.0 Hz, 3H), 2.27 (t, J = 7.5 Hz, 2H), 1.58 (d, J = 1.0 Hz, 3H), 1.56 - 1.50 (m, 2H), 1.42 - 1.36 (m, 2H), 1.25 (s, 6H); MS m/z $[\text{M} + \text{H}]^+$ 670.53.

15 【0860】 [제조예 5-108'] (S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-11-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)undecanamide
hydrochloride



【0861】

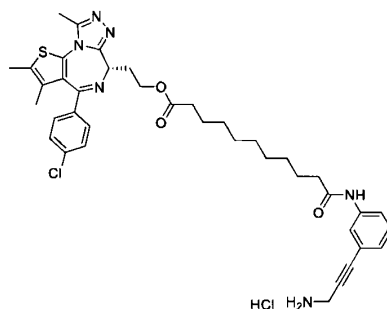
【0862】 Methyl 11-aminoundecanoate로부터 제조예 5-

5 107'과 동일한 방법으로 실시예 5-108'을 합성하였다.

【0863】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.05 (s, 1H), 8.34 (s, 3H), 8.15 (t, $J = 5.6$ Hz, 1H), 7.91 (s, 1H), 7.44 (d, $J = 8.8$ Hz, 4H), 7.38 (d, $J = 8.6$ Hz, 2H), 7.29 (t, $J = 7.9$ Hz, 1H), 7.07 (d, $J = 7.7$ Hz, 1H), 4.50 - 4.45 (m, 1H), 3.96 (q, $J = 5.7$ Hz, 2H), 3.25 - 3.17 (m, 2H), 3.15 - 3.05 (m, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 2.26 (t, $J = 7.5$ Hz, 2H), 1.58 (s, 3H), 1.56 - 1.50 (m, 2H), 1.41 - 1.36 (m, 2H), 1.22 (s, 14H); MS m/z $[\text{M} + \text{H}]^+$ 712.58.

【0864】 [제조예 5-109'] (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethyl 11-((3-(3-aminoprop-1-yn-1-yl)phenyl)amino)-11-oxoundecanoate

hydrochloride



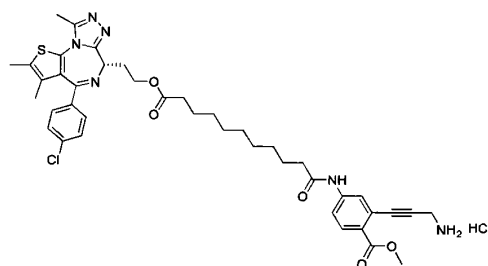
【0865】

【0866】 중간체 5-106'b, undecanedioic acid, 중간체 1-3a를 이용하여 제조예 5-106'의 단계 3 내지 4와 동일한 방법으로 중간체 5-109'a((S)-11-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethoxy)-11-oxoundecanoic acid)를 거쳐 실시예 5-109'을 합성하였다.

【0867】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.03 (s, 1H), 8.28 (s, 3H), 7.97 (d, J = 2.0 Hz, 1H), 7.49 (t, J = 9.1 Hz, 6H), 7.33 (t, J = 7.9 Hz, 1H), 7.11 (dt, J = 7.6, 1.3 Hz, 1H), 4.48 - 4.42 (m, 1H), 4.38 (dt, J = 11.1, 6.2 Hz, 1H), 4.14 (dd, J = 8.6, 5.6 Hz, 1H), 4.01 (q, J = 5.6 Hz, 3H), 2.59 (s, 3H), 2.39 (d, J = 0.9 Hz, 4H), 2.29 (d, J = 7.3 Hz, 2H), 2.26 (d, J = 7.2 Hz, 2H), 1.61 (d, J = 0.9 Hz, 3H), 1.56 (s, 2H), 1.44 (s, 2H), 1.26 (d, J = 7.8 Hz, 4H), 1.18 (s, 6H); MS m/z $[\text{M} + \text{H}]^+$ 713.58.

【0868】 [제조예 5-110'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(11-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethoxy)-11-oxoundecanamido)benzoate hydrochloride



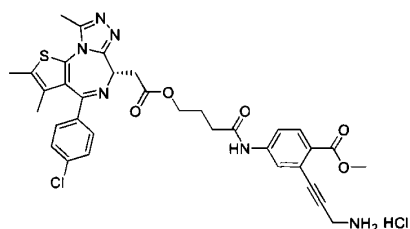
【0869】

【0870】 중간체 5-109'a 와 중간체 3-25a로부터 제조예 5-77'의 단계 2 내지 3과 동일한 방법으로 실시예 5-110'을 합성하였다.

【0871】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.37 (d, $J = 16.6$ Hz, 1H), 8.35 (s, 2H), 8.09 (q, $J = 2.4$ Hz, 1H), 7.88 – 7.83 (m, 1H), 7.54 – 7.38 (m, 5H), 4.41 (dt, $J = 10.8, 7.0$ Hz, 1H), 4.34 (dt, $J = 11.2, 6.1$ Hz, 1H), 4.11 (dd, $J = 8.6, 5.6$ Hz, 1H), 4.04 – 3.98 (m, 2H), 3.79 (s, 3H), 2.64 – 2.58 (m, 2H), 2.56 (d, $J = 1.3$ Hz, 3H), 2.35 (s, 3H), 2.30 (t, $J = 7.3$ Hz, 2H), 2.21 (t, $J = 7.3$ Hz, 2H), 1.57 (s, 3H), 1.52 (t, $J = 7.2$ Hz, 2H), 1.39 (d, $J = 8.0$ Hz, 2H), 1.20 (s, 4H), 1.14 (s, 6H); MS m/z $[\text{M} + \text{H}]^+$ 771.53.

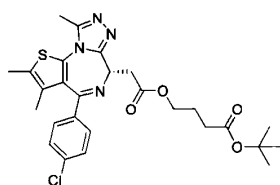
【0872】 [제조예 5-115'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetoxy)butanamido)benzoate

hydrochloride



【0873】

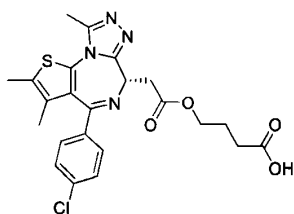
【0874】 단계 1: tert-butyl (S)-4-(2-(4-(4-chlorophenyl)-
2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
5 yl)acetoxy)butanoate (중간체 5-115'a)



【0875】

【0876】 tert-Butyl 4-hydroxybutanoate로부터 제조예 4-
1'의 단계 5과 동일한 방법으로 중간체 5-115'a를 합성하였다.

【0877】 단계 2: (S)-4-(2-(4-(4-chlorophenyl)-2,3,9-
10 trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-
yl)acetoxy)butanoic acid (중간체 5-115'b)



【0878】

【0879】 중간체 5-115'a로부터 제조예 4-1'의 단계 4와

동일한 방법으로 중간체 5-115'b를 합성하였다.

【0880】 단계 3: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetoxy)butanamido)benzoate hydrochloride

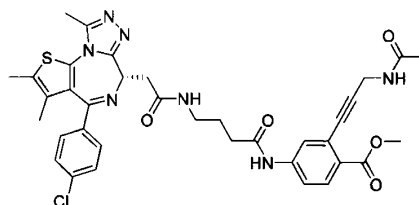
【0881】 중간체 5-115'b와 중간체 3-25a로부터 제조예 5-77'의 단계 2 내지 3과 동일한 방법으로 실시예 5-115'를 합성하였다.

【0882】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.40 (s, 1H), 8.31 (s, 2H), 8.15 (d, J = 2.1 Hz, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.53 – 7.39 (m, 7H), 4.51 – 4.44 (m, 2H), 4.16 (d, J = 5.9 Hz, 3H), 4.07 (d, J = 5.6 Hz, 3H), 3.83 (d, J = 1.5 Hz, 3H), 3.65 – 3.59 (m, 1H), 3.47 – 3.37 (m, 3H), 3.14 (dd, J = 7.3, 4.3 Hz, 1H), 2.69 (d, J = 1.4 Hz, 3H), 2.60 (d, J = 2.6 Hz, 3H), 2.42 – 2.40 (m, 3H), 1.93 (t, J = 6.9 Hz, 2H), 1.62 – 1.60 (m, 3H); MS m/z $[\text{M} + \text{H}]^+$ 673.42.

【0883】 [제조예 5-148'] methyl (S)-2-(3-acetamidoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

yl)acetamido)butanamido)benzoate

【0884】



【0885】

실시예 4-228' (0.02 mmol, 1.0 eq)를 DCM 0.6 mL에 녹인 뒤 0 °C에서 TEA 9 μ l, Ac₂O 2.4 μ l를 적가하고, 실온에서 40 분간 교반하였다. 반응물을 감압증류한 뒤 flash column으로 정제하여 실시예 5-148'을 합성하였다.

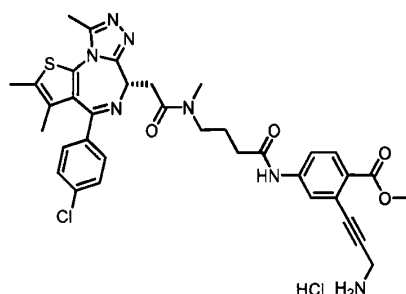
【0886】

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.31 (s, 1H), 8.42 (t, *J* = 5.5 Hz, 1H), 8.30 (t, *J* = 5.7 Hz, 1H), 7.91 (d, *J* = 2.2 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.47 – 7.43 (m, 2H), 7.43 – 7.39 (m, 2H), 4.51 (dd, *J* = 8.1, 6.2 Hz, 1H), 4.13 (d, *J* = 5.5 Hz, 2H), 3.80 (s, 3H), 3.28 – 3.13 (m, 4H), 2.60 (s, 3H), 2.43 – 2.39 (m, 5H), 1.86 (s, 3H), 1.77 (p, *J* = 7.6 Hz, 2H), 1.61 (d, *J* = 0.9 Hz, 3H); MS *m/z* [M+H]⁺ 714.48.

【0887】

[제조예 5-149'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-

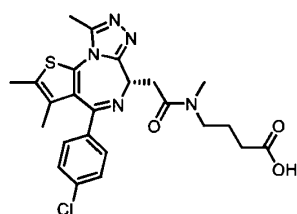
methylacetamido)butanamido)benzoate hydrochloride



【0888】

【0889】 단계 1: (S)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-

5 N-methylacetamido)butanoic acid (중간체 5-149'a)



【0890】

【0891】 Methyl 4-(methylamino)butanoate

hydrochloride로부터 제조예 4-1'의 단계 5, 제조예 3-2'의 단계 1과 동일한 방법을 순차적으로 적용하여 중간체 5-149'a를 합성하였다.

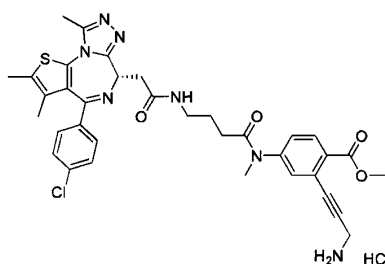
10 【0892】 단계 2: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-methylacetamido)butanamido)benzoate hydrochloride

【0893】 중간체 5-149'a 및 중간체 3-25a로부터 제조예 5-

77'의 단계 2 내지 3과 동일한 방법으로 실시예 5-149'을 합성하였다.

【0894】 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.667 – 10.521 (m, 1H), 8.566 (brs, 3H), 8.160 – 8.138 (m, 1H), 7.889 – 7.823 (m, 1H), 7.525 – 7.512 (m, 1H). 7.508 – 7.409 (m, 4H), 4.572 (m, 1H), 4.052 – 4.032 (m, 2H), 3.841 (s, 3H), 3.713 – 3.501 (m, 2H), 3.407 – 3.391 (m, 2H), 3.148 (s, 3H), 2.640 (s, 3H), 2.499 (s, 3H), 2.430 – 2.360 (m, 2H), 1.827 – 1.810 (m, 1H), 1.793 – 1.635 (m, 1H), 1.626 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 686.2.

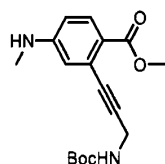
【0895】 [제조예 5-150'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-N-methylbutanamido)benzoate hydrochloride



【0896】

【0897】 단계 1: methyl 2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(methylamino)benzoate

15 (중간체 5-150a)



【0898】

【0899】 중간체 3-25a (0.6 mmol, 1.0 eq), MeB(OH)₂ (2.5 eq),Cu(OAc)₂ (2.5 eq), pyridine (3.5 eq), dioxane 6.0 mL를 혼합 후 반응 용기

내 기체를 Ar 기체로 치환하였다. 반응물을 110 °C에서 밤새 교반하였다.

5 반응물을 celite를 통해 감압 여과 후 증발하였다. 혼합물을 flash column으로 정제하여 중간체 5-150a를 합성하였다.

【0900】 단계 2: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-

(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-N-

10 methylbutanamido)benzoate hydrochloride

【0901】 중간체 5-150a로부터 실시예 5-77'의 단계 2 내지

3과 동일한 방법으로 실시예 5-150'을 합성하였다.

【0902】 ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.57 (brs, 3H), 8.26(t, *J* = 13 Hz, 1H), 7.93 (d, *J* = 21 Hz, 1H), 7.61 (m, 1H), 7.49 (m, 3H), 7.42

15 (m, 2H), 4.54 (m, 1H), 4.02 (m, 2H), 3.88 (s, 3H), 3.25 (m, 5H), 3.16 (m,

2H), 2.64 (s, 3H), 2.42 (s, 3H), 2.33 (m, 2H), 1.68 (m, 2H), 1.62 (s, 3H); MS

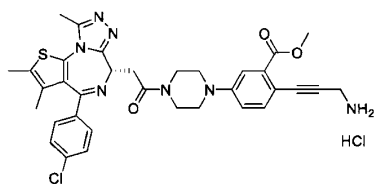
m/z [M+H]⁺ 686.3.

【0903】 [제조예 III']

【0904】 BRD4(Bromodomain-containing protein 4)

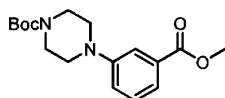
억제제로서의 활성을 나타내는 화합물(JQ1)이 본 발명의 화학식 III에 해당하는 화합물들과 연결된 TBM-UBM 화합물을 아래와 같이 합성하였다.

【0905】 [제조예 4-2'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate hydrochloride



【0906】

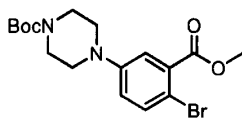
【0907】 단계 1: tert-butyl 4-(3-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (중간체 4-2a)



【0908】

【0909】 Methyl 3-iodobenzoate로부터 제조예 4-226'의 단계 1과 동일한 방법으로 중간체 4-2a를 합성하였다.

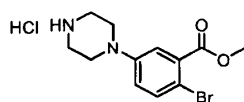
【0910】 단계 2: tert-butyl 4-(4-bromo-3-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (중간체 4-2b)



【0911】

【0912】 중간체 4-2a (2.0 mmol, 1.0 eq)를 dry DCM에 녹인 후 NBS (1.2 eq)를 첨가하여 실온에서 30 분 교반하였다. 반응물은 DCM, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 4-2b를 합성하였다.

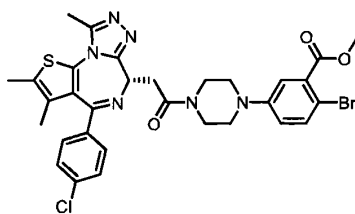
- 5 【0913】 단계 3: methyl 2-bromo-5-(piperazin-1-yl)benzoate hydrochloride(중간체 4-2c)



【0914】

【0915】 중간체 4-2b로부터 제조예 1-1의 단계 2과 동일한 방법으로 중간체 4-2c을 합성하였다.

- 10 【0916】 단계 4: methyl (S)-2-bromo-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate (중간체 4-2'a)



【0917】

- 【0918】 중간체 4-2c로부터 제조예 4-1'의 단계 5와 동일한
15 방법으로 중간체 4-2'a을 합성하였다.

【0919】 단계 5: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate hydrochloride

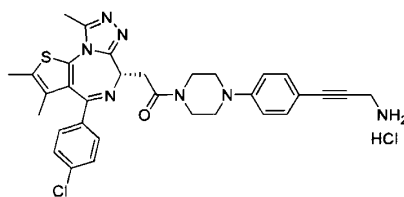
【0920】 중간체 4-2'a로부터 제조예 5-140'의 단계 4 내지 5와 동일한 방법으로 실시예 4-2'을 합성하였다.

5 【0921】 MS m/z [M+H]⁺ 656.41.

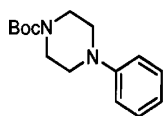
【0922】 [제조예 4-226'] (S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one hydrochloride

10

【0923】



【0924】 단계 1: tert-butyl 4-phenylpiperazine-1-carboxylate (중간체 4-226a)

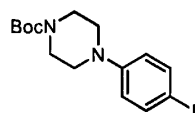


【0925】

【0926】 Iodobenzene (1.4 mmol, 1.0 eq), tert-butyl piperazine-1-carboxylate (1.1 eq), Pd(OH)₂ (0.1 eq), BINAP (0.1 eq), CS₂CO₃ (2.0 eq), dry toluene을 혼합한 뒤 반응 용기 내 기체를 Ar 기체로 치환한 후 100 °C에서 밤새 교반하였다. 반응물은 celite 여과 후 감압 하에

농축하여 flash column로 정제해 중간체 4-226a를 합성하였다.

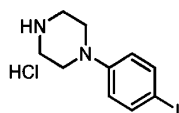
【0927】 단계 2: tert-butyl 4-(4-iodophenyl)piperazine-1-carboxylate (중간체 4-226b)



【0928】

5 【0929】 중간체 4-226a (2.0 mmol, 1.0 eq)를 dry DCM에 녹인 후 NIS (1.2 eq)를 첨가하여 실온에서 30 분 교반하였다. 반응물은 DCM, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 4-226b를 합성하였다.

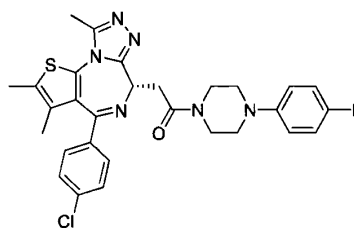
【0930】 단계 3: 1-(4-iodophenyl)piperazine
10 hydrochloride(중간체 4-226c)



【0931】

【0932】 중간체 4-226b로부터 제조예 1-1의 단계 2와 동일한 방법으로 중간체 4-226c을 합성하였다.

【0933】 단계 4: (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-
15 6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-1-(4-(4-iodophenyl)piperazin-1-yl)ethan-1-one (중간체 4-226'a)



【0934】

【0935】 중간체 4-226c 로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 4-226'a를 합성하였다.

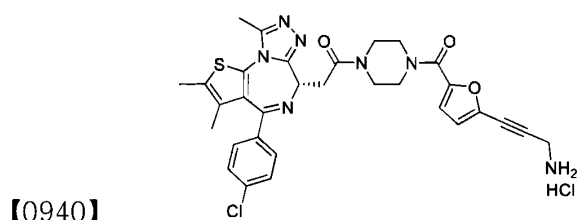
【0936】 단계 5: (S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one hydrochloride

【0937】 중간체 4-226'a로부터 제조예 1-1 와 동일한 방법으로 실시예 4-226'을 합성하였다.

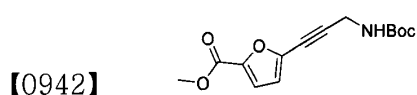
【0938】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.34 - 8.12 (s, 3H), 7.48 - 7.39 (m, 4H), 7.33 - 7.25 (m, 1H), 7.03 - 6.98 (m, 1H), 6.97 - 6.94 (m, 1H), 4.59 (tt, J = 6.9, 2.6 Hz, 1H), 4.06 - 4.02 (m, 2H), 3.82 - 3.76 (m, 1H), 3.66 - 3.56 (m, 2H), 3.53 (s, 3H), 3.51 - 3.41 (m, 2H), 3.40 - 3.28 (m, 2H), 3.19 (d, J = 26.3 Hz, 2H), 2.60 (s, 3H), 2.38 (s, 3H), 1.59 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 598.45.

【0939】 [제조예 4-227'] (S)-1-(4-(5-(3-aminoprop-1-yn-1-yl)furan-2-carbonyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-

trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one hydrochloride

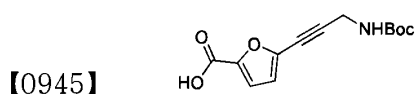


【0941】 단계 1: methyl 5-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)furan-2-carboxylate (중간체 4-227a)



【0943】 Methyl 5-bromo-2-furancarboxylate로부터 제조예 4-179'의 단계 2와 동일한 방법으로 중간체 4-227a을 합성하였다.

10 【0944】 단계 2: 5-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)furan-2-carboxylic acid (중간체 4-227b)



【0946】 중간체 4-227a로부터 제조예 3-2'의 단계 1과 동일한 방법으로 중간체 4-227b을 합성하였다.

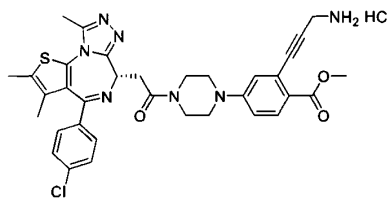
15 【0947】 단계 3: (S)-1-(4-(5-(3-aminoprop-1-yn-1-yl)furan-2-carbonyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-

trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one hydrochloride

【0948】 중간체 5-140'b와 중간체 4-227b로부터 제조예 5-7'와 동일한 방법으로 실시예 4-227'을 합성하였다.

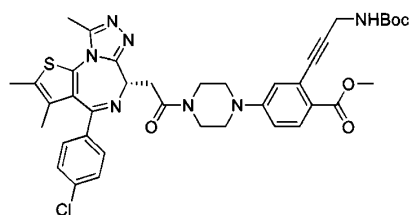
5 【0949】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.41 (s, 3H), 7.51 – 7.45 (m, 2H), 7.45 – 7.38 (m, 2H), 7.09 (d, $J = 3.6$ Hz, 1H), 7.01 (d, $J = 3.6$ Hz, 1H), 4.56 (t, $J = 6.7$ Hz, 1H), 4.06 (q, $J = 5.7$ Hz, 2H), 3.75 (d, $J = 4.4$ Hz, 2H), 3.66 – 3.62 (m, 4H), 3.43 – 3.36 (m, 4H), 2.57 (s, 3H), 2.38 (s, 3H), 1.59 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 616.33.

10 【0950】 [제조예 5-7'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate hydrochloride



【0951】

15 【0952】 단계 1: methyl (S)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate (중간체 5-7'a)



【0953】

【0954】 중간체 5-7b로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-7'a를 합성하였다.

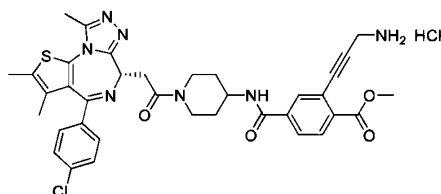
【0955】 단계 2: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-
5 (4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-
yl)benzoate hydrochloride

【0956】 중간체 5-7'a로부터 제조예 1-1의 단계 2와 동일한 방법으로 실시예 5-7'을 합성하였다.

10 【0957】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.33 (s, 3H), 7.84 (d, J = 9.0 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H), 7.10 - 7.07 (m, 1H), 7.03 (d, J = 2.6 Hz, 1H), 4.60 (t, J = 6.8 Hz, 1H), 4.04 (d, J = 5.7 Hz, 2H), 3.80 (s, 3H), 3.71 - 3.61 (m, 8H), 3.39 - 3.34 (m, 2H), 2.60 (d, J = 1.1 Hz, 3H), 2.42 (d, J = 0.9 Hz, 3H), 1.63 (d, J = 1.0 Hz, 3H); MS
15 m/z $[\text{M} + \text{H}]^+$ 656.42.

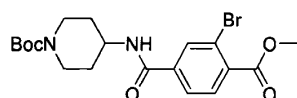
【0958】 [제조예 5-22'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-

yl)carbamoyl)benzoate hydrochloride



【0959】

【0960】 단계 1: tert-butyl 4-(3-bromo-4-oxycarbonyl)benzamido)piperidine-1-carboxylate (중간체 5-22a)

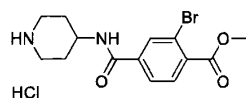


5

【0961】

【0962】 3-Bromo-4-(methoxycarbonyl)benzoic acid (0.2 mmol, 1.0 eq), tert-butyl 4-aminopiperidine-1-carboxylate를 출발 물질로 하여 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-22a을 합성하였다.

10 【0963】 단계 2: methyl 2-bromo-4-(piperidin-4-ylcarbamoyl)benzoate hydrochloride (중간체 5-22b)



【0964】

【0965】 중간체 5-22a로부터 제조예 1-1의 단계 2와 동일한 방법으로 중간체 5-22b을 합성하였다.

15 【0966】 단계 3: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-
 ((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

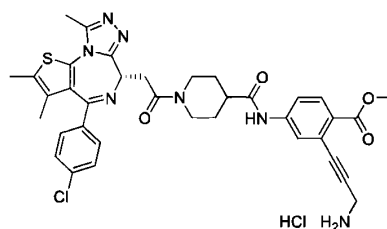
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)carbamoyl)benzoate hydrochloride

【0967】 중간체 5-22b로부터 제조예 4-2'의 단계 4 내지 5와 동일한 방법으로 중간체 5-22'a (methyl (S)-2-bromo-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)carbamoyl)benzoate)를 합성한 후 실시예 5-22'을 합성하였다.

【0968】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.75 (dd, J = 7.6, 3.6 Hz, 1H), 8.56 (s, 3H), 8.10 (dd, J = 5.2, 1.7 Hz, 1H), 8.04 - 7.96 (m, 2H), 7.53 - 7.50 (m, 2H), 7.46 (dd, J = 8.6, 4.8 Hz, 2H), 4.65 - 4.62 (m, 1H), 4.35 (d, J = 13.0 Hz, 1H), 4.17 (s, 1H), 4.06 (d, J = 5.7 Hz, 2H), 3.91 (d, J = 1.5 Hz, 3H), 3.68 (dd, J = 16.5, 7.5 Hz, 1H), 3.44 (dt, J = 16.4, 6.6 Hz, 1H), 3.28 (t, J = 12.6 Hz, 1H), 2.79 (q, J = 12.4, 12.0 Hz, 1H), 2.64 (s, 3H), 2.43 (d, J = 0.9 Hz, 3H), 1.96 (d, J = 12.5 Hz, 1H), 1.84 (s, 1H), 1.64 (s, 3H), 1.42 (td, J = 12.7, 11.5, 5.9 Hz, 1H); MS m/z $[\text{M} + \text{H}]^+$ 698.50.

【0969】 [제조예 5-23'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-

carboxamido)benzoate hydrochloride



【0970】

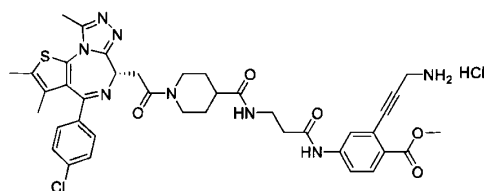
【0971】 중간체 5-25'b, 중간체 3-25a로부터 제조예 5-7'과 동일한 방법으로 실시예 5-23'을 합성하였다.

5 【0972】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.57 (d, $J = 8.6$ Hz, 1H), 8.41 (s, 3H), 8.17 (dd, $J = 20.9, 2.2$ Hz, 1H), 7.91 (dd, $J = 8.7, 3.5$ Hz, 1H), 7.61 (ddd, $J = 24.0, 8.7, 2.2$ Hz, 1H), 7.51 (d, $J = 8.7$ Hz, 2H), 7.45 (t, $J = 8.9$ Hz, 2H), 4.60 (t, $J = 6.7$ Hz, 1H), 4.42 (d, $J = 3.7$ Hz, 1H), 4.23 (d, $J = 13.5$ Hz, 1H), 4.06 (q, $J = 5.6$ Hz, 2H), 3.84 (d, $J = 1.8$ Hz, 3H), 3.64 (ddd, $J = 20.5, 16.4, 7.4$ Hz, 1H), 3.50 – 3.34 (m, 1H), 3.22 (q, $J = 11.5$ Hz, 1H), 2.71 (t, $J = 12.5$ Hz, 2H), 2.61 (s, 3H), 2.42 (s, 3H), 1.95 (d, $J = 13.3$ Hz, 1H), 1.84 (s, 1H), 1.70 (t, $J = 11.0$ Hz, 1H), 1.64 (s, 3H), 1.52 – 1.42 (m, 1H); MS m/z $[\text{M} + \text{H}]^+$ 698.3.

15 【0973】 [제조예 5-25'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-

carboxamido)propanamido)benzoate hydrochloride

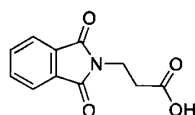
【0974】



【0975】 단계 1: 3-(1,3-dioxoisindolin-2-yl)propanoic acid

(중간체 5-25a)

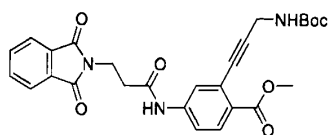
【0976】

【0977】 β -Alanine (2.0 mmol, 2.0 eq), phthalic anhydride (1.0

eq)를 acetic acid 0.6 mL에 녹인 후 120 °C에서 밤새 교반하였다. 반응물은 DCM, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 5-25a를 합성하였다.

【0978】 단계 2: methyl 2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(3-(1,3-dioxoisindolin-2-yl)propanamido)benzoate (중간체 5-25b)

【0979】



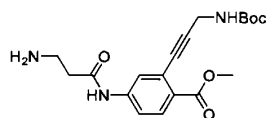
【0980】 중간체 5-25a과 중간체 3-25a로부터 제조예 4-1'의

15 단계 5와 동일한 방법으로 중간체 5-25b를 합성하였다.

【0981】 단계 3: methyl 4-(3-aminopropanamido)-2-(3-

((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate (중간체 5-25c)

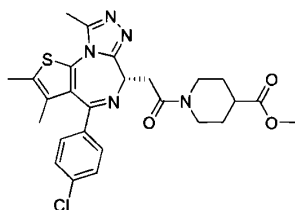
【0982】



【0983】 중간체 5-25b로부터 제조예 5-116의 단계 3과 동일한 방법으로 중간체 5-25c를 합성하였다.

5 【0984】 단계 4: methyl (S)-1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxylate (중간체 5-25'a)

【0985】

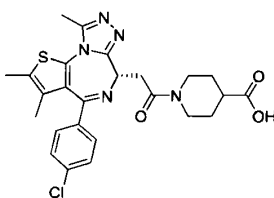


【0986】 Methyl piperidine-4-carboxylate로부터 제조예 4-

10 1'의 단계 5와 동일한 방법으로 중간체 5-25'a를 합성하였다.

【0987】 단계 5: (S)-1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxylic acid (중간체 5-25'b)

【0988】



【0989】 중간체 5-25'a로부터 제조예 3-2'의 단계 1과 동일한 방법으로 중간체 5-25'b를 합성하였다.

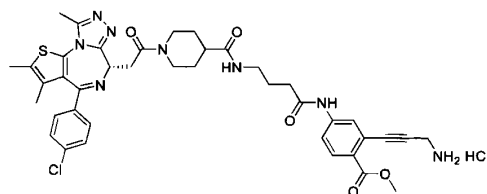
【0990】 단계 6: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)propanamido)benzoate hydrochloride

【0991】 중간체 5-25'b와 중간체 5-25c로부터 제조예 5-7'과 동일한 방법으로 실시예 5-25'을 합성하였다.

【0992】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.44 (s, 1H), 8.34 (s, 3H), 8.13 (t, J = 2.3 Hz, 1H), 8.00 (dd, J = 10.2, 5.4 Hz, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.56 (dd, J = 8.7, 2.2 Hz, 1H), 7.50 (d, J = 4.7 Hz, 2H), 7.43 (t, J = 7.3 Hz, 2H), 4.57 (t, J = 6.7 Hz, 1H), 4.33 (t, J = 14.5 Hz, 1H), 4.14 (s, 1H), 4.06 (t, J = 5.7 Hz, 2H), 3.83 (s, 3H), 3.62 (s, 1H), 3.58 (s, 2H), 3.34 (d, J = 6.6 Hz, 2H), 3.14 (s, 1H), 2.63 (dp, J = 5.5, 1.8 Hz, 2H), 2.60 (d, J = 2.0 Hz, 3H), 2.54 (d, J = 2.7 Hz, 1H), 2.42 (d, J = 0.8 Hz, 3H), 2.36 (p, J = 1.9 Hz, 1H), 2.00 (d, J = 7.6 Hz, 1H), 1.76 (d, J = 13.0 Hz, 1H), 1.68 (d, J = 4.8 Hz, 1H), 1.63 (d, J = 0.9 Hz, 3H); MS m/z $[\text{M} + \text{H}]^+$ 769.43.

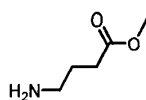
【0993】 [제조예 5-26'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-

carboxamido)butanamido)benzoate hydrochloride



【0994】

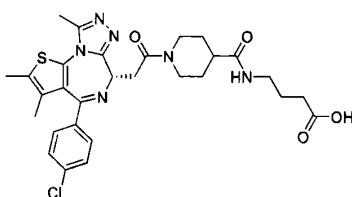
【0995】 단계 1: methyl 4-aminobutanoate (중간체 5-26a)



【0996】

5 【0997】 4-Aminobutanoic acid (14.0 mmol, 1.0 eq)를 MeOH 20.0 mL에 녹인 후 반응 용기 내 기체를 Ar 기체로 치환하였다. 0 °C에서 반응물에 SOCl₂ 1.7 mL를 적가한 후 실온에서 밤새 교반하였다. 반응물을 감압증류한 뒤 EtOAc로 재결정화 하여 중간체 5-26a를 합성하였다.

10 【0998】 단계 2: (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)butanoic acid (중간체 5-26'b)



【0999】

【1000】 중간체 5-25'b와 중간체 5-26a로부터 제조예 5-25'의 단계 4 내지 5와 동일한 방법으로 중간체 5-26'b를 합성하였다.

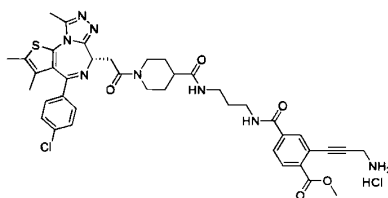
15 【1001】 단계 3: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-

(4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)butanamido)benzoate hydrochloride

【1002】 중간체 5-26'b, 중간체 3-25a로부터 제조예 5-7'과
5 동일한 방법으로 실시예 5-26'을 합성하였다.

【1003】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.50 (s, 1H), 8.39 (s, 3H), 8.08 (s, 1H), 7.95 – 7.88 (m, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.50 – 7.38 (m, 4H), 4.59 – 4.52 (m, 1H), 4.30 (s, 2H), 4.02 (s, 2H), 3.77 (s, 3H), 3.63 – 3.47 (m, 1H), 3.43 – 3.30 (m, 1H), 3.16 – 3.01 (m, 4H), 2.62 – 2.56 (m, 3H), 2.37 (s, 3H), 1.67 (s, 4H), 1.57 (s, 3H), 1.32 (dd, *J* = 10.4, 6.7 Hz, 2H) 1.26 – 1.13 (m, 2H), 1.09 – 0.99 (m, 2H); MS *m/z* [M+H]⁺ 783.31.

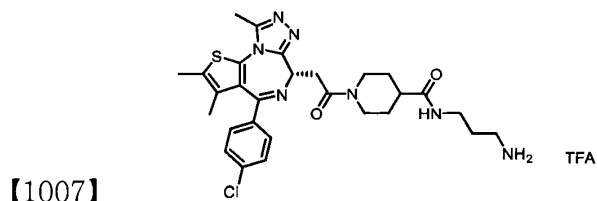
【1004】 [제조예 5-27'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)propyl)carbamoyl)benzoate hydrochloride



【1005】

【1006】 단계 1: (S)-N-(3-aminopropyl)-1-(2-(4-(4-

chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamide trifluoroacetic acid(중간체 5-27'b)



5 【1008】 중간체 5-25'b, tert-butyl (3-aminopropyl)carbamate로부터 제조예 5-140'의 단계 1 내지 2와 동일한 방법으로 중간체 5-27'b를 합성하였다.

 【1009】 단계 2: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)propyl)carbamoyl)benzoate hydrochloride

10

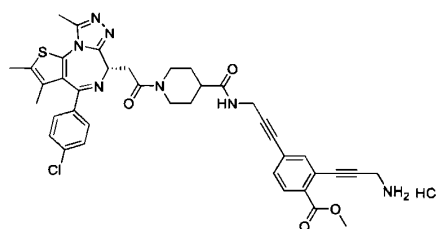
 【1010】 중간체 5-27'b, 3-iodo-4-(methoxycarbonyl)benzoic acid로부터 제조예 5-7'과 동일한 방법으로 실시예 5-27'을 합성하였다.

 【1011】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.76 (d, $J = 3.9$ Hz, 1H), 8.37 (s, 3H), 8.02 (d, $J = 1.9$ Hz, 1H), 7.97 - 7.85 (m, 3H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.40 (dd, $J = 12.3, 8.5$ Hz, 2H), 4.54 (t, $J = 6.7$ Hz, 1H), 4.32 (s, 1H), 4.11 (s, 1H), 4.02 (q, $J = 5.6$ Hz, 2H), 3.85 (s, 3H), 3.58 - 3.47 (m, 4H), 3.25 (d, $J = 6.0$ Hz, 2H), 3.12 - 3.00 (m, 4H), 2.56 (s, 3H), 2.38 (s,

15

3H), 1.77 – 1.71 (m, 1H), 1.63 (d, $J = 3.7$ Hz, 2H), 1.59 (s, 3H), 1.41 – 1.30 (m, 1H), 1.25 – 1.18 (m, 1H); MS m/z $[M+H]^+$ 783.61.

【1012】 [제조예 5-28'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)prop-1-yn-1-yl)benzoate hydrochloride



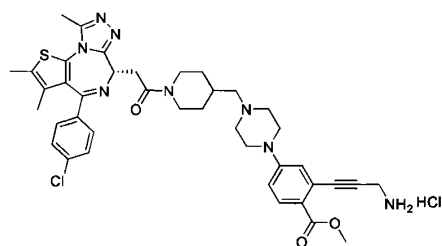
【1013】

【1014】 중간체 5-25'b와 중간체 5-116c로부터 제조예 5-7'과 동일한 방법으로 실시예 5-28'을 합성하였다.

10 【1015】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.45 (s, 4H), 7.86 (dd, $J = 8.2, 2.8$ Hz, 1H), 7.57 (t, $J = 2.0$ Hz, 1H), 7.55 – 7.50 (m, 1H), 7.49 – 7.45 (m, 3H), 7.41 (dd, $J = 12.6, 8.4$ Hz, 1H), 4.57 (t, $J = 6.7$ Hz, 1H), 4.33 (t, $J = 13.2$ Hz, 1H), 4.13 (dd, $J = 7.7, 5.6$ Hz, 4H), 4.00 (t, $J = 5.7$ Hz, 4H), 3.83 (s, 4H), 3.62 – 3.37 (m, 3H), 3.13 (q, $J = 11.1, 9.5$ Hz, 1H), 2.59
15 (s, 3H), 2.40 – 2.38 (m, 3H), 1.59 (s, 3H); MS m/z $[M+H]^+$ 736.46.

【1016】 [제조예 5-29'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)piperazin-1-yl)benzoate hydrochloride



【1017】

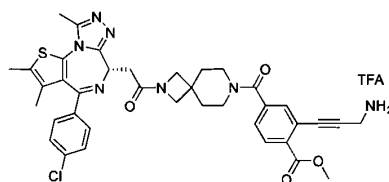
【1018】 JQ1 carboxylic acid와 중간체 5-29d로부터 제조예 5-7'과 동일한 방법으로 실시예 5-29'을 합성하였다.

【1019】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 9.46 (s, 1H), 8.31 (s, 3H), 7.85 (d, $J = 8.9$ Hz, 1H), 7.53 – 7.47 (m, 1H), 7.44 (dd, $J = 8.5, 2.6$ Hz, 2H), 7.15 (d, $J = 9.0$ Hz, 1H), 7.10 (s, 1H), 4.58 (t, $J = 6.7$ Hz, 1H), 4.38 (d, $J = 12.7$ Hz, 1H), 4.20 (s, 1H), 4.04 (dd, $J = 10.6, 6.3$ Hz, 1H), 3.81 (s, 2H), 3.65 (s, 2H), 2.61 – 2.59 (m, 3H), 2.44 – 2.40 (m, 3H), 1.88 (s, 1H), 1.76 (d, $J = 12.0$ Hz, 1H), 1.63 (s, 3H), 1.27 – 1.22 (m, 3H); MS m/z $[\text{M} + \text{H}]^+$ 753.54.

【1020】 [제조예 5-39'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,7-

diazaspiro[3.5]nonane-7-carbonyl)benzoate trifluoroacetic acid

【1021】

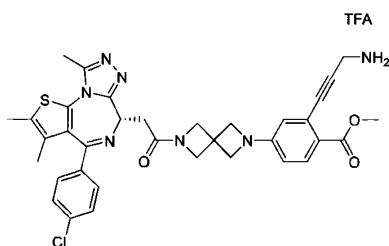


【1022】 중간체 5-39c로부터 제조예 5-85'의 단계 4 내지 5와 동일한 방법으로 실시예 5-39'을 합성하였다.

5 【1023】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.29 (s, 3H), 7.94 (d, $J = 8.0$ Hz, 1H), 7.56 (d, $J = 1.7$ Hz, 1H), 7.52 (dd, $J = 8.0, 1.7$ Hz, 1H), 7.45 (d, $J = 9.6$ Hz, 2H), 7.39 (s, 2H), 4.03 (s, 3H), 3.85 (s, 3H), 3.61 (s, 2H), 3.22 (t, $J = 14.2$ Hz, 4H), 3.10 (d, $J = 21.5$ Hz, 1H), 2.56 (s, 3H), 2.37 (s, 3H), 1.79 (s, 2H), 1.69 (s, 2H), 1.58 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 724.47.

10 【1024】 [제조예 5-40'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,6-diazaspiro[3.3]heptan-2-yl)benzoate trifluoroacetic acid

【1025】



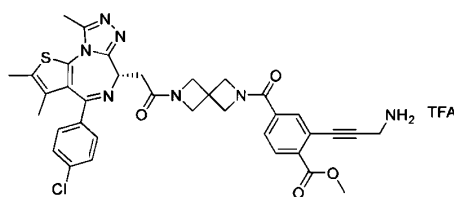
15 【1026】 중간체 5-40b로부터 제조예 5-85'의 단계 4 내지 5와

동일한 방법으로 실시예 5-40'을 합성하였다.

【1027】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.26 (s, 3H), 7.76 (s, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 6.54 – 6.43 (m, 2H), 4.59 – 4.40 (m, 3H), 4.15 – 3.96 (m, 8H), 3.73 (s, 3H), 3.22 (dd, J = 15.5, 7.2 Hz, 1H), 3.09 (dd, J = 15.8, 7.0 Hz, 1H), 2.56 (s, 3H), 2.37 (s, 3H), 1.58 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 668.53.

【1028】 **【제조예 5-41'】 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,6-diazaspiro[3.3]heptane-2-carbonyl)benzoate trifluoroacetic acid**

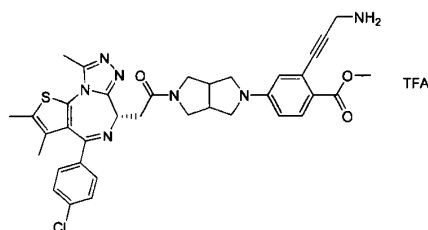
【1029】



【1030】 중간체 5-41c로부터 제조예 5-85'의 단계 4 내지 5와 동일한 방법으로 실시예 5-41'을 합성하였다.

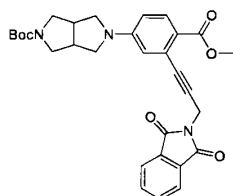
【1031】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.29 (s, 3H), 7.94 (dd, J = 8.3, 4.8 Hz, 1H), 7.80 (s, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.44 (dd, J = 18.8, 8.3 Hz, 2H), 7.41 – 7.36 (m, 2H), 4.55 – 4.40 (m, 3H), 4.25 (s, 8H), 4.07 – 4.00 (m, 3H), 3.85 (s, 3H), 3.22 – 3.13 (m, 1H), 3.13 – 3.03 (m, 1H), 2.56 (s, 3H), 2.37 (s, 3H), 1.57 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 696.60.

【1032】 [제조예 5-44'] methyl 2-(3-aminoprop-1-yn-1-yl)-
4-(5-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)hexahydropyrrolo[3,4-
c]pyrrol-2(1H)-yl)benzoate trifluoroacetic acid



5 【1033】

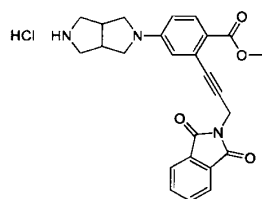
【1034】 단계 1: tert-butyl 5-(3-(3-(1,3-dioxoisindolin-2-
yl)prop-1-yn-1-yl)-4-(methoxycarbonyl)phenyl)hexahydropyrrolo[3,4-
c]pyrrole-2(1H)-carboxylate (중간체 5-44a)



【1035】

10 【1036】 중간체 5-35a, tert-butyl hexahydropyrrolo[3,4-
c]pyrrole-2(1H)-carboxylate를 출발물질로 하여 제조예 5-168의 단계
1과 동일한 방법으로 중간체 5-44a를 합성하였다.

【1037】 단계 2: methyl 2-(3-(1,3-dioxoisindolin-2-
yl)prop-1-yn-1-yl)-4-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-
15 yl)benzoate hydrochloride (중간체 5-44b)



【1038】

【1039】 중간체 5-44a를 출발물질로 하여 제조예 1-1의 단계 1과 동일한 방법으로 중간체 5-44b를 합성하였다.

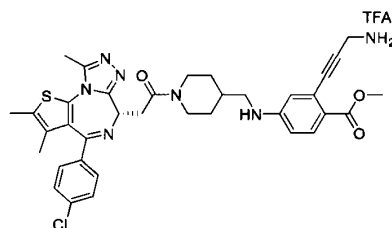
【1040】 단계 3: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)benzoate trifluoroacetic acid

【1041】 중간체 5-44b를 출발물질로 하여 제조예 5-85'의 단계 4 내지 5와 동일한 방법으로 제조예 5-44'을 합성하였다.

【1042】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.26 (s, 3H), 7.82 – 7.74 (m, 1H), 7.49 – 7.44 (m, 1H), 7.42 – 7.37 (m, 2H), 7.37 – 7.32 (m, 2H), 6.63 – 6.58 (m, 1H), 4.52 – 4.49 (m, 1H), 4.00 (s, 2H), 3.74 (d, $J = 2.0$ Hz, 3H), 3.58 (td, $J = 13.3, 12.0, 6.4$ Hz, 4H), 3.34 – 3.28 (m, 2H), 3.21 (h, $J = 5.6$ Hz, 2H), 3.15 (s, 1H), 3.03 (s, 1H), 2.55 (d, $J = 1.0$ Hz, 3H), 2.38 – 2.36 (m, 3H), 1.60 – 1.58 (m, 3H); MS m/z $[\text{M} + \text{H}]^+$ 682.41.

【1043】 [제조예 5-85'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-

yl)methyl)amino)benzoate trifluoroacetic acid

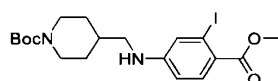


【1044】

【1045】 단계 1: tert-butyl 4-(((3-iodo-4-

(methoxycarbonyl)phenyl)amino)methyl)piperidine-1-carboxylate (중간체

5-85a)



【1046】

【1047】 Methyl 4-amino-2-iodobenzoate (0.9 mmol, 1.0 eq),

boc-piperidine carboxaldehyde (1.2 eq)를 dry DCM에 녹인 후 실온에서

15 분 교반하였다. Sodium triacetoxyborohydride (1.4 eq)를 첨가한 뒤

10 실온에서 15 시간 교반하였다. 반응물은 DCM, H₂O로 추출 후 유기층을

Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을

통해 정제해 중간체 5-85a를 합성하였다.

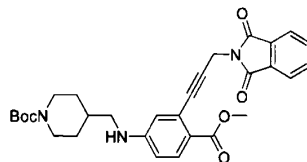
【1048】 단계 2: tert-butyl 4-(((3-(3-(1,3-dioxoisindolin-2-

yl)prop-1-yn-1-yl)-4-

15 (methoxycarbonyl)phenyl)amino)methyl)piperidine-1-carboxylate (중간체

5-85b)

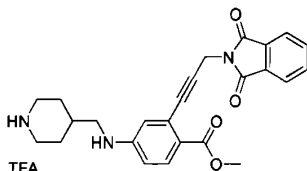
【1049】



【1050】 중간체 5-85a (0.2 mmol, 1.0 eq), n-propargylphthalimide (1.5 eq), Pd(PPh₃)₄ (0.01 eq), CuI (0.03 eq), TEA 0.2 mL, DMF 0.8 mL를 혼합한 뒤 반응 용기 내 기체를 Ar 기체로 치환한 후
 5 실온에서 밤새 교반하였다. 반응물은 DCM, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 5-85b를 합성하였다.

【1051】 단계 3: methyl 2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-((piperidin-4-ylmethyl)amino)benzoate
 10 trifluoroacetic acid (중간체 5-85c)

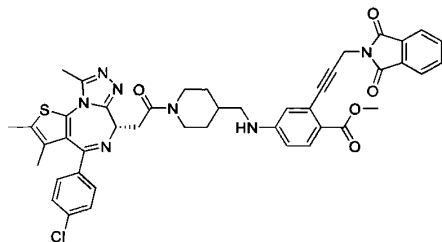
【1052】



【1053】 중간체 5-85b로부터 제조예 4-1'의 단계 4와 동일한 방법으로 중간체 5-85c를 합성하였다.

【1054】 단계 4: methyl (S)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)amino)-2-(3-(1,3-dioxoisindolin-2-

yl)prop-1-yn-1-yl)benzoate (중간체 5-85'a)



【1055】

【1056】 중간체 5-85c로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-85'a를 합성하였다.

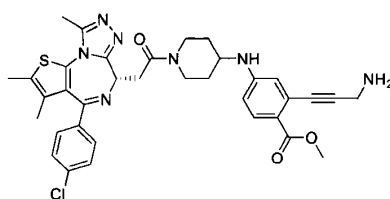
5 【1057】 단계 5: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)amino)benzoate trifluoroacetic acid

10 【1058】 중간체 5-85'a (0.1 mmol, 1.0 eq), hydrazine monohydrate (3.0 eq), EtOH 1.0 mL, 40 °C에서 16 시간 교반하였다. 반응물은 감압 증류 후 prep HPLC로 정제해 실시예 5-85'를 합성하였다.

15 【1059】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.27 (s, 3H), 7.72 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.49 (dd, *J* = 8.9, 1.8 Hz, 2H), 7.43 (dd, *J* = 8.6, 6.6 Hz, 2H), 6.82 (s, 1H), 6.71 – 6.65 (m, 2H), 4.58 (t, *J* = 6.7 Hz, 1H), 4.39 (d, *J* = 12.9 Hz, 1H), 4.18 (d, *J* = 13.6 Hz, 1H), 4.03 (q, *J* = 5.6 Hz, 2H), 3.75 (s, 3H), 3.69 – 3.58 (m, 2H), 3.12 (s, 2H), 3.00 (s, 2H), 2.63 (ddt, *J* = 7.5, 3.7, 1.9 Hz, 2H), 2.60 (d, *J* = 2.6 Hz, 3H), 2.42 (d, *J* = 1.0 Hz, 3H), 1.85 (s,

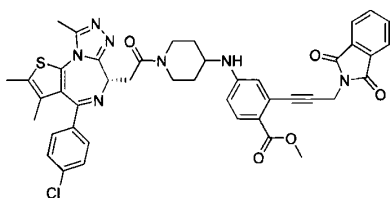
2H), 1.76 (s, 1H), 1.63 (s, 3H); MS m/z [M+ H]⁺ 684.51.

【1060】 [제조예 5-86'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)amino)benzoate



【1061】

【1062】 단계 1: methyl (S)-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)amino)-2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)benzoate (중간체 5-86'a)

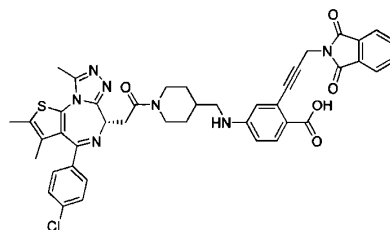


【1063】

【1064】 중간체 5-86c로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-86'a를 합성하였다.

【1065】 단계 2: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-

yl)prop-1-yn-1-yl)benzoic acid (중간체 5-139'a)



【1071】

【1072】 중간체 5-85'a로부터 제조예 3-2'의 단계 1과 동일한 방법으로 중간체 5-139'a를 합성하였다.

5 **【1073】** 단계 2: (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)amino)benzoic acid trifluoroacetic acid

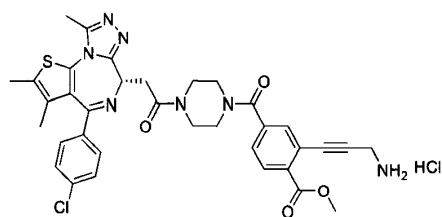
【1074】 중간체 5-139'a로부터 제조예 5-85'의 단계 5와
10 동일한 방법으로 실시예 5-139'을 합성하였다.

[1075] ^1H NMR (500 MHz, DMSO- d_6) δ 8.31 (s, 3H), 7.84 – 7.79 (m, 1H), 7.49 (dd, J = 8.7, 2.8 Hz, 3H), 7.43 (dd, J = 8.7, 7.1 Hz, 3H), 7.17 (s, 1H), 6.86 (dd, J = 8.8, 2.3 Hz, 1H), 6.67 (d, J = 2.1 Hz, 1H), 6.58 (s, 1H), 4.61 – 4.54 (m, 1H), 4.40 (d, J = 12.9 Hz, 1H), 4.19 (d, J = 12.9 Hz, 1H), 3.92 (d, J = 5.8 Hz, 2H), 3.66 – 3.61 (m, 2H), 3.09 (s, 3H), 2.62 (d, J = 1.8 Hz, 2H), 2.60 (d, J = 3.5 Hz, 3H), 2.42 (d, J = 1.0 Hz, 3H), 1.89 – 1.76 (m, 3H), 1.63 (d, J = 0.9 Hz, 3H); MS m/z $[\text{M} + \text{H}]^+$ 670.53.

【1076】 [제조예 5-140'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazine-1-carbonyl)benzoate hydrochloride

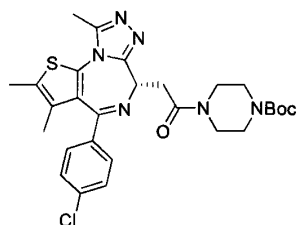
5

【1077】



【1078】 단계 1: tert-butyl (S)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazine-1-carboxylate (중간체 5-140'a)

【1079】

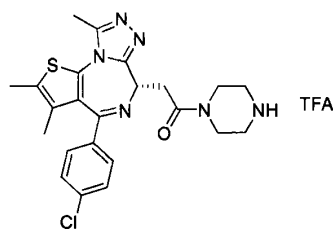


10

【1080】 tert-Butyl piperazine-1-carboxylate로부터 제조예

4-1'의 단계 5와 동일한 방법으로 중간체 5-140'a를 합성하였다.

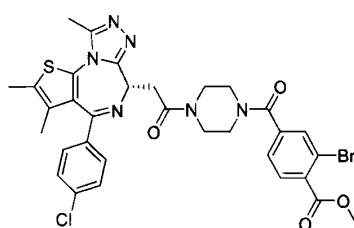
【1081】 단계 2: (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-1-(piperazin-1-yl)ethan-1-one trifluoroacetic acid (중간체 5-140'b)



【1082】

【1083】 중간체 5-140'a로부터 제조예 4-1'의 단계 4와 동일한 방법으로 실시예 5-140'b을 합성하였다.

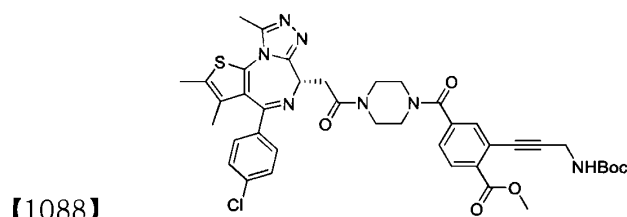
【1084】 단계 3: methyl (S)-2-bromo-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazine-1-carbonyl)benzoate (중간체 5-140'c)



【1085】

【1086】 중간체 5-140'b와 3-bromo-4-(methoxycarbonyl)benzoic acid로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-140'c를 합성하였다.

【1087】 단계 4: methyl (S)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazine-1-carbonyl)benzoate (중간체 5-140'd)



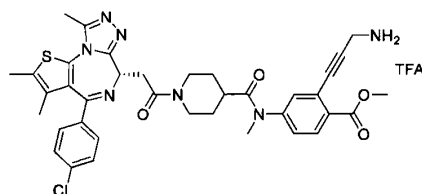
【1089】 중간체 5-140'c로부터 제조예 4-177'의 단계 2와 동일한 방법으로 중간체 5-140'd를 합성하였다.

【1090】 단계 5: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazine-1-carbonyl)benzoate hydrochloride

【1091】 중간체 5-140'd로부터 제조예 1-1의 단계 2와 동일한 방법으로 실시예 5-140'을 합성하였다.

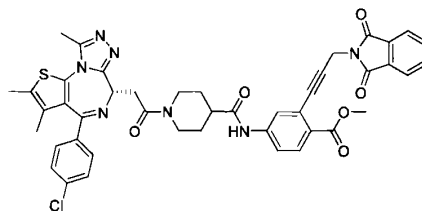
【1092】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.41 (s, 3H), 7.94 (s, 1H), 7.64 (s, 1H), 7.58 (d, $J = 8.1$ Hz, 1H), 7.46 (d, $J = 8.3$ Hz, 2H), 7.40 (d, $J = 8.1$ Hz, 2H), 4.56 (t, $J = 6.7$ Hz, 1H), 4.06 – 4.00 (m, 2H), 3.86 (s, 3H), 3.81 – 3.68 (m, 4H), 3.54 – 3.43 (m, 5H), 3.27 – 3.19 (m, 1H), 2.57 (s, 3H), 2.38 (s, 3H), 1.59 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 684.51.

【1093】 [제조예 5-152'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-N-methylpiperidine-

4-carboxamido)benzoate trifluoroacetic acid

【1094】

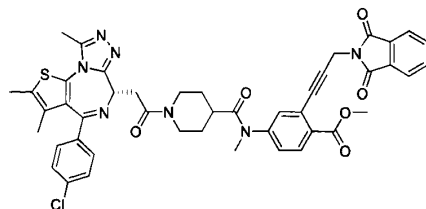
【1095】 단계 1: methyl (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)benzoate (중간체 5-152'a)



【1096】

【1097】 실시예 5-23' (0.04 mmol, 1.0 eq), N-hydroxyphthalimide (1.0 eq)를 0.1 M phosphate buffer (pH 7.0) 2.0 mL에 녹인 후 실온에서 16 시간 교반하였다. 반응물은 DCM, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 중간체 5-152'a를 합성하였다.

【1098】 단계 2: methyl (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-N-methylpiperidine-4-carboxamido)-2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)benzoate (중간체 5-152'b)



【1099】

【1100】 중간체 5-152'a로부터 제조예 5-153'의 단계 1과 동일한 방법으로 중간체 5-152'b를 합성하였다.

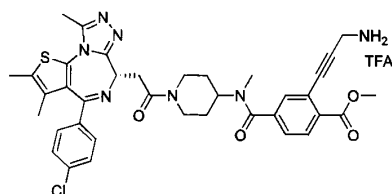
【1101】 단계 3: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-N-methylpiperidine-4-carboxamido)benzoate trifluoroacetic acid

【1102】 중간체 5-152'b로부터 제조예 5-85'의 단계 5와 동일한 방법으로 실시예 5-152'를 합성하였다.

10 **【1103】** ^1H NMR (500 MHz, DMSO-*d*₆) δ 7.96 (s, 1H), 7.57 (s, 1H), 7.52 – 7.44 (m, 4H), 7.39 (s, 1H), 4.57 – 4.51 (m, 1H), 4.32 – 4.31 (m, 1H), 4.09 (s, 2H), 3.87 (s, 3H), 3.72 – 3.56 (m, 4H), 3.44 (s, 3H), 2.58 (s, 3H), 2.39 (s, 3H), 1.77 – 1.67 (m, 1H), 1.60 (s, 3H), 1.42 – 1.31 (m, 1H), 1.00 – 0.95 (m, 1H), 0.89 – 0.80 (s, 1H); MS m/z $[\text{M} + \text{H}]^+$ 712.58.

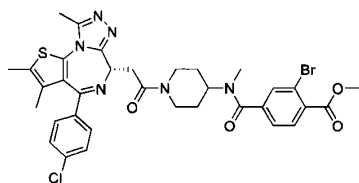
15 【1104】 [제조예 5-153'] methyl (S)-2-(3-aminoprop-1-yn-
1-yl)-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-

yl)(methyl)carbamoyl)benzoate trifluoroacetic acid



【1105】

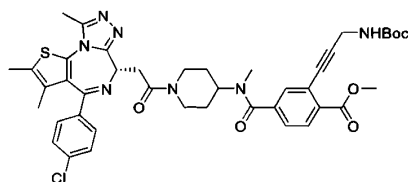
【1106】 단계 1: methyl (S)-2-bromo-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)(methyl)carbamoyl)benzoate (중간체 5-153'a)



【1107】

【1108】 중간체 5-22'a (0.06 mmol, 1.0 eq)를 dry DMF 0.5 mL에 녹인 후 NaH (1.3 eq), MeI (5.0 eq)를 첨가하여 실온에서 2 시간 교반하였다. 반응물은 EtOAc, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해 중간체 5-153'a를 합성하였다.

【1109】 단계 2: methyl (S)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)(methyl)carbamoyl)benzoate (중간체 5-153'b)



【1110】

【1111】 중간체 5-153'a로부터 제조예 4-179'의 단계 2와 동일한 방법으로 중간체 5-153'b을 합성하였다.

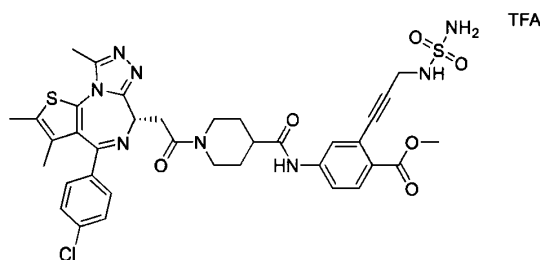
【1112】 단계 3: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-
5 ((1-(2-(4-(4-chlorophenyl))-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-
yl)(methyl)carbamoyl)benzoate trifluoroacetic acid

【1113】 중간체 5-153'b (0.5 mmol, 1.0 eq)를 DCM 3.0 mL에
녹인 후 HCl solution (4.0 M in dioxane, excess)를 적가하여 실온에서 2
10 시간 교반하였다. 반응물은 감압증류한 뒤 prep HPLC를 통해 정제해
실시예 5-153'를 합성하였다.

【1114】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.30 (s, 3H), 7.98 (d,
 $J=8.1$ Hz, 1H), 7.62 – 7.55 (m, 2H), 7.52 – 7.40 (m, 5H), 4.58 (s, 2H), 4.07
(d, $J=5.6$ Hz, 2H), 3.89 (s, 3H), 3.68 (d, $J=9.6$ Hz, 2H), 3.51 (s, 3H), 2.89
15 (d, $J=13.5$ Hz, 2H), 2.75 (s, 2H), 2.60 (s, 3H), 2.42 (s, 3H), 1.63 (s, 3H);
MS m/z $[\text{M}+\text{H}]^+$ 712.48.

【1115】 [제조예 5-154'] methyl (S)-4-(1-(2-(4-(4-
chlorophenyl))-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-

a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-(sulfamoylamino)prop-1-yn-1-yl)benzoate trifluoroacetic acid



【1116】

【1117】 실시예 5-23' (0.043 mmol, 1.0 eq), TEA (2.5 eq),

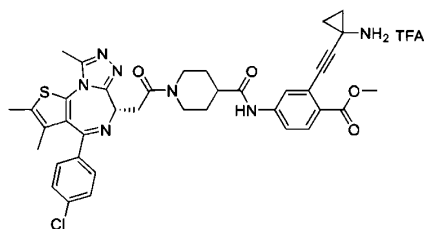
5 DCM 0.8 mL을 혼합한 용액에 sulfamoyl chloride (0.048 mmol, 1.1 eq)을 DCM 0.2 mL에 녹여 0 °C에서 적가한 후 실온에서 밤새 교반하였다. 반응물은 EtOAc, H₂O로 추출 후 유기층을 Na₂SO₄로 건조하였다. 혼합물을 감압여과 후 증류한 뒤 prep HPLC로 정제해 실시예 5-154'을 합성하였다.

【1118】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.36 (d, *J* = 15.9

10 Hz, 1H), 7.95 (d, *J* = 2.1 Hz, 1H), 7.87 (dd, *J* = 8.7, 3.7 Hz, 1H), 7.68 – 7.60 (m, 1H), 7.51 – 7.43 (m, 4H), 7.14 – 7.11 (m, 1H), 6.67 (s, 3H), 4.59 (t, *J* = 6.7 Hz, 1H), 4.45 – 4.39 (m, 1H), 4.25 – 4.20 (m, 1H), 3.97 (d, *J* = 5.7 Hz, 2H), 3.82 (s, 3H), 3.65 – 3.56 (m, 1H), 3.22 – 3.20 (m, 1H), 2.73 – 2.62 (m, 3H), 2.60 (s, 3H), 2.42 (s, 3H), 1.96 – 1.92 (m, 1H), 1.87 – 1.81 (m, 1H), 1.73 – 1.66 (m, 1H), 1.64 (s, 3H), 1.47 (t, *J* = 14.9 Hz, 1H), MS *m/z* [M+H]⁺ 777.32,

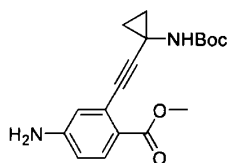
【1119】 [제조예 5-155'] methyl (S)-2-((1-

aminocyclopropyl)ethynyl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)benzoate trifluoroacetic acid



【1120】

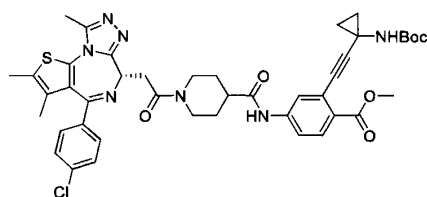
5 【1121】 단계 1: methyl 4-amino-2-((1-((tert-butoxycarbonyl)amino)cyclopropyl)ethynyl)benzoate (중간체 5-155a)



【1122】

 【1123】 Methyl 4-amino-2-iodobenzoate와 tert-butyl (1-ethynylcyclopropyl)carbamate로부터 제조예 1-1과 동일한 방법으로
10 실시에 5-155a을 합성하였다.

 【1124】 단계 2: methyl (S)-2-((1-((tert-butoxycarbonyl)amino)cyclopropyl)ethynyl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)benzoate (중간체
15 5-155'a)



【1125】

【1126】 중간체 5-25'b 와 중간체 5-155a로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-155'a를 합성하였다.

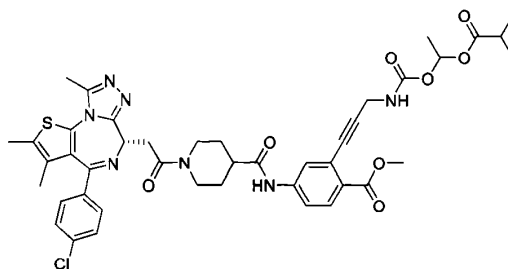
【1127】 단계 3: methyl (S)-2-((1-aminocyclopropyl)ethynyl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)benzoate trifluoroacetic acid

【1128】 중간체 5-155'a로부터 제조예 5-153'의 단계 3과 동일한 방법으로 실시예 5-155'을 합성하였다.

【1129】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.43 (d, $J = 10.9$ Hz, 1H), 8.77 (s, 2H), 8.14 (dd, $J = 22.6, 2.2$ Hz, 1H), 7.92 (dd, $J = 8.7, 3.5$ Hz, 1H), 7.59 – 7.48 (m, 3H), 7.45 (t, $J = 8.6$ Hz, 2H), 4.60 (d, $J = 6.8$ Hz, 1H), 3.82 (d, $J = 2.3$ Hz, 3H), 3.61 (dd, $J = 16.3, 7.5$ Hz, 1H), 3.44 – 3.36 (m, 1H), 3.22 (q, $J = 11.2$ Hz, 1H), 2.69 (t, $J = 12.1$ Hz, 2H), 2.61 (s, 3H), 2.42 (d, $J = 1.0$ Hz, 3H), 1.94 (d, $J = 12.6$ Hz, 1H), 1.83 (s, 1H), 1.74 – 1.66 (m, 1H), 1.64 (s, 3H), 1.48 (d, $J = 15.8$ Hz, 1H), 1.42 – 1.38 (m, 2H), 1.36 – 1.33 (m, 2H), 1.26 – 1.21 (m, 2H); MS m/z $[\text{M} + \text{H}]^+$ 724.47.

【1130】 [제조예 5-157'] methyl 4-(1-(2-((S)-4-(4-

chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate



【1131】

5 【1132】 실시예 5-23' (0.027 mmol, 1.0 eq), HOBt (1.0 eq), DIPEA (3.0 eq), DMF 0.5 mL을 혼합한 용액에 1-(((4-nitrophenoxy)carbonyl)oxy)ethyl isobutyrate (1.0 eq)을 0 °C에서 첨가하고 20 분간 교반하였다. 반응물은 감압여과 후, flash column로 정제하고 prep HPLC로 추가 정제해 실시예 5-157'를 합성하였다.

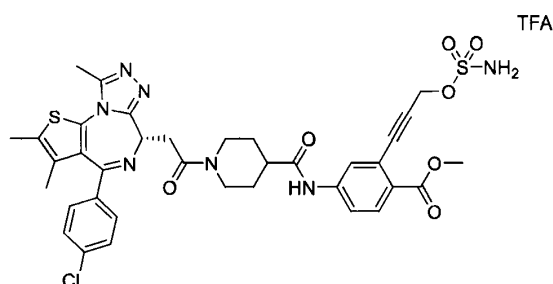
10 【1133】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.33 (d, *J* = 16.3 Hz, 1H), 8.07 – 8.01 (m, 1H), 7.93 (dd, *J* = 6.5, 2.2 Hz, 1H), 7.86 (dd, *J* = 8.7, 3.6 Hz, 1H), 7.63 (dt, *J* = 8.7, 2.5 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.41 (m, 2H), 6.70 (q, *J* = 5.4 Hz, 1H), 4.59 (t, *J* = 6.7 Hz, 1H), 4.46 – 4.38 (m, 1H), 4.27 – 4.19 (m, 1H), 4.13 – 4.02 (m, 2H), 3.80 (d, *J* = 1.2

15 Hz, 3H), 3.22 (q, *J* = 11.6 Hz, 1H), 2.75 – 2.64 (m, 2H), 2.61 (s, 3H), 2.42 (s, 3H), 1.97 – 1.91 (m, 1H), 1.87 – 1.80 (m, 1H), 1.74 – 1.67 (m, 1H), 1.64 (s, 3H), 1.52 – 1.44 (m, 1H), 1.41 (d, *J* = 5.4 Hz, 3H), 1.06 (dd, *J* =

7.0, 4.5 Hz, 6H); MS m/z [M+H]⁺ 856.44

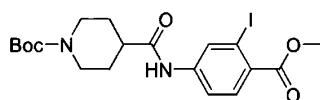
【1134】 [제조예 5-158'] methyl (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-

5 (sulfamoyloxy)prop-1-yn-1-yl)benzoate trifluoroacetic acid



【1135】

【1136】 단계 1: tert-butyl 4-((3-iodo-4-(methoxycarbonyl)phenyl)carbamoyl)piperidine-1-carboxylate (중간체 5-158'a)



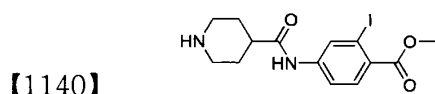
10

【1137】

【1138】 1-(tert-Butoxycarbonyl)piperidine-4-carboxylic acid와 methyl 4-amino-2-iodobenzoate를 출발물질로 하여 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-158'a를 합성하였다.

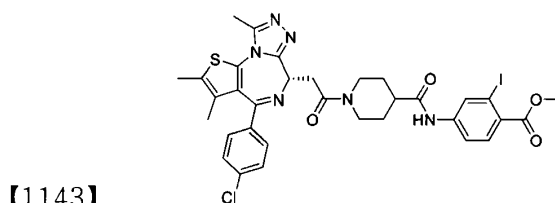
【1139】 단계 2: methyl 2-iodo-4-(piperidine-4-carboxamido)benzoate dihydrochloride (중간체 5-158'b)

15



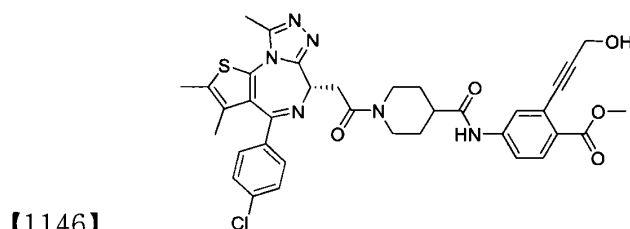
【1141】 중간체 5-158'a로부터 제조예 1-1의 단계 2와 동일한 방법으로 중간체 5-158'b를 합성하였다.

【1142】 단계 3: methyl (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-iodobenzoate (중간체 5-158'c)



【1144】 JQ1 carboxylic acid와 중간체 5-158'b로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-158'c를 합성하였다.

10 【1145】 단계 4: methyl (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-hydroxyprop-1-yn-1-yl)benzoate (중간체 5-158'd)



15 【1147】 중간체 5-158'c (0.3 mmol, 1 eq), propargylalcohol

(3.0 eq), Pd(PPh₃)₄ (0.02 eq), CuI (0.1 eq), TEA 1.0 mL, DMF 1.0 mL를 혼합한 뒤 반응 용기 내 기체를 Ar 기체로 치환한 후 상온조건에서 밤새 교반하였다. 혼합물을 flash column을 통해 정제해 중간체 5-158'd를 합성하였다.

5 **【1148】** 단계 5: methyl (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-(sulfamoyloxy)prop-1-yn-1-yl)benzoate trifluoroacetic acid

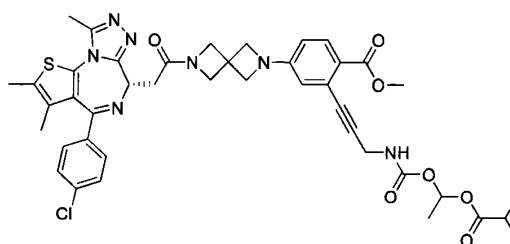
【1149】 중간체 5-158'd로부터 제조예 5-154'와 동일한
10 방법으로 실시예 5-158'를 합성하였다.

【1150】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.40 (d, *J* = 16.9 Hz, 1H), 8.00 (dd, *J* = 7.6, 2.2 Hz, 1H), 7.91 (dd, *J* = 8.7, 3.8 Hz, 1H), 7.72 (s, 2H), 7.69 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.53 – 7.42 (m, 4H), 7.28 (s, 1H), 6.69 (s, 1H), 5.02 (s, 2H), 4.59 (t, *J* = 6.7 Hz, 1H), 4.42 (s, 1H), 4.23 (s,
15 1H), 3.82 (d, *J* = 1.1 Hz, 3H), 3.67 – 3.54 (m, 1H), 2.68 (s, 2H), 2.60 (s, 3H), 2.42 (s, 3H), 1.91 (s, 1H), 1.84 (s, 1H), 1.70 (d, *J* = 13.0 Hz, 1H), 1.64 (s, 3H), 1.47 (d, *J* = 6.3 Hz, 1H).

【1151】 MS *m/z* [M+H]⁺ 778.42.

【1152】 [제조예 5-162'] methyl 4-(6-(2-((S)-4-(4-
20 chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-

a][1,4]diazepin-6-yl)acetyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate

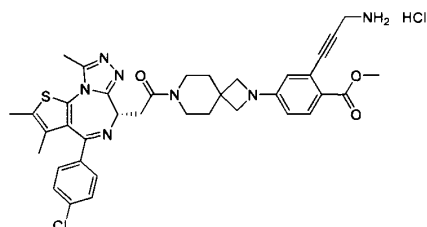


【1153】

【1154】 실시예 5-40'으로부터 제조예 5-157'과 동일한
5 방법으로 실시예 5-162'를 합성하였다.

【1155】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.98 (t, $J = 5.8$ Hz, 1H), 7.72 (d, $J = 8.5$ Hz, 1H), 7.50 – 7.45 (m, 2H), 7.42 – 7.37 (m, 2H), 6.66 (q, $J = 5.4$ Hz, 1H), 6.46 – 6.41 (m, 2H), 4.57 – 4.47 (m, 2H), 4.45 (t, $J = 7.1$ Hz, 1H), 4.11 (d, $J = 3.1$ Hz, 2H), 4.09 – 4.06 (m, 3H), 4.05 – 4.03
10 (m, 3H), 3.70 (s, 3H), 3.21 (dd, $J = 15.5, 6.9$ Hz, 1H), 3.11 (dd, $J = 15.5, 7.2$ Hz, 1H), 2.57 (s, 3H), 2.37 (d, $J = 1.1$ Hz, 3H), 1.59 (d, $J = 1.0$ Hz, 3H), 1.37 (d, $J = 5.4$ Hz, 3H), 1.03 (dd, $J = 7.0, 3.9$ Hz, 6H).

【1156】 [제조예 5-168'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
15 f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,7-

diazaspiro[3.5]nonan-2-yl)benzoate hydrochloride

【1157】

【1158】 JQ1 carboxylic acid와 중간체 5-168b로부터 제조예

5-85'의 단계 4 내지 5와 동일한 방법으로 제조예 5-168'을 합성하였다.

5 【1159】 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.76 (d, $J = 2.3$ Hz, 1H), 7.49 (s, 2H), 7.45 (s, 2H), 6.45 (s, 2H), 4.58 (t, $J = 1.7$ Hz, 1H), 3.74 (m, 6H), 3.64 (m, 5H), 3.48 (m, 2H), 3.28 (m, 2H), 2.60 (s, 3H), 2.42 (s, 3H), 1.88 (s, 2H), 1.70 (s, 2H), 1.63 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 696.2.

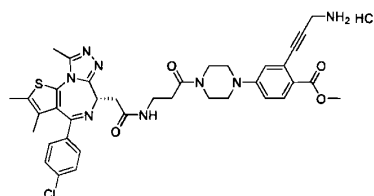
【1160】 【제조예 IV'】

10 【1161】 BRD4(Bromodomain-containing protein 4) 억제제로서의 활성을 나타내는 화합물(JQ1)이 본 발명의 화학식 IV에 해당하는 화합물들과 연결된 TBM-UBM 화합물을 아래와 같이 합성하였다.

【1162】 【제조예 5-32'】 methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

15

yl)acetamido)propanoyl)piperazin-1-yl)benzoate hydrochloride

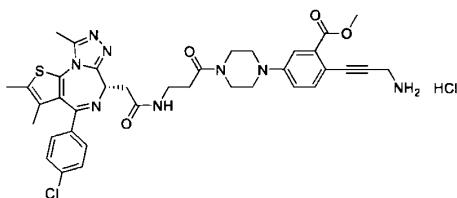


【1163】

【1164】 중간체 4-124'a 와 중간체 5-7b로부터 제조예 5-7'과 동일한 방법으로 실시예 5-32'를 합성하였다.

5 【1165】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.34 (s, 3H), 8.24 (t, J = 5.8 Hz, 1H), 7.78 (d, J = 8.9 Hz, 1H), 7.46 – 7.43 (m, 2H), 7.39 (d, J = 8.6 Hz, 2H), 7.00 (dd, J = 9.0, 2.7 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 4.47 (t, J = 7.1 Hz, 1H), 3.98 (q, J = 5.6 Hz, 2H), 3.75 (s, 3H), 3.59 – 3.54 (m, 3H), 3.39 – 3.26 (m, 9H), 3.19 (d, J = 7.2 Hz, 2H), 2.55 (s, 3H), 2.37 (s, 3H),
10 1.58 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 727.47.

【1166】 [제조예 5-33'] methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanoyl)piperazin-1-yl)benzoate hydrochloride



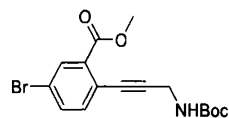
15

【1167】

【1168】 단계 1: methyl 5-bromo-2-(3-((tert-

butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate (중간체 5-33a)

【1169】



【1170】

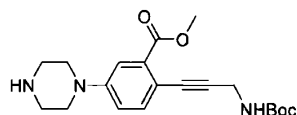
Methyl 5-bromo-2-iodobenzoate로부터 제조예 1-1의 단계 1과 동일한 방법으로 중간체 5-33a를 합성하였다.

5

【1171】

단계 2: methyl 2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-5-(piperazin-1-yl)benzoate (중간체 5-33b)

【1172】



【1173】

중간체 5-33a 와 piperazine로부터 제조예 5-40의 단계 1과 동일한 방법으로 중간체 5-33b를 합성하였다.

10

【1174】

단계 3: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanoyl)piperazin-1-yl)benzoate hydrochloride

15

【1175】

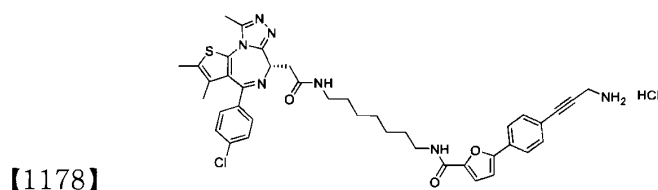
중간체 4-124'a와 중간체 5-33b로부터 제조예 1-1'와 동일한 방법으로 실시예 5-33'를 합성하였다.

【1176】

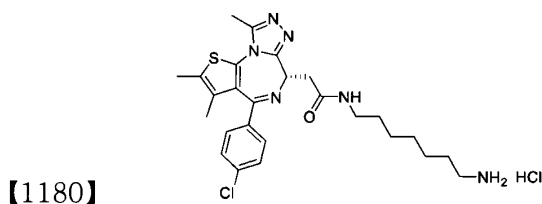
^1H NMR (500 MHz, DMSO- d_6) δ 8.26 (d, J = 26.6 Hz, 3H), 7.45 (dd, J = 8.9, 1.7 Hz, 2H), 7.43 - 7.36 (m, 3H), 7.29 (d, J = 2.8

Hz, 1H), 7.13 (dd, $J = 8.8, 2.6$ Hz, 1H), 7.07 (s, 1H), 4.48 (t, $J = 7.1$ Hz, 1H), 3.95 (q, $J = 5.6$ Hz, 1H), 3.81 (s, 3H), 3.36 – 3.27 (m, 5H), 3.27 – 3.18 (m, 5H), 2.56 (d, $J = 1.3$ Hz, 3H), 2.51 (q, $J = 6.4, 6.0$ Hz, 3H), 2.37 (s, 3H), 1.58 (s, 3H); MS m/z $[M+H]^+$ 727.47.

- 5 **【1177】** **【제조예 5-111'】** (S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide hydrochloride



- 10 **【1179】** 단계 1: (S)-N-(7-aminoheptyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride (중간체 5-111'a)



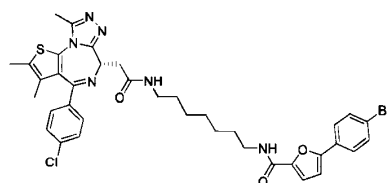
- 【1181】** tert-Butyl (7-aminopropyl)carbamate로부터 제조예

- 15 1-1'과 동일한 방법으로 중간체 5-111'a를 합성하였다.

【1182】 단계 2: (S)-5-(4-bromophenyl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide (중간체 5-111'b)

5

【1183】



【1184】 중간체 5-111'a와 5-(4-Bromophenyl)-2-furoic acid로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-111'b를 합성하였다.

【1185】 단계 3: (S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide hydrochloride

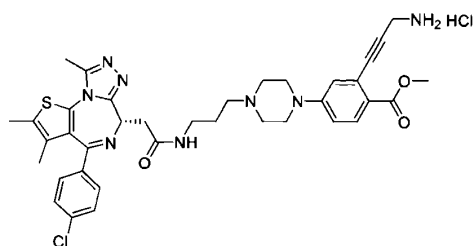
【1186】 중간체 5-111'b로부터 제조예 1-1과 동일한 방법으로 실시예 5-111'를 합성하였다.

15

【1187】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.48 (t, $J = 5.8$ Hz, 1H), 8.14 (t, $J = 5.7$ Hz, 1H), 7.87 - 7.83 (m, 2H), 7.46 - 7.41 (m, 5H), 7.39 - 7.36 (m, 2H), 7.09 (q, $J = 3.5$ Hz, 2H), 4.46 (dd, $J = 8.1, 6.1$ Hz, 1H), 3.49 (s, 2H), 3.19 (d, $J = 5.8$ Hz, 3H), 3.14 - 3.09 (m, 2H), 3.05 (dq, $J =$

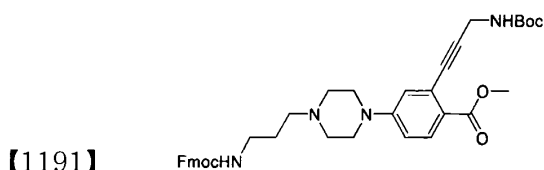
12.9, 6.2 Hz, 2H), 2.54 (d, J = 2.0 Hz, 3H), 2.35 (d, J = 3.1 Hz, 3H), 1.57 (s, 3H), 1.52 (d, J = 8.1 Hz, 2H), 1.48 (d, J = 7.6 Hz, 2H), 1.40 (s, 2H), 1.19 (s, 4H); MS m/z $[M+H]^+$ 736.56.

【1188】 [제조예 5-164'] methyl (S)-2-(3-aminoprop-1-yn-
5 1-yl)-4-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)piperazin-1-
yl)benzoate hydrochloride



【1189】

【1190】 단계 1: methyl 4-(4-(3-(((9H-fluoren-9-
10 yl)methoxy)carbonyl)amino)propyl)piperazin-1-yl)-2-(3-((tert-
butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate (중간체 5-164a)

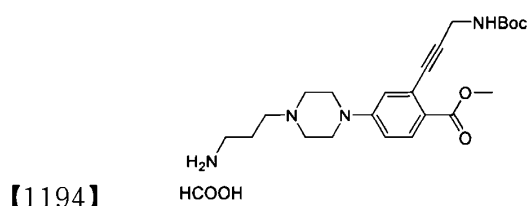


【1191】

【1192】 중간체 5-7b (0.1 mmol, 1.0 eq)을 DCM 3.0 mL에 녹인
후 0 °C에서 NaBH(OAc)₃ (3.0 eq), (9H-fluoren-9-yl)methyl (3-
15 oxopropyl)carbamate (1.2 eq), acetic acid (1.0 eq)를 천천히 첨가해 12
시간 교반하였다. 반응물은 DCM, H₂O로 추출 후 유기층을 Na₂SO₄로

건조하였다. 혼합물을 감압여과 후 증류한 뒤 flash column을 통해 정제해
중간체 5-164a를 합성하였다.

- 【1193】 단계 2: methyl 4-(4-(3-aminopropyl)piperazin-1-yl)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate formic
5 acid (중간체 5-164b)



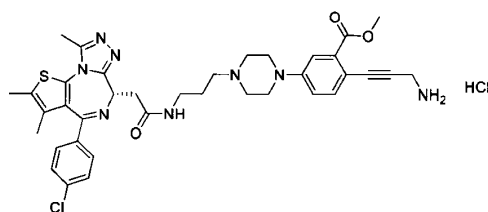
- 【1195】 중간체 5-164a (0.1 mmol, 1.0 eq)을 piperidine/DMF
(1:1) 2.0 mL에 녹인 후 실온에서 0.5 시간 교반하였다. 반응물은 감압
농축한 뒤 prep HPLC를 통해 정제해 중간체 5-164b를 합성하였다.
- 10 【1196】 단계 3: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)piperazin-1-yl)benzoate hydrochloride

- 【1197】 JQ1 carboxylic acid와 중간체 5-164b로부터 제조예
15 5-77'의 단계 2 내지 2과 동일한 방법으로 실시예 5-164'을 합성하였다.

- 【1198】 ^1H NMR (400 MHz, DMSO- d_6) δ 11.37 (s, 1H), 8.65 - 8.47 (m, 3H), 7.84 (d, J = 2.2 Hz, 1H), 7.53 (d, J = 2.2 Hz, 2H), 7.44 (d, J = 2.1 Hz, 2H), 7.19 (s, 1H), 7.18 - 7.12 (m, 1H), 4.59 - 4.57 (m, 1H), 4.05

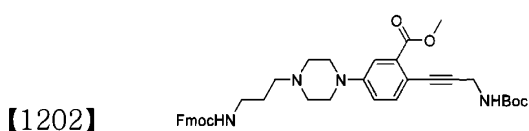
- 3.99 (m, 4H), 3.81 (s, 3H), 3.61 - 3.56 (m, 2H), 3.43 - 3.39 (m, 2H), 3.30 - 3.27 (m, 3H), 3.17 - 3.12 (m, 5H), 2.64 (s, 3H), 2.42 (m, 3H), 1.96 - 1.91 (m, 2H), 1.62 (s, 3H); MS m/z [M+H]⁺ 713.5.

【1199】 [제조예 5-165'] methyl (S)-2-(3-aminoprop-1-yn-
5 1-yl)-5-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-
f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)piperazin-1-
yl)benzoate hydrochloride



【1200】

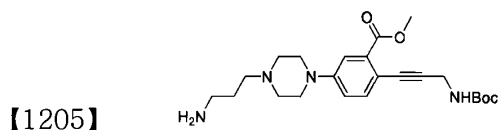
【1201】 단계 1: methyl 5-(4-(3-(((9H-fluoren-9-
10 yl)methoxy)carbonyl)amino)propyl)piperazin-1-yl)-2-(3-((tert-
butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate(중간체 5-165a)



【1202】

【1203】 5-33b를 출발물질로 하여 제조예 5-164' 단계 1과
동일한 방법으로 중간체 5-165a를 합성하였다.

15 【1204】 단계 2: methyl 5-(4-(3-aminopropyl)piperazin-1-
yl)-2-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)benzoate (중간체
5-165b)



【1206】 중간체 5-165a를 출발물질로 하여 실시예 5-29의 단계 4와 동일한 방법으로 중간체 5-165b를 합성하였다.

【1207】 단계 3: methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)piperazin-1-yl)benzoate hydrochloride

【1208】 중간체 5-165b를 출발물질로 하여 실시예 5-77'의 단계 2와 동일한 방법으로 실시예 5-165'을 합성하였다.

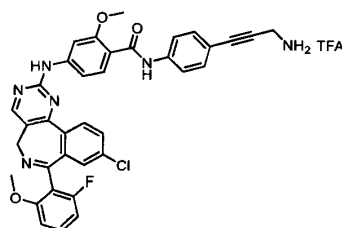
【1209】 ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.21 (t, $J = 1.4$ Hz, 1H), 7.48 (d, $J = 2.1$ Hz, 2H), 7.42 (d, $J = 2.1$ Hz, 2H), 7.32 (d, $J = 2.2$ Hz, 1H), 7.25 (s, 1H), 7.11 (m, 1H), 4.50 (t, $J = 1.7$ Hz, 1H), 3.82 (s, 3H), 3.48 (s, 2H), 3.24 - 3.20 (m, 6H), 3.15 (m, 2H), 2.59 (s, 3H), 2.41 (s, 4H), 2.37 (s, 3H), 2.34 (m, 2H), 1.62 (s, 5H); MS m/z $[\text{M} + \text{H}]^+$ 713.4.

【1210】 [제조예 I'']

【1211】 Aurora A 키나제 억제제로서의 활성을 나타내는 화합물(Alisertib)이 본 발명의 화학식 I에 해당하는 화합물들과 연결된 TBM-UBM 화합물을 아래와 같이 합성하였다.

【1212】 [제조예 1-1''] N-(4-(3-aminoprop-1-yn-1-

yl)phenyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid



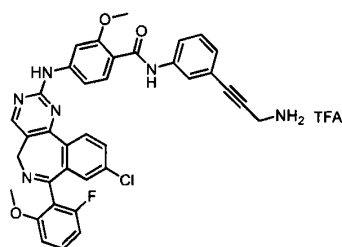
【1213】

- 5 【1214】 상업적으로 구입 가능한 Alisertib(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoic acid)와 중간체 1-1a로부터 제조예 5-155'의 단계 2 내지 3과 동일한 방법으로 실시예 1-1''을 합성하였다.

 【1215】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.23 (s, 1H), 10.10 (s, 1H), 8.71 (d, *J* = 3.6 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 8.22 (s, 3H), 7.98 (s, 1H), 7.79 (dd, *J* = 9.5, 6.9 Hz, 3H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.41 (dddd, *J* = 12.3, 9.9, 8.5, 1.8 Hz, 4H), 3.98 – 3.94 (m, 2H), 3.92 (s, 3H); MS *m/z* [M+H]⁺ 647.45.

- 【1216】 [제조예 1-3''] N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide

trifluoroacetic acid



【1217】

【1218】 Alisertib과 중간체 1-3a로부터 제조예 5-155'의 단계

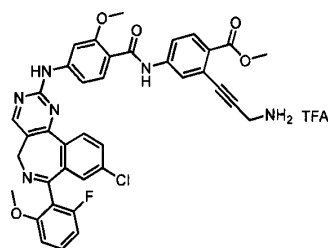
2 내지 3과 동일한 방법으로 실시예 1-3''을 합성하였다.

5 【1219】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.27 (s, 1H), 10.07 (s, 1H), 8.74 (s, 1H), 8.31 (d, $J = 8.8$ Hz, 4H), 8.11 (s, 1H), 8.01 (s, 1H), 7.83 (dd, $J = 8.5, 2.2$ Hz, 1H), 7.74 (d, $J = 8.6$ Hz, 1H), 7.66 – 7.63 (m, 1H), 7.48 (dd, $J = 8.6, 1.9$ Hz, 1H), 7.45 – 7.37 (m, 2H), 7.23 (s, 1H), 7.18 (d, $J = 7.7$ Hz, 1H), 4.03 (d, $J = 5.6$ Hz, 2H), 3.96 (s, 6H), 3.80 (s, 2H); MS m/z

10 $[\text{M} + \text{H}]^+$ 647.45.

【1220】 [제조예 3-25''] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-

methoxybenzamido)benzoate trifluoroacetic acid



【1221】

【1222】 Alisertib과 중간체 3-25a로부터 제조예 5-155'의

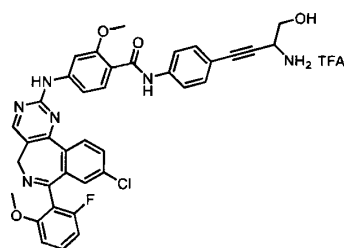
단계 2 내지 3과 동일한 방법으로 실시예 3-25''을 합성하였다.

5 【1223】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.30 (d, $J = 4.6$ Hz, 2H), 8.75 (s, 1H), 8.35 (s, 2H), 8.30 (d, $J = 2.6$ Hz, 3H), 8.02 (s, 1H), 7.93 (d, $J = 8.6$ Hz, 1H), 7.83 (dd, $J = 8.5, 2.2$ Hz, 1H), 7.73 (td, $J = 6.4, 3.3$ Hz, 2H), 7.48 (dd, $J = 8.6, 1.9$ Hz, 1H), 7.43 (td, $J = 8.4, 6.8$ Hz, 1H), 7.23 (s, 1H), 7.04 – 6.77 (m, 1H), 4.08 (s, 2H), 3.96 (s, 6H), 3.85 (s, 5H); MS m/z

10 $[\text{M} + \text{H}]^+$ 705.39.

【1224】 【제조예 3-49''】 N-(4-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide

trifluoroacetic acid

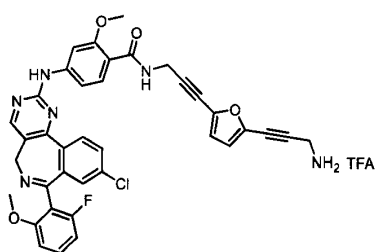


【1225】

【1226】 Alisertib과 중간체 3-49c로부터 제조예 5-155'의 단계 2 내지 3과 동일한 방법으로 실시예 3-49''을 합성하였다.

5 【1227】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.23 (s, 1H), 10.10 (s, 1H), 8.70 (s, 1H), 8.40 (d, $J = 5.3$ Hz, 3H), 8.27 (d, $J = 8.5$ Hz, 1H), 7.97 (s, 1H), 7.82 – 7.76 (m, 4H), 7.70 (d, $J = 8.6$ Hz, 1H), 7.46 – 7.35 (m, 5H), 7.19 (s, 1H), 4.32 – 4.26 (m, 1H), 3.92 (s, 3H), 3.74 (dd, $J = 11.3, 4.4$ Hz, 1H), 3.63 (dd, $J = 11.2, 7.0$ Hz, 1H); MS m/z $[\text{M} + \text{H}]^+$ 677.52.

10 【1228】 【제조예 4-1''】 N-(3-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid

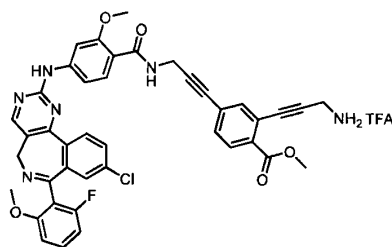


【1229】

【1230】 Alisertib로부터 중간체 4-1d로부터 제조예 5-155'의 단계 2 내지 3과 동일한 방법으로 실시예 4-1''을 합성하였다.

【1231】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.22 (s, 1H), 8.70 (s, 1H), 8.52 (t, $J = 5.7$ Hz, 1H), 8.28 (s, 2H), 8.26 (s, 3H), 7.96 (s, 1H), 7.83 (d, $J = 8.7$ Hz, 1H), 7.79 (dd, $J = 8.5, 2.2$ Hz, 1H), 7.42 – 7.34 (m, 3H), 7.19 (s, 1H), 6.91 (d, $J = 3.6$ Hz, 1H), 6.84 (d, $J = 3.6$ Hz, 1H), 4.32 (d, $J = 5.7$ Hz, 2H), 4.04 (d, $J = 5.5$ Hz, 2H), 3.90 (s, 6H); MS m/z $[\text{M} + \text{H}]^+$ 675.42.

【1232】 [제조예 5-116''] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)prop-1-yn-1-yl)benzoate trifluoroacetic acid



【1233】

【1234】 Alisertib과 중간체 5-116c로부터 제조예 5-155'의 단계 2 내지 3과 동일한 방법으로 실시예 5-116''을 합성하였다.

【1235】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.21 (d, $J = 2.6$ Hz, 1H), 8.70 (s, 1H), 8.52 (t, $J = 5.7$ Hz, 1H), 8.29 – 8.19 (m, 5H), 7.96 (s, 1H), 7.85 (dd, $J = 11.4, 8.4$ Hz, 2H), 7.79 (dd, $J = 8.5, 2.3$ Hz, 1H), 7.59 –

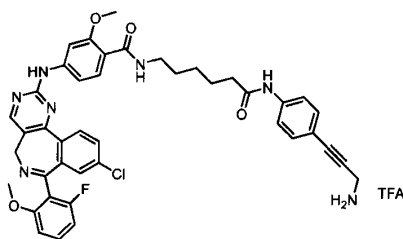
7.51 (m, 2H), 7.42 – 7.35 (m, 3H), 7.19 (s, 1H), 4.33 (d, $J = 5.7$ Hz, 2H), 4.01 (q, $J = 5.6$ Hz, 2H), 3.91 (s, 3H), 3.82 (s, 3H); MS m/z $[M + H]^+$ 743.45.

【1236】 【제조예 II'】

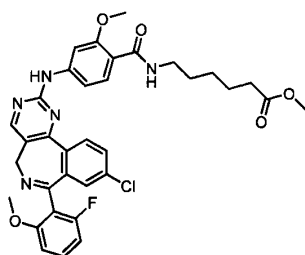
【1237】 Aurora A 키나제 억제제로서의 활성을 나타내는
5 화합물(Alisertib)이 본 발명의 화학식 II에 해당하는 화합물들과 연결된
TBM-UBM 화합물을 아래와 같이 합성하였다.

【1238】 【제조예 4-165''】 N-(6-((4-(3-aminoprop-1-yn-1-yl)phenyl)amino)-6-oxohexyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
10

【1239】



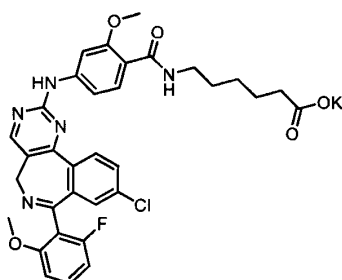
【1240】 단계 1: methyl 6-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)hexanoate(중간체 4-165''a)



【1241】

【1242】 Alisertib와 methyl 6-aminohexanoate를 출발물질로 하여 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 4-165''a를 합성하였다.

5 【1243】 단계 2: potassium 6-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)hexanoate (중간체 4-165''b)



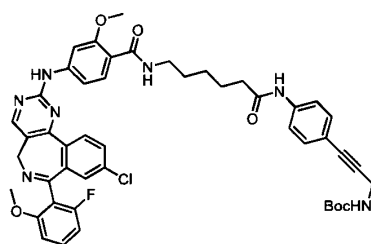
【1244】

【1245】 중간체 4-165''a (0.04 mmol, 1.0 eq), potassium trimethylsilanolate (4.0 eq), THF 0.5 mL를 혼합한 뒤 실온에서 3 시간 교반하였다. 반응물을 감압여과 후 추가정제 없이 중간체 4-165''b를 합성하였다.

【1246】 단계 3: tert-butyl (3-(4-(6-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-

yl)amino)-2-methoxybenzamido)hexanamido)phenyl)prop-2-yn-1-yl)carbamate (중간체 4-165''c)

【1247】

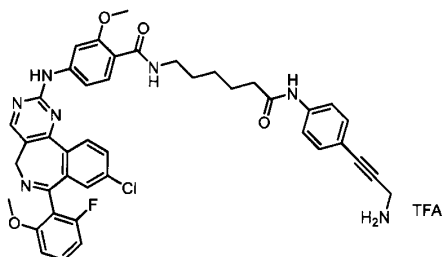


【1248】 중간체 4-165''b와 1-1a를 출발물질로 하여 제조예

5 4-1'의 단계 1과 동일한 방법으로 중간체 4-165''c를 합성하였다.

【1249】 단계 4: N-(6-((4-(3-aminoprop-1-yn-1-yl)phenyl)amino)-6-oxohexyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid

【1250】



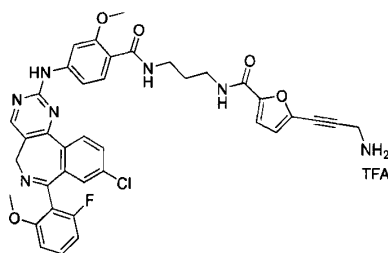
10

【1251】 중간체 4-165''c로부터 제조예 5-153'의 단계 3과 동일한 방법으로 실시예 4-165''을 합성하였다.

【1252】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.15 (s, 1H), 10.07 (s, 1H), 8.68 (s, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.20 (s, 3H), 8.01 (s, 1H),

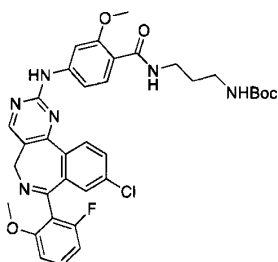
7.91 (s, 1H), 7.80 – 7.77 (m, 1H), 7.77 – 7.74 (m, 2H), 7.63 – 7.60 (m, 2H), 7.38 (d, $J = 7.0$ Hz, 1H), 7.37 – 7.34 (m, 4H), 3.94 (d, $J = 5.7$ Hz, 2H), 3.87 (s, 6H), 2.31 (d, $J = 7.7$ Hz, 4H), 1.60 (d, $J = 7.4$ Hz, 2H), 1.51 (t, $J = 7.3$ Hz, 2H), 1.32 (d, $J = 7.2$ Hz, 2H); MS m/z $[M+H]^+$ 760.44.

- 5 **【1253】** **[제조예 4-166"] 5-(3-aminoprop-1-yn-1-yl)-N-(3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propyl)furan-2-carboxamide trifluoroacetic acid**



【1254】

- 10 **【1255】** 단계 1: tert-butyl (3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propyl)carbamate (중간체 4-166"a)

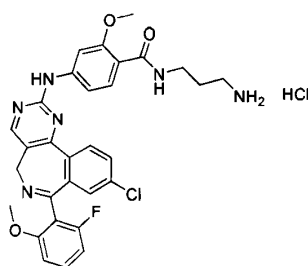


【1256】

- 【1257】** tert-Butyl (3-aminopropyl)carbamate를 사용하여

제조예 4-165''의 단계 1과 동일한 방법으로 중간체 4-166''a를 합성하였다.

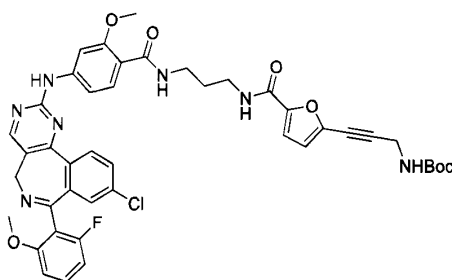
【1258】 단계 2: N-(3-aminopropyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide hydrochloride(중간체 4-166''b)



【1259】

【1260】 중간체 4-166''a로부터 제조예 1-1의 단계 2와 동일한 방법으로 중간체 4-166''b를 합성하였다.

【1261】 단계 3: tert-butyl (3-(5-((3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propyl)carbamoyl)furan-2-yl)prop-2-yn-1-yl)carbamate (중간체 4-166''c)



【1262】

【1263】 중간체 4-166''b와 중간체 4-227b로부터 제조예 1-

1'의 단계 1과 동일한 방법으로 중간체 4-166''c를 합성하였다.

【1264】 단계 4: 5-(3-aminoprop-1-yn-1-yl)-N-(3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propyl)furan-2-

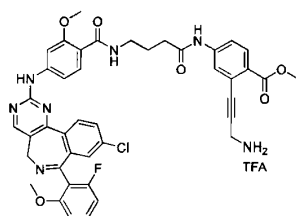
5 carboxamide trifluoroacetic acid

【1265】 중간체 4-166''c로부터 제조예 5-153'의 단계 3과 동일한 방법으로 실시예 4-166''을 합성하였다.

【1266】 ^1H NMR (500 MHz, DMSO- d_6) δ 10.20 (s, 1H), 8.72 (s, 1H), 8.60 (t, $J = 6.0$ Hz, 1H), 8.39 – 8.25 (m, 6H), 7.97 (s, 1H), 7.84 – 7.81 (m, 2H), 7.44 – 7.40 (m, 2H), 7.22 (s, 1H), 7.19 (d, $J = 3.6$ Hz, 1H), 7.01 (d, $J = 3.6$ Hz, 1H), 4.11 (d, $J = 5.6$ Hz, 2H), 3.94 (s, 6H), 3.30 (dt, $J = 12.9, 6.4$ Hz, 6H), 1.70 (q, $J = 6.7$ Hz, 2H); MS m/z $[\text{M} + \text{H}]^+$ 722.47.

【1267】 [제조예 4-228''] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)butanamido)benzoate trifluoroacetic acid

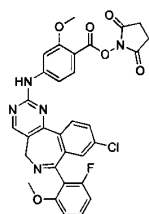
【1268】



【1269】 단계 1: 2,5-dioxopyrrolidin-1-yl 4-((9-chloro-7-

(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoate (중간체 4-228''a)

【1270】

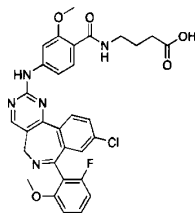


【1271】 Alisertib로부터 제조예 4-177'의 단계 1과 같은

5 방법으로 중간체 4-228''a를 합성하였다.

【1272】 단계 2: 4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)butanoic acid (중간체 4-228''b)

【1273】



10 【1274】 중간체 4-228''a와 4-aminobutanoic acid로부터

제조예 4-1'의 단계 1과 동일한 방법으로 중간체 4-228''b를 합성하였다.

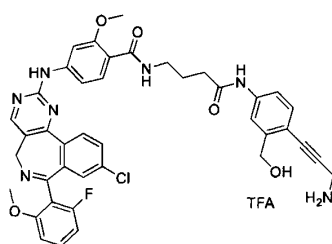
【1275】 단계 3: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-

15 methoxybenzamido)butanamido)benzoate trifluoroacetic acid

【1276】 중간체 4-228''b, 중간체 3-25a로부터 제조예 5-153'의 단계 3과 동일한 방법으로 실시예 4-228''을 합성하였다.

【1277】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.40 (s, 1H), 10.19 (s, 1H), 8.72 (s, 1H), 8.29 (d, $J = 8.6$ Hz, 5H), 8.16 – 8.13 (m, 2H), 7.94 (s, 1H), 7.89 (d, $J = 8.6$ Hz, 1H), 7.84 – 7.79 (m, 2H), 7.52 (dd, $J = 8.7, 2.2$ Hz, 1H), 7.44 – 7.39 (m, 2H), 7.22 (s, 1H), 4.07 (d, $J = 5.7$ Hz, 2H), 3.91 (s, 3H), 3.81 (s, 6H), 3.35 (q, $J = 6.6$ Hz, 4H), 2.41 (t, $J = 7.3$ Hz, 2H), 1.84 (q, $J = 7.2$ Hz, 2H); MS m/z $[\text{M} + \text{H}]^+$ 760.51.

【1278】 [제조예 5-8''] N-(4-((4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)amino)-4-oxobutyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid



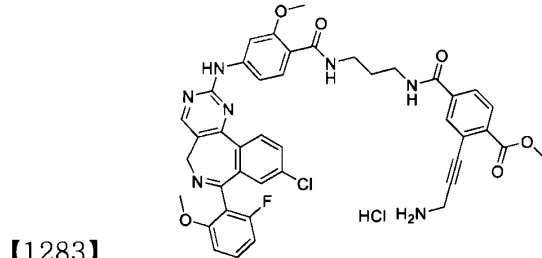
【1279】

【1280】 Alisertib과 중간체 3-3c로부터 제조예 4-125'과 동일한 방법으로 제조하고, prep HPLC 추가정제하여 실시예 5-8''을 합성하였다.

【1281】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.19 (s, 1H), 10.16

(s, 1H), 8.72 (s, 1H), 8.30 (d, $J = 8.5$ Hz, 1H), 8.25 (s, 4H), 8.14 (t, $J = 5.8$ Hz, 1H), 7.95 (s, 1H), 7.84 – 7.77 (m, 2H), 7.76 (d, $J = 2.2$ Hz, 1H), 7.62 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.41 (ddd, $J = 8.6, 6.9, 1.7$ Hz, 3H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.21 (d, $J = 9.2$ Hz, 1H), 4.62 (s, 2H), 4.01 (q, $J = 5.6$ Hz, 2H),
 5 3.92 (s, 6H), 3.16 (s, 4H), 2.38 (s, 2H), 1.84 (s, 2H); MS m/z $[M+H]^+$ 762.54.

【1282】 **【제조예 5-18'】** methyl 2-(3-aminoprop-1-yn-1-yl)-
 4-((3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-
 benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-
 10 methoxybenzamido)propyl)carbamoyl)benzoate hydrochloride



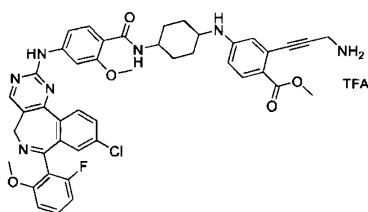
【1284】 Alisertib로부터 제조예 5-18'과 동일한 방법으로
 실시예 5-18''을 합성하였다.

【1285】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.22 (s, 1H), 8.89
 15 (t, $J = 5.8$ Hz, 1H), 8.73 (s, 1H), 8.45 (s, 3H), 8.34 – 8.27 (m, 2H), 8.09 (t,
 $J = 1.2$ Hz, 1H), 7.99 (d, $J = 1.2$ Hz, 2H), 7.96 (s, 1H), 7.88 – 7.79 (m, 3H),
 7.48 – 7.38 (m, 3H), 7.25 (s, 1H), 4.06 (q, $J = 5.6$ Hz, 2H), 3.94 (s, 6H),

3.89 (s, 3H), 3.87 (s, 2H), 3.34 (q, $J = 7.4$ Hz, 4H), 1.75 (t, $J = 6.7$ Hz, 2H);

MS m/z $[M+H]^+$ 790.41.

- 【1286】** **[제조예 5-35'']** methyl 2-(3-aminoprop-1-yn-1-yl)-
4-((4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-
5 benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-
methoxybenzamido)cyclohexyl)amino)benzoate trifluoroacetic acid



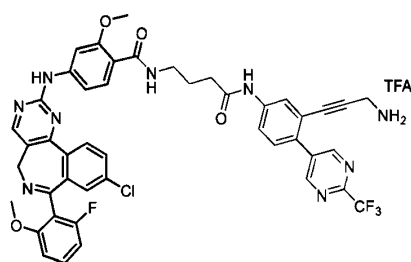
【1287】

- 【1288】** Alisertib로부터 제조예 5-35'의 단계 4 내지 5와
동일한 방법으로 실시예 5-35''을 합성하였다.

- 10 **【1289】** ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.19 (s, 1H), 8.69
(d, $J = 3.5$ Hz, 1H), 8.29 – 8.21 (m, 6H), 7.99 (d, $J = 7.1$ Hz, 2H), 7.81 (d,
 $J = 8.6$ Hz, 1H), 7.78 (dd, $J = 8.5, 2.2$ Hz, 2H), 7.68 (dd, $J = 8.9, 1.5$ Hz,
1H), 7.42 – 7.35 (m, 3H), 6.69 (s, 2H), 3.99 (q, $J = 5.7$ Hz, 2H), 3.95 (s,
3H), 3.89 (s, 1H), 3.71 (s, 1H), 3.44 (s, 1H), 2.59 (dp, $J = 5.5, 1.8$ Hz, 2H),
15 1.94 (d, $J = 11.0$ Hz, 2H), 1.71 (t, $J = 13.3$ Hz, 4H), 1.49 (d, $J = 9.0$ Hz, 2H);
MS m/z $[M+H]^+$ 802.50.

- 【1290】** **[제조예 5-81'']** N-(4-((3-(3-aminoprop-1-yn-1-
yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)amino)-4-oxobutyl)-4-

((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid



【1291】

【1292】 Alisertib로부터 제조예 5-81'과 동일한 방법으로

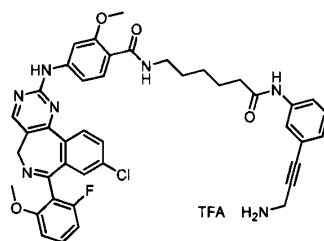
5 실시예 5-81''을 합성하였다.

【1293】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.34 (s, 1H), 10.19 (s, 1H), 9.28 (s, 2H), 8.72 (s, 1H), 8.29 (d, $J = 8.6$ Hz, 1H), 8.26 – 8.17 (m, 4H), 8.14 (t, $J = 5.8$ Hz, 1H), 7.94 (s, 1H), 7.85 – 7.76 (m, 2H), 7.66 – 7.60 (m, 2H), 7.45 – 7.37 (m, 3H), 7.22 (s, 1H), 3.98 – 3.93 (m, 2H), 3.92 (s, 6H),
10 3.37 (d, $J = 6.4$ Hz, 4H), 2.42 (d, $J = 7.4$ Hz, 2H), 1.87 (t, $J = 7.1$ Hz, 2H);
MS m/z $[\text{M} + \text{H}]^+$ 878.42.

【1294】 [제조예 5-104''] N-(6-((3-(3-aminoprop-1-yn-1-yl)phenyl)amino)-6-oxohexyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-

methoxybenzamide trifluoroacetic acid

【1295】

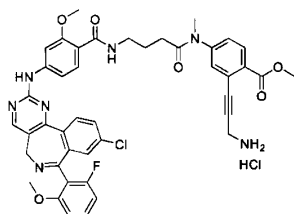


【1296】 중간체 4-165''b와 중간체 1-3a로부터 제조예 4-165''의 단계 3 내지 4와 동일한 방법으로 실시예 5-104''을 합성하였다.

5 【1297】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.15 (s, 1H), 10.01 (s, 1H), 8.68 (s, 1H), 8.26 (d, $J = 8.5$ Hz, 2H), 8.23 (s, 3H), 8.01 (t, $J = 5.8$ Hz, 1H), 7.93 (t, $J = 1.9$ Hz, 1H), 7.91 (s, 1H), 7.78 (dd, $J = 8.5, 2.2$ Hz, 1H), 7.75 (d, $J = 8.6$ Hz, 1H), 7.43 – 7.39 (m, 2H), 7.37 (dt, $J = 8.7, 1.8$ Hz, 2H), 7.29 (t, $J = 7.9$ Hz, 1H), 7.07 (dt, $J = 7.6, 1.4$ Hz, 1H), 3.97 (d, $J = 5.7$ Hz, 2H), 3.86 (s, 3H), 2.29 (t, $J = 7.4$ Hz, 4H), 1.60 (d, $J = 7.5$ Hz, 2H), 1.50 (d, 10 $J = 7.5$ Hz, 2H), 1.32 (d, $J = 7.4$ Hz, 2H); MS m/z $[\text{M} + \text{H}]^+$ 760.44.

【1298】 [제조예 5-150''] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)-N-

methylbutanamido)benzoate hydrochloride



【1299】

【1300】 Alisertib로부터 제조예 5-150'과 동일한 방법으로 실시예 5-150''을 합성하였다.

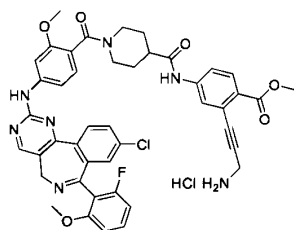
5 【1301】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.15 (s, 1H), 8.69 (s, 1H), 8.29 – 8.23 (m, 5H), 7.99 (s, 1H), 7.89 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.79 (dd, J = 8.5, 2.2 Hz, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.54 (d, J = 2.3 Hz, 1H), 7.47 (dd, J = 8.5, 2.2 Hz, 1H), 7.42 – 7.34 (m, 3H), 7.19 (s, 1H), 4.02 (q, J = 5.6 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 6H), 3.23 – 3.16 (m, 7H),
10 2.23 (s, 2H), 1.71 (p, J = 6.9 Hz, 2H); MS m/z $[\text{M} + \text{H}]^+$ 804.39

【1302】 【제조예 III'】

【1303】 Aurora A 키나제 억제제로서의 활성을 나타내는 화합물(Alisertib)이 본 발명의 화학식 III에 해당하는 화합물들과 연결된 TBM-UBM 화합물을 아래와 같이 합성하였다.

15 【1304】 【제조예 5-23''】 methyl 2-(3-aminoprop-1-yn-1-yl)-4-(1-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-

methoxybenzoyl)piperidine-4-carboxamido)benzoate hydrochloride



【1305】

【1306】 Alisertib로부터 제조예 5-23'과 동일한 방법으로 실시예 5-23''을 합성하였다.

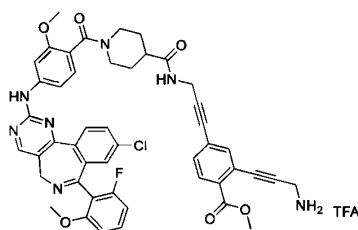
5 【1307】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.46 (s, 1H), 10.04 (s, 1H), 8.66 (s, 1H), 8.33 (s, 3H), 8.26 (d, $J = 8.5$ Hz, 2H), 8.12 (d, $J = 16.3$ Hz, 1H), 7.86 (d, $J = 8.7$ Hz, 2H), 7.78 (dd, $J = 8.5, 2.2$ Hz, 1H), 7.54 - 7.52 (m, 1H), 7.39 (td, $J = 8.4, 6.9$ Hz, 2H), 7.34 (s, 1H), 7.19 (d, $J = 10.7$ Hz, 1H), 7.13 - 7.02 (m, 1H), 4.51 (s, 1H), 4.01 (t, $J = 5.6$ Hz, 2H), 3.79 (s, 10 3H), 3.77 (s, 3H), 2.76 (t, $J = 12.4$ Hz, 2H), 2.59 (dp, $J = 5.5, 1.9$ Hz, 2H), 1.87 (s, 2H), 1.71 (s, 2H); MS m/z $[\text{M} + \text{H}]^+$ 816.48.

【1308】 [제조예 5-28''] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)piperidine-4-carboxamido)prop-1-yn-1-yl)benzoate

15

trifluoroacetic acid

【1309】



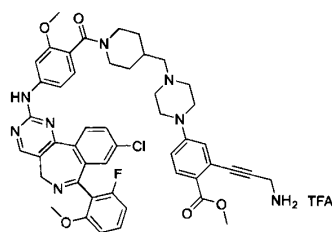
【1310】 Alisertib로부터 제조예 5-28'과 동일한 방법으로 실시예 5-28''을 합성하였다.

5 【1311】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.02 (s, 1H), 8.65 (s, 1H), 8.40 (s, 1H), 8.26 (s, 3H), 8.24 (s, 2H), 7.86 (d, $J = 8.1$ Hz, 1H), 7.84 (s, 1H), 7.79 – 7.75 (m, 1H), 7.55 (s, 1H), 7.52 (d, $J = 8.2$ Hz, 1H), 7.41 – 7.35 (m, 1H), 7.33 (s, 1H), 7.17 (d, $J = 7.5$ Hz, 1H), 7.16 – 7.07 (m, 1H), 7.12 – 7.00 (m, 1H), 4.46 (s, 1H), 4.11 (s, 2H), 4.01 (q, $J = 5.6$ Hz, 2H), 3.82 (s, 3H), 3.76 (s, 6H), 2.93 (d, $J = 47.2$ Hz, 2H), 2.72 (t, $J = 12.7$ Hz, 2H), 1.75 (d, $J = 12.7$ Hz, 2H), 1.65 – 1.29 (m, 2H); MS m/z $[\text{M} + \text{H}]^+$ 854.44.

15 【1312】 [제조예 5-29''] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-((1-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)benzoate

trifluoroacetic acid

【1313】

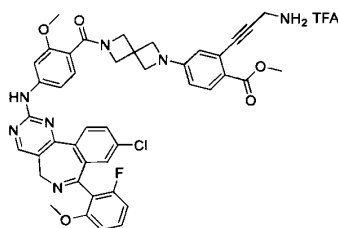


【1314】 Alisertib와 중간체 5-29d로부터 제조예 5-155'의

단계 2 내지 3과 동일한 방법으로 실시예 5-29''을 합성하였다.

5 【1315】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.04 (s, 1H), 9.60 (s, 1H), 8.66 (s, 1H), 8.30 (s, 3H), 8.25 (d, $J = 8.5$ Hz, 1H), 7.81 (d, $J = 8.9$ Hz, 2H), 7.77 (d, $J = 8.8$ Hz, 1H), 7.39 (td, $J = 8.4, 6.8$ Hz, 1H), 7.33 (s, 1H), 7.17 (d, $J = 9.3$ Hz, 1H), 7.11 (d, $J = 2.6$ Hz, 1H), 7.09 (d, $J = 2.6$ Hz, 1H), 7.06 (d, $J = 2.7$ Hz, 2H), 4.48 (d, $J = 12.7$ Hz, 1H), 4.00 (d, $J = 5.6$ Hz, 3H),
10 3.77 (s, 6H), 3.40 (d, $J = 13.0$ Hz, 2H), 3.18 (s, 3H), 3.08 (s, 5H), 2.91 (s, 1H), 2.73 (t, $J = 12.4$ Hz, 1H), 2.08 (s, 1H), 1.83 (d, $J = 11.0$ Hz, 1H), 1.64 (d, $J = 24.6$ Hz, 1H), 1.16 (d, $J = 37.6$ Hz, 3H), 1.00 (d, $J = 6.1$ Hz, 1H); MS m/z $[\text{M} + \text{H}]^+$ 871.53.

15 【1316】 [제조예 5-40''] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(6-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)-2,6-

diazaspiro[3.3]heptan-2-yl)benzoate trifluoroacetic acid**【1317】**

【1318】 Alisertib로부터 제조예 5-40'과 동일한 방법으로 실시예 5-40''을 합성하였다.

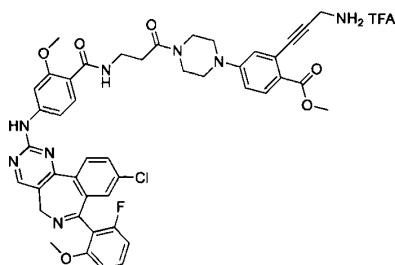
5 **【1319】** ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.08 (s, 1H), 8.67 (s, 1H), 8.30 – 8.16 (m, 5H), 7.87 (s, 1H), 7.80 – 7.73 (m, 3H), 7.42 – 7.35 (m, 1H), 7.32 (dd, $J = 8.5, 1.8$ Hz, 1H), 7.25 (d, $J = 8.4$ Hz, 1H), 7.18 (s, 1H), 6.45 (dd, $J = 8.8, 2.5$ Hz, 1H), 6.41 (d, $J = 2.4$ Hz, 1H), 4.17 (s, 2H), 4.12 (s, 2H), 4.09 (d, $J = 8.7$ Hz, 2H), 4.05 (s, 2H), 3.99 (q, $J = 5.6$ Hz, 2H),
10 3.81 (s, 3H), 3.73 (s, 3H); MS m/z $[\text{M} + \text{H}]^+$ 786.41.

【1320】 [제조예 IV'']

【1321】 Aurora A 키나제 억제제로서의 활성을 나타내는 화합물(Alisertib)이 본 발명의 화학식 IV에 해당하는 화합물들과 연결된 TBM-UBM 화합물을 아래와 같이 합성하였다.

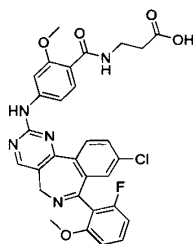
15 **【1322】** [제조예 5-32''] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-

methoxybenzamido)propanoyl)piperazin-1-yl)benzoate trifluoroacetic acid



【1323】

- 【1324】 단계 1: 3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propanoic acid (중간체 5-32''a)



【1325】

【1326】 Alisertib로부터 제조예 4-124'의 단계 1과 동일한 방법으로 중간체 5-32''a를 합성하였다.

- 【1327】 단계 2: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propanoyl)piperazin-1-yl)benzoate trifluoroacetic acid

【1328】 중간체 5-32''a 와 중간체 5-7b로부터 제조예 1-1'와

동일한 방법으로 합성한 후 prep HPLC 로 추가 정제하여 실시예 5-32''를 합성하였다.

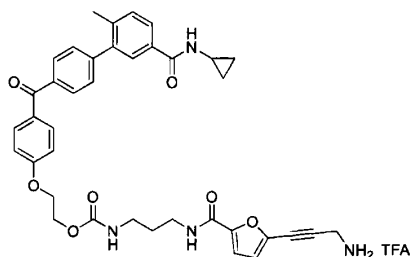
5 **【1329】** ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.18 (s, 1H), 8.69 (s, 1H), 8.39 (t, *J* = 5.9 Hz, 1H), 8.27 (s, 1H), 8.25 (s, 3H), 7.94 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.77 (d, *J* = 8.9 Hz, 2H), 7.41 – 7.38 (m, 1H), 7.37 (dd, *J* = 8.5, 1.8 Hz, 2H), 7.19 (s, 1H), 7.01 (dd, *J* = 9.1, 2.7 Hz, 1H), 6.95 (d, *J* = 2.7 Hz, 1H), 3.99 (q, *J* = 5.6 Hz, 2H), 3.88 (s, 3H), 3.74 (s, 6H), 3.50 (d, *J* = 6.3 Hz, 8H), 3.34 (s, 2H), 3.31 (d, *J* = 5.5 Hz, 2H), 2.62 – 2.59 (m, 2H); MS *m/z* [M+H]⁺ 845.55.

10 **【1330】** **【제조예 I'''】**

【1331】 p38 MAPK 억제제로서의 활성을 나타내는 화합물(N-cyclopropyl-4'-(4-(2-hydroxyethoxy)benzoyl)-6-methyl-[1,1'-biphenyl]-3-carboxamide)이 본 발명의 화학식 I에 해당하는 화합물들과 연결된 TBM-UBM 화합물을 아래와 같이 합성하였다.

15 **【1332】** **【제조예 4-166'''】** 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (3-(5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamido)propyl)carbamate

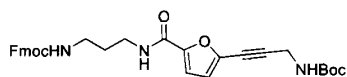
trifluoroacetic acid



【1333】

【1334】 단계 1: tert-butyl (3-(5-((3-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)propyl)carbamoyl)furan-2-yl)prop-2-yn-1-yl)carbamate (중간체 4-166a)

【1335】



【1336】

(9H-Fluoren-9-yl)methyl (3-aminopropyl)carbamate를 출발물질로 하여 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 4-166a를 합성하였다.

10

【1337】

단계

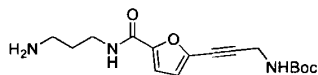
2:

tert-butyl

(3-(5-((3-

aminopropyl)carbamoyl)furan-2-yl)prop-2-yn-1-yl)carbamate (중간체 4-166b)

【1338】



【1339】

중간체 4-166a를 출발물질로 하여 제조예 5-29의 단계 4와 동일한 방법으로 중간체 4-166b를 합성하였다.

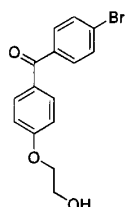
【1340】

단계

3:

(4-bromophenyl)(4-(2-

hydroxyethoxy)phenyl)methanone (중간체 4-166'''a)



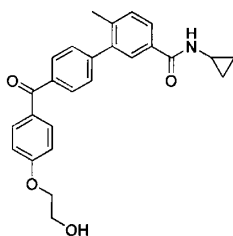
【1341】

【1342】 (4-Bromophenyl)(4-hydroxyphenyl)methanone (1.0

mmol, 1.0 eq), 2-bromoethan-1-ol (1.5 eq), K_2CO_3 (2.0 eq)를 acetone

5 용매 하에 85 °C에서 16 시간 교반하였다. 반응물은 flash column을 통해 정제하여 화합물을 합성하였다.

【1343】 단계 4: N-cyclopropyl-4'-(4-(2-hydroxyethoxy)benzoyl)-6-methyl-[1,1'-biphenyl]-3-carboxamide (중간체 4-166'''b)



10

【1344】

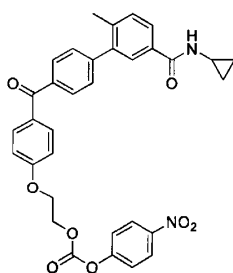
【1345】 중간체 4-166'''a (0.7 mmol, 1.0 eq), N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (1.5 eq), $Pd(PPh_3)_4$ (0.1 eq), K_2CO_3 (2.0 eq), DMF 3.0 mL를 혼합한 뒤 반응 용기 내 기체를 Ar 기체로 치환한 후 90 °C에서 16 시간 가열하였다, 15 반응물은 EtOAc, H_2O 로 추출 후 유기층을 Na_2SO_4 로 건조하였다. 혼합물을

감압여과 후 증류한 뒤 flash column을 통해 정제해 화합물을 합성하였다.

【1346】 단계 5: 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (4-nitrophenyl) carbonate (중간체 4-166'''c)

5

【1347】

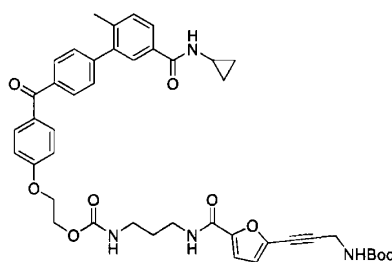


【1348】

중간체 4-166'''b (0.7 mmol, 1.0 eq), 4-nitrophenyl chloroformate (1.1 eq), TEA (2.0 eq)를 THF 용매하에 0 ℃에서 2 시간 교반하였다. 반응물은 flash column을 통해 정제하여 화합물을 합성하였다.

【1349】 단계 6: tert-butyl (3-(5-((3-(((2-(4-(5'-
10 (cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethoxy)carbonyl)amino)propyl)carbamoyl)furan-2-yl)prop-2-yn-1-yl)carbamate (중간체 4-166'''d)

【1350】



【1351】

중간체 4-166'''c (0.5 mmol, 1.0 eq), 중간체 4-166b

(1.0 eq), DIPEA (3.0 eq)를 DMF 용매 하에 실온에서 90 분간 교반하였다.

반응물은 flash column을 통해 정제하여 화합물을 합성하였다.

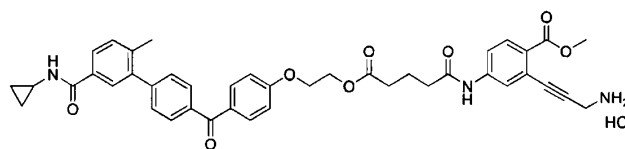
【1352】 단계 7: 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (3-(5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamido)propyl)carbamate trifluoroacetic acid

【1353】 중간체 4-166'''d를 출발물질로 하여 제조예 5-155' 단계 3과 동일한 방법으로 실시예 4-166'''을 합성하였다.

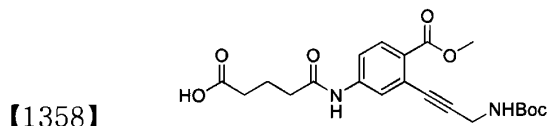
【1354】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.50 (t, $J = 5.8$ Hz, 1H), 8.46 (d, $J = 4.2$ Hz, 1H), 8.35 (s, 2H), 7.79 (dd, $J = 8.5, 6.4$ Hz, 5H), 7.74 (d, $J = 1.9$ Hz, 1H), 7.57 (d, $J = 8.3$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 1H), 7.34 (t, $J = 5.7$ Hz, 1H), 7.17 – 7.12 (m, 3H), 6.99 (d, $J = 3.7$ Hz, 1H), 4.33 – 4.26 (m, 4H), 4.10 (s, 2H), 3.21 (q, $J = 6.7$ Hz, 2H), 3.04 – 2.98 (m, 2H), 2.85 (td, $J = 7.3, 3.8$ Hz, 1H), 2.31 (s, 3H), 1.62 (p, $J = 7.0$ Hz, 2H), 0.68 (td, $J = 7.1, 4.7$ Hz, 2H), 0.59 – 0.54 (m, 2H); MS m/z $[\text{M} + \text{H}]^+$ 663.53.

【1355】 [제조예 5-106'''] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethoxy)-5-oxopentanamido)benzoate hydrochloride

【1356】



【1357】 단계 1: 5-((3-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)-4-(methoxycarbonyl)phenyl)amino)-5-oxopentanoic acid (중간체 5-106a)



5 【1359】 중간체 3-25a를 출발물질로 하여 제조예 5-106'의 단계 3과 동일한 방법으로 중간체 5-106a를 합성하였다.

【1360】 단계 2: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethoxy)-5-oxopentanamido)benzoate hydrochloride

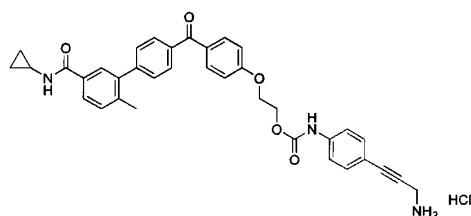
10 【1361】 중간체 5-106a, 중간체 4-166'''c로부터 제조예 5-77'의 단계 2과 동일한 방법으로 실시예 5-106'''을 합성하였다.

【1362】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.36 (s, 1H), 8.42 (d, $J = 4.2$ Hz, 1H), 8.08 (d, $J = 2.2$ Hz, 1H), 7.84 (d, $J = 8.7$ Hz, 1H), 7.78 – 7.72 (m, 5H), 7.70 (d, $J = 2.0$ Hz, 1H), 7.55 – 7.50 (m, 2H), 7.48 (dd, $J = 8.7, 2.2$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.12 – 7.06 (m, 2H), 4.39 – 4.35 (m, 2H), 4.31 – 4.26 (m, 2H), 3.99 (s, 2H), 3.78 (s, 3H), 2.82 (tt, $J = 7.3, 4.0$ Hz, 1H), 2.41 – 2.35 (m, 4H), 2.27 (s, 3H), 1.81 (p, $J = 7.5$ Hz, 2H), 0.67 – 0.62 (m, 2H), 0.54 – 0.50 (m, 2H); MS m/z $[\text{M} + \text{H}]^+$ 716.48.

【1363】 [제조예 II''']

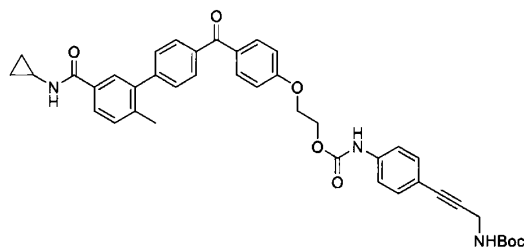
【1364】 p38 MAPK 억제제로서의 활성을 나타내는 화합물(N-cyclopropyl-4'-(4-(2-hydroxyethoxy)benzoyl)-6-methyl-[1,1'-biphenyl]-3-carboxamide)이 본 발명의 화학식 II에 해당하는 화합물들과 연결된 TBM-UBM 화합물을 아래와 같이 합성하였다.

5 **【1365】** [제조예 1-1'''] 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (4-(3-aminoprop-1-yn-1-yl)phenyl)carbamate hydrochloride



【1366】

【1367】 단계 1: 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (4-(3-((tert-butoxycarbonyl)amino)prop-1-yn-1-yl)phenyl)carbamate (중간체 1-1'''a)



【1368】

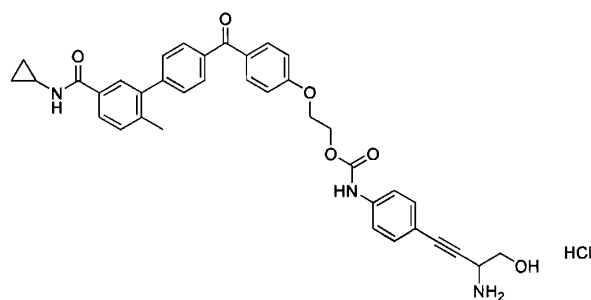
【1369】 중간체 4-166'''c와 중간체 1-1a를 출발물질로 하여
15 제조예 5-140'''의 단계 4와 동일한 방법으로 중간체 1-1'''a를 합성하였다.

【1370】 단계 2: 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (4-(3-aminoprop-1-yn-1-yl)phenyl)carbamate

【1371】 중간체 1-1'''a로부터 제조예 1-1의 단계 1과 동일한
5 방법으로 실시예 1-1'''을 합성하였다.

【1372】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.42 (d, $J = 4.3$ Hz, 1H), 8.24 (s, 3H), 7.90 (t, $J = 5.7$ Hz, 1H), 7.86 (d, $J = 8.2$ Hz, 1H), 7.75 (ddd, $J = 8.4, 4.5, 2.4$ Hz, 5H), 7.71 (d, $J = 2.0$ Hz, 1H), 7.57 (d, $J = 1.7$ Hz, 1H), 7.52 (dd, $J = 6.8, 4.8$ Hz, 3H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.13 – 7.08 (m, 2H), 4.33 (d, $J = 4.7$ Hz, 2H), 4.27 (s, 2H), 4.06 (d, $J = 5.7$ Hz, 2H), 4.00 (s, 2H), 3.83 (d, $J = 3.7$ Hz, 3H), 2.81 (td, $J = 7.3, 3.8$ Hz, 1H), 2.28 (s, 3H), 0.67 – 0.63 (m, 2H), 0.52 (dt, $J = 6.9, 4.4$ Hz, 2H); MS m/z $[\text{M} + \text{H}]^+$ 684.51

【1373】 [제조예 3-49'''] 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (4-(3-amino-4-
15 hydroxybut-1-yn-1-yl)phenyl)carbamate hydrochloride



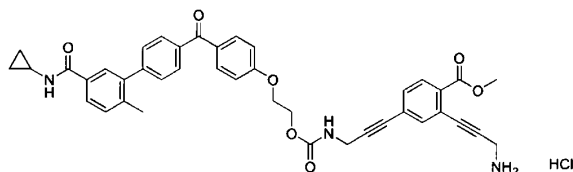
【1374】

【1375】 단계 1: 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (4-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)carbamate hydrochloride

【1376】 중간체 3-49b를 출발물질로 하여 제조예 1-1'''의
5 단계 1 내지 2와 동일한 방법으로 실시예 3-49'''을 합성하였다.

【1377】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.13 (s, 1H), 8.46 (d, $J = 4.3$ Hz, 1H), 8.40 (s, 2H), 7.80 (dd, $J = 12.2, 8.5$ Hz, 5H), 7.74 (d, $J = 1.9$ Hz, 1H), 7.55 (dd, $J = 16.1, 8.6$ Hz, 4H), 7.41 (dd, $J = 11.5, 8.4$ Hz, 3H), 7.16 (d, $J = 8.9$ Hz, 2H), 5.74 (t, $J = 5.3$ Hz, 1H), 4.52 – 4.45 (m, 2H),
10 4.41 – 4.35 (m, 2H), 4.31 (s, 1H), 3.79 – 3.73 (m, 1H), 3.67 – 3.60 (m, 1H), 2.88 – 2.82 (m, 1H), 2.31 (s, 3H), 0.68 (dd, $J = 7.1, 2.4$ Hz, 2H), 0.56 (dd, $J = 4.1, 2.4$ Hz, 2H); MS m/z $[\text{M} + \text{H}]^+$ 618.47.

【1378】 [제조예 5-116'''] methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(((2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate
15 hydrochloride



【1379】

【1380】 단계 1: methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-

(((2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate hydrochloride

【1381】 중간체 5-116c를 출발물질로 하여 제조예 1-1'''의
5 단계 1 내지 2와 동일한 방법으로 실시예 5-116'''을 합성하였다.

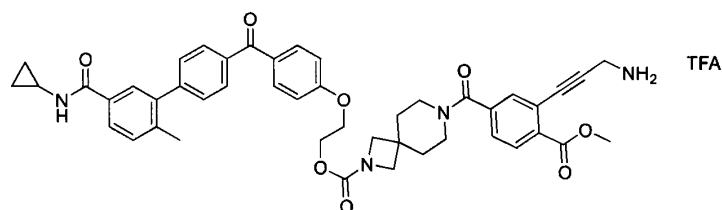
【1382】 ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.42 (d, *J* = 4.3 Hz, 1H), 8.24 (s, 3H), 7.90 (t, *J* = 5.7 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.75 (ddd, *J* = 8.4, 4.5, 2.4 Hz, 5H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.57 (d, *J* = 1.7 Hz, 1H), 7.52 (dd, *J* = 6.8, 4.8 Hz, 3H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.13 – 7.08 (m, 10 2H), 4.33 (d, *J* = 4.7 Hz, 2H), 4.27 (s, 2H), 4.06 (d, *J* = 5.7 Hz, 2H), 4.00 (s, 2H), 3.83 (d, *J* = 3.7 Hz, 3H), 2.81 (td, *J* = 7.3, 3.8 Hz, 1H), 2.28 (s, 3H), 0.67 – 0.63 (m, 2H), 0.52 (dt, *J* = 6.9, 4.4 Hz, 2H); MS *m/z* [M+H]⁺ 684.51

【1383】 [제조예 III''']

【1384】 p38 MAPK 억제제로서의 활성을 나타내는 화합물(N-cyclopropyl-4'-(4-(2-hydroxyethoxy)benzoyl)-6-methyl-[1,1'-biphenyl]-3-carboxamide)이 본 발명의 화학식 III에 해당하는 화합물들과 연결된 TBM-UBM 화합물을 아래와 같이 합성하였다.

【1385】 [제조예 5-39'''] 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl 7-(3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)benzoyl)-2,7-

diazaspiro[3.5]nonane-2-carboxylate trifluoroacetic acid



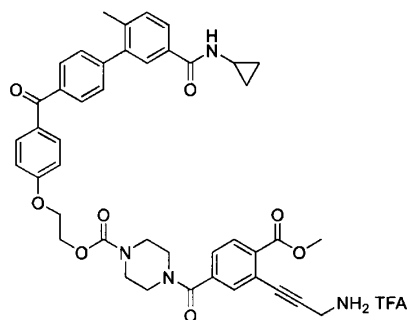
【1386】

【1387】 중간체 5-39c를 출발물질로 하여 제조예 5-140'''의 단계 4 내지 5와 동일한 방법으로 실시예 5-39'''을 합성하였다.

5 【1388】 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.46 (d, $J = 4.3$ Hz, 1H), 8.31 (s, 2H), 7.82 – 7.76 (m, 5H), 7.74 (d, $J = 1.9$ Hz, 1H), 7.61 – 7.55 (m, 3H), 7.52 – 7.46 (m, 2H), 7.42 (d, $J = 8.3$ Hz, 1H), 7.14 (d, $J = 8.9$ Hz, 2H), 4.33 (s, 2H), 4.29 (s, 2H), 3.99 (s, 2H), 3.66 (s, 7H), 3.17 (d, $J = 8.5$ Hz, 2H), 2.85 (td, $J = 7.3, 3.8$ Hz, 1H), 2.31 (s, 3H), 1.75 (s, 2H), 1.65 (s, 10 2H), 0.70 – 0.65 (m, 2H), 0.56 (dt, $J = 7.2, 4.4$ Hz, 2H); MS m/z $[\text{M} + \text{H}]^+$ 783.51.

【1389】 [제조예 5-140'''] 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl 4-(3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)benzoyl)piperazine-1-

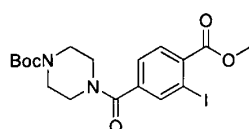
carboxylate trifluoroacetic acid



【1390】

【1391】 단계 1 tert-butyl 4-(3-iodo-4-

(methoxycarbonyl)benzoyl)piperazine-1-carboxylate (중간체 5-140a)



5

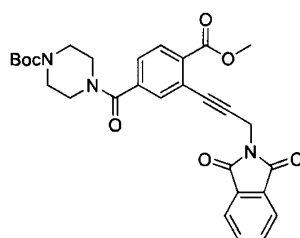
【1392】

【1393】 tert-Butyl piperazine-1-carboxylate, 3-iodo-4-

(methoxycarbonyl)benzoic acid를 출발물질로 하여 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-140a를 합성하였다.

【1394】 단계 2: tert-butyl 4-(3-(3-(1,3-dioxoisindolin-2-

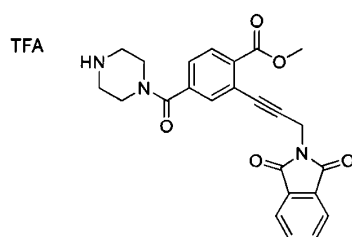
10 yl)prop-1-yn-1-yl)-4-(methoxycarbonyl)benzoyl)piperazine-1-carboxylate (중간체 5-140b)



【1395】

【1396】 중간체 5-140a로부터 제조예 5-35' 단계 1과 동일한 방법으로 중간체 5-140b를 합성하였다.

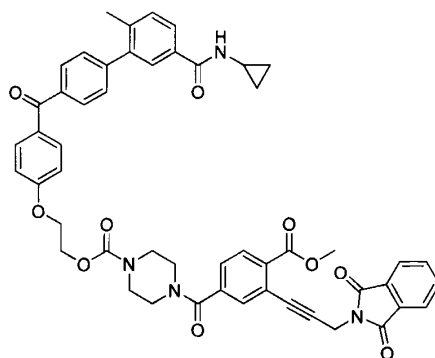
【1397】 단계 3: methyl 2-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-(piperazine-1-carbonyl)benzoate trifluoroacetic acid (중간체 5-140c)



【1398】

【1399】 중간체 5-140b로부터 제조예 4-1'의 단계 4와 동일한 방법으로 중간체 5-140c를 합성하였다.

【1400】 단계 4: 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl 4-(3-(3-(1,3-dioxoisindolin-2-yl)prop-1-yn-1-yl)-4-(methoxycarbonyl)benzoyl)piperazine-1-carboxylate (중간체 5-140''a)



【1401】

【1402】 중간체 5-140c, 4-166'''c로부터 제조예 4-1'의 단계 5와 동일한 방법으로 중간체 5-140'''a를 합성하였다.

【1403】 단계 5: 2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl 4-(3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)benzoyl)piperazine-1-carboxylate trifluoroacetic acid

【1404】 중간체 5-140'''a로부터 제조예 5-85'의 단계 5와 동일한 방법으로 실시예 5-140'''을 합성하였다.

【1405】 ^1H NMR (500 MHz, DMSO- d_6) δ 8.42 (d, J = 4.3 Hz, 1H), 8.26 (s, 3H), 8.17 (d, J = 8.5 Hz, 1H), 8.06 – 8.00 (m, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.78 – 7.73 (m, 5H), 7.71 (d, J = 2.0 Hz, 1H), 7.57 (d, J = 1.7 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.13 (dd, J = 8.9, 2.6 Hz, 1H), 4.36 (d, J = 5.0 Hz, 2H), 4.30 (s, 2H), 4.03 (q, J = 5.7 Hz, 2H), 3.84 (s, 3H), 3.34 (s, 4H), 3.24 (s, 4H), 2.81 (dt, J = 7.4, 3.7 Hz, 1H), 2.28 (s, 3H), 0.65 (td, J = 7.1, 4.7 Hz, 2H), 0.54 – 0.48 (m, 2H); MS m/z $[\text{M} + \text{H}]^+$ 743.55.

【1406】

【1407】 [실험예]

【1408】 [실험예 1]

20 【1409】 MM.1S 세포주에서 BRD4 분해자의 분해 효과 확인

【1410】 상기 제조예 I' 내지 제조예 IV'의 화합물들 (BRD4 degraders)이 BRD4 단백질의 양을 감소시키는 것을 확인하기 위하여, 다발성 골수종 환자의 혈액에서 유래된 B세포인 MM.1S 세포주를 사용하여 실험을 수행하였다.

5 【1411】 구체적으로, 10% 소 태아 혈청 및 Penicillin/Streptomycin (100 U/ml)이 보충된 RPMI-1640 배지에서 MM.1S 세포를 배양한 뒤 6 웰 플레이트에 옮기고 24시간이 경과한 후에 BRD4 분해자들을 배양액에 희석하여 10 μ M씩 처리하였다. 처리 후 CO₂ 배양기에서 24시간 동안 배양하였다. 단백질 면역 블로팅(Western Blot)을
10 통해 각 화합물의 세포 내 BRD4 단백질에 대한 분해능을 확인하였다. 실험 조건에 따라 세포의 배양이 끝난 후, 세포를 수거하여 1,800 rpm에서 3분동안 원심분리 하였다. 침전물을 RIPA(25 mM Tris-HCl pH 7.6, 150 mM NaCl, 1% NP-40, 1% sodium deoxycholate, 0.1% SDS, 1x Protease Inhibitor Cocktail)로 세포를 용해하고, 5X sample buffer를 첨가한 뒤
15 100 °C에서 15 분 동안 가열하였다. 준비된 샘플을 Sodium Dodecyl Sulfate Poly Acrylamide Gel Electrophoresis(SDS-PAGE)로 전기 영동 한 후, 겔 내 단백질을 Trans-Blot Turbo를 이용하여 PVDF 막(membrane)에 전사하였다. 막에 5% 소 혈청 알부민(BSA) 용액을 처리해 2시간 동안 상온에서 blocking 한 후, 5% BSA 용액에 BRD4 및 β -actin 항체를
20 희석하여 4°C에서 막(membrane)과 하룻밤동안 반응시켰다. 그 후

- PBST(0.5% Tween20)로 5회에 걸쳐 세척한 후, HRP 접합된(Horse radish peroxidase-conjugated) 2차 항체를 PBST에 희석시켜 실온에서 2시간 동안 반응시키고 다시 PBST 용액으로 5회 세척하였다. HRP 기질을 사용하여 효소-기질 반응시킨 후 chemi-doc 장비로 신호를 측정하였고,
- 5 제조예 화합물들에서 검출된 BRD4 단백질에 해당하는 밴드 (band)의 농도계 (densitometry)를 정량 분석하여 각 BRD4 분해자들의 분해능이 40% 미만 감소하였을 경우는 +, 40% 이상 70% 미만 감소하였을 경우는 ++, 70% 이상 감소하였을 경우는 +++로 하기 표 16 내지 표 19에 표기하였다. 하기 표에 기재된 바와 같이 본 발명에 따른 제조예 I' 내지
- 10 제조예 IV'의 화합물들은 우수한 분해능을 갖는 것을 확인하였다.

【표 16】

번호	BRD4 분해능(%)	번호	BRD4 분해능(%)
1-1'	++	3-25'	+++
1-3'	++	3-26'	++
3-1'	+++	3-27'	++
3-2'	++	3-49'	++
3-3'	+++	3-51'	+++
3-8'	+	3-57'	++
4-1'	++	4-147'	++
4-10'	+++	4-179'	+
4-128'	++	4-223'	++
4-129'	+++	5-116'	+++

【표 17】

번호	BRD4 분해능(%)	번호	BRD4 분해능(%)
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4-124'	+++	5-35'	+++
4-125'	+++	5-53'	++
4-126'	++	5-59'	+++
4-148'	+	5-61'	++
4-149'	+++	5-63'	++
4-161'	+++	5-65'	+
4-162'	+++	5-75'	+++
4-163'	+++	5-77'	+
4-164'	++	5-78'	+
4-165'	+++	5-81'	+++
4-166'	+++	5-89'	+
4-167'	++	5-90'	+++
4-225'	+++	5-96'	+++
4-228'	+++	5-104'	++
4-235'	++	5-106'	+
5-1'	+++	5-107'	++
5-2'	++	5-108'	+++
5-4'	++	5-109'	+++
5-5'	++	5-110'	++
5-6'	++	5-115'	+++
5-8'	++	5-148'	+
5-9'	++	5-149'	+++
5-12'	+++	5-150'	+++
5-18'	+++		

【표 18】

번호	BRD4 분해능(%)	번호	BRD4 분해능(%)
4-2'	+++	5-44'	++
4-226'	+++	5-85'	+++
4-227'	++	5-86'	+++
5-7'	+	5-139'	+

5-22'	+++	5-140'	+++
5-23'	+++	5-152'	+++
5-25'	+++	5-153'	+++
5-26'	++	5-154'	+++
5-27'	++	5-155'	++
5-28'	+++	5-157'	+++
5-29'	+++	5-158'	+++
5-39'	++	5-162'	+++
5-40'	+++	5-168'	+++
5-41'	+++		

【표 19】

번호	BRD4 분해능(%)	번호	BRD4 분해능(%)
5-32'	+++	5-164'	+++
5-33'	++	5-165'	+++
5-111'	++		

【1412】 [실험예 2]

【1413】 MM.1S 세포주에서 Aurora A 분해자의 분해 효과 확인

【1414】 상기 제조예 I' 내지 제조예 IV''의 화합물들(Aurora A degraders)이 Aurora A 단백질의 양을 감소시키는 것을 확인하기 위하여, 다발성 골수종 환자의 혈액에서 유래된 B세포인 MM.1S 세포주를 사용하여 실험을 수행하였다.

【1415】 구체적으로, 10% 소 태아 혈청(FBS), 1% 페니실린, 스트렙토마이신 (100U/ml) 이 포함된 RPMI-1640 배지에서 MM.1S 세포를 배양한 뒤, 6 웰 플레이트에 옮기고 24시간이 경과한 후에 Aurora A

분해자들을 RPMI 배양액에 희석하여 5 μ M 농도로 세포에 처리하였다. 처리 후 CO₂ 배양기에서 24시간 동안 배양하였다. 단백질 면역 블로팅(Western Blot)을 통해 각 화합물의 세포 내 Aurora A 단백질에 대한 분해능을 확인하였다. 실험 조건에 따라 세포의 배양이 끝난 후, 세포를 수거하여

5 1,800 rpm에서 3분동안 원심분리 하였다. 침전물을 RIPA(25 mM Tris-HCl pH 7.6, 150 mM NaCl, 1% NP-40, 1% sodium deoxycholate, 0.1% SDS, 1x Protease Inhibitor Cocktail)로 세포를 용해하고, 5X sample buffer를 첨가한 뒤 100 °C에서 15 분 동안 가열하였다. 준비된 샘플을 Sodium Dodecyl Sulfate Poly Acrylamide Gel Electrophoresis(SDS-PAGE)로 전기 영동 한

10 후, 겔 내 단백질을 Trans-Blot Turbo를 이용하여 PVDF 막(membrane)에 전사하였다. 막에 5% 소 혈청 알부민(BSA) 용액을 처리해 2시간 동안 상온에서 blocking 한 후, 5% BSA 용액에 Aurora A 및 β -actin 항체를 희석하여 4°C에서 막(membrane)과 하룻밤동안 반응시켰다. 그 후 PBST(0.5% Tween20)로 5회에 걸쳐 세척한 후, HRP 접합된(Horse radish

15 peroxidase-conjugated) 2차 항체를 PBST에 희석시켜 실온에서 2시간 동안 반응시키고 다시 PBST 용액으로 5회 세척하였다. HRP 기질을 사용하여 효소-기질 반응시킨 후 chemi-doc 장비로 신호를 측정하였고, 제조예 화합물들에서 검출된 Aurora A 단백질에 해당하는 밴드 (band)의 농도계 (densitometry)를 정량 분석하여 각 Aurora A 분해자들의 분해능이

20 40% 미만 감소하였을 경우는 +, 40% 이상 70% 미만 감소하였을 경우는

++, 70% 이상 감소하였을 경우는 +++로 하기 표 20 내지 표 23에 표기하였다. 대조군인 화학식 2의 화합물은 0%의 분해능을 보인 반면, 본 발명에 따른 제조예 I' 내지 IV'의 화합물들은 우수한 분해능을 갖는 것을 확인하였다.

5 【표 20】

번호	Aurora A 분해능(%)	번호	Aurora A 분해능(%)
1-1''	+++	3-25''	+
1-3''	+++	3-49''	+++
4-1''	+++	5-116''	+++

【표 21】

번호	Aurora A 분해능(%)	번호	Aurora A 분해능(%)
4-165''	+++	5-35''	+++
4-166''	+	5-81''	+++
4-228''	++	5-104''	+++
5-8''	+	5-150''	+
5-18''	+++		

【표 22】

번호	Aurora A 분해능(%)	번호	Aurora A 분해능(%)
5-23''	+	5-29''	+++
5-28''	+++	5-40''	+++

【표 23】

번호	Aurora A 분해능(%)	번호	Aurora A 분해능(%)
5-32''	++		

【1416】 [실험예 3]

【1417】 대식세포에서 p38 분해자의 분해 효과 확인

【1418】 상기 제조예 I''' 내지 제조예 III'''의 화합물들(p38
degraders)이 p-p38(phospho-p38) 단백질의 양을 감소시키는 것을
5 확인하기 위하여 대식세포 Raw 264.7를 사용하여 실험을 수행하였다. p38
MAPK alpha는 상위 조절인자인 MKK3, MKK6 등에 의해 트레오닌
180(Thr180)과 티로신 182(Tyr182) 잔기가 인산화되는 과정을 거쳐
활성화되므로 일반적으로 이들 잔기의 인산화는 p38 MAPK alpha의
활성화가 일어난 p-p38(phosphor-p38) MAPK를 특이적으로 인지하는
10 항체(Cellsignaling 사의 3D7 rabbit 단일클론 항체)를 사용하여 이를
검출하였다.

【1419】 구체적으로, 10% 소 태아 혈청(FBS), 1% 페니실린,
스트렙토마이신 (100U/ml) 이 포함된 DMEM 배지에서 RAW 264.7 세포를
배양한 뒤, 6 웰 플레이트에 옮기고 24시간이 경과한 후에 p38 분해자들을
15 DMEM 배양액에 희석하여 10 μ M 농도로 처리하였다. 처리 후 CO₂
배양기에서 24시간 동안 배양하였다. 단백질 면역 블로팅(Western Blot)을
통해 각 화합물의 세포 내 p38 및 p-p38 단백질에 대한 분해능을
확인하였다. 실험 조건에 따라 세포의 배양이 끝난 후, 세포를 수거하여

1,800 rpm에서 3분동안 원심분리 하였다. 침전물을 RIPA(25 mM Tris-HCl
pH 7.6, 150 mM NaCl, 1% NP-40, 1% sodium deoxycholate, 0.1% SDS, 1x
Protease Inhibitor Cocktail)로 세포를 용해하고, 5X sample buffer를 첨가한
뒤 100 °C에서 15 분 동안 가열하였다. 준비된 샘플을 Sodium Dodecyl
5 Sulfate Poly Acrylamide Gel Electrophoresis(SDS-PAGE)로 전기 영동 한
후, 겔 내 단백질을 Trans-Blot Turbo를 이용하여 PVDF 막(membrane)에
전사하였다. 막에 5% 소 혈청 알부민(BSA) 용액을 처리하여 2시간 동안
상온에서 blocking 한 후, 5% BSA 용액에 p-p38, p38 및 β -actin 항체를
희석하여 4°C에서 막(membrane)과 하룻밤동안 반응시켰다. 그 후
10 PBST(0.5% Tween20를 포함하는 phosphate-based Saline)로 5회에 걸쳐
세척한 후, HRP(Horse radish peroxidase) 접합된 2차 항체를 PBST에
희석시켜 실온에서 2시간 동안 반응시키고 다시 PBST 용액으로 5회
세척하였다. HRP 기질을 사용하여 효소-기질 반응시킨 후 chemi-doc
장비로 신호를 측정하였고, 제조에 화합물들에서 검출된 p-p38, p38
15 단백질에 해당하는 밴드 (band)의 농도계 (densitometry)를 정량 분석하여
각 p38 분해자들의 분해능이 40% 미만 감소하였을 경우는 +, 40% 이상
70% 미만 감소하였을 경우는 ++, 70% 이상 감소하였을 경우는 +++로
하기 표 24 내지 표 26에 표기하였다. 하기 표에 기재된 바와 같이 본
발명에 따른 제조예 I''' 내지 제조예 III'''의 화합물들은 우수한 분해능을
20 갖는 것을 확인하였다.

【표 24】

번호	p38 분해능(%)	번호	p38 분해능(%)
1-1'''	+++	5-116'''	+++
3-49'''	+++		

【표 25】

번호	p38 분해능(%)	번호	p38 분해능(%)
4-166'''	+++	5-106'''	+++

【표 26】

번호	p38 분해능(%)	번호	p38 분해능(%)
5-140'''	+++		

【1420】 [실험예 4]

5 【1421】 Pulldown assay를 이용한 유비퀴틴의 직접적 결합 확인

【1422】 본 발명의 화학식 I 내지 화학식 IV로 표시되는 화합물들이 다양한 E3 리가아제 복합체에 의해 유비퀴틴과 결합 및 다중유비퀴틴화(polyubiquitination)을 일으키는지 확인하기 위하여, *in vitro* ubiquitination assay를 수행하였다. E3 리가아제는 ITCH/AIP4, NEDD4, cIAP-1/HUAP-2 단백질을(제조사 R&D System)을 이용하였다.

【1423】 구체적으로, 첫번째 레인은 10X buffer, 100μg의 유비퀴틴이 사용되었고, 두번째-여섯번째 레인은 10X buffer와 100μg의 유비퀴틴, 5nM의 E1, 100nM의 E2, 14nM의 E3, 1mM의 ATP가 사용되었다. 세번째 레인에는 음성 대조군으로 비오틴 40μM이 되도록 추가하였고, 네번째, 다섯번째 레인에는 각각 비오틴이 결합된 제조예 4-228, 4-166의

화합물을 40 μ M이 되도록 추가하였다. 각 샘플은 37 $^{\circ}$ C incubator에서 3시간
 반응시킨 후, 각 샘플의 5 μ l는 input 결과를 위하여 5X sample buffer를
 추가하여 100 $^{\circ}$ C, 10분동안 가열하였다. 나머지 샘플액은 Streptavidin이
 결합된 Agarose bead를 추가하여 4 $^{\circ}$ C에서 3시간 동안 반응시킨 후
 5 TritonX-100 lysis buffer로 5회 세척한 후 2X sample buffer를 추가하여
 100 $^{\circ}$ C, 10분동안 가열하였다. Input 샘플과 pulldown 샘플을 SDS-PAGE로
 전기 영동한 후, 겔 내 단백질을 Trans-Blot Turbo를 이용하여 PVDF 막에
 전사하였다. 막에 5% 소혈청 알부민(BSA) 용액을 처리해 1시간 동안
 상온에서 blocking 한 후, 5% BSA 용액에 유비퀴틴 항체, K63 연결
 10 다중유비퀴틴 항체, K48 연결 다중유비퀴틴 항체를 각각 희석하여 4 $^{\circ}$ C에서
 PVDF 막과 하룻밤 동안 반응시켰다. 그 후 PBST (0.5% Tween20를
 포함하는 phosphate-based Saline)로 5회 걸쳐 세척한 후, HRP (Horse
 radish peroxidase) 접합된 2차 항체를 PBST에 희석시켜 실온에서 2시간
 동안 반응시키고 다시 PBST 용액으로 5회 세척하였다. HRP 기질을
 15 사용하여 효소-기질 반응시킨 후 chemo-doc 장비로 신호를 측정하여 그
 결과는 도 2에 나타내었다.

【1424】 그 결과, 도 2에 도시된 바와 같이, 본 발명의 화학식
 I 내지 화학식 IV로 표시되는 화합물들이 유비퀴틴과 직접적으로 결합하는
 수용체(accepter)임을 확인하였다.

20

【1425】 [실예 5]

【1426】 원형 단백질 분석법을 이용한 유비퀴틴과의 직접적 결합 확인

【1427】 본 발명의 화학식 V 내지 VIII로 표시되는 화합물들이 유비퀴틴과 직접적으로 결합함을 확인하기 위하여, *in vitro ubiquitination* assay를 진행한 후 유비퀴틴, BRD4 저해제 및 유비퀴틴에 결합한 제조예 I' 내지 제조예 IV'''의 화합물들(BRD4 분해자)을 원형 단백질 분석법을 이용하여 검출하였다. 원형 단백질 분석법은 프로테아제 전처리 없이 질량 분석을 하여 단백질에 결합된 화합물을 측정할 수 있는 방법이다. *In vitro* 상에서 유비퀴틴과 BRD4 분해자를 결합시키기 위하여 E3 리가아제인 ITCH/AIP4 단백질(제조사 R&D System)을 이용하여 실험을 수행되었다.

【1428】 구체적으로, 각 분해자 10 μ M을 10X buffer와 1mg/ml의 유비퀴틴, 5nM의 E1, 100nM의 E2, 14nM의 E3, 1mM의 ATP와 혼합하여 37 $^{\circ}$ C 인큐베이터에서 4시간 반응시켰다. 반응된 샘플들에 UPLC-Q/TOF 또는 MALDI-TOF 분석을 위하여 아세트니트릴과 포름산을 추가하여 각각 최종농도가 50% 아세트니트릴, 0.1% 포름산이 되게 하였다. UPLC-Q/TOF의 경우 질량 분석법을 수행하기 위하여 ESI가 설치된 Micromass Q-TOF micro Synapt High-definition 질량 분석기를 사용하였다. 최적의 분석 조건을 위해 모세관 전압 2.7kV, 에너지원 온도 120 $^{\circ}$ C, 용출 온도 400 $^{\circ}$ C, cone 가스 속도 10L/h, 용출 가스 속도 800L/h, 최저 전압 2V, 최고 전압 30V 조건으로 수행하였다. 질량 분석의 정확성을

위하여 양이온 모드에서 기준값과 비교하며 진행하였다. 실험 결과는 MassLynx 4.0 프로그램을 이용하여 분석하여 질량 분석 값을 도 3에 나타내었다. 또한, MALDI-TOF는 MALDI-TOF/TOF 5800 시스템(AB SCIEX, USA)을 사용하여 선형 양이온 모드에서 질량 스펙트럼을
5 획득하였다. 실험결과는 TOF/TOFTM Series Explorer™ 소프트웨어 버전 4.0을 이용하여 분석하였다.

【1429】 그 결과, 도 3에 도시된 바와 같이, 화학식 1(JQ1) 대조군에서는 유비퀴틴과 결합된 크기의 분자량 peak가 검출되지 않았으나, BRD4 분해자와 반응시킨 유비퀴틴 분자량이 분해자의 크기만큼 증가한
10 peak 검출을 통해 유비퀴틴과 BRD4 분해자가 직접적으로 결합함을 확인하였다.

【1430】

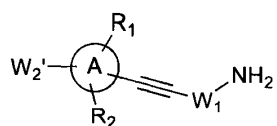
【1431】 상기에서는 본 발명의 바람직한 실시예를 예시적으로 설명하였으나, 본 발명의 범위는 상기와 같은 특정 실시예에만 한정되지
15 아니하며, 해당 분야에서 통상의 지식을 가진 자라면 본 발명의 청구범위에 기재된 범주 내에서 적절하게 변경이 가능할 것이다.

【청구의 범위】

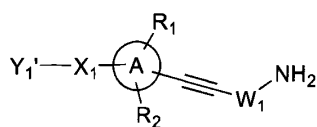
【청구항 1】

하기 화학식 I 내지 화학식 IV로 표시되는 화합물 또는 이의
약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭:

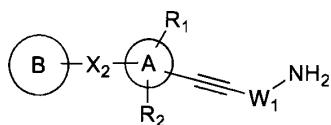
5 [화학식 I]



[화학식 II]

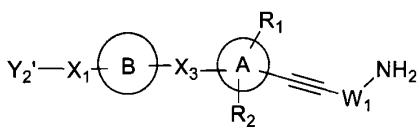


[화학식 III]



10

[화학식 IV]



상기 화학식 I 내지 화학식 IV에서, 각각 독립적으로,

W1은 중수소, 알킬, C(O)OR', C(O)N(R')(R''), 알킬렌-C(O)OR',

15 알킬렌-C(O)N(R')(R''), 알킬렌-OR', 알킬렌-SR', 알킬렌-N(R')(R''),

알킬렌-OP(O)(OR')(OR''), 알킬렌-P(O)(OR')(OR'') 및 알킬렌-OP(O)(R')(R'')으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, -알킬렌-, -알킬렌-O-, -알킬렌-OSO₂- 및 -알킬렌-N(R')SO₂-로 구성되는 군에서 선택되는 어느 하나이고;

- 5 A는 아릴, 헤테로아릴, 시클로알킬, 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이고;

- R₁ 및 R₂는, 각각 독립적으로, 수소, 알킬, 알케닐, 알키닐, 할로젠, 옥소, CN, NO₂, OR', SR', N(R')(R''), O-(알킬렌)-OR', -N(R')-(알킬렌)-OR', C(O)R', C(NH)R', C(S)R', C(O)OR', C(O)N(R')(R''), P(O)(R')(R''),
 10 P(O)(OR')(OR''), C(NH)N(R')(R''), C(S)OR', C(S)N(R')(R''), C(O)O-(알킬렌)-OC(O)R', C(O)O-(알킬렌)-메타크릴로일옥시, (알킬렌)-OR', (알킬렌)-SR', (알킬렌)-N(R')(R''), (알키닐렌)-N(R')(R''), (알킬렌)-P(O)(R')(R'')-, (알킬렌)-P(O)(OR')(OR''), (알킬렌)-OP(O)(R')(R''), (알킬렌)-OP(O)(OR')(OR''), (알킬렌)-OP(O)(벤질옥시)₂, (알킬렌)-OP(O)(페녹시)₂,
 15 (알킬렌)-OP(O)(페녹시)(NH-CH(R')C(O)OR''), (알킬렌)-C(O)OR', (알케닐렌)-C(O)OR', (알키닐렌)-C(O)OR', (알킬렌)-C(O)N(R')(R''), (알케닐렌)-C(NH)N(R')(R''), (알키닐렌)-C(S)N(R')(R''), (알킬렌)-C(O)R', (알킬렌)-C(NH)R', (알킬렌)-C(S)R', 아릴, 헤테로아릴, 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이고, 상기 R₁ 및
 20 R₂는 각각 독립적으로 1개 이상의 할로젠으로 치환될 수 있으며, 각각

독립적으로 상기 R_1 및 R_2 가 아릴, 헤테로아릴, 헤테로시클로알킬 또는 헤테로시클로알케닐인 경우에는 1개 이상의 위치에서 1개 이상의 할로젠으로 치환 또는 비치환된 알킬 또는 $N(R')(R'')$ 로 치환될 수 있고;

X_1 은 직접 결합이거나, 또는 $-N(R')-$, $-O-$, $-S-$, $-C(O)-$, $-SO-$,
 5 SO_2- , $=N-O-$ 및 $-O-N=$ 로 구성되는 X_{1a} 군, $-OC(O)-$, $-C(O)O-$, $-N(R')C(O)-$, $-C(O)N(R')-$, $-N(R')SO-$, $-SON(R')-$, $-N(R')SO_2-$ 및 $-SO_2N(R')-$ 로 구성되는 X_{1b} 군 및 -알킬렌-, -알케닐렌- 및 -알키닐렌-으로 구성되는 X_{1c} 군으로부터 선택되는 어느 하나이거나, 또는 둘 이상이 서로 연결된 것이고;

10 X_2 는 직접 결합이거나, 또는 $-N(R')-$, $-O-$, $-S-$, $-C(O)-$, $-SO-$, SO_2- , $=N-O-$ 및 $-O-N=$ 로 구성되는 X_{2a} 군, $-OC(O)-$, $-N(R')C(O)-$, $-N(R')C(O)O-$, $-N(R')SO_2-O-$ 및 $-N(R')C(S)O-$ 로 구성되는 X_{2b} 군, $-C(O)O-$, $-C(O)N(R')-$, $-O-SO_2-N(R')-$, $-O-C(S)N(R')-$ 및 $-O-C(O)N(R')-$ 로 구성되는 X_{2c} 군 및 -알킬렌-, -알케닐렌- 및 -알키닐렌-으로 구성되는
 15 X_{2d} 군으로부터 선택되는 어느 하나이거나, 또는 둘 이상이 서로 연결된 것이고;

X_3 은 직접 결합이거나, 또는 -알킬렌-, $-O-$, $-S-$, $-C(O)-$, $-N(R')-$, $-SO-$, $-SO_2-$ 및 이들의 조합으로 구성되는 군으로부터 선택되는 어느 하나이고;

20 B는 히드록시, 알콕시 및 옥소로 구성되는 군에서 선택되는 적어도

- 하나로 치환 또는 비치환된, 아릴, 헤테로아릴, 시클로알킬, 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이거나, 또는 히드록시, 알콕시 및 옥소로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 아릴, 헤테로아릴, 시클로알킬,
- 5 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 둘 이상이 직접 연결, -알킬렌-, -O-, -S-, -C(O)-, -N(R')-, -SO-, -SO₂- 또는 이들의 조합으로 연결된 것일 수 있고;

- W₂'은 수소이거나, 또는 중수소, 할로젠, 알킬, 알킬렌-C(O)OR', 알킬렌-C(O)N(R')(R''), 알킬렌-OR', 알킬렌-SR', 알킬렌-N(R')(R''),
- 10 알킬렌-OP(O)(OR')(OR''), 알킬렌-P(O)(OR')(OR''), 알킬렌-OP(O)(R')(R''), -N(R')(R''), -OR', -SR', -C(O)R', -SOR', -SO₂R', =N-OR', -C(O)OR', -C(O)N(R')(R''), -OC(O)OR', -OC(O)N(R')(R''), -N(R')C(O)O(R''), -N(R')SO(R'), -SON(R')(R''), -N(R')SO₂(R'') 및 -SO₂N(R')(R'')으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 알킬, 알케닐 및
- 15 알키닐로 구성되는 군에서 선택되는 어느 하나이고;

- Y₁'은 할로젠, -N(R')(R''), -OR', -SR', -C(O)R', -SOR', SO₂R', =N-OR', -C(O)OR', -C(O)N(R')(R''), -N(R')SO(R'), -SON(R')(R''), -OC(O)OR', -OC(O)N(R')(R''), -N(R')C(O)O(R''), -N(R')SO₂(R'') 및 -SO₂N(R')(R'')으로
- 20 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 알킬, 알케닐, 알키닐, (CH₃CH₂O)-(CH₂CH₂O)_{n-1}CH₂- 및 (CH₃CH₂O)-(CH₂CH₂O)_{n-}

$_1\text{CH}_2\text{CH}_2$ -로 구성되는 군에서 선택되는 어느 하나이고, 여기서 n 은 1~4이고;

Y_2' 은 할로젠, $-\text{N}(\text{R}')(\text{R}'')$, $-\text{OR}'$, $-\text{SR}'$, $-\text{C}(\text{O})\text{R}'$, $-\text{SOR}'$, $\text{SO}_2\text{R}'$, $=\text{N}-\text{OR}'$, $-\text{C}(\text{O})\text{OR}'$, $-\text{C}(\text{O})\text{N}(\text{R}')(\text{R}'')$, $-\text{OC}(\text{O})\text{OR}'$, $-\text{OC}(\text{O})\text{N}(\text{R}')(\text{R}'')$, $-\text{N}(\text{R}')\text{C}(\text{O})\text{O}(\text{R}'')$, $-\text{N}(\text{R}')\text{SO}(\text{R}')$, $-\text{SON}(\text{R}')(\text{R}'')$, $-\text{N}(\text{R}')\text{SO}_2(\text{R}'')$ 및 $-\text{SO}_2\text{N}(\text{R}')(\text{R}'')$ 으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 알킬, 알케닐, 알키닐, 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이며;

상기 작용기들에서 R' 및 R'' 은 각각 독립적으로 수소 또는 알킬임.

10

【청구항 2】

청구항 1에 있어서,

상기 화학식 I 내지 화학식 IV에서, 각각 독립적으로,

상기 W_1 은 $\text{C}(\text{O})\text{OR}'$, $\text{C}(\text{O})\text{N}(\text{R}')(\text{R}'')$, 알킬렌- OR' , 알킬렌- SR' 및
15 알킬렌- $\text{OP}(\text{O})(\text{OR}')(\text{OR}'')$ 으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, -알킬렌-, -알킬렌-O-, -알킬렌- OSO_2 - 및 -알킬렌- $\text{N}(\text{R}')\text{SO}_2$ -로 구성되는 군에서 선택되는 어느 하나이고;

상기 A는 아릴, N, O 및 S로 구성되는 군에서 선택되는 적어도 하나를 포함하는 5원 내지 10원의 헤테로아릴, 3원 내지 10원의 시클로알킬,
20 N, O 및 S로 구성되는 군에서 선택되는 적어도 하나를 포함하는 3원 내지

10원의 헤테로시클로알킬 및 N, O 및 S로 구성되는 군에서 선택되는 적어도 하나를 포함하는 3원 내지 10원의 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이고;

상기 R_1 및 R_2 는, 각각 독립적으로, 수소, 알킬, 알케닐, 할로젠, OR' ,
 5 $N(R')(R'')$, $O-(알킬렌)-OR'$, $C(O)R'$, $C(O)OR'$, $C(O)N(R')(R'')$,
 $C(NH)N(R')(R'')$, $C(O)O-(알킬렌)-OC(O)R'$, $C(O)O-(알킬렌)-$
 메타크릴로일옥시, $(알킬렌)-OR'$, $(알킬렌)-SR'$, $(알킬렌)-N(R')(R'')$,
 $(알킬렌)-N(R')(R'')$, $(알킬렌)-OP(O)(OR')(OR'')$, $(알킬렌)-$
 $OP(O)(벤질옥시)_2$, $(알킬렌)-OP(O)(페녹시)_2$, $(알킬렌)-OP(O)(페녹시)(NH-$
 10 $CH(R')C(O)OR'')$, $(알킬렌)-C(O)OR'$, 아릴, 헤테로아릴, 헤테로시클로알킬
 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이고, 상기 R_1
 및 R_2 는 각각 독립적으로 1개 이상의 할로젠으로 치환될 수 있으며, 각각
 독립적으로 상기 R_1 및 R_2 가 아릴, 헤테로아릴, 헤테로시클로알킬, 또는
 헤테로시클로알케닐인 경우에는 1개 이상의 위치에서 1개 이상의
 15 할로젠으로 치환 또는 비치환된 알킬 또는 $N(R')(R'')$ 로 치환될 수 있고;

상기 X_1 은 직접 결합이거나, 상기 $X1a$ 군 및 상기 $X1b$ 군으로부터
 선택되는 어느 하나이거나, 또는 상기 $X1a$ 군 및 상기 $X1b$ 군으로부터
 선택되는 어느 하나와 상기 $X1c$ 군으로부터 선택되는 어느 하나가 $X1a-$
 $X1c$ 또는 $X1b-X1c$ 의 형태로 연결된 것이고;

20 상기 X_2 는 직접 결합이거나, 상기 $X2a$ 군, 상기 $X2b$ 군 및 상기

X2c 군으로부터 선택되는 어느 하나이거나, 또는 둘 이상이 서로 연결된 것이거나, 또는 상기 X2b 군, 상기 X2c 군 및 상기 X2d 군에서 선택되는 어느 하나 또는 둘 이상이 X2b-X2d-X2b, X2b-X2d-X2c, X2c-X2d-X2b 또는 X2c-X2d-X2c의 형태로 연결된 것이고;

- 5 상기 X₃은 직접 결합이거나, 또는 -C(O)-, -N(R')- 및 이들의 조합으로 구성되는 군으로부터 선택되는 어느 하나이고;

상기 B는 히드록시, 알콕시 및 옥소로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 아릴, 5원 내지 10원의 헤테로아릴, 3원 내지 10원의 헤테로시클로알킬 및 3원 내지 10원의 헤테로시클로알케닐로

10 구성되는 군에서 선택되는 어느 하나이거나, 또는 히드록시 및 옥소로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 아릴, 5원 내지 10원의 헤테로아릴, 3원 내지 10원의 헤테로시클로알킬 및 3원 내지 10원의 헤테로시클로알케닐로 구성되는 군에서 선택되는 둘 이상이 직접, -알킬렌-, -C(O)-, -N(R')-, 또는 이들의 조합으로 연결된 것일 수 있고;

- 15 상기 W₂'은 수소이거나, 또는 중수소, 할로젠, 알킬, 알킬렌-C(O)OR', 알킬렌-C(O)N(R')(R''), 알킬렌-OR', 알킬렌-SR', 알킬렌-N(R')(R''), 알킬렌-OP(O)(OR')(OR''), 알킬렌-P(O)(OR')(OR''), 알킬렌-OP(O)(R')(R''), -N(R')(R''), -OR', -SR', -C(O)R', -SOR', -SO₂R', =N-OR', -C(O)OR', -C(O)N(R')(R''), -OC(O)OR', -OC(O)N(R')(R''), -N(R')C(O)O(R''),
- 20 -N(R')SO(R''), -SON(R')(R''), -N(R')SO₂(R'') 및 -SO₂N(R')(R'')으로

구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 알케닐 및 알키닐로 구성되는 군에서 선택되는 어느 하나이고;

상기 Y_1' 은 할로젠, $-N(R')(R'')$, $-OR'$, $-SR'$, $-C(O)R'$, $-SOR'$, SO_2R' , $=N-OR'$, $-C(O)OR'$, $-C(O)N(R')(R'')$, $-OC(O)OR'$, $-OC(O)N(R')(R'')$, $-N(R')C(O)O(R'')$, $-N(R')SO(R')$, $-SON(R')(R'')$, $-N(R')SO_2(R'')$ 및 $-SO_2N(R')(R'')$ 으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 알킬, 알케닐, 알키닐, $(CH_3CH_2O)-(CH_2CH_2O)_{n-1}CH_2-$ 및 $(CH_3CH_2O)-(CH_2CH_2O)_{n-1}CH_2CH_2-$ 로 구성되는 군에서 선택되는 어느 하나이고, 여기서 n 은 1~2이며;

상기 Y_2' 은 할로젠, $-N(R')(R'')$, $-OR'$, $-SR'$, $-C(O)R'$, $-SOR'$, SO_2R' , $=N-OR'$, $-C(O)OR'$, $-C(O)N(R')(R'')$, $-OC(O)OR'$, $-OC(O)N(R')(R'')$, $-N(R')C(O)O(R'')$, $-N(R')SO(R')$, $-SON(R')(R'')$, $-N(R')SO_2(R'')$ 및 $-SO_2N(R')(R'')$ 으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 알킬, 알케닐, 알키닐 및 헤테로시클로알킬로 구성되는 군에서 선택되는 어느 하나

인 것인 화합물 또는 이의 약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭.

【청구항 3】

청구항 2에 있어서,

상기 화학식 I 내지 화학식 IV에서, 각각 독립적으로,

상기 W_1 은 알킬렌-OR' 및 알킬렌-OP(O)(OR')(OR'')으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, -알킬렌-, -알킬렌-O-, -알킬렌-OSO₂- 및 -알킬렌-N(R')SO₂-로 구성되는 군에서 선택되는 어느

5 하나이고;

상기 A는 벤젠, 퓨란, 벤조퓨란, 피리딘, 티오펜, 이미다졸 및 옥사졸로 구성되는 군에서 선택되는 어느 하나이고;

상기 R_1 및 R_2 는, 각각 독립적으로, 수소, 알킬, OR', C(O)R', C(O)OR', C(O)N(R')(R''), (알킬렌)-OR', (알킬렌)-SR', (알킬렌)-OP(O)(OR')(OR''), 헤테로아릴 및 헤테로시클로알킬로 구성되는 군에서 선택되는 어느 하나이고, 상기 R_1 및 R_2 는 각각 독립적으로 1개 이상의 할로젠으로 치환될 수 있으며, 각각 독립적으로 상기 R_1 및 R_2 가 헤테로아릴, 또는 헤테로시클로알킬인 경우에는 1개 이상의 위치에서 1개 이상의 할로젠으로 치환 또는 비치환된 알킬 또는 N(R')(R'')로 치환될 수

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있고;

상기 X_1 은 직접 결합이거나, 또는 상기 X_{1a} 군은 -N(R')- 및 -O-로 구성되고, 상기 X_{1b} 군은 -C(O)O-, -N(R')C(O)- 및 -C(O)N(R')-로 구성되고,

상기 X_2 는 직접 결합이거나, 또는 상기 X_{2a} 군은 N(R')-, -O-, -C(O)- 및 =N-O-로 구성되고, 상기 X_{2b} 군은 -N(R')C(O)-로 구성되고,

20

상기 X2c 군은 $-C(O)N(R')-$ 로 구성되고,

상기 B는 히드록시 및 옥소로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 5원 내지 10원의 헤테로아릴, 3원 내지 10원의 헤테로시클로알킬 및 3원 내지 10원의 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이거나, 또는 비치환된, 5원 내지 10원의 헤테로아릴, 3원 내지 10원의 헤테로시클로알킬 및 3원 내지 10원의 헤테로시클로알케닐로 구성되는 군에서 선택되는 둘 이상이 직접, $-알킬렌-$, $-C(O)-$, $-N(R')-$ 또는 이들의 조합으로 연결된 것일 수 있고;

W_2' 은 수소이거나, 또는 할로젠, 알킬렌-OR', 알킬렌-OP(O)(OR')(OR''), $-N(R')(R'')$, $-OR'$ 및 $-C(O)OR'$ 으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된 알킬일고;

Y_1' 은 할로젠, $-N(R')(R'')$, $-OR'$ 및 $-C(O)OR'$ 으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 알킬, 알케닐 및 알킬닐로 구성되는 군에서 선택되는 어느 하나이며;

Y_2' 은 할로젠, $-N(R')(R'')$, $-OR'$ 및 $-C(O)OR'$ 으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 알킬 및 헤테로시클로알킬로 구성되는 군에서 선택되는 어느 하나

인 것인 화합물 또는 이의 약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭.

【청구항 4】

청구항 3에 있어서,

- 상기 화합물은 하기 표 1 내지 표 4에 기재된 화합물들로 구성되는 군에서 선택되는 적어도 하나인 것인 화합물 또는 이의 약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭.

[표 1]

번호	화합물
1-1	4-(3-aminoprop-1-yn-1-yl)aniline hydrochloride
1-3	3-(3-aminoprop-1-yn-1-yl)aniline hydrochloride
3-1	methyl 5-amino-2-(3-aminoprop-1-yn-1-yl)benzoate
3-2	5-amino-2-(3-aminoprop-1-yn-1-yl)benzoic acid
3-3	(5-amino-2-(3-aminoprop-1-yn-1-yl)phenyl)methanol
3-6	(5-amino-2-(3-aminoprop-1-yn-1-yl)phenyl)methanethiol
3-7	5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl dimethyl phosphate
3-8	5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl dihydrogen phosphate
3-9	5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl di-tert-butyl phosphate
3-10	5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl dibenzyl phosphate
3-11	5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl diisopropyl phosphate
3-12	isopropyl (((5-amino-2-(3-aminoprop-1-yn-1-yl)benzyl)oxy)(phenoxy)phosphoryl)-L-alaninate
3-25	methyl 4-amino-2-(3-aminoprop-1-yn-1-yl)benzoate hydrochloride
3-26	4-amino-2-(3-aminoprop-1-yn-1-yl)benzoic acid
3-27	(4-amino-2-(3-aminoprop-1-yn-1-yl)phenyl)methanol
3-28	(4-amino-2-(3-aminoprop-1-yn-1-yl)phenyl)methanethiol

3-30	4-amino-2-(3-aminoprop-1-yn-1-yl)benzyl dimethyl phosphate
3-31	4-amino-2-(3-aminoprop-1-yn-1-yl)benzyl di-tert-butyl phosphate
3-32	4-amino-2-(3-aminoprop-1-yn-1-yl)benzyl dihydrogen phosphate
3-33	4-amino-2-(3-aminoprop-1-yn-1-yl)benzyl diphenyl phosphate
3-34	4-amino-2-(3-aminoprop-1-yn-1-yl)benzyl diisopropyl phosphate
3-35	isopropyl ((4-amino-2-(3-aminoprop-1-yn-1-yl)phenethoxy)(phenoxy)phosphoryl)-L-alaninate
3-49	2-amino-4-(4-aminophenyl)but-3-yn-1-ol hydrochloride
3-51	2-amino-4-(3-aminophenyl)but-3-yn-1-ol
3-53	2-amino-4-(4-aminophenyl)but-3-yn-1-yl di-tert-butyl phosphate
3-55	2-amino-4-(3-aminophenyl)but-3-yn-1-yl di-tert-butyl phosphate
3-57	2-amino-4-(4-aminophenyl)but-3-yn-1-yl dihydrogen phosphate
3-60	2-amino-4-(3-aminophenyl)butyl dihydrogen phosphate
4-1	3,3'-(furan-2,5-diyl)bis(prop-2-yn-1-amine)
4-10	3,3'-(thiophene-2,5-diyl)bis(prop-2-yn-1-amine)
4-13	3,3'-(1H-pyrrole-2,5-diyl)bis(prop-2-yn-1-amine)
4-16	3,3'-(furan-2,4-diyl)bis(prop-2-yn-1-amine)
4-19	3,3'-(thiophene-2,4-diyl)bis(prop-2-yn-1-amine)
4-25	3,3'-(furan-2,4-diyl)bis(prop-2-yn-1-amine)
4-28	3,3'-(thiophene-2,4-diyl)bis(prop-2-yn-1-amine)
4-31	3,3'-(1H-pyrrole-2,4-diyl)bis(prop-2-yn-1-amine)
4-34	3,3'-(furan-3,4-diyl)bis(prop-2-yn-1-amine)
4-40	3,3'-(1H-pyrrole-3,4-diyl)bis(prop-2-yn-1-amine)
4-43	3,3'-(furan-2,3-diyl)bis(prop-2-yn-1-amine)
4-52	3,3'-(furan-2,3-diyl)bis(prop-2-yn-1-amine)
4-61	4-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)but-3-yn-1-amine

4-62	4-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)but-3-yn-1-amine
4-63	4-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)but-3-yn-1-amine
4-64	5-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)pent-4-yn-1-amine
4-65	5-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)pent-4-yn-1-amine
4-66	5-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)pent-4-yn-1-amine
4-67	6-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)hex-5-yn-1-amine
4-68	6-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)hex-5-yn-1-amine
4-69	6-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)hex-5-yn-1-amine
4-70	7-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)hept-6-yn-1-amine
4-71	7-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)hept-6-yn-1-amine
4-72	7-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)hept-6-yn-1-amine
4-73	8-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)oct-7-yn-1-amine
4-74	8-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)oct-7-yn-1-amine
4-75	8-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)oct-7-yn-1-amine
4-128	3,3'-(1,4-phenylene)bis(prop-2-yn-1-amine)
4-129	3,3'-(1,3-phenylene)bis(prop-2-yn-1-amine)
4-130	3,3'-(1H-imidazole-2,5-diyl)bis(prop-2-yn-1-amine)
4-131	3,3'-(oxazole-2,5-diyl)bis(prop-2-yn-1-amine)
4-147	4,4'-(furan-2,5-diyl)bis(but-3-yn-1-amine)
4-177	3,3'-(pyridine-2,5-diyl)bis(prop-2-yn-1-amine)
4-178	3,3'-(pyridine-2,6-diyl)bis(prop-2-yn-1-amine)

4-179	3,3'-(pyridine-2,5-diyl)bis(prop-2-yn-1-amine)
4-180	3-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1,1-d2-1-amine
4-181	2-amino-4-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)but-3-ynoic acid
4-182	methyl 2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-carboxylate
4-183	dimethyl 2,5-bis(3-aminoprop-1-yn-1-yl)furan-3,4-dicarboxylate
4-184	methyl 2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-carboxylate
4-185	(2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-yl)methanol
4-186	(2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-yl)methanol
4-187	(2,5-bis(3-aminoprop-1-yn-1-yl)furan-3,4-diyl)dimethanol
4-188	(2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-yl)methyl dihydrogen phosphate
4-189	(2,5-bis(3-aminoprop-1-yn-1-yl)furan-3-yl)methyl dihydrogen phosphate
4-200	4-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)but-3-yn-1-amine
4-201	4-(5-(3-aminoprop-1-yn-1-yl)furan-3-yl)but-3-yn-1-amine
4-202	4,4'-(furan-2,4-diyl)bis(but-3-yn-1-amine)
4-218	3,3'-(5-methylthiophene-2,4-diyl)bis(prop-2-yn-1-amine)
4-219	4-(5-(3-aminoprop-1-yn-1-yl)-2-methylthiophen-3-yl)but-3-yn-1-amine
4-223	3-(5-(3-(aminooxy)prop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-amine
5-52	ethyl 2,5-bis(3-aminoprop-1-yn-1-yl)oxazole-4-carboxylate
5-116	methyl 2,4-bis(3-aminoprop-1-yn-1-yl)benzoate dihydrochloride

[표 2]

번호	화합물
4-6	2-(3-aminoprop-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-109	methyl 2-(4-aminobut-1-yn-1-yl)-5-(3-

	aminopropanamido)benzoate
4-110	2-(4-aminobut-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-111	3-amino-N-(4-(4-aminobut-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-112	methyl 2-(5-aminopent-1-yn-1-yl)-5-(3-aminopropanamido)benzoate
4-113	2-(5-aminopent-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-114	3-amino-N-(4-(5-aminopent-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-115	methyl 2-(6-aminohex-1-yn-1-yl)-5-(3-aminopropanamido)benzoate
4-116	2-(6-aminohex-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-117	3-amino-N-(4-(6-aminohex-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-118	methyl 2-(7-aminohept-1-yn-1-yl)-5-(3-aminopropanamido)benzoate
4-119	2-(7-aminohept-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-120	3-amino-N-(4-(7-aminohept-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-121	methyl 2-(8-aminooct-1-yn-1-yl)-5-(3-aminopropanamido)benzoate
4-122	2-(8-aminooct-1-yn-1-yl)-5-(3-aminopropanamido)benzoic acid
4-123	3-amino-N-(4-(8-aminooct-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-124	3-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)propanamide
4-125	3-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)propanamide
4-126	methyl 2-(3-aminoprop-1-yn-1-yl)-5-(3-aminopropanamido)benzoate
4-127	3-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3,5-bis(hydroxymethyl)phenyl)propanamide
4-148	N-(4-aminobut-2-yn-1-yl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-149	N-(4-aminobutyl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide

4-150	5-(4-aminobut-1-yn-1-yl)-N-(4-aminobut-2-yn-1-yl)furan-2-carboxamide
4-161	3-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)propanamide
4-162	4-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)butanamide dihydrochloride
4-163	5-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)pentanamide
4-164	5-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)pentanamide
4-165	6-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)hexanamide
4-166	5-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)furan-2-carboxamide dihydrochloride
4-167	N-(5-aminopentyl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-168	4-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)butanamide
4-169	5-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)pentanamide
4-170	5-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-methoxyphenyl)pentanamide
4-171	6-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)hexanamide
4-192	N-(4-aminobutyl)-5-(3-aminoprop-1-yn-1-yl)-3-methylfuran-2-carboxamide
4-199	4-amino-N-((5-(3-aminoprop-1-yn-1-yl)furan-2-yl)methyl)butanamide
4-203	N-(4-aminobutyl)-4-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-204	4-(4-aminobut-1-yn-1-yl)-N-(4-aminobutyl)furan-2-carboxamide
4-205	4-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)furan-2-carboxamide
4-206	N-(5-aminopentyl)-4-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-209	N-(4-aminobutyl)-5-(3-aminoprop-1-yn-1-yl)benzofuran-2-carboxamide
4-210	5-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)benzofuran-2-carboxamide

4-214	N-(4-aminobutyl)-5-(3-aminoprop-1-yn-1-yl)-7-methoxybenzofuran-2-carboxamide
4-215	N-(4-aminobutyl)-5-(3-aminoprop-1-yn-1-yl)-6-methoxybenzofuran-2-carboxamide
4-216	5-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)-6-methoxybenzofuran-2-carboxamide
4-217	5-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)-7-methoxybenzofuran-2-carboxamide
4-224	N-(7-aminoheptyl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-225	N-(9-aminononyl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
4-228	methyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate dihydrochloride
4-229	N-(4-aminobutyl)-4-(3-aminoprop-1-yn-1-yl)benzamide
4-231	5-(3-aminoprop-1-yn-1-yl)-N-(2-aminopyridin-4-yl)furan-2-carboxamide
4-232	5-(3-(aminooxy)prop-1-yn-1-yl)-N-(3-aminopropyl)furan-2-carboxamide
4-233	methyl 2-amino-4-(5-((3-aminopropyl)carbamoyl)furan-2-yl)but-3-ynoate
4-234	methyl 2-(3-(aminooxy)prop-1-yn-1-yl)-5-((3-aminopropyl)carbamoyl)furan-3-carboxylate
4-235	N-(8-aminooctyl)-5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamide
5-1	ethyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-2	isopropyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-3	cyclopropyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-4	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-aminopropanamido)benzoate
5-5	methyl 4-(5-aminopentanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-6	methyl 4-(6-aminohexanamido)-2-(3-aminoprop-1-yn-1-

	yl)benzoate
5-8	4-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)butanamide trifluoroacetic acid
5-9	5-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)pentanamide
5-10	methyl 4-((4-aminobutyl)amino)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-11	methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-aminopropyl)amino)benzoate
5-12	methyl 4-(4-aminobutoxy)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-13	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-aminopropoxy)benzoate
5-14	methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-aminopropanoyl)oxy)benzoate
5-15	methyl 4-((4-aminobutanoyl)oxy)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-16	methyl 4-((5-aminopentanoyl)oxy)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-17	methyl 4-((6-aminohexanoyl)oxy)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-18	methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-aminopropyl)carbamoyl)benzoate dihydrochloride
5-19	methyl 4-((2-aminoethyl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-20	methyl 4-((4-aminobutyl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-21	methyl 4-((5-aminopentyl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-30	methyl 4-((4-aminobut-2-yn-1-yl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-31	methyl (Z)-4-((4-aminobut-2-en-1-yl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-34	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(((1r,4r)-4-hydroxycyclohexyl)amino)benzoate
5-35	methyl 4-((4-aminocyclohexyl)amino)-2-(3-aminoprop-1-yn-1-yl)benzoate

5-49	methyl 4-(4-aminobicyclo[2.2.2]octane-1-carboxamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-50	methyl 4-(1-(2-aminoethyl)cyclopropane-1-carboxamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-53	4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoic acid
5-54	difluoromethyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-55	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-(trifluoromethyl)cyclopropane-1-carbonyl)phenyl)butanamide
5-56	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-fluorocyclopropane-1-carbonyl)phenyl)butanamide
5-57	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-fluorocyclobutane-1-carbonyl)phenyl)butanamide
5-58	1,1-difluoroethyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-59	4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzamide
5-60	4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)-N-methylbenzamide
5-61	4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)-N,N-dimethylbenzamide
5-62	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-hydroxyphenyl)butanamide
5-63	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-methoxyphenyl)butanamide
5-64	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-methoxyethoxy)phenyl)butanamide
5-65	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-methylphenyl)butanamide
5-66	N-(4-acetyl-3-(3-aminoprop-1-yn-1-yl)phenyl)-4-aminobutanamide
5-67	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-hydroxyethyl)phenyl)butanamide
5-68	4-amino-N-(4-(aminomethyl)-3-(3-aminoprop-1-yn-1-yl)phenyl)butanamide
5-69	4-amino-N-(4-amino-3-(3-aminoprop-1-yn-1-yl)phenyl)butanamide

5-70	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)butanamide
5-71	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)butanamide
5-72	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(3-(methylamino)oxetan-3-yl)phenyl)butanamide
5-73	(E)-4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-fluoroprop-1-en-1-yl)phenyl)butanamide
5-74	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-carbamimidoylphenyl)butanamide
5-75	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(trifluoromethyl)phenyl)butanamide
5-76	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-chlorophenyl)butanamide
5-77	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-fluorophenyl)butanamide
5-78	methyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)-6-methylbenzoate
5-79	methyl 4-(5-aminopent-1-yn-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-80	methyl 4-(4-aminobut-1-yn-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-81	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)butanamide dihydrochloride
5-82	4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzyl dihydrogen phosphate
5-83	4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzyl di-tert-butyl phosphate
5-87	methyl 4-(4-aminobutanamido)-2-(3,4-diamino-4-oxobut-1-yn-1-yl)benzoate
5-89	methyl 3-(4-aminobutanamido)-5-(3-aminoprop-1-yn-1-yl)benzoate
5-90	methyl 2-(4-aminobutanamido)-4-(3-aminoprop-1-yn-1-yl)benzoate
5-92	methyl 4-(4-aminobutanamido)-2-((1-aminocyclopropyl)ethynyl)benzoate

5-93	2-amino-4-(5-(4-aminobutanamido)-2-(methoxycarbonyl)phenyl)but-3-ynoic acid
5-94	methyl 2-(3-amino-4-methoxy-4-oxobut-1-yn-1-yl)-4-(4-aminobutanamido)benzoate
5-95	methyl 2-(3-amino-4-hydroxybut-1-yn-1-yl)-4-(4-aminobutanamido)benzoate
5-96	methyl 6-(4-aminobutanamido)-3-(3-aminoprop-1-yn-1-yl)picolinate
5-97	dimethyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)isophthalate
5-98	methyl 2-(4-aminobutanamido)-6-(3-aminoprop-1-yn-1-yl)nicotinate
5-99	2-(4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)phenyl)acetic acid
5-100	ethyl 2-(4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)phenyl)acetate
5-101	acetoxymethyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-102	(methacryloyloxy)methyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-103	(pivaloyloxy)methyl 4-(4-aminobutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-104	6-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)hexanamide
5-106	5-((3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)phenyl)amino)-5-oxopentanoic acid
5-107	8-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)octanamide
5-108	11-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)undecanamide
5-109	11-((3-(3-aminoprop-1-yn-1-yl)phenyl)amino)-11-oxoundecanoic acid hydrochloride
5-110	11-((3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)phenyl)amino)-11-oxoundecanoic acid hydrochloride
5-113	methyl 4-(5-((7-aminoheptyl)amino)-5-oxopentanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-115	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-hydroxybutanamido)benzoate

5-121	N-(7-aminoheptyl)-2,4-bis(3-aminoprop-1-yn-1-yl)benzamide
5-122	methyl 4-(3-(4-aminobutanamido)prop-1-yn-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-123	4-amino-N-(3-(3-(3-aminoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl)butanamide
5-126	20-amino-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-3,6,9,12,15,18-hexaoxaicosanamide
5-127	20-amino-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-3,6,9,12,15,18-hexaoxaicosanamide
5-135	8-amino-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)octanamide
5-148	methyl 2-(3-acetamidoprop-1-yn-1-yl)-4-(4-aminobutanamido)benzoate
5-149	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(methylamino)butanamido)benzoate
5-150	methyl 4-(4-amino-N-methylbutanamido)-2-(3-aminoprop-1-yn-1-yl)benzoate hydrochloride
5-169	2-(3-aminoprop-1-yn-1-yl)-N-(3-aminopropyl)oxazole-5-carboxamide
5-170	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-morpholinophenyl)butanamide
5-171	4-amino-N-(3-(3-aminoprop-1-yn-1-yl)-4-(4-methylpiperazin-1-yl)phenyl)butanamide

[표 3]

번호	화합물
4-2	methyl 2-(3-aminoprop-1-yn-1-yl)-5-(piperazin-1-yl)benzoate hydrochloride
4-3	2-(3-aminoprop-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-4	(2-(3-aminoprop-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol
4-94	methyl 2-(4-aminobut-1-yn-1-yl)-5-(piperazin-1-yl)benzoate
4-95	2-(4-aminobut-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-96	(2-(4-aminobut-1-yn-1-yl)-5-(piperazin-1-

	yl)phenyl)methanol
4-97	methyl 2-(5-aminopent-1-yn-1-yl)-5-(piperazin-1-yl)benzoate
4-98	2-(5-aminopent-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-99	(2-(5-aminopent-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol
4-100	methyl 2-(6-aminohex-1-yn-1-yl)-5-(piperazin-1-yl)benzoate
4-101	2-(6-aminohex-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-102	(2-(6-aminohex-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol
4-103	methyl 2-(7-aminohept-1-yn-1-yl)-5-(piperazin-1-yl)benzoate
4-104	2-(7-aminohept-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-105	(2-(7-aminohept-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol
4-106	methyl 2-(8-aminooct-1-yn-1-yl)-5-(piperazin-1-yl)benzoate
4-107	2-(8-aminooct-1-yn-1-yl)-5-(piperazin-1-yl)benzoic acid
4-108	(2-(8-aminooct-1-yn-1-yl)-5-(piperazin-1-yl)phenyl)methanol
4-134	3-(4-([1,4'-bipiperidin]-4-yl)phenyl)prop-2-yn-1-amine
4-135	3-(4-(1-(azetidin-3-yl)piperidin-4-yl)phenyl)prop-2-yn-1-amine
4-136	3-(4-(piperidin-4-yl)phenyl)prop-2-yn-1-amine
4-146	3-(4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)prop-2-yn-1-amine
4-226	3-(4-(piperazin-1-yl)phenyl)prop-2-yn-1-amine
4-227	(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)(piperazin-1-yl)methanone
5-7	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperazin-1-yl)benzoate hydrochloride
5-22	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidin-4-ylcarbamoyl)benzoate
5-23	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidine-4-

	carboxamido)benzoate hydrochloride
5-24	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2-(piperidine-4-carboxamido)acetamido)benzoate
5-25	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(piperidine-4-carboxamido)propanamido)benzoate
5-26	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(piperidine-4-carboxamido)butanamido)benzoate
5-27	methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-(piperidine-4-carboxamido)propyl)carbamoyl)benzoate
5-28	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(piperidine-4-carboxamido)prop-1-yn-1-yl)benzoate dihydrochloride
5-29	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(piperidin-4-ylmethyl)piperazin-1-yl)benzoate dihydrochloride
5-36	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidin-4-yloxy)benzoate
5-37	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(azetidin-3-yl)piperazin-1-yl)benzoate
5-38	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,7-diazaspiro[3.5]nonan-7-yl)benzoate
5-39	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,7-diazaspiro[3.5]nonane-7-carbonyl)benzoate dihydrochloride
5-40	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptan-2-yl)benzoate dihydrochloride
5-41	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptane-2-carbonyl)benzoate dihydrochloride
5-42	methyl 4-((2-azaspiro[3.3]heptan-6-yl)carbamoyl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-43	methyl 4-(((2-azaspiro[3.3]heptan-6-ylidene)amino)oxy)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-44	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)benzoate
5-45	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzoate
5-46	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(azetidin-3-yl)piperidin-1-yl)benzoate
5-47	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(piperidin-4-

	yl)azetidin-1-yl)benzoate
5-48	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3,6-diazabicyclo[3.1.1]heptan-3-yl)benzoate
5-85	methyl 2-(3-aminoprop-1-yn-1-yl)-4-((piperidin-4-ylmethyl)amino)benzoate
5-86	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperidin-4-ylamino)benzoate dihydrochloride
5-88	4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperidin-4-ol
5-112	methyl 3-(3-aminoprop-1-yn-1-yl)-6-(piperidine-4-carboxamido)picolinate
5-118	methyl 2-(3-aminoprop-1-yn-1-yl)-5-(3,6-diazabicyclo[3.1.1]heptan-3-yl)benzoate
5-119	methyl 2-(3-aminoprop-1-yn-1-yl)-5-(3-oxopiperazin-1-yl)benzoate
5-120	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(piperidine-4-carbonyl)piperazin-1-yl)benzoate
5-124	(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-yl)(4-(piperidin-4-ylmethyl)piperazin-1-yl)methanone
5-125	(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-yl)(piperazin-1-yl)methanone
5-129	5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(piperidin-4-yl)furan-2-carboxamide
5-131	N-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperidine-4-carboxamide
5-134	N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperidine-4-carboxamide
5-139	2-(3-aminoprop-1-yn-1-yl)-4-((piperidin-4-ylmethyl)amino)benzoic acid
5-140	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(piperazine-1-carbonyl)benzoate
5-152	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(N-methylpiperidine-4-carboxamido)benzoate
5-153	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(methyl(piperidin-4-yl)carbamoyl)benzoate
5-154	methyl 4-(piperidine-4-carboxamido)-2-(3-(sulfamoylamino)prop-1-yn-1-yl)benzoate

5-155	methyl 2-((1-aminocyclopropyl)ethynyl)-4-(piperidine-4-carboxamido)benzoate
5-156	methyl 2-(3-(((4-chlorophenyl)(5-fluoro-2-hydroxyphenyl)methylene)amino)prop-1-yn-1-yl)-4-(piperidine-4-carboxamido)benzoate
5-157	methyl 2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)-4-(piperidine-4-carboxamido)benzoate
5-158	methyl 4-(piperidine-4-carboxamido)-2-(3-(sulfamoyloxy)prop-1-yn-1-yl)benzoate
5-159	methyl 2-(3-amino-4-mercaptobut-1-yn-1-yl)-4-(piperidin-4-ylcarbamoyl)benzoate
5-160	5-(3-(3-aminoprop-1-yn-1-yl)phenyl)-N-(piperidin-4-yl)furan-2-carboxamide
5-162	methyl 2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)-4-(2,6-diazaspiro[3.3]heptan-2-yl)benzoate
5-167	methyl 3-(3-aminoprop-1-yn-1-yl)-6-(piperidine-4-carboxamido)picolinate
5-168	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(2,7-diazaspiro[3.5]nonan-2-yl)benzoate dihydrochloride

[표 4]

번호	화합물
4-207	N-(4-aminobut-2-yn-1-yl)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carboxamide
4-208	N-(4-aminobutyl)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carboxamide
4-211	5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(3-aminopropyl)furan-2-carboxamide
5-32	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-aminopropanoyl)piperazin-1-yl)benzoate
5-33	methyl 2-(3-aminoprop-1-yn-1-yl)-5-(4-(3-aminopropanoyl)piperazin-1-yl)benzoate
5-51	methyl 4-(5-amino-1,3,4-oxadiazol-2-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-111	N-(7-aminoheptyl)-5-(4-(3-aminoprop-1-yn-1-

	yl)phenyl)furan-2-carboxamide
5-114	methyl 4-(4-(6-aminohexanoyl)piperazin-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-117	methyl 4-(4-aminopiperidin-1-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-128	(4-aminopiperidin-1-yl)(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-yl)methanone
5-130	N-(4-aminobutyl)-1-(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carbonyl)piperidine-4-carboxamide
5-132	1-(4-aminobutanoyl)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperidine-4-carboxamide
5-133	1-(4-aminobutanoyl)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperidine-4-carboxamide
5-136	N-(7-aminoheptyl)-5-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)furan-2-carboxamide
5-137	N-(4-aminobutyl)-5-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)furan-2-carboxamide
5-138	N-(7-aminoheptyl)-5-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)furan-2-carboxamide
5-141	methyl 4-(5-((4-aminobutyl)carbamoyl)furan-2-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-142	N-(4-aminobutyl)-5-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)furan-2-carboxamide
5-143	N-(4-aminobutyl)-5-(3-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carboxamide
5-144	methyl 5-(5-((4-aminobutyl)carbamoyl)furan-2-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-145	methyl 5-(5-((7-aminoheptyl)carbamoyl)furan-2-yl)-2-(3-aminoprop-1-yn-1-yl)benzoate
5-164	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-aminopropyl)piperazin-1-yl)benzoate
5-165	methyl 2-(3-aminoprop-1-yn-1-yl)-5-(4-(3-aminopropyl)piperazin-1-yl)benzoate

【청구항 5】

청구항 1에 있어서,

상기 화합물은 유비퀴틴 결합 화합물인 것인 화합물 또는 이의
약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭.

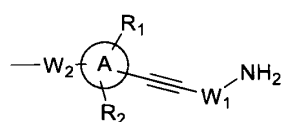
5 【청구항 6】

TBM-UBM의 화학 구조를 가지고,

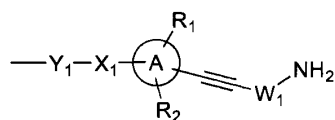
상기 TBM은 표적 단백질 또는 폴리펩티드에 결합하는
부분(moiety)이고,

상기 UBM은 하기 화학식 V 내지 화학식 VIII로 표시되는 화학
10 구조인 것인, 화합물 또는 이의 약학적으로 허용 가능한 염, 이성질체,
용매화물, 수화물 또는 프로드럭:

[화학식 V]

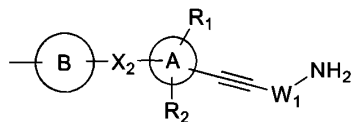


[화학식 VI]

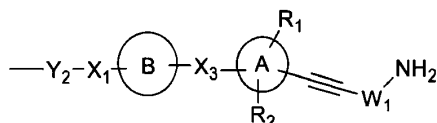


15

[화학식 VII]



[화학식 VIII]



5 상기 화학식 V 내지 화학식 VIII에서, 각각 독립적으로,

W_1 은 중수소, 알킬, $C(O)OR'$, $C(O)N(R')(R'')$, 알킬렌- $C(O)OR'$,
 알킬렌- $C(O)N(R')(R'')$, 알킬렌- OR' , 알킬렌- SR' , 알킬렌- $N(R')(R'')$,
 알킬렌- $OP(O)(OR')(OR'')$, 알킬렌- $P(O)(OR')(OR'')$ 및 알킬렌-
 $OP(O)(R')(R'')$ 으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는
 10 비치환된, -알킬렌-, -알킬렌-O-, -알킬렌- OSO_2 - 및 -알킬렌- $N(R')SO_2$ -로
 구성되는 군에서 선택되는 어느 하나이고;

 A는 아릴, 헤테로아릴, 시클로알킬, 헤테로시클로알킬 및
 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이고;

R_1 및 R_2 는, 각각 독립적으로, 수소, 알킬, 알케닐, 알키닐, 할로젠,
 15 옥소, CN, NO_2 , OR' , SR' , $N(R')(R'')$, O-(알킬렌)- OR' , - $N(R')$ -(알킬렌)- OR' ,
 $C(O)R'$, $C(NH)R'$, $C(S)R'$, $C(O)OR'$, $C(O)N(R')(R'')$, $P(O)(R')(R'')$,
 $P(O)(OR')(OR'')$, $C(NH)N(R')(R'')$, $C(S)OR'$, $C(S)N(R')(R'')$, $C(O)O$ -(알킬렌)-

OC(O)R' , $\text{C(O)O-(알킬렌)-메타크릴로일옥시}$, (알킬렌)-OR' , (알킬렌)-SR' ,
 (알킬렌)-N(R')(R'') , (알키닐렌)-N(R')(R'') , $\text{(알킬렌)-P(O)(R')(R'')-}$,
 $\text{(알킬렌)-P(O)(OR')(OR'')}$, $\text{(알킬렌)-OP(O)(R')(R'')}$, (알킬렌)-
 OP(O)(OR')(OR'') , $\text{(알킬렌)-OP(O)(벤질옥시)}_2$, $\text{(알킬렌)-OP(O)(페녹시)}_2$,
5 $\text{(알킬렌)-OP(O)(페녹시)(NH-CH(R')C(O)OR'')}$, (알킬렌)-C(O)OR' ,
 (알케닐렌)-C(O)OR' , (알키닐렌)-C(O)OR' , $\text{(알킬렌)-C(O)N(R')(R'')}$,
 $\text{(알케닐렌)-C(NH)N(R')(R'')}$, $\text{(알키닐렌)-C(S)N(R')(R'')}$, (알킬렌)-C(O)R' ,
 (알킬렌)-C(NH)R' , (알킬렌)-C(S)R' , 아릴, 헤테로아릴, 헤테로시클로알킬 및
헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이고, 상기 R_1 및
10 R_2 는 각각 독립적으로 1개 이상의 할로겐으로 치환될 수 있으며, 각각
독립적으로 상기 R_1 및 R_2 가 아릴, 헤테로아릴, 헤테로시클로알킬 또는
헤테로시클로알케닐인 경우에는 1개 이상의 위치에서 1개 이상의
할로겐으로 치환 또는 비치환된 알킬 또는 N(R')(R'') 로 치환될 수 있고;

X_1 은 직접 결합이거나, 또는 $-\text{N(R')-}$, $-\text{O-}$, $-\text{S-}$, $-\text{C(O)-}$, $-\text{SO-}$,
15 SO_2- , $=\text{N-O-}$ 및 $-\text{O-N=}$ 로 구성되는 X_{1a} 군, $-\text{OC(O)-}$, $-\text{C(O)O-}$, $-\text{N(R')C(O)-}$,
 $-\text{C(O)N(R')-}$, $-\text{N(R')SO-}$, $-\text{SON(R')-}$, $-\text{N(R')SO}_2-$ 및 $-\text{SO}_2\text{N(R')-}$ 로
구성되는 X_{1b} 군 및 $-\text{알킬렌-}$, $-\text{알케닐렌-}$ 및 $-\text{알키닐렌-}$
으로 구성되는 X_{1c} 군으로부터 선택되는 어느 하나이거나, 또는 둘 이상이
서로 연결된 것이고;

20 X_2 는 직접 결합이거나, 또는 $-\text{N(R')-}$, $-\text{O-}$, $-\text{S-}$, $-\text{C(O)-}$, $-\text{SO-}$,

SO₂-, =N-O- 및 -O-N=로 구성되는 X2a 군, -OC(O)-, -N(R')C(O)-, -N(R')C(O)O-, -N(R')SO₂-O- 및 -N(R')C(S)O-로 구성되는 X2b 군, -C(O)O-, -C(O)N(R')-, -O-SO₂-N(R')-, -O-C(S)N(R')- 및 -O-C(O)N(R')-로 구성되는 X2c 군 및 -알킬렌-, -알케닐렌- 및 -알키닐렌-으로 구성되는 X2d 군으로부터 선택되는 어느 하나이거나, 또는 둘 이상이 서로 연결된 것이고;

X₃은 직접 결합이거나, 또는 -알킬렌-, -O-, -S-, -C(O)-, -N(R')-, -SO-, -SO₂- 및 이들의 조합으로 구성되는 군으로부터 선택되는 어느 하나이고;

10 B는 히드록시, 알콕시 및 옥소로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 아릴, 헤테로아릴, 시클로알킬, 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이거나, 또는 히드록시, 알콕시 및 옥소로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 아릴, 헤테로아릴, 시클로알킬, 15 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 둘 이상이 직접 연결, -알킬렌-, -O-, -S-, -C(O)-, -N(R')-, -SO-, -SO₂- 또는 이들의 조합으로 연결된 것일 수 있고;

W₂는 직접 결합이거나, 또는 중수소, 알킬, C(O)OR', C(O)N(R')(R''), 알킬렌-C(O)OR', 알킬렌-C(O)N(R')(R''), 알킬렌-OR', 알킬렌-SR', 알킬렌-N(R')(R''), 알킬렌-OP(O)(OR')(OR''), 알킬렌-P(O)(OR')(OR'') 및 알킬렌-

OP(O)(R')(R'')으로 구성된 군에서 선택되는 적어도 하나로 치환 또는
 비치환된, -알킬렌-, -알케닐렌- 및 -알키닐렌-으로 구성되는 군에서
 선택되는 어느 하나이고;

Y₁은 직접 결합, 알킬렌, 알케닐렌, 알키닐렌, -(CH₂CH₂O)_nCH₂- 및
 5 -(CH₂CH₂O)_nCH₂CH₂-로 구성되는 군에서 선택되는 어느 하나이고, 여기서
 n은 1~4이고;

Y₂는 직접 결합, 알킬렌, 알케닐렌, 알키닐렌, 헤테로시클로알킬렌 및
 헤테로시클로알케닐렌로 구성되는 군에서 선택되는 어느 하나이고;

상기 TBM과 UBM은 공유 결합으로 연결되며, 상기 공유 결합
 10 부위가 직접 결합이거나, 또는 -N(R')-, -O-, -C(R')(R'')-O-, -S-, -C(O)-,
 -SO-, SO₂-, =N-O-, -O-N=, -OC(O)-, -C(O)O-, -N(R')C(O)-, -
 C(O)N(R')-, -OC(O)O-, -OC(O)N(R')-, -N(R')C(O)O-, -N(R')SO-, -
 SON(R')-, -N(R')SO₂- 및 -SO₂N(R')-로 구성되는 군에서 선택되는 어느
 하나를 형성하도록 TBM과 UBM은 각각 변형될 수 있으며;

15 상기 작용기들에서 R' 및 R''은 각각 독립적으로 수소 또는 알킬임.

【청구항 7】

청구항 6에 있어서,

상기 화학식 V 내지 화학식 VIII에서, 각각 독립적으로,

20 상기 W₁은 C(O)OR', C(O)N(R')(R''), 알킬렌-OR', 알킬렌-SR' 및

알킬렌-OP(O)(OR')(OR'')으로 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, -알킬렌-, -알킬렌-O-, -알킬렌-OSO₂- 및 -알킬렌-N(R')SO₂-로 구성되는 군에서 선택되는 어느 하나이고;

상기 A는 아릴, N, O 및 S로 구성되는 군에서 선택되는 적어도 하나를 포함하는 5원 내지 10원의 헤테로아릴, 3원 내지 10원의 시클로알킬, N, O 및 S로 구성되는 군에서 선택되는 적어도 하나를 포함하는 3원 내지 10원의 헤테로시클로알킬 및 N, O 및 S로 구성되는 군에서 선택되는 적어도 하나를 포함하는 3원 내지 10원의 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이고;

상기 R₁ 및 R₂는, 각각 독립적으로, 수소, 알킬, 알케닐, 할로젠, OR', N(R')(R''), O-(알킬렌)-OR', C(O)R', C(O)OR', C(O)N(R')(R''), C(NH)N(R')(R''), C(O)O-(알킬렌)-OC(O)R', C(O)O-(알킬렌)-메타크릴로일옥시, (알킬렌)-OR', (알킬렌)-SR', (알킬렌)-N(R')(R''), (알킬렌)-N(R')(R''), (알킬렌)-OP(O)(OR')(OR''), (알킬렌)-OP(O)(벤질옥시)₂, (알킬렌)-OP(O)(페녹시)₂, (알킬렌)-OP(O)(페녹시)(NH-CH(R')C(O)OR''), (알킬렌)-C(O)OR', 아릴, 헤테로아릴, 헤테로시클로알킬 및 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이고, 상기 R₁ 및 R₂는 각각 독립적으로 1개 이상의 할로젠으로 치환될 수 있으며, 각각 독립적으로 상기 R₁ 및 R₂가 아릴, 헤테로아릴, 헤테로시클로알킬, 또는 헤테로시클로알케닐인 경우에는 1개 이상의 위치에서 1개 이상의

할로겐으로 치환 또는 비치환된 알킬 또는 $N(R')(R'')$ 로 치환될 수 있고;

상기 X_1 은 직접 결합이거나, 상기 $X1a$ 군 및 상기 $X1b$ 군으로부터
 선택되는 어느 하나이거나, 또는 상기 $X1a$ 군 및 상기 $X1b$ 군으로부터
 선택되는 어느 하나와 상기 $X1c$ 군으로부터 선택되는 어느 하나가 $X1a$ -
 5 $X1c$ 또는 $X1b$ - $X1c$ 의 형태로 연결된 것이고;

상기 X_2 는 직접 결합이거나, 상기 $X2a$ 군, 상기 $X2b$ 군 및 상기
 $X2c$ 군으로부터 선택되는 어느 하나이거나, 또는 둘 이상이 서로 연결된
 것이거나, 또는 상기 $X2b$ 군, 상기 $X2c$ 군 및 상기 $X2d$ 군에서 선택되는
 어느 하나 또는 둘 이상이 $X2b$ - $X2d$ - $X2b$, $X2b$ - $X2d$ - $X2c$, $X2c$ - $X2d$ - $X2b$
 10 또는 $X2c$ - $X2d$ - $X2c$ 의 형태로 연결된 것이고;

상기 X_3 은 직접 결합이거나, 또는 $-C(O)-$, $-N(R')-$ 및 이들의
 조합으로 구성되는 군으로부터 선택되는 어느 하나이고;

상기 B 는 히드록시, 알콕시 및 옥소로 구성되는 군에서 선택되는
 적어도 하나로 치환 또는 비치환된, 아릴, 5원 내지 10원의 헤테로아릴, 3원
 15 내지 10원의 헤테로시클로알킬 및 3원 내지 10원의 헤테로시클로알케닐로
 구성되는 군에서 선택되는 어느 하나이거나, 또는 히드록시 및 옥소로
 구성되는 군에서 선택되는 적어도 하나로 치환 또는 비치환된, 아릴, 5원
 내지 10원의 헤테로아릴, 3원 내지 10원의 헤테로시클로알킬 및 3원 내지
 10원의 헤테로시클로알케닐로 구성되는 군에서 선택되는 둘 이상이 직접, -
 20 알킬렌-, $-C(O)-$, $-N(R')-$, 또는 이들의 조합으로 연결된 것일 수 있고;

W_2 는 직접 결합이거나, 또는 알킬렌-OR', 알킬렌-SR' 및 알킬렌-OP(O)(OR')(OR'') 으로 구성된 군에서 선택되는 적어도 하나로 치환 또는 비치환된, -알케닐렌- 및 -알키닐렌-으로 구성되는 군에서 선택되는 어느 하나이고;

- 5 Y_1 은 직접 결합, 알킬렌, 알케닐렌, 알키닐렌, $-(CH_2CH_2O)_nCH_2-$ 및 $-(CH_2CH_2O)_nCH_2CH_2-$ 로 구성되는 군에서 선택되는 어느 하나이고, 여기서 n 은 1~2이고;

Y_2 는 직접 결합, 알킬렌, 알케닐렌, 알키닐렌 및 헤테로시클로알킬렌으로 구성되는 군에서 선택되는 어느 하나이고;

- 10 상기 TBM과 UBM이 연결되는 공유 결합 부위가 직접 결합이거나, 또는 $-N(R')-$, $-O-$, $-C(R')(R'')-O-$, $-OC(O)-$, $-OC(O)N(R')-$ 및 $-C(O)N(R')-$ 로 구성되는 군에서 선택되는 어느 하나를 형성하도록 TBM과 UBM은 각각 변형될 수 있는 것

- 인 화합물 또는 이의 약학적으로 허용 가능한 염, 이성질체,
15 용매화물, 수화물 또는 프로드럭.

【청구항 8】

청구항 7에 있어서,

상기 화학식 V 내지 화학식 VIII에서, 각각 독립적으로,

- 20 상기 W_1 은 알킬렌-OR' 및 알킬렌-OP(O)(OR')(OR'')으로 구성되는

군에서 선택되는 적어도 하나로 치환 또는 비치환된, -알킬렌-, -알킬렌-O-,
-알킬렌-OSO₂- 및 -알킬렌-N(R')SO₂-로 구성되는 군에서 선택되는 어느
하나이고;

상기 A는 벤젠, 퓨란, 벤조퓨란, 피리딘, 티오펜, 이미다졸 및
5 옥사졸로 구성되는 군에서 선택되는 어느 하나이고;

상기 R₁ 및 R₂는, 각각 독립적으로, 수소, 알킬, OR', C(O)R',
C(O)OR', C(O)N(R')(R''), (알킬렌)-OR', (알킬렌)-SR', (알킬렌)-
OP(O)(OR')(OR''), 헤테로아릴 및 헤테로시클로알킬로 구성되는 군에서
선택되는 어느 하나이고, 상기 R₁ 및 R₂는 각각 독립적으로 1개 이상의
10 할로겐으로 치환될 수 있으며, 각각 독립적으로 상기 R₁ 및 R₂가
헤테로아릴, 또는 헤테로시클로알킬인 경우에는 1개 이상의 위치에서 1개
이상의 할로겐으로 치환 또는 비치환된 알킬 또는 N(R')(R'')로 치환될 수
있고;

상기 X₁은 직접 결합이거나, 또는 상기 X_{1a} 군은 -N(R')- 및 -O-로
15 구성되고, 상기 X_{1b} 군은 -C(O)O-, -N(R')C(O)- 및 -C(O)N(R')-로
구성되고,

상기 X₂는 직접 결합이거나, 또는 상기 X_{2a} 군은 N(R')-, -O-, -
C(O)- 및 =N-O-로 구성되고, 상기 X_{2b} 군은 -N(R')C(O)-로 구성되고,
상기 X_{2c} 군은 -C(O)N(R')-로 구성되고,

20 상기 B는 히드록시 및 옥소로 구성되는 군에서 선택되는 적어도

하나로 치환 또는 비치환된, 5원 내지 10원의 헤테로아릴, 3원 내지 10원의 헤테로시클로알킬 및 3원 내지 10원의 헤테로시클로알케닐로 구성되는 군에서 선택되는 어느 하나이거나, 또는 비치환된, 5원 내지 10원의 헤테로아릴, 3원 내지 10원의 헤테로시클로알킬 및 3원 내지 10원의 헤테로시클로알케닐로 구성되는 군에서 선택되는 둘 이상이 직접, -알킬렌-,
 5 -C(O)-, -N(R')- 또는 이들의 조합으로 연결된 것일 수 있고;

W_2 는 직접 결합이거나, 또는 알킬렌-OR' 및 알킬렌-OP(O)(OR')(OR'')으로 구성된 군에서 선택되는 적어도 하나로 치환 또는 비치환된, -알키닐렌-이고;

10 Y_1 은 직접 결합, 알킬렌, 알케닐렌 및 알키닐렌으로 구성되는 군에서 선택되는 어느 하나이고;

Y_2 는 직접 결합, 알킬렌 및 헤테로시클로알킬렌으로 구성되는 군에서 선택되는 어느 하나이고;

상기 TBM과 UBM이 연결되는 공유 결합 부위가 직접 결합이거나,
 15 또는 -O-, -C(R')(R'')-O-, -OC(O)-, -OC(O)N(R')- 및 -C(O)N(R')-로 구성되는 군에서 선택되는 어느 하나를 형성하도록 TBM과 UBM은 각각 변형될 수 있는 것

인 화합물 또는 이의 약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭.

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【청구항 9】

청구항 6 내지 청구항 8 중 어느 한 항에 있어서,

- 상기 화합물은 TBM이 결합하는 표적 단백질 또는 폴리펩티드를 분해하는 것인, 화합물 또는 이의 약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭.

【청구항 10】

청구항 6 내지 청구항 8 중 어느 한 항에 있어서,

- 상기 TBM이 결합하는 표적 단백질 또는 폴리펩티드는 B7.1 및 B7, 10 TINFR1m, TNFR2, NADPH 옥시다아제, Bcl2Bax를 포함하는 세포사멸 기전에 연관된 단백질들, Ras, Raf. 를 포함하는 MAP/ERK 신호 경로 관련 단백질, NF- κ B신호 경로에 연관된 단백질들, mTOR 신호 경로에 연관된 단백질들, wnt 신호 경로에 연관된 단백질들, AKT 신호 경로에 연관된 단백질들, JAK-STAT 신호 경로에 연관된 단백질들, NOX 복합체들과 그에 15 신호 경로에 연관된 단백질들. 혈관 내피 성장 인자 및 수용체와 그에 신호 경로에 연관된 단백질들, TLR 수용체 및 그에 신호 경로에 연관된 단백질들, G 단백질 연결 수용체들과 그 신호 경로에 연관된 단백질들, TCR-MHC 복합체 연관 수용체들과 신호 경로에 연관된 단백질들, 세포주기 검문 지점 단백질들과 그 신호 경로에 연관된 단백질들, 유전자 전사 및 번역을 20 조절하는 인자를 포함하는 단백질, 유전자 복제에 연관된 단백질 및 그 조절

인자 단백질들. 유전자 발현을 위한 히스톤 단백질 조절 인자를 포함하는 단백질, 후성 유전을 조절하는 인자 및 관련 단백질들. 세포 고격을 구성하고 그를 조절하는 단백질들, 세포내 수송을 조절 하는 단백질과 그를 조절하는 단백질들, C5a 수용체, 도파민 수용체들, 5HT 수용체들, 케모킨

5 수용체들, 히스타민 수용체들, CD40/CD40L, CD23, CD124, CD4, CD5, VCAM, VLA-4 인테그린, 셀렉틴, ICOS, ICAM1, IL-2 수용체, IL-1 수용체, TNF-알파 수용체, 및 그 밖의 사이토카인 수용체들 및 케모카인 수용체, 옥시토신 수용체, 글리신 수용체, 노르아드레날린 재흡수 수용체, 엔도텔린 수용체, 에스트로겐 수용체, 안드로겐 수용체, 아데노신 수용체, NGF에 대한

10 TrkA 수용체, 비트로넥틴 수용체, 인테그린 수용체, 뉴로키닌 및 수용체, 상피세포 성장인자 수용체들, 퓨린성 수용체(P2Y1, P2Y2, P2Y4, P2Y6, P2X1-7), EGF 수용체, HMG-CoA 환원효소, PDE V 포스포디에스테라아제 유형, PDE IV 포스포디에스테라아제 유형 4, PDE I, PDEII, PDEIII, 스쿠알렌 시클라아제 저해제, 산화질소(NO) 신타아제, 시클로옥시게나아제 1,

15 시클로옥시게나아제 2, 5-리폭시게나아제, 트립신분해효소 세린 프로테아제, 티미딜산염 신타아제, 퓨린 뉴클레오시드 인산화효소, GAPDH 트라이파노소마성, 글리코겐 인산화효소, 탄산 탈수효소, 이의 유사체, P-당단백질 및 MRP, 티로신 키나아제, 티로신 키나아제 p56 lck, Cat+ 통로, 이노신 일인산염 탈수소효소, 인터류킨-1 전환 효소, 카스파제글리신아미드

20 리보뉴클레오티드 포르밀 전달효소, 폴리(ADP-리보오스) 중합효소,

아세틸콜린 에스테라제, 사이클린 의존성 키나아제, 마이크로솜 전달 단백질
 저해제, 담즙산 수송 저해제, 5 알파 환원효소 저해제, 안지오텐신 11,
 아데노신 수용체, 아데노신 키나아제 및 AMP 탈아미노효소,
 파르네실전달효소, 게라닐게라닐 전달효소, 베타-아밀로이드, 티로신
 5 키나아제 Her-21 neu, 텔로머라아제 저해, 세포질 포스포리파아제A2,
 그리고 티로신 키나아제, 아세틸-CoA 카르복실라아제, 아데닐로숙신산염
 합성효소, 프로토포피리노겐 옥시다아제 및 에놀피루빌쉬키 메이트-인산염
 신타아제, 액디손 20-모노산소첨가효소, GABA 게이팅된 염화물 통로의
 이온 통로, 전압-민감성 나트륨 통로 단백질, 나트륨 통로, 칼슘 방출 통로
 10 단백질들, 염화물 통로 단백질들과 이 단백질로부터 유도된 폴리펩타이드, ,
 HCV NS3 프로테아제, HCV NS3 RNA 헬리카아제, 리노바이러스 3C
 프로테아제, 단순 헤르페스 바이러스-1(HSV-I) 프로테아제,
 시토메갈로바이러스(CMV) 프로테아제, 다중 약제 내성(MDR) 단백질들, HIV
 1 프로테아제, HIV 1 인테그라아제, 인플루엔자, 뉴라미니다아제, B형 간염
 15 역전사효소와 같은 세균 혹은 바이러스 단백질들과 그로부터 유도된 폴리
 펩타이드들, 혈관작용성 장펩티드, 프리온, 신경펩티드 Y 및 수용체들과
 같은 단백질들과 폴리 펩타이드들로 구성되는 군에서 선택되는 적어도
 하나인 것인 화합물 또는 이의 약학적으로 허용 가능한 염, 이성질체,
 용매화물, 수화물 또는 프로드럭.

【청구항 11】

청구항 6 내지 청구항 8 중 어느 한 항에 있어서,

상기 TBM이 결합하는 표적 단백질 또는 폴리펩티드는
브로모도메인-내포 단백질, Aurora 키나제 A 및 p38 MAP 키나아제로
5 구성되는 군에서 선택되는 적어도 하나인 것인 화합물 또는 이의
약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭.

【청구항 12】

청구항 6 내지 청구항 8 중 어느 한 항에 있어서,

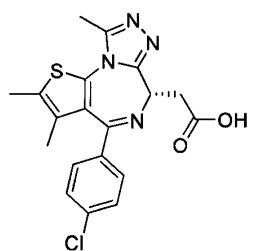
10 상기 TBM은 BRD4 저해제, Aurora A 저해제 및 p38 저해제로
구성되는 군에서 선택되는 어느 하나인 것인 화합물 또는 이의 약학적으로
허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭.

【청구항 13】

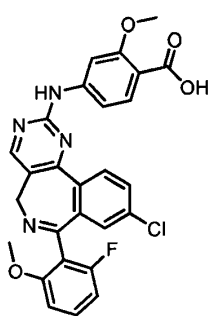
15 청구항 6 내지 청구항 8 중 어느 한 항에 있어서,

상기 TBM은 하기 화학식 1 내지 화학식 3으로 구성되는 군에서
선택되는 어느 하나의 화학 구조를 갖는 것인 화합물 또는 이의 약학적으로
허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭:

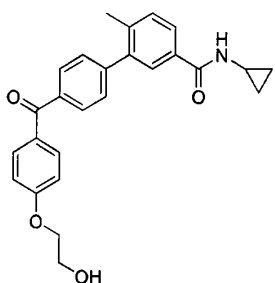
[화학식 1]



[화학식 2]



[화학식 3]



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【청구항 14】

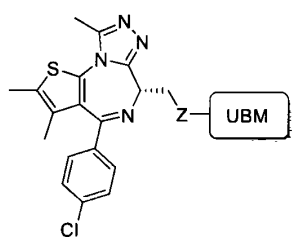
청구항 6 내지 청구항 8 중 어느 한 항에 있어서,

상기 화합물은 하기 화학식 4 내지 화학식 6으로 구성되는 군에서

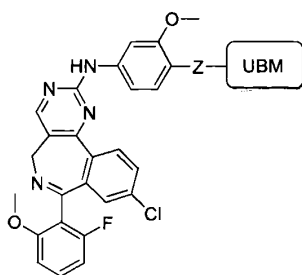
10 선택되는 어느 하나의 화학 구조를 갖는 것인 화합물 또는 이의 약학적으로

허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭:

[화학식 4]

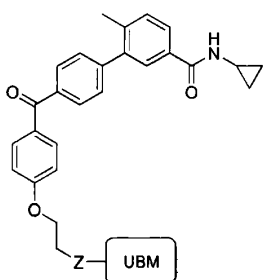


[화학식 5]



5

[화학식 6]



상기 화학식 4 내지 화학식 6에서, Z는 각각 독립적으로 직접
 결합이거나, 또는 -N(R')-, -O-, -C(R')(R'')-O-, -S-, -C(O)-, -SO-, SO₂-,
 10 =N-O-, -O-N=, -OC(O)-, -C(O)O-, -N(R')C(O)-, -C(O)N(R')-, -
 OC(O)O-, -OC(O)N(R')-, -N(R')C(O)O-, -N(R')SO-, -SON(R')-, -

$N(R')SO_2-$ 및 $-SO_2N(R')$ -로 구성되는 군에서 선택되는 어느 하나이고;

상기 작용기들에서 R' 및 R''는 각각 독립적으로 수소 또는 알킬임.

【청구항 15】

5 청구항 6 내지 청구항 8 중 어느 한 항에 있어서,

상기 화합물은 하기 표 5 내지 표 15에 기재된 화합물들로 구성되는 군에서 선택되는 적어도 하나인 것인 화합물 또는 이의 약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭.

[표 5]

번호	화합물
1-1'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
1-3'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
3-1'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoate hydrochloride
3-2'	(S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoic acid hydrochloride
3-3'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-

	a][1,4]diazepin-6-yl)acetamide hydrochloride
3-6'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(mercaptomethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
3-7'	(S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl dimethyl phosphate
3-8'	(S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl dihydrogen phosphate trifluoroacetic acid
3-9'	(S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl di-tert-butyl phosphate
3-10'	(S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl dibenzyl phosphate
3-11'	(S)-2-(3-aminoprop-1-yn-1-yl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl diisopropyl phosphate
3-12'	isopropyl (((2-(3-aminoprop-1-yn-1-yl)-5-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzyl)oxy)(phenoxy)phosphoryl)-L-alaninate
3-25'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoate hydrochloride
3-26'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)benzoic acid hydrochloride
3-27'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(hydroxymethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-

	a)[1,4]diazepin-6-yl)acetamide hydrochloride
3-28'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(mercaptomethyl)phenyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a])[1,4]diazepin-6-yl)acetamide
3-30'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a])[1,4]diazepin-6-yl)acetamido)benzyl dimethyl phosphate
3-31'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a])[1,4]diazepin-6-yl)acetamido)benzyl di-tert-butyl phosphate
3-32'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a])[1,4]diazepin-6-yl)acetamido)benzyl dihydrogen phosphate
3-33'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a])[1,4]diazepin-6-yl)acetamido)benzyl diphenyl phosphate
3-34'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a])[1,4]diazepin-6-yl)acetamido)benzyl diisopropyl phosphate
3-35'	isopropyl (((2-(3-aminoprop-1-yn-1-yl)-4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a])[1,4]diazepin-6-yl)acetamido)benzyl)oxy)(phenoxy)phosphoryl)-L-alaninate
3-49'	N-(4-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)-2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a])[1,4]diazepin-6-yl)acetamide hydrochloride
3-51'	N-(3-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)-2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a])[1,4]diazepin-6-yl)acetamide hydrochloride
3-53'	2-amino-4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a])[1,4]diazepin-6-yl)acetamido)phenyl)but-3-yn-1-yl di-tert-butyl phosphate

3-55'	2-amino-4-(3-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)but-3-yn-1-yl di-tert-butyl phosphate
3-57'	2-amino-4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)but-3-yn-1-yl dihydrogen phosphate trifluoroacetic acid
3-60'	2-amino-4-(3-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)phenyl)butyl dihydrogen phosphate
4-1'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-10'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-13'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-16'	(S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-19'	(S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-25'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)furan-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-28'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)thiophen-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-

	thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-31'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-34'	(S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)furan-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-40'	(S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)-1H-pyrrol-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-43'	(S)-N-(3-(3-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-52'	(S)-N-(3-(2-(3-aminoprop-1-yn-1-yl)furan-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-61'	(S)-N-(3-(5-(4-aminobut-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-62'	(S)-N-(3-(5-(4-aminobut-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-63'	(S)-N-(3-(5-(4-aminobut-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-64'	(S)-N-(3-(5-(5-aminopent-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

	yl)acetamide
4-65'	(S)-N-(3-(5-(5-aminopent-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-66'	(S)-N-(3-(5-(5-aminopent-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-67'	(S)-N-(3-(5-(6-aminohex-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-68'	(S)-N-(3-(5-(6-aminohex-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-69'	(S)-N-(3-(5-(6-aminohex-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-70'	(S)-N-(3-(5-(7-aminohept-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-71'	(S)-N-(3-(5-(7-aminohept-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-72'	(S)-N-(3-(5-(7-aminohept-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-73'	(S)-N-(3-(5-(8-aminooct-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

4-74'	(S)-N-(3-(5-(8-aminooct-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-75'	(S)-N-(3-(5-(8-aminooct-1-yn-1-yl)-1H-pyrrol-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-128'	((S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-129'	(S)-N-(3-(3-(3-aminoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-130'	(S)-N-(3-(2-(3-aminoprop-1-yn-1-yl)-1H-imidazol-5-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-131'	(S)-N-(3-(2-(3-aminoprop-1-yn-1-yl)oxazol-5-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-147'	(S)-N-(4-(5-(4-aminobut-1-yn-1-yl)furan-2-yl)but-3-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-177'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)pyridin-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-178'	(S)-N-(3-(6-(3-aminoprop-1-yn-1-yl)pyridin-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

4-179'	(S)-N-(3-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
4-180'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)-3,3-d2)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-181'	2-amino-4-(5-(3-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-2-yl)but-3-ynoic acid
4-182'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-3-carboxylate
4-183'	dimethyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-3,4-dicarboxylate
4-184'	methyl (S)-5-(3-aminoprop-1-yn-1-yl)-2-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-3-carboxylate
4-185'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)-4-(hydroxymethyl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-186'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-187'	(S)-N-(3-(5-(3-aminoprop-1-yn-1-yl)-3,4-bis(hydroxymethyl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide

4-188'	(S)-(5-(3-aminoprop-1-yn-1-yl)-2-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-3-yl)methyl dihydrogen phosphate
4-189'	(S)-(2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)furan-3-yl)methyl dihydrogen phosphate
4-200'	(S)-N-(4-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)but-3-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-201'	(S)-N-(3-(4-(4-aminobut-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-202'	(S)-N-(4-(4-(4-aminobut-1-yn-1-yl)furan-2-yl)but-3-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-218'	(S)-N-(3-(4-(3-aminoprop-1-yn-1-yl)-5-methylthiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-219'	(S)-N-(3-(4-(4-aminobut-1-yn-1-yl)-5-methylthiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
4-223'	(S)-N-(3-(5-(3-(aminooxy)prop-1-yn-1-yl)thiophen-2-yl)prop-2-yn-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide hydrochloride
5-52'	ethyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-1-yn-1-yl)oxazole-4-carboxylate
5-116'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)prop-

	1-yn-1-yl)benzoate hydrochloride
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[표 6]

번호	화합물
1-1''	N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
1-3''	N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
3-25''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)benzoate trifluoroacetic acid
3-49''	N-(4-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
4-1''	N-(3-(5-(3-aminoprop-1-yn-1-yl)furan-2-yl)prop-2-yn-1-yl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
5-116''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)prop-1-yn-1-yl)benzoate trifluoroacetic acid

[표 7]

번호	화합물
1-1'''	2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (4-(3-aminoprop-1-yn-1-yl)phenyl)carbamate hydrochloride
3-49'''	2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-

	4-carbonyl)phenoxy)ethyl (4-(3-amino-4-hydroxybut-1-yn-1-yl)phenyl)carbamate hydrochloride
5-116'''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(((2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate hydrochloride

[표 8]

번호	화합물
4-6'	(S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid
4-109'	methyl (S)-2-(4-aminobut-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate
4-110'	(S)-2-(4-aminobut-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid
4-111'	(S)-N-(4-(4-aminobut-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-112'	methyl (S)-2-(5-aminopent-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate
4-113'	(S)-2-(5-aminopent-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid
4-114'	(S)-N-(4-(5-aminopent-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-115'	methyl (S)-2-(6-aminohex-1-yn-1-yl)-5-(3-(2-(4-(4-

	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate
4-116'	(S)-2-(6-aminohex-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid
4-117'	(S)-N-(4-(6-aminohex-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-118'	methyl (S)-2-(7-aminohept-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate
4-119'	(S)-2-(7-aminohept-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid
4-120'	(S)-N-(4-(7-aminohept-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-121'	methyl (S)-2-(8-aminooct-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate
4-122'	(S)-2-(8-aminooct-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoic acid
4-123'	(S)-N-(4-(8-aminooct-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-124'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide hydrochloride

4-125'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide hydrochloride
4-126'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate hydrochloride
4-127'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3,5-bis(hydroxymethyl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide
4-148'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-yn-1-yl)furan-2-carboxamide hydrochloride
4-149'	((S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide hydrochloride
4-150'	(S)-5-(4-aminobut-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-yn-1-yl)furan-2-carboxamide
4-161'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamide hydrochloride
4-162'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride
4-163'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide hydrochloride

4-164'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide hydrochloride
4-165'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamide hydrochloride
4-166'	((S)-5-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)furan-2-carboxamide hydrochloride
4-167'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentyl)furan-2-carboxamide hydrochloride
4-168'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
4-169'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide
4-170'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-methoxyphenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide
4-171'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-methoxyphenyl)-6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamide
4-192'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)-3-methylfuran-2-carboxamide
4-199'	(S)-N-((5-(3-aminoprop-1-yn-1-yl)furan-2-yl)methyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

	f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
4-203'	(S)-4-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
4-204'	(S)-4-(4-aminobut-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
4-205'	(S)-4-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)furan-2-carboxamide
4-206'	(S)-4-(3-aminoprop-1-yn-1-yl)-N-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentyl)furan-2-carboxamide
4-209'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)benzofuran-2-carboxamide
4-210'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)benzofuran-2-carboxamide
4-214'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)-7-methoxybenzofuran-2-carboxamide
4-215'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)-6-methoxybenzofuran-2-carboxamide
4-216'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)-6-methoxybenzofuran-2-carboxamide
4-217'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)-7-methoxybenzofuran-2-carboxamide

4-224'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide
4-225'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(9-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)nonyl)furan-2-carboxamide hydrochloride
4-228'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride
4-229'	(S)-4-(3-aminoprop-1-yn-1-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)benzamide
4-231'	(S)-5-(3-aminoprop-1-yn-1-yl)-N-(2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pyridin-4-yl)furan-2-carboxamide
4-232'	(S)-5-(3-(aminooxy)prop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)furan-2-carboxamide
4-233'	methyl 2-amino-4-(5-((3-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)carbamoyle)furan-2-yl)but-3-ynoate
4-234'	methyl (S)-2-(3-(aminooxy)prop-1-yn-1-yl)-5-((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)carbamoyle)furan-3-carboxylate
4-235'	((S)-5-(3-aminoprop-1-yn-1-yl)-N-(8-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)octyl)furan-2-carboxamide hydrochloride
5-1'	ethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

	yl)acetamido)butanamido)benzoate hydrochloride
5-2'	isopropyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride
5-3'	cyclopropyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-4'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanamido)benzoate hydrochloride
5-5'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamido)benzoate hydrochloride
5-6'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamido)benzoate hydrochloride
5-8'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride
5-9'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanamide hydrochloride
5-10'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)amino)benzoate
5-11'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

	yl)acetamido)propyl)amino)benzoate
5-12'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butoxy)benzoate hydrochloride
5-13'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propoxy)benzoate
5-14'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanoyl)oxy)benzoate
5-15'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanoyl)oxy)benzoate
5-16'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentanoyl)oxy)benzoate
5-17'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanoyl)oxy)benzoate
5-18'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)carbamoyl)benzoate hydrochloride
5-19'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)ethyl)carbamoyl)benzoate
5-20'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

	yl)acetamido)butyl)carbamoyle)benzoate
5-21'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pentyl)carbamoyle)benzoate
5-30'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-yn-1-yl)carbamoyle)benzoate
5-31'	methyl (S,Z)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-en-1-yl)carbamoyle)benzoate
5-34'	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(((1S,4r)-4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetoxy)cyclohexyl)amino)benzoate
5-35'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)cyclohexyl)amino)benzoate trifluoroacetic acid
5-49'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)bicyclo[2.2.2]octane-1-carboxamido)benzoate
5-50'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(1-(2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)ethyl)cyclopropane-1-carboxamido)benzoate
5-53'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoic acid hydrochloride
5-54'	difluoromethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

	yl)acetamido)butanamido)benzoate
5-55'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-(trifluoromethyl)cyclopropane-1-carbonyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-56'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-fluorocyclopropane-1-carbonyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-57'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(1-fluorocyclobutane-1-carbonyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-58'	1,1-difluoroethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-59'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzamide hydrochloride
5-60'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-N-methylbenzamide
5-61'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-N,N-dimethylbenzamide hydrochloride
5-62'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-hydroxyphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-63'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-methoxyphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide trifluoroacetic acid
5-64'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-

	methoxyethoxy)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-65'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-methylphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride
5-66'	(S)-N-(4-acetyl-3-(3-aminoprop-1-yn-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-67'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-hydroxyethyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-68'	(S)-N-(4-(aminomethyl)-3-(3-aminoprop-1-yn-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-69'	(S)-N-(4-amino-3-(3-aminoprop-1-yn-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-70'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-71'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-72'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(3-(methylamino)oxetan-3-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-73'	(S,E)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-fluoroprop-1-en-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide

5-74'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-carbamimidoylphenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-75'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(trifluoromethyl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride
5-76'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-chlorophenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-77'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-fluorophenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride
5-78'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-6-methylbenzoate hydrochloride
5-79'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)pent-1-yn-1-yl)benzoate
5-80'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-1-yn-1-yl)benzoate
5-81'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide hydrochloride
5-82'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzyl dihydrogen phosphate
5-83'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-

	2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzyl di-tert-butyl phosphate
5-87'	methyl 4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-2-(3,4-diamino-4-oxobut-1-yn-1-yl)benzoate
5-89'	methyl (S)-3-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride
5-90'	methyl (S)-4-(3-aminoprop-1-yn-1-yl)-2-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate hydrochloride
5-92'	methyl (S)-2-((1-aminocyclopropyl)ethynyl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-93'	2-amino-4-(5-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)-2-(methoxycarbonyl)phenyl)but-3-ynoic acid
5-94'	methyl 2-(3-amino-4-methoxy-4-oxobut-1-yn-1-yl)-4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-95'	methyl 2-(3-amino-4-hydroxybut-1-yn-1-yl)-4-(4-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-96'	methyl (S)-3-(3-aminoprop-1-yn-1-yl)-6-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)picolinate hydrochloride
5-97'	dimethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-

	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)isophthalate
5-98'	methyl (S)-6-(3-aminoprop-1-yn-1-yl)-2-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)nicotinate
5-99'	(S)-2-(2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)phenyl)acetic acid
5-100'	ethyl (S)-2-(2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)phenyl)acetate
5-101'	acetoxymethyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-102'	(methacryloyloxy)methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-103'	(pivaloyloxy)methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-104'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanamide hydrochloride
5-106'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethoxy)-5-oxopentanamido)benzoate hydrochloride
5-107'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-8-(2-(4-(4-

	chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)octanamide hydrochloride
5-108'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-11-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)undecanamide hydrochloride
5-109'	(S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethyl 11-((3-(3-aminoprop-1-yn-1-yl)phenyl)amino)-11-oxoundecanoate hydrochloride
5-110'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(11-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethoxy)-11-oxoundecanamido)benzoate hydrochloride
5-113'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-((7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)amino)-5-oxopentanamido)benzoate
5-115'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetoxo)butanamido)benzoate hydrochloride
5-121'	(S)-2,4-bis(3-aminoprop-1-yn-1-yl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)benzamide
5-122'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)prop-1-yn-1-yl)benzoate
5-123'	(S)-N-(3-(3-(3-aminoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-126'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-20-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

	f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-3,6,9,12,15,18-hexaoxaicosanamide
5-127'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)phenyl)-20-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-3,6,9,12,15,18-hexaoxaicosanamide
5-135'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-8-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)octanamide
5-148'	methyl (S)-2-(3-acetamidoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamido)benzoate
5-149'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-methylacetamido)butanamido)benzoate hydrochloride
5-150'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-N-methylbutanamido)benzoate hydrochloride
5-169'	(S)-2-(3-aminoprop-1-yn-1-yl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)oxazole-5-carboxamide
5-170'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-morpholinophenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide
5-171'	(S)-N-(3-(3-aminoprop-1-yn-1-yl)-4-(4-methylpiperazin-1-yl)phenyl)-4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanamide

[표 9]

번호	화합물
4-	N-(6-((4-(3-aminoprop-1-yn-1-yl)phenyl)amino)-6-

165''	oxohexyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
4-166''	5-(3-aminoprop-1-yn-1-yl)-N-(3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propyl)furan-2-carboxamide trifluoroacetic acid
4-228''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)butanamido)benzoate trifluoroacetic acid
5-8''	N-(4-((4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)amino)-4-oxobutyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
5-18''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-((3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propyl)carbamoyl)benzoate hydrochloride
5-35''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-((4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)cyclohexyl)amino)benzoate trifluoroacetic acid
5-81''	N-(4-((3-(3-aminoprop-1-yn-1-yl)-4-(2-(trifluoromethyl)pyrimidin-5-yl)phenyl)amino)-4-oxobutyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
5-104''	N-(6-((3-(3-aminoprop-1-yn-1-yl)phenyl)amino)-6-oxohexyl)-4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamide trifluoroacetic acid
5-150''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-

	e]azepin-2-yl)amino)-2-methoxybenzamido)-N-methylbutanamido)benzoate trifluoroacetic acid
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[표 10]

번호	화합물
4-166'''	2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl (3-(5-(3-aminoprop-1-yn-1-yl)furan-2-carboxamido)propyl)carbamate trifluoroacetic acid
5-106'''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethoxy)-5-oxopentanamido)benzoate hydrochloride

[표 11]

번호	화합물
4-2'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate hydrochloride
4-3'	(S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoic acid
4-4'	(S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-94'	methyl (S)-2-(4-aminobut-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate
4-95'	(S)-2-(4-aminobut-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-

	1-yl)benzoic acid
4-96'	(S)-1-(4-(4-(4-aminobut-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-97'	methyl (S)-2-(5-aminopent-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate
4-98'	(S)-2-(5-aminopent-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoic acid
4-99'	(S)-1-(4-(4-(5-aminopent-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-100'	methyl (S)-2-(6-aminohex-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate
4-101'	(S)-2-(6-aminohex-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoic acid
4-102'	(S)-1-(4-(4-(6-aminohex-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-103'	methyl (S)-2-(7-aminohept-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate
4-104'	(S)-2-(7-aminohept-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-

	1-yl)benzoic acid
4-105'	(S)-1-(4-(4-(7-aminohept-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-106'	methyl (S)-2-(8-aminooct-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate
4-107'	(S)-2-(8-aminooct-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoic acid
4-108'	(S)-1-(4-(4-(8-aminooct-1-yn-1-yl)-3-(hydroxymethyl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-134'	(S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)-[1,4'-bipiperidin]-1'-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-135'	(S)-1-(3-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperidin-1-yl)azetidin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-136'	(S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperidin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-146'	(S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
4-226'	(S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one hydrochloride

4-227'	(S)-1-(4-(5-(3-aminoprop-1-yn-1-yl)furan-2-carbonyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one hydrochloride
5-7'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)benzoate hydrochloride
5-22'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)carbamoyl)benzoate hydrochloride
5-23'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)benzoate hydrochloride
5-24'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)acetamido)benzoate
5-25'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)propanamido)benzoate hydrochloride
5-26'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)butanamido)benzoate hydrochloride
5-27'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)propyl)carbamoyl)benzoate hydrochloride
5-28'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)prop-1-yn-1-yl)benzoate hydrochloride

5-29'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)piperazin-1-yl)benzoate hydrochloride
5-36'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)oxy)benzoate
5-37'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)azetidin-3-yl)piperazin-1-yl)benzoate
5-38'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,7-diazaspiro[3.5]nonan-7-yl)benzoate
5-39'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,7-diazaspiro[3.5]nonane-7-carbonyl)benzoate trifluoroacetic acid
5-40'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,6-diazaspiro[3.3]heptan-2-yl)benzoate trifluoroacetic acid
5-41'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,6-diazaspiro[3.3]heptane-2-carbonyl)benzoate trifluoroacetic acid
5-42'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-((2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2-azaspiro[3.3]heptan-6-yl)carbonyl)benzoate
5-43'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((2-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

	f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2-azaspiro[3.3]heptan-6-ylidene)amino)oxy)benzoate
5-44'	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)benzoate trifluoroacetic acid
5-45'	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)octahydropyrrolo[3,4-c]pyrrole-2-carbonyl)benzoate
5-46'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)azetidin-3-yl)piperidin-1-yl)benzoate
5-47'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)azetidin-1-yl)benzoate
5-48'	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(6-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)benzoate
5-85'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)amino)benzoate trifluoroacetic acid
5-86'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)amino)benzoate
5-88'	(S)-1-(4-(4-(3-aminoprop-1-yn-1-yl)phenyl)-4-hydroxypiperidin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one

5-112'	methyl (S)-3-(3-aminoprop-1-yn-1-yl)-6-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)picolinate
5-118'	methyl 2-(3-aminoprop-1-yn-1-yl)-5-(6-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)benzoate
5-119'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-3-oxopiperazin-1-yl)benzoate
5-120'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carbonyl)piperazin-1-yl)benzoate
5-124'	(S)-1-(4-((4-(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carbonyl)piperazin-1-yl)methyl)piperidin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
5-125'	(S)-1-(4-(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carbonyl)piperazin-1-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)ethan-1-one
5-129'	(S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)furan-2-carboxamide
5-131'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamide
5-134'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamide

5-139'	(S)-2-(3-aminoprop-1-yn-1-yl)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)methyl)amino)benzoic acid trifluoroacetic acid
5-140'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperazine-1-carbonyl)benzoate hydrochloride
5-152'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-N-methylpiperidine-4-carboxamido)benzoate trifluoroacetic acid
5-153'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(((1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)(methyl)carbamoyl)benzoate trifluoroacetic acid
5-154'	methyl (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-(sulfamoylamino)prop-1-yn-1-yl)benzoate trifluoroacetic acid
5-155'	methyl (S)-2-((1-aminocyclopropyl)ethynyl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)benzoate
5-156'	methyl (S)-2-(3-(((4-chlorophenyl)(5-fluoro-2-hydroxyphenyl)methylene)amino)prop-1-yn-1-yl)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)benzoate
5-157'	methyl 4-(1-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)-2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate
5-158'	methyl (S)-4-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

	yl)acetyl)piperidine-4-carboxamido)-2-(3-(sulfamoyloxy)prop-1-yn-1-yl)benzoate trifluoroacetic acid
5-159'	methyl 2-(3-amino-4-mercaptobut-1-yn-1-yl)-4-((1-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)carbamoyl)benzoate
5-160'	(S)-5-(3-(3-aminoprop-1-yn-1-yl)phenyl)-N-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidin-4-yl)furan-2-carboxamide
5-162'	methyl 4-(6-(2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,6-diazaspiro[3.3]heptan-2-yl)-2-(3-(((1-(isobutyryloxy)ethoxy)carbonyl)amino)prop-1-yn-1-yl)benzoate
5-167'	methyl (S)-3-(3-aminoprop-1-yn-1-yl)-6-(1-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)piperidine-4-carboxamido)picolinate
5-168'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)-2,7-diazaspiro[3.5]nonan-2-yl)benzoate hydrochloride

[표 12]

번호	화합물
5-23''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(1-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)piperidine-4-carboxamido)benzoate hydrochloride
5-28''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(3-(1-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)piperidine-4-carboxamido)prop-1-yn-1-yl)benzoate trifluoroacetic acid
5-29''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-((1-(4-((9-chloro-

	7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)benzoate trifluoroacetic acid
5-40''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(6-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzoyl)-2,6-diazaspiro[3.3]heptan-2-yl)benzoate trifluoroacetic acid

[표 13]

번호	화합물
5-39'''	2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl 7-(3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)benzoyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate trifluoroacetic acid
5-140'''	2-(4-(5'-(cyclopropylcarbamoyl)-2'-methyl-[1,1'-biphenyl]-4-carbonyl)phenoxy)ethyl 4-(3-(3-aminoprop-1-yn-1-yl)-4-(methoxycarbonyl)benzoyl)piperazine-1-carboxylate trifluoroacetic acid

[표 14]

번호	화합물
4-207'	(S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)but-2-yn-1-yl)furan-2-carboxamide
4-208'	(S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
4-211'	(S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)furan-2-carboxamide
5-32'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-

	f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanoyl)piperazin-1-yl)benzoate hydrochloride
5-33'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propanoyl)piperazin-1-yl)benzoate hydrochloride
5-51'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)-1,3,4-oxadiazol-2-yl)benzoate
5-111'	(S)-5-(4-(3-aminoprop-1-yn-1-yl)phenyl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide hydrochloride
5-114'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(6-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)hexanoyl)piperazin-1-yl)benzoate
5-117'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)piperidin-1-yl)benzoate
5-128'	(S)-N-(1-(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carbonyl)piperidin-4-yl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide
5-130'	(S)-1-(5-(4-(3-aminoprop-1-yn-1-yl)phenyl)furan-2-carbonyl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)piperidine-4-carboxamide
5-132'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)phenyl)-1-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanoyl)piperidine-4-carboxamide

5-133'	(S)-N-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-1-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butanoyl)piperidine-4-carboxamide
5-136'	(S)-5-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide
5-137'	(S)-5-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
5-138'	(S)-5-(6-(3-aminoprop-1-yn-1-yl)pyridin-3-yl)-N-(7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)heptyl)furan-2-carboxamide
5-141'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(5-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)carbonyl)furan-2-yl)benzoate
5-142'	(S)-5-(4-(3-aminoprop-1-yn-1-yl)-3-(hydroxymethyl)phenyl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
5-143'	(S)-5-(3-(3-aminoprop-1-yn-1-yl)phenyl)-N-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)furan-2-carboxamide
5-144'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(5-((4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butyl)carbonyl)furan-2-yl)benzoate
5-145'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(5-((7-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-

	yl)acetamido)heptyl)carbamoyl)furan-2-yl)benzoate
5-164'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)piperazin-1-yl)benzoate hydrochloride
5-165'	methyl (S)-2-(3-aminoprop-1-yn-1-yl)-5-(4-(3-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)propyl)piperazin-1-yl)benzoate hydrochloride

[표 15]

번호	화합물
5-32''	methyl 2-(3-aminoprop-1-yn-1-yl)-4-(4-(3-(4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-benzo[c]pyrimido[4,5-e]azepin-2-yl)amino)-2-methoxybenzamido)propanoyl)piperazin-1-yl)benzoate trifluoroacetic acid

【청구항 16】

청구항 1 내지 청구항 8 중 어느 한 항의 화합물 또는 이의
 5 약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭을
 유효성분으로 포함하는, 표적 단백질 또는 폴리펩티드 분해를 통한 질환의
 예방 또는 치료용 약학적 조성물.

【청구항 17】

10 청구항 6 내지 청구항 8 중 어느 한 항의 화합물 또는 이의
 약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭을

유효성분으로 포함하고,

상기 화합물에서 상기 TBM은 BRD4 저해제인 것인, 브로모도메인-
내포 단백질 관련 질환의 예방 또는 치료용 약학적 조성물.

5 **【청구항 18】**

청구항 6 내지 청구항 8 중 어느 한 항의 화합물 또는 이의
약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭을
유효성분으로 포함하고,

상기 화합물에서 상기 TBM은 Aurora A 저해제인 것인, 세포 증식성
10 장애의 예방 또는 치료용 약학적 조성물.

【청구항 19】

청구항 6 내지 청구항 8 중 어느 한 항의 화합물 또는 이의
약학적으로 허용 가능한 염, 이성질체, 용매화물, 수화물 또는 프로드럭을
15 유효성분으로 포함하고,

상기 화합물에서 상기 TBM은 p38 저해제인 것인, 염증 및 염증
관련 질환의 예방 또는 치료용 약학적 조성물.