(19) 대한민국특허청(KR)
(12) 공개특허공보(A)

(11) 공개번호 10-2024-0093742
(43) 공개일자 2024년06월24일

(51) 국제특허분류(Int. Cl.)
C12N 15/113 (2010.01) *A61P 25/28* (2006.01)
(52) CPC특허분류
C12N 15/113 (2013.01)
A61K 31/7088 (2013.01)
(21) 출원번호 10-2024-7016358(분할)
(22) 출원일자(국제) 2014년07월21일
심사청구일자 없음
(62) 원출원 특허 10-2023-7013823
원출원일자(국제) 2014년07월21일
심사청구일자 2023년05월24일
(85) 번역문제출일자 2024년05월17일
(86) 국제출원번호 PCT/US2014/047486
(87) 국제공개번호 WO 2015/010135
국제공개일자 2015년01월22일
(30) 우선권주장
61/856,551 2013년07월19일 미국(US)
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(54) 발명의 명칭 **타우 발현 조절 조성물**

(57) 요 약

타우 mRNA 및 단백질의 발현을 감소시키기 위한 방법 및 안티센스 화합물이 본원에서 제공된다. 본원의 방법, 화합물, 및 조성물은 타우 연관된 질환, 장애, 및 병태를 치료, 예방, 및 개선하는데 유용하다.

(52) CPC특허분류
A61P 25/28 (2018.01)
C12N 2310/11 (2013.01)
C12N 2310/315 (2013.01)
C12N 2310/3341 (2013.01)
C12N 2310/3525 (2013.01)
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(30) 우선권주장
61/879,621 2013년09월18일 미국(US)
61/885,371 2013년10월01일 미국(US)
62/014,486 2014년06월19일 미국(US)

명 세 서

청구범위

청구항 1

변형된 올리고뉴클레오타이드를 포함하는 화합물의 용도.

발명의 설명

기 술 분 야

[0001] **서열목록**

[0002] 본 발명은 전자 형식으로 서열목록과 함께 출원된다. 서열목록은 그 크기가 916 Kb인 파일명 BIOL0227WOSEQ_ST25.txt (2014년 6월 17일에 만들어짐)로서 제공되어 있다. 상기 서열목록의 전자 형식의 정보는 본 명세서에 그의 전문이 참고로 편입된다.

[0003] **기술 분야**

[0004] 동물에서 타우 mRNA 및 단백질의 발현을 감소시키기 위한 방법, 화합물, 및 조성물이 본원에서 제공된다. 그러한 방법은 동물에서 타우 발현을 억제함으로써 타우병증, 알츠하이머 질환, 전두측두엽 치매 (FTD), FTDP-17, 진행성 핵상안근 마비 (PSP), 만성 외상성 뇌증 (CTE), 뇌피질 기저 신경절 퇴행증 (CBD), 간질, 및 드라벳 증후군을 포함하는 신경퇴행성 질병을 치료, 예방, 또는 개선하는데 유용하다.

배 경 기 술

[0005] 타우의 1차 기능은 유사분열, 세포질분열, 및 소포 이동과 관련된 세포골격의 중요한 구조적 성분인 미세소관에 연결하고 이를 안정시키는 것이다. 타우는 다수 조직에서 발견되나, 뉴런의 축삭에 특히 많다. 인간에게는 엑손 2, 3, 및 10의 대안적 스플라이싱에 의하여 생성된, 6개의 타우 이소형이 있다. 단백질의 N 말단에서의 엑손 2, 3의 스플라이싱은 0, 1, 또는 2개의 29 아미노산 산성 도메인의 포함을 야기하고, 이는 각각 0N, 1N, 또는 2N 타우라고 지칭된다. 타우 기능에 대한 이러한 도메인의 영향은 완전히 명백하지는 않으나, 원형질막과 상호작용하는 역할을 할 수 있다. C 말단에서의 엑손 10의 포함은 엑손 10에 의하여 암호화된 미세소관 연결 도메인의 포함을 야기한다. 타우의 다른 곳에서 3개의 미세소관 연결 도메인이 있으므로, 이러한 타우 이소형 (엑손 10 포함)은 4R 타우라고 지칭되며, 여기서 'R'은 미세소관 연결 도메인의 반복 수를 나타낸다. 엑손 10이 없는 타우는 3R 타우라 불리운다. 더욱 많은 미세소관 연결 도메인 (3R과 비교한 4R)은 미세소관에 대한 연결을 증가시키므로, 4R 타우는 미세소관 연결 및 조립을 뚜렷하게 증가시킬 것이다. 3R/4R 타우 비율은 3R 타우를 독점적으로 발현하는 태아 조직 및 대략적으로 평형한 수준의 3R/4R 타우를 발현하는 성체 인간 조직과 함께 발달적으로 조절된다. 3R/4R 타우의 표준 비율로부터의 편차는 신경퇴행성 FTD 타우병증의 특성이다. 성체 동물에서 후기 단계에서의 3R/4R 타우 비율의 변화가 어떻게 타우 발병에 영향을 줄 것인지에 대한 것은 알려져 있지 않다.

[0006] 세린-트레오닌 유도 인산화는 타우의 미세소관 연결 능력을 조절한다. 과인산화는 미세소관으로부터의 타우 분리를 촉진한다. 타우의 다른 번역-후 변형이 기술되어 왔으나; 이러한 것들의 중요성은 명백하지 않다. 타우의 인산화는 또한 태아 조직에서 더 높은 인산화 및 성체에서 훨씬 낮은 인산화와 함께 발달적으로 조절된다. 신경퇴행성 장애의 한 특성은 비정상적으로 증가된 타우 인산화이다.

[0007] 미세소관 네트워크는 세포의 모폴로지를 유지시키고 이송 기작을 작동시키는데 필요한 구조적 통합을 포함하는, 세포내 많은 중요 과정과 연관된다. 타우의 미세소관으로의 연결이 미세소관을 안정시키므로, 타우는 이러한 과정 중 일부의 중요 매개자일 가능성이 있으며, 신경 퇴행성 질환에서 정상 타우의 파괴는 이러한 중요 세포 과정의 일부를 파괴할 수 있다.

[0008] 타우가 신경퇴행성 증후군에서 중요할 수 있다는 초기 지표 중 하나는, 타우가 알츠하이머 질환에서 신경섬유 포함물의 중요 구성성분이라는 것에 대한 인식이다. 사실, 신경섬유 포함물은 과인산화된 타우 단백질의 군체이다. 플라크를 함유하는 아밀로이드 베타와 함께, 신경섬유 포함물은 알츠하이머 질환의 특징이고, 인지 장애와 뚜렷하게 연관된다. AD에서의 타우 누적 중 95%는 뉴런 과정에서 발견되고, 신경염성 이영양증으로 불리운다. 이러한 미세소관 연관 단백질이 미세소관으로부터 유리되고 단백질의 누적을 형성하는 과정 및 이것이 어떻게

뉴런 독성과 관련있는지에 대한 자세한 이해는 없는 상황이다.

[0009] 뉴런 타우 포함물은 알츠하이머 질환 뿐만 아니라, 전두측두엽 치매 (FTD), PSP, 및 CBD의 병리학적 특성이다. 타우 및 신경퇴행 사이의 연관은 타우 유전자의 돌연변이가 FTD의 서브세트(subset)를 야기한다는 발견에 의하여 공고해졌다. 이러한 유전적 데이터는 또한 타우의 3R:4R 비율의 중요성을 강조하였다. FTD 야기하는 타우 돌연변이의 많은 것은 타우 스플라이싱에 있어 변화를 야기하고, 이는 엑손 10의 우선적 포함을 야기하며, 이로써 증가된 4R 타우를 야기한다. 전제 타우 수준은 정상이다. 타우 이소형 변화, 아미노산 변화, 또는 둘 다가 신경퇴행을 야기하는지에 대해서는 미지인 채로 남아있다. 최근 데이터는, PSP가 또한 증가된 4R:3R 타우 비율과 연관될 수 있다는 것을 암시한다.

[0010] 신경퇴행에서의 타우 비율의 영향에 대한 이해를 돕기 위하여, 스플라이싱 타우 돌연변이 (N279K) 중 하나에 기반한 마우스 모델이 타우 프로모터 및 엑손 10의 측면 인트론 서열을 포함하는 미니유전자를 사용하여 생성되었다. 인간에서와 같이, 이러한 마우스는 WT 타우를 발현하는 형질전환체와 비교하여 4R 타우의 증가된 수준을 나타내며, 뇌 및 척수에서의 군집된 타우의 누적뿐만 아니라, 행동 및 운동적 이상을 발병시킨다.

[0011] 단백질 "타우"는 알츠하이머 질환, 전두측두엽 치매, 진행성 핵상안근 마비, 뇌피질기저 신경절 퇴행, 권투선수 치매, 염색체 연관 파킨슨증, 리티코-보딕(lytico-bodig) 질환, 엉킴-우세 치매, 신경절교종, 신경절세포종, 뇌막혈관종증, 아급성 경화성 범뇌염, 연뇌증, 결절성 경화증, 할러포르덴-스파츠(Hallervorden-Spatz) 질환, 피크 질환, 호은성 입자 질환, 피질기저 신경퇴행, 또는 전측두엽 신경퇴행, 및 다른 것들을 포함하는 뇌의 다수 질환과 연관되어 있다. AD와 같은 타우-연관된 장애는 노인들에서의 치매의 가장 흔한 원인이다. AD는 전세계에서 1500만명, 및 85세 초과 인구 중 40%에 영향을 주는 것으로 추정된다. AD는 다음 두개의 병리학적 특징으로 특성화된다: 타우 신경섬유 포함물 (NFT) 및 아밀로이트-β (Aβ) 플라크.

[0012] 현재 그러한 신경퇴행성 질환을 치료하기 위하여 수용가능한 선택사항에 대한 부족이 존재한다. 따라서, 본원에서는 그러한 질환에 치료 방법을 제공하기 위한 목적이 존재한다.

[0013] **요약**

[0014] 타우 mRNA 및 단백질의 발현을 조절하기 위한 방법, 화합물, 및 조성물이 본원에서 제공된다. 특정 구현예에서, 타우 mRNA 및 단백질의 발현을 조절하기에 유용한 화합물은 안티센스 화합물이다. 특정 구현예에서, 안티센스 화합물은 안티센스 올리고뉴클레오타이드이다.

[0015] 특정 구현예에서, 조절은 세포 또는 조직에서 발생할 수 있다. 특정 구현예에서, 상기 세포 또는 조직은 동물 내의 것이다. 특정 구현예에서, 상기 동물은 인간이다. 특정 구현예에서, 타우 mRNA 수준은 감소된다. 특정 구현예에서, 타우 단백질 수준은 감소된다. 그러한 감소는 시간-의존적 방식 또는 용량-의존적 방식으로 발생할 수 있다.

[0016] 질환, 장애, 및 병태를 예방, 치료, 및 지연하는데 유용한 방법, 화합물, 및 조성물이 또한 제공된다. 특정 구현예에서, 그러한 타우 연관된 질환, 장애, 및 병태는 신경퇴행성 질환이다. 특정 구현예에서, 그러한 신경퇴행성 질환, 장애, 및 병태는 타우병증, 알츠하이머 질환, 전두측두엽 치매 (FTD), FTDP-17, 진행성 핵상안근 마비 (PSP), 만성 외상성 뇌증 (CTE), 뇌피질 기저 신경절 퇴행증 (CBD), 간질, 및 드라벳 증후군을 포함한다.

[0017] 그러한 질환, 장애, 및 병태는 하나 이상의 위험인자, 원인 또는 결과를 공통적으로 가질 수 있다. 신경퇴행성 장애의 발달에 대한 특정 위험 인자 및 원인은 노화, 개인 또는 가족력, 또는 유전적 소인을 포함한다. 신경퇴행성 장애의 발달과 연관된 특정 증후군 및 결과는 비제한적으로 하기를 포함한다: 과인산화된 타우의 존재, 신경섬유 포함물의 존재, 신경 기능의 감소, 기억 감퇴, 운동 기능 감소, 운동 협응 감소 및 착란.

[0018] 특정 구현예에서, 치료 방법은 타우 안티센스 화합물을 이를 필요로 하는 개체에게 투여하는 단계를 포함한다. 특정 구현예에서, 치료 방법은 타우 안티센스 올리고뉴클레오타이드를 이를 필요로 하는 개체에게 투여하는 단계를 포함한다.

[0019] 본 개시사항은 하기 비제한적 수의 구현예를 제공한다.

[0020] 구현예 1: 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 20-2443 및 서열 번호: 2478-2483의 핵염기 서열 중 임의의 것의 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 갖는 변형된 올리고뉴클레오타이드를 포함하는 화합물.

[0021] 구현예 2: 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 2444-2477 및 서열 번호: 2484-2565의 핵염기 서열 중 임의의 것의 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 갖는 변형된 올리고뉴클레오타이드를 포함하는 화합물.

[0022] 구현예 3: 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 20-2565의 핵염기 서열 중 임의의 것의 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 갖는 변형된 올리고뉴클레오타이드를 포함하는 화합물.

[0023] 구현예 4: 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 1의 핵염기 135783-135980와 동등한 길이 부분에 상보적인 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 갖는 변형된 올리고뉴클레오타이드를 포함하는 화합물.

[0024] 구현예 5: 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 1의 핵염기 135853-135872와 동등한 길이 부분에 상보적인 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 갖는 변형된 올리고뉴클레오타이드를 포함하는 화합물.

[0025] 구현예 6: 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 1의 핵염기 135783-135929와 동등한 길이 부분에 상보적인 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 갖는 변형된 올리고뉴클레오타이드를 포함하는 화합물.

[0026] 구현예 7: 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 1의 핵염기 135783-135914와 동등한 길이 부분에 상보적인 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 갖는 변형된 올리고뉴클레오타이드를 포함하는 화합물.

[0027] 구현예 8: 구현예 4 내지 7의 화합물에 있어서, 상기 변형된 올리고뉴클레오타이드는 서열 번호: 1에 적어도 80%, 적어도 81%, 적어도 82%, 적어도 83%, 적어도 84%, 적어도 85%, 적어도 86%, 적어도 87%, 적어도 88%, 적어도 89%, 적어도 90%, 적어도 91%, 적어도 92%, 적어도 93%, 적어도 94%, 적어도 95%, 적어도 96%, 적어도 97%, 적어도 98%, 적어도 99%, 또는 100% 상보적일 수 있다.

[0028] 구현예 9: 선행 구현예들 중 어느 하나에서, 단일 가닥 변형된 올리고뉴클레오타이드로 구성된, 화합물.

[0029] 구현예 10: 선행 구현예들 중 어느 하나에서, 적어도 하나의 뉴클레오사이드간 연결은 변형된 뉴클레오사이드간 연결인, 화합물.

[0030] 구현예 11: 구현예 10에 있어서, 적어도 하나의 뉴클레오사이드간 연결은 포스포로티오에이트 뉴클레오사이드간 연결인 화합물.

[0031] 구현예 12: 청구항 10에 있어서, 각각의 변형된 뉴클레오사이드간 연결은 포스포로티오에이트 뉴클레오사이드간 연결인 화합물.

[0032] 구현예 13: 선행 구현예들 중 어느 하나에서, 적어도 하나의 뉴클레오사이드간 연결은 포스포디에스테르 뉴클레오사이드간 연결인, 화합물.

[0033] 구현예 14: 선행 구현예들 중 어느 하나에서, 적어도 하나의 뉴클레오사이드간 연결은 포스포로티오에이트 연결이고, 적어도 하나의 뉴클레오사이드간 연결은 포스포디에스테르 연결인 화합물.

[0034] 구현예 15: 선행 구현예들 중 어느 하나에서, 적어도 하나의 뉴클레오사이드는 변형된 핵염기를 포함하는, 화합물.

[0035] 구현예 16: 구현예 15에 있어서, 상기 변형된 핵염기는 5-메틸시토신인, 화합물.

[0036] 구현예 17: 선행 구현예들 중 어느 하나에서, 상기 변형된 올리고뉴클레오타이드의 적어도 하나의 뉴클레오사이드는 변형된 당을 포함하는, 화합물.

[0037] 구현예 18: 구현예 17에 있어서, 상기 적어도 하나의 변형된 당은 이환식 당인, 화합물.

[0038] 구현예 19: 구현예 18에 있어서, 상기 이환식 당은 당 4'-CH2-N(R)-O-2' 가교의 2' 및 4' 위치 사이에서 화학적 연결을 포함하며, 이때 R은 독립적으로, H, C1-C12 알킬, 또는 보호기인, 화합물.

[0039] 구현예 20: 구현예 18에 있어서, 상기 이환식 당은4'-CH2-N(R)-O-2' 가교를 포함하며, 이때 R은 독립적으로, H, C1-C12 알킬, 또는 보호기인, 화합물.

[0040] 구현예 21: 구현예 17에 있어서, 적어도 하나의 변형된 당은 2'-O-메톡시에틸 기를 포함하는, 화합물.

[0041] 구현예 22: 구현예 17에 있어서, 상기 변형된 당은 2'-O$(CH_2)_2$-OCH_3 기를 포함하는, 화합물.

[0042] 구현예 23: 선행 구현예들 중 어느 하나에서, 상기 변형된 올리고뉴클레오타이드는:

[0043] 10 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0044] 5개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0045] 5개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절을 포함하고;

[0046] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함하는, 화합물.

[0047] 구현예 24: 선행 구현예들 중 어느 하나에서, 상기 변형된 올리고뉴클레오타이드는:

[0048] 9 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0049] 5개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0050] 5개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절을 포함하고;

[0051] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함하는, 화합물.

[0052] 구현예 25: 선행 구현예들 중 어느 하나에서, 상기 변형된 올리고뉴클레오타이드는:

[0053] 7 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0054] 5개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0055] 6개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절을 포함하고;

[0056] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함하는, 화합물.

[0057] 구현예 26: 선행 구현예들 중 어느 하나에서, 상기 변형된 올리고뉴클레오타이드는:

[0058] 8 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0059] 5개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0060] 5개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절을 포함하고;

[0061] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함하는, 화합물.

[0062] 구현예 27: 선행 구현예들 중 어느 하나에서, 상기 변형된 올리고뉴클레오타이드는:

[0063] 8 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0064] 4개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0065] 6개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절을 포함하고;

[0066] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함하는, 화합물.

[0067] 구현예 28: 선행 구현예들 중 어느 하나에서, 상기 변형된 올리고뉴클레오타이드는:

[0068] 8 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0069] 6개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0070] 4개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절;

[0071] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함하는, 화합물.

[0072] 구현예 29: 선행 구현예들 중 어느 하나에서, 상기 변형된 올리고뉴클레오타이드는 20 개의 연결된 뉴클레오사이드로 이루어지는, 화합물.

[0073] 구현예 30: 선행 구현예들 중 어느 하나에서, 상기 변형된 올리고뉴클레오타이드는 19개의 연결된 뉴클레오사이드로 이루어지는, 화합물.

[0074] 구현예 31: 선행 구현예들 중 어느 하나에서, 상기 변형된 올리고뉴클레오타이드는 18개의 연결된 뉴클레오사이드로 이루어지는, 화합물.

[0075] 구현예 32: 선행 구현예들 중 어느 하나의 화합물 또는 이의 염 및 약제학적으로 허용가능한 담체 또는 희석제 중 적어도 하나를 포함하는 조성물.

[0076] 구현예 33: 선행 구현예들 중 어느 하나의 화합물 또는 조성물을 동물에 투여하는 단계를 포함하는 방법.

[0077] 구현예 34: 구현예 33에 있어서, 상기 동물은 인간인, 방법.

[0078] 구현예 35: 구현예 33에 있어서, 상기 화합물의 투여는 타우 연관된 질환, 장애 또는 병태를 예방, 치료, 개선 또는 이의 진행을 지연시키는, 방법.

[0079] 구현예 36: 구현예 35에 있어서, 상기 질환, 장애, 및 병태는 타우병증, 알츠하이머 질환, 전두측두엽 치매 (FTD), FTDP-17, 진행성 핵상안근 마비 (PSP), 만성 외상성 뇌증 (CTE), 뇌피질 기저 신경절 퇴행증 (CBD), 간질, 또는 드라벳 증후군인, 방법.

[0080] 구현예 37: 신경퇴행성 장애를 치료하기 위한 약제의 제조를 위한 선행 구현예들 중 어느 하나의 화합물 또는 조성물의 용도.

[0081] 구현예 38: ISIS 613099 어진, 화합물.

[0082] 구현예 39: ISIS 613361 어진, 화합물.

[0083] 구현예 40: ISIS 613370 어진, 화합물.

[0084] 구현예 41: ISIS 623782로 이루어진, 화합물.

[0085] 구현예 42: ISIS 623996로 이루어진, 화합물.

[0086] 구현예 43: 구현예 38 내지 42 중 어느 하나의 화합물 또는 이의 염 및 약제학적으로 허용가능한 담체 또는 희석제 중 적어도 하나를 포함하는, 조성물.

[0087] 구현예 44: 구현예 38 내지 43 중 어느 하나의 화합물 또는 조성물을 투여하는 단계를 포함하는, 방법.

[0088] 구현예 45: 구현예 44에 있어서, 상기 동물은 인간인, 방법.

[0089] 구현예 46: 구현예 44에 있어서, 상기 화합물의 투여는 타우 연관된 질환, 장애 또는 병태를 예방, 치료, 개선 또는 이의 진행을 지연시키는, 방법.

[0090] 구현예 47: 구현예 46에 있어서, 상기 질환, 장애, 및 병태는 타우병증, 알츠하이머 질환, 전두측두엽 치매 (FTD), FTDP-17, 진행성 핵상안근 마비 (PSP), 만성 외상성 뇌증 (CTE), 뇌피질 기저 신경절 퇴행증 (CBD), 간질, 또는 드라벳 증후군인, 방법.

[0091] 구현예 48: 신경퇴행성 장애를 치료하기 위한 약제의 제조를 위한 구현예 38 내지 43 중 어느 하나의 화합물 또는 조성물의 용도.

발명을 실시하기 위한 구체적인 내용

[0092] 전술된 일반적인 설명 및 하기 상세한 설명 모두는 단지 예시적이고 설명적인 것이며, 청구될 때 본 발명을 제한하지 않음이 이해되어야 한다. 본원에서, 단수의 사용은 달리 구체적으로 언급되지 않으면 복수를 포함한다. 본원에서 사용된 바와 같이, "또는"의 사용은 다른 식으로 명시되지 않는 한, "및/또는"을 의미한다. 또한, 본원에서 사용된 바와 같이, "및"의 사용은 다른 식으로 명시되지 않는 한, "및/또는"을 의미한다. 더욱이, 용어 "포함하는" 및 "포함한다" 및 "포함하였다"와 같은 다른 형태의 사용은 비제한적이다. 또한, "요소" 또는 "성분"은 다른 식으로 구체적으로 명시되지 않는 한, 하나의 단위를 포함하는 요소 및 성분들 및 하나 초과의 하부단위를 포함하는 요소 및 성분들 둘 다를 포괄한다.

[0093] 본 명세서에서 사용된 섹션 제목들은 단지 조직적 목적을 위한 것이며, 기술된 요지를 제한하는 것으로 해석되지는 않는다. 허용되는 경우에, 모든 특허, 특허출원, 공개된 특허출원 및 다른 저널 출판물을 포함하여 (단, 이들로 제한되지는 않는다) 본 출원에서 인용된 모든 문서, 또는 문서의 일부분, 유전자 은행 (GENBANK) 수탁 번호 및 국립 바이오테크롤로지 정보 센터 (NCBI) 및 본 명세서에서 전체적으로 언급된 다른 데이터와 같은 데이터베이스를 통해 수득될 수 있는 관련된 서열 정보는 그 전체로, 또한 본원에서 거론된 문서의 일부분에 대한 참고로 포함된다.

[0094] *정의*

[0095] 구체적인 정의가 제공되지 않는 한, 본 명세서에 기술된 분석 화학, 합성 유기 화학, 및 의학 및 약제학적 화학과 관련하여 이용된 명명법, 및 그의 절차 및 기술은 본 기술분야에서 잘 알려지고 통상적으로 사용되는 것들이다. 화학적 합성 및 화학적 분석을 위해서는 표준 기술이 사용될 수 있다.

[0096] 다른 식으로 지적되지 않는 한, 하기 용어들은 하기의 의미를 갖는다:

[0097] "2'-O-메톡시에틸" (또한 2'-MOE 및 2'-OCH_2CH_2-OCH_3 및 MOE)은 푸로실 환의 2' 위치의 O-메톡시-에틸 변형을 나타낸다. 2'-O-메톡시에틸 변형된 당은 변형된 당이다.

[0098] "2'-MOE 뉴클레오사이드" (또한 2'-O-메톡시에틸 뉴클레오사이드)는 2'-MOE 변형된 당 모이어티를 포함하는 뉴클레오사이드를 의미한다.

[0099] 본원에서 사용된 바와 같이, "2'-치환된 뉴클레오사이드" 는 OH 이외의 푸라노 환의 2' 위치에서 치환체를 포함하는 뉴클레오사이드를 의미한다. 특정 구현예에서, 2' 치환된 뉴클레오사이드는 이환식 당 변형을 갖는 뉴클레오사이드를 포함한다.

[0100] "5-메틸시토신"은 5' 위치에 부착된 메틸기로 변형된 시토신을 의미한다. 5-메틸시토신은 변형된 핵염기이다.

[0101] "약"은 값의 ±7% 범위 내를 의미한다. 예를 들어, "화합물은 타우 억제의 적어도 약 70%만큼 영향을 미칠 수 있다"라고 언급된 경우에, 이것은 상기 타우 수준이 63%-77% 범위 내로 억제될 수 있음을 시사한다.

[0102] "수반하여 투여된다"는 둘 다의 약물학적 효과가 환자에게서 동시에 나타나도록 하는 임의의 방식으로의 두 가지 약제학적 제제의 공동-투여를 나타낸다. 수반되는 투여는 두 가지 약제학적 제제를 단일 약제학적 조성물로, 단일 투약형으로, 또는 동일한 투여 경로에 의해서 투여할 것을 필요로 하지 않는다. 두 가지 약제학적 제제의 효과는 그들 자체가 동시에 나타날 필요는 없다. 효과는 단지 기간의 중복이 필요할 뿐이며, 동일한 시간에 걸칠 필요는 없다.

[0103] "투여하는"은 약제학적 제제를 동물에게 제공하는 것을 의미하며, 의료 전문가에 의한 투여 및 자가-투여를 포함하지만 이들로 제한되지는 않는다.

[0104] "개선"은 연관된 질환, 장애 또는 상태의 적어도 하나의 지표, 징후 또는 증상을 약화시키는 것을 나타낸다. 지표의 중증도는 본 기술분야에서 숙련된 전문가에게 공지되어 있는 주관적 또는 객관적 척도에 의해서 결정될 수 있다.

[0105] "동물"은 마우스, 랫트, 토끼, 개, 고양이, 돼지, 및 원숭이 및 침팬지를 포함한 (단, 이들로 제한되지는 않는다) 비-인간 영장류를 포함하는 (단, 이들로 제한되지는 않는다) 인간 또는 비-인간 동물을 나타낸다.

[0106] "항체"는 일부 경우에서 항원과 특이적으로 반응함으로써 특징화되는 분자를 지칭하며, 여기서 항체 및 항원은 각각 다른 용어에서 정의된다. 항체는 완전한 항체 분자 또는 이의 임의의 단편 또는 영역, 예컨대 중쇄, 경쇄,

Fab 영역, 및 Fc 영역을 지칭할 수 있다.

[0107] "안티센스 활성"은 안티센스 화합물의 그의 표적 핵산에 대한 혼성화에 기인할 수 있는 특정 검출 가능하거나 측정 가능한 활성을 의미한다. 특정 구현예에서, 안티센스 활성은 표적 핵산 또는 이러한 표적 핵산에 의해서 암호화된 단백질의 양 또는 발현의 감소이다.

[0108] "안티센스 화합물"은 수소 결합을 통해서 표적 핵산에 대한 혼성화를 겪을 수 있는 올리고머 화합물을 의미한다. 안티센스 화합물의 예시는 단일 가닥 및 이중 가닥 화합물, 예컨대 안티센스 올리고뉴클레오타이드, siRNA, shRNA, ssRNA, 및 점유도-기반 화합물을 포함한다.

[0109] "안티센스 억제"는 안티센스 화합물의 부재 하에서의 표적 핵산 수준에 비하여, 표적 핵산에 대해 상보적인 안티센스 화합물의 존재 하에서의 표적 핵산 수준의 감소를 의미한다.

[0110] "안티센스 기전"은 표적 핵산을 갖는 화합물의 혼성화를 포함하는 모든 기전이며, 여기서 상기 혼성화의 결과 또는 효과는 예를 들어 전사 또는 스플라이싱을 포함하는 세포 기작의 수반된 스톨링(stalling)을 갖는 표적 저하 또는 표적 점유이다.

[0111] "안티센스 올리고뉴클레오타이드"는 표적 핵산의 상응하는 분절에 대한 혼성화를 허용하는 핵염기 서열을 갖는 단일-가닥 올리고뉴클레오타이드를 의미한다.

[0112] "염기 상보성"은 표적 핵산 (즉, 혼성화)에서의 상응하는 핵염기를 갖는 안티센스 올리고뉴클레오타이드의 핵염기의 정확한 염기 짝짓기에 대한 능력을 지칭하며, 이는 상응하는 핵염기 사이의 왓슨-크릭, 후그스텐 또는 역방향 후그스텐 수소 결합에 의하여 매개된다.

[0113] "이환식 당"은 두 개의 원자의 가교화 (bridging)에 의해서 변형된 푸로실 환을 의미한다. 이환식 당은 변형된 당이다.

[0114] "이환식 핵산" (또는 BNA)는 당 환의 두 개의 탄소 원자를 연결하는 가교를 포함하는 당 모이어티를 갖고, 이로써 이환식 환계를 형성하는 뉴클레오사이드를 의미한다. 특정 구현예에서, 상기 가교는 상기 당 환의 4'-탄소 및 2' 탄소를 연결한다.

[0115] "캡 (cap) 구조" 또는 "말단 캡 모이어티"는 안티센스 화합물의 어느 하나의 말단에 포함된 화학적 변형을 의미한다.

[0116] "cEt" 및 "제한된 에틸"은 4'-탄소 및 2' 탄소를 연결하는 가교를 포함하는 당 모이어티를 갖는 이환식 뉴클레오사이드를 의미하며, 이때 상기 가교는 하기 화학식: 4'-CH(CH_3)-O-2'를 갖는다.

[0117] "제한된 에틸 뉴클레오사이드" (또한 cEt 뉴클레오사이드)는 4'-CH(CH_3)-O-2' 가교를 포함하는 이환식 모이어티를 포함하는 뉴클레오사이드를 의미한다.

[0118] "화학적으로 구분되는 영역"은 특정 점에서 동일한 안티센스 화합물의 또 다른 영역과 화학적으로 상이한 안티센스 화합물의 영역을 나타낸다. 예를 들어, 2'-O-메톡시에틸 뉴클레오사이드를 갖는 영역은 2'-O-메톡시에틸 변형이 없는 뉴클레오사이드를 갖는 영역과 화학적으로 구분된다.

[0119] "키메라 안티센스 화합물"은 적어도 두 개의 화학적으로 구분되는 영역을 갖고, 각 위치는 다수의 서브유닛을 갖는 안티센스 화합물을 의미한다.

[0120] "공동-투여"는 개체에게 두 개 이상의 약제학적 제제를 투여하는 것을 의미한다. 두 개 이상의 약제학적 제제는 단일 약제학적 조성물 내에 존재할 수 있거나, 별개의 약제학적 조성물 내에 존재할 수 있다. 상기 두 개 이상의 약제학적 조성물 각각은 동일하거나 상이한 투여 경로를 통해서 투여될 수 있다. 공동-투여는 병행 또는 순차적 투여를 포괄한다.

[0121] "상보성"은 제1 핵산과 제2 핵산의 핵염기 사이의 짝짓기 능력을 의미한다.

[0122] "포함하다", "포함하다" 및 "포함하는" 은 언급된 단계 또는 요소, 또는 단계 또는 요소의 집합의 포함을 의미하지만, 임의의 다른 단계 또는 요소의 집합을 암시하는 것으로 이해될 것이다.

[0123] "인접 핵염기"는 서로에 대해 바로 인접한 핵염기를 의미한다.

[0124] "설계" 또는 "~하도록 설계된"은 선택된 핵산 분자와 특이적으로 혼성화하는 올리고머 화합물을 설계하는 과정

을 지칭한다.

[0125] "희석제"는 약물학적 활성을 결여하고 있지만, 약제학적으로 필요하거나 바람직한 조성물 내의 성분을 의미한다. 예를 들어, 주사용 약물에서, 희석제는 액체, 예를 들어, 식염수일 수 있다.

[0126] "용량"은 단일 투여에서, 또는 명시된 기간 동안에 제공된 약제학적 제제의 명시된 양을 의미한다. 특정 구현예에서, 용량은 1, 또는 2 이상의 볼러스 (bolus), 정제, 또는 주사제로 투여될 수 있다. 예를 들어, 피하 투여를 원하는 특정 구현예에서, 원하는 용량은 단일 주사에 의해서 쉽게 수용되지 않는 용적을 필요로 하며, 따라서 2 이상의 주사제를 사용하여 원하는 용량을 달성할 수 있다. 특정 구현예에서, 약제학적 작용제는 장시간에 걸쳐서, 또는 연속적으로 주입함으로써 투여된다. 용량은 시간, 일, 주, 또는 개월 당 약제학적 제제의 양으로 언급될 수 있다.

[0127] 병태를 치료 또는 예방의, 또는 이의 활성을 조절하는 맥락에서, "효과적인 양"은 그러한 조절, 치료, 또는 예방을 필요로 하는 대상체에 약제학적 제제의 그와 같은 양을, 그러한 병태의 치료 또는 예방 또는 개선을 위하여, 또는 그러한 병태의 효과 조절에 대해 효과적인, 단일 투여 또는 일련의 것 중 부분으로 투여하는 것을 의미한다. 유효량은 치료될 개체의 건강 및 신체 조건, 치료될 개체의 분류군, 조성물의 제형, 개체의 의학적 상태의 평가, 및 그 밖의 다른 관련된 인자에 따라 개체들 사이에서 달라질 수 있다.

[0128] "효능"은 원하는 효과를 생성하는 능력을 의미한다.

[0129] "발현"은 유전자 암호화된 정보가 세포 내에서 존재 및 작동하는 구조로 전환되는 모든 기능을 포함한다. 그러한 구조는 비제한적으로 전사 및 번역의 생성물을 포함한다.

[0130] "완전히 상보적" 또는 "100% 상보적"은 제1 핵산의 각각의 핵염기가 제2 핵산 내에 상보적인 핵염기를 갖는 것을 의미한다. 특정 구현예에서, 제1 핵산은 안티센스 화합물이고, 표적 핵산은 제2 핵산이다.

[0131] "갭머 (gapmer)"는 RNase H 분해를 지지하는 다수의 뉴클레오사이드를 갖는 내부 영역이 하나 또는 그 이상의 뉴클레오사이드를 갖는 외부 영역들 사이에 배치된 키메라 안티센스 화합물을 의미하며, 이때 상기 내부 영역을 포함하는 뉴클레오사이드는 상기 외부 영역을 포함하는 뉴클레오사이드 또는 뉴클레오사이드들과 화학적으로 구분된다. 내부 영역은 "갭"로 지칭될 수 있으며, 외부 영역은 "윙 (wing)"로 지칭될 수 있다.

[0132] "갭-한정된 (gap-narrowed)"은 1 내지 6 개의 뉴클레오사이드를 갖는 5' 및 3' 윙 분절들 사이에, 및 이들에 바로 인접하여 배치된 9개 이하의 인접 2'-데옥시리보뉴클레오사이드의 갭 분절을 갖는 키메라 안티센스 화합물을 의미한다.

[0133] "갭-확장된 (gap-widened)"은 1 내지 6 개의 뉴클레오사이드를 갖는 5' 및 3' 윙 분절들 사이에, 및 이들에 바로 인접하여 배치된 12 개 또는 그 이상의 인접 2'-데옥시리보뉴클레오사이드의 갭 분절을 갖는 키메라 안티센스 화합물을 의미한다.

[0134] "혼성화"는 상보적 핵산 분자의 어닐링 (annealing)을 의미한다. 특정 구현예에서, 상보적 핵산 분자는 비제한적으로 안티센스 화합물 및 표적 핵산을 포함한다. 특정 구현예에서, 상보적 핵산 분자는 비제한적으로 안티센스 올리고뉴클레오타이드 및 핵산 표적을 포함한다.

[0135] "타우 연관된 질환을 갖는 동물을 동정하는 것"은 타우 연관된 질환으로 진단되었거나 타우 연관된 질병을 발병할 소인이 있는 동물을 동정하는 것을 의미한다. 타우 연관된 질병을 발병할 소인이 있는 개체는 노화, 개인 또는 가족력, 또는 유전적 소인 중 하나 이상의 타우 연관된 질병 소인을 포함하는, 타우 연관된 질병 발병에 대한 하나 이상의 위험 인자를 갖는 개체를 포함한다. 그러한 동정은 개체의 병력 및 표준 임상 시험 또는 평가, 예컨대 유전자 시험을 평가하는 단계를 포함하는 임의의 방법에 의하여 수반될 수 있다.

[0136] "바로 인접한"은 바로 인접한 요소들 사이에 개입성 요소가 없는 것을 의미한다.

[0137] "개체" 는 치료 또는 요법을 위해서 선택된 인간 또는 비-인간 동물을 의미한다.

[0138] "타우 억제"는 타우 mRNA 및/또는 단백질의 발현 수준을 감소시키는 것을 의미한다. 특정 구현예에서, 타우 mRNA 및/또는 단백질 수준은, 타우 안티센스 화합물, 예컨대 안티센스 올리고뉴클레오타이드의 부재 하에서 타우 mRNA 및/또는 단백질 수준의 발현과 비교하여, 타우를 표적화하는 안티센스 올리고뉴클레오타이드를 포함하는 타우를 표적화하는 안티센스 화합물의 존재 하에서 억제된다.

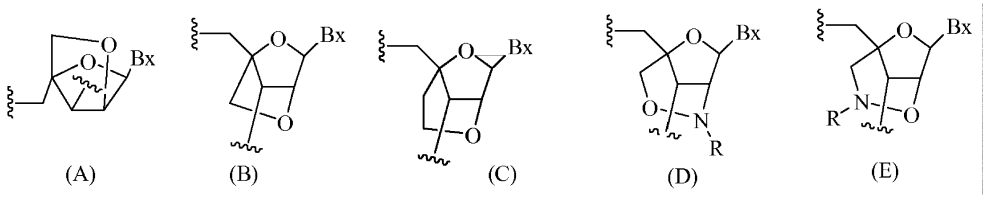
[0139] "발현 또는 활성을 억제하는"은 발현 또는 활성의 감소 또는 차단을 나타내며, 반드시 발현 또는 활성의 전체

제거를 나타내지는 않는다.

[0140] "뉴클레오사이드간 연결"은 뉴클레오사이드들 사이의 화학적 결합을 나타낸다.

[0141] "연결된 뉴클레오사이드"는 뉴클레오사이드간 연결에 의하여 함께 연결된 인접한 뉴클레오사이드를 의미한다.

[0142] "잠금(locked) 핵산" 또는 " LNA" 또는 "LNA 뉴클레오사이드"는 뉴클레오사이드 당 단위의 4' 및 2' 위치 사이의 두 개의 탄소 원자를 연결하는 가교를 갖는 핵산 모노머를 의미한다. 이환식 당의 예시는, 비제한적으로, 하기 묘사된 (A) α-L-메틸렌옥시 (4'-CH_2-O-2') LNA, (B) β-D-메틸렌옥시 (4'-CH_2-O-2') LNA, (C) 에틸렌옥시 (4'-$(CH_2)_2$-O-2') LNA, (D) 아미노옥시 (4'-CH_2-O-N(R)-2') LNA, 및 (E) 옥시아미노 (4'-CH_2-N(R)-O-2') LNA를 포함한다.

[0143] 

[0144] 본원에서 사용된 바와 같이, LNA 화합물은, 비제한적으로, 당의 4' 및 2' 위치 사이의 적어도 하나의 가교를 갖는 화합물을 포함하고, 여기서 상기 가교 중 각각은 독립적으로, -$[C(R_1)(R_2)]_n$-, -$C(R_1)$=$C(R_2)$-, -$C(R_1)$=N-, -C(=NR_1)-, -C(=O)-, -C(=S)-, -O-, -$Si(R_1)_2$-, -$S(=O)_x$- 및 -$N(R_1)$-로부터 독립적으로 선택된 1 또는 2 내지 4개의 연결기를 포함한다; 여기서 x는 0, 1, 또는 2이고; n은 1, 2, 3, 또는 4이고; R_1 및 R_2 각각은, 독립적으로, H, 보호기, 하이드록실, C_1-C_{12} 알킬, 치환된 C_1-C_{12} 알킬, C_2-C_{12} 알케닐, 치환된 C_2-C_{12} 알케닐, C_2-C_{12} 알키닐, 치환된 C_2-C_{12} 알키닐, C_5-C_{20} 아릴, 치환된 C_5-C_{20} 아릴, 헤테로환 라디칼, 치환된 헤테로환 라디칼, 헤테로아릴, 치환된 헤테로아릴, C_5-C_7 지환식 라디칼, 치환된 C_5-C_7 지환식 라디칼, 할로겐, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, 아실 (C(=O)-H), 치환된 아실, CN, 설포닐 ($S(=O)_2$-J_1), 또는 설폭실 (S(=O)-J_1)이고; 그리고 J_1 및 J_2 각각은 독립적으로, H, C_1-C_{12} 알킬, 치환된 C_1-C_{12} 알킬, C_2-C_{12} 알케닐, 치환된 C_2-C_{12} 알케닐, C_2-C_{12} 알키닐, 치환된 C_2-C_{12} 알키닐, C_5-C_{20} 아릴, 치환된 C_5-C_{20} 아릴, 아실 (C(=O)-H), 치환된 아실, 헤테로환 라디칼, 치환된 헤테로환 라디칼, C_1-C_{12} 아미노알킬, 치환된 C_1-C_{12} 아미노알킬 또는 보호기이다.

[0145] LNA 정의 내에 포괄된 4' - 2' 가교기의 예시는, 다음 화학식 중 하나를 포함하지만 이들로 제한되는 것은 아니다: -$[C(R_1)(R_2)]_n$-, -$[C(R_1)(R_2)]_n$-O-, -$C(R_1R_2)$-$N(R_1)$-O- 또는 -$C(R_1R_2)$-O-$N(R_1)$-. 더욱이, LNA의 정의 내에서 포괄된 다른 가교 그룹은 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-$N(R_1)$-2' 및 4'-CH_2-$N(R_1)$-O-2'- 가교이고, 이때 R_1 및 R_2 각각은 독립적으로, H, 보호기, 또는 C_1-C_{12} 알킬이다.

[0146] 또한 본 발명에 따른 LNA의 정의 내에 포함된 것은 리보실 당 환의 2'-하이드록실 기가 당 환의 4' 탄소 원자와 연결되어, 이로써 이환식 당 모이어티를 형성하는 메틸렌옥시 (4'-CH_2-O-2') 가교를 형성하는 LNA이다. 상기 가교는 또한 2' 산소 원자 및 4' 탄소 원자를 연결하는 메틸렌 (-CH_2-)기일 수 있으며, 이에 대해 용어 메틸렌옥시 (4'-CH_2-O-2') LNA가 사용된다. 더욱이, 이러한 위치에서 에틸렌 가교 그룹을 갖는 이환식 당 모이어티의 경우에서, 용어 에틸렌옥시 (4'-CH_2CH_2-O-2') LNA가 사용된다. α -L- 메틸렌옥시 (4'-CH_2-O-2'), 메틸렌옥시 (4'-CH_2-O-2') LNA의 이성질체는 또한 본원에 사용된 바와 같이 LNA의 정의 내에 포괄된다.

[0147] "미스매치 (mismatch)" 또는 "비-상보적 핵염기"는 제1 핵산의 핵염기가 제2 또는 표적 핵산의 상응하는 핵염기와 짝짓기 할 수 없는 경우를 지칭한다.

[0148] "변형된 뉴클레오사이드간 연결"은 천연적으로 발생하는 뉴클레오사이드간 결합 (즉, 포스포디에스테르 뉴클레오사이드간 결합)으로부터의 치환 또는 특정 변화를 지칭한다.

[0149] "변형된 핵염기"는 아데닌, 시토신, 구아닌, 티미딘, 또는 우라실 이외의 임의의 핵염기를 의미한다. "비변형된 핵염기"는 퓨린 염기인 아데닌 (A) 및 구아닌 (G), 및 피리미딘 염기인 티민 (T), 시토신 (C), 및 우라실 (U)을

의미한다.

[0150] "변형된 뉴클레오사이드"는 독립적으로, 변형된 당 모이어티 및/또는 변형된 핵염기를 갖는 뉴클레오사이드를 의미한다.

[0151] "변형된 뉴클레오타이드"는 독립적으로, 변형된 당 모이어티, 변형된 뉴클레오사이드간 연결, 및/또는 변형된 핵염기를 갖는 뉴클레오타이드를 의미한다.

[0152] "변형된 올리고뉴클레오타이드"는 적어도 하나의 뉴클레오사이드간 연결, 변형된 당, 및/또는 변형된 핵염기를 포함하는 올리고뉴클레오타이드를 의미한다.

[0153] "변형된 당"은 천연 당 모이어티로부터의 치환 및/또는 변화를 나타낸다.

[0154] "모노머"는 올리고머의 단일 단위를 의미한다. 모노머는 비제한적으로, 천연 발생하거나 변형된 뉴클레오사이드 및 뉴클레오타이드를 포함한다.

[0155] "모티프"는 안티센스 화합물 내에서 비변형 및 변형된 뉴클레오사이드의 패턴을 의미한다.

[0156] "천연 당 모이어티"는 DNA (2'-H) 또는 RNA (2'-OH)에서 발견되는 당 모이어티를 의미한다.

[0157] "천연적으로 발생하는 뉴클레오사이드간 연결"은 3' 내지 5' 포스포디에스테르 연결을 의미한다.

[0158] "비-상보적 핵염기"는 다른 하나와 수소 결합을 형성하거나 달리 혼성화를 지지하지 않는 핵염기 쌍을 지칭한다.

[0159] "핵산"은 모노머 뉴클레오타이드로 구성된 분자를 나타낸다. 핵산은 비제한적으로 리보핵산 (RNA), 데옥시리보핵산 (DNA), 단일-가닥 핵산, 이중-가닥 핵산, 소형 개입성 리보핵산 (siRNA), 및 마이크로RNAs (miRNA)가 포함한다.

[0160] "핵염기"는 또 다른 핵산의 염기와 짝짓기 할 수 있는 헤테로환 모이어티를 의미한다.

[0161] "핵염기 상보성"은 다른 핵염기와 염기 짝짓기를 할 수 있는 핵염기를 지칭한다. 예를 들어, DNA에서, 아데닌 (A)은 티민 (T)과 상보적이다. 예를 들어, RNA에서, 아데닌 (A)은 우라실 (U)와 상보적이다. 특정 구현예에서, 상보적 핵염기는 이의 표적 핵산의 핵염기와 염기 짝짓기를 할 수 있는 안티센스 화합물의 핵염기를 지칭한다. 예를 들어, 만약 안티센스 화합물의 특정 위치에서의 핵염기가 표적 핵산의 특정 위치에서의 핵염기와 수소 결합을 할 수 있다면, 상기 올리고뉴클레오타이드 및 상기 표적 핵산 사이의 수소 결합 위치는 그러한 핵염기 쌍에서 상보적이라고 고려된다.

[0162] "핵염기 서열"은 임의의 당, 연결 및/또는 핵염기 변형에 독립적인 인접 핵염기의 순서를 의미한다.

[0163] "뉴클레오사이드"는 당에 연결된 핵염기를 의미한다.

[0164] "뉴클레오사이드 모방체"는 당 또는 당 및 염기, 및 필수적은 아니나 하나 이상의 위치에서의 연결을, 예를 들어, 모폴리노, 사이클로헥세닐, 사이클로헥실, 테트라하이드로피라닐, 바이사이클로 또는 트리사이클로 당 모방체, *예를 들어*, 비-푸라노즈 당 단위를 갖는 뉴클레오사이드 모방체와 같은 올리고머 화합물로 대체하기 위하여 사용된 이들 구조를 포함한다. 뉴클레오타이드 모방체는 뉴클레오사이드 및 하나 이상의 위치에서의 연결을, 예를 들어, 펩타이드 핵산 또는 모폴리노 (-N(H)-C(=O)-O- 또는 다른 비-포스포디에스테르 연결에 의해서 연결된 모폴리노)와 같은 올리고머 화합물로 대체하기 위하여 사용된 이들 구조를 포함한다. 당 대용물은 조금 더 넓은 용어 뉴클레오사이드 모방체와 중복되나, 오직 당 단위 (푸라노스 환)의 대체를 지시하도록 의도된다. 본원에 제공된 테트라히드로피라닐 환은 당 대용물의 예로 예시되고, 이때 푸라노스 당 그룹은 테트라히드로피라닐 환계(ring system)로 대체되었다. "모방체"는 당, 핵염기, 및/또는 뉴클레오사이드간 연결을 대체하는 그룹을 지칭한다. 일반적으로, 모방체는 당 또는 당-뉴클레오사이드간 연결 조합물을 대신하여 사용되고, 핵염기는 선택된 표적으로의 혼성화를 위하여 유지된다.

[0165] "뉴클레오타이드"는 뉴클레오사이드의 당 부분에 공유 연결된 인산기를 갖는 뉴클레오사이드를 의미한다.

[0166] "오프-타겟 효과"는 의도된 표적 핵산 이외의 유전자의 RNA 또는 단백질 발현 조절과 연관된 원하지 않거나 유해한 생물학적 효과를 지칭한다.

[0167] "올리고머 화합물" 또는 "올리고머"는 적어도 하나의 핵산 분자의 영역에 혼성화할 수 있는, 연결된 모노머 하부단위의 중합체를 의미한다.

[0168] "올리고뉴클레오타이드"는 각각 서로 독립적으로 변형되거나 비변형될 수 있는, 연결된 뉴클레오사이드의 중합체를 의미한다.

[0169] "비경구 투여"는 주사 (예컨대 볼러스 주사) 또는 주입을 통한 투여를 의미한다. 비경구 투여에는 피하 투여, 정맥내 투여, 근육내 투여, 동맥내 투여, 복강내 투여, 또는 두개내 투여, 예를 들어, 척추강내 또는 뇌실내 투여가 포함된다.

[0170] "펩타이드"는 아미드 결합에 의해 적어도 두 개의 아미노산을 연결시킴으로써 형성된 분자를 의미한다. 제한 없이, 본원에서 사용된 바와 같이, 펩티드는 폴리펩티드 및 단백질을 지칭한다.

[0171] "약제학적 제제"는 개체에게 투여하였을 때 치료학적 이점을 제공하는 물질을 의미한다. 예를 들어, 특정 구현예에서, 타우에 표적화된 안티센스 올리고뉴클레오타이드가 약제학적 제제이다.

[0172] "약제학적 조성물"은 개체에게 투여하는데 적합한 물질의 혼합물을 의미한다. 예를 들어, 약제학적 조성물은 안티센스 올리고뉴클레오타이드 및 멸균 수용액을 포함할 수 있다.

[0173] "약제학적으로 허용가능한 유도체"는 본 명세서에 기술된 화합물의 약제학적으로 허용가능한 염, 공액체, 프로드러그 (prodrug) 또는 이성질체를 포괄한다.

[0174] "약제학적으로 허용가능한 염"은 안티센스 화합물의 생리적으로 및 약제학적으로 허용가능한 염, 즉, 모체 올리고뉴클레오타이드의 원하는 생물학적 활성을 보유하며, 원치 않는 독물학적 효과를 그에 부여하지 않는 염을 의미한다.

[0175] "포스포로티오에이트 연결"은 포스포디에스테르 결합이 비-가교화 산소 원자들 중의 하나를 황 원자로 대체시킴으로써 변형된 뉴클레오사이드 간의 연결을 의미한다. 포스포로티오에이트 연결은 변형된 뉴클레오사이드간 연결이다.

[0176] "부분"은 핵산의 인접 (즉, 연결된) 핵염기의 규정된 수를 의미한다. 특정 구현예에서, 부분은 표적 핵산의 인접 핵염기의 규정된 수이다. 특정 구현예에서, 부분은 안티센스 화합물의 인접 핵염기의 규정된 수이다.

[0177] "예방하다" 또는 "예방하는"은 질환, 장애 또는 병태의 시작 또는 발전을 몇 분 내지 몇주, 몇달, 또는 무한대의 기간 동안 지연시키거나 미연에 방지하는 것을 지칭한다.

[0178] "프로드러그"은 내인성 효소 또는 다른 화합물질 및/또는 조건의 작용에 의해 신체 또는 세포 내에서 활성 형태 (즉, 약물)로 전환되는 불활성 형태로 제조된 치료제를 의미한다.

[0179] "예방학적 유효량"은 동물에게 예방학적 또는 예방적인 이점을 제공하는 약제학적 제제의 양을 의미한다.

[0180] "영역"은 적어도 하나의 식별가능한 구조, 기능 또는 특성을 갖는 표적 핵산의 부분으로서 정의된다.

[0181] "리보뉴클레오타이드"는 뉴클레오타이드의 당 부분의 2' 위치에 하이드록시를 갖는 뉴클레오타이드를 의미한다. 리보뉴클레오타이드는 다양한 치환체 중 임의의 것으로 변형될 수 있다.

[0182] "염"은 안티센스 화합물의 생리적으로 및 약제학적으로 허용가능한 염, 즉, 모체 올리고뉴클레오타이드의 원하는 생물학적 활성을 보유하며, 원치 않는 독물학적 효과를 그에 부여하지 않는 염을 의미한다.

[0183] "분절"은 표적 핵산 내의 더 작거나 하부-부분의 영역으로서 정의된다.

[0184] 본원에 기술된 "짧아진" 또는 "절단된" 버전의 안티센스 올리고뉴클레오타이드는하나, 또는 둘 이상의 결실된 뉴클레오사이드를 갖는다.

[0185] "부작용"은 원하는 효과 이외에 치료에 기인하는 생리적 반응을 의미한다. 특정 구현예에서, 부작용은 비제한적으로 주사 부위 반응, 간 기능 시험 이상, 신장 기능 이상, 간독성, 신장 독성, 중추신경계 이상, 근병증, 및 권태감을 포함한다.

[0186] "단일-가닥 올리고뉴클레오타이드"는 상보적 가닥에 혼성화되지 않은 올리고뉴클레오타이드를 의미한다.

[0187] 본원에서 사용된 바와 같이, "부위"는 표적 핵산 내의 특별한 핵염기 위치로 정의된다.

[0188] "진행 지연"은 상기 질환의 발병에서의 감소를 의미한다.

[0189] "특이적으로 혼성화할 수 있는"은 특이적 연결이 바람직한 조건 하에서, 즉 체내 검정 및 치료학적 치료의 경우에 생리적 조건 하에서, 비-표적 핵산에 대해서는 최소의 효과를 나타내거나 효과를 나타내지 않으면서, 안티센

스 올리고뉴클레오타이드 및 표적 핵산 사이에서 원하는 효과를 유도하기에 충분한 정도의 상보성을 갖는 안티센스 화합물을 지칭한다.

[0190] "엄격한 혼성화 조건" 또는 "엄격한 조건"은 올리고머 화합물이 이의 표적 서열에 혼성화할 것이나, 다른 서열에는 이의 최소 수로 혼성화할 것인 조건을 의미한다.

[0191] "대상체" 는 치료 또는 요법을 위해서 선택된 인간 또는 비-인간 동물을 의미한다.

[0192] "표적"은 이의 조절을 원하는 단백질을 지칭한다.

[0193] "표적 유전자"는 표적을 암호화하는 유전자를 지칭한다.

[0194] "표적화" 또는 "표적화된"은 표적 핵산에 특이적으로 혼성화하여 원하는 효과를 유도할 것인, 안티센스 화합물의 설계 및 선택의 과정을 의미한다.

[0195] "표적 핵산", "표적 RNA", 및 "표적 RNA 전사체" 및 "핵산 표적"은 모두 안티센스 화합물에 의해서 표적화될 수 있는 핵산을 의미한다.

[0196] "표적 영역"은 하나 이상의 안티센스 화합물이 표적화된, 표적 핵산의 부분을 의미한다.

[0197] "표적 분절"은 안티센스 화합물이 표적화된, 표적 핵산의 뉴클레오타이드의 서열을 의미한다. "5' 표적 부위"는 표적 분절의 5'-모스트(most) 뉴클레오타이드를 나타낸다. "3' 표적 부위"는 표적 분절의 3'-모스트 뉴클레오타이드를 나타낸다.

[0198] "타우"는 인간 미세소관-연관된 단백질 타우(MAPT)를 포함하는 포유류 미세소관-연관된 단백질 타우 (MAPT)를 의미한다.

[0199] "타우 연관된 질환"은 임의의 타우 핵산 또는 이의 발현 생성물과 연관된 임의의 질환을 의미한다. 그러한 질환은 신경퇴행성 질환을 포함할 수 있다. 그러한 신경퇴행성 질환은 타우병증, 알츠하이머 질환, 전두측두엽 치매 (FTD), FTDP-17, 진행성 핵상안근 마비 (PSP), 만성 외상성 뇌증 (CTE), 뇌피질 기저 신경절 퇴행증 (CBD), 간질, 및 드라벳 증후군을 포함한다.

[0200] "타우 mRNA"는 타우를 암호화하는 임의의 DNA 서열의 메신저 RNA 발현 생성물을 의미한다.

[0201] "타우 핵산"은 타우를 암호화하는 임의의 핵산을 의미한다. 예를 들어, 특정 구현예에서, 타우 핵산은 타우를 암호화한 DNA 서열, 타우를 암호화한 DNA (인트론 및 엑손을 포함하는 게놈 DNA를 포함)로부터 전사된 RNA 서열, 및 타우를 암호화한 mRNA 서열을 포함한다. "타우 mRNA"는 타우 단백질을 암호화한 mRNA를 의미한다.

[0202] "타우 단백질"은 타우 핵산의 폴리펩티드 발현 생성물을 의미한다.

[0203] "치료학적 유효량"은 개체에게 치료학적 이점을 제공하는 치료학적 제제의 양을 의미한다.

[0204] "치료하다" 또는 "치료하는" 또는 "치료"는 질병 또는 병태의 변경 또는 개선을 달성하기 위해서 조성물을 투여하는 것을 지칭한다.

[0205] "비변형된 핵염기"는 퓨린 염기인 아데닌 (A) 및 구아닌 (G), 및 피리미딘 염기인 티민 (T), 시토신 (C), 및 우라실 (U)을 의미한다.

[0206] "비변형 뉴클레오타이드"는 천연적으로 발생하는 핵염기, 당 모이어티, 및 뉴클레오사이드간 연결으로 구성된 뉴클레오타이드를 의미한다. 특정 구현예에서, 비변형 뉴클레오타이드는 RNA 뉴클레오타이드 (즉, β-D-리보뉴클레오사이드) 또는 DNA 뉴클레오타이드 (즉, β-D-데옥시리보뉴클레오사이드)이다.

[0207] "윙 분절"은 예컨대 개선된 억제 활성, 표적 핵산에 대한 증가된 결합 친화도, 또는 체내 핵염기에 의한 저하에 대한 저항성과 같은 올리코뉴클레오타이드 특성을 부여하기 위하여 변형된 다수의 뉴클레오사이드를 의미한다.

[0208] *특정 구현예*

[0209] 특정 구현예는 타우 mRNA 및 단백질 발현을 억제하기 위한 방법, 화합물, 및 조성물을 제공한다. 특정 구현예는 타우 mRNA 및 단백질 수준을 감소시키기 위한 방법, 화합물, 및 조성물을 제공한다.

[0210] 특정 구현예는 타우 핵산에 표적화된 안티센스 화합물을 제공한다. 특정 구현예에서, 타우 핵산은 뉴클레오타이드 9240000-9381000로부터 절단된 유전자 은행 수탁 번호 유전자 은행 수탁 번호 NT_010783.15 (본원에서 서열번호: 1과 같이 포함), 유전자 은행 수탁 번호 NM_001123066.3 (본원에서 서열 번호: 2와 같이 포함) 엑손 3,

4, 6, 8, 10, 및 12를 건너뛰는 유전자 은행 수탁 번호 NM_016841.4, 변이체 mRNA 서열 (본원에서 서열 번호: 3과 같이 포함) 뉴클레오타이드 2624000-2761000로부터 절단된 유전자 은행 수탁 번호 NT_010783.14 (본원에서 서열 번호: 4와 같이 포함) 유전자 은행 수탁 번호 DR002467.1 (본원에서 서열 번호: 5와 같이 포함) 유전자 은행 수탁 번호 NM_001203251.1 (본원에서 서열 번호: 6과 같이 포함) 및 유전자 은행 수탁 번호 NM_016835.4 (본원에서 서열 번호: 7과 같이 포함)에 제시된 서열이다.

[0211] 특정 구현예는 이를 필요로 하는 개체에서 타우와 연관된 질환, 장애 및 병태의 치료, 예방, 또는 개선을 위한 방법을 제공한다. 타우 연관된 질환, 장애 또는 병태의 치료, 예방, 또는 개선용 약제의 제조를 위한 방법이 또한 고려된다. 타우 연관된 질환, 장애, 및 병태는 신경퇴행성 질환을 포함한다. 특정 구현예에서, 타우 연관된 질환은 타우병증, 알츠하이머 질환, 전두측두엽 치매 (FTD), FTDP-17, 진행성 핵상안근 마비 (PSP), 만성 외상성 뇌증 (CTE), 뇌피질 기저 신경절 퇴행증 (CBD), 간질, 또는 드라벳 증후군을 포함한다.

[0212] 특정 구현예는 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 20-2443 및 서열 번호: 2478-2483의 핵염기 서열 중 임의의 것 중 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 갖는 변형된 올리고뉴클레오타이드를 포함하는 화합물을 제공한다.

[0213] 특정 구현예는 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 2444-2477 및 서열 번호: 2484-2565의 핵염기 서열 중 임의의 것 중 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 갖는 변형된 올리고뉴클레오타이드를 포함하는 화합물을 제공한다.

[0214] 특정 구현예는 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 20-2565의 핵염기 서열 중 임의의 것 중 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 갖는 변형된 올리고뉴클레오타이드를 포함하는 화합물을 제공한다.

[0215] 특정 구현예는 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 1의 핵염기 135783-135980와 동등한 길이 부분에 상보적인 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 포함하는 변형된 올리고뉴클레오타이드를 포함하는 화합물을 제공한다.

[0216] 특정 구현예는 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 1의 핵염기 135853-135872와 동등한 길이 부분에 상보적인 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 포함하는 변형된 올리고뉴클레오타이드를 포함하는 화합물을 제공한다.

[0217] 특정 구현예는 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 1의 핵염기 135783-135929와 동등한 길이 부분에 상보적인 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 포함하는 변형된 올리고뉴클레오타이드를 포함하는 화합물을 제공한다.

[0218] 특정 구현예는 12 내지 30 개의 연결된 뉴클레오사이드로 이루어지고, 서열 번호: 1의 핵염기 135783-135914와 동등한 길이 부분에 상보적인 적어도 8개, 적어도 9개, 적어도 10개, 적어도 11개, 적어도 12개, 적어도 13개, 적어도 14개, 적어도 15개, 적어도 16개, 적어도 17개, 적어도 18개, 적어도 19개, 또는 적어도 20개의 인접 핵염기를 포함하는 핵염기 서열을 포함하는 변형된 올리고뉴클레오타이드를 포함하는 화합물을 제공한다.

[0219] 특정 구현예에서, 상기 변형된 올리고뉴클레오타이드의 핵염기 서열은 서열 번호: 1에 적어도 80%, 적어도 81%, 적어도 82%, 적어도 83%, 적어도 84%, 적어도 85%, 적어도 86%, 적어도 87%, 적어도 88%, 적어도 89%, 적어도 90%, 적어도 91%, 적어도 92%, 적어도 93%, 적어도 94%, 적어도 95%, 적어도 96%, 적어도 97%, 적어도 98%, 적어도 99%, 또는 100% 상보적이다.

[0220] 특정 구현예에서, 화합물은 단일-가닥 변형된 올리고뉴클레오타이드로 이루어진다.

[0221] 특정 구현예에서, 변형된 올리고뉴클레오타이드의 적어도 하나의 뉴클레오사이드간 연결은 변형된 뉴클레오사이드간 연결이다.

[0222] 특정 구현예에서, 적어도 하나의 뉴클레오사이드간 연결은 포스포로티오에이트 뉴클레오사이드간 연결이다.

[0223] 특정 구현예에서, 각각의 뉴클레오사이드간 연결은 포스포로티오에이트 뉴클레오사이드간 연결이다.

[0224] 특정 구현예에서, 적어도 하나의 뉴클레오사이드간 연결은 포스포디에스테르 뉴클레오사이드간 연결이다.

[0225] 특정 구현예에서, 적어도 하나의 뉴클레오사이드간 연결은 포스포로티오에이트 연결이고, 적어도 하나의 뉴클레오사이드간 연결은 포스포디에스테르 연결이다.

[0226] 특정 구현예에서, 적어도 하나의 뉴클레오사이드는 변형된 핵염기를 포함한다.

[0227] 특정 구현예에서, 변형된 핵염기는 5-메틸시토신이다.

[0228] 특정 구현예에서, 상기 변형된 올리고뉴클레오타이드의 적어도 하나의 뉴클레오사이드는 변형된 당을 포함한다.

[0229] 특정 구현예에서, 상기 적어도 하나의 변형된 당은 이환식 당이다.

[0230] 특정 구현예에서, 상기 이환식 당은 당 4'-CH2-N(R)-O-2' 가교의 2' 및 4' 위치 사이에서 화학적 연결을 포함하며, 이때 R은 독립적으로, H, C1-C12 알킬, 또는 보호기이다.

[0231] 특정 구현예에서, 상기 이환식 당은 4'-CH2-N(R)-O-2' 가교를 포함하며, 이때 R은 독립적으로, H, C1-C12 알킬, 또는 보호기이다.

[0232] 특정 구현예에서, 상기 적어도 하나의 변형된 당은 2'-O-메톡시에틸 기를 포함한다.

[0233] 특정 구현예에서, 상기 변형된 당 모이어티는 $2'\text{-}O(CH_2)_2\text{-}OCH_3$ 기를 포함한다.

[0234] 특정 구현예에서, 상기 변형된 올리고뉴클레오타이드는:

[0235] 10 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0236] 5개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0237] 5개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절을 포함하고;

[0238] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함한다.

[0239] 특정 구현예에서, 상기 변형된 올리고뉴클레오타이드는:

[0240] 9 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0241] 5개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0242] 5개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절을 포함하고;

[0243] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함한다.

[0244] 특정 구현예에서, 상기 변형된 올리고뉴클레오타이드는:

[0245] 7 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0246] 5개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0247] 6개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절을 포함하고;

[0248] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함한다.

[0249] 특정 구현예에서, 상기 변형된 올리고뉴클레오타이드는:

[0250] 8 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0251] 5개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0252] 5개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절을 포함하고;

[0253] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함한다.

[0254] 특정 구현예에서, 상기 변형된 올리고뉴클레오타이드는:

[0255] 8 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0256] 4개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0257] 6개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절을 포함하고;

[0258] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함한다.

[0259] 특정 구현예에서, 상기 변형된 올리고뉴클레오타이드는:

[0260] 8 개의 연결된 데옥시뉴클레오사이드로 이루어진 갭 분절;

[0261] 6개의 연결된 뉴클레오사이드로 이루어진 5' 윙 분절; 및

[0262] 4개의 연결된 뉴클레오사이드로 이루어진 3' 윙 분절;

[0263] 여기서 상기 갭 분절은 상기 5' 윙 분절과 상기 3' 윙 분절 사이에 위치하고, 각 윙 분절의 각각의 뉴클레오사이드는 변형된 당을 포함한다.

[0264] 특정 구현예에서, 변형된 올리고뉴클레오타이드는 20 개의 연결된 뉴클레오사이드로 이루어진다.

[0265] 특정 구현예에서, 변형된 올리고뉴클레오타이드는 19 개의 연결된 뉴클레오사이드로 이루어진다.

[0266] 특정 구현예에서, 변형된 올리고뉴클레오타이드는 18 개의 연결된 뉴클레오사이드로 이루어진다.

[0267] 특정 구현예는 본원에 개시된 임의의 화합물 또는 이의 염, 및 약제학적으로 허용가능한 담체 또는 희석제 중 적어도 하나를 포함하는 조성물을 제공한다.

[0268] 특정 구현예는 본원에 기재된 바와 같은 임의의 화합물 또는 조성물을 동물에게 투여하는 단계를 포함하는 방법을 제공한다.

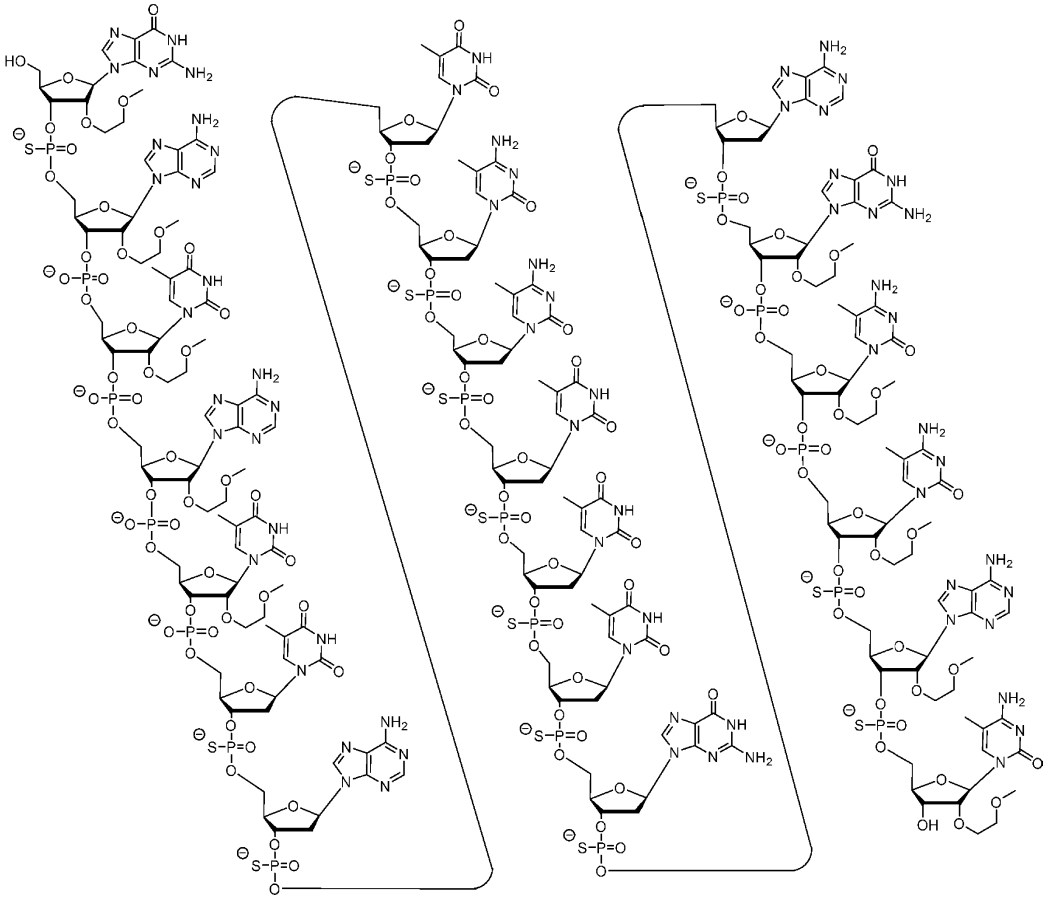
[0269] 특정 구현예에서, 상기 동물은 인간이다.

[0270] 특정 구현예에서, 상기 화합물의 투여는 타우 연관된 질환, 장애 또는 병태를 예방, 치료, 개선 또는 이의 진행을 지연시키는, 방법.

[0271] 특정 구현예에서, 상기 질환, 장애, 또는 병태는 타우병증, 알츠하이머 질환, 전두측두엽 치매 (FTD), FTDP-17, 진행성 핵상안근 마비 (PSP), 만성 외상성 뇌증 (CTE), 뇌피질 기저 신경절 퇴행증 (CBD), 간질, 또는 드라벳 증후군이다.

[0272] 특정 구현예는 신경퇴행성 장애를 치료하기 위한 약제의 제조를 위한, 본원에 개시된 화합물 또는 조성물의 용도를 제공한다.

[0273] 특정 구현예는 하기 화학식 (Ia)에 따른 화합물 또는 이들의 약학적으로 허용가능한 염을 제공한다:

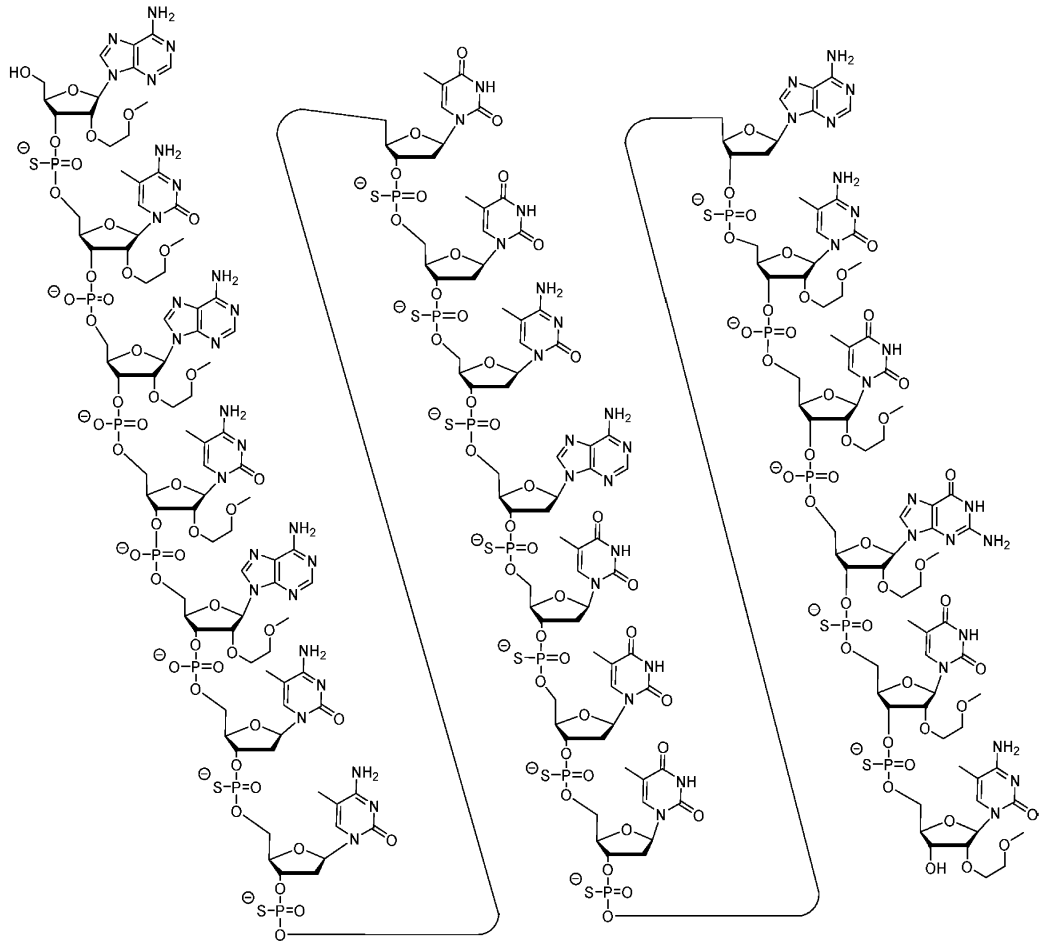


(Ia)

[0274]

[0275] 특정 구현예에서, 상기 화학식 (Ia)를 갖는 화합물을 포함하는 약제학적 조성물이 제공된다.

[0276] 특정 구현예는 하기 화학식 (IIa)에 따른 화합물 또는 이들의 약학적으로 허용가능한 염을 제공한다:

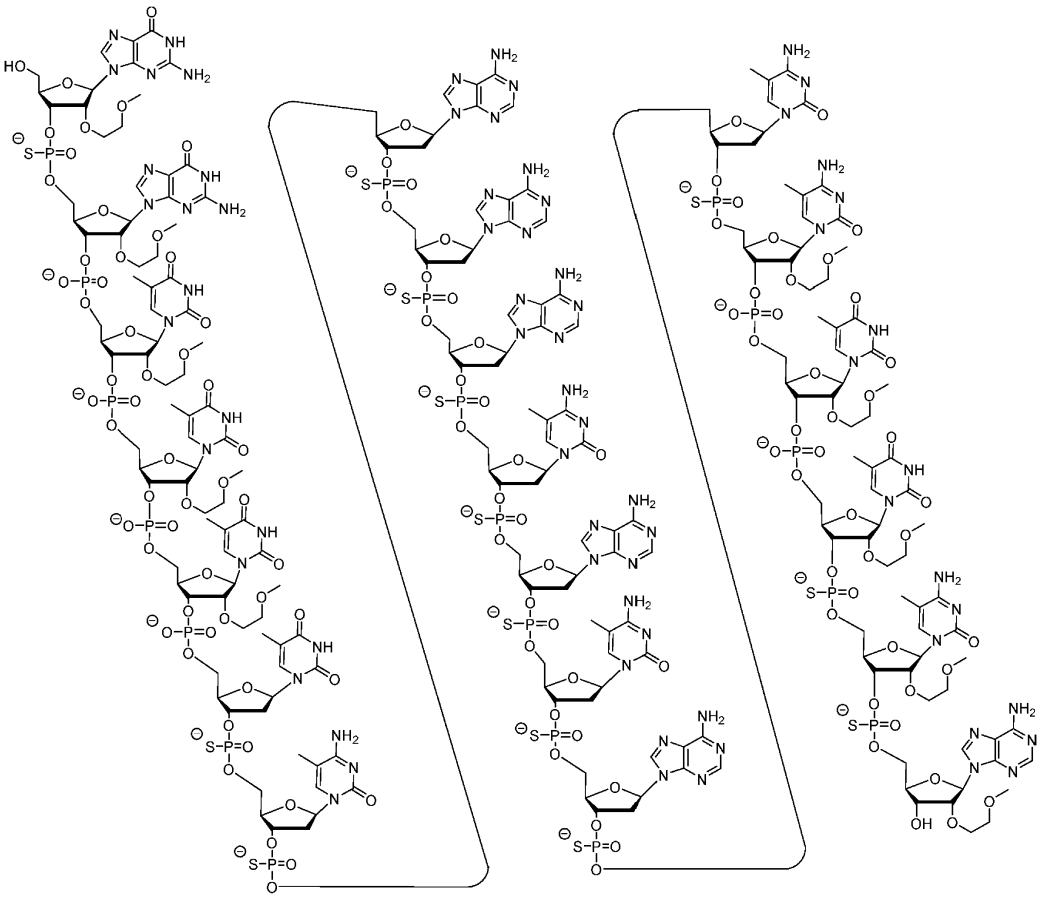


(IIa)

[0277]

[0278] 특정 구현예에서, 상기 화학식 (IIa)를 갖는 화합물을 포함하는 약제학적 조성물이 제공된다.

[0279] 특정 구현예는 하기 화학식 (IIIa)에 따른 화합물 또는 이들의 약학적으로 허용가능한 염을 제공한다.

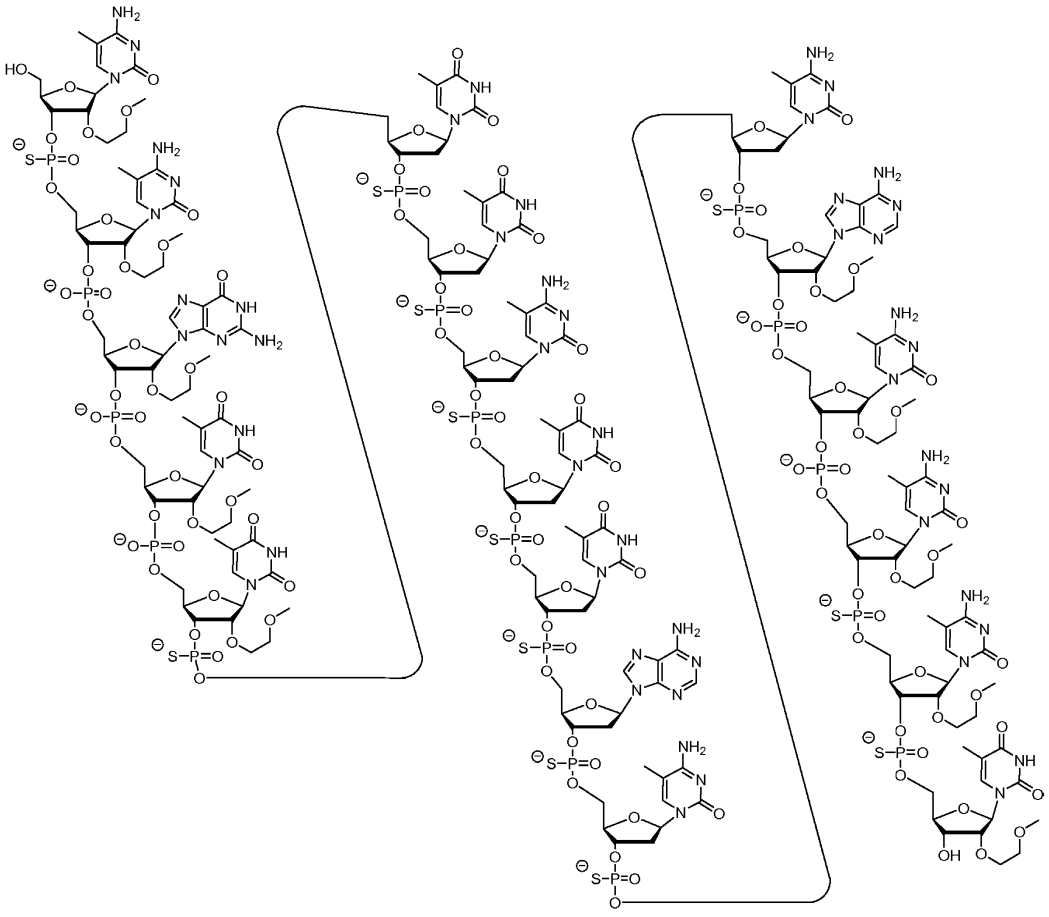


(IIIa)

[0280]

[0281] 특정 구현예에서, 상기 화학식 (IIIa)를 갖는 화합물을 포함하는 약제학적 조성물이 제공된다.

[0282] 특정 구현예는 하기 화학식 (IVa)에 따른 화합물 또는 이들의 약학적으로 허용가능한 염을 제공한다.

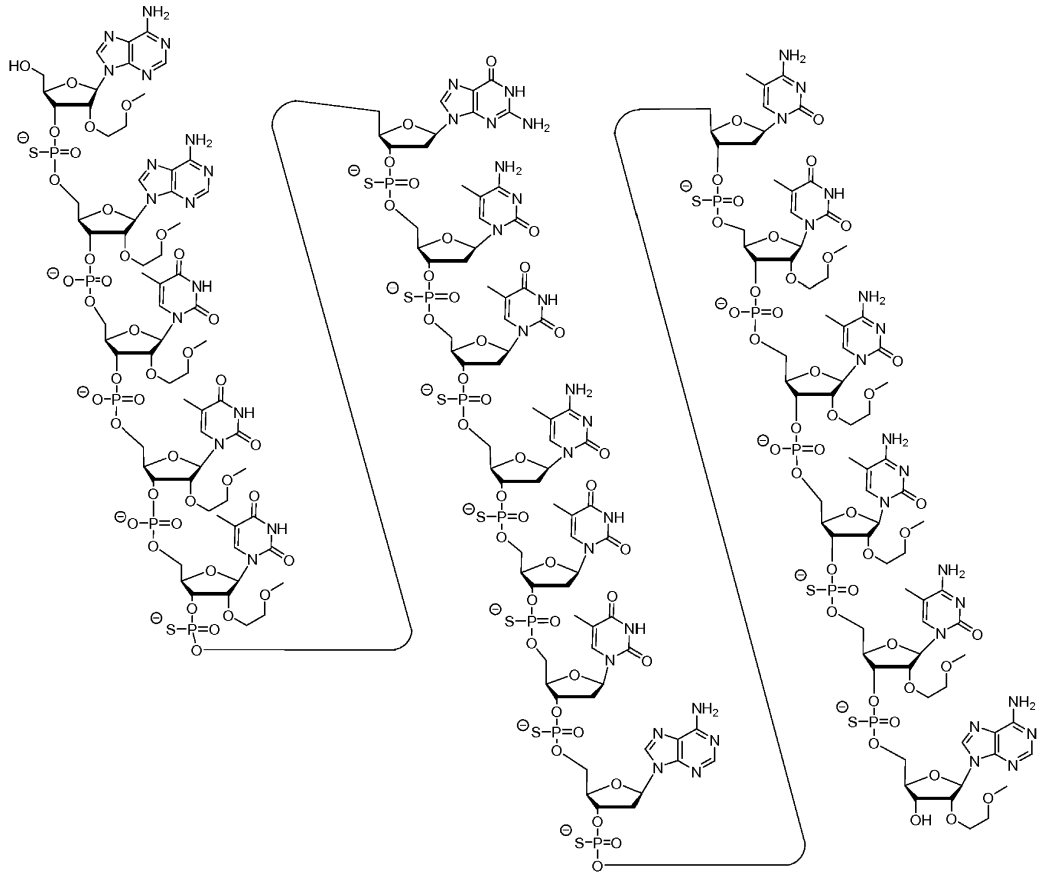


(IVa)

[0283]

[0284] 특정 구현예에서, 상기 화학식 (IVa)를 갖는 화합물을 포함하는 약제학적 조성물이 제공된다.

[0285] 특정 구현예는 하기 화학식 (Va)에 따른 화합물 또는 이들의 약학적으로 허용가능한 염을 제공한다:



(Va)

[0286]

[0287] 특정 구현예에서, 상기 화학식 (Va)를 갖는 화합물을 포함하는 약제학적 조성물이 제공된다.

[0288] *안티센스 화합물*

[0289] 올리고머 화합물은, 비제한적으로, 올리고뉴클레오타이드, 올리고뉴클레오사이드, 올리고뉴클레오타이드 유사체, 올리고뉴클레오타이드 모방체, 안티센스 화합물, 안티센스 올리고뉴클레오타이드, 및 siRNA를 포함한다. 올리고머 화합물은 표적 핵산에 대한 "안티센스"일 수 있고, 이것은 수소 결합을 통해 표적 핵산에 대한 혼성화를 경험할 수 있다는 것을 의미한다.

[0290] 특정 구현예에서, 안티센스 화합물은, 5'에서 3' 방향으로 쓰여질 때, 그것이 표적화된 표적 핵산의 표적 분절의 역보체를 포함하는 핵염기 서열을 갖는다. 그와 같은 특정 구현예에서, 안티센스 올리고뉴클레오타이드는, 5'에서 3' 방향으로 쓰여질 때, 그것이 표적화된 표적 핵산의 표적 분절의 역보체를 포함하는 핵염기 서열을 갖는다.

[0291] 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 12 내지 30 개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 12 내지 25 개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 12 내지 22 개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 14 내지 20 개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 15 내지 25 개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 18 내지 22 개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 19 내지 21 개의 하부단위이다. 특정 구현예에서, 안티센스 화합물은 길이가 8 내지 80개, 12 내지 50개, 13 내지 30개, 13 내지 50개, 14 내지 30개, 14 내지 50개, 15 내지 30개, 15 내지 50개, 16 내지 30개, 16 내지 50개, 17 내지 30개, 17 내지 50개, 18 내지 30개, 18 내지 50개, 19 내지 30개, 19 내지 50개, 또는 20 내지 30개 연결된 하부단위이다.

[0292] 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 12개의 하부단위이다. 특정 구현예에서,

타우 핵산에 표적화된 안티센스 화합물은 그 길이가 13개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 14개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 15개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 16개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 17개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 18개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 19개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 20개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 21개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 22개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 23개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 24개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 25개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 26개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 27개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 28개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 29개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 30개의 하부단위이다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 그 길이가 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 또는 80개 연결된 하부단위 또는 상기 값 중 임의의 2개에 의하여 정의된 범위 내이다. 특정 구현예에서, 안티센스 화합물은 안티센스 올리고뉴클레오타이드이고, 상기 연결된 하부단위는 뉴클레오사이드이다.

[0293] 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 단축되거나 절단될 수 있다. 예를 들어, 단일 하부단위는 5' 말단 (5' 절단), 또는 대안적으로 3' 말단 (3' 절단)로부터 결실될 수 있다. 타우 핵산에 표적화된 단축된 또는 절단된 안티센스 화합물은 상기 안티센스 화합물의 5' 말단으로부터 결실된 2 개의 하부단위를 가질 수 있고, 또는 대안적으로 이의 3' 말단으로부터 결실된 2개의 하부단위를 가질 수 있다. 대안적으로, 결실된 뉴클레오사이드는 안티센스 화합물을 통하여, 예를 들면, 5' 말단으로부터 결실된 하나의 뉴클레오사이드 및 3' 말단로부터 결실된 하나의 뉴클레오사이드을 갖는 안티센스 화합물에서, 분산될 수 있다.

[0294] 단일 부가적 하부단위가 늘어난 안티센스 화합물에 존재할 때, 부가적 하부단위는 안티센스 화합물의 5' 또는 3' 말단에서 위치할 수 있다. 2 개 이상의 부가적 하부단위가 존재할 때, 부가된 뉴클레오사이드는, 예를 들면, 안티센스 화합물의 5' 말단 (5' 부가), 또는 대안적으로 3' 말단 (3' 부가)에 부가된 2개의 하부단위를 갖는 안티센스 화합물에서 서로 인접할 수 있다. 대안적으로, 부가된 하부단위는 안티센스 화합물을 통하여, 예를 들면, 5' 말단에 부가된 하나의 하부단위 및 3' 말단에 부가된 하나의 하부단위를 갖는 안티센스 화합물에서 분산될 수 있다.

[0295] 안티센스 화합물, 예컨대 안티센스 올리고뉴클레오타이드의 길이를 증가 또는 감소시키고/거나 활성을 제거하지 않으면서 미스매치 염기를 도입하는 것이 가능하다. 예를 들어, 다음을 참고: Woolf et al. (Proc. Natl. Acad. Sci. USA 89:7305-7309, 1992), 일련의 길이가 13-25개의 핵염기인 안티센스 올리고뉴클레오타이드가 난모세포 주사 모델에서 표적 RNA의 절단을 유도하는 그들의 능력에 대해 시험되었다. 안티센스 올리고뉴클레오타이드의 말단 근처의 8 또는 11 미스매치 염기를 가지며 그 길이가 25개 핵염기인 안티센스 올리고뉴클레오타이드는 미스매치를 함유하지 않는 안티센스 올리고뉴클레오타이드보다 더 적을지라도 표적 mRNA의 직접적인 특이적 절단이 가능했다. 마찬가지로, 표적 특이적 절단은 1 또는 3 미스매치를 갖는 것을 포함하는 13개 핵염기 안티센스 올리고뉴클레오타이드를 사용하여 달성되었다.

[0296] Gautschi et al (J.Natl. Cancer Inst. 93:463-471, March 2001)는 bcl-2 및 bcl-xL 둘 다의 *시험관내* 및 체내 발현을 감소시키기 위해 bcl-2 mRNA에 대해100% 상보성을 가지며 bcl-xL mRNA에 대한 3 개의 미스매치를 갖는 올리고뉴클레오타이드의 능력을 실증했다. 더욱이, 이러한 올리고뉴클레오타이드는 체내 강력한 항-종양 활성을 실증했다.

[0297] Maher 및 Dolnick (Nuc. Acid. Res. 16:3341-3358,1988) 는 토끼 망상적혈구 검정에서 인간 DHFR의 번역을 저지하는 그것의 능력에 대한, 각각의 탠덤 안티센스 올리고뉴클레오타이드의 2개 또는 3개 서열로 구성된, 일련의 탠덤 14 핵염기 안티센스 올리고뉴클레오타이드 및, 28 및 42 핵염기 안티센스 올리고뉴클레오타이드를 시험했다. 각각의 3 개의 14 핵염기 안티센스 올리고뉴클레오타이드 단독은 28 또는 42 핵염기 안티센스 올리고뉴클

레오타이드보다 더 보통의 수준일지라로 번역을 억제할 수 있었다.

[0298] *안티센스 화합물 모티프*

[0299] 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 안티센스 화합물 특성 예컨대 증대된 억제 활성, 증가된 표적 핵산에 대한 결합 친화도, 또는 체내 뉴클레아제에 의한 분해에 대한 내성을 부여하기 위해 패턴, 또는 모티프에서 배열된 화학적으로 변형된 하부단위를 갖는다.

[0300] 키메라 안티센스 화합물은 전형적으로 뉴클레아제 분해에 대한 증가된 내성, 증가된 세포 흡수, 표적 핵산의 증가된 결합 친화도, 및/또는 증가된 억제 활성을 부여하기위해 변형된 적어도 하나의 영역을 함유한다. 키메라 안티센스 화합물의 제 2 영역은 RNA:DNA 듀플렉스의 RNA 가닥을 절단하는 세포 엔도뉴클레아제 RNase H의 기질로서 임의로 쓰일 수 있다.

[0301] 갭머 모티프를 갖는 안티센스 화합물은 키메라 안티센스 화합물로 간주된다. 갭머에서 RNaseH 절단을 지지하는 복수의 뉴클레오타이드를 갖는 내부 영역은 내부 영역의 뉴클레오사이드로부터 화학적으로 뚜렷한 복수의 뉴클레오타이드를 갖는 외부 영역 사이에 배치된다. 갭머 모티프를 갖는 안티센스 올리고뉴클레오타이드의 경우에, 갭 분절은 일반적으로 엔도뉴클레아제 절단의 기질로서 쓰이지만, 윙 분절은 변형된 뉴클레오사이드를 포함한다. 특정 구현예에서, 갭머의 영역은 각각의 뚜렷한 영역을 포함하는 당 모이어티의 유형에 의해 분화된다. 갭머의 영역을 분화시키기 위해 사용된 당 모이어티의 유형은 일부 구현예에서 하기를 포함할 수 있다: β-D-리보뉴클레오사이드, β-D-데옥시리보뉴클레오사이드, 2'-변형된 뉴클레오사이드 (그와 같은 2'-변형된 뉴클레오사이드는 기타 중에서 2'-MOE 및 2'-O-CH_3를 포함할 수 있다), 및 이환식 당 변형된 뉴클레오사이드 (그와 같은 이환식 당 변형된 뉴클레오사이드는 4'-(CH_2)n-O-2' 가교(여기서 n=1 또는 n=2 및 4'-CH_2-O-CH_2-2')을 갖는 것을 포함할 수 있다). 특정 구현예에서, 윙은, 예를 들면 2'-MOE 및 제한된 에틸을 포함하는 몇 개의 변형된 당 모이어티를 포함할 수 있다. 특정 구현예에서, 윙은 몇 개의 변형된 및 비변형된 당 모이어티를 포함할 수 있다. 특정 구현예에서, 윙은 2'-MOE 뉴클레오사이드, 및 2'-데옥시뉴클레오사이드의 다양한 조합을 포함할 수 있다.

[0302] 각각의 뚜렷한 영역은 균일한 당 모이어티, 변이체, 또는 교차 당 모이어티를 포함할 수 있다. 윙-갭-윙 모티프는 "X-Y-Z"로서 빈번히 기재되고, 여기서 "X"는 5'-윙의 길이를 나타내고, "Y"는 갭의 길이를 나타내고, 그리고 "Z"는 3'-윙의 길이를 나타낸다. "X" 및 "Z"는 균일한, 변이체, 또는 교대 당 모이어티를 포함할 수 있다. 특정 구현예에서, "X" 및 "Y"는 하나 이상의 2'-데옥시뉴클레오사이드를 포함할 수 있다. "Y"는 2'-데옥시뉴클레오사이드를 포함할 수 있다. 본원에서 사용된 바와 같이, "X-Y-Z"로서 기재된 갭머는, 갭이 각각의 5'-윙 및 3' 윙에 바로 인접하여 배치되는 정도의 배치를 갖는다. 따라서, 개재(intervening) 뉴클레오타이드는 5'-윙 및 갭, 또는 갭 및 3'-윙 사이에 존재하지 않는다. 본원에 기재된 안티센스 화합물의 임의의 것은 갭머 모티프를 가질 수 있다. 특정 구현예에서, "X" 및 "Z"는 동일하고, 다른 구현예에서는 상이하다.

[0303] 특정 구현예에서, 본원에 제공된 갭머는 예를 들어 5-10-5의 모티프를 갖는 20 량체(20 - mers)를 포함한다.

[0304] 특정 구현예에서, 본원에 제공된 갭머는 예를 들어 5-9-5의 모티프를 갖는 19량체(19 - mers)를 포함한다.

[0305] 특정 구현예에서, 본원에 제공된 갭머는 예를 들어 5-8-5의 모티프를 갖는 18량체(18-mers)를 포함한다.

[0306] 특정 구현예에서, 본원에 제공된 갭머는 예를 들어 4-8-6의 모티프를 갖는 18량체(18-mers)를 포함한다.

[0307] 특정 구현예에서, 본원에 제공된 갭머는 예를 들어 6-8-4의 모티프를 갖는 18량체(18-mers)를 포함한다.

[0308] 특정 구현예에서, 본원에 제공된 갭머는 예를 들어 5-7-6의 모티프를 갖는 18량체(18-mers)를 포함한다.

[0309] *표적 핵산, 표적 영역 및 뉴클레오타이드 서열*

[0310] 타우를 암호화하는 뉴클레오타이드 서열은 비제한적으로 하기를 포함한다: 뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자 은행 수탁 번호 NT_010783.15 (본원에서 서열 번호: 1과 같이 포함) 유전자 은행 수탁 번호 NM_001123066.3 (본원에서 서열 번호: 2와 같이 포함) 엑손 3, 4, 6, 8, 10, 및 12를 건너뛰는 유전자 은행 수탁 번호 NM_016841.4, 변이체 mRNA 서열 (본원에서 서열 번호: 3과 같이 포함) 뉴클레오타이드 2624000-2761000로부터 절단된 유전자 은행 수탁 번호 NT_010783.14 (본원에서 서열 번호: 4와 같이 포함) 유전자 은행 수탁 번호 DR002467.1 (본원에서 서열 번호: 5와 같이 포함) 유전자 은행 수탁 번호 NM_001203251.1 (본원에서 서열 번호: 6과 같이 포함) 및 유전자 은행 수탁 번호 NM_016835.4 (본원에서 서열 번호: 7과 같이 포함).

[0311] 본원에 함유된 실시예에서 각각의 서열 번호로 제시된 서열은 당 모이어티, 뉴클레오사이드간 연결, 또는 핵염기에 대한 임의의 변형에 독립적인 것으로 이해된다. 그것으로서, 서열번호에 의해 규정된 안티센스 화합물은 당 모이어티, 뉴클레오사이드간 연결, 또는 핵염기에 대한 하나 이상의 변형을 독립적으로 포함할 수 있다. ISIS 번호 (Isis No)에 의해 기재된 안티센스 화합물은 핵염기 서열 및 모티프의 조합을 나타낸다.

[0312] 특정 구현예에서, 표적 영역은 표적 핵산의 구조적으로 규정된 영역이다. 예를 들면, 표적 영역은 3' UTR, 5' UTR, 엑손, 인트론, 엑손/인트론 접합, 암호화 영역, 번역 개시 영역, 번역 종료 영역, 또는 다른 규정된 핵산 영역을 포괄할 수 있다. 타우에 대한 구조적으로 규정된 영역은 서열 데이타베이스 예컨대 NCBI로부터의 승인 번호에 의해 수득될 수 있고 그와 같은 정보는 본원에 참고로 포함되어 있다. 특정 구현예에서, 표적 영역은 표적 영역내의 하나의 표적 분절의 5' 표적 부위로부터 동일한 표적 영역내의 다른 표적 분절의 3' 표적 부위까지의 서열을 포괄할 수 있다.

[0313] 표적화는 안티센스 화합물이 혼성화하는 적어도 하나의 표적 분절의 결정을 포함하고, 이로써 원하는 효과가 발생한다. 특정 구현예에서, 원하는 효과는 mRNA 표적 핵산 수준의 감소이다. 특정 구현예에서, 원하는 효과는 표적 핵산 또는 표적 핵산과 연관된 표현형 변화에 의해 암호화된 단백질의 수준의 감소이다.

[0314] 표적 영역은 하나 이상의 표적 분절을 함유할 수 있다. 표적 영역 내의 다중 표적 분절은 중복일 수 있다. 대안적으로, 이들은 비-중복일 수 있다. 특정 구현예에서, 표적 영역 내의 표적 분절은 약 300개 이하의 뉴클레오타이드에 의해 분리된다. 특정 구현예에서, 표적 영역 내의 표적 분절은 표적 핵산 상의 약 250, 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, 또는 10 또는 그 이하의 뉴클레오타이드이고, 이전의 값의 임의의 2개에 의해 규정된 범위인 수많은 뉴클레오타이드에 의해 분리된다. 특정 구현예에서, 표적 영역 내의 표적 분절은 표적 핵산 상의 약 5개 이하의 뉴클레오타이드에 의해 분리된다. 특정 구현예에서, 표적 분절은 인접한다. 본원에서 열거된 5' 표적 부위 또는 3' 표적 부위의 임의의 것인 개시 핵산을 갖는 범위에 의해 규정된 표적 영역이 고려된다.

[0315] 적당한 표적 분절은 5' UTR, 암호화 영역, 3' UTR, 인트론, 엑손, 또는 엑손/인트론 접합 내에서 발견될 수 있다. 시작 코돈 또는 정지 코돈을 함유하는 표적 분절은 또한 적당한 표적 분절이다. 적당한 표적 분절은 특정의 구조적으로 규정된 영역 예컨대 시작 코돈 또는 정지 코돈을 명시적으로 제외할 수 있다.

[0316] 적당한 표적 분절의 결정은 게놈 도처의 다른 서열에 대한 표적 핵산의 서열의 비교를 포함할 수 있다. 예를 들면, BLAST 알고리즘은 상이한 핵산 중에서 유사성의 영역을 확인하기 위해 사용될 수 있다. 이러한 비교는 선택된 표적 핵산 이외의 서열 (즉, 비-표적 또는 오프-타겟(off-target) 서열)과 비특이적 방식으로 혼성화할 수 있는 안티센스 화합물의 서열의 선택을 방지할 수 있다

[0317] 활성 표적 영역 내의 안티센스 화합물의 활성의 변화 (예를 들면, 표적 핵산 수준의 퍼센트 감소에 의해 규정된 바와 같이) 가 있을 수 있다. 특정 구현예에서, 타우 mRNA 수준의 감소는 타우 발현의 억제를 가리킨다. 타우 단백질의 수준 감소는 또한 표적 mRNA 발현의 억제를 가리킨다. 과인산화된 타우에 대한 세포 염색 양성 백분율의 감소는 타우 발현의 억제를 가리킨다. 더욱이, 표현형 변화는 타우 발현의 억제를 가리킨다. 신경학적 기능에서의 개선은 타우 발현의 억제를 가리킨다. 기억 및 운동 기능에서의 개선은 타우 발현의 억제를 가리킨다. 신경섬유 포함물의 감소는 타우 발현의 억제를 가리킨다.

[0318] *혼성화*

[0319] 일부 구현예에서, 혼성화는 본원에 개시된 안티센스 화합물 및 타우 핵산 사이에서 발생한다. 혼성화의 가장 일반적인 기전은 핵산 분자의 상보적 핵염기 사이의 수소 결합 (예를 들면, 왓슨-크릭(Watson-Crick), 후그스텐(Hoogsteen) 또는 역전된 후그스텐(Hoogsteen) 수소 결합)을 수반한다.

[0320] 혼성화는 가변 조건 하에서 발생할 수 있다. 엄격한 조건은 서열-의존적이고 혼성화될 핵산 분자의 성질 및 조성에 의해 결정된다.

[0321] 서열이 표적 핵산과 특이적으로 혼성화할 수 있는 지를 측정하는 방법은 당해기술에 공지되어 있다. 특정 구현예에서, 본원에서 제공된 안티센스 화합물은 타우 핵산과 특이적으로 혼성화할 수 있다.

[0322] *상보성*

[0323] 안티센스 화합물 및 표적 핵산은, 충분한 수의 안티센스 화합물의 핵염기가 표적 핵산의 상응하는 핵염기와 수소연결하여 이로써 원하는 효과가 발생할 수 있을 때 (예를 들면, 표적 핵산, 예컨대 타우 핵산의 안티센스 억

제), 서로 상보적이다.

[0324] 안티센스 화합물 및 타우 핵산 사이에서의 비-상보적 핵염기는, 상기 안티센스 화합물이 표적 핵산에 특이적으로 혼성화 가능하도록 남아있는 경우 용인될 수 있다. 더욱이, 안티센스 화합물은 타우 핵산의 하나 이상의 분절 상에서 혼성화될 수 있고 이로써 개재 또는 인접한 분절은 혼성화 사건 (예를 들면, 루프 구조, 미스매치 또는 헤어핀 구조)에 관여하지 않는다.

[0325] 특정 구현예에서, 본원에서 제공된 안티센스 화합물, 또는 명시된 이의 부분은 타우 핵산, 표적 영역, 표적 분절, 또는 명시된 이의 부분에 대해 적어도, 70%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 또는 100% 상보적이다. 표적 핵산을 갖는 안티센스 화합물의 퍼센트 상보성은 보통의 방법을 사용하여 측정될 수 있다.

[0326] 예를 들면, 20개 안티센스 화합물의 핵염기 중 18개는 표적 영역에 대해 상보적이고 따라서 특이적으로 혼성화하는, 안티센스 화합물은 90 퍼센트 상보성을 나타낼 것이다. 이러한 예시에서, 잔류 비-상보적 핵염기는 무리를 이루거나 상보적 핵염기와 함께 사이에 배치될 수 있고, 서로 또는 상보적 핵염기에 인접할 필요가 없다. 그것으로서, 표적 핵산에 완전한 상보성을 갖는 2 개의 영역에 의해 플랭킹된 4 개의 비-상보적 핵염기를 갖는 길이가 18개의 핵염기인 안티센스 화합물은 표적 핵산에 77.8% 전체 상보성을 가질 것이며, 따라서 본 발명의 범위 내에 있을 것이다. 표적 핵산의 영역을 갖는 안티센스 화합물의 퍼센트 상보성은 당해기술에서 공지된 BLAST 프로그램 (기본적 국소 정렬 연구 도구) 및 PowerBLAST 프로그램을 사용하여 보통 측정될 수 있다 (Altschul 등, J. Mol. Biol., Biol., 1990, 215, 403 410; Zhang 및 Madden, Genome Res., 1997, 7, 649 656). 퍼센트 상동성, 서열 동일성 또는 상보성은 Smith 및 Waterman (Adv. Appl. Math., 1981, 2, 482 489)의 알고리즘을 사용하는 디폴트 세팅을 사용하여, 예를 들면, Gap 프로그램 (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison Wis.)에 의해 측정될 수 있다.

[0327] 특정 구현예에서, 본원에서 제공된 안티센스 화합물, 또는 이의 명시된 부분은 표적 핵산, 또는 명시된 이의 부분에 대해 완전 상보적 (즉, 100% 상보적)이다. 예를 들면, 안티센스 화합물은 타우 핵산, 또는 이의 표적 영역, 또는 표적 분절 또는 표적 서열에 대해 완전히 상보적일 수 있다. 본원에서 사용된 바와 같이, "완전히 상보적"은, 안티센스 화합물의 각각의 핵염기가 표적 핵산의 상응하는 핵염기와 정확한 염기 짝짓기를 할수 있다는 것을 의미한다. 예를 들면, 20 핵염기 안티센스 화합물은, 안티센스 화합물에 대해 완전히 상보적인 표적 핵산의 상응하는 20 핵염기 부분이 있는 한, 400 핵염기 길이인 표적 서열에 대해 완전히 상보적이다. 완전 상보성은 제 1 및/또는 제 2 핵산의 명시된 부분을 참조하여 또한 사용될 수 있다. 예를 들면, 30 핵염기 안티센스 화합물의 20 핵염기 부분은 400개 핵염기 길이인 표적 서열에 대해 "완전히 상보적"일 수 있다. 30 핵염기 올리고뉴클레오타이드의 20 핵염기 부분은, 표적 서열이 상응하는 20 핵염기 부분을 갖고, 이때 각각의 핵염기가 안티센스 화합물의 20 핵염기 부분에 대해 상보적이라면, 표적 서열에 대해 완전히 상보적이다. 동시에, 전체 30 핵염기 안티센스 화합물은, 안티센스 화합물의 잔류 10 핵염기가 표적 서열에 대해 또한 상보적인지에 따라 표적 서열에 대해 또한 완전히 상보적이거나 그렇지 않을 수 있다.

[0328] 비-상보적 핵염기의 위치는 안티센스 화합물의 5' 말단 또는 3' 말단에 있을 수 있다. 대안적으로, 비-상보적 핵염기 또는 핵염기들은 안티센스 화합물의 내부 위치에 있을 수 있다. 두개 이상의 비-상보적 핵염기가 존재할 때, 이들은 인접하거나(즉, 연결되거나), 또는 비-인접할 수 있다. 일 구현예에서, 비-상보적 핵염기는 갭머 안티센스 올리고뉴클레오타이드의 윙 분절에 위치한다.

[0329] 특정 구현예에서, 길이가 11, 12, 13, 14, 15, 16, 17, 18, 19, 또는 20개이거나, 또는 최대로 상기 길이인 안티센스 화합물은 표적 핵산, 예컨대 타우 핵산, 또는 명시된 이의 부분에 대해 4 이하, 3 이하, 2 이하, 또는 1 이하의 비-상보적 핵염기(들)을 포함한다.

[0330] 특정 구현예에서, 길이가 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 또는 30개이거나, 또는 최대로 상기 길이인 안티센스 화합물은 표적 핵산, 예컨대 타우 핵산, 또는 명시된 이의 부분에 대해 6 이하, 5 이하, 4 이하, 3 이하, 2 이하, 또는 1 이하의 비-상보적 핵염기(들)을 포함한다.

[0331] 본원에서 제공된 안티센스 화합물은 또한 표적 핵산의 부분에 대해 상보적인 것을 포함한다. 본원에서 사용된 바와 같이, "부분"은 표적 핵산의 영역 또는 분절 내의 규정된 수의 인접한 (즉, 연결된) 핵염기를 의미한다. "부분"은 또한 규정된 수의 안티센스 화합물의 인접한 핵염기를 의미할 수 있다. 특정 구현예에서, 안티센스 화합물은 표적 분절의 적어도 8 핵염기 부분에 대해 상보적이다. 특정 구현예에서, 안티센스 화합물은 표적 분절의 적어도 9 핵염기 부분에 대해 상보적이다. 특정 구현예에서, 안티센스 화합물은 표적 분절의 적어도 10 핵

염기 부분에 대해 상보적이다. 특정 구현예에서, 안티센스 화합물은 표적 분절의 적어도 11 핵염기 부분에 대해 상보적이다. 특정 구현예에서, 안티센스 화합물은 표적 분절의 적어도 12 핵염기 부분에 대해 상보적이다. 특정 구현예에서, 안티센스 화합물은 표적 분절의 적어도 13 핵염기 부분에 대해 상보적이다. 특정 구현예에서, 안티센스 화합물은 표적 분절의 적어도 14 핵염기 부분에 대해 상보적이다. 특정 구현예에서, 안티센스 화합물은 표적 분절의 적어도 15 핵염기 부분에 대해 상보적이다. 표적 분절의 적어도 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 또는 그 초과, 또는 이들 값의 임의의 2 개에 의해 규정된 범위의 핵염기 부분에 대해 상보적인 안티센스 화합물이 또한 고려된다.

[0332] *동일성*

[0333] 본원에서 제공된 안티센스 화합물은 특정한 뉴클레오타이드 서열, 서열번호, 또는 특정 ISIS 번호로 나타내는 화합물, 또는 이의 부분에 대한 규정된 퍼센트 동일성을 또한 가질 수 있다. 본원에서 사용된 바와 같이, 안티센스 화합물은, 동일한 핵염기 짝짓기 능력을 갖는다면, 본원에 개시된 서열과 동일하다. 예를 들면, 우라실 및 티미딘 둘 다 아데닌과 쌍을 이루므로, 개시된 DNA 서열에서 티미딘 대신에 우라실을 함유하는 RNA가 DNA 서열과 동일한 것으로 간주된다. 본원에 기재된 안티센스 화합물 뿐만 아니라 본원에서 제공된 안티센스 화합물에 대해 비-동일한 염기를 갖는 화합물의 단축된 및 늘어난 버전이 또한 고려된다. 비-동일한 염기는 안티센스 화합물에 도처에서 분산되거나 서로 인접할 수 있다. 안티센스 화합물의 퍼센트 동일성은 비교되는 서열에 대해 동일한 염기 짝짓기를 갖는 염기의 수에 따라 산출된다.

[0334] 특정 구현예에서, 안티센스 화합물, 또는 이의 일부는, 본원에 개시된 안티센스 화합물 또는 서열번호, 또는 이의 부분의 하나 이상과 적어도 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% 또는 100% 동일하다.

[0335] 특정 구현예에서, 안티센스 화합물의 부분은 표적 핵산의 동등한 길이 부분과 비교된다. 특정 구현예에서, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 또는 25 핵염기 부분은 표적 핵산 부분과 동등한 길이 부분과 비교된다.

[0336] 특정 구현예에서, 안티센스 올리고뉴클레오타이드의 부분은 표적 핵산 부분과 동등한 길이 부분과 비교된다. 특정 구현예에서, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 또는 25 핵염기 부분은 표적 핵산 부분과 동등한 길이 부분과 비교된다.

[0337] *변형*

[0338] 뉴클레오사이드는 염기-당 조합이다. 뉴클레오사이드의 핵염기 (또한 염기로서 공지됨) 부분은 보통 헤테로환 염기 모이어티이다. 뉴클레오타이드는 뉴클레오사이드의 당 부분에 공유 연결된 인산기를 추가로 포함하는 뉴클레오사이드이다. 펜토푸라노실 당을 포함하는 뉴클레오사이드에 대해, 인산기는 당의 2', 3' 또는 5' 하이드록실 모이어티에 연결될 수 있다. 올리고뉴클레오타이드는 서로에 대한 인접한 뉴클레오사이드의 공유연결을 통해 형성되어, 선형 중합체 올리고뉴클레오타이드를 형성한다. 올리고뉴클레오타이드 구조 내에, 인산기는 통상적으로 올리고뉴클레오타이드의 뉴클레오사이드간 연결을 형성하는 것으로 간주된다.

[0339] 안티센스 화합물에 대한 변형은 뉴클레오사이드간 연결, 당 모이어티, 또는 핵염기에 대한 치환 또는 변화를 포괄한다. 변형된 안티센스 화합물은 바람직한 특성 예컨대, 예를 들면, 증대된 세포 흡수, 핵산 표적에 대한 증대된 친화도, 뉴클레아제의 존재에서의 증가된 안정성, 또는 증가된 억제 활성 때문에 원산 형태와 비교하여 종종 바람직하다.

[0340] 화학적으로 변형된 뉴클레오사이드는 그것의 표적 핵산에 대해, 단축된 또는 절단된 안티센스 올리고뉴클레오타이드의 결합 친화도를 증가시키기 위해 또한 이용될 수 있다. 결과적으로, 비교할만한 결과는 그와 같은 화학적으로 변형된 뉴클레오사이드를 갖는 더 짧은 안티센스 화합물로 종종 수득될 수 있다.

[0341] *변형된 뉴클레오사이드간 연결*

[0342] RNA 및 DNA의 "천연적으로 발생하는 뉴클레오사이드간 연결"은 3' 내지 5' 포스포디에스테르 연결을 의미한다. 하나 이상의 변형된, 즉 비-천연 발생, 뉴클레오사이드간 연결을 갖는 안티센스 화합물은 바람직한 특성 예컨대, 예를 들면, 증대된 세포 흡수, 표적 핵산에 대한 증대된 친화도, 및 뉴클라아제의 존재에서 증가된 안정성 때문에 천연 발생 뉴클레오사이드간 연결을 갖는 안티센스 화합물과 비교하여 종종 선택된다.

[0343] 변형된 뉴클레오사이드간 연결을 갖는 올리고뉴클레오타이드는 인 원자를 보유하는 뉴클레오사이드간 연결 뿐만 아니라 인 원자를 갖지 않는 뉴클레오사이드간 연결을 포함한다. 대표적인 인을 함유하는 뉴클레오사이드간 연결은, 비제한적으로, 포스포디에스테르, 포스포트리에스테르, 메틸포스포네이트, 포스포르아미데이트, 및 포스

포로티오에이트를 포함한다. 인-함유 및 비-인-함유 연결의 제조 방법은 공지되어 있다.

[0344] 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물은 하나 이상의 변형된 뉴클레오사이드간 연결을 포함한다. 특정 구현예에서, 변형된 뉴클레오사이드간 연결은 안티센스 화합물 도처에 배치된다. 특정 구현예에서, 변형된 뉴클레오사이드간 연결은 포스포로티오에이트 연결이다. 특정 구현예에서, 안티센스 화합물의 각 뉴클레오사이드간 연결은 포스포로티오에이트 뉴클레오사이드간 연결이다.

[0345] *변형된 당 모이어티*

[0346] 안티센스 화합물은 하나 이상의 뉴클레오사이드를 함유할 수 있으며, 여기서 당 그룹은 변형되었던 것이다. 그와 같은 당 변형된 뉴클레오사이드는 안티센스 화합물에 대한 증대된 뉴클레아제 안정성, 증가된 결합 친화도, 또는 일부 다른 유익한 생물학적 특성을 부여할 수 있다. 특정 구현예에서, 뉴클레오사이드는 화학적으로 변형된 리보푸라노스 환 모이어티를 포함한다. 화학적으로 변형된 리보푸라노스 고리의 예는 비제한적으로 하기를 포함한다: 치환체 그룹의 부가 (5' 및 2' 치환체 그룹, 이확신 핵산 (BNA)를 형성하기 위한 비-제미널(geminal) 고리 원자의 가교, 리보실 환 산소 원자의 S, N(R), 또는 C(R_1)(R_2)로의 교체 포함) (R, R_1 및 R_2 각각은 독립적으로 H, C_1-C_{12} 알킬 또는 보호기로부터 선택된다) 및 이들의 조합. 화학적으로 변형된 당의 예시는 하기를 포함한다: 2'-F-5'-메틸 치환된 뉴클레오사이드 (참고, PCT 국제 출원 WO 2008/101157, 다른 개시된 5', 2'-비스 치환된 뉴클레오사이드에 대해 8/21/08에 공개됨), 또는 2'-위치에서 추가 치환에 의해 S에 의한 리보실 환 산소 원자의 교체 (참고, 공개된 미국 특허 출원 US2005/0130923, 2005년 6월 16일에 공개됨), 또는 대안적으로, BNA의 5'-치환 (참고, PCT 국제 출원 WO 2007/134181, 11/22/07에 공개됨, LNA는, 예를 들면, 5'-메틸 또는 5'-비닐 그룹으로 치환됨).

[0347] 변형된 당 모이어티를 갖는 뉴클레오사이드의 예는 5'-비닐, 5'-메틸 (*R* 또는 *S*), 4'-S, 2'-F, 2'-OCH_3, 2'-OCH_2CH_3, 2'-OCH_2CH_2F 및 2'-$O(CH_2)_2OCH_3$ 치환체 그룹을 포함하는 뉴클레오사이드를 비제한적으로 포함한다. 2' 위치에서의 치환체는 알릴, 아미노, 아지도, 티오, O-알릴, O-C_1-C_{10} 알킬, OCF_3, OCH_2F, $O(CH_2)_2SCH_3$, $O(CH_2)_2$-O-$N(R_m)(R_n)$, O-CH_2-C(=O)-$N(R_m)(R_n)$, 및 O-CH_2-C(=O)-$N(R_1)$-$(CH_2)_2$-$N(R_m)(R_n)$, 여기서 각각의 R_1, R_m 및 R_n은 독립적으로, H 또는 치환된 또는 비치환된 C_1-C_{10} 알킬이다.

[0348] 본원에서 사용된 바와 같이, "이환식 뉴클레오사이드"는 이환식 당 모이어티를 포함하는 변형된 뉴클레오사이드를 지칭한다. 이환식 뉴클레오사이드의 예는 4' 및 2' 리보실 환 원자 사이의 가교를 포함하는 뉴클레오사이드를 비제한적으로 포함한다. 특정 구현예에서-, 본원에서 제공된 안티센스 화합물은 4' 내지 2' 이환식 가교를 포함하는 하나 이상의 이환식 뉴클레오사이드를 포함한다. 그와 같은 4' 내지 2' 이환식 뉴클레오사이드의 하기 식 중의 하나를 비제한적으로 포함한다: 4'-(CH_2)-O-2' (LNA); 4'-(CH_2)-S-2'; 4'-$(CH_2)_2$-O-2' (ENA); 4'-$CH(CH_3)$--O-2' 및 4'-C-H(CH_2OCH_3)--O-2' 및 그의 유사체 (참고, 미국 특허 7,399,845, 2008년 7월 15일 발표); 4'-$C(CH_3)(CH_3)$--O-2' 및 그의 유사체 (참고, 공개된 PCT 국제 출원 WO2009/006478, 2009년 1월 8일 공개); 4'-CH_2-$N(OCH_3)$-2' 및 그의 유사체 (참고, 공개된 PCT 국제 출원 WO2008/150729, 2008년 12월 11일 공개); 4'-CH_2-O-$N(CH_3)$-2' (참고, 공개된 미국 특허 출원 US2004/0171570, 2004년 9월 2일 공개); 4'-CH_2-N(R)-O-2' (여기서 R은 H, C_1-C_{12} 알킬, 또는 보호기이다) (참고, 미국 특허 7,427,672, 2008년 12월 23일 발표); 4'-CH_2-C-(H)(CH_3)-2' (참고, Chattopadhyaya *et al., J. Org. Chem.,* 2009, *74*, 118-134); 및 4'-CH_2-C-(=CH_2)-2' (및 이의 유사체, 참고: 공개 국제 출원 WO 2008/154401, 2008년 12월 8일 발표).

[0349] 이환식 뉴클레오타이드와 관련된 추가적인 보고는 다음 출판 문헌에서 발견될 수 있다 (예를 들어 Singh *et al.*, *Chem. Commun.*, 1998, *4*, 455-456; Koshkin *et al.*, *Tetrahedron*, 1998, *54*, 3607-3630; Wahlestedt *et al.*, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, *97*, 5633-5638; Kumar *et al.*, *Bioorg. Med. Chem. Lett.*, 1998, *8*, 2219-2222; Singh *et al.*, *J. Org. Chem.*, 1998, *63*, 10035-10039; Srivastava *et al.*, *J. Am. Chem. Soc.*, 2007, *129(26)* 8362-8379; Elayadi *et al.*, *Curr. Opinion Invest. Drugs,* 2001, *2*, 558-561; Braasch *et al.*, *Chem. Biol.*, 2001, *8*, 1-7; 및 Orum *et al.*, *Curr. Opinion Mol. Ther.*, 2001, *3*, 239-243; 미국 특허 번호 6,268,490; 6,525,191; 6,670,461; 6,770,748; 6,794,499; 7,034,133; 7,053,207; 7,399,845; 7,547,684; 및 7,696,345; 미국 특허 공보 번호 US2008-0039618; US2009-0012281; 미국 특허 일련 번호 60/989,574; 61/026,995; 61/026,998; 61/056,564; 61/086,231; 61/097,787; 및 61/099,844; 공개 PCT 국제

출원 WO 1994/014226; WO 2004/106356; WO 2005/021570; WO 2007/134181; WO 2008/150729; WO 2008/154401; 및 WO 2009/006478. 각각의 상기 이환식 뉴클레오사이드는 예를 들면 α-L-리보푸라노스 및 β-D-리보푸라노스를 포함하는 하나 이상의 입체화학적 당 배치를 갖도록 제조될 수 있다 (참고 PCT 국제 출원 PCT/DK98/00393, WO 99/14226로서 1999년 3월 25일 공개).

[0350] 특정 구현예에서, BNA 뉴클레오사이드의 이환식 당 모이어티는, 비제한적으로, 펜토푸라노실 당 모이어티의 4' 및 2' 위치 사이의 적어도 하나의 가교를 갖는 화합물을 포함하고, 여기서 그와 같은 가교는 독립적으로, $-[C(R_a)(R_b)]_n-$, $-C(R_a)=C(R_b)-$, $-C(R_a)=N-$, $-C(=O)-$, $-C(=NR_a)-$, $-C(=S)-$, $-O-$, $-Si(R_a)_2-$, $-S(=O)_x-$, 및 $-N(R_a)-$로부터 독립적으로 선택된 1 또는 2 내지 4 연결된 그룹을 포함한다;

[0351] 여기서:

[0352] x는 0, 1, 또는 2이고;

[0353] n은 1, 2, 3, 또는 4이고;

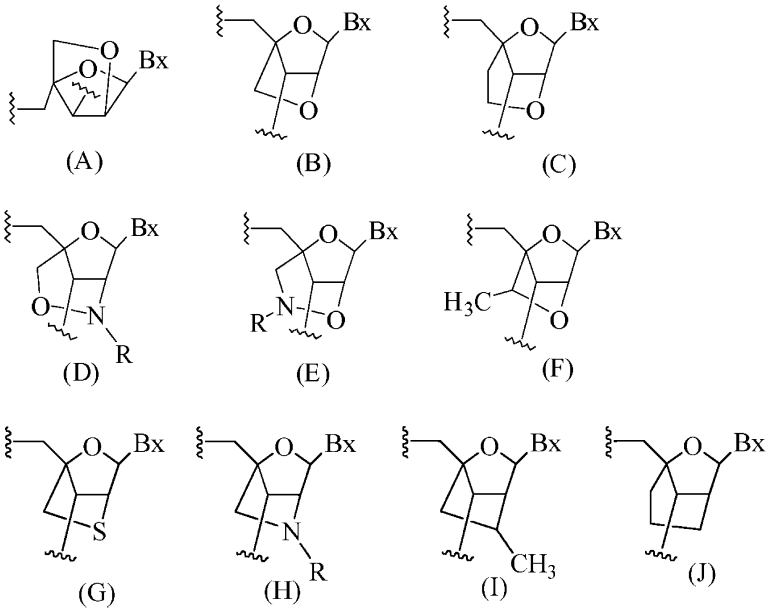
[0354] 각각의 R_a 및 R_b는, 독립적으로, H, 보호기, 하이드록실, C_1-C_{12} 알킬, 치환된 C_1-C_{12} 알킬, C_2-C_{12} 알케닐, 치환된 C_2-C_{12} 알케닐, C_2-C_{12} 알키닐, 치환된 C_2-C_{12} 알키닐, C_5-C_{20} 아릴, 치환된 C_5-C_{20} 아릴, 헤테로사이클 라디칼, 치환된 헤테로사이클 라디칼, 헤테로아릴, 치환된 헤테로아릴, C_5-C_7 지환족 라디칼, 치환된 C_5-C_7 지환족 라디칼, 할로겐, OJ_1, NJ_1J_2, SJ_1, N_3, $COOJ_1$, 아실 (C(=O)-H), 치환된 아실, CN, 설포닐 ($S(=O)_2-J_1$), 또는 설폭실 ($S(=O)-J_1$)이고;

[0355] 각각의 J_1 및 J_2는, 독립적으로, H, C_1-C_{12} 알킬, 치환된 C_1-C_{12} 알킬, C_2-C_{12} 알케닐, 치환된 C_2-C_{12} 알케닐,C_2-C_{12} 알키닐, 치환된 C_2-C_{12} 알키닐, C_5-C_{20} 아릴, 치환된 C_5-C_{20} 아릴, 아실 (C(=O)-H), 치환된 아실, 헤테로사이클 라디칼, 치환된 헤테로사이클 라디칼, C_1-C_{12} 아미노알킬, 치환된 C_1-C_{12} 아미노알킬, 또는 보호기이다.

[0356] 특정 구현예에서, 이환식 당 모이어티의 가교는, $-[C(R_a)(R_b)]_n-$, $-[C(R_a)(R_b)]_n-O-$, $-C(R_aR_b)-N(R)-O-$ 또는 $-C(R_aR_b)-O-N(R)-$이다. 특정 구현예에서, 가교는 4'-CH_2-2', 4'-$(CH_2)_2$-2', 4'-$(CH_2)_3$-2', 4'-CH_2-O-2', 4'-$(CH_2)_2$-O-2', 4'-CH_2-O-N(R)-2' 및 4'-CH_2-N(R)-O-2'-이고, 여기서 각각의 R은, 독립적으로, H, 보호기, 또는 C_1-C_{12} 알킬이다.

[0357] 특정 구현예에서, 이환식 뉴클레오사이드는 이성질체 배치에 의해 추가로 규정된다. 예를 들면, 4'-2' 메틸렌-옥시 가교를 포함하는 뉴클레오사이드는, α-L 배치 또는 β-D 배치로 존재한다. 이전에, α-L-메틸렌옥시 (4'-CH_2-O-2') BNA'는 안티센스 활성을 보여준 안티센스 올리고뉴클레오타이드에 통합되었다 (Frieden *et al.,* *Nucleic Acids Research,* 2003, *21*, 6365-6372).

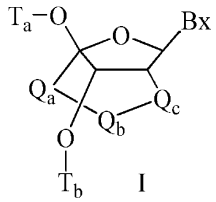
[0358] 특정 구현예에서, 이환식 뉴클레오사이드는, 비제한적으로, (A) α-L-메틸렌옥시 (4'-CH_2-O-2') BNA, (B) β-D-메틸렌옥시 (4'-CH_2-O-2') BNA, (C) 에틸렌옥시 (4'-$(CH_2)_2$-O-2') BNA, (D) 아미노옥시 (4'-CH_2-O-N(R)-2') BNA, (E) 옥시아미노 (4'-CH_2-N(R)-O-2') BNA, 및 (F) 메틸(메틸렌옥시) (4'-$CH(CH_3)$-O-2') BNA, (G) 메틸렌-티오 (4'-CH_2-S-2') BNA, (H) 메틸렌-아미노 (4'-CH_2-N(R)-2') BNA, (I) 메틸 카보사이클릭 (4'-CH_2-$CH(CH_3)$-2') BNA, 및 (J) 프로필렌 카보사이클릭 (4'-$(CH_2)_3$-2') BNA를, 이하에서 묘사된 바와 같이 포함한다.



[0359]

[0360] 여기서 Bx는 염기 모이어티이고 R은, 독립적으로, H, 보호기 또는 C_1-C_{12} 알킬이다.

[0361] 특정 구현예에서, 하기 화학식 I을 갖는 이환식 뉴클레오사이드가 제공된다:



I

[0362]

[0363] 여기서:

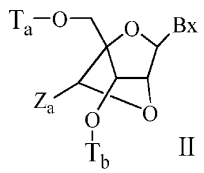
[0364] Bx는 헤테로환 염기 모이어티이고;

[0365] $-Q_a-Q_b-Q_c-$는 $-CH_2-N(R_c)-CH_2-$, $-C(=O)-N(R_c)-CH_2-$, $-CH_2-O-N(R_c)-$, $-CH_2-N(R_c)-O-$ 또는 $-N(R_c)-O-CH_2$이고;

[0366] R_c 는 C_1-C_{12} 알킬 또는 아미노 보호기이고; 그리고

[0367] T_a 및 T_b 각각은, 독립적으로 H, 하이드록실 보호기, 공액체 그룹, 반응성 인 그룹, 인 모이어티, 또는 지지 매질에 대한 공유 부착(covalent attachment)이다.

[0368] 특정 구현예에서, 하기 화학식 II을 갖는 이환식 뉴클레오사이드가 제공된다:



II

[0369]

[0370] 여기서:

[0371] Bx는 헤테로환 염기 모이어티이고;

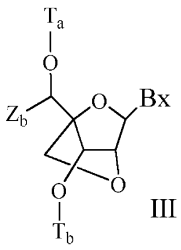
[0372] T_a 및 T_b 각각은, 독립적으로 H, 하이드록실 보호기, 공액체 그룹, 반응성 인 그룹, 인 모이어티, 또는 지지 매질에 대한 공유 부착(covalent attachment)이고;

[0373] Z_a는 C_1-C_6 알킬, C_2-C_6 알케닐, C_2-C_6 알키닐, 치환된 C_1-C_6 알킬, 치환된 C_2-C_6 알케닐, 치환된 C_2-C_6 알키닐, 아

실, 치환된 아실, 치환된 아미드, 티올, 또는 치환된 티오이다.

[0374] 일 구현예에서, 각각의 치환된 그룹은, 독립적으로, 할로겐, 옥소, 하이드록실, OJ_c, NJ_cJ_d, SJ_c, N_3, $OC(=X)J_c$, 및 $NJ_eC(=X)NJ_cJ_d$로부터 독립적으로 선택된 치환체 그룹으로 모노 또는 폴리 치환되고, 여기서 각각의 J_c, J_d 및 J_e는, 독립적으로, H, C_1-C_6 알킬, 또는 치환된 C_1-C_6 알킬이고 X는 O 또는 NJ_c이다.

[0375] 특정 구현예에서, 하기 화학식 III을 갖는 이환식 뉴클레오사이드가 제공된다:



III

[0376]

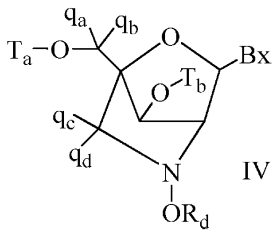
[0377] 여기서:

[0378] Bx는 헤테로환 염기 모이어티이고;

[0379] T_a 및 T_b 각각은, 독립적으로 H, 하이드록실 보호기, 공액체 그룹, 반응성 인 그룹, 인 모이어티, 또는 지지 매질에 대한 공유 부착(covalent attachment)이고;

[0380] Z_b는 C_1-C_6 알킬, C_2-C_6 알케닐, C_2-C_6 알키닐, 치환된 C_1-C_6 알킬, 치환된 C_2-C_6 알케닐, 치환된 C_2-C_6 알키닐, 아실, 또는 치환된 아실 (C(=O)-)이다.

[0381] 특정 구현예에서, 하기 화학식 IV을 갖는 이환식 뉴클레오사이드가 제공된다:



IV

[0382]

[0383] 여기서:

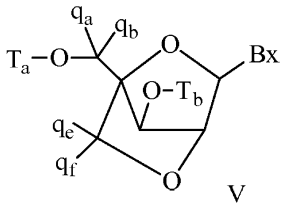
[0384] Bx는 헤테로환 염기 모이어티이고;

[0385] T_a 및 T_b 각각은, 독립적으로 H, 하이드록실 보호기, 공액체 그룹, 반응성 인 그룹, 인 모이어티, 또는 지지 매질에 대한 공유 부착(covalent attachment)이고;

[0386] R_d는 C_1-C_6 알킬, 치환된 C_1-C_6 알킬, C_2-C_6 알케닐, 치환된 C_2-C_6 알케닐, C_2-C_6 알키닐 또는 치환된 C_2-C_6 알키닐이고;

[0387] 각각의 q_a, q_b, q_c 및 q_d는 독립적으로, H, 할로겐, C_1-C_6 알킬, 치환된 C_1-C_6 알킬, C_2-C_6 알케닐, 치환된 C_2-C_6 알케닐, C_2-C_6 알키닐 또는 치환된 C_2-C_6 알키닐, C_1-C_6 알콕실, 치환된 C_1-C_6 알콕실, 아실, 치환된 아실, C_1-C_6 아미노알킬 또는 치환된 C_1-C_6 아미노알킬이다;

[0388] 특정 구현예에서, 하기 화학식 V을 갖는 이환식 뉴클레오사이드가 제공된다:



V

[0389]

[0390] 여기서:

[0391] Bx는 헤테로환 염기 모이어티이고;

[0392] T_a 및 T_b 각각은, 독립적으로 H, 하이드록실 보호기, 공액체 그룹, 반응성 인 그룹, 인 모이어티, 또는 지지 매질에 대한 공유 부착(covalent attachment)이고;

[0393] q_a, q_b, q_e 및 q_f 각각은, 독립적으로, 수소, 할로겐, C_1-C_{12} 알킬, 치환된 C_1-C_{12} 알킬, C_2-C_{12} 알케닐, 치환된 C_2-C_{12} 알케닐, C_2-C_{12} 알키닐, 치환된 C_2-C_{12} 알키닐, C_1-C_{12} 알콕실, 치환된 C_1-C_{12} 알콕실, OJ_j, SJ_j, SOJ_j, SO_2J_j, NJ_jJ_k, N_3, CN, $C(=O)OJ_j$, $C(=O)NJ_jJ_k$, $C(=O)J_j$, $O-C(=O)-NJ_jJ_k$, $N(H)C(=NH)NJ_jJ_k$, $N(H)C(=O)-NJ_jJ_k$ 또는 $N(H)C(=S)NJ_jJ_k$이고;

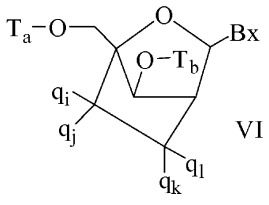
[0394] 또는 q_e 및 q_f는 함께 $=C(q_g)(q_h)$이고;

[0395] q_g 및 q_h 각각은, 독립적으로, H, 할로겐, C_1-C_{12} 알킬, 또는 치환된 C_1-C_{12} 알킬이다.

[0396] 메틸렌옥시 (4'-CH_2-O-2') BNA 모노머 아데닌, 시토신, 구아닌, 5-메틸-시토신, 티민, 및 우라실의 합성 및 제조는, 그것의 올리고머화, 및 핵산 인식 특성과 함께 기재되었다 (참고, 예를 들면, Koshkin *et al.*, *Tetrahedron*, 1998, *54*, 3607-3630). BNA 및 이의 제조는 WO 98/39352 및 WO 99/14226에 또한 설명되어 있었다.

[0397] 메틸렌옥시 (4'-CH_2-O-2') BNA, 및 2'-티오-BNA의 유사체가 또한 제조되었다 (참고, 예를 들면, Kumar *et al.*, *Bioorg. Med. Chem. Lett.*, 1998, *8*, 2219-2222). 올리고데옥시리보뉴클레오타이드 듀플렉스를 핵산 폴리머라제의 기질로서 포함하는 락킹된(locked) 뉴클레오사이드 유사체의 제조가 또한 기재되었다 (참고, Wengel *et al.*, WO 99/14226). 더욱이, 2'-아미노-BNA, 신규 형태적으로 제한된 고-친화도 올리고뉴클레오타이드 유사체의 합성은 당해기술에 기재되었다 (참고, 예를 들면, Singh *et al.*, *J. Org. Chem.*, 1998, *63*, 10035-10039). 또한, 2'-아미노- 및 2'-메틸아미노-BNA'가 제조되었고 상보적 RNA 및 DNA 가닥을 갖는 그것의 듀플렉스의 열 안정성은 이전에 보고되었다.

[0398] 특정 구현예에서, 하기 화학식 VI을 갖는 이환식 뉴클레오사이드가 제공된다:



VI

[0399]

[0400] 여기서:

[0401] Bx는 헤테로환 염기 모이어티이고;

[0402] T_a 및 T_b 각각은, 독립적으로 H, 하이드록실 보호기, 공액체 그룹, 반응성 인 그룹, 인 모이어티, 또는 지지 매질에 대한 공유 부착(covalent attachment)이고;

[0403] q_i, q_j, q_k 및 q_l 각각은, 독립적으로, 수소, 할로겐, C_1-C_{12} 알킬, 치환된 C_1-C_{12} 알킬, C_2-C_{12} 알케닐, 치환된 C_2-

C_{12} 알케닐, C_2-C_{12} 알키닐, 치환된 C_2-C_{12} 알키닐, C_1-C_{12} 알콕실, 치환된 C_1-C_{12} 알콕실, OJ_j, SJ_j, SOJ_j, SO_2J_j, NJ_jJ_k, N_3, CN, $C(=O)OJ_j$, $C(=O)NJ_jJ_k$, $C(=O)J_j$, $O-C(=O)-NJ_jJ_k$, $N(H)C(=NH)NJ_jJ_k$, $N(H)C(=O)-NJ_jJ_k$ 또는 $N(H)C(=S)NJ_jJ_k$이고; 그리고

[0404] q_i 및 q_j 또는 q_l 및 q_k는 함께 $=C(q_g)(q_h)$이고, 여기서 q_g 및 q_h은 각각 독립적으로 H, 할로겐, C_1-C_{12} 알킬 또는 치환된 C_1-C_{12} 알킬이다.

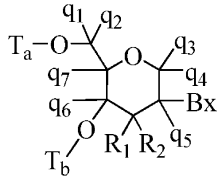
[0405] $4'-(CH_2)_3-2'$ 가교를 갖는 하나의 탄소환 이환식 뉴클레오사이드 및 알케닐 유사체 가교 $4'-CH=CH-CH_2-2'$가 기재되었다 (참고, 예를 들면, Freier *et al., Nucleic Acids Research*, 1997, *25*(*22*), 4429-4443 및 Albaek *et al., J. Org. Chem.*, 2006, *71*, 7731-7740). 탄소환 이환식 뉴클레오사이드의 합성 및 제조는 그것의 올리고머화 및 생화학적 연구와 함께 또한 기재되었다 (참고, 예를 들면, Srivastava *et al., J. Am. Chem. Soc.*, 2007, *129(26)*, 8362-8379).

[0406] 본원에서 사용된 바와 같이, "4'-2' 이환식 뉴클레오사이드" 또는 "4' 내지 2' 이환식 뉴클레오사이드"는 당 환의 2' 탄소 원자 및 4' 탄소 원자를 연결하는, 푸라노스 환의 두개의 탄소를 연결하는 가교를 포함하는 이환식 뉴클레오사이드를 의미한다.

[0407] 본원에서 사용된 바와 같이, "일환식 뉴클레오사이드"는 이환식 당 모이어티가 아닌 변형된 당 모이어티를 포함하는 뉴클레오사이드를 의미한다. 특정 구현예에서, 뉴클레오사이드의 당 모이어티, 또는 당 모이어티 유사체는 임의의 위치에서 변형 또는 치환될 수 있다.

[0408] 본원에서 사용된 바와 같이, "2'-변형된 당"는 2' 위치에서 변형된 푸라노실 당을 의미한다. 특정 구현예에서, 그와 같은 변형은 하기로부터 선택된 치환체를 포함한다: 치환된 및 비치환된 알콕시, 치환된 및 비치환된 티오알킬, 치환된 및 비치환된 아미노 알킬, 치환된 및 비치환된 알킬, 치환된 및 비치환된 알릴, 및 치환된 및 비치환된 알키닐을 비제한적으로 포함하는 할라이드. 특정 구현예에서, 2' 변형은 하기를 비제한적으로 포함하는 치환체로부터 선택된다: $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nF$, $O(CH_2)_nONH_2$, $OCH_2C(=O)N(H)CH_3$, 및 $O(CH_2)_nON[(CH_2)_nCH_3]_2$ (여기서 n 및 m은 1 내지 약 10이다). 다른 2' 치환체 그룹은 또한 하기로부터 선택될 수 있다: C_1-C_{12} 알킬, 치환된 알킬, 알케닐, 알키닐, 알카릴, 아랄킬, O-알카릴 또는 O-아랄킬, SH, SCH_3, OCN, Cl, Br, CN, F, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, 헤테로사이클로알킬, 헤테로사이클로알카릴, 아미노알킬아미노, 폴리-알킬아미노. 치환된 실릴, RNA 절단 그룹, 리포터 그룹, 삽입제, 약력학적 특성을 개선하는 그룹, 및 안티센스 화합물의 약동학적 특성을 개선하는 그룹, 및 유사한 특성을 갖는 다른 치환체. 특정 구현예에서, 변형된 뉴클레오사이드는 2'-MOE 측쇄를 포함한다 (참고, 예를 들면, Baker *et al., J. Biol. Chem.*, 1997, *272*, 11944-12000). 그와 같은 2'-MOE 치환은 비변형된 뉴클레오사이드 및 다른 변형된 뉴클레오사이드, 예컨대 2'- *O*-메틸, *O*-프로필, 및 *O*-아미노프로필과 비교하여 개선된 결합 친화도를 갖는 것으로 기재되었다. 2'-MOE 치환체를 갖는 올리고뉴클레오타이드는 또한 체내 사용을 위해 유망한 특징을 갖는 유전자 발현의 안티센스 억제제인 것으로 보여졌다 (참고, 예를 들면, Martin, *Helv. Chim. Acta*, 1995, *78*, 486-504; Altmann *et al.*, *Chimia*, 1996, *50*, 168-176; Altmann *et al.*, *Biochem. Soc. Trans.*, 1996, *24*, 630-637; 및 Altmann *et al.*, *Nucleosides Nucleotides*, 1997, *16*, 917-926).

[0409] 본원에서 사용된 바와 같이, "변형된 테트라하이드로피란 뉴클레오사이드" 또는 "변형된 THP 뉴클레오사이드"는 정상 뉴클레오사이드 (당 대용물)에서 펜토푸라노실 잔기를 대체하기 위해 치환된 6-원 테트라하이드로피란 "당"을 갖는 뉴클레오사이드를 의미한다. 변형된 THP 뉴클레오사이드는, 비제한적으로, 헥시톨 핵산 (HNA), 아니톨 핵산 (ANA), 만니톨 핵산 (MNA) (참고 Leumann, *Bioorg. Med. Chem.*, 2002, *10*, 841-854), 플루오로 HNA (F-HNA)로서 본 분야에서 지칭되는 것들, 또는 하기 화학식 VII을 갖는 화합물을 포함한다:



VII

[0410]

[0411] 여기서 독립적으로 화학식 VII의 각각의 상기 적어도 하나의 테트라하이드로피란 뉴클레오사이드 유사체에 대해:

[0412] Bx는 헤테로환 염기 모이어티이고;

[0413] T_a 및 T_b 각각은, 독립적으로, 테트라하이드로피란 뉴클레오사이드 유사체를 안티센스 화합물에 연결시키는 뉴클레오사이드간 연결기이거나 T_a 및 T_b 중 하나는 테트라하이드로피란 뉴클레오사이드 유사체를 안티센스 화합물에 연결시키는 뉴클레오사이드간 연결기이고, T_a 및 T_b 중 다른 것은 H, 하이드록실 보호기, 연결된 공액체 그룹, 또는 5' 또는 3'-말단기이고;

[0414] q_1, q_2, q_3, q_4, q_5, q_6 및 q_7은 각각 독립적으로, H, C_1-C_6 알킬, 치환된 C_1-C_6 알킬, C_2-C_6 알케닐, 치환된 C_2-C_6 알케닐, C_2-C_6 알키닐 또는 치환된 C_2-C_6 알키닐이고; 그리고 각각의 R_1 및 R_2는 수소, 히드록실, 할로겐, 치환된 또는 비치환된 알콕시, NJ_1J_2, SJ_1, N_3, $OC(=X)J_1$, $OC(=X)NJ_1J_2$, $NJ_3C(=X)NJ_1J_2$ 및 CN으로부터 선택되고, 여기서 X는 O, S 또는 NJ_1이고, 그리고 각각의 J_1, J_2 및 J_3 는 독립적으로, H 또는 C_1-C_6 알킬이다.

[0415] 특정 구현예에서, 화학식 VII의 변형된 THP 뉴클레오사이드가 제공되며, 여기서 q_1, q_2, q_3, q_4, q_5, q_6 및 q_7는 각각 H이다. 특정 구현예에서, q_1, q_2, q_3, q_4, q_5, q_6 및 q_7 중 적어도 하나는 H 이외의 것이다. 특정 구현예에서, q_1, q_2, q_3, q_4, q_5, q_6 및 q_7 중 적어도 하나는 메틸이다. 특정 구현예에서, 식 VII의 THP 뉴클레오사이드가 제공되고, 여기서 R_1 및 R_2 중 하나는 플루오로이다. 특정 구현예에서, R_1은 플루오로이고 R_2는 H이고; R_1은 메톡시이고 R_2는 H이고, 그리고 R_1은 H이고, R_2는 메톡시에톡시이다.

[0416] 본원에서 사용된 바와 같이, "2'-변형된" 또는 "2'-치환된"은 H 또는 OH 이외의 2' 위치에서 치환체를 포함하는 당을 포함하는 뉴클레오사이드를 의미한다. 2'-변형된 뉴클레오사이드는, 비제한적으로, 이환식 뉴클레오사이드 (여기서 당 환의 2 개의 탄소 원자를 연결하는 가교는 당 환의 2' 탄소 및 다른 탄소를 연결한다); 및 비-가교 2' 치환체, 예컨대 알릴, 아미노, 아지도, 티오, O-알릴, O-C_1-C_{10} alkyl, -OCF_3, O-$(CH_2)_2$-O-CH_3, 2'-$O(CH_2)_2SCH_3$, O-$(CH_2)_2$-O-$N(R_m)(R_n)$, 또는 O-CH_2-C(=O)-$N(R_m)(R_n)$를 갖는 뉴클레오사이드 (여기서 각각의 R_m 및 R_n는, 독립적으로, H 또는 치환된 또는 비치환된 C_1-C_{10} 알킬이다)를 포함한다. 2'-변형된 뉴클레오사이드는 예를 들면, 당의 다른 위치에서 및/또는 핵염기에서 다른 변형을 추가로 포함할 수 있다.

[0417] 본원에서 사용된 바와 같이, "2'-F"는 2' 위치에서 플루오로 기를 포함하는 당을 지칭한다.

[0418] 본원에서 사용된 바와 같이, "2'-OMe" 또는 "2'-OCH_3" 또는 "2'-O-메틸" 각각은 당 환의 2' 위치에서-OCH_3 기를 포함하는 당을 포함하는 뉴클레오사이드를 지칭한다.

[0419] 본원에서 사용된 바와 같이, "MOE" 또는 "2'-MOE" 또는 "2'-$OCH_2CH_2OCH_3$" 또는 "2'-O-메톡시에틸" 각각은 당 환의 2' 위치에서 -$OCH_2CH_2OCH_3$ 기를 포함하는 당을 포함하는 뉴클레오사이드를 지칭한다.

[0420] 본원에서 사용된 바와 같이, "올리고뉴클레오타이드"는 복수의 연결된 뉴클레오사이드를 포함하는 화합물을 지칭한다. 특정 구현예에서, 복수의 뉴클레오사이드 중 하나 이상이 변형된다. 특정 구현예에서, 올리고뉴클레오타이드는 하나 이상의 리보뉴클레오사이드(RNA) 및/또는 데옥시리보뉴클레오사이드(DNA)를 포함한다.

[0421] 많은 다른 이환식 및 삼환식 당 대용물 고리계는 또한 당해기술에 공지되어 있고 안티센스 화합물에 통합시키기 위한 뉴클레오사이드를 변형하기 위해 사용될 수 있다 (참고, 예를 들면, 검토 논문: Leumann, *Bioorg. Med. Chem.*, 2002, *10*, 841-854).

[0422] 그와 같은 고리계는 활성을 향상시키기 위해 다양한 부가적 치환을 경험할 수 있다.

[0423] 변형된 당류의 제조 방법은 당해분야의 숙련가에게 잘 공지되어 있다.

[0424] 변형된 당 모이어티를 갖는 뉴클레오타이드에서, 핵염기 모이어티 (천연, 변형된, 또는 이들의 조합)은 적절한 핵산 표적과의 혼성화를 위해 유지된다.

[0425] 특정 구현예에서, 안티센스 화합물은 변형된 당 모이어티를 갖는 하나 이상의 뉴클레오사이드를 포함한다. 특정 구현예에서, 변형된 당 모이어티는 2'-MOE이다. 특정 구현예에서, 2'-MOE 변형된 뉴클레오사이드는 갭머 모티프

에서 배열된다. 특정 구현예에서, 상기 변형된 당 모이어티는 (4'-CH(CH_3)-O-2')) 가교기를 갖는 이환식 뉴클레오사이드이다. 특정 구현예에서, 상기 (4'-CH(CH_3)-O-2') 변형된 뉴클레오사이드는 갭머 모티프의 윙에 걸쳐 배열된다.

[0426] *약제학적 조성물을 제형화하기 위한 조성물 및 방법*

[0427] 안티센스 올리고뉴클레오타이드는 약제학적 조성물 또는 제형의 제조를 위한 약제학적으로 허용가능한 활성 또는 불활성 물질과 혼합될 수 있다. 조성물 및 약제학적 조성물의 제형 방법은 수많은 기준에 의존하고, 이 기준은, 비제한적으로, 투여 경로, 질환 정도, 또는 투여될 복용량을 포함한다.

[0428] 타우 핵산에 표적화된 안티센스 화합물은 안티센스 화합물을 적당한 약제학적으로 허용가능한 희석제 또는 담체와 조합함으로써 약제학적 조성물에서 이용될 수 있다. 약제학적으로 허용가능한 희석제는 포스페이트-완충 식염수 (PBS)를 포함한다. PBS는 비경구로 전달될 조성물에서 사용하기에 적당한 희석제이다. 따라서, 일 구현예에서, 타우 핵산에 표적화된 안티센스 화합물 및 약제학적으로 허용가능한 희석제를 포함하는 약제학적 조성물이 본원에 기재된 방법에서 이용된다. 특정 구현예에서, 약제학적으로 허용가능한 희석제는 PBS이다. 특정 구현예에서, 안티센스 화합물은 안티센스 올리고뉴클레오타이드이다.

[0429] 안티센스 화합물을 포함하는 약제학적 조성물은 임의의 약제학적으로 허용가능한 염, 에스테르, 또는 그와 같은 에스테르의 염, 또는 인간을 포함하는 동물에게 투여시, (직접적으로 또는 간접적으로) 생물학적 활성 대사물 또는 그의 잔류물을 제공할 수 있는 임의의 다른 올리고뉴클레오타이드을 포함한다. 따라서, 예를 들면, 본 개시내용은 또한 안티센스 화합물의 약제학적으로 허용가능한 염, 프로드러그, 그와 같은 프로드러그의 약제학적으로 허용가능한 염, 및 다른 생체동등물에 관한 것이다. 적당한 약제학적으로 허용가능한 염은, 비제한적으로, 나트륨 및 칼륨 염을 포함한다.

[0430] 프로드러그는 활성 안티센스 화합물을 형성하도록 내인성 뉴클레아제에 의해 절단된 안티센스 화합물의 하나 또는 둘 모두의 말단에서 부가적 뉴클레오사이드의 통합을 포함한다.

[0431] *공액된 안티센스 화합물*

[0432] 안티센스 화합물은 수득한 안티센스 올리고뉴클레오타이드의 활성, 세포 분포 또는 세포 흡수를 향상시키는 하나 이상의 모이어티 또는 공액체에 공유연결될 수 있다. 전형적인 공액체 그룹은 콜레스테롤 모이어티 및 지질 모이어티를 포함한다. 부가적 공액체 그룹은 탄수화물, 인지질, 비오틴, 펜아진, 엽산, 펜안트리딘, 안트라퀴논, 아크리딘, 플루오레신, 로다민, 쿠마린, 및 염료를 포함한다.

[0433] 안티센스 화합물은 또한 뉴클레아제 안정성과 같은 특성을 개선하기 위해 안티센스 화합물의 하나 또는 둘 모두 말단에 일반적으로 부착된 하나 이상의 안정화 그룹을 갖도록 또한 변형될 수 있다. 안정화 그룹에 캡 구조가 포함된다. 이들 말단 변형은 엑소뉴클레아제 분해로부터 말단 핵산을 갖는 안티센스 화합물을 보호하고, 세포 내에서 전달 및/또는 국지화를 도울 수 있다. 캡은 5'-말단 (5'-캡), 또는 3'-말단 (3'-캡)에서 존재할 수 있고, 또는 말단 둘에서 존재할 수 있다. 캡 구조는 당해기술에서 잘 공지되어 있고, 예를 들면, 역전된 데옥시 무염기성 캡을 포함한다. 뉴클레아제 안정성을 부여하기 위해 안티센스 화합물의 하나 또는 둘 모두의 말단을 캡핑하기 위해 사용될 수 있는 추가의 3' 및 5'-안정화 그룹은 WO 03/004602 (2003년 1월 16일 공개)에서 개시된 것을 포함한다.

[0434] *세포 배양물 및 안티센스 화합물 치료*

[0435] 타우 핵산의 수준, 활성 또는 발현에 대한 안티센스 화합물의 효과는 다양한 세포 유형에서 *시험관내에서* 시험될 수 있다. 그와 같은 분석을 위해 사용된 세포 유형은 상업적 판매인 (*예를 들면* American Type Culture Collection, Manassus, VA; Zen-Bio, Inc., Research Triangle Park, NC; Clonetics Corporation, Walkersville, MD)으로부터 이용가능하고 상업적으로 이용가능한 시약을 사용하여 판매인의 지침에 따라 배양된다 (예를 들면 Invitrogen Life Technologies, Carlsbad, CA). 예시적인 세포 유형은, 비제한적으로, HepG2 세포 Hep3B 세포, 및 일차 간세포를 포함한다.

[0436] *안티센스 올리고뉴클레오타이드의 시험관내 시험*

[0437] 다른 안티센스 화합물에 의한 치료를 위해 적절하게 변형될 수 있는 안티센스 올리고뉴클레오타이드에 의한 세포의 치료 방법이 본원에 기재되어 있다.

[0438] 세포는, 세포가 배양물에서 대략 60-80% 밀집도에 도달할 때 안티센스 올리고뉴클레오타이드로 처리될 수 있다.

[0439] 안티센스 올리고뉴클레오타이드를 배양 세포에 도입하기 위해 통상적으로 사용된 하나의 시약은 양이온성 지질 형질감염 시약 LIPOFECTIN (Invitrogen, Carlsbad, CA)을 포함한다. 안티센스 올리고뉴클레오타이드는 안티센스 올리고뉴클레오타이드의 원하는 최종 농도 및 2 내지 12 ug/mL / 100 nM 안티센스 올리고뉴클레오타이드 범위인 LIPOFECTIN 농도를 달성하기 위해 OPTI-MEM 1 (Invitrogen, Carlsbad, CA) 중에서 LIPOFECTIN와 혼합된다.

[0440] 안티센스 올리고뉴클레오타이드를 배양 세포에 도입하기 위해 사용된 또 하나의 시약은 LIPOFECTAMINE (Invitrogen, Carlsbad, CA)을 포함한다. 안티센스 올리고뉴클레오타이드는 안티센스 올리고뉴클레오타이드의 원하는 농도 및 2 내지 12 ug/mL / 100 nM 안티센스 올리고뉴클레오타이드 범위인 LIPOFECTAMINE 농도를 달성하기 위해 OPTI-MEM 1 감소된 혈청 배지 (Invitrogen, Carlsbad, CA)에서 LIPOFECTAMINE와 혼합된다.

[0441] 안티센스 올리고뉴클레오타이드를 배양 세포에 도입하기 위해 사용된 또 하나의 기술은 전기천공을 포함한다.

[0442] 세포는 통상적인 방법에 의해 안티센스 올리고뉴클레오타이드로 처리된다. 세포는 전형적으로 안티센스 올리고뉴클레오타이드 처리 16-24 시간 후에 수확되고, 그 시간에 표적 핵산의 RNA 또는 단백질 수준은 당해분야에서 공지되고 본원에 기재된 방법으로 측정된다. 일반적으로, 처리가 다중 복제물에서 수행될 때, 데이타는 복제물 처리의 평균치로서 제공된다.

[0443] 사용된 안티센스 올리고뉴클레오타이드의 농도는 세포주 내지 세포주 사이에서 변화한다. 특정한 세포주에 대한 최적의 안티센스 올리고뉴클레오타이드 농도를 측정하는 방법은 당해기술에 공지되어 있다. 안티센스 올리고뉴클레오타이드는 LIPOFECTAMINE으로 형질감염될 때 1 nM 내지 300 nM 범위의 농도에서 전형적으로 사용된다. 안티센스 올리고뉴클레오타이드는 전기천공을 사용하여 형질감염될 때 625 내지 20,000 nM 범위의 고농도에서 사용된다.

[0444] *RNA 단리*

[0445] RNA 분석은 총 세포 RNA 또는 폴리(A)+ mRNA에 대해 수행될 수 있다. RNA 단리의 방법은 당해기술에 공지되어 있다. RNA는 제조자의 추천된 프로토콜에 따라 당해기술에서 공지된 방법, 예를 들면, TRIZOL 시약 (Invitrogen, Carlsbad, CA)을 사용하여 제조된다.

[0446] *표전 수준 또는 발현의 억제 분석*

[0447] 타우 핵산의 수준 또는 발현의 억제는 당해기술에서 공지된 다양한 방식으로 검정될 수 있다. 예를 들면, 표적 핵산 수준은, 예를 들면, 노던 블랏 분석, 경쟁적 폴리머라제 연쇄 반응 (PCR), 또는 정량적 실시간 PCR에 의해 정량화될 수 있다. RNA 분석은 총 세포 RNA 또는 폴리(A)+ mRNA에 대해 수행될 수 있다. RNA 단리의 방법은 당해기술에 공지되어 있다. 노던 블랏 분석은 당해기술에서 또한 통상적이다. 정량적 실시간 PCR은 상업적으로 이용가능한 ABI PRISM 7600, 7700, 또는 7900 서열 검출 시스템 (PE-Applied Biosystems, Foster City, CA로부터 이용가능)을 사용하여 편리하게 달성될 수 있고 제조자의 지침에 따라 사용된다.

[0448] *표적 RNA 수준의 정량적 실시간 PCR 분석*

[0449] 표적 RNA 수준의 정량화는 제조자의 지침에 따라 ABI PRISM 7600, 7700, 또는 7900 서열 검출 시스템 (PE-Applied Biosystems, Foster City, CA)을 사용하여 정량적 실시간 PCR에 의해 달성될 수 있다. 정량적 실시간 PCR의 방법은 당해기술에 공지되어 있다.

[0450] 실시간 PCR 전에, 단리된 RNA에 대해 역전사효소 (RT) 반응이 수행되고, 이 반응은 상보적 DNA (cDNA)를 생산하고 이후 실시간 PCR 증폭에 대한 기질로서 사용된다. RT 및 실시간 PCR 반응은 동일 샘플 웰에서 순차적으로 수행된다. RT 및 실시간 PCR 시약은 Invitrogen (Carlsbad, CA)로부터 수득될 수 있다. RT, 실시간-PCR 반응은 당해분야의 숙련가에게 공지된 방법에 의해 수행된다.

[0451] 실시간 PCR에 의해 수득된 유전자 (또는 RNA)는, 발현이 일정한 유전자, 예컨대 사이클로필린 A의 발현 수준을 사용하거나, RIBOGREEN (Invitrogen, Inc. Carlsbad, CA)을 사용하여 총 RNA를 정량화하여 정규화된다. 사이클로필린 A 발현은 실시간 PCR에 의해, 표적과 동시에, 다중화, 또는 별도로 시행하여 정량화된다. 총 RNA는 리보그린 RNA 정량화 시약 (Invetrogen, Inc. Eugene, OR)을 사용하여 정량화된다. RIBOGREEN에 의한 RNA 정량화의 방법은 하기에서 교시된다: Jones, L.J., 등, (Analytical Biochemistry, 1998, 265, 368-374). CYTOFLUOR 4000 기기 (PE Applied Biosystems)는 RIBOGREEN 형광을 측정하기위해 사용된다.

[0452] 프로브 및 프라이머는 타우 핵산에 대한 혼성화를 위해 설계된다. 실시간 PCR 프로브 및 프라이머를 설계하는 방법은 당해기술에 공지되어 있고 소프트웨어 예컨대 PRIMER EXPRESS 소프트웨어 (Applied Biosystems, Foster

City, CA)의 사용을 포함할 수 있다

[0453] *단백질 수준 분석*

[0454] 타우 핵산의 안티센스 억제는 타우 단백질 수준을 측정하여 평가될 수 있다. 타우의 단백질 수준은 당해기술에 공지된 다양한 방식, 예컨대 면역침전, 웨스턴 블랏 분석 (면역블로팅), 효소-연결 면역흡착 검정 (ELISA), 정량적 단백질 검정, 단백질 활성 검정 (예를 들면, 카스파제 활성 검정), 면역조직화학, 면역세포화학 또는 형광-활성화된 세포 분류 (FACS)으로 평가 또는 정량화될 수 있다. 표적에 대해 지향된 항체는 다양한 공급원, 예컨대 항체의 MSRS 카탈로그 (Aerie Corporation, Birmingham, MI)으로부터 확인 및 수득될 수 있고, 또는 당해기술에 잘 공지된 종래의 모노클로날 또는 폴리클로날 항체 생성 방법을 통해 제조될 수 있다.

[0455] *안티센스 화합물의 체내 시험*

[0456] 안티센스 화합물, 예를 들면, 안티센스 올리고뉴클레오타이드는, 타우의 발현을 억제하고 표현형 변화를 생성하기 위해 그것의 능력을 평가하기 위해 동물에서 시험된다. 특정 구현예에서, 인식은 신규 목적 인식 및 네스트레트(nestlet) 구축 활성에 의하여 측정된다. 특정 구현예에서, 운동 기능은 동물에서의 보행 개시 분석, 로타로드(rotarod), 악력, 폴 크라이밍(pole climb), 오픈 필드 수행, 발란스 빔, 뒷발 발자국 시험에 의하여 측정될 수 있다. 특정 구현예에서, 안티센스 화합물, 예를 들면, 안티센스 올리고뉴클레오타이드는, 과인산화된 타우 및 신경섬유 매듭을 감소시키는 이들의 능력을 평가하기 위하여 동물에서 시험된다. 특정 구현예에서, 안티센스 화합물, 예를 들면, 안티센스 올리고뉴클레오타이드는, 펜틸렌테트라졸 (PTZ) 유도 발작(seizure) 모델에서의 발작의 중증도를 예방하고/하거나 감소시키는 이들의 능력을 평가하기 위하여 동물에서 시험된다.

[0457] 시험은 정상동물, 또는 실험 질환 모델에서 수행될 수 있다. 동물에의 투여에 대해, 안티센스 올리고뉴클레오타이드는 약제학적으로 허용가능한 희석제, 예컨대 포스페이트-완충 식염수에서 제형화된다. 투여는, 예를 들어 복강내, 정맥내 및 피하와 같은 비경구 투여 경로를 포함한다. 안티센스 올리고뉴클레오타이드 투여 및 투여 빈도의 산출은 당업자의 능력 내에 있으며, 투여 경로 및 동물 체중과 같은 인자에 따라 달라진다. 안티센스 올리고뉴클레오타이드에 의한 치료 기간 후, RNA는 CNS 조직 또는 CSF로부터 단리되고 타우 핵산 발현에서의 변화가 측정된다.

[0458] *특정 징후*

[0459] 특정 구현예에서, 개체를 치료하는 방법이 본원에서 제공되고, 이 방법은 본원에 기재된 바와 같은 하나 이상의 약제학적 조성물을 투여하는 단계를 포함한다. 특정 구현예에서, 개체는 신경변성 질환을 갖는다. 특정 구현예에서, 상기 개체는 비제한적으로 타우병증, 알츠하이머 질환, 전두측두엽 치매 (FTD), FTDP-17, 진행성 핵상안근 마비 (PSP), 만성 외상성 뇌증 (CTE), 뇌피질 기저 신경절 퇴행증 (CBD), 간질, 및 드라벳 증후군을 포함하는 신경변성 질환이 발병할 위험에 처해있다. 특정 구현예에서, 개체는 타우 관련된 질환을 갖는 것으로 동정된다. 특정 구현예에서, 개체에서 타우 발현은 방지적으로 감소시키는 방법이 제공된다. 특정 구현예는 타우 핵산에 표적화된 안티센스 화합물의 치료학적 유효량을 개체에 투여함으로써 이를 필요로하는 개체를 치료하는 것을 포함한다.

[0460] 일 구현예에서, 타우 핵산에 표적화된 안티센스 화합물의 치료학적 유효량의 투여는 개체에서 타우 수준을 모니터링하여 안티센스 화합물 투여에 대한 개체의 반응을 측정하는 것을 수반한다. 안티센스 화합물 투여에 대한 개체의 반응은 치료적 처치의 양 및 기간을 결정하는 의료진에 의하여 사용될 수 있다.

[0461] 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물의 투여는 적어도 15, 20, 25, 30, 35, 40, 45, 50, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 또는 100%, 또는 상기 값 중 임의의 2개에 의하여 정의된 범위 내로 타우 발현의 감소를 초래한다. 특정 구현예에서, 타우 핵산에 표적화된 안티센스 화합물의 투여는 동물에서 개선된 운동 기능을 초래한다. 특정 구현예에서, 타우 안티센스 화합물의 투여는 적어도 15, 20, 25, 30, 35, 40, 45, 50, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 또는 100%, 또는 상기 값 중 임의의 2개에 의하여 정의된 범위 내로 운동 기능을 개선한다.

[0462] 특정 구현예에서, 타우에 표적화된 안티센스 화합물을 포함하는 약제학적 조성물은 타우병증, 알츠하이머 질환, 전두측두엽 치매 (FTD), FTDP-17, 진행성 핵상안근 마비 (PSP), 만성 외상성 뇌증 (CTE), 뇌피질 기저 신경절 퇴행증 (CBD), 간질, 및 드라벳 증후군을 포함하는 신경변성 질환을 앓고 있거나 이에 취약한 환자를 치료하는

약제의 제조에 사용된다.

[0463] *특정 빈발 영역*

[0464] **1. 서열 번호: 1의 핵염기 135783-135980**

[0465] 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 서열 번호: 1의 표적 핵염기 135783-135980 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자 은행 수탁 번호 유전자 은행 수탁 번호 NT_010783.15)를 표적화하기 위하여 설계된다. 특정 구현예에서, 핵염기 135783-135980은 빈발 영역이다. 특정 구현예에서, 핵염기 135783-135980은 안티센스 올리고뉴클레오타이드에 의하여 표적화된다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 그 길이가 18, 19, 또는 20개의 핵염기이다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머, 5-9-5 MOE 갭머, 5-7-6 MOE 갭머 및 5-8-5 MOE 갭머이다. 특정 구현예에서, 안티센스 화합물의 뉴클레오사이드는 포스포로티오에이트 뉴클레오사이드간 연결으로 연결된다. 특정 구현예에서, 안티센스 화합물의 각각의 뉴클레오사이드간 연결은 포스포디에스테르 뉴클레오사이드간 연결이다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드의 뉴클레오사이드는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결에 의하여 연결된다 (예컨대 안티센스 올리고뉴클레오타이드는 "혼합 뼈대"를 갖는다).

[0466] 특정 구현예에서, 핵염기 135783-135980은 하기 ISIS 번호에 의하여 표적화된다: 424879, 424880, 548937, 613114-613120, 622096-622150, 623988-623996, 664511-664542, 및 664661-664819.

[0467] 특정 구현예에서, 핵염기 135783-135980은 하기 서열 번호에 의하여 표적화된다: 56, 57, 248, 462-467, 1668-1698, 2025-2048, 2301-2309, 2331- 2443, 및 2478-2483.

[0468] 특정 구현예에서, 핵염기 135783-135980를 표적화하는 안티센스 올리고뉴클레오타이드는 시험관내 및/또는 시험관내에서의 타우 mRNA 및 또는 단백질 수준의 적어도 12%, 적어도 13%, 적어도 14%, 적어도 15%, 적어도 16%, 적어도 17%, 적어도 18%, 적어도 19%, 20%, 적어도 21%, 적어도 22%, 적어도 23%, 적어도 24%, 적어도 25%, 적어도 26%, 적어도 27%, 적어도 28%, 적어도 29%, 적어도 30%, 적어도 31%, 적어도 32%, 적어도 33%, 적어도 34%, 적어도 35%, 적어도 36%, 적어도 37%, 적어도 38%, 적어도 39%, 적어도 40%, 적어도 41%, 적어도 42%, 적어도 43%, 적어도 44%, 적어도 45%, 적어도 46%, 적어도 47%, 적어도 48%, 적어도 49%, 적어도 50%, 적어도 51%, 적어도 52%, 적어도 53%, 적어도 54%, 적어도 55%, 적어도 56%, 적어도 57%, 적어도 58%, 적어도 59%, 적어도 60%, 적어도 61%, 적어도 62%, 적어도 63%, 적어도 64%, 적어도 65%, 적어도 66%, 적어도 67%, 적어도 68%, 적어도 69%, 적어도 70%, 적어도 71%, 적어도 72%, 적어도 73%, 적어도 74%, 적어도 75%, 적어도 76%, 적어도 77%, 적어도 78%, 적어도 79%, 적어도 80%, 적어도 81%, 적어도 82%, 적어도 83%, 적어도 84%, 적어도 85%, 적어도 86%, 적어도 87%, 적어도 88%, 적어도 89%, 적어도 90%, 적어도 91%, 적어도 92%, 또는 적어도 93%의 감소를 달성한다.

[0469] **2. 서열 번호: 1의 핵염기 135853-135872**

[0470] 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 서열 번호: 1의 표적 핵염기 135853-135872 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자 은행 수탁 번호 유전자 은행 수탁 번호 NT_010783.15)를 표적화하기 위하여 설계된다. 특정 구현예에서, 핵염기 135853-135872는 빈발 영역이다. 특정 구현예에서, 핵염기 135853-135872은 안티센스 올리고뉴클레오타이드에 의하여 표적화된다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 그 길이가 18, 19, 또는 20개의 핵염기이다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머, 5-9-5 MOE 갭머, 5-7-6 MOE 갭머 또는 5-8-5 MOE 갭머이다. 특정 구현예에서, 안티센스 화합물의 뉴클레오사이드는 포스포로티오에이트 뉴클레오사이드간 연결으로 연결된다. 특정 구현예에서, 안티센스 화합물의 각각의 뉴클레오사이드간 연결은 포스포디에스테르 뉴클레오사이드간 연결이다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드의 뉴클레오사이드는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결에 의하여 연결된다 (예컨대 안티센스 올리고뉴클레오타이드는 "혼합 뼈대"를 갖는다).

[0471] 특정 구현예에서, 핵염기 135853-135872은 하기 ISIS 번호에 의하여 표적화된다: 424879, 424880, 613117, 613118, 622114-622125, 623993-623996, 664522-664542, 664676-664713, 664729-664766, 및 664783-664819.

[0472] 특정 구현예에서, 핵염기 135853-135872은 하기 서열 번호에 의하여 표적화된다: 56, 57, 248, 464-465, 1668-1673, 2039-2048, 2306-2309, 2345-2443, 및 2478-2483.

[0473] 특정 구현예에서, 핵염기 135853-135872를 표적화하는 안티센스 올리고뉴클레오타이드는 시험관내 및/또는 시험관내에서의 타우 mRNA 및 또는 단백질 수준의 적어도 36%, 적어도 37%, 적어도 38%, 적어도 39%, 적어도 40%, 적어도 41%, 적어도 42%, 적어도 43%, 적어도 44%, 적어도 45%, 적어도 46%, 적어도 47%, 적어도 48%, 적어도 49%, 적어도 50%, 적어도 51%, 적어도 52%, 적어도 53%, 적어도 54%, 적어도 55%, 적어도 56%, 적어도 57%, 적어도 58%, 적어도 59%, 적어도 60%, 적어도 61%, 적어도 62%, 적어도 63%, 적어도 64%, 적어도 65%, 적어도 66%, 적어도 67%, 적어도 68%, 적어도 69%, 적어도 70%, 적어도 71%, 적어도 72%, 적어도 73%, 적어도 74%, 적어도 75%, 적어도 76%, 적어도 77%, 적어도 78%, 적어도 79%, 적어도 80%, 적어도 81%, 적어도 82%, 적어도 83%, 적어도 84%, 적어도 85%, 적어도 86%, 또는 적어도 87%의 감소를 달성한다.

[0474] **3. 서열 번호: 1의 핵염기 135783-135929**

[0475] 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 서열 번호: 1의 표적 핵염기 135783-135929 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자 은행 수탁 번호 유전자 은행 수탁 번호 NT_010783.15)를 표적화하기 위하여 설계된다. 특정 구현예에서, 핵염기 135783-135929는 빈발 영역이다. 특정 구현예에서, 핵염기 135783-135929 안티센스 올리고뉴클레오타이드에 의하여 표적화된다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 그 길이가 18, 19, 또는 20개의 핵염기이다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머, 5-9-5 MOE 갭머, 5-7-6 MOE 갭머 또는 5-8-5 MOE 갭머이다. 특정 구현예에서, 안티센스 화합물의 뉴클레오사이드는 포스포로티오에이트 뉴클레오사이드간 연결으로 연결된다. 특정 구현예에서, 안티센스 화합물의 각각의 뉴클레오사이드간 연결은 포스포디에스테르 뉴클레오사이드간 연결이다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드의 뉴클레오사이드는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결에 의하여 연결된다 (예컨대 안티센스 올리고뉴클레오타이드는 "혼합 뼈대"를 갖는다).

[0476] 특정 구현예에서, 핵염기 135783-135929는 하기 ISIS 번호에 의하여 표적화된다: 424879, 424880, 548937, 613114-613119, 622096-622138, 623988-623996, 664511-664542, 및 664661-664819.

[0477] 특정 구현예에서, 핵염기 135783-135929는 하기 서열 번호에 의하여 표적화된다: 56, 57, 248, 462-466, 1668-1686, 2025-2048, 2301-2309, 2331-2443, 및 2478-2483.

[0478] 특정 구현예에서, 핵염기 135783-135929를 표적화하는 안티센스 올리고뉴클레오타이드는 시험관내 및/또는 시험관내에서의 타우 mRNA 및 또는 단백질 수준의 적어도 12%, 적어도 13%, 적어도 14%, 적어도 15%, 적어도 16%, 적어도 17%, 적어도 18%, 적어도 19%, 20%, 적어도 21%, 적어도 22%, 적어도 23%, 적어도 24%, 적어도 25%, 적어도 26%, 적어도 27%, 적어도 28%, 적어도 29%, 적어도 30%, 적어도 31%, 적어도 32%, 적어도 33%, 적어도 34%, 적어도 35%, 적어도 36%, 적어도 37%, 적어도 38%, 적어도 39%, 적어도 40%, 적어도 41%, 적어도 42%, 적어도 43%, 적어도 44%, 적어도 45%, 적어도 46%, 적어도 47%, 적어도 48%, 적어도 49%, 적어도 50%, 적어도 51%, 적어도 52%, 적어도 53%, 적어도 54%, 적어도 55%, 적어도 56%, 적어도 57%, 적어도 58%, 적어도 59%, 적어도 60%, 적어도 61%, 적어도 62%, 적어도 63%, 적어도 64%, 적어도 65%, 적어도 66%, 적어도 67%, 적어도 68%, 적어도 69%, 적어도 70%, 적어도 71%, 적어도 72%, 적어도 73%, 적어도 74%, 적어도 75%, 적어도 76%, 적어도 77%, 적어도 78%, 적어도 79%, 적어도 80%, 적어도 81%, 적어도 82%, 적어도 83%, 적어도 84%, 적어도 85%, 적어도 86%, 적어도 87%, 적어도 88%, 적어도 89%, 적어도 90%, 적어도 91%, 적어도 92%, 또는 적어도 93%의 감소를 달성한다.

[0479] **4. 서열 번호: 1의 핵염기 135783-135914**

[0480] 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 서열 번호: 1의 표적 핵염기 135783-135914 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자 은행 수탁 번호 유전자 은행 수탁 번호 NT_010783.15)를 표적화하기 위하여 설계된다. 특정 구현예에서, 핵염기 135783-135914는 빈발 영역이다. 특정 구현예에서, 핵염기 135783-135914는 안티센스 올리고뉴클레오타이드에 의하여 표적화된다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 그 길이가 18, 19, 또는 20개의 핵염기이다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드는 갭머이다. 특정 구현예에서, 갭머는 5-10-5 MOE 갭머, 5-9-5 MOE 갭머, 5-7-6 MOE 갭머 또는 5-8-5 MOE 갭머이다. 특정 구현예에서, 안티센스 화합물의 뉴클레오사이드는 포스포로티오에이트 뉴클레오사이드간 연결으로 연결된다. 특정 구현예에서, 안티센스 화합물의 각각의 뉴클레오사이드간 연결은 포스포디에스테르 뉴클레오사이드간 연결이다. 특정 구현예에서, 안티센스 올리고뉴클레오타이드의 뉴클레오사이드는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결에 의하여 연결된다 (예컨대 안티센스 올리고뉴클레오타이드는 "혼합

뼈대"를 갖는다).

[0481] 특정 구현예에서, 핵염기 135783-135914은 하기 ISIS 번호에 의하여 표적화된다: 424879, 424880, 548937, 613114-613119, 622096-622133, 623988-623996, 664511-664542, 664661-664819.

[0482] 특정 구현예에서, 핵염기 135783-135914는 하기 서열 번호에 의하여 표적화된다: 56, 57, 248, 462-466, 1668-1681, 2025-2048, 2301-2309, 2331-2443, 및 2478-2483.

[0483] 특정 구현예에서, 핵염기 135783-135914은 하기 ISIS 번호에 의하여 표적화된다: 424879, 424880, 548937, 613114-613119, 622096- 622133, 및 623988- 623996.

[0484] 특정 구현예에서, 핵염기 135783-135914는 하기 서열 번호에 의하여 표적화된다: 56, 57, 248, 462-466, 1668-1681, 2025-2048, 및 2301-2309.

[0485] 특정 구현예에서, 핵염기 135783-135914를 표적화하는 안티센스 올리고뉴클레오타이드는 시험관내 및/또는 시험관내에서의 타우 mRNA 및 또는 단백질 수준의 적어도 12%, 적어도 13%, 적어도 14%, 적어도 15%, 적어도 16%, 적어도 17%, 적어도 18%, 적어도 19%, 20%, 적어도 21%, 적어도 22%, 적어도 23%, 적어도 24%, 적어도 25%, 적어도 26%, 적어도 27%, 적어도 28%, 적어도 29%, 적어도 30%, 적어도 31%, 적어도 32%, 적어도 33%, 적어도 34%, 적어도 35%, 적어도 36%, 적어도 37%, 적어도 38%, 적어도 39%, 적어도 40%, 적어도 41%, 적어도 42%, 적어도 43%, 적어도 44%, 적어도 45%, 적어도 46%, 적어도 47%, 적어도 48%, 적어도 49%, 적어도 50%, 적어도 51%, 적어도 52%, 적어도 53%, 적어도 54%, 적어도 55%, 적어도 56%, 적어도 57%, 적어도 58%, 적어도 59%, 적어도 60%, 적어도 61%, 적어도 62%, 적어도 63%, 적어도 64%, 적어도 65%, 적어도 66%, 적어도 67%, 적어도 68%, 적어도 69%, 적어도 70%, 적어도 71%, 적어도 72%, 적어도 73%, 적어도 74%, 적어도 75%, 적어도 76%, 적어도 77%, 적어도 78%, 적어도 79%, 적어도 80%, 적어도 81%, 적어도 82%, 적어도 83%, 적어도 84%, 적어도 85%, 적어도 86%, 적어도 87%, 적어도 88%, 적어도 89%, 적어도 90%, 적어도 91%, 적어도 92%, 또는 적어도 93%의 감소를 달성한다.

[0486] **실시예**

[0487] ***참조에 의한 비제한 개시내용 및 편입***

[0488] 본 명세서에 기술된 특정 화합물, 조성물 및 방법은 특정 구현예에 따라 구체성을 갖고 기술되어 있지만, 하기 실시예는 단지 본 명세서에 기술된 화합물들을 설명하는데 도움이 되며, 이들을 제한하고자 의도되는 것은 아니다. 본 출원에서 열거된 각각의 참조문헌은 본 발명에 온전히 참고로 포함된다.

[0489] **실시예 1: MOE 갭머에 의한 HepG2 세포에서의 인간 타우의 안티센스 억제**

[0490] 안티센스 올리고뉴클레오타이드는 타우 핵산을 표적화하도록 설계되었으며, 시험관내에서 타우 mRNA에 대한 그들의 효과에 대해서 시험되었다. 100 nM 안티센스 올리고뉴클레오타이드와 리포펙틴 시약을 사용하여 배양된 HepG2 세포를 형질감염시켰다. 대략 24 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104 (정방향 서열 GGAGATCATATAGACAATCAAGTGCAA, 본 발명에서는 서열 번호: 10으로 지정됨; 역방향 서열 AGCTTGTGGGTTTCAATCTTTTTATT, 본 발명에서는 서열 번호: 11로 지정됨; 프로브 서열 CACCCACGTCCCTGGCGGA, 본 발명에서는 서열 번호: 12로 지정됨)가 mRNA 수준을 측정하기 위하여 사용되었다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한, 타우의 억제율로서 표현된다.

[0491] 하기 표에서 새롭게 설계된 키메라 안티센스 올리고뉴클레오타이드는 5-10-5 MOE 갭머 (gapmer)로서 설계되었다. 갭머는 길이가 20개의 뉴클레오사이드이고, 여기에서 중앙 갭 분절은 10 개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5 개의 뉴클레오사이드를 포함하는, 양 측면 (5' 및 3' 방향으로) 상의 윙 분절에 의하여 플랭킹된다. 5' 윙 분절 내의 각각의 뉴클레오사이드 및 3' 윙 분절 내의 각각의 뉴클레오사이드는 2'-MOE 변형을 갖는다. 각각의 갭머에서의 뉴클레오사이드간 연결은 포스포로티오에이트 연결이다. 각각의 갭머에서의 모든 시토신 잔기는 5-메틸시토신이다. "개시 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 5'-모스트(most) 뉴클레오사이드를 나타낸다. "정지 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 3'-모스트(most) 뉴클레오사이드를 나타낸다. 하기 표 1에 열거된 각각의 갭머는 본원에 개시된 서열 번호: 1과 같이 지정된 인간 타우 게놈 서열 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자은행 수탁 번호 NT_010783.15) 또는 서열 번호: 2와 같이 지정된 인간 타우 mRNA 서열 (유전자은행 수탁 번호 NM_001123066.

3)에 표적화된다. 'n/a'는 올리고뉴클레오타이드가 100% 상보성을 갖는 유전자 서열을 표적화하지 않는다는 것이다. 하기 표 2에 열거된 서열은 100% 상보성을 갖는 서열 번호: 1 또는 2를 표적화하지 않지만, 대신 서열 번호: 3 (엑손 3, 4, 6, 8, 10, 및 12를 건너뛰는, 변이체 mRNA, 유전자 은행 수탁 번호 NM_016841.4) 또는 서열 번호: 4 (뉴클레오타이드 2624000 내지 2761000로부터 절단된 유전자 은행 수탁 번호 NT_010783.14)을 표적화한다.

[0492] **표 1**

[0493] 서열 번호: 1 및 2를 표적화하는 5-10-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	서열 번호
424863	n/a	n/a	TTGTAGACTATTTGCACACT	59	2240	2259	20
433519	28769	28788	CACAGGCAGATGCGAACCCT	57	n/a	n/a	21
433520	47181	47200	TGGTGGAGACAAGACATTCT	57	n/a	n/a	22
433521	71387	71406	CCATCCCCTAATAGTTAGCA	29	n/a	n/a	23
433522	72861	72880	CATGAGGCTTGGGATCTGAA	49	n/a	n/a	24
433474	73879	73898	GTGATCTTCCATCACTTCGA	61	345	364	25
433523	73980	73999	GTCCACTAACCTTTCAGGCC	63	n/a	n/a	26
433518	83423	83442	AGCATCAGAGGTTTCAGAGC	46	501	520	27
424852	83437	83456	GTTGGAGTGCTCTTAGCATC	58	515	534	28
433513	85934	85953	GGCAGCCTGCTTGCCGGGAG	68	573	592	29
433524	87927	87946	GAGGATTTCCTTGGAGAGAG	53	n/a	n/a	30
433525	89950	89969	GTTCACTGACCTTGGGTCAC	38	n/a	n/a	31
433526	91248	91267	ATGATTTCTAGAGGTCATGC	61	n/a	n/a	32
433514	95121	95140	AGAGGAAATCCACAGGGAGG	43	1120	1139	33
433515	95372	95391	TTCAGAGGGCTCTGGAAGGT	58	1371	1390	34
433527	95790	95809	ACACCATGAGGGCACCCGTC	65	n/a	n/a	35
433528	98549	98568	ACCATGCGAGCTGATAAAAT	46	n/a	n/a	36
433516	101406	101425	AAGGTTTTAGCAGAGGAACG	50	1514	1533	37
433517	101507	101526	AGGAAGGTGGCTCTGGGCAC	73	1615	1634	38
433476	103087	103106	CCAGAGCTGGGTGGTGTCTT	60	n/a	n/a	39
433477	108040	108059	GGTGGAGTACGGACCACTGC	71	2006	2025	40
433478	108054	108073	AAGACGGCGACTTGGGTGGA	65	2020	2039	41
424857	108148	108167	TGGTGCTTCAGGTTCTCAGT	54	2114	2133	42
433529	121819	121838	TTATCTGCACCTTTGGTAGC	29	n/a	n/a	43
424859	121828	121847	TCTTATTAATTATCTGCACC	50	2149	2168	44
424860	121838	121857	AGATCCAGCTTCTTATTAAT	36	2159	2178	45
424861	121846	121865	CGTTGCTAAGATCCAGCTTC	48	2167	2186	46
424862	121865	121884	GAGCCACACTTGGACTGGAC	79	2186	2205	47
433530	122497	122516	GGTGGCGCAGGCTAAGCATA	52	n/a	n/a	48
424864	125798	125817	GAGCCACACTTGGAGGTCAC	63	2279	2298	49
433531	125834	125853	ACAGGGCTACCTGGTTTATG	53	n/a	n/a	50
424866	130141	130160	ATTTTACTTCCACCTGGCCA	70	2329	2348	51

[0494]

433479	130188	130207	GGACCCAATCTTCGACTGGA	70	2376	2395	52
424926	135467	135486	GTGGGTTTCAATCTGCAAGA	39	n/a	n/a	53
424869	135475	135494	GTCAGCTTGTGGGTTTCAAT	74	2438	2457	54
433480	135673	135692	GATCACAAACCCTGCTTGGC	60	2636	2655	55
424879	135848	135867	TGATTTTGAAGTCCCGAGCC	64	2811	2830	56
424880	135853	135872	ATCACTGATTTTGAAGTCCC	54	2816	2835	57
433481	136033	136052	CAGAAGCAGCTTTCAGAGCC	38	2996	3015	58
433482	136118	136137	AAATCCTTTGTTGCTGCCAC	37	3081	3100	59
424882	136425	136444	CCCACAGGCTGCCCTGCAGA	57	3388	3407	60
433483	136491	136510	GGAGGTCATCCACGAAGTGC	67	3454	3473	61
433484	136577	136596	GGAAGCCCCTCAACTCAGGC	28	3540	3559	62
433485	136655	136674	GGTCTGCAAAGTGGCCAAAA	49	3618	3637	63
424883	136675	136694	TGGTTAGCCCTAAAGTCCCA	54	3638	3657	64
433486	136686	136705	ACAAAGAGAACTGGTTAGCC	39	3649	3668	65
424884	136703	136722	AAGAGGCACAAGTCCTTACA	40	3666	3685	66
433487	136748	136767	CAGAGATGCCAGTGGCCCAG	70	3711	3730	67
433488	137083	137102	GGAACCGAATCAGATCATGA	54	4046	4065	68
433489	137387	137406	TGGAGGGCTGATACTATGCA	45	4350	4369	69
433490	137430	137449	AAAAGAACCATTTCCAAGGG	41	4393	4412	70
433491	137540	137559	ATCCAACTACAACTCAACAG	17	4503	4522	71
424894	137579	137598	ATCATAGTCACTCTGGTGAA	56	4542	4561	72
433492	137694	137713	GCCACACGAGTCCCAGTGTG	45	4657	4676	73
433493	137731	137750	AAAACTTGGGAGGCCCCAGC	50	4694	4713	74
433494	138173	138192	GATCCAGGACAGGCAATTCA	58	5136	5155	75
433495	138205	138224	TCCTCAGGCAGGCAGCTTGG	49	5168	5187	76
433496	138303	138322	TTCTCATGGCAGCAGATGGA	51	5266	5285	77
433497	138338	138357	TTAGGCAGCAATGTTTTGCA	18	5301	5320	78
433498	138503	138522	AGAGTTCTGGGCCCAGAGAC	73	5466	5485	79
433499	138675	138694	AGGAAGAGGAACCGAGGTGC	59	5638	5657	80
433500	138774	138793	TCTTAGGCTGGCCCCAAGAG	36	5737	5756	81
433501	138812	138831	TCAATTTATCTGCCAGCACT	28	5775	5794	82
433502	138845	138864	TCCTCATTTAAGATCACAAG	36	5808	5827	83
433503	138983	139002	ATGGAACTATTGATAAAGTG	47	5946	5965	84
433504	139003	139022	CACCACTGAAGTCAATTTAA	23	5966	5985	85
433505	139112	139131	AGTTTAAGTGCTGCACCCCA	52	6075	6094	86
433506	139137	139156	GAAATCATGAAAAGGGTTAC	25	6100	6119	87
433507	139154	139173	CTCTAGCAAATGTGGTTGAA	42	6117	6136	88
433508	139229	139248	AGCCAGCTGCCTGGGAAAGC	70	6192	6211	89
433509	139359	139378	TAGAGGGAAGGATGCCAAGG	56	6322	6341	90
433510	139406	139425	GTGTGTCTGGAGCCAGTGTG	49	6369	6388	91
424910	139675	139694	GAAATCATGGGACTTGCAAG	52	6638	6657	92
433512	139729	139748	AAAGCTAAGCTAAGATGATT	31	6692	6711	93
424913	139797	139816	TTACAGCAACAGTCAGTGTA	42	6760	6779	94

[0495]

[0496] **표 2**

[0497] 서열 번호: 3 및 4를 표적화하는 5-10-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	표적 서열 번호	표적 개시 부위	서열	억제율%	서열 번호
424917	3	968	TTGTAGACTATTTGCACCTT	51	95
433475	3	443	TCTTCAGCTTTCAGGCCAGC	68	96
433511	4	135519	AGAAGTTTTATGAAGCCGCA	13	97

[0498]

[0499] **실시예 2: 5-10-5 MOE 갭머에 의한 HepG2 세포에서의 인간 타우의 용량-의존적 안티센스 억제**

[0500] 타우 mRNA의 뚜렷한 시험관내 억제를 나타내는 상기 기술된 연구로부터의 갭머는 HepG2 세포에서의 다양한 용량에서 선택 및 시험되었다. 세포를 웰당 10,000 세포의 밀도로 플레이팅하고, 리포펙틴 시약을 사용하여 하기 표에 명시된 바와 같이 12.5 nM, 25.0 nM, 50.0 nM, 100.0 nM, 또는 200.0 nM 농도의 안티센스 올리고뉴클레오타

이드로 형질감염시켰다. 대략 16 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104를 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한, 타우의 억제율로서 표현된다. 타우 mRNA 수준은 안티센스 올리고뉴클레오타이드 처리된 세포에서 용량-의존적 방식으로 뚜렷하게 감소되었다.

[0501] **표 3**

ISIS 번호	12.5 nM	25.0 nM	50.0 nM	100.0 nM	200.0 nM
424862	17	24	41	64	84
424866	14	25	47	63	84
433498	27	42	61	79	82
433508	25	31	53	66	83
433517	25	34	57	72	78
433487	18	30	38	60	76
433477	23	31	51	71	80
433475	18	33	57	71	85
433513	24	30	50	71	77
433483	23	28	41	58	74
433527	19	32	46	60	77

[0502]

[0503] **실시예 3: 5-10-5 MOE 갭머에 의한 SH-SY5Y 세포에서의 인간 타우 안티센스 억제**

[0504] 안티센스 올리고뉴클레오타이드는 인간 타우 핵산을 표적화하도록 설계되었으며, 시험관내에서 타우 mRNA에 대한 그들의 효과에 대해서 시험하였다. 안티센스 올리고뉴클레오타이드는 유사한 배양 조건을 갖는 일련의 실험에서 시험되었다. 각 실험에 대한 결과는 하기 나타낸 개별 표에서 제시된다. 배양된 SH-SY5Y 세포를 전기천공을 사용하여 7,000 nM 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 24 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한 타우의 억제율로서 표현된다.

[0505] 하기 표에서 새롭게 설계된 키메라 안티센스 올리고뉴클레오타이드는 5-10-5 MOE 갭머 (gapmer)로서 설계되었다. 갭머는 길이가 20개의 뉴클레오사이드이고, 여기에서 중앙 갭 분절은 10 개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5 개의 뉴클레오사이드를 포함하는, 양 측면 (5' 및 3' 방향으로) 상의 윙 분절에 의하여 플랭킹된다. 5' 윙 분절 내의 각각의 뉴클레오사이드 및 3' 윙 분절 내의 각각의 뉴클레오사이드는 2'-MOE 변형을 갖는다. 각각의 갭머에서의 뉴클레오사이드간 연결은 포스포로티오에이트 연결이다. 각각의 갭머에서의 모든 시토신 잔기는 5-메틸시토신이다. "개시 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 5'-모스트(most) 뉴클레오사이드를 나타낸다. "정지 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 3'-모스트(most) 뉴클레오사이드를 나타낸다. 하기 표에 열거된 각각의 갭머는 본원에 개시된 서열 번호: 1과 같이 지정된 인간 타우 게놈 서열(뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자은행 수탁 번호 NT_010783.15) 또는 서열 번호: 2와 같이 지정된 인간 타우 mRNA 서열(유전자은행 수탁 번호 NM_001123066.3)에 표적화된다. 'n/a'는 안티센스 올리고뉴클레오타이드가 100% 상보성을 갖는 특정 유전자 서열을 표적화하지 않는다는 것이다.

[0506] **표 4**

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	서열 번호
548786	73867	73886	CACTTCGAACTCCTGGCGGG	73	333	352	98
548787	73869	73888	ATCACTTCGAACTCCTGGCG	64	335	354	99
548788	73871	73890	CCATCACTTCGAACTCCTGG	78	337	356	100
548789	73873	73892	TTCCATCACTTCGAACTCCT	49	339	358	101
548790	73875	73894	TCTTCCATCACTTCGAACTC	33	341	360	102
548791	73877	73896	GATCTTCCATCACTTCGAAC	54	343	362	103
433474	73879	73898	GTGATCTTCCATCACTTCGA	86	345	364	25
548792	73906	73925	CCTGTCCCCCAACCCGTACG	38	372	391	104

[0507]

548793	73908	73927	TTCCTGTCCCCCAACCCGTA	58	374	393	105
548794	73910	73929	CTTTCCTGTCCCCCAACCCG	55	376	395	106
548795	73912	73931	ATCTTTCCTGTCCCCCAACC	14	378	397	107
548796	73914	73933	TGATCTTTCCTGTCCCCCAA	59	380	399	108
548797	73916	73935	CCTGATCTTTCCTGTCCCCC	67	382	401	109
548798	73918	73937	CCCCTGATCTTTCCTGTCCC	67	384	403	110
548799	73920	73939	CCCCCCTGATCTTTCCTGTC	33	386	405	111
548800	73922	73941	AGCCCCCCTGATCTTTCCTG	45	388	407	112
548801	73924	73943	GTAGCCCCCCTGATCTTTCC	62	390	409	113
548802	73926	73945	GTGTAGCCCCCCTGATCTTT	42	392	411	114
548803	73928	73947	TGGTGTAGCCCCCCTGATCT	58	394	413	115
548804	73930	73949	CATGGTGTAGCCCCCCTGAT	62	396	415	116
548805	73932	73951	TGCATGGTGTAGCCCCCCTG	82	398	417	117
548806	73934	73953	GGTGCATGGTGTAGCCCCCC	79	400	419	118
548807	73936	73955	TTGGTGCATGGTGTAGCCCC	58	402	421	119
548808	73938	73957	TCTTGGTGCATGGTGTAGCC	60	404	423	120
548809	73940	73959	GGTCTTGGTGCATGGTGTAG	67	406	425	121
548810	73945	73964	CTCTTGGTCTTGGTGCATGG	61	411	430	122
548811	73958	73977	CGTCCGTGTCACCCTCTTGG	73	424	443	123
548812	98559	98578	GCTTTTACTGACCATGCGAG	68	1449	1468	124
548813	98561	98580	TTGCTTTTACTGACCATGCG	64	1451	1470	125
548814	98563	98582	CTTTGCTTTTACTGACCATG	40	1453	1472	126
548815	98565	98584	GTCTTTGCTTTTACTGACCA	60	1455	1474	127
548816	98567	98586	CCGTCTTTGCTTTTACTGAC	50	1457	1476	128
548817	98569	98588	TCCCGTCTTTGCTTTTACTG	46	1459	1478	129
548818	98571	98590	AGTCCCGTCTTTGCTTTTAC	41	1461	1480	130
548819	98573	98592	CCAGTCCCGTCTTTGCTTTT	37	1463	1482	131
548820	98577	98596	GCTTCCAGTCCCGTCTTTGC	43	1467	1486	132
548821	98579	98598	TCGCTTCCAGTCCCGTCTTT	35	1469	1488	133
548822	98581	98600	CATCGCTTCCAGTCCCGTCT	73	1471	1490	134
548823	98583	98602	GTCATCGCTTCCAGTCCCGT	63	1473	1492	135
548824	98585	98604	TTGTCATCGCTTCCAGTCCC	50	1475	1494	136
548825	98587	98606	TTTTGTCATCGCTTCCAGTC	46	1477	1496	137
548826	103023	103042	GGCCCTTCTGGCCTGGAGGG	64	1747	1766	138
548827	103025	103044	CTGGCCCTTCTGGCCTGGAG	29	1749	1768	139
548828	103027	103046	GCCTGGCCCTTCTGGCCTGG	40	1751	1770	140
548829	103029	103048	TGGCCTGGCCCTTCTGGCCT	12	1753	1772	141
548830	103031	103050	GTTGGCCTGGCCCTTCTGGC	53	1755	1774	142
548831	103052	103071	TTTTGCTGGAATCCTGGTGG	20	1776	1795	143
548832	103054	103073	GTTTTTGCTGGAATCCTGGT	29	1778	1797	144
548833	103056	103075	GGGTTTTTGCTGGAATCCTG	51	1780	1799	145
548834	103075	103094	GGTGTCTTTGGAGCGGGCGG	44	1799	1818	146
548835	103077	103096	GTGGTGTCTTTGGAGCGGGC	30	1801	1820	147

[0508]

548836	103079	103098	GGGTGGTGTCTTTGGAGCGG	38	1803	1822	148
548837	103081	103100	CTGGGTGGTGTCTTTGGAGC	29	1805	1824	149
548838	103083	103102	AGCTGGGTGGTGTCTTTGGA	37	1807	1826	150
548839	103085	103104	AGAGCTGGGTGGTGTCTTTG	0	1809	1828	151
548840	107921	107940	ATCCCCTGATTTTGGAGGTT	27	1887	1906	152
548841	107923	107942	CGATCCCCTGATTTTGGAGG	65	1889	1908	153
548842	107925	107944	TGCGATCCCCTGATTTTGGA	53	1891	1910	154
548843	107927	107946	GCTGCGATCCCCTGATTTTG	23	1893	1912	155
548844	107929	107948	CCGCTGCGATCCCCTGATTT	32	1895	1914	156
548845	107931	107950	AGCCGCTGCGATCCCCTGAT	51	1897	1916	157
548846	107933	107952	GTAGCCGCTGCGATCCCCTG	14	1899	1918	158
548847	107968	107987	CGGCTGCCGGGAGTGCCTGG	33	1934	1953	159
548848	107970	107989	AGCGGCTGCCGGGAGTGCCT	52	1936	1955	160
548849	107972	107991	GGAGCGGCTGCCGGGAGTGC	44	1938	1957	161
548850	108047	108066	CGACTTGGGTGGAGTACGGA	10	2013	2032	162
548851	108049	108068	GGCGACTTGGGTGGAGTACG	29	2015	2034	163
548852	108051	108070	ACGGCGACTTGGGTGGAGTA	39	2017	2036	164
548853	108053	108072	AGACGGCGACTTGGGTGGAG	6	2019	2038	165
548854	108055	108074	GAAGACGGCGACTTGGGTGG	0	2021	2040	166
548855	108057	108076	CGGAAGACGGCGACTTGGGT	40	2023	2042	167
548856	108059	108078	GGCGGAAGACGGCGACTTGG	38	2025	2044	168
548857	108061	108080	TTGGCGGAAGACGGCGACTT	41	2027	2046	169
548858	108063	108082	TCTTGGCGGAAGACGGCGAC	35	2029	2048	170
548859	108065	108084	GCTCTTGGCGGAAGACGGCG	54	2031	2050	171
548860	108067	108086	CGGCTCTTGGCGGAAGACGG	58	2033	2052	172
548861	108069	108088	GGCGGCTCTTGGCGGAAGAC	55	2035	2054	173
433498	138503	138522	AGAGTTCTGGGCCCAGAGAC	53	5466	5485	79

[0509]

[0510] **표 5**

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	서열 번호
548885	n/a	n/a	GGGAGATTCTTTCAGGCCAG	0	444	463	174
548893	n/a	n/a	GAGCTTTGAGTTGAGGGACC	0	1432	1451	175
548894	n/a	n/a	GACCATGCGAGCTTTGAGTT	13	1440	1459	176
548895	n/a	n/a	TACTGACCATGCGAGCTTTG	33	1444	1463	177
548881	6183	6202	ATAGTCGACAGAGGCGAGGA	43	283	302	178
548882	73840	73859	CATCCTGGTTCAAAGTTCAC	30	306	325	179
548883	73846	73865	CTCAGCCATCCTGGTTCAAA	39	312	331	180
548884	73847	73866	GCTCAGCCATCCTGGTTCAA	53	313	332	181
548886	83401	83420	GGTTCCTCAGATCCGTCCTC	53	479	498	182
548887	83438	83457	TGTTGGAGTGCTCTTAGCAT	33	516	535	183

[0511]

548888	85939	85958	TGCGCGGCAGCCTGCTTGCC	32	578	597	184
548889	94699	94718	ACCACCTTACCACTTTCAGG	35	698	717	185
548890	94775	94794	GGGAGCCCCAGGCATGCCGG	45	774	793	186
548891	95125	95144	TTGGAGAGGAAATCCACAGG	13	1124	1143	187
548892	95131	95150	GAAACTTTGGAGAGGAAATC	0	1130	1149	188
548896	98557	98576	TTTTACTGACCATGCGAGCT	40	1447	1466	189
548897	101425	101444	AAGGCAAGGCCTATTTTTCA	34	1533	1552	190
548898	101469	101488	TGGATCAGAGGGTCTGAGCT	40	1577	1596	191
548899	101501	101520	GTGGCTCTGGGCACACAGCA	63	1609	1628	192
548900	108037	108056	GGAGTACGGACCACTGCCAC	37	2003	2022	193
433477	108040	108059	GGTGGAGTACGGACCACTGC	21	2006	2025	40
548862	108071	108090	CAGGCGGCTCTTGGCGGAAG	24	2037	2056	194
548863	108073	108092	TGCAGGCGGCTCTTGGCGGA	34	2039	2058	195
548864	108075	108094	TCTGCAGGCGGCTCTTGGCG	40	2041	2060	196
548865	108129	108148	TGGAGCCGATCTTGGACTTG	23	2095	2114	197
548866	108131	108150	AGTGGAGCCGATCTTGGACT	4	2097	2116	198
548901	108134	108153	CTCAGTGGAGCCGATCTTGG	28	2100	2119	199
548902	108136	108155	TTCTCAGTGGAGCCGATCTT	9	2102	2121	200
548903	108155	108174	TCCCGGCTGGTGCTTCAGGT	33	2121	2140	201
548904	121675	121694	TTTCGGACTTGGCAGAGGCA	50	n/a	n/a	202
548905	121728	121747	GAGTGACATGCGCCACCCTG	65	n/a	n/a	203
548906	121736	121755	CTTTCGATGAGTGACATGCG	19	n/a	n/a	204
548907	121794	121813	AAAAGGATGAGTGACACGCC	58	n/a	n/a	205
548908	121916	121935	GTGAAGGTACTCACACTGCC	34	n/a	n/a	206
548909	121917	121936	TGTGAAGGTACTCACACTGC	21	n/a	n/a	207
548910	121992	122011	CTATGCAGTGTCTCGCAAGT	39	n/a	n/a	208
548911	122001	122020	GGATTTATTCTATGCAGTGT	38	n/a	n/a	209
548912	122002	122021	AGGATTTATTCTATGCAGTG	37	n/a	n/a	210
548913	122015	122034	TGAGAGCCCAAGAAGGATTT	15	n/a	n/a	211
548914	122022	122041	CAGATCCTGAGAGCCCAAGA	33	n/a	n/a	212
548915	122025	122044	AGCCAGATCCTGAGAGCCCA	55	n/a	n/a	213
548916	122137	122156	GGACCCAGAAATGCTGGGAC	18	n/a	n/a	214
548917	125555	125574	AAATGTGTTGTCGAAATTCT	0	n/a	n/a	215
548918	125568	125587	AGTCAGGGTGGAAAAATGTG	0	n/a	n/a	216
548919	125578	125597	AGCACATCCTAGTCAGGGTG	39	n/a	n/a	217
548920	125587	125606	GCCATGAGGAGCACATCCTA	45	n/a	n/a	218
548921	125600	125619	GTGGTTCCCAGCTGCCATGA	38	n/a	n/a	219
548922	125603	125622	ACAGTGGTTCCCAGCTGCCA	38	n/a	n/a	220
548923	125619	125638	CCCAGGCCCTTATTGGACAG	19	n/a	n/a	221
548867	125778	125797	CTTGCTCAGGTCAACTGGTT	45	2259	2278	222
548925	125812	125831	GGATGTTGCCTAATGAGCCA	35	2293	2312	223
548926	130194	130213	GTCCAGGGACCCAATCTTCG	87	2382	2401	224
548927	130196	130215	TTGTCCAGGGACCCAATCTT	48	2384	2403	225

[0512]

548928	135478	135497	AAGGTCAGCTTGTGGGTTTC	52	2441	2460	226
548868	135518	135537	CTCCGCCCCGTGGTCTGTCT	37	2481	2500	227
548869	135520	135539	ATCTCCGCCCCGTGGTCTGT	25	2483	2502	228
548870	135522	135541	CGATCTCCGCCCCGTGGTCT	48	2485	2504	229
548871	135524	135543	CACGATCTCCGCCCCGTGGT	38	2487	2506	230
548872	135526	135545	TACACGATCTCCGCCCCGTG	33	2489	2508	231
548873	135528	135547	TGTACACGATCTCCGCCCCG	22	2491	2510	232
548874	135530	135549	CTTGTACACGATCTCCGCCC	38	2493	2512	233
548875	135532	135551	GACTTGTACACGATCTCCGC	13	2495	2514	234
548876	135534	135553	GCGACTTGTACACGATCTCC	40	2497	2516	235
548877	135536	135555	TGGCGACTTGTACACGATCT	33	2499	2518	236
548878	135538	135557	ACTGGCGACTTGTACACGAT	25	2501	2520	237
548879	135540	135559	CCACTGGCGACTTGTACACG	19	2503	2522	238
548929	135546	135565	CAGACACCACTGGCGACTTG	33	2509	2528	239
548930	135593	135612	GCTGCCGGTGGAGGAGACAT	29	2556	2575	240
548931	135594	135613	TGCTGCCGGTGGAGGAGACA	19	2557	2576	241
548932	135600	135619	TGTCGATGCTGCCGGTGGAG	20	2563	2582	242
548933	135601	135620	ATGTCGATGCTGCCGGTGGA	20	2564	2583	243
548934	135610	135629	GAGTCTACCATGTCGATGCT	23	2573	2592	244
548880	135654	135673	CCAGGGAGGCAGACACCTCG	28	2617	2636	245
548935	135662	135681	CTGCTTGGCCAGGGAGGCAG	14	2625	2644	246
548936	135674	135693	TGATCACAAACCCTGCTTGG	25	2637	2656	247
548937	135786	135805	CCGAACTGCGAGGAGCAGCT	66	2749	2768	248
433498	138503	138522	AGAGTTCTGGGCCCAGAGAC	34	5466	5485	79

[0513]

[0514] **실시예 4: 5-10-5 MOE 갭머에 의한 SH-SY5Y 세포에서의 인간 타우의 용량-의존적 안티센스 억제**

[0515] 타우 mRNA의 뚜렷한 *시험관내* 억제를 나타내는 상기 기술된 연구로부터의 갭머는 SH-SY-5Y 세포에서의 다양한 용량에서 선택 및 시험되었다. 세포를 웰당 20,000 세포의 밀도로 플레이팅하고, 하기 표에 명시된 바와 같이 전기천공을 사용하여 1.25 μM, 2.50 μM, 5.00 μM, 10.00 μM, 및 20.00 μM 농도의 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 16 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한 타우의 억제율로서 표현된다. 타우 mRNA 수준은 안티센스 올리고뉴클레오타이드 처리된 세포에서 용량-의존적 방식으로 뚜렷하게 감소되었다.

[0516] **표 6**

ISIS 번호	1.25 μM	2.50 μM	5.00 μM	10.00 μM	20.00 μM
433474	29	54	74	83	88
433477	0	0	11	33	59
433498	0	10	30	53	71
548786	9	29	51	66	82
548787	19	27	61	85	87
548788	31	31	54	72	94
548805	19	48	62	81	96
548806	25	50	75	80	95
548811	21	42	60	74	94
548812	47	39	64	77	91
548822	0	32	52	62	91
548899	19	50	69	87	93
548905	11	32	57	80	95
548907	14	28	44	80	91
548937	24	43	66	82	91

[0517]

[0518] **실시예 5: 5-10-5 MOE 갭머에 의한 SH-SY5Y 세포에서의 인간 타우 안티센스 억제**

[0519] 안티센스 올리고뉴클레오타이드는 인간 타우 핵산을 표적화하도록 설계되었으며, 시험관내에서 타우 mRNA에 대한 그들의 효과에 대해서 시험하였다. 웰당 20,000 세포의 밀도로 배양된 SH-SY5Y 세포를 전기천공을 사용하여 6,000 nM 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 24 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한, 타우의 억제율로서 표현된다.

[0520] 하기 표에서 새롭게 설계된 키메라 안티센스 올리고뉴클레오타이드는 5-10-5 MOE 갭머 (gapmer)로서 설계되었다. 갭머는 길이가 20개의 뉴클레오사이드이고, 여기에서 중앙 갭 분절은 10 개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5 개의 뉴클레오사이드를 포함하는, 양 측면 (5' 및 3' 방향으로) 상의 윙 분절에 의하여 플랭킹된다. 5' 윙 분절 내의 각각의 뉴클레오사이드 및 3' 윙 분절 내의 각각의 뉴클레오사이드는 2'-MOE 변형을 갖는다. 각각의 갭머에서의 뉴클레오사이드간 연결은 포스포로티오에이트 연결이다. 각각의 갭머에서의 모든 시토신 잔기는 5-메틸시토신이다. "개시 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 5'-모스트(most) 뉴클레오사이드를 나타낸다. "정지 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 3'-모스트(most) 뉴클레오사이드를 나타낸다. 하기 표에 열거된 각각의 갭머는 본원에 개시된 서열 번호: 1과 같이 지정된 인간 타우 게놈 서열 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자 은행 수탁 번호 NT_010783.15)에 표적화된다.

[0521] **표 7**

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호
433474	73879	73898	GTGATCTTCCATCACTTCGA	63	25
559166	26760	26779	TGCTTACACACCACACACAC	0	249
	26944	26963			
559167	26761	26780	ATGCTTACACACCACACACA	4	250
	26945	26964			
559168	26762	26781	CATGCTTACACACCACACAC	0	251
	26946	26965			
559169	81022	81041	TACAGATATATGATTGGATG	0	252
	81125	81144			
559170	81023	81042	GTACAGATATATGATTGGAT	0	253
	81126	81145			
559171	81024	81043	TGTACAGATATATGATTGGA	0	254
	81127	81146			
559172	81025	81044	ATGTACAGATATATGATTGG	0	255
	81128	81147			
559173	81026	81045	TATGTACAGATATATGATTG	0	256
	81129	81148			
559174	81027	81046	TTATGTACAGATATATGATT	0	257
	81130	81149			
559175	81028	81047	ATTATGTACAGATATATGAT	0	258
	81131	81150			
559176	81029	81048	GATTATGTACAGATATATGA	0	259
	81132	81151			
559177	81030	81049	GGATTATGTACAGATATATG	0	260
	81133	81152			
559178	81031	81050	TGGATTATGTACAGATATAT	0	261
	81134	81153			
559179	81032	81051	ATGGATTATGTACAGATATA	0	262
	81135	81154			
559180	81033	81052	AATGGATTATGTACAGATAT	0	263
	81136	81155			
559181	81034	81053	GAATGGATTATGTACAGATA	0	264
	81137	81156			
559182	81035	81054	AGAATGGATTATGTACAGAT	0	265
	81138	81157			
559183	81036	81055	AAGAATGGATTATGTACAGA	0	266
	81139	81158			
559184	81037	81056	GAAGAATGGATTATGTACAG	0	267
	81140	81159			
559185	81038	81057	GGAAGAATGGATTATGTACA	0	268

[0522]

	81141	81160			
559186	81039	81058	GGGAAGAATGGATTATGTAC	0	269
	81142	81161			
559187	81040	81059	AGGGAAGAATGGATTATGTA	0	270
	81143	81162			
559188	81041	81060	GAGGGAAGAATGGATTATGT	0	271
	81144	81163			
559189	81042	81061	CGAGGGAAGAATGGATTATG	0	272
	81145	81164			
559190	81043	81062	CCGAGGGAAGAATGGATTAT	33	273
	81146	81165			
559191	81044	81063	ACCGAGGGAAGAATGGATTA	12	274
	81147	81166			
559192	81045	81064	AACCGAGGGAAGAATGGATT	1	275
	81148	81167			
559193	81046	81065	GAACCGAGGGAAGAATGGAT	0	276
	81149	81168			
559194	81047	81066	TGAACCGAGGGAAGAATGGA	0	277
	81150	81169			
559195	81048	81067	ATGAACCGAGGGAAGAATGG	0	278
	81151	81170			
559196	81049	81068	GATGAACCGAGGGAAGAATG	0	279
	81152	81171			
559197	81050	81069	GGATGAACCGAGGGAAGAAT	0	280
	81153	81172			
559198	81051	81070	TGGATGAACCGAGGGAAGAA	0	281
	81154	81173			
559199	81052	81071	ATGGATGAACCGAGGGAAGA	0	282
	81155	81174			
559200	81053	81072	GATGGATGAACCGAGGGAAG	0	283
	81156	81175			
559201	81054	81073	GGATGGATGAACCGAGGGAA	1	284
	81157	81176			
559202	81055	81074	TGGATGGATGAACCGAGGGA	0	285
	81158	81177			
559203	81056	81075	ATGGATGGATGAACCGAGGG	0	286
	81159	81178			
559204	81057	81076	GATGGATGGATGAACCGAGG	0	287
	81160	81179			
559205	81058	81077	GGATGGATGGATGAACCGAG	0	288
	81161	81180			
559206	81096	81115	AAGGATGAAGGAAGGGATGG	0	289
	81199	81218			

[0523]

559207	81097	81116	GAAGGATGAAGGAAGGGATG	0	290
	81200	81219			
559208	81098	81117	GGAAGGATGAAGGAAGGGAT	0	291
	81201	81220			
559209	81100	81119	TAGGAAGGATGAAGGAAGGG	0	292
	81203	81222			
559210	81101	81120	ATAGGAAGGATGAAGGAAGG	0	293
	81204	81223			
559211	81102	81121	GATAGGAAGGATGAAGGAAG	0	294
	81205	81224			
559212	81103	81122	TGATAGGAAGGATGAAGGAA	0	295
	81206	81225			
559213	81104	81123	ATGATAGGAAGGATGAAGGA	0	296
	81207	81226			
559214	81105	81124	GATGATAGGAAGGATGAAGG	0	297
	81208	81227			
559215	81106	81125	GGATGATAGGAAGGATGAAG	0	298
	81209	81228			
559216	81107	81126	TGGATGATAGGAAGGATGAA	0	299
	81210	81229			
559217	81108	81127	ATGGATGATAGGAAGGATGA	0	300
	81211	81230			
559218	81109	81128	GATGGATGATAGGAAGGATG	0	301
	81212	81231			
559219	81110	81129	GGATGGATGATAGGAAGGAT	0	302
	81213	81232			
559220	81111	81130	TGGATGGATGATAGGAAGGA	0	303
	81214	81233			
559221	81112	81131	TTGGATGGATGATAGGAAGG	0	304
	81215	81234			
559222	81113	81132	ATTGGATGGATGATAGGAAG	0	305
	81216	81235			
559223	81114	81133	GATTGGATGGATGATAGGAA	0	306
	81217	81236			
559224	81115	81134	TGATTGGATGGATGATAGGA	0	307
	81218	81237			
559225	81116	81135	ATGATTGGATGGATGATAGG	0	308
	81219	81238			
559226	81117	81136	TATGATTGGATGGATGATAG	0	309
	81220	81239			
559227	80890	80909	AGATATGGGTGGATGGATGG	0	310
	81472	81491			
559228	80891	80910	AAGATATGGGTGGATGGATG	0	311

[0524]

	81473	81492			
559229	80892	80911	GAAGATATGGGTGGATGGAT	0	312
	81474	81493			
559230	98881	98900	ACACACCTTCATTTACTGTC	79	313
	98918	98937			
559231	98882	98901	AACACACCTTCATTTACTGT	56	314
	98919	98938			
559232	98883	98902	AAACACACCTTCATTTACTG	59	315
	98920	98939			
559233	98884	98903	CAAACACACCTTCATTTACT	51	316
	98921	98940			
559234	98885	98904	TCAAACACACCTTCATTTAC	25	317
	98922	98941			
559235	98887	98906	TTTCAAACACACCTTCATTT	25	318
	98924	98943			
559236	98888	98907	TTTTCAAACACACCTTCATT	14	319
	98925	98944			
559237	98889	98908	GTTTTCAAACACACCTTCAT	42	320
	98926	98945			
559238	98890	98909	GGTTTTCAAACACACCTTCA	79	321
	98927	98946			
559239	98891	98910	TGGTTTTCAAACACACCTTC	87	322
	98928	98947			
559240	111795	111814	GAAAACAGAGAAAAGCACAA	12	323
	111819	111838			
559241	119594	119613	AGAAGTGATATCATATCCTA	63	324
	119905	119924			
559242	119595	119614	AAGAAGTGATATCATATCCT	74	325
	119906	119925			

[0525]

[0526] **실시예 6: 5-10-5 MOE 갭머에 의한 SH-SY5Y 세포에서의 인간 타우의 용량-의존적 안티센스 억제**

[0527] 타우 mRNA의 뚜렷한 *시험관내* 억제를 나타내는 상기 기술된 연구로부터의 갭머는 SH-SY-5Y 세포에서의 다양한 용량에서 선택 및 시험되었다. 세포를 웰당 20,000 세포의 밀도로 플레이팅하고, 하기 표에 명시된 바와 같이 전기천공을 사용하여 0.625 μM, 1.25 μM, 2.500 μM, 5.00 μM, 10.00 μM, 및 20.00 μM 농도의 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 16 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한 타우의 억제율로서 표현된다. 타우 mRNA 수준은 안티센스 올리고뉴클레오타이드 처리된 세포에서 용량-의존적 방식으로 뚜렷하게 감소되었다.

[0528] **표 8**

ISIS 번호	0.625 μM	1.25 μM	2.50 μM	5.00 μM	10.00 μM	20.00 μM
433474	17	39	53	73	81	88
559230	30	50	67	81	92	94
559231	0	16	26	44	63	83
559232	10	12	23	30	62	79
559233	5	10	21	38	62	81
559237	0	16	27	31	58	88
559238	25	18	72	77	86	86
559239	26	47	64	80	88	93
559241	0	18	34	61	74	95
559242	13	20	23	47	71	83

[0529]

[0530] **실시예 7: 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 MOE 갭머에 의한 SH-SY5Y 세포에서의 인간 타우 안티센스 억제**

[0531] 안티센스 올리고뉴클레오타이드는 타우 핵산을 표적화하도록 설계되었으며, 시험관내에서 타우 mRNA에 대한 그들의 효과에 대해서 시험되었다. 안티센스 올리고뉴클레오타이드는 유사한 배양 조건을 갖는 일련의 실험에서 시험되었다. 각 실험에 대한 결과는 하기 나타낸 개별 표에서 제시된다. 배양된 SH-SY5Y 세포를 전기천공을 사용하여 8,000 nM 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 24 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한, 타우의 억제율로서 표현된다.

[0532] 하기 표에서 새롭게 설계된 키메라 안티센스 올리고뉴클레오타이드는 5-10-5 MOE 갭머 (gapmer)로서 설계되었다. 갭머는 길이가 20개의 뉴클레오사이드이고, 여기에서 중앙 갭 분절은 10 개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5 개의 뉴클레오사이드를 포함하는, 양 측면 (5' 및 3' 방향으로) 상의 윙 분절에 의하여 플랭킹된다. 5' 윙 분절 내의 각각의 뉴클레오사이드 및 3' 윙 분절 내의 각각의 뉴클레오사이드는 2'-MOE 변형을 갖는다. 각각의 갭머에서의 뉴클레오사이드간 연결은 포스포로티오에이트 연결 또는 포스포디에스테르 연결이다. 각각의 갭머에서의 모든 시토신 잔기는 5-메틸시토신이다. '화학' 칼럼은 각 올리고뉴클로타이드의 뉴클레오사이드간 연결을 개시한다. 's'는 포스포로티오에이트 연결을 , 'o'는 포스포디에스테르 연결을 나타낸다. "개시 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 5'-모스트(most) 뉴클레오사이드를 나타낸다. "정지 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 3'-모스트(most) 뉴클레오사이드를 나타낸다.

[0533] 하기 표에 열거된 각각의 갭머는 본원에 개시된 서열 번호: 1과 같이 지정된 인간 타우 게놈 서열 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자은행 수탁 번호 NT_010783.15) 또는 서열 번호: 2와 같이 지정된 인간 타우 mRNA 서열 (유전자 은행 수탁 번호 NM_001123066.3) 또는 서열 번호: 3 (유전자은행 수탁 번호 NM_016841.4)에 표적화된다. 하기 표 10, 12, 및 16에 열거된 각각의 올리고뉴클레오타이드는 본원에 개시된 서열 번호: 5 (유전자은행 수탁 번호 DR002467.1)와 같이 지정된 변이체 mRNA 서열, 서열 번호: 6 (유전자은행 수탁 번호 NM_001203251.1) 또는 서열 번호: 7 (유전자은행 수탁 번호 NM_016835.4)를 표적화한다. 올리고뉴클레오타이드는 100% 상보성과 함께 표적화하는 주요 유전자 서열에 따라 다양한 표에서 제시된다. 'n/a'는 안티센스 올리고뉴클레오타이드가 100% 상보성을 갖는 특정 유전자 서열을 표적화하지 않는다는 것이다.

[0534] **표 9**

[0535] 서열번호 1 및 3을 표적화하는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 5-10-5 MOE 갭머에 의한 타우 mRNA 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 3 개시 부위	서열 번호: 3 정지 부위	결합 화학성질	서열 번호
433475	n/a	n/a	TCTTCAGCTTTCAGGCCAGC	41	443	462	sssssssssssssssssss	96
613242	n/a	n/a	CTTCAGCTTTCAGGCCAGCG	54	442	461	soooossssssssssooss	326
613243	n/a	n/a	TCTTCAGCTTTCAGGCCAGC	43	443	462	soooossssssssssooss	96
613244	n/a	n/a	CCATGCGAGCTTGGGTCACG	64	511	530	soooossssssssssooss	327
613245	n/a	n/a	CAGCCCCCTTGGCTTTTTTG	30	565	584	soooossssssssssooss	328
613247	n/a	n/a	TTGCACCTTCCCGCCTCCCG	53	957	976	soooossssssssssooss	329
613240	5897	5916	TGCCGCTCGGCCGTCCGGCG	9	n/a	n/a	soooossssssssssooss	330
613249	6292	6311	GCCCGGCGCACGAAGCCCCA	80	n/a	n/a	soooossssssssssooss	331
613250	7099	7118	AGAAAGAAATCCGCCCCGAG	45	n/a	n/a	soooossssssssssooss	332
613251	11709	11728	ATAATGGAATACTTATTGCA	54	n/a	n/a	soooossssssssssooss	333
613252	11819	11838	GCAGGAGCATGGCACCTGGA	79	n/a	n/a	soooossssssssssooss	334
613253	12081	12100	ACTCGCTGACATGGTGTTTG	87	n/a	n/a	soooossssssssssooss	335
613254	13386	13405	GATGACTCCACAATGTAAAC	75	n/a	n/a	soooossssssssssooss	336
613255	16760	16779	CCTATAGGATTATCCAGGAA	88	n/a	n/a	soooossssssssssooss	337
613256	16987	17006	CATTTCTCATCAGCCATCGA	81	n/a	n/a	soooossssssssssooss	338
613257	17428	17447	ACCAAAGACTTCAGATCAGC	88	n/a	n/a	soooossssssssssooss	339
613412	73879	73898	GTGATCTTCCATCACTTCGA	82	345	364	soooossssssssssooss	25
613246	103087	103106	CCAGAGCTGGGTGGTGTCTT	51	686	705	soooossssssssssooss	39
613181	138046	138065	AGCTTCTGGGAGCTGCAGAT	80	3737	3756	soooossssssssssooss	340
613182	138083	138102	AGAGGAACCCAGTCTGAGGG	49	3774	3793	soooossssssssssooss	341

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613183	138116	138135	AGGCTGCGCTGCCCCTCCAG	68	3807	3826	soooossssssssssooss	342
613184	138149	138168	AATCCCTGCTGTGGTCGCAG	63	3840	3859	soooossssssssssooss	343
613185	138182	138201	TCTAGAGCAGATCCAGGACA	53	3873	3892	soooossssssssssooss	344
613186	138215	138234	AAGTCATCCTTCCTCAGGCA	63	3906	3925	soooossssssssssooss	345
613187	138248	138267	CAAGGCTTTGGGAACAGTGT	78	3939	3958	soooossssssssssooss	346
613188	138250	138269	GTCAAGGCTTTGGGAACAGT	84	3941	3960	soooossssssssssooss	347
613189	138281	138300	TTGTGCAAGGTCAGCGGGCT	75	3972	3991	soooossssssssssooss	348
613190	138314	138333	CGGCTTCCCTTTTCTCATGG	75	4005	4024	soooossssssssssooss	349
613191	138347	138366	TGAGTTTCTTTAGGCAGCAA	82	4038	4057	soooossssssssssooss	350
613192	138380	138399	AACCAGAAGTGGCAGAATTG	47	4071	4090	soooossssssssssooss	351
613193	138413	138432	CAAGTCCCTCAGGGTTGCCT	78	4104	4123	soooossssssssssooss	352
613194	138454	138473	CGAAGCTGCCAGCCCCAGGG	70	4145	4164	soooossssssssssooss	353
613195	138487	138506	AGACTTCCTTTCAGGTAAAG	77	4178	4197	soooossssssssssooss	354
613196	138503	138522	AGAGTTCTGGGCCCAGAGAC	58	4194	4213	soooossssssssssooss	79
613197	138520	138539	AGGGAGGCTCTTGGTGGAGA	35	4211	4230	soooossssssssssooss	355
613198	138553	138572	ACTTAGGAGAATTGCTGGGA	75	4244	4263	soooossssssssssooss	356
613199	138586	138605	CCCACATTTCCTTCTCCTTC	72	4277	4296	soooossssssssssooss	357
613200	138636	138655	ACTGTTGGCAGTAATGAGGG	71	4327	4346	soooossssssssssooss	358
613201	138674	138693	GGAAGAGGAACCGAGGTGCG	61	4365	4384	soooossssssssssooss	359
613202	138707	138726	CATGGTGCTGAAGAGCAGGG	71	4398	4417	soooossssssssssooss	360
613203	138740	138759	GGGAGATCCCAGAGCCTTCC	53	4431	4450	soooossssssssssooss	361
613204	138773	138792	CTTAGGCTGGCCCCAAGAGC	64	4464	4483	soooossssssssssooss	362
613205	138806	138825	TATCTGCCAGCACTGATCAC	56	4497	4516	soooossssssssssooss	363
613206	138839	138858	TTTAAGATCACAAGCCAGCG	62	4530	4549	soooossssssssssooss	364
613207	138872	138891	GAGGAGTGCCCAGCCCTGGG	54	4563	4582	soooossssssssssooss	365
613208	138905	138924	CTGGCTCTGCAGGTGGGAGA	44	4596	4615	soooossssssssssooss	366
613209	138938	138957	TACAGTATATCCTATCTAGC	57	4629	4648	soooossssssssssooss	367
613210	138971	138990	ATAAAGTGAGTCAGCAGCTT	71	4662	4681	soooossssssssssooss	368
613211	139004	139023	TCACCACTGAAGTCAATTTA	72	4695	4714	soooossssssssssooss	369
613212	139037	139056	AGCACAACAAGCAATAGCAA	80	4728	4747	soooossssssssssooss	370
613213	139070	139089	ACTATCTTACACATTCCTCC	48	4761	4780	soooossssssssssooss	371
613214	139103	139122	GCTGCACCCCAAGATCTCCC	79	4794	4813	soooossssssssssooss	372
613215	139136	139155	AAATCATGAAAAGGGTTACG	61	4827	4846	soooossssssssssooss	373
613216	139169	139188	GTGGCTGCTCCCTCCCTCTA	60	4860	4879	soooossssssssssooss	374
613217	139188	139207	CCCAAGGGCCTCTAACTCCG	64	4879	4898	soooossssssssssooss	375
613218	139202	139221	TGGAAAAGAGAAACCCCAAG	56	4893	4912	soooossssssssssooss	376
613219	139229	139248	AGCCAGCTGCCTGGGAAAGC	63	4920	4939	soooossssssssssooss	89
613220	139235	139254	TGAACTAGCCAGCTGCCTGG	46	4926	4945	soooossssssssssooss	377
613221	139268	139287	TATTCCTACGCCTGCACCTG	54	4959	4978	soooossssssssssooss	378
613222	139301	139320	AGAGGGCAGCAGGCCAAAGC	48	4992	5011	soooossssssssssooss	379
613223	139337	139356	TTAGGGAGGCATGATTGTGG	55	5028	5047	soooossssssssssooss	380
613224	139368	139387	CCAACGGCTTAGAGGGAAGG	61	5059	5078	soooossssssssssooss	381
613225	139370	139389	TGCCAACGGCTTAGAGGGAA	65	5061	5080	soooossssssssssooss	382

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613226	139403	139422	TGTCTGGAGCCAGTGTGAGA	56	5094	5113	soooossssssssssooss	383
613227	139436	139455	CGAGTGATCTCAGCTCCAAA	79	5127	5146	soooossssssssssooss	384
613228	139502	139521	TGATCACCTCTGCCCTCGCC	72	5193	5212	soooossssssssssooss	385
613229	139535	139554	TGAAGCTGCAGGTCTGTAGA	57	5226	5245	soooossssssssssooss	386
613230	139568	139587	CTTTTCAAAGCTGAAGAGAA	57	5259	5278	soooossssssssssooss	387
613231	139601	139620	AGGTGAGGCTCTAGGCCAGT	76	5292	5311	soooossssssssssooss	388
613232	139636	139655	CAACATGGCAAACTCATGGG	76	5327	5346	soooossssssssssooss	389
613233	139669	139688	ATGGGACTTGCAAGTGCCAG	83	5360	5379	soooossssssssssooss	390
613234	139702	139721	CCTCCCCCCACCCTCAGAAT	15	5393	5412	soooossssssssssooss	391
613235	139735	139754	AGACAGAAAGCTAAGCTAAG	50	5426	5445	soooossssssssssooss	392
613236	139768	139787	TTAAAACACACAATACACTA	46	5459	5478	soooossssssssssooss	393
613237	139801	139820	ACTTTTACAGCAACAGTCAG	54	5492	5511	soooossssssssssooss	394
613238	139834	139853	TTTAATCAGAGTAATAACTT	12	5525	5544	soooossssssssssooss	395

[0538]

[0539] **표 10**

[0540] 서열 번호: 5 및 6을 표적화하는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 5-10-5 MOE 갭머에 의한 타우 mRNA 억제

ISIS 번호	표적 서열 번호	표적 개시 부위	서열	억제율%	결합 화학성질	서열 번호
613239	5	3	TGCCCTTCGCGGTCCCTTCG	2	soooosssssssssooss	396
613241	5	424	CTGTCCCCCAAACCCGTACG	56	soooosssssssssooss	397
613248	6	524	GCTTCCGCTGTTGGAGTGCT	62	soooosssssssssooss	398

[0541]

[0542] **표 11**

[0543] 서열 번호: 1 및 3을 표적화하는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 5-10-5 MOE 갭머에 의한 타우 mRNA 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 3 개시 부위	서열 번호: 3 정지 부위	결합 화학성질	서열 번호
433475	n/a	n/a	TCTTCAGCTTTCAGGCCAGC	17	443	462	sssssssssssssssss	96
613027	5901	5920	GCCCTGCCGCTCGGCCGTCC	29	1	20	soooosssssssssooss	399
613028	5934	5953	TTCTCCTCCGGCCACTAGTG	22	34	53	soooosssssssssooss	400
613029	5987	6006	GAACGCGAGCCTCCCCAGGG	1	87	106	soooosssssssssooss	401
613030	6020	6039	GAGGCCGGCGGGCGGCGCAG	2	120	139	soooosssssssssooss	402
613031	6053	6072	GAGGGCGCGCGCCGGCGAAG	0	153	172	soooosssssssssooss	403
613032	6086	6105	TTGGTGCCGGAGCTGGTGGG	54	186	205	soooosssssssssooss	404
613033	6119	6138	GGCAGAAGGTGGGCGGTGGC	74	219	238	soooosssssssssooss	405
613034	6185	6204	TGATAGTCGACAGAGGCGAG	71	285	304	soooosssssssssooss	406
613035	73867	73886	CACTTCGAACTCCTGGCGGG	67	333	352	soooosssssssssooss	98

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613036	73869	73888	ATCACTTCGAACTCCTGGCG	72	335	354	soooossssssssssooss	99
613037	73871	73890	CCATCACTTCGAACTCCTGG	69	337	356	soooossssssssssooss	100
613412	73879	73898	GTGATCTTCCATCACTTCGA	72	345	364	soooossssssssssooss	25
613038	73906	73925	CCTGTCCCCCAACCCGTACG	44	372	391	soooossssssssssooss	104
613039	73932	73951	TGCATGGTGTAGCCCCCCTG	80	398	417	soooossssssssssooss	117
613040	73934	73953	GGTGCATGGTGTAGCCCCCC	73	400	419	soooossssssssssooss	118
613041	73939	73958	GTCTTGGTGCATGGTGTAGC	77	405	424	soooossssssssssooss	407
613042	73958	73977	CGTCCGTGTCACCCTCTTGG	79	424	443	soooossssssssssooss	123
613044	83397	83416	CCTCAGATCCGTCCTCAGTG	67	n/a	n/a	soooossssssssssooss	408
613045	83430	83449	TGCTCTTAGCATCAGAGGTT	89	n/a	n/a	soooossssssssssooss	409
613046	85902	85921	CTAAGGGTGCTGTCACATCT	69	n/a	n/a	soooossssssssssooss	410
613047	85934	85953	GGCAGCCTGCTTGCCGGGAG	51	n/a	n/a	soooossssssssssooss	29
613048	85935	85954	CGGCAGCCTGCTTGCCGGGA	51	n/a	n/a	soooossssssssssooss	411
613049	85968	85987	TGGTTCCTTCTGGGATCTCC	76	n/a	n/a	soooossssssssssooss	412
613051	94719	94738	CTCGGAGGAAGCCTTCCTGG	53	n/a	n/a	soooossssssssssooss	413
613052	94752	94771	TGAGCTGGTGGCTCAGACCT	41	n/a	n/a	soooossssssssssooss	414
613053	94825	94844	CCTGTCCCCGAAGGTTGGCG	61	n/a	n/a	soooossssssssssooss	415
613054	94875	94894	GGTGCTTGAGCAGCTCAGGG	70	n/a	n/a	soooossssssssssooss	416
613055	94908	94927	GCGGCCCCTCCTGGTGCAGG	47	n/a	n/a	soooossssssssssooss	417
613056	94941	94960	CCGGCCTCTCTTTGCCCCCT	31	n/a	n/a	soooossssssssssooss	418
613057	94974	94993	CGTCGCGGTCTTCATCCACC	42	n/a	n/a	soooossssssssssooss	419
613058	95038	95057	GGCCGCCCATCTTGGGCTGG	0	n/a	n/a	soooossssssssssooss	420
613059	95071	95090	ATGCTGGTGGCTTCTCTGGC	53	n/a	n/a	soooossssssssssooss	421
613060	95098	95117	ATGGCACCCTCCGCTGGGAA	39	n/a	n/a	soooossssssssssooss	422
613061	95121	95140	AGAGGAAATCCACAGGGAGG	30	n/a	n/a	soooossssssssssooss	33
613062	95154	95173	GCTCTGAGGCTGGGATCTCT	70	n/a	n/a	soooossssssssssooss	423
613063	95187	95206	GCCCTTTGGCCCGCCCTACA	67	n/a	n/a	soooossssssssssooss	424
613064	95235	95254	CGTTGGGTGTGATTTCCACG	61	n/a	n/a	soooossssssssssooss	425
613065	95268	95287	AATGCTCCTCCGAGTGCGCC	85	n/a	n/a	soooossssssssssooss	426
613066	95313	95332	CCTCTGGCCCCTCTCCAGGG	43	n/a	n/a	soooossssssssssooss	427
613067	95346	95365	CTTTTGTGTCCTCTCCCAAA	42	n/a	n/a	soooossssssssssooss	428
613068	95379	95398	GCTGCTTTTCAGAGGGCTCT	51	n/a	n/a	soooossssssssssooss	429
613069	95412	95431	GGCTGACGGGCTTCCCCCGC	61	n/a	n/a	soooossssssssssooss	430
613070	95429	95448	TTTGAGTTGAGGGACCCGGC	33	n/a	n/a	soooossssssssssooss	431
613073	98559	98578	GCTTTTACTGACCATGCGAG	79	522	541	soooossssssssssooss	124
613074	98581	98600	CATCGCTTCCAGTCCCGTCT	78	544	563	soooossssssssssooss	134
613075	98587	98606	TTTTGTCATCGCTTCCAGTC	35	550	569	soooossssssssssooss	137
613076	101406	101425	AAGGTTTTAGCAGAGGAACG	63	n/a	n/a	soooossssssssssooss	37
613077	101457	101476	TCTGAGCTACCAGGAGTGGG	65	n/a	n/a	soooossssssssssooss	432
613078	101491	101510	GCACACAGCAGGGCTGGAGG	68	n/a	n/a	soooossssssssssooss	433
613079	101501	101520	GTGGCTCTGGGCACACAGCA	77	n/a	n/a	soooossssssssssooss	192
613080	101507	101526	AGGAAGGTGGCTCTGGGCAC	69	n/a	n/a	soooossssssssssooss	38
613081	101537	101556	GGGAAGTGACAGAAGAGACG	46	n/a	n/a	soooossssssssssooss	434

[0545]

613082	101570	101589	GTTTCATCTCCTTTGCTCCA	57	n/a	n/a	soooossssssssssooss	435
613083	102995	103014	CCGCGGTGTGGCGATCTTCG	9	594	613	soooossssssssssooss	436
613084	103028	103047	GGCCTGGCCCTTCTGGCCTG	14	627	646	soooossssssssssooss	437
613085	103075	103094	GGTGTCTTTGGAGCGGGCGG	37	674	693	soooossssssssssooss	146
613086	105445	105464	CTTCTCTGGACTTGCTTAGT	45	n/a	n/a	soooossssssssssooss	438
613087	105475	105494	CTCTCAGATCTGGGCCCTGC	41	n/a	n/a	soooossssssssssooss	439
613088	105478	105497	CCTCTCTCAGATCTGGGCCC	49	n/a	n/a	soooossssssssssooss	440
613089	107932	107951	TAGCCGCTGCGATCCCCTGA	19	719	738	soooossssssssssooss	441
613090	107968	107987	CGGCTGCCGGGAGTGCCTGG	31	755	774	soooossssssssssooss	159
613091	108021	108040	CCACCTTCTTGGGCTCCCGG	17	808	827	soooossssssssssooss	442
613092	108040	108059	GGTGGAGTACGGACCACTGC	20	827	846	soooossssssssssooss	40
613093	108054	108073	AAGACGGCGACTTGGGTGGA	0	841	860	soooossssssssssooss	41
613094	108101	108120	CAGGTCTGGCATGGGCACGG	67	888	907	soooossssssssssooss	443
613095	108134	108153	CTCAGTGGAGCCGATCTTGG	31	921	940	soooossssssssssooss	199
613096	108167	108186	CACCTTCCCGCCTCCCGGCT	47	954	973	soooossssssssssooss	444
613097	121845	121864	GTTGCTAAGATCCAGCTTCT	49	n/a	n/a	soooossssssssssooss	445
613098	121865	121884	GAGCCACACTTGGACTGGAC	85	n/a	n/a	soooossssssssssooss	47
613099	121878	121897	GATATTATCCTTTGAGCCAC	88	n/a	n/a	soooossssssssssooss	446
613101	125784	125803	GGTCACCTTGCTCAGGTCAA	68	993	1012	soooossssssssssooss	447
613102	125817	125836	ATGATGGATGTTGCCTAATG	14	1026	1045	soooossssssssssooss	448
613103	130141	130160	ATTTTACTTCCACCTGGCCA	22	1057	1076	soooossssssssssooss	51

[0546]

[0547] **표 12**

[0548] 서열 번호: 6 및 7을 표적화하는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 5-10-5 MOE 갭머에 의한 타우 mRNA 억제

ISIS 번호	표적 서열 번호	표적 개시 부위	서열	억제율%	결합 화학성질	서열 번호
613043	6	442	GAGATTCTTTCAGGCCAGCG	17	soooossssssssssooss	449
613050	7	685	TTTCAGGCTCTTGGGTCACG	0	soooossssssssssooss	450
613071	7	1430	GCTTTGAGTTGAGGGACCCG	23	soooossssssssssooss	451
613072	7	1444	TACTGACCATGCGAGCTTTG	73	soooossssssssssooss	177
613100	7	2178	TATTTGCACACTGCCGCCTC	13	soooossssssssssooss	452

[0549]

[0550] **표 13**

[0551] 서열번호 1 및 3을 표적화하는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 5-10-5 MOE 갭머에 의한 타우 mRNA 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 3 개시 부위	서열 번호: 3 정지 부위	결합 화학성질	서열 번호

[0552]

433475	n/a	n/a	TCTTCAGCTTTCAGGCCAGC	23	443	462	sssssssssssssssss	96
613412	73879	73898	GTGATCTTCCATCACTTCGA	76	345	364	soooossssssssssooss	25
613104	130143	130162	AGATTTTACTTCCACCTGGC	59	1059	1078	soooossssssssssooss	453
613105	130176	130195	CGACTGGACTCTGTCCTTGA	47	1092	1111	soooossssssssssooss	454
613106	130225	130244	TATTTCCTCCGCCAGGGACG	90	1141	1160	soooossssssssssooss	455
613107	135483	135502	CGCGGAAGGTCAGCTTGTGG	43	1174	1193	soooossssssssssooss	456
613108	135516	135535	CCGCCCCGTGGTCTGTCTTG	44	1207	1226	soooossssssssssooss	457
613109	135549	135568	CCCCAGACACCACTGGCGAC	36	1240	1259	soooossssssssssooss	458
613110	135590	135609	GCCGGTGGAGGAGACATTGC	51	1281	1300	soooossssssssssooss	459
613111	135654	135673	CCAGGGAGGCAGACACCTCG	61	1345	1364	soooossssssssssooss	245
613112	135697	135716	AATTATTGACCGCCCCAGGG	33	1388	1407	soooossssssssssooss	460
613113	135730	135749	TTTTTCCACACTCTCTCATT	41	1421	1440	soooossssssssssooss	461
613114	135783	135802	AACTGCGAGGAGCAGCTGGG	51	1474	1493	soooossssssssssooss	462
613115	135786	135805	CCGAACTGCGAGGAGCAGCT	78	1477	1496	soooossssssssssooss	248
613116	135816	135835	CAAAAGCAGGTTAAGTGATT	28	1507	1526	soooossssssssssooss	463
613117	135849	135868	CTGATTTTGAAGTCCCGAGC	69	1540	1559	soooossssssssssooss	464
613118	135869	135888	ATTTGCTCTTACTCCCATCA	80	1560	1579	soooossssssssssooss	465
613119	135882	135901	TTGGAAAGATGAAATTTGCT	52	1573	1592	soooossssssssssooss	466
613120	135948	135967	TGTTGGATGTGGCCATGTTT	63	1639	1658	soooossssssssssooss	467
613121	136049	136068	GTCCCTTGAAATCCCCCAGA	45	1740	1759	soooossssssssssooss	468
613122	136082	136101	CCACAACAGGGCCAGAGGTG	55	1773	1792	soooossssssssssooss	469
613123	136115	136134	TCCTTTGTTGCTGCCACTGC	59	1806	1825	soooossssssssssooss	470
613124	136148	136167	GCCTGTGGCTCCACGAACAC	72	1839	1858	soooossssssssssooss	471
613125	136181	136200	CCCCGTCACACTCACACAAG	43	1872	1891	soooossssssssssooss	472
613126	136214	136233	GGCCTCCCCCGTGGCCTCCC	37	1905	1924	soooossssssssssooss	473
613127	136247	136266	TGCTTCCTCTCCCCTCTGCC	41	1938	1957	soooossssssssssooss	474
613128	136295	136314	GATGTCTACTCTCCAGCACG	32	1986	2005	soooossssssssssooss	475
613129	136328	136347	ATAGGCCTTGGCTCTCCCAG	73	2019	2038	soooossssssssssooss	476
613130	136361	136380	AGGACAGGCGGCCGCTCAGA	46	2052	2071	soooossssssssssooss	477
613131	136394	136413	TGACCCACAGCAGGCCCCCA	14	2085	2104	soooossssssssssooss	478
613132	136427	136446	CTCCCACAGGCTGCCCTGCA	46	2118	2137	soooossssssssssooss	479
613133	136460	136479	CAGCTTGCCTTCTCTTTTTA	58	2151	2170	soooossssssssssooss	480
613134	136491	136510	GGAGGTCATCCACGAAGTGC	45	2182	2201	soooossssssssssooss	61
613135	136493	136512	AAGGAGGTCATCCACGAAGT	41	2184	2203	soooossssssssssooss	481
613136	136515	136534	GACATCAAGGTCAGTCTTTT	80	2206	2225	soooossssssssssooss	482
613137	136541	136560	AGGGAGGAAGAGGCCAGCGC	60	2232	2251	soooossssssssssooss	483
613138	136574	136593	AGCCCCTCAACTCAGGCCCC	53	2265	2284	soooossssssssssooss	484
613139	136607	136626	TCAATAAAACAGGGTTTCTG	38	2298	2317	soooossssssssssooss	485
613140	136640	136659	CAAAATCATGGCAGCAGTTC	26	2331	2350	soooossssssssssooss	486
613141	136673	136692	GTTAGCCCTAAAGTCCCAGG	76	2364	2383	soooossssssssssooss	487
613142	136706	136725	CCCAAGAGGCACAAGTCCTT	57	2397	2416	soooossssssssssooss	488
613143	136739	136758	CAGTGGCCCAGGCTTGGAAA	63	2430	2449	soooossssssssssooss	489
613144	136748	136767	CAGAGATGCCAGTGGCCCAG	43	2439	2458	soooossssssssssooss	67

[0553]

613145	136772	136791	TGCCTCCCAGACCCCCACAC	23	2463	2482	soooossssssssooss	490
613146	136805	136824	AGTGGCCGTGGGAAGGACAG	17	2496	2515	soooossssssssooss	491
613147	136838	136857	ACAACAGCACAGCGGCGCAG	61	2529	2548	soooossssssssooss	492
613148	136845	136864	ACGGCAGACAACAGCACAGC	59	2536	2555	soooossssssssooss	493
613149	136899	136918	GAATTCGGGACATTGTGACG	42	2590	2609	soooossssssssooss	494
613150	136933	136952	CAGGGTCATTACTGAGAAGG	39	2624	2643	soooossssssssooss	495
613151	136966	136985	CTCAGTATGGAGTAGGTACC	52	2657	2676	soooossssssssooss	496
613152	136999	137018	TGTGCCTGGACTTTGCCTTC	61	2690	2709	soooossssssssooss	497
613153	137032	137051	GGAACTGAGAGTGAGAGGCT	62	2723	2742	soooossssssssooss	498
613154	137077	137096	GAATCAGATCATGAGATTCG	30	2768	2787	soooossssssssooss	499
613155	137110	137129	CACATCTGTGACGGGAGGAG	26	2801	2820	soooossssssssooss	500
613156	137143	137162	CACCTAGGGTCACAGCTGAG	33	2834	2853	soooossssssssooss	501
613157	137176	137195	GAAAGGGCTCTCTCCATGTC	54	2867	2886	soooossssssssooss	502
613158	137214	137233	GTGGGCTCAGCACAGGAAGG	23	2905	2924	soooossssssssooss	503
613159	137229	137248	ACCCAGCCTGCTGCTGTGGG	36	2920	2939	soooossssssssooss	504
613160	137247	137266	ACCACTGACAACCAAGACAC	22	2938	2957	soooossssssssooss	505
613161	137280	137299	GCCCTGGGTGCCTTGCCCTT	53	2971	2990	soooossssssssooss	506
613162	137322	137341	ACAAGCTAGGGTGCAAGTGG	47	3013	3032	soooossssssssooss	507
613163	137364	137383	GGAGCTGAGCAGCGGGCTGG	45	3055	3074	soooossssssssooss	508
613164	137401	137420	CCCTTTGTCGGGTGTGGAGG	8	3092	3111	soooossssssssooss	509
613165	137453	137472	TGGCTTCCAGCTGGGACTGG	65	3144	3163	soooossssssssooss	510
613166	137486	137505	ATATGTTCAGCTGCTCCAGC	58	3177	3196	soooossssssssooss	511
613167	137529	137548	ACTCAACAGGGTGCAGATGG	54	3220	3239	soooossssssssooss	512
613168	137562	137581	GAATCCAAGCATAAACAGAC	55	3253	3272	soooossssssssooss	513
613169	137595	137614	TTTTTTTCTTTTCACTATCA	34	3286	3305	soooossssssssooss	514
613170	137629	137648	AGCATTTCAAGATACATGCG	59	3320	3339	soooossssssssooss	515
613171	137692	137711	CACACGAGTCCCAGTGTGGG	11	3383	3402	soooossssssssooss	516
613172	137761	137780	TTGGGTCCCAGGTGCTGAGG	40	3452	3471	soooossssssssooss	517
613173	137794	137813	ACGGCCTCCTTAGCTGCTAG	73	3485	3504	soooossssssssooss	518
613174	137827	137846	TAATCCTGTGCTTCAGGCCT	32	3518	3537	soooossssssssooss	519
613175	137881	137900	TGACACAGGGAGCCCCAAGG	40	3572	3591	soooossssssssooss	520
613176	137914	137933	AGCCAGACCAGCCACAAGAC	16	3605	3624	soooossssssssooss	521
613177	137947	137966	GCTATGACCAGAGAGAACCA	29	3638	3657	soooossssssssooss	522
613178	137967	137986	GGACTGCCATGAGACTTCGG	26	3658	3677	soooossssssssooss	523
613179	137980	137999	TAAGCCTCCTTTGGGACTGC	64	3671	3690	soooossssssssooss	524
613180	138013	138032	AGTGGCTTCCTTTTTCTTGT	69	3704	3723	soooossssssssooss	525

[0554]

[0555] **표 14**

[0556] 서열번호 1 및 3을 표적화하는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 5-10-5 MOE 갭머에 의한 타우 mRNA 억제

[0557]

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 3 개시 부위	서열 번호: 3 정지 부위	결합 화학성질	서열 번호

433475	n/a	n/a	TCTTCAGCTTTCAGGCCAGC	23	433	452	sssssssssssssssss	96
613258	18371	18390	GGCAATGCCTGGAAGAAACT	75	n/a	n/a	soooossssssssssooss	526
613259	18411	18430	CGCTGGTGAGAGTGTGACTG	69	n/a	n/a	soooossssssssssooss	527
613260	18449	18468	ATCCGAGGGTGAGATGATAA	75	n/a	n/a	soooossssssssssooss	528
613261	19611	19630	AATAATTTCTCCAGGCTCAT	62	n/a	n/a	soooossssssssssooss	529
613262	20955	20974	GCTGACTTCGATTTGTTATT	84	n/a	n/a	soooossssssssssooss	530
613263	22139	22158	TATCATATGGCACAAATTCT	32	n/a	n/a	soooossssssssssooss	531
613264	23662	23681	CTACCTGGGACCACACCTTA	61	n/a	n/a	soooossssssssssooss	532
613265	25046	25065	GGGTGGAGAGCCTGATGGTC	47	n/a	n/a	soooossssssssssooss	533
613266	25418	25437	CTGTGAGCATCATGAAAGCC	56	n/a	n/a	soooossssssssssooss	534
613267	25606	25625	TTTTATTATGAGGGAGATCA	48	n/a	n/a	soooossssssssssooss	535
613268	26186	26205	AATAGTAGAGAAATGGAAAT	39	n/a	n/a	soooossssssssssooss	536
613269	26690	26709	TAACATGACAGGGTTAGGCC	67	n/a	n/a	soooossssssssssooss	537
613270	26917	26936	GCCCACACACATGCTCATGC	57	n/a	n/a	soooossssssssssooss	538
613271	27160	27179	TGTGTTCAGTTACATGCCTT	82	n/a	n/a	soooossssssssssooss	539
613272	27569	27588	GACCACCATGGTGGGCTGAC	39	n/a	n/a	soooossssssssssooss	540
613273	28227	28246	GGCACCTCTCTGCAGACTTT	85	n/a	n/a	soooossssssssssooss	541
613274	30102	30121	TGCTTCACACACCACAATGG	60	n/a	n/a	soooossssssssssooss	542
613275	31769	31788	AACATTGCCGAGCACCAGCC	63	n/a	n/a	soooossssssssssooss	543
613276	31832	31851	GACTCAGGAACATGTTAGCT	70	n/a	n/a	soooossssssssssooss	544
613277	32045	32064	CACGGCTCAGCAGAGGAGAC	23	n/a	n/a	soooossssssssssooss	545
613278	32324	32343	GCTGCTATCCTTCCTGGGCC	57	n/a	n/a	soooossssssssssooss	546
613279	32760	32779	GGAAATGAAAGCTTCCCACG	61	n/a	n/a	soooossssssssssooss	547
613280	33359	33378	AACAGTCAGAATACCCCCAA	72	n/a	n/a	soooossssssssssooss	548
613281	34056	34075	TATAGGTAGAATATAAAACT	17	n/a	n/a	soooossssssssssooss	549
613282	35266	35285	TATGAACAAAACTGCAGGAC	45	n/a	n/a	soooossssssssssooss	550
613283	35839	35858	AGCCTCCAGAGTGACAGGTG	63	n/a	n/a	soooossssssssssooss	551
613284	36223	36242	CCATAAGCCACTCCTGGTTG	0	n/a	n/a	soooossssssssssooss	552
613285	36410	36429	CAGCTTGGAAGATACAGGAG	63	n/a	n/a	soooossssssssssooss	553
613286	38647	38666	CAAACTTAAGAAAAGTTGCA	67	n/a	n/a	soooossssssssssooss	554
613287	39104	39123	TGCTGGCAAAGAAGACAGGA	69	n/a	n/a	soooossssssssssooss	555
613288	40506	40525	CCACTGATGGCCGGGTGCAG	27	n/a	n/a	soooossssssssssooss	556
613289	42727	42746	TGGGTGTCAAATGGCTGGCT	55	n/a	n/a	soooossssssssssooss	557
613290	42955	42974	TAGAAAGCTATTTAATAAAT	0	n/a	n/a	soooossssssssssooss	558
613291	43109	43128	AGCCGTACATCAATGGTACA	71	n/a	n/a	soooossssssssssooss	559
613292	46627	46646	GGCCCTACCATGGTCGATTT	57	n/a	n/a	soooossssssssssooss	560
613293	47399	47418	ATCAGTGCCAGAGACAGAGG	5	n/a	n/a	soooossssssssssooss	561
613294	48115	48134	TATTATTAACGAACAAAAAA	0	n/a	n/a	soooossssssssssooss	562
613295	48223	48242	AGAGCAATACTTTGTGCTTA	51	n/a	n/a	soooossssssssssooss	563
613296	48608	48627	AGACTCCTCAAATGTGCGCC	53	n/a	n/a	soooossssssssssooss	564

[0558]

613297	49204	49223	GAATGACGGCCGCCTCCTCT	39	n/a	n/a	soooossssssssssooss	565
613298	49696	49715	TATGGAGGGCTTCTGGCCTC	18	n/a	n/a	soooossssssssssooss	566
613299	51161	51180	GAGAAAGAGCGAGTAATTAG	44	n/a	n/a	soooossssssssssooss	567
613300	52250	52269	TAGCTAGAAACTGTGTCCCT	41	n/a	n/a	soooossssssssssooss	568
613301	53908	53927	CTGTGAGATCATCCCCTGGT	51	n/a	n/a	soooossssssssssooss	569
613302	54457	54476	CAGCGCAGTGCAGGGAGTCA	41	n/a	n/a	soooossssssssssooss	570
613303	55975	55994	GGGTACACAGAGAGGCCACT	53	n/a	n/a	soooossssssssssooss	571
613304	56155	56174	GAACGATGCACTGCCTTGGC	54	n/a	n/a	soooossssssssssooss	572
613305	57402	57421	CACCATATTACACCAGTTGT	60	n/a	n/a	soooossssssssssooss	573
613306	57696	57715	CTGAAATGAATCCCCTGAAC	0	n/a	n/a	soooossssssssssooss	574
613307	57733	57752	GTGTCCACGAATGCCCCTGG	40	n/a	n/a	soooossssssssssooss	575
613308	58392	58411	ACGGATGGTTGCTGCTGATG	47	n/a	n/a	soooossssssssssooss	576
613309	61917	61936	GTCCCTTTTGCTCCCAAAGA	18	n/a	n/a	soooossssssssssooss	577
613310	62489	62508	CAGTCTTTTAATAAGTGAAA	50	n/a	n/a	soooossssssssssooss	578
613311	63219	63238	TTAGCTAAATTGAGGCCCGG	31	n/a	n/a	soooossssssssssooss	579
613312	63257	63276	GGAAAGGTATTGCCTCCTGA	42	n/a	n/a	soooossssssssssooss	580
613313	63627	63646	GGTGACTACGCAGCCTGGAC	57	n/a	n/a	soooossssssssssooss	581
613314	64559	64578	TTCAGGGCAATCCTTGAGGT	41	n/a	n/a	soooossssssssssooss	582
613315	64872	64891	TGCTAATGCTTTGGGACCTA	44	n/a	n/a	soooossssssssssooss	583
613316	66922	66941	TGGGTAGAGAGCAACTGTTC	32	n/a	n/a	soooossssssssssooss	584
613317	67104	67123	ACACCCCTTCTCTGCACATC	25	n/a	n/a	soooossssssssssooss	585
613318	68893	68912	CTGCTAGAGTTCGCCAACAG	59	n/a	n/a	soooossssssssssooss	586
613319	69457	69476	TCTTATTCTCTAGGTGGGCT	70	n/a	n/a	soooossssssssssooss	587
613320	70922	70941	CAGTGCAAGTGGGTATGAAG	30	n/a	n/a	soooossssssssssooss	588
613321	70928	70947	CAGATGCAGTGCAAGTGGGT	44	n/a	n/a	soooossssssssssooss	589
613322	71310	71329	GAAAAACTTTGTCCATAATT	41	n/a	n/a	soooossssssssssooss	590
613323	71665	71684	TAATGAATGTATAACAGAAA	0	n/a	n/a	soooossssssssssooss	591
613324	71702	71721	AAAAGGCAGATACTTTGTGG	56	n/a	n/a	soooossssssssssooss	592
613325	72456	72475	CAGAGGTGTGAAAGTAAAAG	0	n/a	n/a	soooossssssssssooss	593
613326	72566	72585	CAGCTAAAGCTTTGTGAACA	31	n/a	n/a	soooossssssssssooss	594
613327	72612	72631	TGCAGCCCAGGTGAGCCAGC	49	n/a	n/a	soooossssssssssooss	595
613328	73748	73767	GCCTCTCCTCCCAGTTCATG	12	n/a	n/a	soooossssssssssooss	596
613329	75140	75159	GTTTTCTTATTTTTAGCATT	87	n/a	n/a	soooossssssssssooss	597
613330	76340	76359	GGAGGGACGAGAAACAGCAG	0	n/a	n/a	soooossssssssssooss	598
613331	79041	79060	AGCTTCCAGCATGAACATAG	77	n/a	n/a	soooossssssssssooss	599
613332	79971	79990	GAGCCCTGATATGATAGAGG	57	n/a	n/a	soooossssssssssooss	600
613333	80360	80379	TGTACCATGCCTGGCAGATG	78	n/a	n/a	soooossssssssssooss	601
613334	81325	81344	GTTAGATGTATGTATGATGG	0	n/a	n/a	soooossssssssssooss	602
613412	73879	73898	GTGATCTTCCATCACTTCGA	80	345	364	soooossssssssssooss	25

[0559]

[0560] **표 15**

[0561] 서열번호 1 및 3을 표적화하는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 5-10-5 MOE 갭머에 의한 타우 mRNA 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 3 개시 부위	서열 번호: 3 정지 부위	결합 화학성질	서열 번호
433475	n/a	n/a	TCTTCAGCTTTCAGGCCAGC	31	443	462	ssssssssssssssssss	96
613335	82136	82155	GCCTCCTCCTAGAGCTCCTG	81	n/a	n/a	soooossssssssssooss	603
613336	83231	83250	CGGCCTCGCAACAAACCCAC	55	n/a	n/a	soooossssssssssooss	604
613337	83820	83839	TCCACTGACCTGCCCCTTCC	66	n/a	n/a	soooossssssssssooss	605
613338	84269	84288	TTTGCAACTTGTTCCTGCTT	84	n/a	n/a	soooossssssssssooss	606
613339	85073	85092	TCTTGGGTGCAGGCGGAGCA	53	n/a	n/a	soooossssssssssooss	607
613340	86117	86136	ACCCAAGATTCCCAGGAGCC	77	n/a	n/a	soooossssssssssooss	608
613341	86191	86210	AGGCCCTAAATGCTCTGAGA	75	n/a	n/a	soooossssssssssooss	609
613342	86251	86270	AGAAGTCTCTGGAACTGACG	70	n/a	n/a	soooossssssssssooss	610
613343	86714	86733	TCACCAAACCAATGGCTGGC	67	n/a	n/a	soooossssssssssooss	611
613344	86774	86793	GGTGAAATCCTGGCTAGGCC	89	n/a	n/a	soooossssssssssooss	612
613345	88487	88506	TGCAGATTCGGCCTGAGTTT	72	n/a	n/a	soooossssssssssooss	613
613346	89131	89150	CCAAACAAGAAAGACTGAGA	55	n/a	n/a	soooossssssssssooss	614
613347	89994	90013	CCATGTCCCTCCCCCCAACC	12	n/a	n/a	soooossssssssssooss	615
613348	90126	90145	ATTAGAAAAAAACCACTAGG	37	n/a	n/a	soooossssssssssooss	616
613349	92246	92265	AGCTTACTAGAGTGCTCTTG	81	n/a	n/a	soooossssssssssooss	617
613350	92915	92934	ATTTTTTTCTGGTTCATTCA	71	n/a	n/a	soooossssssssssooss	618
613351	94316	94335	CGCTTAAGAGAGGGAGCATC	72	n/a	n/a	soooossssssssssooss	619
613352	94673	94692	GTGGAGATACGCAGTGGTGG	68	n/a	n/a	soooossssssssssooss	620
613353	95790	95809	ACACCATGAGGGCACCCGTC	82	n/a	n/a	soooossssssssssooss	35
613354	95918	95937	CCCAAACCTGGCTCTGTCAC	65	n/a	n/a	soooossssssssssooss	621
613355	97224	97243	ATCAACCAGCACCATCCACG	65	n/a	n/a	soooossssssssssooss	622
613356	97314	97333	GGGTCTGTAAGCCTAAAGTG	53	n/a	n/a	soooossssssssssooss	623
613357	97315	97334	TGGGTCTGTAAGCCTAAAGT	56	n/a	n/a	soooossssssssssooss	624
613358	97368	97387	TATACTATGTGGCAGAATCA	48	n/a	n/a	soooossssssssssooss	625
613359	97478	97497	CACATTCCCTCTACCCCATG	57	n/a	n/a	soooossssssssssooss	626
613360	97507	97526	TCATAGATTTTCTTCTTTGG	75	n/a	n/a	soooossssssssssooss	627
613361	98881	98900	ACACACCTTCATTTACTGTC	95	n/a	n/a	soooossssssssssooss	313
	98918	98937			n/a	n/a	soooossssssssssooss	
613362	98882	98901	AACACACCTTCATTTACTGT	83	n/a	n/a	soooossssssssssooss	314
	98919	98938			n/a	n/a	soooossssssssssooss	
613363	98883	98902	AAACACACCTTCATTTACTG	79	n/a	n/a	soooossssssssssooss	315
	98920	98939			n/a	n/a	soooossssssssssooss	
613364	98884	98903	CAAACACACCTTCATTTACT	63	n/a	n/a	soooossssssssssooss	316
	98921	98940			n/a	n/a	soooossssssssssooss	
613365	98885	98904	TCAAACACACCTTCATTTAC	59	n/a	n/a	soooossssssssssooss	317
	98922	98941			n/a	n/a	soooossssssssssooss	
613366	98886	98905	TTCAAACACACCTTCATTTA	67	n/a	n/a	soooossssssssssooss	628

[0562]

	98923	98942			n/a	n/a	soooossssssssssooss	
613367	98887	98906	TTTCAAACACACCTTCATTT	72	n/a	n/a	soooossssssssssooss	318
	98924	98943			n/a	n/a	soooossssssssssooss	
613368	98888	98907	TTTTCAAACACACCTTCATT	59	n/a	n/a	soooossssssssssooss	319
	98925	98944			n/a	n/a	soooossssssssssooss	
613369	98889	98908	GTTTTCAAACACACCTTCAT	90	n/a	n/a	soooossssssssssooss	320
	98926	98945			n/a	n/a	soooossssssssssooss	
613370	98890	98909	GGTTTTCAAACACACCTTCA	96	n/a	n/a	soooossssssssssooss	321
	98927	98946			n/a	n/a	soooossssssssssooss	
613371	98891	98910	TGGTTTTCAAACACACCTTC	95	n/a	n/a	soooossssssssssooss	322
	98928	98947			n/a	n/a	soooossssssssssooss	
613372	99560	99579	CCCCAGCTGGCCGAGGCCCA	81	n/a	n/a	soooossssssssssooss	629
613373	99816	99835	GAGAAGGGTCCTGTCCCAGA	76	n/a	n/a	soooossssssssssooss	630
613374	100743	100762	AGTAAGTTGATGGAGATCAT	83	n/a	n/a	soooossssssssssooss	631
613375	102894	102913	CACCAGCCCCACTCCGCCAC	61	n/a	n/a	soooossssssssssooss	632
613376	103875	103894	TGCTCTGTCTCCAGAGACAT	70	n/a	n/a	soooossssssssssooss	633
613377	104615	104634	ATCCAAGATCCAGGCCAGGC	63	n/a	n/a	soooossssssssssooss	634
613378	105870	105889	AGAGACCCAGGGTGACCAGT	76	n/a	n/a	soooossssssssssooss	635
613379	106909	106928	CAAATTTCTCGATCCCCTTC	18	n/a	n/a	soooossssssssssooss	636
613380	108411	108430	CCTGAGGAGGGCACTCACAG	61	n/a	n/a	soooossssssssssooss	637
613381	108891	108910	GTGGCTACCCACGGCCACAG	1	n/a	n/a	soooossssssssssooss	638
613382	108939	108958	CTACCAGGAGCACACACAGA	65	n/a	n/a	soooossssssssssooss	639
613383	109303	109322	CCCTAAGCCATGGTGGGTTT	72	n/a	n/a	soooossssssssssooss	640
613384	109995	110014	CCCTTGTCCCCACAGCCACA	72	n/a	n/a	soooossssssssssooss	641
613385	110198	110217	GGGTCACCTGTGAGTTATTT	62	n/a	n/a	soooossssssssssooss	642
613386	113567	113586	AGCTGCCTCCAGTTGTTTAT	85	n/a	n/a	soooossssssssssooss	643
613387	114056	114075	ACTTTAGCTCCATCTTCTCA	49	n/a	n/a	soooossssssssssooss	644
613388	114755	114774	CTATAATGGTCAGTGGTGTA	67	n/a	n/a	soooossssssssssooss	645
613389	115899	115918	TGAAGGAGAGGCTGTGGTGA	41	n/a	n/a	soooossssssssssooss	646
613390	117387	117406	TGTGACAACAAAGTTGTCCT	46	n/a	n/a	soooossssssssssooss	647
613391	117654	117673	CCCTGCAATCAACACAGGAG	65	n/a	n/a	soooossssssssssooss	648
613392	119050	119069	TCTAACATGCACATATTTAC	60	n/a	n/a	soooossssssssssooss	649
613393	119190	119209	AGCACTGGGTGTTTACAACA	84	n/a	n/a	soooossssssssssooss	650
613394	119594	119613	AGAAGTGATATCATATCCTA	85	n/a	n/a	soooossssssssssooss	324
	119905	119924			n/a	n/a	soooossssssssssooss	
613395	119595	119614	AAGAAGTGATATCATATCCT	68	n/a	n/a	soooossssssssssooss	325
	119906	119925			n/a	n/a	soooossssssssssooss	
613396	120782	120801	ACCCGGTGACCTTTCCTCTC	67	n/a	n/a	soooossssssssssooss	651
613397	121728	121747	GAGTGACATGCGCCACCCTG	87	n/a	n/a	soooossssssssssooss	203
613398	121794	121813	AAAAGGATGAGTGACACGCC	66	n/a	n/a	soooossssssssssooss	205
613399	121940	121959	GCCACAGCACGGCGCATGGG	89	n/a	n/a	soooossssssssssooss	652
613400	124954	124973	GCACCGCTCCCTCTGGGAAT	49	n/a	n/a	soooossssssssssooss	653
613401	125298	125317	AAATCTTGCTGGAAAGGCAG	64	n/a	n/a	soooossssssssssooss	654

[0563]

613402	125428	125447	GACCCAGACATTTGCTCAGC	86	n/a	n/a	soooossssssssssooss	655
613403	125982	126001	GGGCTCCCGCAAGTTTCACA	71	n/a	n/a	soooossssssssssooss	656
613404	127460	127479	GAGAGGCCCTGTGGACAGCT	75	n/a	n/a	soooossssssssssooss	657
613405	130381	130400	CCCACTGGATGCTGCTGAGG	34	n/a	n/a	soooossssssssssooss	658
613406	131662	131681	GTGCCTAGTAACCCATTTAG	54	n/a	n/a	soooossssssssssooss	659
613407	131796	131815	CACCCACAGCAAGACCTAGA	49	n/a	n/a	soooossssssssssooss	660
613408	133056	133075	ACACAGAGAAGCTTCCAGAG	70	n/a	n/a	soooossssssssssooss	661
613409	133304	133323	AGCTATCACATGGACGAGTT	67	n/a	n/a	soooossssssssssooss	662
613410	133548	133567	CATTTAATACAGGCTTTGAT	38	n/a	n/a	soooossssssssssooss	663
613411	134599	134618	AGCCACTGATGCCCAGACAT	69	n/a	n/a	soooossssssssssooss	664
613412	73879	73898	GTGATCTTCCATCACTTCGA	82	345	364	soooossssssssssooss	25

[0564]

[0565] **표 16**

[0566] 서열번호 5 및 6을 표적화하는 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 5-10-5 MOE 갭머에 의한 타우 mRNA 억제

ISIS 번호	표적 서열 번호	표적 개시 부위	서열	억제율%	결합 화학성질	서열 번호
613239	5	3	TGCCCTTCGCGGTCCCTTCG	11	soooossssssssssooss	396
613241	5	424	CTGTCCCCCAAACCCGTACG	48	soooossssssssssooss	397
613248	6	524	GCTTCCGCTGTTGGAGTGCT	59	soooossssssssssooss	398

[0567]

[0568] **실시예 8: 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 5-10-5 MOE 갭머에 의한 SH-SY5Y 세포에서의 인간 타우 안티센스 억제**

[0569] 타우 mRNA의 뚜렷한 *시험관내* 억제를 나타내는 상기 기술된 연구로부터의 갭머는 SH-SY-5Y 세포에서의 다양한 용량에서 선택 및 시험되었다. 세포를 웰당 20,000 세포의 밀도로 플레이팅하고, 하기 표에 명시된 바와 같이 전기천공을 사용하여 1.25 μM, 2.500 μM, 5.00 μM, 10.00 μM, 및 20.00 μM 농도의 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 16 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한 타우의 억제율로서 표현된다. 타우 mRNA 수준은 안티센스 올리고뉴클레오타이드 처리된 세포에서 용량-의존적 방식으로 뚜렷하게 감소되었다.

[0570] **표 17**

ISIS 번호	1.25 μM	2.50 μM	5.00 μM	10.00 μM	20.00 μM
613118	46	47	73	92	93
613136	36	70	83	88	92
613115	32	49	82	86	94
613329	73	80	92	94	92
613273	46	24	48	60	85
613262	31	72	76	87	94
613271	44	66	84	89	94
613370	92	92	95	98	98
613361	88	86	89	94	96
613371	80	88	91	95	97
613369	58	85	89	95	96
613399	61	77	90	94	96
613344	80	79	93	95	95
613397	64	74	79	93	95
613412	45	66	70	81	96

[0571]

[0572] 표 18

ISIS 번호	1.25 μM	2.50 μM	5.00 μM	10.00 μM	20.00 μM
613255	54	61	80	91	90
613065	22	61	62	83	89
613257	45	69	82	86	91
613098	70	57	83	92	98
613253	44	67	74	86	91
613039	21	77	85	90	95
613188	0	35	72	86	87
613042	33	45	73	90	94
613233	21	54	69	75	89
613073	59	67	83	92	97
613187	8	54	74	61	84
613402	10	58	62	81	87
613045	57	72	92	96	95
613412	20	52	67	84	90
613099	71	66	89	91	95

[0573]

[0574] **실시예 9: SH-SY5Y 세포에서의, 5-10-5 MOE, 5-8-5 MOE, 4-8-6 MOE, 또는 6-8-4 MOE 갭머에 의한 인간 타우 안티센스 억제**

[0575] 안티센스 올리고뉴클레오타이드는 타우 핵산을 표적화하도록 설계되었으며, 시험관내에서 타우 mRNA에 대한 그들의 효과에 대해서 시험되었다. 안티센스 올리고뉴클레오타이드는 유사한 배양 조건을 갖는 일련의 실험에서 시험되었다. ISIS 613412는 또한 검정에 포함되었다. 각 실험에 대한 결과는 하기 나타낸 개별 표에서 제시된다. 웰당 20,000 세포의 밀도로 배양된 SH-SY5Y 세포를 전기천공을 사용하여 8,000 nM 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 24 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한, 타우의 억제율로서 표현된다.

[0576] 하기 표에서 새롭게 설계된 키메라 안티센스 올리고뉴클레오타이드는 5-8-5 MOE, 4-8-6 MOE, 또는 6-8-4 MOE 갭머로서 설계되었다. 5-8-5 MOE 갭머는 길이가 18개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 8개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 4-8-6 MOE 갭머는 길이가 18개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 8개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 4개 및 6개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 6-8-4 MOE 갭머는 길이가 18개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 8개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 6개 및 4개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 5' 윙 분절 내의 각각의 뉴클레오사이드 및 3' 윙 분절 내의 각각의 뉴클레오사이드는 2'-MOE 변형을 갖는다. 하기 표에서의 각각의 갭머에 대한 뉴클레오사이드간 연결 모티프는, ISIS 613412를 제외하고, 5'-sooosssssssssssooss-3' 이며, 여기서 각 "s"는 포스포로티오에이트 뉴클레오사이드간 연결을 나타내고, 각 "o"는 포스포디에스테르 뉴클레오사이드간 연결을 나타낸다. ISIS 613412에 대한 뉴클레오사이드간 연결 모티프는 5'-soooosssssssssssooss-3' 이며, 여기서 각 "s"는 포스포로티오에이트 뉴클레오사이드간 연결을 나타내고, 각 "o"는 포스포디에스테르 뉴클레오사이드간 연결을 나타낸다. 각각의 갭머에서의 모든 시토신 잔기는 5-메틸시토신이다. "개시 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 5'-모스트(most) 뉴클레오사이드를 나타낸다. "정지 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 3'-모스트(most) 뉴클레오사이드를 나타낸다. 하기 표에 열거된 각 서열은 서열 번호: 1 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자 은행 수탁 번호 NT_010783.15) 또는 서열 번호: 4 (뉴클레오타이드 2624000-2761000로부터 절단된 유전자 은행 수탁 번호 NT_010783.14), 서열 번호: 5 (유전자 은행 수탁 번호 DR002467.1) 또는 서열 번호: 6 (유전자은행 수탁 번호 NM_001203251.1)에 표적화된다. n/a' 는 안티센스 올리고뉴클레오타이드가 100% 상보성을 갖는 특정 유전자 서열을 표적화하지 않는다는 것이다.

[0577] 표 19

[0578] 서열 번호: 1 및 서열 번호: 4를 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 4 개시 부위	서열 번호: 4 정지 부위	모티프	서열 번호
613412	73879	73898	GTGATCTTCCATCACTTCGA	83	69842	69861	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	89	94855	94872	5-8-5	665
	98928	98945			94892	94909		
621197	n/a	n/a	TCGCCAACAGACATGTGA	39	64850	64867	5-8-5	666

[0579]

621196	67898	67915	TGAAGGAGCCTGGGAAGT	15	63891	63908	5-8-5	667
621198	69079	69096	AGCAGAGATGTGGCTGGG	50	65044	65061	5-8-5	668
621199	69622	69639	GTGAGGTTGAAAAGTTTC	34	65587	65604	5-8-5	669
621200	69802	69819	TGGTTTCTGATGGTTTTT	43	65767	65784	5-8-5	670
621201	70023	70040	GTTGGAACTCCTGGGATC	27	65988	66005	5-8-5	671
621202	70259	70276	TCAGCATTTTTCTCCTCT	47	66224	66241	5-8-5	672
621203	70531	70548	CTGGAATGGTACGATCTC	52	66496	66513	5-8-5	673
621204	70750	70767	CCACTCTGGTGCAGGACG	29	66715	66732	5-8-5	674
621205	70930	70947	CAGATGCAGTGCAAGTGG	43	66895	66912	5-8-5	675
621206	71110	71127	GGGTTTCACCAGACCTCA	29	67075	67092	5-8-5	676
621207	71306	71323	CTTTGTCCATAATTTTTT	34	67271	67288	5-8-5	677
621208	71487	71504	TATAGCATGAGCATTTGT	42	67452	67469	5-8-5	678
621209	71667	71684	TAATGAATGTATAACAGA	2	67632	67649	5-8-5	679
621210	71850	71867	TCCTCCTGGCTGCCCTGT	33	67815	67832	5-8-5	680
621211	72030	72047	CATCCTGCCATACCAGAC	32	67995	68012	5-8-5	681
621212	72224	72241	TATCCGCCTCTCAAAGTG	0	68189	68206	5-8-5	682
621213	72410	72427	CACATTTGCATATTTTCA	65	68373	68390	5-8-5	683
621214	72590	72607	TCGGGTTGCCCCATTCAA	27	68553	68570	5-8-5	684
621215	72770	72787	AACCACCATTTACTCACA	35	68733	68750	5-8-5	685
621216	72950	72967	ACCGGCACCCACCAGGTC	22	68913	68930	5-8-5	686
621217	73130	73147	AGGGACAGCATCAGCAGA	22	69093	69110	5-8-5	687
621218	73437	73454	AGGCATGTGGCAGGTGCC	12	69400	69417	5-8-5	688
621219	73617	73634	ACCAACACCGCAGCAGTT	35	69580	69597	5-8-5	689
621220	73797	73814	GTTCTGAGGAGTGTTGGG	0	69760	69777	5-8-5	690
621221	73978	73995	ACTAACCTTTCAGGCCAG	33	69941	69958	5-8-5	691
621222	74273	74290	TAAATTATTTTAGAGACG	0	70236	70253	5-8-5	692
621223	74467	74484	CAAGGTAAATTTCTTTCT	69	70430	70447	5-8-5	693
621224	74647	74664	TCAGGCCTGATCTAAGTA	14	70610	70627	5-8-5	694
621225	74827	74844	TCCCCAACCATGTGGTCT	40	70790	70807	5-8-5	695
621226	75007	75024	TGCCAGCCACACCCATGG	52	70970	70987	5-8-5	696
621227	75187	75204	AACTCCACGGCTTCCATG	50	71150	71167	5-8-5	697
621228	75371	75388	AGATAGAAATCTGAAACG	34	71334	71351	5-8-5	698
621229	75551	75568	GCTGGGCCGAGCTGCATT	66	71514	71531	5-8-5	699
621230	75891	75908	GGATTCAAAGGAGAAAAC	35	71854	71871	5-8-5	700
621231	76192	76209	ATTATTATTTGACATGGG	75	72155	72172	5-8-5	701
621232	76373	76390	AGGGTAGGCAGTGTTGTG	4	72336	72353	5-8-5	702
621233	76553	76570	CTCTCTTTGTCAGGAAAA	58	72516	72533	5-8-5	703
621234	76942	76959	CCTTTTTTTTTAGGACGG	0	72905	72922	5-8-5	704
621235	77222	77239	GAGTTGACTGGGCACGGT	33	73185	73202	5-8-5	705
621236	77414	77431	TCATCTGTGAAGCGGACG	81	73377	73394	5-8-5	706
621237	77594	77611	GGCACAATCCATATGAGG	56	73557	73574	5-8-5	707
621238	77781	77798	GTTATTTTGGAACAGTTT	87	73744	73761	5-8-5	708
621239	78117	78134	CTGGACTTTATTTCATTT	77	74080	74097	5-8-5	709

[0580]

621240	78319	78336	CAGTATATATAGTGCATA	76	74282	74299	5-8-5	710
621241	78499	78516	CAAAACAGCTCCTTGTAA	14	74462	74479	5-8-5	711
621242	78679	78696	ACTTTCATCTACTTTTCA	32	74642	74659	5-8-5	712
621243	78859	78876	CCAATCTGTCCCCAGCTT	42	74822	74839	5-8-5	713
621244	79039	79056	TCCAGCATGAACATAGCT	65	75002	75019	5-8-5	714
621245	79219	79236	TAGAGTCAGTTTCAGGAT	75	75182	75199	5-8-5	715
621246	79399	79416	GGTGGTATCACCAACAGC	35	75362	75379	5-8-5	716
621247	79589	79606	TTAAGGAATGGCTCTGGG	42	75552	75569	5-8-5	717
621248	79769	79786	GAACATGAGACATCTTGA	8	75732	75749	5-8-5	718
621249	79949	79966	AGCTGTGCCCAGTTAAAA	53	75912	75929	5-8-5	719
621250	80129	80146	TCTGGTCATATGAGGAAA	55	76092	76109	5-8-5	720
621251	80309	80326	AGTCATTATCATGTCACC	89	76272	76289	5-8-5	721
621252	80489	80506	GCTGAGCGAATTACCTAA	75	76452	76469	5-8-5	722
621253	80669	80686	CCTCTGTATGACAGAAAT	48	76632	76649	5-8-5	723
621254	80849	80866	GGTAACATGTAAAGCTTC	79	76812	76829	5-8-5	724
621255	81033	81050	TGGATTATGTACAGATAT	28	76996	77013	5-8-5	725
	81136	81153			77099	77116		
621256	81110	81127	ATGGATGATAGGAAGGAT	20	77073	77090	5-8-5	726
	81213	81230			77176	77193		
621257	81393	81410	GATGGAGGAAGGAATGAT	5	77356	77373	5-8-5	727
621258	81629	81646	CTGGATGGTTACATGGAT	31	77592	77609	5-8-5	728
621259	81812	81829	ATAATTGATGTATAATTA	0	77775	77792	5-8-5	729
621260	81992	82009	GTTCTGCCCCACCTGGGC	56	77955	77972	5-8-5	730
621261	82198	82215	GCCTCTCAGGGCCTCCGT	76	78161	78178	5-8-5	731
621262	82378	82395	GAAGGATGGCCACACAGA	39	78341	78358	5-8-5	732
621263	82558	82575	ATGGGCTTATCAATGCAT	85	78521	78538	5-8-5	733
621264	82738	82755	GAGGCCCAAATGATCACA	56	78701	78718	5-8-5	734
621265	82918	82935	GCTCAGGGCAGACACGGT	66	78881	78898	5-8-5	735
621266	83098	83115	CTTAACCAGCTAGTGGTG	38	79061	79078	5-8-5	736
621267	83278	83295	GTCCTGTGGAGCTGAAAA	54	79241	79258	5-8-5	737
621268	83486	83503	GGCTGGAGGCATGGAGGG	7	79449	79466	5-8-5	738
621269	83666	83683	TGCCTCCAGAGCACACAC	55	79629	79646	5-8-5	739
621270	83846	83863	AGGATACTAAACCAAGAT	24	79809	79826	5-8-5	740
621271	84026	84043	CACAGATGGGAAGCAAGA	20	79989	80006	5-8-5	741
621272	84206	84223	CATGAGGCAACAATCCAA	70	80169	80186	5-8-5	742

[0581]

[0582] **표 20**

[0583] 서열 번호: 1을 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호
613412	73879	73898	GTGATCTTCCATCACTTCGA	80	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	92	5-8-5	665

[0584]

	98928	98945				
621273	84386	84403	GCCGTAAGACCCAGCTCT	58	5-8-5	743
621274	84566	84583	GAAGAAGTACTGAGAAAG	14	5-8-5	744
621275	84746	84763	TAAGAACCTCAGCGGCAA	56	5-8-5	745
621276	84926	84943	TGAGGGAGCACTGAGAGT	21	5-8-5	746
621277	85106	85123	AGTTCAATGAAGGACATT	69	5-8-5	747
621278	85287	85304	ACTGTTGGATGGGTCCAC	70	5-8-5	748
621279	85467	85484	TTGGTCCATTTTGATTGG	0	5-8-5	749
621280	85647	85664	CGGCAGCCCTGTGTAAAC	48	5-8-5	750
621281	85828	85845	CCTTTGCTTCTTGCGCAG	66	5-8-5	751
621282	86014	86031	AGGGCCTTGACTGCCTGG	15	5-8-5	752
621283	86194	86211	AAGGCCCTAAATGCTCTG	57	5-8-5	753
621284	86384	86401	CGCTCAGGTGATCTTGGG	76	5-8-5	754
621285	86564	86581	CTGATTGATTCCCCATCA	64	5-8-5	755
621286	86746	86763	TTCTTGTTGGGCAACTGG	59	5-8-5	756
621287	86928	86945	GAAATGCACTCAGAAGGG	52	5-8-5	757
621288	87108	87125	CCTCAGTGAAATAACTGT	55	5-8-5	758
621289	87288	87305	TGGCTGCAACTTTGAATG	0	5-8-5	759
621290	87470	87487	CTGGAGATGGCAGGCTGG	39	5-8-5	760
621291	87653	87670	CCCGTGGGCCCCATGTGG	1	5-8-5	761
621292	87834	87851	ATTGAGGACACCTGGTGT	6	5-8-5	762
621293	88014	88031	AAGGTCTGCATTGTCAGT	61	5-8-5	763
621294	88194	88211	CTGCTGGCCTCTCTGTAC	56	5-8-5	764
621295	88374	88391	TCGGACACGGTCACTGCC	60	5-8-5	765
621296	88554	88571	GTGCCTTGTCATGTGACA	79	5-8-5	766
621297	88734	88751	GGAAGCCATGTGGTAGCC	50	5-8-5	767
621298	88918	88935	CAGAGGCCACTGCCTCTG	0	5-8-5	768
621299	89098	89115	TTAATAGTACCAAAATCA	25	5-8-5	769
621300	89278	89295	TACATTTCCTTCCTCCCA	10	5-8-5	770
621301	89470	89487	CGGAGTCAGGCAGATGGG	43	5-8-5	771
621302	89650	89667	GCTATGACCTAGTAGGAA	84	5-8-5	772
621303	89830	89847	ATTGTTTACTAGAAACCA	39	5-8-5	773
621304	90010	90027	GGGCAGAGCCCACCCCAT	40	5-8-5	774
621305	90190	90207	AGGCTGGACAAGGCTAGC	63	5-8-5	775
621306	90531	90548	CATATTTGAGTTTCTTTT	62	5-8-5	776
621307	90711	90728	AATGATTACACAAAGCTG	61	5-8-5	777
621308	90891	90908	GAACAGTGTCTTTCCAGC	73	5-8-5	778
621309	91071	91088	ATGTGCCTTTCTGTGCCA	89	5-8-5	779
621310	91251	91268	AATGATTTCTAGAGGTCA	54	5-8-5	780
621311	91431	91448	CCATGATTCCAGGCTGCT	80	5-8-5	781
621312	91816	91833	CAGCCAGGCTAGTCTTGC	80	5-8-5	782
621313	92037	92054	AGGAGAATGTTCTTTTTT	53	5-8-5	783
621314	92219	92236	TTACTGTACTCTGATATA	41	5-8-5	784

[0585]

621315	92399	92416	CCTTATGGGAGCCCTTTG	54	5-8-5	785
621316	92579	92596	CAGAGCGCAGCAGCACCT	64	5-8-5	786
621317	92759	92776	CTCACCAGCTCTGCTTTA	53	5-8-5	787
621318	92939	92956	CAGCTGATCAAGGGCACA	84	5-8-5	788
621319	93123	93140	AGACCTGCCATAAGACTC	39	5-8-5	789
621320	93380	93397	CTGACTAAAATGTTATTT	34	5-8-5	790
621321	93570	93587	ACAGGCATGAGTTTTTTT	61	5-8-5	791
621322	93840	93857	CCCCTTTTTTTTGGTTTG	2	5-8-5	792
621323	94020	94037	TCTGGAGCCGCCCTGGGC	36	5-8-5	793
621324	94200	94217	ATGACAGCTCTCCTGGTC	38	5-8-5	794
621325	94380	94397	ACTCTCAACTCCTCTGGT	49	5-8-5	795
621326	94576	94593	TCCTGTTGGAGGAGGCGC	7	5-8-5	796
621327	95433	95450	CCTTTGAGTTGAGGGACC	60	5-8-5	797
621328	95613	95630	GCCTGAGCACGGGAGGAG	41	5-8-5	798
621329	95793	95810	GACACCATGAGGGCACCC	69	5-8-5	799
621330	95986	96003	AGCACCTCCTGGGAGGCG	18	5-8-5	800
621331	96166	96183	GGTGGCATGTGGACCAGG	50	5-8-5	801
621332	96346	96363	TGTGGCTCTGAGGTCTCC	72	5-8-5	802
621333	96526	96543	GCCTCTGTCTTAACTTTT	50	5-8-5	803
621334	96778	96795	TTAGGGTACAGTGGTGTG	18	5-8-5	804
621335	96958	96975	CCTCTAGTAGGCCAGTAT	62	5-8-5	805
621336	97141	97158	AATCAAGTAAGTTTGGGA	57	5-8-5	806
621337	97321	97338	CAACTGGGTCTGTAAGCC	47	5-8-5	807
621338	97506	97523	TAGATTTTCTTCTTTGGT	45	5-8-5	808
621339	97686	97703	GGGCACGAATTCTCACTG	53	5-8-5	809
621340	97866	97883	TCCAGAATAGGAGAGGCT	9	5-8-5	810
621341	98046	98063	ACACTGCAGCCAGGCTTG	63	5-8-5	811
621342	98226	98243	TGCAGTCTCCCTAACCCA	59	5-8-5	812
621343	98406	98423	CTCTTTTCCCTTGAATCT	33	5-8-5	813
621344	98607	98624	GTCAGCTTACCTTGGCTT	44	5-8-5	814
621345	98802	98819	CAACTGCTCTTCCCTGGG	68	5-8-5	815
621346	98982	98999	TCTGGGTGCAGTTTATGC	80	5-8-5	816
621347	99162	99179	AGAATTTATGCTGGAAAT	38	5-8-5	817
621348	99342	99359	GGCCAGCTCTCCAAATCC	56	5-8-5	818
621349	99522	99539	CCCTAGACTCTGGGCAAC	66	5-8-5	819

[0586]

[0587] **표 21**

[0588] 서열 번호: 1을 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호
613412	73879	73898	GTGATCTTCCATCACTTCGA	91	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	96	5-8-5	665

[0589]

	98928	98945				
620965	20187	20204	TCTAAGTAATTCGATATG	27	5-8-5	820
620966	20375	20392	AAACAGAAACTAGGGTGG	63	5-8-5	821
620967	20571	20588	TCCCGCTGGGATCCATGG	40	5-8-5	822
620968	20751	20768	TGTTGCCATTGGGCAGCC	0	5-8-5	823
620969	20931	20948	GACCTTCTAATTAGTCCA	58	5-8-5	824
620970	21291	21308	GCGATTCTCTCCTGTCTC	53	5-8-5	825
620971	21567	21584	ACTCAGATTTATTATTTT	87	5-8-5	826
620972	21747	21764	AAAGTACTATCCACTTGT	77	5-8-5	827
620973	21927	21944	CAAATCCTGGGTTCGAAT	39	5-8-5	828
620974	22107	22124	AGGTCTCTGCCCATGAAA	59	5-8-5	829
620975	22287	22304	AGATTTCTCCCTTCACCC	46	5-8-5	830
620976	22467	22484	TTAACATGATGGTGGTTT	86	5-8-5	831
620977	22652	22669	CATTGTGGAAATTAAACA	50	5-8-5	832
620978	22837	22854	TGTAGTCAATATTGAACT	86	5-8-5	833
620979	23269	23286	TTTTGAGAGCAGGTCTCG	61	5-8-5	834
620980	23449	23466	ATGGCAAACAGTACATGT	80	5-8-5	835
620981	23631	23648	AGGATTTAAGTGATTTTC	66	5-8-5	836
620982	23826	23843	TACAAAGACCCCTTTTCC	51	5-8-5	837
620983	24016	24033	AGCTGCCAGCAGTCCTTG	81	5-8-5	838
620984	24196	24213	CTGCTGTAGGAAATGACC	77	5-8-5	839
620985	24377	24394	AGCTCCAACCAGCTTTCT	58	5-8-5	840
620986	24557	24574	GTCCTGATTAACAGCTAA	69	5-8-5	841
620987	24744	24761	GTCTGTCTGCTGCCATCC	81	5-8-5	842
620988	24924	24941	GTAACTGATATGGTAACA	85	5-8-5	843
620989	25286	25303	AGCCCTCTTTGTACAGGA	75	5-8-5	844
620990	25466	25483	CTGTTCCAGTTGATCCAG	53	5-8-5	845
620991	25668	25685	GCAGTCTTTTTAAATTAA	80	5-8-5	846
620992	25848	25865	CCTCTGCTCACATAGAAA	64	5-8-5	847
620993	26028	26045	AGTACCTGCCTTGTTCCT	52	5-8-5	848
620994	26208	26225	AAGCATGGTAATACAAAA	78	5-8-5	849
620995	26404	26421	TTGATTAAAAAAAATAGC	4	5-8-5	850
620996	26584	26601	TTCATCCTTTCCAAGTGT	58	5-8-5	851
620997	26764	26781	CATGCTTACACACCACAC	23	5-8-5	852
	26948	26965				
620998	26762	26779	TGCTTACACACCACACAC	38	5-8-5	853
	26946	26963				
620999	27140	27157	ATATGCTGAACACACACA	75	5-8-5	854
621000	27320	27337	CCACCGAGGTCTCATTGG	52	5-8-5	855
621001	27500	27517	GGGAGACCTCCCTTTCAA	0	5-8-5	856
621002	27680	27697	TCTCTGGGTGTAGAGACG	54	5-8-5	857
621003	27861	27878	GCAGGCTCGGGCTCCACG	61	5-8-5	858
621004	28041	28058	CCTTGTCAGATGGTTGAT	55	5-8-5	859

[0590]

621005	28221	28238	TCTGCAGACTTTTCTCAA	22	5-8-5	860
621006	28426	28443	CTGGAGGGAGGTGATGTG	7	5-8-5	861
621007	28616	28633	GAAAGCTGCTGCTGAGGG	63	5-8-5	862
621008	28981	28998	GGGCAAAGATAATTCGAA	61	5-8-5	863
621009	29165	29182	CCTCACCCTGGGCAAGAA	68	5-8-5	864
621010	29409	29426	TTGCTGCTCGGGAGGCCG	14	5-8-5	865
621011	29589	29606	AAATGAAAGATGCTGGCT	23	5-8-5	866
621012	29953	29970	CAGAGAGGTCCAGCTACT	58	5-8-5	867
621013	30133	30150	AGCTCACTACAGCAGGCA	93	5-8-5	868
621014	30607	30624	TATTTCTTGCAATTCTTT	78	5-8-5	869
621015	30787	30804	GGAGGACTGTCTCTAGAG	59	5-8-5	870
621016	30967	30984	TCCGGCCTGGCGAACTGA	40	5-8-5	871
621017	31278	31295	CCTGCAAAGCTAATTTTA	18	5-8-5	872
621018	31458	31475	GAGCCCCCTTTAAGCCTT	65	5-8-5	873
621019	31654	31671	GTACAAAGACTGTGTACG	47	5-8-5	874
621020	31834	31851	GACTCAGGAACATGTTAG	81	5-8-5	875
621021	32023	32040	TGAGGCAGCAATGCTGGG	34	5-8-5	876
621022	32203	32220	CACTGGGAGGTGTATAGA	0	5-8-5	877
621023	32383	32400	GCGAGGTGGGTGAAGGTT	25	5-8-5	878
621024	32563	32580	AAAAACTTTGGCAGTCAG	80	5-8-5	879
621025	32743	32760	GGTCTGCCCTGCACCAGG	59	5-8-5	880
621026	32923	32940	CTGAGCTCTCCGAGCTGC	61	5-8-5	881
621027	33103	33120	GTGAGGTGGTATCATTGG	51	5-8-5	882
621028	33283	33300	CTAGCTTGAATTCCTCCA	81	5-8-5	883
621029	33463	33480	AATCTGTGACTCAAGAAC	47	5-8-5	884
621030	33708	33725	GGGCCGTCTCTATTAAAA	56	5-8-5	885
621031	33888	33905	GGTATAATTTGTTTGGAC	85	5-8-5	886
621032	34068	34085	CTTTATTGCATATAGGTA	86	5-8-5	887
621033	34248	34265	ATCCAGTCCCAACATTGG	30	5-8-5	888
621034	34428	34445	CGGTCTCTCTGACTTGCC	78	5-8-5	889
621035	34620	34637	GAGGGCATTCCTCAAAGG	10	5-8-5	890
621036	34800	34817	AGTTCTCTGATTCTCAAA	63	5-8-5	891
621037	34980	34997	CCCCCAGTGCCCACAAGT	48	5-8-5	892
621038	35160	35177	CTAAAAGCTAAAGTGGGT	49	5-8-5	893
621039	35340	35357	AGGACCTGGCAGAGCTGC	73	5-8-5	894
621040	35520	35537	AAATCGAACACTTACATA	20	5-8-5	895
621041	35721	35738	TTGCCATCTTGGACAGGG	89	5-8-5	896

[0591]

[0592] 표 22

[0593] 서열 번호: 1을 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호
613412	73879	73898	GTGATCTTCCATCACTTCGA	85	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	93	5-8-5	665
	98928	98945				
620888	98881	98898	ACACCTTCATTTACTGTC	95	5-8-5	897
	98918	98935				
620889	98890	98907	TTTTCAAACACACCTTCA	74	5-8-5	898
	98927	98944				
620890	98892	98909	GGTTTTCAAACACACCTT	96	5-8-5	899
	98929	98946				
620891	98893	98910	TGGTTTTCAAACACACCT	96	5-8-5	900
	98930	98947				
620892	6191	6208	TACCTGATAGTCGACAGA	53	5-8-5	901
620893	6371	6388	GTCCCTTTCCAGGCCGCC	70	5-8-5	902
620894	6551	6568	CGCCCATTGCGGCAAAAG	73	5-8-5	903
620895	6736	6753	CACTGCTCGGGAGGTGCA	62	5-8-5	904
620896	6938	6955	TGTTCTCAGGCACGGCGC	74	5-8-5	905
620897	7121	7138	GCCCTGCGCTCCGAGCGC	44	5-8-5	906
620898	7301	7318	AAAAAAGATGGCACCTCG	30	5-8-5	907
620899	7481	7498	ACAAAGCAAAGAGCCCCC	59	5-8-5	908
620900	7687	7704	TCACGCCCGTTCCATGCG	43	5-8-5	909
620901	7867	7884	CCGGATGGGTAGCCAGCG	47	5-8-5	910
620902	8047	8064	CCCTCTCCGGACACCTGT	69	5-8-5	911
620903	8227	8244	AAATACACCCAGGGCCGC	51	5-8-5	912
620904	8408	8425	GATAGAATTAACCAGAAA	33	5-8-5	913
620905	8588	8605	AGCCTCGCAGTACCCAGG	39	5-8-5	914
620906	8775	8792	TCGCGAGATGGCAATACG	55	5-8-5	915
620907	8956	8973	TTCCTCCATTAACAGCGC	49	5-8-5	916
620908	9157	9174	CCCGCCTGCTGGGAATGG	65	5-8-5	917
620909	9337	9354	AGAACTCAAATTGGTCCT	67	5-8-5	918
620910	9517	9534	TATAAGCAGCTTATACAG	34	5-8-5	919
620911	9697	9714	CCAAGCCAGGTTATTGCT	70	5-8-5	920
620912	9877	9894	TCTAACAATTTATGGGCA	81	5-8-5	921
620913	10057	10074	AACAAATGGACTGTAACA	59	5-8-5	922
620914	10240	10257	TTCAAGGAGGGAGTAAGG	12	5-8-5	923
620915	10420	10437	AGGAAAGTGGTGGTGGAG	22	5-8-5	924
620916	10600	10617	TGCAGCCCAGCTGGTGAG	35	5-8-5	925
620917	10781	10798	TCCTTGTAGGATGTTTAA	30	5-8-5	926

[0594]

620918	10961	10978	ACCTGCTACATAGCGGAA	87	5-8-5	927
620919	11141	11158	TTATAGATCATATCTGGG	82	5-8-5	928
620920	11321	11338	AAACAGAGCACCAATGTA	36	5-8-5	929
620921	11501	11518	ACCTCAGAGACTTGACCT	54	5-8-5	930
620922	11681	11698	CCCAGGAAGTGAGAAAAG	20	5-8-5	931
620923	11864	11881	CAGTTGGGAGCCATCTGG	51	5-8-5	932
620924	12044	12061	ATTGGGCTCAGCATGGAG	30	5-8-5	933
620925	12224	12241	TCCTTAACCATTAGGCCA	70	5-8-5	934
620926	12404	12421	TGGCCCTAGTGAGTACCG	75	5-8-5	935
620927	12597	12614	GCCCAGTTTGGTGCAGGG	79	5-8-5	936
620928	12777	12794	GGCGGGAAGGCAGGTCAG	51	5-8-5	937
620929	12957	12974	CAGTTTACCAATGTCAGC	77	5-8-5	938
620930	13137	13154	ATATATTGTTACTTAGTC	83	5-8-5	939
620931	13317	13334	CATAGGCAAAACAGACAA	68	5-8-5	940
620932	13504	13521	TAGTTGAATGTTTTGGAA	73	5-8-5	941
620933	13702	13719	ACGGCGGAGGCTGAGGCG	10	5-8-5	942
620934	13882	13899	AGGTGCAAGCTGGCCGGG	44	5-8-5	943
620935	14062	14079	TGATACCCTGTAAGAATA	82	5-8-5	944
620936	14243	14260	AATATAGCAAAGGGAATT	54	5-8-5	945
620937	14423	14440	TAGAGATAATTATGTCCC	73	5-8-5	946
620938	14609	14626	GCAATTACAGAGCCAGGG	76	5-8-5	947
620939	14789	14806	GCAGAACTGGATCCGATC	69	5-8-5	948
620940	15035	15052	CAAAGCCAGGATGGTCTC	92	5-8-5	949
620941	15246	15263	CCAAAGAGATTCCTTTTT	79	5-8-5	950
620942	15924	15941	GGCCTCATTTATATATAT	20	5-8-5	951
620943	16156	16173	TATGGGACAATCATAGCT	56	5-8-5	952
620944	16336	16353	AATTCTGATACATTGTCA	81	5-8-5	953
620945	16516	16533	GATGACTCTTCCAAATGG	70	5-8-5	954
620946	16696	16713	TCACTTCATTATTCAAGC	84	5-8-5	955
620947	16876	16893	GTGCAGCCGCCACTGGCC	86	5-8-5	956
620948	17085	17102	CGATAAGATCTTTTTAAA	25	5-8-5	957
620949	17266	17283	GACAGTATAATCTCCATT	69	5-8-5	958
620950	17446	17463	AGGCTAAAGTCAGCCCAC	29	5-8-5	959
620951	17639	17656	CTTGCACCCTGGTTTGGG	40	5-8-5	960
620952	17819	17836	TCCCTGTCTGGTTAGGAA	80	5-8-5	961
620953	17999	18016	ACGCGCCTGCCCCGTGCC	50	5-8-5	962
620954	18179	18196	CTCAAACCTGGCCACGCT	64	5-8-5	963
620955	18359	18376	GAAACTGGCGGGTCTGTT	64	5-8-5	964
620956	18539	18556	GGGAGGAATTTGGCAATG	37	5-8-5	965
620957	18719	18736	AAAGAGCACGGCATCTAT	76	5-8-5	966
620958	18905	18922	AAACTGTGAGGCACTGGG	87	5-8-5	967
620959	19088	19105	CATTTGACATTGGCCTGT	72	5-8-5	968
620960	19283	19300	ATTATTATCAGCATCTTC	77	5-8-5	969

[0595]

620961	19467	19484	TTGCAGAGGCAGGAAGGC	67	5-8-5	970
620962	19647	19664	AGCAGCCTGGTTTAGAGG	31	5-8-5	971
620963	19827	19844	TCCACATCTTCCAGCCTC	74	5-8-5	972
620964	20007	20024	ATACAGACTCAGTCTCCT	79	5-8-5	973

[0596]

[0597] 표 23

[0598] 서열 번호: 1을 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호
613412	73879	73898	GTGATCTTCCATCACTTCGA	78	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	93	5-8-5	665
	98928	98945				
621042	35901	35918	AGTCGACCGCACTCCTGC	42	5-8-5	974
621043	36106	36123	GCCCTGAGGGTCCACAGG	20	5-8-5	975
621044	36286	36303	AGGGCAGTGTCCTACCTC	50	5-8-5	976
621045	36466	36483	GTCCTCCCTTCCCCACAA	29	5-8-5	977
621046	36653	36670	CTGAATTCCTATCATGCG	51	5-8-5	978
621047	36833	36850	GAGAAAGAAGAGTGTGGT	23	5-8-5	979
621048	37024	37041	CTTAGGACAGATTCCTAG	29	5-8-5	980
621049	37204	37221	GTCAGAAGTGTTTTCCCA	80	5-8-5	981
621050	37413	37430	TCCAATTTTAAACTTAAA	28	5-8-5	982
621051	37750	37767	CTACTGTTTAAAAAGGCT	66	5-8-5	983
621052	38013	38030	GTAAACACCATCTCTAAA	19	5-8-5	984
621053	38193	38210	CTCTGATACTATTATAAG	31	5-8-5	985
621054	38374	38391	CTGAGCTATTTGAGAATT	21	5-8-5	986
621055	38557	38574	TCTGCATATATAATTATA	57	5-8-5	987
621056	38737	38754	CACATTGTTTAGATTTTC	79	5-8-5	988
621057	38922	38939	TTAGCACACCTGAAACGC	51	5-8-5	989
621058	39102	39119	GGCAAAGAAGACAGGAGA	68	5-8-5	990
621059	39541	39558	TGCTGAGGATGCTTTTTT	72	5-8-5	991
621060	39721	39738	GCTGGAAGATGAGGTGGT	47	5-8-5	992
621061	39901	39918	TGGGTGTTGGAGAAAACT	24	5-8-5	993
621062	40100	40117	GCTTTAAAAGCTCCTCAG	65	5-8-5	994
621063	40347	40364	CGAGCACTTGTAGTTCCA	35	5-8-5	995
621064	40528	40545	GCAGTGCTTTAAAAATAT	22	5-8-5	996
621065	40709	40726	GAAATTTCATGAAATATG	37	5-8-5	997
621066	40889	40906	TTACTTGCAATTGAAAGA	6	5-8-5	998
621067	41069	41086	GGAAAGACTACTCAGAGC	57	5-8-5	999
621068	41249	41266	GATGAAAGAGAATAACAA	20	5-8-5	1000
621069	41429	41446	ACCCATTATCTGCTCCCC	66	5-8-5	1001
621070	41611	41628	TTTTCAGTAACAACATAA	51	5-8-5	1002
621071	41944	41961	CCTTTAGCTTTCCTTTTC	47	5-8-5	1003

[0599]

621072	42124	42141	CAAATTCTGTTTCTGTAA	47	5-8-5	1004
621073	42304	42321	GCAAAAATAAGTGAACTG	38	5-8-5	1005
621074	42492	42509	TTGCAGTGACTTCTTGGG	71	5-8-5	1006
621075	42672	42689	AAACCCCTTCAACATCAG	45	5-8-5	1007
621076	42853	42870	ACAAGAGAAACATTTTAC	53	5-8-5	1008
621077	43033	43050	CACTTAGTAACCAAGCAA	53	5-8-5	1009
621078	43213	43230	CATAGATGATATATTTTG	78	5-8-5	1010
621079	43393	43410	AAATCTTGAACTCCTGAA	58	5-8-5	1011
621080	43620	43637	GGAGTTTTTGTGTTTCTT	77	5-8-5	1012
621081	43804	43821	AAATTCTTAATGGTTCAG	75	5-8-5	1013
621082	44051	44068	AGATAGATCTCGGCTCAC	81	5-8-5	1014
621083	44231	44248	AACCTTTAATAAACTTTT	43	5-8-5	1015
621084	44617	44634	GTCCAAGAGGTTTTTTTT	41	5-8-5	1016
621085	44809	44826	GCAGTCACTGCATTCCAG	27	5-8-5	1017
621086	45050	45067	CAAAAACAGGGCTAGGCA	21	5-8-5	1018
621087	45230	45247	TTCCCTGAACAAATGGCA	59	5-8-5	1019
621088	45412	45429	CTCAAATGTAACATTTTA	84	5-8-5	1020
621089	45592	45609	TACACCTGGCCCATGACC	41	5-8-5	1021
621090	45772	45789	AAGTTCTGGCTCAAGCAA	21	5-8-5	1022
621091	45955	45972	ACAACTCTCTGGAAAAAA	30	5-8-5	1023
621092	46135	46152	AGTCCACGCCTGCATCTG	63	5-8-5	1024
621093	46315	46332	CAAGGCAACAGAGAGGCA	42	5-8-5	1025
621094	46495	46512	AACATGCATATAATTACC	40	5-8-5	1026
621095	46675	46692	TTGGAGGGACAATTCTCA	46	5-8-5	1027
621096	46855	46872	CGAAGAGGCCAGGACTGC	34	5-8-5	1028
621097	47036	47053	TTTGGCTCTGGTGATGGT	45	5-8-5	1029
621098	47216	47233	ACCAGGCAAAGGGACACC	68	5-8-5	1030
621099	47396	47413	TGCCAGAGACAGAGGTTG	68	5-8-5	1031
621100	47576	47593	CACACGCATGGCTTCATG	55	5-8-5	1032
621101	47756	47773	GAGGAAGGCATGAACTAA	60	5-8-5	1033
621102	47936	47953	TCCCATGCCCACGCATGT	26	5-8-5	1034
621103	48116	48133	ATTATTAACGAACAAAAA	2	5-8-5	1035
621104	48302	48319	ATGTCCAGATGTGGATCG	52	5-8-5	1036
621105	48482	48499	ATCAGACAGAAGAGCCAT	55	5-8-5	1037
621106	48678	48695	GCACAGTGCAACAGTGGG	78	5-8-5	1038
621107	49171	49188	GGCTTTCCCTTCCCTTCT	33	5-8-5	1039
621108	49361	49378	AGCTGGGAAAGTGGCAGG	23	5-8-5	1040
621109	49561	49578	ATGACAACTTGATTTGGG	65	5-8-5	1041
621110	49741	49758	GACCGCAACCTTGCCAAA	43	5-8-5	1042
621111	50111	50128	CTTTCAGAGACAGGCTCG	41	5-8-5	1043
621112	50298	50315	GGGCTCACCCCTGTAGTT	9	5-8-5	1044
621113	50766	50783	CTCTTAAGGCCGAGTGCA	39	5-8-5	1045
621114	50970	50987	TGCTAGGCAAAAAAACAA	35	5-8-5	1046

[0600]

621115	51150	51167	TAATTAGAAACCTCCTCG	10	5-8-5	1047
621116	51330	51347	CAGGTCATATATGAAATC	33	5-8-5	1048
621117	51521	51538	TGTGCTTCCGAAAGTAGT	63	5-8-5	1049
621118	51702	51719	GCATCAAATCCATGCATT	38	5-8-5	1050

[0601]

[0602] **표 24**

[0603] 서열 번호: 1을 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호
613412	73879	73898	GTGATCTTCCATCACTTCGA	71	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	84	5-8-5	665
	98928	98945				
621119	51894	51911	ACTCTGAAGCACAGACAG	21	5-8-5	1051
621120	52081	52098	CTTACCTGGGCTGGATGG	5	5-8-5	1052
621121	52261	52278	TTCTGTCTATAGCTAGAA	32	5-8-5	1053
621122	52441	52458	AGATGGCTTCCTATTGTT	32	5-8-5	1054
621123	52621	52638	TGGTTTGGTCAGGCCTCA	51	5-8-5	1055
621124	52803	52820	ATTGTAACTCAAAGTGGG	50	5-8-5	1056
621125	53004	53021	AAACTCTACACCCCTGGG	17	5-8-5	1057
621126	53264	53281	CATACCAGGAAGGAAGGA	17	5-8-5	1058
621127	53444	53461	TGGACATATCAGAATTTG	64	5-8-5	1059
621128	53624	53641	CCCTTATTAGTGTCTACA	68	5-8-5	1060
621129	53805	53822	ACACTCTAGAGAGGTCCA	68	5-8-5	1061
621130	53985	54002	GACAGTACCCACGACACG	32	5-8-5	1062
621131	54165	54182	CCCCATTCTGGATCCTGG	40	5-8-5	1063
621132	54348	54365	ATTGTCTGTAAAATGTGG	57	5-8-5	1064
621133	54528	54545	ATTCTGTCTGACAGAGAC	40	5-8-5	1065
621134	54711	54728	CGATGGTGCACATCTATA	45	5-8-5	1066
621135	54891	54908	CAGTGTCCGCTGAACACA	37	5-8-5	1067
621136	55073	55090	AGGAGGATTAGGAAGAAA	14	5-8-5	1068
621137	55261	55278	CAAGGAAGGCGATCTGGG	17	5-8-5	1069
621138	55623	55640	GGTGGCACTTGAACAAGC	61	5-8-5	1070
621139	55803	55820	GGTGGAAAGGGAACCCGG	43	5-8-5	1071
621140	55983	56000	CCCCACGGGTACACAGAG	20	5-8-5	1072
621141	56163	56180	CGCTGCGAACGATGCACT	63	5-8-5	1073
621142	56343	56360	GAATGGTCCTTCTTACAG	13	5-8-5	1074
621143	56526	56543	CTGGGAAAACCAAGGCAA	57	5-8-5	1075
621144	56706	56723	CCCAGGCTGAGGAAGGAC	40	5-8-5	1076
621145	56886	56903	GATTGGCTTTTACATCTT	48	5-8-5	1077
621146	57289	57306	CGGTTTGAGTACAGTGGT	50	5-8-5	1078
621147	57470	57487	CTAACATCTTAGGGCACA	73	5-8-5	1079
621148	57650	57667	TTCCTCTGATGTCAGAAT	51	5-8-5	1080

[0604]

621149	58090	58107	CCCCCTCGGTCGCCCAGG	37	5-8-5	1081
621150	58271	58288	TGTTTTAACTAAAAGCTT	24	5-8-5	1082
621151	58451	58468	GTATGAGGGCATAGATGA	26	5-8-5	1083
621152	58631	58648	ATCACACCACAGAATGTT	29	5-8-5	1084
621153	58812	58829	TACTCTTCTGTGGCAGCT	66	5-8-5	1085
621154	59198	59215	CAACAGCAAGGCCAGGCG	44	5-8-5	1086
621155	59380	59397	TAGATAATTTGAAATTTA	0	5-8-5	1087
621156	59786	59803	ACCTTAATCCCAGTATTT	12	5-8-5	1088
621157	59966	59983	TGCTTATGGTCCAGCTGT	40	5-8-5	1089
621158	60146	60163	GAGCCAGGCTTCAAAACC	26	5-8-5	1090
621159	60326	60343	TCCAGCACATTTAGGCGG	32	5-8-5	1091
621160	60522	60539	ATCTCAATAAAGCTATCG	70	5-8-5	1092
621161	60702	60719	CGCCCGCGGTGACTCAGC	32	5-8-5	1093
621162	60906	60923	GGAGTCAAGAGTCCAGGG	44	5-8-5	1094
621163	61109	61126	AGAAGGAATGATGAGGAA	24	5-8-5	1095
621164	61290	61307	GCAGTACAGTTTGGTAAT	32	5-8-5	1096
621165	61476	61493	TGGCTACTCTCTCAGGAG	9	5-8-5	1097
621166	61656	61673	GACCCTAGGTGGGTAAAG	21	5-8-5	1098
621167	61836	61853	GTCCCCTGAGGTGTTGTG	0	5-8-5	1099
621168	62016	62033	CCCAGACAACCTTCACCT	34	5-8-5	1100
621169	62208	62225	TGGGTTAAGACTCTGTCT	11	5-8-5	1101
621170	62467	62484	TGGAGCCGAGTGCGGTGG	12	5-8-5	1102
621171	62657	62674	TCTCTTCTGGATATTTCG	49	5-8-5	1103
621172	62843	62860	CGATTTAAAATGAATGAT	20	5-8-5	1104
621173	63023	63040	AGAACAAAGATAACAGTT	0	5-8-5	1105
621174	63218	63235	GCTAAATTGAGGCCCGGG	42	5-8-5	1106
621175	63398	63415	CTTTCTCCTTTCCTCAAT	26	5-8-5	1107
621176	63578	63595	TCTAAGCGAGACACACAG	26	5-8-5	1108
621177	63758	63775	TGATTTCTCTGGAAGAAC	27	5-8-5	1109
621178	63938	63955	GCCTGTGTCTTCTAACTC	32	5-8-5	1110
621179	64184	64201	GGCTGAGAAGCTGGGACC	40	5-8-5	1111
621180	64365	64382	TTTTTACTTGAGATGTCA	38	5-8-5	1112
621181	64543	64560	GTAGGTGTCATCATCATC	83	5-8-5	1113
621182	64723	64740	CAACACTGACTGAGCACA	56	5-8-5	1114
621183	64903	64920	GCATTGGCTGGGCTAGGT	73	5-8-5	1115
621184	65092	65109	TATTTACTATGCAAAATA	18	5-8-5	1116
621185	65273	65290	AGCACCACAGAGCAGATG	19	5-8-5	1117
621186	65453	65470	CTCAGTGTGGAGTTCTGC	44	5-8-5	1118
621187	65634	65651	CATTTTTCAACCACTTAA	44	5-8-5	1119
621188	65815	65832	GTAAGGCTTTGTGGGCCA	32	5-8-5	1120
621189	66148	66165	TACTTTGCATTATTTATT	44	5-8-5	1121
621190	66535	66552	TTGGCTTTCATTATAATT	13	5-8-5	1122
621191	66736	66753	GGACGGTTGGGAAATAGG	18	5-8-5	1123

[0605]

621192	66916	66933	GAGCAACTGTTCATAGGG	49	5-8-5	1124
621193	67096	67113	TCTGCACATCGACACATC	34	5-8-5	1125
621194	67538	67555	AGGCTAGGCCCCATGGCT	21	5-8-5	1126
621195	67718	67735	GCACCCCCATCCTTCAGC	30	5-8-5	1127

[0606]

[0607] **표 25**

[0608] 서열 번호: 1을 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호:
613412	73879	73898	GTGATCTTCCATCACTTCGA	87	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	96	5-8-5	665
	98928	98945				
621350	99702	99719	CCAGGAGATGAAGTAGCA	75	5-8-5	1128
621351	n/a	n/a	ACTCTTGGGAAACAAAGT	31	5-8-5	1129
621352	100065	100082	GGAAGCAGCCAGGGACGG	38	5-8-5	1130
621353	100288	100305	CTGCCTGGCCAATTAAAT	28	5-8-5	1131
621354	100468	100485	CAAACTAATATTAACACT	0	5-8-5	1132
621355	100648	100665	TACTCAATTCCAGGCAAG	71	5-8-5	1133
621356	100836	100853	AATGGAAGTTCTAGTACG	57	5-8-5	1134
621357	101188	101205	CAATCACAGTTCTTTTTC	45	5-8-5	1135
621358	101381	101398	GTCTTAAACATAAACATA	77	5-8-5	1136
621359	101759	101776	TGAGAGGGATGGCCCCCA	67	5-8-5	1137
621360	n/a	n/a	CGCATAACACCACGCCCG	90	5-8-5	1138
621361	102169	102186	GCCAAAATCAGGAATGGG	94	5-8-5	1139
621362	102349	102366	GGCAGTCCCTGGGTTCCG	77	5-8-5	1140
621363	102529	102546	GTTGAACCTGACCAAGGA	89	5-8-5	1141
621364	102709	102726	AGCATGAGTTGTGCCAAG	89	5-8-5	1142
621365	102889	102906	CCCACTCCGCCACCTTGA	67	5-8-5	1143
621366	103091	103108	TACCAGAGCTGGGTGGTG	13	5-8-5	1144
621367	103271	103288	ACATTTGCCTCAGAAATC	5	5-8-5	1145
621368	103593	103610	GATTCAGGCTGGGAGTGG	11	5-8-5	1146
621369	103773	103790	CTCCGAGAGCTGCCACTT	51	5-8-5	1147
621370	103966	103983	TGCAGCAGACTCCTAACG	33	5-8-5	1148
621371	104389	104406	AGGAATCTCACTTTTGTC	25	5-8-5	1149
621372	104569	104586	AGGCTGCCCGTGCCACCA	30	5-8-5	1150
621373	104749	104766	TTAGTGAATGGCCATCCT	33	5-8-5	1151
621374	105023	105040	AAACTGCTTGAATTTGGG	31	5-8-5	1152
621375	105203	105220	TGTGAGTCCCCTGTAATC	18	5-8-5	1153
621376	105383	105400	TAAACAGGGCCTTAATGA	0	5-8-5	1154
621377	105563	105580	TCCTCCCGGCTCTAGAAA	10	5-8-5	1155
621378	105745	105762	GGAGACAGCCAGGCATGG	18	5-8-5	1156
621379	106173	106190	ATAATGTTTTTTATAGAG	0	5-8-5	1157
621380	106365	106382	GACTGGATTTTTGTATTT	30	5-8-5	1158

[0609]

621381	106545	106562	CGGAGTCTTATTCTGATG	39	5-8-5	1159
621382	106725	106742	CCGCAGCAATGCCCCTGC	65	5-8-5	1160
621383	106905	106922	TCTCGATCCCCTTCAAGA	23	5-8-5	1161
621384	107085	107102	CTGGGTGTCCTTTACCCT	5	5-8-5	1162
621385	107265	107282	CCTGCTCCACGCCTGCCT	82	5-8-5	1163
621386	107445	107462	TCAGGGCCTTTATCCTAA	51	5-8-5	1164
621387	107625	107642	TCGGCTCCACAGTCTTTG	60	5-8-5	1165
621388	107805	107822	CACCACTGGGTTAGGCAG	38	5-8-5	1166
621389	108170	108187	TCACCTTCCCGCCTCCCG	16	5-8-5	1167
621390	108359	108376	TTGAAGAGGGTCCAGAGG	3	5-8-5	1168
621391	108548	108565	TGCCCAGAAGGCAGGTGG	38	5-8-5	1169
621392	108728	108745	GGCCCCCGAAGTCTGTGC	62	5-8-5	1170
621393	108908	108925	CGGTGCAGGACAGAGGTG	57	5-8-5	1171
621394	109135	109152	CGCGCACCACCACCACGC	78	5-8-5	1172
621395	109315	109332	TCAGGCTGGGCCCTAAGC	50	5-8-5	1173
621396	109495	109512	TCACCCTTCCCCAGCTCC	45	5-8-5	1174
621397	109675	109692	TCAGACCCAAGTGATAAG	64	5-8-5	1175
621398	109855	109872	GCAGGGTCTACACATGCG	76	5-8-5	1176
621399	110045	110062	CTGAGATGTTCTCTTCCT	73	5-8-5	1177
621400	110225	110242	AGCTGCGGTACAGGACAG	68	5-8-5	1178
621401	110405	110422	CCAGTGAGGGCCCCTCTG	20	5-8-5	1179
621402	110585	110602	GCCCCCAGAGGTGCATGG	58	5-8-5	1180
621403	110769	110786	GGAGCAGCAGACACATGC	79	5-8-5	1181
621404	110949	110966	GGAAGCTACTTCCCATGC	43	5-8-5	1182
621406	111495	111512	GGAGGAGGCCTGACACCC	58	5-8-5	1183
621407	111675	111692	TTTCCCTTTGGTGTTAGC	91	5-8-5	1184
621408	111856	111873	CCCCAAAGCAATCTATGT	47	5-8-5	1185
621409	112036	112053	TCTGGAGGGAACACTGCC	60	5-8-5	1186
621410	112216	112233	GGTTGAGGTTGAGGGTAG	37	5-8-5	1187
621411	112396	112413	ACTCCCGCAGGCCAAACA	36	5-8-5	1188
621412	112603	112620	GAGTGCCAACAGGCCCAG	75	5-8-5	1189
621413	112784	112801	TTCTAAGTACAATTTGGG	67	5-8-5	1190
621414	112984	113001	TTACTGGTTGTGTTTTCT	94	5-8-5	1191
621415	113164	113181	GAGTCTCAGTCTCACTGT	76	5-8-5	1192
621416	113347	113364	CATTCCTCCTGCTGCTGT	83	5-8-5	1193
621417	113540	113557	GCTCTGAAGAGCTCCACG	83	5-8-5	1194
621418	113720	113737	CTCTCTTCAGGGCCACCG	82	5-8-5	1195
621419	113900	113917	CTCTCTCGCCCTGCATGG	48	5-8-5	1196
621420	114080	114097	CTGGACATCCTCCGAGAA	27	5-8-5	1197
621421	114260	114277	CACCCAGGCTGCGGCCCA	64	5-8-5	1198
621422	114440	114457	CTGTGGTGCAAGCCTGTG	42	5-8-5	1199
621423	114639	114656	AGACGAGAGTGCGCCCAC	78	5-8-5	1200
621424	115155	115172	CCACATAAATGTTCTACA	94	5-8-5	1201

[0610]

621425	115335	115352	GGTACAGGAAAAGATGCC	88	5-8-5	1202
621426	115515	115532	ATCAGCTTAGGAACTGAC	85	5-8-5	1203

[0611]

[0612] 표 26

[0613] 서열 번호: 1을 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호:
613412	73879	73898	GTGATCTTCCATCACTTCGA	86	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	97	5-8-5	665
	98928	98945				
621427	115695	115712	GTGCCTCACAGTTGGCTC	39	5-8-5	1204
621428	115896	115913	GAGAGGCTGTGGTGAGGT	25	5-8-5	1205
621429	116077	116094	GAAATCAGAATCCTGAAA	66	5-8-5	1206
621430	116259	116276	ATGTGGCTTTTTCTTGTT	64	5-8-5	1207
621431	116595	116612	GTTTTTTTCTGGCCGGGC	90	5-8-5	1208
621432	116955	116972	TTTTCAGTGGATAAGGCT	78	5-8-5	1209
621433	117135	117152	ACATAAACTCCTTCTTTG	53	5-8-5	1210
621434	117315	117332	TGGTGAATGTTGAAATTC	78	5-8-5	1211
621435	117495	117512	AGGACAAGGAGGCCATGT	56	5-8-5	1212
621436	117787	117804	TCAAATGACAGATTCTCA	78	5-8-5	1213
621437	117967	117984	CATCCCTACTTTCTCCCT	24	5-8-5	1214
621438	118420	118437	TAGAATCTTGCCTTGTCG	34	5-8-5	1215
621439	118600	118617	GATACAGACATACATTGT	68	5-8-5	1216
621440	118831	118848	AATTCTTTGTGATGATGG	82	5-8-5	1217
621441	119044	119061	GCACATATTTACATTTTA	94	5-8-5	1218
621442	119224	119241	GGTGAGAGAGCCAGCCTC	59	5-8-5	1219
621443	119404	119421	CAAACAGCCTCCCATGAA	38	5-8-5	1220
621444	119584	119601	ATATCCTAAGCATTGTCT	71	5-8-5	1221
621445	119880	119897	TACAGTGGCTCCTGTAAT	18	5-8-5	1222
621446	120060	120077	GCTCATCAAAGCAAAAAC	84	5-8-5	1223
621447	120248	120265	CTGGGCTGTCGGATCTGG	69	5-8-5	1224
621448	120439	120456	AAGCCACCATGCCTGTAA	89	5-8-5	1225
621449	120660	120677	ACACCATCACGGCTCAGT	56	5-8-5	1226
621450	120840	120857	AGGGAGTTGGAAAAACTG	46	5-8-5	1227
621451	121209	121226	CAGGTTTGAGAAGCCCTG	0	5-8-5	1228
621452	121389	121406	AGACCCACCGGCACATTC	56	5-8-5	1229
621453	121569	121586	ATTTCCAGCGGGCTTTAC	62	5-8-5	1230
621454	121761	121778	GCTTGCTCGCAAGGACGC	93	5-8-5	1231
621455	121941	121958	CCACAGCACGGCGCATGG	65	5-8-5	1232
621456	122121	122138	ACACCCCCTCCTAGAATA	0	5-8-5	1233
621457	122301	122318	ACCACCTTCAGCCCAACT	22	5-8-5	1234
621458	122481	122498	TAAGCTGGAGGCTTAGGA	40	5-8-5	1235
621459	122678	122695	GAACCTCCCGCCTTAGTC	19	5-8-5	1236

[0614]

621460	122913	122930	TATATGATTGTTTTTTGA	0	5-8-5	1237
621461	123093	123110	AGGAGCCTCGGGTGCCCA	30	5-8-5	1238
621462	123273	123290	TCAGGCCAGGCATTTTCT	58	5-8-5	1239
621463	123453	123470	CACTTAGCAGACACTGGT	77	5-8-5	1240
621464	123633	123650	TCCTCTGGCCGAGCTCAC	58	5-8-5	1241
621465	123824	123841	ACAGCGCGGGACACACGG	77	5-8-5	1242
621466	124004	124021	GCATCTCTTCTCACCAGG	13	5-8-5	1243
621467	124184	124201	GGATACCTGGAGGGCAGG	13	5-8-5	1244
621468	124379	124396	TGAGGCCAGCACTGAGGG	29	5-8-5	1245
621469	124559	124576	ACTGGAACCATCCCGAAT	37	5-8-5	1246
621470	124752	124769	GCAGTGGCCTTGTGTGGG	19	5-8-5	1247
621471	124932	124949	ACCCTGAGCTGCCAGCTG	53	5-8-5	1248
621472	125112	125129	CTGCACACTCAGTGTCCT	78	5-8-5	1249
621473	125292	125309	CTGGAAAGGCAGGAGTGG	33	5-8-5	1250
621474	125472	125489	AAGAGCCTCTGGGAAAAA	50	5-8-5	1251
621475	125652	125669	GGTGTAACTCAATGAGAA	41	5-8-5	1252
621476	125832	125849	GGCTACCTGGTTTATGAT	32	5-8-5	1253
621477	126012	126029	GGAGCGAGCTGGAGCCAC	75	5-8-5	1254
621478	126332	126349	GCTCACTCCGCTCACTGC	74	5-8-5	1255
621479	126527	126544	CTAGGTCTTATTCTATTT	38	5-8-5	1256
621480	127208	127225	AGGTTTTTGTTGTGTGTT	54	5-8-5	1257
621481	127396	127413	CCTCTTCACCTTAAAAAA	24	5-8-5	1258
621482	127591	127608	AAACAAAGTCACAGAGGG	67	5-8-5	1259
621483	127934	127951	AGGATCACTTTCTTTTCT	31	5-8-5	1260
621484	128271	128288	TTGCTGAGTCTCACTCTG	87	5-8-5	1261
621485	128451	128468	CAGAATCTATAGCTGTGT	51	5-8-5	1262
621486	128631	128648	ATACTTTCCACAGGGAGA	45	5-8-5	1263
621487	128811	128828	GAAGAAGGGTCCCTCTCT	38	5-8-5	1264
621488	128993	129010	ATGAGAGTACAACTCCAT	44	5-8-5	1265
621489	129269	129286	ACCCTTTCAGGCCGGGCG	44	5-8-5	1266
621490	129678	129695	TAAGTAAAGTCTGTTTTT	47	5-8-5	1267
621491	129861	129878	TAGAATGGTGTTTGGATA	42	5-8-5	1268
621492	130040	130057	GCAGTCTACAGGGCAAAG	79	5-8-5	1269
621493	130234	130251	ACCTTTTTATTTCCTCCG	14	5-8-5	1270
621494	130414	130431	AGCTCCAGGTGATTGAGA	68	5-8-5	1271
621495	130691	130708	GTCGCCATGTAAGAAATG	46	5-8-5	1272
621496	130902	130919	AGGGAGACTGATATGGTT	31	5-8-5	1273
621497	131113	131130	ATATTGCTTGACCTCAGG	18	5-8-5	1274
621498	131543	131560	AGTGGTTCTCGCTTTTTT	75	5-8-5	1275
621499	131725	131742	CAAGACAGGCAGGCAGAG	19	5-8-5	1276
621500	131905	131922	GTGCTTGGCTGCGCTTCT	45	5-8-5	1277
621501	132085	132102	CAGACCTCTATCTTTTAG	24	5-8-5	1278
621502	132266	132283	AGGAGGGTCTTTCCCGTG	57	5-8-5	1279

[0615]

[0616]

621503	132446	132463	AACTGGGCCACCATGAGA	30	5-8-5	1280

[0617] **표 27**

[0618] 서열 번호: 1을 표적화하는 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호:
621519	5901	5918	CCTGCCGCTCGGCCGTCC	19	5-8-5	1281
621520	5904	5921	CGCCCTGCCGCTCGGCCG	0	5-8-5	1282
621521	5919	5936	GTGGGCGCGCGCGAGCGC	7	5-8-5	1283
621522	5922	5939	CTAGTGGGCGCGCGCGAG	6	5-8-5	1284
621523	5925	5942	CCACTAGTGGGCGCGCGC	0	5-8-5	1285
621524	5928	5945	CGGCCACTAGTGGGCGCG	18	5-8-5	1286
621525	5931	5948	CTCCGGCCACTAGTGGGC	39	5-8-5	1287
621526	5934	5951	CTCCTCCGGCCACTAGTG	37	5-8-5	1288
621527	5937	5954	CTTCTCCTCCGGCCACTA	15	5-8-5	1289
621528	5940	5957	AGCCTTCTCCTCCGGCCA	0	5-8-5	1290
621529	5943	5960	GGGAGCCTTCTCCTCCGG	0	5-8-5	1291
621530	5946	5963	CGCGGGAGCCTTCTCCTC	28	5-8-5	1292
621531	5949	5966	CTCCGCGGGAGCCTTCTC	0	5-8-5	1293
621532	5952	5969	GGCCTCCGCGGGAGCCTT	0	5-8-5	1294
621533	5955	5972	CGCGGCCTCCGCGGGAGC	0	5-8-5	1295
621534	5958	5975	CAGCGCGGCCTCCGCGGG	0	5-8-5	1296
621535	5961	5978	GGGCAGCGCGGCCTCCGC	31	5-8-5	1297
621536	5964	5981	GGCGGGCAGCGCGGCCTC	17	5-8-5	1298
621537	5987	6004	ACGCGAGCCTCCCCAGGG	10	5-8-5	1299
621538	5990	6007	GGAACGCGAGCCTCCCCA	33	5-8-5	1300
621539	5993	6010	GCGGGAACGCGAGCCTCC	0	5-8-5	1301
621540	5996	6013	GCAGCGGGAACGCGAGCC	0	5-8-5	1302
621541	5999	6016	CGAGCAGCGGGAACGCGA	0	5-8-5	1303
621542	6002	6019	GCGCGAGCAGCGGGAACG	9	5-8-5	1304
621543	6005	6022	CAGGCGCGAGCAGCGGGA	22	5-8-5	1305
621544	6008	6025	GCGCAGGCGCGAGCAGCG	1	5-8-5	1306
621545	6011	6028	GCGGCGCAGGCGCGAGCA	11	5-8-5	1307
621546	6014	6031	CGGGCGGCGCAGGCGCGA	47	5-8-5	1308
621547	6017	6034	CGGCGGGCGGCGCAGGCG	15	5-8-5	1309
621548	6020	6037	GGCCGGCGGGCGGCGCAG	0	5-8-5	1310
621549	6023	6040	TGAGGCCGGCGGGCGGCG	5	5-8-5	1311
621550	6026	6043	TCCTGAGGCCGGCGGGCG	20	5-8-5	1312
621551	6029	6046	CGTTCCTGAGGCCGGCGG	13	5-8-5	1313
621552	6045	6062	GCCGGCGAAGAGGGCGCG	0	5-8-5	1314
621553	6048	6065	CGCGCCGGCGAAGAGGGC	0	5-8-5	1315
621554	6051	6068	GCGCGCGCCGGCGAAGAG	0	5-8-5	1316
621555	6054	6071	AGGGCGCGCGCCGGCGAA	32	5-8-5	1317

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621556	6057	6074	GCGAGGGCGCGCGCCGGC	15	5-8-5	1318
621557	6060	6077	ACTGCGAGGGCGCGCGCC	30	5-8-5	1319
621558	6063	6080	GTGACTGCGAGGGCGCGC	38	5-8-5	1320
621559	6066	6083	GCGGTGACTGCGAGGGCG	30	5-8-5	1321
621560	6069	6086	GTGGCGGTGACTGCGAGG	37	5-8-5	1322
621561	6072	6089	TGGGTGGCGGTGACTGCG	48	5-8-5	1323
621562	6075	6092	TGGTGGGTGGCGGTGACT	34	5-8-5	1324
621563	6078	6095	AGCTGGTGGGTGGCGGTG	54	5-8-5	1325
621564	6081	6098	CGGAGCTGGTGGGTGGCG	36	5-8-5	1326
621565	6084	6101	TGCCGGAGCTGGTGGGTG	52	5-8-5	1327
621566	6087	6104	TGGTGCCGGAGCTGGTGG	64	5-8-5	1328
621567	6090	6107	TGTTGGTGCCGGAGCTGG	74	5-8-5	1329
621568	6093	6110	TGCTGTTGGTGCCGGAGC	50	5-8-5	1330
621569	6096	6113	CGCTGCTGTTGGTGCCGG	47	5-8-5	1331
621570	6111	6128	GGGCGGTGGCAGCGGCGC	86	5-8-5	1332
621571	6114	6131	GGTGGGCGGTGGCAGCGG	61	5-8-5	1333
621572	6117	6134	GAAGGTGGGCGGTGGCAG	19	5-8-5	1334
621573	6120	6137	GCAGAAGGTGGGCGGTGG	22	5-8-5	1335
621574	6123	6140	GCGGCAGAAGGTGGGCGG	18	5-8-5	1336
621575	6126	6143	GCGGCGGCAGAAGGTGGG	62	5-8-5	1337
621576	6129	6146	GTGGCGGCGGCAGAAGGT	79	5-8-5	1338
621577	6132	6149	GTGGTGGCGGCGGCAGAA	70	5-8-5	1339
621578	6135	6152	GCTGTGGTGGCGGCGGCA	78	5-8-5	1340
621579	6138	6155	GTGGCTGTGGTGGCGGCG	78	5-8-5	1341
621580	6141	6158	AAGGTGGCTGTGGTGGCG	72	5-8-5	1342
613412	73879	73898	GTGATCTTCCATCACTTCGA	78	5-8-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	94	5-8-5	665
	98928	98945				
621504	132626	132643	AAACCCTTCTCACAAAAC	17	5-8-5	1343
621505	132812	132829	CCTCCTGGTCCCTCCTCG	12	5-8-5	1344
621506	132992	133009	CCTATCCAGACCCACTCA	10	5-8-5	1345
621507	133179	133196	CACAACCACCCCGGGACG	8	5-8-5	1346
621508	133359	133376	GGACCAGGATGGTGTTTT	44	5-8-5	1347
621509	133539	133556	GGCTTTGATAAAAATATT	8	5-8-5	1348
621510	133788	133805	CGCCTCCGGGATCAAGCA	47	5-8-5	1349
621511	133968	133985	GGTTCGCATTTAAGCTAG	28	5-8-5	1350
621512	134148	134165	ACGGTCATTCTCAGCCCT	59	5-8-5	1351
621513	134333	134350	TAACCTCCAGAGCAACTG	26	5-8-5	1352
621514	134513	134530	GGCAGGTGGGCCACAAAA	17	5-8-5	1353
621515	134696	134713	TCAAAAGGCATGCACATT	44	5-8-5	1354
621516	134876	134893	TAGTATTCCGTCGCCACG	40	5-8-5	1355
621517	135057	135074	GAGCTGTTGTTTTTATTG	7	5-8-5	1356
621518	135369	135386	GCCAGGGACTGTTTTTTG	62	5-8-5	1357

[0620]

[0621] 표 28

[0622] 서열 번호: 1 및 2를 표적화하는 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	모티프	서열 번호:
621596	n/a	n/a	TCACCTGATAGTCGACAG	70	292	309	5-8-5	1358
621597	n/a	n/a	AGTTCACCTGATAGTCGA	61	295	312	5-8-5	1359
621598	n/a	n/a	CAAAGTTCACCTGATAGT	44	298	315	5-8-5	1360
621599	n/a	n/a	GTTCAAAGTTCACCTGAT	72	301	318	5-8-5	1361
621629	n/a	n/a	GATTCTTTCAGGCCAGCG	42	442	459	5-8-5	1362
621630	n/a	n/a	GGAGATTCTTTCAGGCCA	0	445	462	5-8-5	1363
621649	n/a	n/a	ATCTTCCGCTGTTGGAGT	43	527	544	5-8-5	1364
621650	n/a	n/a	CACATCTTCCGCTGTTGG	3	530	547	5-8-5	1365
621651	n/a	n/a	TGTCACATCTTCCGCTGT	0	533	550	5-8-5	1366
621652	n/a	n/a	TGCTGTCACATCTTCCGC	30	536	553	5-8-5	1367
621653	n/a	n/a	AGGGTGCTGTCACATCTT	61	540	557	5-8-5	1368
621581	6144	6161	GAGAAGGTGGCTGTGGTG	14	244	261	5-8-5	1369
621582	6147	6164	GAGGAGAAGGTGGCTGTG	53	247	264	5-8-5	1370
621583	6153	6170	GCGGAGGAGGAGAAGGTG	25	253	270	5-8-5	1371
621584	6156	6173	ACAGCGGAGGAGGAGAAG	2	256	273	5-8-5	1372
621585	6159	6176	AGGACAGCGGAGGAGGAG	38	259	276	5-8-5	1373
621586	6162	6179	GAGAGGACAGCGGAGGAG	53	262	279	5-8-5	1374
621587	6165	6182	CGGGAGAGGACAGCGGAG	43	265	282	5-8-5	1375
621588	6168	6185	GGACGGGAGAGGACAGCG	69	268	285	5-8-5	1376
621589	6171	6188	CGAGGACGGGAGAGGACA	0	271	288	5-8-5	1377
621590	6174	6191	AGGCGAGGACGGGAGAGG	13	274	291	5-8-5	1378
621591	6177	6194	CAGAGGCGAGGACGGGAG	10	277	294	5-8-5	1379
621592	6180	6197	CGACAGAGGCGAGGACGG	57	280	297	5-8-5	1380
621593	6183	6200	AGTCGACAGAGGCGAGGA	61	283	300	5-8-5	1381
621594	6186	6203	GATAGTCGACAGAGGCGA	65	286	303	5-8-5	1382
621595	6189	6206	CCTGATAGTCGACAGAGG	51	289	306	5-8-5	1383
621600	73838	73855	CTGGTTCAAAGTTCACCT	52	304	321	5-8-5	1384
621601	73841	73858	ATCCTGGTTCAAAGTTCA	62	307	324	5-8-5	1385
621602	73844	73861	GCCATCCTGGTTCAAAGT	42	310	327	5-8-5	1386
621603	73847	73864	TCAGCCATCCTGGTTCAA	38	313	330	5-8-5	1387
621604	73850	73867	GGCTCAGCCATCCTGGTT	65	316	333	5-8-5	1388
621605	73867	73884	CTTCGAACTCCTGGCGGG	20	333	350	5-8-5	1389
621606	73870	73887	TCACTTCGAACTCCTGGC	51	336	353	5-8-5	1390
621607	73873	73890	CCATCACTTCGAACTCCT	68	339	356	5-8-5	1391
621608	73876	73893	CTTCCATCACTTCGAACT	28	342	359	5-8-5	1392
613412	73879	73898	GTGATCTTCCATCACTTCGA	75	345	364	5-8-5	25
621609	73879	73896	GATCTTCCATCACTTCGA	68	345	362	5-8-5	1393

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621610	73882	73899	CGTGATCTTCCATCACTT	13	348	365	5-8-5	1394
621611	73906	73923	TGTCCCCCAACCCGTACG	46	372	389	5-8-5	1395
621612	73909	73926	TCCTGTCCCCCAACCCGT	54	375	392	5-8-5	1396
621613	73912	73929	CTTTCCTGTCCCCCAACC	43	378	395	5-8-5	1397
621614	73915	73932	GATCTTTCCTGTCCCCCA	71	381	398	5-8-5	1398
621615	73918	73935	CCTGATCTTTCCTGTCCC	71	384	401	5-8-5	1399
621616	73921	73938	CCCCCTGATCTTTCCTGT	54	387	404	5-8-5	1400
621617	73924	73941	AGCCCCCCTGATCTTTCC	40	390	407	5-8-5	1401
621618	73927	73944	TGTAGCCCCCCTGATCTT	35	393	410	5-8-5	1402
621619	73930	73947	TGGTGTAGCCCCCCTGAT	31	396	413	5-8-5	1403
621620	73933	73950	GCATGGTGTAGCCCCCCT	71	399	416	5-8-5	1404
621621	73936	73953	GGTGCATGGTGTAGCCCC	62	402	419	5-8-5	1405
621622	73939	73956	CTTGGTGCATGGTGTAGC	54	405	422	5-8-5	1406
621623	73942	73959	GGTCTTGGTGCATGGTGT	65	408	425	5-8-5	1407
621624	73945	73962	CTTGGTCTTGGTGCATGG	63	411	428	5-8-5	1408
621625	73948	73965	CCTCTTGGTCTTGGTGCA	49	414	431	5-8-5	1409
621626	73951	73968	CACCCTCTTGGTCTTGGT	65	417	434	5-8-5	1410
621627	73956	73973	CGTGTCACCCTCTTGGTC	49	422	439	5-8-5	1411
621628	73959	73976	GTCCGTGTCACCCTCTTG	70	425	442	5-8-5	1412
621631	83395	83412	AGATCCGTCCTCAGTGGG	48	473	490	5-8-5	1413
621632	83398	83415	CTCAGATCCGTCCTCAGT	38	476	493	5-8-5	1414
621633	83401	83418	TTCCTCAGATCCGTCCTC	11	479	496	5-8-5	1415
621634	83404	83421	CGGTTCCTCAGATCCGTC	57	482	499	5-8-5	1416
621635	83407	83424	GCCCGGTTCCTCAGATCC	38	485	502	5-8-5	1417
621636	83410	83427	AGAGCCCGGTTCCTCAGA	63	488	505	5-8-5	1418
621637	83413	83430	TTCAGAGCCCGGTTCCTC	50	491	508	5-8-5	1419
621638	83416	83433	GGTTTCAGAGCCCGGTTC	48	494	511	5-8-5	1420
621639	83419	83436	AGAGGTTTCAGAGCCCGG	41	497	514	5-8-5	1421
621640	83422	83439	ATCAGAGGTTTCAGAGCC	40	500	517	5-8-5	1422
621641	83425	83442	AGCATCAGAGGTTTCAGA	23	503	520	5-8-5	1423
621642	83428	83445	CTTAGCATCAGAGGTTTC	50	506	523	5-8-5	1424
621643	83431	83448	GCTCTTAGCATCAGAGGT	69	509	526	5-8-5	1425
621644	83434	83451	AGTGCTCTTAGCATCAGA	80	512	529	5-8-5	1426
621645	83437	83454	TGGAGTGCTCTTAGCATC	50	515	532	5-8-5	1427
621646	83440	83457	TGTTGGAGTGCTCTTAGC	59	518	535	5-8-5	1428
621647	83443	83460	CGCTGTTGGAGTGCTCTT	70	521	538	5-8-5	1429
621648	83446	83463	TTCCGCTGTTGGAGTGCT	52	524	541	5-8-5	1430
621654	85904	85921	CTAAGGGTGCTGTCACAT	64	543	560	5-8-5	1431
621655	85907	85924	CCACTAAGGGTGCTGTCA	44	546	563	5-8-5	1432
621656	85910	85927	CATCCACTAAGGGTGCTG	55	549	566	5-8-5	1433
621657	85913	85930	CCTCATCCACTAAGGGTG	41	552	569	5-8-5	1434
620887	98891	98908	GTTTTCAAACACACCTTC	81	n/a	n/a	5-8-5	665
	98928	98945			n/a	n/a		

[0624]

[0625] 표 29

[0626] 서열 번호: 1 및 2를 표적화하는 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	모티프	서열 번호
621672	n/a	n/a	GCTGTGGTTCCTTCTGGG	51	613	630	5-8-5	1435
621676	n/a	n/a	TCAGGCTCTTGGGTCACG	0	685	702	5-8-5	1436
621677	n/a	n/a	CTTTCAGGCTCTTGGGTC	0	688	705	5-8-5	1437
621678	n/a	n/a	CCACTTTCAGGCTCTTGG	51	691	708	5-8-5	1438
613412	73879	73898	GTGATCTTCCATCACTTCGA	79	345	364	5-10-5	25
621658	85916	85933	CTCCCTCATCCACTAAGG	27	555	572	5-8-5	1439
621659	85919	85936	GAGCTCCCTCATCCACTA	35	558	575	5-8-5	1440
621660	85922	85939	CGGGAGCTCCCTCATCCA	25	561	578	5-8-5	1441
621661	85925	85942	TGCCGGGAGCTCCCTCAT	40	564	581	5-8-5	1442
621662	85928	85945	GCTTGCCGGGAGCTCCCT	47	567	584	5-8-5	1443
621663	85931	85948	CCTGCTTGCCGGGAGCTC	46	570	587	5-8-5	1444
621664	85934	85951	CAGCCTGCTTGCCGGGAG	45	573	590	5-8-5	1445
621665	85937	85954	CGGCAGCCTGCTTGCCGG	1	576	593	5-8-5	1446
621666	85940	85957	GCGCGGCAGCCTGCTTGC	31	579	596	5-8-5	1447
621667	85943	85960	GCTGCGCGGCAGCCTGCT	50	582	599	5-8-5	1448
621668	85962	85979	TCTGGGATCTCCGTGTGG	39	601	618	5-8-5	1449
621669	85965	85982	CCTTCTGGGATCTCCGTG	56	604	621	5-8-5	1450
621670	85968	85985	GTTCCTTCTGGGATCTCC	79	607	624	5-8-5	1451
621671	85971	85988	GTGGTTCCTTCTGGGATC	49	610	627	5-8-5	1452
621673	89894	89911	CAATGCCTGCTTCTTCAG	31	630	647	5-8-5	1453
621674	89899	89916	GTCTCCAATGCCTGCTTC	43	635	652	5-8-5	1454
621675	89902	89919	GGTGTCTCCAATGCCTGC	74	638	655	5-8-5	1455
621679	94695	94712	TTACCACTTTCAGGCTCT	63	694	711	5-8-5	1456
621680	94700	94717	CCACCTTACCACTTTCAG	28	699	716	5-8-5	1457
621681	94703	94720	GGACCACCTTACCACTTT	62	702	719	5-8-5	1458
621682	94706	94723	CCTGGACCACCTTACCAC	33	705	722	5-8-5	1459
621683	94709	94726	CTTCCTGGACCACCTTAC	18	708	725	5-8-5	1460
621684	94712	94729	AGCCTTCCTGGACCACCT	61	711	728	5-8-5	1461
621685	94715	94732	GGAAGCCTTCCTGGACCA	54	714	731	5-8-5	1462
621686	94718	94735	GGAGGAAGCCTTCCTGGA	24	717	734	5-8-5	1463
621687	94721	94738	CTCGGAGGAAGCCTTCCT	48	720	737	5-8-5	1464
621688	94724	94741	GCTCTCGGAGGAAGCCTT	27	723	740	5-8-5	1465
621689	94727	94744	CTGGCTCTCGGAGGAAGC	19	726	743	5-8-5	1466
621690	94730	94747	GGCCTGGCTCTCGGAGGA	46	729	746	5-8-5	1467
621691	94749	94766	TGGTGGCTCAGACCTGGG	49	748	765	5-8-5	1468
621692	94752	94769	AGCTGGTGGCTCAGACCT	50	751	768	5-8-5	1469
621693	94755	94772	ATGAGCTGGTGGCTCAGA	17	754	771	5-8-5	1470
621694	94758	94775	GACATGAGCTGGTGGCTC	54	757	774	5-8-5	1471
621695	94761	94778	CCGGACATGAGCTGGTGG	26	760	777	5-8-5	1472

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621696	94764	94781	ATGCCGGACATGAGCTGG	12	763	780	5-8-5	1473
621697	94767	94784	GGCATGCCGGACATGAGC	11	766	783	5-8-5	1474
621698	94770	94787	CCAGGCATGCCGGACATG	41	769	786	5-8-5	1475
621699	94773	94790	GCCCCAGGCATGCCGGAC	57	772	789	5-8-5	1476
621700	94776	94793	GGAGCCCCAGGCATGCCG	47	775	792	5-8-5	1477
621701	94793	94810	GGCCCTCAGGCAGGAGGG	0	792	809	5-8-5	1478
621702	94825	94842	TGTCCCCGAAGGTTGGCG	50	824	841	5-8-5	1479
621703	94828	94845	TCCTGTCCCCGAAGGTTG	38	827	844	5-8-5	1480
621704	94831	94848	AGGTCCTGTCCCCGAAGG	41	830	847	5-8-5	1481
621705	94834	94851	CTCAGGTCCTGTCCCCGA	60	833	850	5-8-5	1482
621706	94837	94854	GTCCTCAGGTCCTGTCCC	0	836	853	5-8-5	1483
621707	94840	94857	TGTGTCCTCAGGTCCTGT	23	839	856	5-8-5	1484
621708	94843	94860	CTCTGTGTCCTCAGGTCC	55	842	859	5-8-5	1485
621709	94846	94863	GCCCTCTGTGTCCTCAGG	35	845	862	5-8-5	1486
621710	94849	94866	GCCGCCCTCTGTGTCCTC	45	848	865	5-8-5	1487
621711	94852	94869	GCGGCCGCCCTCTGTGTC	0	851	868	5-8-5	1488
621712	94855	94872	GTGGCGGCCGCCCTCTGT	0	854	871	5-8-5	1489
621713	94875	94892	TGCTTGAGCAGCTCAGGG	67	874	891	5-8-5	1490
621714	94878	94895	TGGTGCTTGAGCAGCTCA	51	877	894	5-8-5	1491
621715	94882	94899	AAGCTGGTGCTTGAGCAG	27	881	898	5-8-5	1492
621716	94885	94902	TAGAAGCTGGTGCTTGAG	14	884	901	5-8-5	1493
621717	94888	94905	TCCTAGAAGCTGGTGCTT	0	887	904	5-8-5	1494
621718	94891	94908	GTCTCCTAGAAGCTGGTG	45	890	907	5-8-5	1495
621719	94894	94911	CAGGTCTCCTAGAAGCTG	47	893	910	5-8-5	1496
621720	94897	94914	GTGCAGGTCTCCTAGAAG	41	896	913	5-8-5	1497
621721	94900	94917	CTGGTGCAGGTCTCCTAG	36	899	916	5-8-5	1498
621722	94903	94920	CTCCTGGTGCAGGTCTCC	41	902	919	5-8-5	1499
621723	94906	94923	CCCCTCCTGGTGCAGGTC	39	905	922	5-8-5	1500
621724	94909	94926	CGGCCCCTCCTGGTGCAG	19	908	925	5-8-5	1501
621725	94912	94929	CGGCGGCCCCTCCTGGTG	22	911	928	5-8-5	1502
621726	94915	94932	CAGCGGCGGCCCCTCCTG	35	914	931	5-8-5	1503
621727	94918	94935	CTTCAGCGGCGGCCCCTC	46	917	934	5-8-5	1504
621728	94921	94938	CCCCTTCAGCGGCGGCCC	36	920	937	5-8-5	1505
621729	94924	94941	TGCCCCCTTCAGCGGCGG	17	923	940	5-8-5	1506
621730	94927	94944	CCCTGCCCCCTTCAGCGG	15	926	943	5-8-5	1507
621731	94930	94947	GCCCCCTGCCCCCTTCAG	27	929	946	5-8-5	1508
621732	94933	94950	TTTGCCCCCTGCCCCCTT	49	932	949	5-8-5	1509
621733	94936	94953	CTCTTTGCCCCCTGCCCC	22	935	952	5-8-5	1510
621734	94939	94956	CCTCTCTTTGCCCCCTGC	28	938	955	5-8-5	1511
620887	98891	98908	GTTTTCAAACACACCTTC	90	n/a	n/a	5-8-5	665
	98928	98945			n/a	n/a		

[0628]

[0629] 표 30

[0630] 서열 번호: 1을 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호:
613412	73879	73898	GTGATCTTCCATCACTTCGA	82	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	92	5-8-5	665
	98928	98945				
621735	94942	94959	CGGCCTCTCTTTGCCCCC	34	5-8-5	1512
621736	94945	94962	CCCCGGCCTCTCTTTGCC	27	5-8-5	1513
621737	94948	94965	GCTCCCCGGCCTCTCTTT	44	5-8-5	1514
621738	94951	94968	CTTGCTCCCCGGCCTCTC	38	5-8-5	1515
621739	94954	94971	CTCCTTGCTCCCCGGCCT	37	5-8-5	1516
621740	94957	94974	CTCCTCCTTGCTCCCCGG	33	5-8-5	1517
621741	94960	94977	CACCTCCTCCTTGCTCCC	37	5-8-5	1518
621742	94963	94980	ATCCACCTCCTCCTTGCT	32	5-8-5	1519
621743	94967	94984	CTTCATCCACCTCCTCCT	51	5-8-5	1520
621744	94970	94987	GGTCTTCATCCACCTCCT	61	5-8-5	1521
621745	94973	94990	CGCGGTCTTCATCCACCT	71	5-8-5	1522
621746	94976	94993	CGTCGCGGTCTTCATCCA	48	5-8-5	1523
621747	95038	95055	CCGCCCATCTTGGGCTGG	12	5-8-5	1524
621748	95041	95058	AGGCCGCCCATCTTGGGC	18	5-8-5	1525
621749	95044	95061	GGGAGGCCGCCCATCTTG	21	5-8-5	1526
621750	95060	95077	CTCTGGCGGCTGTCTGGG	47	5-8-5	1527
621751	95063	95080	CTTCTCTGGCGGCTGTCT	41	5-8-5	1528
621752	95066	95083	TGGCTTCTCTGGCGGCTG	53	5-8-5	1529
621753	95069	95086	TGGTGGCTTCTCTGGCGG	26	5-8-5	1530
621754	95072	95089	TGCTGGTGGCTTCTCTGG	57	5-8-5	1531
621755	95075	95092	GGATGCTGGTGGCTTCTC	65	5-8-5	1532
621756	95078	95095	CTGGGATGCTGGTGGCTT	66	5-8-5	1533
621757	95081	95098	AGCCTGGGATGCTGGTGG	51	5-8-5	1534
621758	95084	95101	GGAAGCCTGGGATGCTGG	57	5-8-5	1535
621759	95092	95109	CTCCGCTGGGAAGCCTGG	48	5-8-5	1536
621760	95095	95112	ACCCTCCGCTGGGAAGCC	38	5-8-5	1537
621761	95098	95115	GGCACCCTCCGCTGGGAA	54	5-8-5	1538
621762	95101	95118	GATGGCACCCTCCGCTGG	27	5-8-5	1539
621763	95121	95138	AGGAAATCCACAGGGAGG	15	5-8-5	1540
621764	95124	95141	GAGAGGAAATCCACAGGG	29	5-8-5	1541
621765	95127	95144	TTGGAGAGGAAATCCACA	45	5-8-5	1542
621766	95130	95147	ACTTTGGAGAGGAAATCC	38	5-8-5	1543
621767	95134	95151	GGAAACTTTGGAGAGGAA	56	5-8-5	1544
621768	95137	95154	TGTGGAAACTTTGGAGAG	26	5-8-5	1545
621769	95140	95157	CTCTGTGGAAACTTTGGA	69	5-8-5	1546
621770	95143	95160	GATCTCTGTGGAAACTTT	62	5-8-5	1547

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621771	95146	95163	TGGGATCTCTGTGGAAAC	61	5-8-5	1548
621772	95149	95166	GGCTGGGATCTCTGTGGA	47	5-8-5	1549
621773	95152	95169	TGAGGCTGGGATCTCTGT	32	5-8-5	1550
621774	95155	95172	CTCTGAGGCTGGGATCTC	64	5-8-5	1551
621775	95161	95178	GTCGGGCTCTGAGGCTGG	42	5-8-5	1552
621776	95164	95181	CCCGTCGGGCTCTGAGGC	34	5-8-5	1553
621777	95174	95191	CTACACTGGGCCCGTCGG	31	5-8-5	1554
621778	95177	95194	GCCCTACACTGGGCCCGT	48	5-8-5	1555
621779	95180	95197	CCCGCCCTACACTGGGCC	35	5-8-5	1556
621780	95183	95200	TGGCCCGCCCTACACTGG	51	5-8-5	1557
621781	95186	95203	CTTTGGCCCGCCCTACAC	4	5-8-5	1558
621782	95189	95206	GCCCTTTGGCCCGCCCTA	52	5-8-5	1559
621783	95192	95209	CCTGCCCTTTGGCCCGCC	42	5-8-5	1560
621784	95195	95212	CATCCTGCCCTTTGGCCC	49	5-8-5	1561
621785	95198	95215	GGGCATCCTGCCCTTTGG	15	5-8-5	1562
621786	95235	95252	TTGGGTGTGATTTCCACG	52	5-8-5	1563
621787	95253	95270	GCCTGCTCCTTCTGCACG	44	5-8-5	1564
621788	95256	95273	TGCGCCTGCTCCTTCTGC	64	5-8-5	1565
621789	95259	95276	GAGTGCGCCTGCTCCTTC	70	5-8-5	1566
621790	95262	95279	TCCGAGTGCGCCTGCTCC	53	5-8-5	1567
621791	95265	95282	TCCTCCGAGTGCGCCTGC	54	5-8-5	1568
621792	95268	95285	TGCTCCTCCGAGTGCGCC	52	5-8-5	1569
621793	95271	95288	AAATGCTCCTCCGAGTGC	72	5-8-5	1570
621794	95274	95291	CCCAAATGCTCCTCCGAG	75	5-8-5	1571
621795	95277	95294	CTTCCCAAATGCTCCTCC	47	5-8-5	1572
621796	95280	95297	GCCCTTCCCAAATGCTCC	58	5-8-5	1573
621797	95283	95300	GCAGCCCTTCCCAAATGC	39	5-8-5	1574
621798	95286	95303	AATGCAGCCCTTCCCAAA	61	5-8-5	1575
621799	95291	95308	CTGGAAATGCAGCCCTTC	64	5-8-5	1576
621800	95294	95311	CCCCTGGAAATGCAGCCC	49	5-8-5	1577
621801	95297	95314	GGGCCCCTGGAAATGCAG	29	5-8-5	1578
621802	95313	95330	TCTGGCCCCTCTCCAGGG	41	5-8-5	1579
621803	95316	95333	GCCTCTGGCCCCTCTCCA	42	5-8-5	1580
621804	95319	95336	CGGGCCTCTGGCCCCTCT	11	5-8-5	1581
621805	95322	95339	CCCCGGGCCTCTGGCCCC	13	5-8-5	1582
621806	95341	95358	GTCCTCTCCCAAAGAGGG	25	5-8-5	1583
621807	95344	95361	TGTGTCCTCTCCCAAAGA	20	5-8-5	1584
621808	95347	95364	TTTTGTGTCCTCTCCCAA	66	5-8-5	1585
621809	95365	95382	CTCTGGAAGGTCAGCCTC	53	5-8-5	1586
621810	95368	95385	GGGCTCTGGAAGGTCAGC	72	5-8-5	1587
621811	95371	95388	AGAGGGCTCTGGAAGGTC	57	5-8-5	1588

[0632]

[0633] 표 31

[0634] 서열 번호: 1을 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호:
613412	73879	73898	GTGATCTTCCATCACTTCGA	88	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	96	5-8-5	665
	98928	98945				
623737	111219	111236	CCTCCACCCAGCATGGTG	56	5-8-5	1589
623738	111267	111284	TCAAGTCACCCTTTCTCC	78	5-8-5	1590
623739	111368	111385	TTCAGACAATTTTTCTAG	66	5-8-5	1591
623740	111629	111646	TCAGACTCCGCCAGCTTT	79	5-8-5	1592
623741	111678	111695	TCTTTTCCCTTTGGTGTT	34	5-8-5	1593
623742	111753	111770	TTTCCCCCAATGATTTGC	77	5-8-5	1594
623743	112016	112033	CCACGACTCCCACAAGAT	32	5-8-5	1595
623744	112213	112230	TGAGGTTGAGGGTAGGTG	50	5-8-5	1596
623745	112219	112236	AGTGGTTGAGGTTGAGGG	31	5-8-5	1597
623746	112304	112321	CAGGCACTTGGAAACTGC	90	5-8-5	1598
623747	112877	112894	TTGTACTCTTTTTCCCCT	65	5-8-5	1599
623748	112949	112966	TTAGGAGTGCAAGGTTGT	49	5-8-5	1600
623749	113352	113369	TCCTACATTCCTCCTGCT	67	5-8-5	1601
623750	113523	113540	GTTGCAGTGTTCCACTAT	90	5-8-5	1602
623751	113783	113800	CCAGCAGATGCCGACAGC	74	5-8-5	1603
623752	113809	113826	GGGCCCTCACCCCTGCTT	14	5-8-5	1604
623753	113830	113847	CCAAGAAGGGCTGCTGAG	8	5-8-5	1605
623754	114267	114284	AAGCAGCCACCCAGGCTG	17	5-8-5	1606
623755	114739	114756	TATGAGGAGGGAGGAAAG	13	5-8-5	1607
623756	115242	115259	CTGACATCTCAGCCCAAG	93	5-8-5	1608
621425	115335	115352	GGTACAGGAAAAGATGCC	77	5-8-5	1202
623757	115522	115539	CAAGGTGATCAGCTTAGG	82	5-8-5	1609
623758	115526	115543	AGTCCAAGGTGATCAGCT	89	5-8-5	1610
623759	115547	115564	CCCACACAAGCCTCCTCT	66	5-8-5	1611
623760	115791	115808	TTTGTTTGGGTTCAGTTC	59	5-8-5	1612
623761	115803	115820	CCTTGATCTGGTTTTGTT	77	5-8-5	1613
623762	115993	116010	ATCAAGGGAGAGAACGAT	52	5-8-5	1614
623763	116229	116246	AAAAGGCAACAAGCCTTT	0	5-8-5	1615
623764	116769	116786	CGAGGCAAAAAGGGAAAT	45	5-8-5	1616
623765	116791	116808	TAACTTTGAGCTTCCTGG	65	5-8-5	1617
623766	116944	116961	TAAGGCTTAGAAGATTTG	45	5-8-5	1618
623767	116978	116995	GACGATCATTTTTTATTC	72	5-8-5	1619
623768	116983	117000	GGCTTGACGATCATTTTT	77	5-8-5	1620
623769	117421	117438	AGATCTCAGAGTTTGTAG	68	5-8-5	1621
623770	117472	117489	TCGCTGAGGTTCCGCAAC	37	5-8-5	1622
623771	117489	117506	AGGAGGCCATGTGAGGCT	61	5-8-5	1623

[0635]

623772	117547	117564	TGGATAAATCTCTAGTGC	54	5-8-5	1624
623773	117564	117581	CACTCCTCCTTTAGAGAT	38	5-8-5	1625
623774	117599	117616	TTGTAATTCCTTCTCTGG	65	5-8-5	1626
623775	117971	117988	TAACCATCCCTACTTTCT	42	5-8-5	1627
623776	119098	119115	ACTGAAATCGCTCCTTTA	58	5-8-5	1628
623777	119107	119124	CCAATTATGACTGAAATC	32	5-8-5	1629
623778	119313	119330	GGTCAAAGTTATAAATAT	57	5-8-5	1630
623779	119431	119448	GGATTTGATGCAAAGAAA	70	5-8-5	1631
623780	119740	119757	GCGCAACCCAGCTACTCG	7	5-8-5	1632
621445	119880	119897	TACAGTGGCTCCTGTAAT	28	5-8-5	1222
623781	119964	119981	CTGTATACCTATACTTGG	34	5-8-5	1633
623782	120043	120060	CCGTTTTCTTACCACCCT	92	5-8-5	1634
623783	120177	120194	TTACTTGTCTGAATCTTC	83	5-8-5	1635
623784	120204	120221	TTCATCCCGTTTTTTTTC	54	5-8-5	1636
623785	120309	120326	GACCTCAGTGGCTCTTTT	68	5-8-5	1637
623786	120513	120530	TGTCCAGGATAGTTTGAA	44	5-8-5	1638
623787	121033	121050	GCTGAGCAAATGCTCCCG	54	5-8-5	1639
623788	121194	121211	CTGACCCCGTAGGCAGGA	29	5-8-5	1640
623789	121478	121495	ACCAGCCTGAGGTCAAGT	73	5-8-5	1641
623790	121538	121555	CAGGTCCTCACTTCACAA	42	5-8-5	1642
623791	121767	121784	CCGCCTGCTTGCTCGCAA	92	5-8-5	1643
623792	121787	121804	AGTGACACGCCACCCTGG	80	5-8-5	1644
623793	121797	121814	AAAAAGGATGAGTGACAC	28	5-8-5	1645
623794	121807	121824	GGTAGCCAGAAAAAAGGA	49	5-8-5	1646
623795	121812	121829	CCTTTGGTAGCCAGAAAA	63	5-8-5	1647
623796	121817	121834	CTGCACCTTTGGTAGCCA	87	5-8-5	1648
623797	121822	121839	ATTATCTGCACCTTTGGT	67	5-8-5	1649
623798	121824	121841	TAATTATCTGCACCTTTG	49	5-8-5	1650
623799	121905	121922	CACTGCCGCCTCCCGGGA	65	5-8-5	1651
623800	121909	121926	CTCACACTGCCGCCTCCC	75	5-8-5	1652
623801	121911	121928	TACTCACACTGCCGCCTC	54	5-8-5	1653
623679	121913	121930	GGTACTCACACTGCCGCC	81	5-8-5	1654
623802	121915	121932	AAGGTACTCACACTGCCG	69	5-8-5	1655
623803	121920	121937	GTGTGAAGGTACTCACAC	18	5-8-5	1656
623804	121942	121959	GCCACAGCACGGCGCATG	80	5-8-5	1657
623805	121952	121969	AATAATTCAAGCCACAGC	88	5-8-5	1658
623806	121962	121979	ACCACTTCCTAATAATTC	39	5-8-5	1659
623807	121972	121989	ACGCACTCACACCACTTC	83	5-8-5	1660
623808	121982	121999	TCGCAAGTGTACGCACTC	94	5-8-5	1661
623809	121992	122009	ATGCAGTGTCTCGCAAGT	93	5-8-5	1662
623810	122227	122244	TGATGGGTATTCTCAGCT	77	5-8-5	1663

[0636]

[0637] 표 32

[0638] 서열 번호: 1을 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호:
613412	73879	73898	GTGATCTTCCATCACTTCG A	87	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	83	5-8-5	665
	98928	98945				
622186	5897	5914	CCGCTCGGCCGTCCGGCG	6	5-8-5	1664
622187	5900	5917	CTGCCGCTCGGCCGTCCG	6	5-8-5	1665
622174	103089	103106	CCAGAGCTGGGTGGTGTC	12	5-8-5	1666
622182	125760	125777	TGTAGACTATTTGCACCT	74	5-8-5	1667
622120	135855	135872	ATCACTGATTTTGAAGTC	36	5-8-5	1668
622121	135858	135875	CCCATCACTGATTTTGAA	59	5-8-5	1669
622122	135861	135878	ACTCCCATCACTGATTTT	70	5-8-5	1670
622123	135864	135881	CTTACTCCCATCACTGAT	41	5-8-5	1671
622124	135867	135884	GCTCTTACTCCCATCACT	82	5-8-5	1672
622125	135870	135887	TTTGCTCTTACTCCCATC	87	5-8-5	1673
622126	135873	135890	AAATTTGCTCTTACTCCC	62	5-8-5	1674
622127	135876	135893	ATGAAATTTGCTCTTACT	70	5-8-5	1675
622128	135879	135896	AAGATGAAATTTGCTCTT	55	5-8-5	1676
622129	135882	135899	GGAAAGATGAAATTTGCT	84	5-8-5	1677
622130	135885	135902	TTTGGAAAGATGAAATTT	12	5-8-5	1678
622131	135891	135908	CATCAATTTGGAAAGATG	43	5-8-5	1679
622132	135894	135911	ACCCATCAATTTGGAAAG	18	5-8-5	1680
622133	135897	135914	CCCACCCATCAATTTGGA	34	5-8-5	1681
622134	135900	135917	TAGCCCACCCATCAATTT	17	5-8-5	1682
622135	135903	135920	TACTAGCCCACCCATCAA	14	5-8-5	1683
622136	135906	135923	TATTACTAGCCCACCCAT	24	5-8-5	1684
622137	135909	135926	TTTTATTACTAGCCCACC	24	5-8-5	1685
622138	135912	135929	ATATTTTATTACTAGCCC	33	5-8-5	1686
622139	135915	135932	TAAATATTTTATTACTAG	0	5-8-5	1687
622140	135918	135935	TTTTAAATATTTTATTAC	0	5-8-5	1688
622141	135926	135943	ATGTTTTTTTTTAAATAT	0	5-8-5	1689
622142	135939	135956	GCCATGTTTTTGAATGTT	60	5-8-5	1690
622143	135942	135959	GTGGCCATGTTTTTGAAT	28	5-8-5	1691
622144	135945	135962	GATGTGGCCATGTTTTTG	63	5-8-5	1692
622145	135948	135965	TTGGATGTGGCCATGTTT	78	5-8-5	1693
622146	135951	135968	ATGTTGGATGTGGCCATG	71	5-8-5	1694
622147	135954	135971	GAAATGTTGGATGTGGCC	72	5-8-5	1695
622148	135957	135974	GAGGAAATGTTGGATGTG	55	5-8-5	1696
622149	135960	135977	CCTGAGGAAATGTTGGAT	77	5-8-5	1697
622150	135963	135980	TTGCCTGAGGAAATGTTG	55	5-8-5	1698

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622151	139811	139828	CCAAATTCACTTTTACAG	54	5-8-5	1699
622152	139813	139830	TTCCAAATTCACTTTTAC	67	5-8-5	1700
622153	139815	139832	ATTTCCAAATTCACTTTT	52	5-8-5	1701
622154	139817	139834	TTATTTCCAAATTCACTT	52	5-8-5	1702
622155	139819	139836	CTTTATTTCCAAATTCAC	61	5-8-5	1703
622156	139821	139838	AACTTTATTTCCAAATTC	26	5-8-5	1704
622157	139823	139840	ATAACTTTATTTCCAAAT	23	5-8-5	1705
622158	139826	139843	GTAATAACTTTATTTCCA	65	5-8-5	1706
622159	139828	139845	GAGTAATAACTTTATTTC	25	5-8-5	1707
622160	139830	139847	CAGAGTAATAACTTTATT	9	5-8-5	1708
622161	139832	139849	ATCAGAGTAATAACTTTA	23	5-8-5	1709
622162	139834	139851	TAATCAGAGTAATAACTT	14	5-8-5	1710
622163	139836	139853	TTTAATCAGAGTAATAAC	4	5-8-5	1711

[0640]

[0641] **표 33**

[0642] 서열 번호: 5 및 6을 표적화하는 5-10-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 5 개시 부위	서열 번호: 5 정지 부위	서열	억제율%	서열 번호: 6 개시 부위	서열 번호: 6 정지 부위	모티프	서열 번호
622164	n/a	n/a	GCTTCCGCTGTTGGAGTG	22	526	543	5-8-5	1712
622165	n/a	n/a	TCAGCTTCCGCTGTTGGA	15	529	546	5-8-5	1713
622166	n/a	n/a	TCTTCAGCTTCCGCTGTT	0	532	549	5-8-5	1714
622167	n/a	n/a	GCTTCTTCAGCTTCCGCT	43	535	552	5-8-5	1715
622171	n/a	n/a	GCCCCCTTGGCTTTTTTG	16	652	669	5-8-5	1716
622172	n/a	n/a	TCAGCCCCCTTGGCTTTT	15	655	672	5-8-5	1717
622173	n/a	n/a	ACCATCAGCCCCCTTGGC	49	659	676	5-8-5	1718
622175	n/a	n/a	TCACCAGAGCTGGGTGGT	15	778	795	5-8-5	1719
622176	n/a	n/a	GGTTCACCAGAGCTGGGT	80	781	798	5-8-5	1720
622177	n/a	n/a	GGAGGTTCACCAGAGCTG	79	784	801	5-8-5	1721
622178	n/a	n/a	TTTGGAGGTTCACCAGAG	45	787	804	5-8-5	1722
622179	n/a	n/a	GATTTTGGAGGTTCACCA	68	790	807	5-8-5	1723
622180	n/a	n/a	TTGCACCTTCCCGCCTCC	19	1046	1063	5-8-5	1724
622181	n/a	n/a	AGACTATTTGCACCTTCC	70	1053	1070	5-8-5	1725
622183	3	20	CCCTTCGCGGTCCCTTCG	0	n/a	n/a	5-8-5	1726
622184	6	23	CTGCCCTTCGCGGTCCCT	12	n/a	n/a	5-8-5	1727
622185	9	26	GCGCTGCCCTTCGCGGTC	0	n/a	n/a	5-8-5	1728
622188	424	441	GTCCCCCAAACCCGTACG	15	n/a	n/a	5-8-5	1729
622189	427	444	CCTGTCCCCCAAACCCGT	45	n/a	n/a	5-8-5	1730
622190	430	447	TTTCCTGTCCCCCAAACC	57	n/a	n/a	5-8-5	1731
622191	436	453	TTGATCTTTCCTGTCCCC	74	n/a	n/a	5-8-5	1732
622192	439	456	CCCTTGATCTTTCCTGTC	69	n/a	n/a	5-8-5	1733

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622193	442	459	GCCCCCTTGATCTTTCCT	7	n/a	n/a	5-8-5	1734
622194	445	462	GTAGCCCCCTTGATCTTT	3	n/a	n/a	5-8-5	1735
622195	448	465	GGTGTAGCCCCCTTGATC	8	n/a	n/a	5-8-5	1736
622196	451	468	CATGGTGTAGCCCCCTTG	83	n/a	n/a	5-8-5	1737
622168	564	581	ATGCGAGCTTGGGTCACG	65	598	615	5-8-5	1738
622169	567	584	ACCATGCGAGCTTGGGTC	62	601	618	5-8-5	1739
622170	570	587	CTGACCATGCGAGCTTGG	91	604	621	5-8-5	1740

[0644]

[0645] **표 34**

[0646] 서열 번호: 1 및 2를 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	모티프	서열 번호:
613412	73879	73898	GTGATCTTCCATCACTTCGA	91	345	364	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	97	n/a	n/a	5-8-5	665
	98928	98945			n/a	n/a		
621832	n/a	n/a	GAGCTTTGAGTTGAGGGA	14	1434	1451	5-8-5	1741
621833	n/a	n/a	TGCGAGCTTTGAGTTGAG	0	1437	1454	5-8-5	1742
621834	n/a	n/a	CCATGCGAGCTTTGAGTT	10	1440	1457	5-8-5	1743
621835	n/a	n/a	TGACCATGCGAGCTTTGA	83	1443	1460	5-8-5	1744
621836	n/a	n/a	TACTGACCATGCGAGCTT	91	1446	1463	5-8-5	1745
621848	n/a	n/a	GATGTCTTGGCTTTTTTG	3	1492	1509	5-8-5	1746
621849	n/a	n/a	GTGTGGATGTCTTGGCTT	15	1497	1514	5-8-5	1747
621812	95374	95391	TTCAGAGGGCTCTGGAAG	0	1373	1390	5-8-5	1748
621813	95377	95394	CTTTTCAGAGGGCTCTGG	44	1376	1393	5-8-5	1749
621814	95380	95397	CTGCTTTTCAGAGGGCTC	56	1379	1396	5-8-5	1750
621815	95383	95400	AGGCTGCTTTTCAGAGGG	38	1382	1399	5-8-5	1751
621816	95386	95403	AGCAGGCTGCTTTTCAGA	40	1385	1402	5-8-5	1752
621817	95389	95406	AGCAGCAGGCTGCTTTTC	26	1388	1405	5-8-5	1753
621818	95392	95409	AGCAGCAGCAGGCTGCTT	12	1391	1408	5-8-5	1754
621819	95395	95412	CGGAGCAGCAGCAGGCTG	23	1394	1411	5-8-5	1755
621820	95398	95415	CCGCGGAGCAGCAGCAGG	34	1397	1414	5-8-5	1756
621821	95401	95418	CCCCCGCGGAGCAGCAGC	50	1400	1417	5-8-5	1757
621822	95404	95421	CTTCCCCCGCGGAGCAGC	48	1403	1420	5-8-5	1758
621823	95407	95424	GGGCTTCCCCCGCGGAGC	0	1406	1423	5-8-5	1759
621824	95410	95427	GACGGGCTTCCCCCGCGG	7	1409	1426	5-8-5	1760
621825	95413	95430	GCTGACGGGCTTCCCCCG	36	1412	1429	5-8-5	1761
621826	95416	95433	CCGGCTGACGGGCTTCCC	54	1415	1432	5-8-5	1762
621827	95419	95436	GACCCGGCTGACGGGCTT	7	1418	1435	5-8-5	1763
621828	95423	95440	GAGGGACCCGGCTGACGG	6	1422	1439	5-8-5	1764
621829	95426	95443	GTTGAGGGACCCGGCTGA	27	1425	1442	5-8-5	1765
621830	95429	95446	TGAGTTGAGGGACCCGGC	50	1428	1445	5-8-5	1766
621831	95432	95449	CTTTGAGTTGAGGGACCC	50	1431	1448	5-8-5	1767
621837	98559	98576	TTTTACTGACCATGCGAG	77	1449	1466	5-8-5	1768

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621838	98562	98579	TGCTTTTACTGACCATGC	95	1452	1469	5-8-5	1769
621839	98565	98582	CTTTGCTTTTACTGACCA	85	1455	1472	5-8-5	1770
621840	98568	98585	CGTCTTTGCTTTTACTGA	66	1458	1475	5-8-5	1771
621841	98571	98588	TCCCGTCTTTGCTTTTAC	79	1461	1478	5-8-5	1772
621842	98575	98592	CCAGTCCCGTCTTTGCTT	87	1465	1482	5-8-5	1773
621843	98578	98595	CTTCCAGTCCCGTCTTTG	64	1468	1485	5-8-5	1774
621844	98581	98598	TCGCTTCCAGTCCCGTCT	88	1471	1488	5-8-5	1775
621845	98584	98601	TCATCGCTTCCAGTCCCG	90	1474	1491	5-8-5	1776
621846	98587	98604	TTGTCATCGCTTCCAGTC	88	1477	1494	5-8-5	1777
621847	98590	98607	TTTTTGTCATCGCTTCCA	80	1480	1497	5-8-5	1778
621850	101406	101423	GGTTTTAGCAGAGGAACG	75	1514	1531	5-8-5	1779
621851	101409	101426	CAAGGTTTTAGCAGAGGA	83	1517	1534	5-8-5	1780
621852	101412	101429	TTTCAAGGTTTTAGCAGA	35	1520	1537	5-8-5	1781
621853	101415	101432	ATTTTTCAAGGTTTTAGC	79	1523	1540	5-8-5	1782
621854	101418	101435	CCTATTTTTCAAGGTTTT	71	1526	1543	5-8-5	1783
621855	101425	101442	GGCAAGGCCTATTTTTCA	83	1533	1550	5-8-5	1784
621856	101428	101445	TAAGGCAAGGCCTATTTT	23	1536	1553	5-8-5	1785
621857	101431	101448	GGCTAAGGCAAGGCCTAT	69	1539	1556	5-8-5	1786
621858	101457	101474	TGAGCTACCAGGAGTGGG	75	1565	1582	5-8-5	1787
621859	101460	101477	GTCTGAGCTACCAGGAGT	78	1568	1585	5-8-5	1788
621860	101463	101480	AGGGTCTGAGCTACCAGG	82	1571	1588	5-8-5	1789
621861	101466	101483	CAGAGGGTCTGAGCTACC	88	1574	1591	5-8-5	1790
621862	101469	101486	GATCAGAGGGTCTGAGCT	72	1577	1594	5-8-5	1791
621863	101472	101489	TTGGATCAGAGGGTCTGA	83	1580	1597	5-8-5	1792
621864	101478	101495	GGAGGGTTGGATCAGAGG	0	1586	1603	5-8-5	1793
621865	101481	101498	GCTGGAGGGTTGGATCAG	16	1589	1606	5-8-5	1794
621866	101491	101508	ACACAGCAGGGCTGGAGG	34	1599	1616	5-8-5	1795
621867	101494	101511	GGCACACAGCAGGGCTGG	67	1602	1619	5-8-5	1796
621868	101499	101516	CTCTGGGCACACAGCAGG	75	1607	1624	5-8-5	1797
621869	101502	101519	TGGCTCTGGGCACACAGC	90	1610	1627	5-8-5	1798
621870	101505	101522	AGGTGGCTCTGGGCACAC	92	1613	1630	5-8-5	1799
621871	101508	101525	GGAAGGTGGCTCTGGGCA	67	1616	1633	5-8-5	1800
621872	101511	101528	AGAGGAAGGTGGCTCTGG	43	1619	1636	5-8-5	1801
621873	101514	101531	AGGAGAGGAAGGTGGCTC	65	1622	1639	5-8-5	1802
621874	101517	101534	TTTAGGAGAGGAAGGTGG	26	1625	1642	5-8-5	1803
621875	101520	101537	GTATTTAGGAGAGGAAGG	0	1628	1645	5-8-5	1804
621876	101537	101554	GAAGTGACAGAAGAGACG	37	1645	1662	5-8-5	1805
621877	101540	101557	CGGGAAGTGACAGAAGAG	59	1648	1665	5-8-5	1806
621878	101543	101560	GTTCGGGAAGTGACAGAA	65	1651	1668	5-8-5	1807
621879	101546	101563	CCAGTTCGGGAAGTGACA	35	1654	1671	5-8-5	1808
621880	101549	101566	CTGCCAGTTCGGGAAGTG	69	1657	1674	5-8-5	1809
621881	101552	101569	GAACTGCCAGTTCGGGAA	48	1660	1677	5-8-5	1810
621882	101555	101572	CCAGAACTGCCAGTTCGG	66	1663	1680	5-8-5	1811

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621883	101558	101575	GCTCCAGAACTGCCAGTT	69	1666	1683	5-8-5	1812
621884	101561	101578	TTTGCTCCAGAACTGCCA	74	1669	1686	5-8-5	1813
621885	101564	101581	TCCTTTGCTCCAGAACTG	61	1672	1689	5-8-5	1814
621886	101567	101584	ATCTCCTTTGCTCCAGAA	64	1675	1692	5-8-5	1815
621887	101570	101587	TTCATCTCCTTTGCTCCA	36	1678	1695	5-8-5	1816
621888	101573	101590	AGTTTCATCTCCTTTGCT	32	1681	1698	5-8-5	1817

[0649]

[0650] **표 35**

[0651] 서열 번호: 1 및 2를 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	모티프	서열 번호:
613412	73879	73898	GTGATCTTCCATCACTTCGA	87	345	364	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	95	n/a	n/a	5-8-5	665
	98928	98945			n/a	n/a		
621890	n/a	n/a	CCCTTGAGTTTCATCTCC	30	1687	1704	5-8-5	1818
621891	n/a	n/a	GCCCCCTTGAGTTTCATC	8	1690	1707	5-8-5	1819
621892	n/a	n/a	TCAGCCCCCTTGAGTTTC	0	1693	1710	5-8-5	1820
621893	n/a	n/a	CCATCAGCCCCCTTGAGT	4	1696	1713	5-8-5	1821
621894	n/a	n/a	TTACCATCAGCCCCCTTG	75	1699	1716	5-8-5	1822
621912	n/a	n/a	CGCAGAGCTGGGTGGTGT	0	1814	1831	5-8-5	1823
621913	n/a	n/a	AGTCGCAGAGCTGGGTGG	0	1817	1834	5-8-5	1824
621914	n/a	n/a	CTTAGTCGCAGAGCTGGG	21	1820	1837	5-8-5	1825
621915	n/a	n/a	TTGCTTAGTCGCAGAGCT	12	1823	1840	5-8-5	1826
621916	n/a	n/a	GACTTGCTTAGTCGCAGA	29	1826	1843	5-8-5	1827
621925	n/a	n/a	TTCACCTCTCTCAGATCT	4	1871	1888	5-8-5	1828
621926	n/a	n/a	AGGTTCACCTCTCTCAGA	9	1874	1891	5-8-5	1829
621927	n/a	n/a	TGGAGGTTCACCTCTCTC	7	1877	1894	5-8-5	1830
621928	n/a	n/a	TTTTGGAGGTTCACCTCT	11	1880	1897	5-8-5	1831
621889	101576	101593	TTGAGTTTCATCTCCTTT	23	1684	1701	5-8-5	1832
621895	102978	102995	GTTTTACCATCAGCCCCC	88	1702	1719	5-8-5	1833
621896	102995	103012	GCGGTGTGGCGATCTTCG	42	1719	1736	5-8-5	1834
621897	102998	103015	CCCGCGGTGTGGCGATCT	33	1722	1739	5-8-5	1835
621898	103001	103018	CTCCCCGCGGTGTGGCGA	37	1725	1742	5-8-5	1836
621899	103004	103021	CTGCTCCCCGCGGTGTGG	50	1728	1745	5-8-5	1837
621900	103007	103024	GGGCTGCTCCCCGCGGTG	43	1731	1748	5-8-5	1838
621901	103025	103042	GGCCCTTCTGGCCTGGAG	29	1749	1766	5-8-5	1839
621902	103029	103046	GCCTGGCCCTTCTGGCCT	34	1753	1770	5-8-5	1840
621903	103032	103049	TTGGCCTGGCCCTTCTGG	49	1756	1773	5-8-5	1841
621904	103050	103067	GCTGGAATCCTGGTGGCG	58	1774	1791	5-8-5	1842
621905	103053	103070	TTTGCTGGAATCCTGGTG	50	1777	1794	5-8-5	1843
621906	103056	103073	GTTTTTGCTGGAATCCTG	62	1780	1797	5-8-5	1844
621907	103075	103092	TGTCTTTGGAGCGGGCGG	21	1799	1816	5-8-5	1845
621908	103078	103095	TGGTGTCTTTGGAGCGGG	57	1802	1819	5-8-5	1846

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621909	103081	103098	GGGTGGTGTCTTTGGAGC	17	1805	1822	5-8-5	1847
621910	103084	103101	GCTGGGTGGTGTCTTTGG	44	1808	1825	5-8-5	1848
621911	103087	103104	AGAGCTGGGTGGTGTCTT	47	1811	1828	5-8-5	1849
621917	105442	105459	CTGGACTTGCTTAGTCGC	27	1829	1846	5-8-5	1850
621918	105445	105462	TCTCTGGACTTGCTTAGT	0	1832	1849	5-8-5	1851
621919	105448	105465	TCTTCTCTGGACTTGCTT	48	1835	1852	5-8-5	1852
621920	105451	105468	TGGTCTTCTCTGGACTTG	49	1838	1855	5-8-5	1853
621921	105454	105471	GGGTGGTCTTCTCTGGAC	33	1841	1858	5-8-5	1854
621922	105473	105490	CAGATCTGGGCCCTGCAG	36	1860	1877	5-8-5	1855
621923	105476	105493	TCTCAGATCTGGGCCCTG	70	1863	1880	5-8-5	1856
621924	105479	105496	CTCTCTCAGATCTGGGCC	32	1866	1883	5-8-5	1857
621929	107917	107934	TGATTTTGGAGGTTCACC	44	1883	1900	5-8-5	1858
621930	107920	107937	CCCTGATTTTGGAGGTTC	74	1886	1903	5-8-5	1859
621931	107923	107940	ATCCCCTGATTTTGGAGG	26	1889	1906	5-8-5	1860
621932	107926	107943	GCGATCCCCTGATTTTGG	45	1892	1909	5-8-5	1861
621933	107929	107946	GCTGCGATCCCCTGATTT	38	1895	1912	5-8-5	1862
621934	107932	107949	GCCGCTGCGATCCCCTGA	42	1898	1915	5-8-5	1863
621935	107935	107952	GTAGCCGCTGCGATCCCC	31	1901	1918	5-8-5	1864
621936	107938	107955	GCTGTAGCCGCTGCGATC	67	1904	1921	5-8-5	1865
621937	107941	107958	GCTGCTGTAGCCGCTGCG	23	1907	1924	5-8-5	1866
621938	107971	107988	GCGGCTGCCGGGAGTGCC	40	1937	1954	5-8-5	1867
621939	107974	107991	GGAGCGGCTGCCGGGAGT	1	1940	1957	5-8-5	1868
621940	107978	107995	TGCGGGAGCGGCTGCCGG	48	1944	1961	5-8-5	1869
621941	108021	108038	ACCTTCTTGGGCTCCCGG	24	1987	2004	5-8-5	1870
621942	108024	108041	GCCACCTTCTTGGGCTCC	28	1990	2007	5-8-5	1871
621943	108027	108044	ACTGCCACCTTCTTGGGC	19	1993	2010	5-8-5	1872
621944	108030	108047	ACCACTGCCACCTTCTTG	28	1996	2013	5-8-5	1873
621945	108033	108050	CGGACCACTGCCACCTTC	72	1999	2016	5-8-5	1874
621946	108036	108053	GTACGGACCACTGCCACC	57	2002	2019	5-8-5	1875
621947	108039	108056	GGAGTACGGACCACTGCC	25	2005	2022	5-8-5	1876
621948	108042	108059	GGTGGAGTACGGACCACT	30	2008	2025	5-8-5	1877
621949	108045	108062	TTGGGTGGAGTACGGACC	24	2011	2028	5-8-5	1878
621950	108052	108069	CGGCGACTTGGGTGGAGT	1	2018	2035	5-8-5	1879
621951	108055	108072	AGACGGCGACTTGGGTGG	4	2021	2038	5-8-5	1880
621952	108058	108075	GGAAGACGGCGACTTGGG	50	2024	2041	5-8-5	1881
621953	108061	108078	GGCGGAAGACGGCGACTT	66	2027	2044	5-8-5	1882
621954	108064	108081	CTTGGCGGAAGACGGCGA	38	2030	2047	5-8-5	1883
621955	108067	108084	GCTCTTGGCGGAAGACGG	24	2033	2050	5-8-5	1884
621956	108070	108087	GCGGCTCTTGGCGGAAGA	20	2036	2053	5-8-5	1885
621957	108073	108090	CAGGCGGCTCTTGGCGGA	46	2039	2056	5-8-5	1886
621958	108076	108093	CTGCAGGCGGCTCTTGGC	72	2042	2059	5-8-5	1887
621959	108079	108096	TGTCTGCAGGCGGCTCTT	52	2045	2062	5-8-5	1888
621960	108082	108099	GGCTGTCTGCAGGCGGCT	47	2048	2065	5-8-5	1889

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621961	108101	108118	GGTCTGGCATGGGCACGG	73	2067	2084	5-8-5	1890
621962	108137	108154	TCTCAGTGGAGCCGATCT	39	2103	2120	5-8-5	1891
621963	108140	108157	GGTTCTCAGTGGAGCCGA	66	2106	2123	5-8-5	1892
621964	108143	108160	TCAGGTTCTCAGTGGAGC	65	2109	2126	5-8-5	1893
621965	108146	108163	GCTTCAGGTTCTCAGTGG	44	2112	2129	5-8-5	1894

[0654]

[0655] 표 36

[0656] 서열 번호: 1 및 2를 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	모티프	서열 번호:
613412	73879	73898	GTGATCTTCCATCACTTCGA	88	345	364	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	94	n/a	n/a	5-8-5	665
	98928	98945			n/a	n/a		
621973	n/a	n/a	TGCACCTTCCCGCCTCCC	66	2137	2154	5-8-5	1895
621974	n/a	n/a	TATCTGCACCTTCCCGCC	17	2141	2158	5-8-5	1896
621975	n/a	n/a	AATTATCTGCACCTTCCC	27	2144	2161	5-8-5	1897
621994	n/a	n/a	TGCACACTGCCGCCTCCC	74	2230	2247	5-8-5	1898
621995	n/a	n/a	ACTATTTGCACACTGCCG	28	2236	2253	5-8-5	1899
621996	n/a	n/a	TAGACTATTTGCACACTG	29	2239	2256	5-8-5	1900
621997	n/a	n/a	TTGTAGACTATTTGCACA	62	2242	2259	5-8-5	1901
622012	n/a	n/a	CTCCTGGTTTATGATGGA	24	2310	2327	5-8-5	1902
622013	n/a	n/a	GGCCACCTCCTGGTTTAT	21	2316	2333	5-8-5	1903
622014	n/a	n/a	CACCTGGCCACCTCCTGG	44	2321	2338	5-8-5	1904
622041	n/a	n/a	ATCTTTTTATTTCCTCCG	32	2422	2439	5-8-5	1905
622042	n/a	n/a	TTTCAATCTTTTTATTTC	16	2427	2444	5-8-5	1906
621966	108149	108166	GGTGCTTCAGGTTCTCAG	48	2115	2132	5-8-5	1907
621967	108153	108170	GGCTGGTGCTTCAGGTTC	46	2119	2136	5-8-5	1908
621968	108156	108173	CCCGGCTGGTGCTTCAGG	50	2122	2139	5-8-5	1909
621969	108159	108176	CCTCCCGGCTGGTGCTTC	22	2125	2142	5-8-5	1910
621970	108162	108179	CCGCCTCCCGGCTGGTGC	27	2128	2145	5-8-5	1911
621971	108165	108182	TTCCCGCCTCCCGGCTGG	5	2131	2148	5-8-5	1912
621972	108168	108185	ACCTTCCCGCCTCCCGGC	39	2134	2151	5-8-5	1913
621976	121826	121843	ATTAATTATCTGCACCTT	76	2147	2164	5-8-5	1914
621977	121829	121846	CTTATTAATTATCTGCAC	73	2150	2167	5-8-5	1915
621978	121833	121850	GCTTCTTATTAATTATCT	68	2154	2171	5-8-5	1916
621979	121836	121853	CCAGCTTCTTATTAATTA	44	2157	2174	5-8-5	1917
621980	121839	121856	GATCCAGCTTCTTATTAA	31	2160	2177	5-8-5	1918
621981	121842	121859	TAAGATCCAGCTTCTTAT	44	2163	2180	5-8-5	1919
621982	121845	121862	TGCTAAGATCCAGCTTCT	69	2166	2183	5-8-5	1920
621983	121848	121865	CGTTGCTAAGATCCAGCT	82	2169	2186	5-8-5	1921
621984	121864	121881	CCACACTTGGACTGGACG	73	2185	2202	5-8-5	1922
621985	121867	121884	GAGCCACACTTGGACTGG	80	2188	2205	5-8-5	1923
621986	121870	121887	TTTGAGCCACACTTGGAC	59	2191	2208	5-8-5	1924

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621987	121873	121890	TCCTTTGAGCCACACTTG	66	2194	2211	5-8-5	1925
621988	121876	121893	TTATCCTTTGAGCCACAC	77	2197	2214	5-8-5	1926
621989	121879	121896	ATATTATCCTTTGAGCCA	54	2200	2217	5-8-5	1927
621990	121882	121899	TTGATATTATCCTTTGAG	69	2203	2220	5-8-5	1928
621991	121885	121902	TGTTTGATATTATCCTTT	92	2206	2223	5-8-5	1929
621992	121903	121920	CTGCCGCCTCCCGGGACG	51	2224	2241	5-8-5	1930
621993	121906	121923	ACACTGCCGCCTCCCGGG	70	2227	2244	5-8-5	1931
621998	125764	125781	GGTTTGTAGACTATTTGC	76	2245	2262	5-8-5	1932
621999	125767	125784	ACTGGTTTGTAGACTATT	62	2248	2265	5-8-5	1933
622000	125770	125787	TCAACTGGTTTGTAGACT	39	2251	2268	5-8-5	1934
622001	125777	125794	GCTCAGGTCAACTGGTTT	87	2258	2275	5-8-5	1935
622002	125780	125797	CTTGCTCAGGTCAACTGG	53	2261	2278	5-8-5	1936
622003	125783	125800	CACCTTGCTCAGGTCAAC	68	2264	2281	5-8-5	1937
622004	125805	125822	CTAATGAGCCACACTTGG	51	2286	2303	5-8-5	1938
622005	125808	125825	TGCCTAATGAGCCACACT	65	2289	2306	5-8-5	1939
622006	125811	125828	TGTTGCCTAATGAGCCAC	69	2292	2309	5-8-5	1940
622007	125814	125831	GGATGTTGCCTAATGAGC	70	2295	2312	5-8-5	1941
622008	125817	125834	GATGGATGTTGCCTAATG	61	2298	2315	5-8-5	1942
622009	125820	125837	TATGATGGATGTTGCCTA	44	2301	2318	5-8-5	1943
622010	125823	125840	GTTTATGATGGATGTTGC	57	2304	2321	5-8-5	1944
622011	125826	125843	CTGGTTTATGATGGATGT	26	2307	2324	5-8-5	1945
622015	130141	130158	TTTACTTCCACCTGGCCA	36	2329	2346	5-8-5	1946
622016	130144	130161	GATTTTACTTCCACCTGG	49	2332	2349	5-8-5	1947
622017	130147	130164	TCAGATTTTACTTCCACC	76	2335	2352	5-8-5	1948
622018	130150	130167	TTCTCAGATTTTACTTCC	24	2338	2355	5-8-5	1949
622019	130153	130170	AGCTTCTCAGATTTTACT	30	2341	2358	5-8-5	1950
622020	130156	130173	TCAAGCTTCTCAGATTTT	39	2344	2361	5-8-5	1951
622021	130159	130176	AAGTCAAGCTTCTCAGAT	2	2347	2364	5-8-5	1952
622022	130162	130179	TTGAAGTCAAGCTTCTCA	53	2350	2367	5-8-5	1953
622023	130165	130182	TCCTTGAAGTCAAGCTTC	39	2353	2370	5-8-5	1954
622024	130168	130185	CTGTCCTTGAAGTCAAGC	19	2356	2373	5-8-5	1955
622025	130171	130188	ACTCTGTCCTTGAAGTCA	39	2359	2376	5-8-5	1956
622026	130174	130191	TGGACTCTGTCCTTGAAG	36	2362	2379	5-8-5	1957
622027	130177	130194	GACTGGACTCTGTCCTTG	75	2365	2382	5-8-5	1958
622028	130180	130197	TTCGACTGGACTCTGTCC	29	2368	2385	5-8-5	1959
622029	130183	130200	ATCTTCGACTGGACTCTG	33	2371	2388	5-8-5	1960
622030	130186	130203	CCAATCTTCGACTGGACT	49	2374	2391	5-8-5	1961
622031	130189	130206	GACCCAATCTTCGACTGG	74	2377	2394	5-8-5	1962
622032	130192	130209	AGGGACCCAATCTTCGAC	79	2380	2397	5-8-5	1963
622033	130195	130212	TCCAGGGACCCAATCTTC	77	2383	2400	5-8-5	1964
622034	130198	130215	TTGTCCAGGGACCCAATC	68	2386	2403	5-8-5	1965
622035	130201	130218	ATATTGTCCAGGGACCCA	6	2389	2406	5-8-5	1966
622036	130204	130221	GTGATATTGTCCAGGGAC	86	2392	2409	5-8-5	1967

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622037	130207	130224	TGGGTGATATTGTCCAGG	68	2395	2412	5-8-5	1968
622038	130225	130242	TTTCCTCCGCCAGGGACG	77	2413	2430	5-8-5	1969
622039	130228	130245	TTATTTCCTCCGCCAGGG	52	2416	2433	5-8-5	1970
622040	130231	130248	TTTTTATTTCCTCCGCCA	61	2419	2436	5-8-5	1971

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[0660] **표 37**

[0661] 서열 번호: 1 및 2를 표적화하는 5-10-5 MOE 및 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	모티프	서열 번호:
613412	73879	73898	GTGATCTTCCATCACTTCGA	89	345	364	5-10-5	25
620887	98891	98908	GTTTTCAAACACACCTTC	98	n/a	n/a	5-8-5	665
	98928	98945			n/a	n/a		
622043	n/a	n/a	GGGTTTCAATCTTTTTAT	65	2430	2447	5-8-5	1972
622044	135477	135494	GTCAGCTTGTGGGTTTCA	86	2440	2457	5-8-5	1973
622045	135480	135497	AAGGTCAGCTTGTGGGTT	49	2443	2460	5-8-5	1974
622046	135484	135501	GCGGAAGGTCAGCTTGTG	26	2447	2464	5-8-5	1975
622047	135488	135505	TCTCGCGGAAGGTCAGCT	54	2451	2468	5-8-5	1976
622048	135491	135508	CGTTCTCGCGGAAGGTCA	63	2454	2471	5-8-5	1977
622049	135507	135524	TCTGTCTTGGCTTTGGCG	30	2470	2487	5-8-5	1978
622050	135510	135527	TGGTCTGTCTTGGCTTTG	72	2473	2490	5-8-5	1979
622051	135513	135530	CCGTGGTCTGTCTTGGCT	75	2476	2493	5-8-5	1980
622052	135516	135533	GCCCCGTGGTCTGTCTTG	39	2479	2496	5-8-5	1981
622053	135527	135544	ACACGATCTCCGCCCCGT	80	2490	2507	5-8-5	1982
622054	135530	135547	TGTACACGATCTCCGCCC	72	2493	2510	5-8-5	1983
622055	135533	135550	ACTTGTACACGATCTCCG	30	2496	2513	5-8-5	1984
622056	135536	135553	GCGACTTGTACACGATCT	72	2499	2516	5-8-5	1985
622057	135539	135556	CTGGCGACTTGTACACGA	65	2502	2519	5-8-5	1986
622058	135542	135559	CCACTGGCGACTTGTACA	35	2505	2522	5-8-5	1987
622059	135545	135562	ACACCACTGGCGACTTGT	46	2508	2525	5-8-5	1988
622060	135548	135565	CAGACACCACTGGCGACT	61	2511	2528	5-8-5	1989
622061	135551	135568	CCCCAGACACCACTGGCG	74	2514	2531	5-8-5	1990
622062	135554	135571	TGTCCCCAGACACCACTG	38	2517	2534	5-8-5	1991
622063	135572	135589	TGAGATGCCGTGGAGACG	36	2535	2552	5-8-5	1992
622064	135575	135592	TGCTGAGATGCCGTGGAG	34	2538	2555	5-8-5	1993
622065	135599	135616	CGATGCTGCCGGTGGAGG	43	2562	2579	5-8-5	1994
622066	135602	135619	TGTCGATGCTGCCGGTGG	51	2565	2582	5-8-5	1995
622067	135605	135622	CCATGTCGATGCTGCCGG	66	2568	2585	5-8-5	1996
622068	135608	135625	CTACCATGTCGATGCTGC	68	2571	2588	5-8-5	1997
622069	135611	135628	AGTCTACCATGTCGATGC	56	2574	2591	5-8-5	1998
622070	135614	135631	GCGAGTCTACCATGTCGA	68	2577	2594	5-8-5	1999
622071	135654	135671	AGGGAGGCAGACACCTCG	24	2617	2634	5-8-5	2000
622072	135657	135674	GCCAGGGAGGCAGACACC	73	2620	2637	5-8-5	2001
622073	135661	135678	CTTGGCCAGGGAGGCAGA	50	2624	2641	5-8-5	2002

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622074	135664	135681	CTGCTTGGCCAGGGAGGC	44	2627	2644	5-8-5	2003
622075	135667	135684	ACCCTGCTTGGCCAGGGA	18	2630	2647	5-8-5	2004
622076	135678	135695	CCTGATCACAAACCCTGC	65	2641	2658	5-8-5	2005
622077	135681	135698	GGGCCTGATCACAAACCC	82	2644	2661	5-8-5	2006
622078	135697	135714	TTATTGACCGCCCCAGGG	42	2660	2677	5-8-5	2007
622079	135700	135717	CAATTATTGACCGCCCCA	54	2663	2680	5-8-5	2008
622080	135703	135720	CCACAATTATTGACCGCC	95	2666	2683	5-8-5	2009
622081	135706	135723	TCTCCACAATTATTGACC	63	2669	2686	5-8-5	2010
622082	135709	135726	TCCTCTCCACAATTATTG	41	2672	2689	5-8-5	2011
622083	135712	135729	CTCTCCTCTCCACAATTA	76	2675	2692	5-8-5	2012
622084	135715	135732	ATTCTCTCCTCTCCACAA	57	2678	2695	5-8-5	2013
622085	135718	135735	CTCATTCTCTCCTCTCCA	72	2681	2698	5-8-5	2014
622086	135721	135738	TCTCTCATTCTCTCCTCT	69	2684	2701	5-8-5	2015
622087	135724	135741	CACTCTCTCATTCTCTCC	75	2687	2704	5-8-5	2016
622088	135727	135744	CCACACTCTCTCATTCTC	90	2690	2707	5-8-5	2017
622089	135730	135747	TTTCCACACTCTCTCATT	70	2693	2710	5-8-5	2018
622090	135733	135750	TTTTTTCCACACTCTCTC	76	2696	2713	5-8-5	2019
622091	135737	135754	CTTTTTTTTTCCACACTC	84	2700	2717	5-8-5	2020
622092	135740	135757	ATTCTTTTTTTTTCCACA	67	2703	2720	5-8-5	2021
622093	135746	135763	GTCATTATTCTTTTTTTT	54	2709	2726	5-8-5	2022
622094	135749	135766	CGGGTCATTATTCTTTTT	82	2712	2729	5-8-5	2023
622095	135752	135769	GGCCGGGTCATTATTCTT	72	2715	2732	5-8-5	2024
622096	135783	135800	CTGCGAGGAGCAGCTGGG	52	2746	2763	5-8-5	2025
622097	135786	135803	GAACTGCGAGGAGCAGCT	59	2749	2766	5-8-5	2026
622098	135789	135806	ACCGAACTGCGAGGAGCA	77	2752	2769	5-8-5	2027
622099	135792	135809	TTAACCGAACTGCGAGGA	62	2755	2772	5-8-5	2028
622100	135795	135812	CAATTAACCGAACTGCGA	55	2758	2775	5-8-5	2029
622101	135798	135815	AACCAATTAACCGAACTG	59	2761	2778	5-8-5	2030
622102	135801	135818	ATTAACCAATTAACCGAA	71	2764	2781	5-8-5	2031
622103	135804	135821	GTGATTAACCAATTAACC	70	2767	2784	5-8-5	2032
622104	135807	135824	TAAGTGATTAACCAATTA	42	2770	2787	5-8-5	2033
622105	135810	135827	GGTTAAGTGATTAACCAA	42	2773	2790	5-8-5	2034
622106	135813	135830	GCAGGTTAAGTGATTAAC	78	2776	2793	5-8-5	2035
622107	135816	135833	AAAGCAGGTTAAGTGATT	38	2779	2796	5-8-5	2036
622108	135819	135836	ACAAAAGCAGGTTAAGTG	55	2782	2799	5-8-5	2037
622109	135822	135839	GTGACAAAAGCAGGTTAA	82	2785	2802	5-8-5	2038
622110	135825	135842	CGAGTGACAAAAGCAGGT	86	2788	2805	5-8-5	2039
622111	135828	135845	AGCCGAGTGACAAAAGCA	93	2791	2808	5-8-5	2040
622112	135831	135848	CAAAGCCGAGTGACAAAA	73	2794	2811	5-8-5	2041
622113	135834	135851	AGCCAAAGCCGAGTGACA	82	2797	2814	5-8-5	2042
622114	135837	135854	CCGAGCCAAAGCCGAGTG	82	2800	2817	5-8-5	2043
622115	135840	135857	GTCCCGAGCCAAAGCCGA	63	2803	2820	5-8-5	2044
622116	135843	135860	GAAGTCCCGAGCCAAAGC	59	2806	2823	5-8-5	2045

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622117	135846	135863	TTTGAAGTCCCGAGCCAA	76	2809	2826	5-8-5	2046
622118	135849	135866	GATTTTGAAGTCCCGAGC	72	2812	2829	5-8-5	2047
622119	135852	135869	ACTGATTTTGAAGTCCCG	73	2815	2832	5-8-5	2048

[0664]

[0665] 표 38

[0666] 서열 번호: 1을 표적화하는 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호:
620887	98891	98908	GTTTTCAAACACACCTTC	96	5-8-5	665
	98928	98945				
623853	12069	12086	TGTTTGGATTTCTATCGG	82	5-8-5	2049
623854	12077	12094	TGACATGGTGTTTGGATT	47	5-8-5	2050
623855	12079	12096	GCTGACATGGTGTTTGGA	77	5-8-5	2051
623856	12080	12097	CGCTGACATGGTGTTTGG	78	5-8-5	2052
623857	12081	12098	TCGCTGACATGGTGTTTG	83	5-8-5	2053
623858	12082	12099	CTCGCTGACATGGTGTTT	84	5-8-5	2054
623859	12083	12100	ACTCGCTGACATGGTGTT	74	5-8-5	2055
623860	12084	12101	GACTCGCTGACATGGTGT	89	5-8-5	2056
623861	12085	12102	GGACTCGCTGACATGGTG	77	5-8-5	2057
623862	16753	16770	TTATCCAGGAAAAATATT	21	5-8-5	2058
623863	16756	16773	GGATTATCCAGGAAAAAT	86	5-8-5	2059
623864	16758	16775	TAGGATTATCCAGGAAAA	76	5-8-5	2060
623865	16759	16776	ATAGGATTATCCAGGAAA	84	5-8-5	2061
623866	16760	16777	TATAGGATTATCCAGGAA	62	5-8-5	2062
623867	16761	16778	CTATAGGATTATCCAGGA	87	5-8-5	2063
623868	16763	16780	CCCTATAGGATTATCCAG	76	5-8-5	2064
623869	16764	16781	TCCCTATAGGATTATCCA	34	5-8-5	2065
623870	16766	16783	TATCCCTATAGGATTATC	56	5-8-5	2066
623871	16769	16786	AGTTATCCCTATAGGATT	16	5-8-5	2067
623872	16774	16791	AGGCAAGTTATCCCTATA	86	5-8-5	2068
623873	17416	17433	ATCAGCACCTGACTGCGG	78	5-8-5	2069
623874	17421	17438	TTCAGATCAGCACCTGAC	91	5-8-5	2070
623875	17424	17441	GACTTCAGATCAGCACCT	92	5-8-5	2071
623876	17426	17443	AAGACTTCAGATCAGCAC	92	5-8-5	2072
623877	17427	17444	AAAGACTTCAGATCAGCA	95	5-8-5	2073
623878	17428	17445	CAAAGACTTCAGATCAGC	96	5-8-5	2074
623879	17429	17446	CCAAAGACTTCAGATCAG	86	5-8-5	2075
623880	17430	17447	ACCAAAGACTTCAGATCA	65	5-8-5	2076
623881	17431	17448	CACCAAAGACTTCAGATC	51	5-8-5	2077
623882	17432	17449	CCACCAAAGACTTCAGAT	55	5-8-5	2078
623883	17434	17451	GCCCACCAAAGACTTCAG	77	5-8-5	2079
623884	17437	17454	TCAGCCCACCAAAGACTT	56	5-8-5	2080
623885	17442	17459	TAAAGTCAGCCCACCAAA	2	5-8-5	2081

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623886	20943	20960	GTTATTGGGACTGACCTT	69	5-8-5	2082
623887	20948	20965	GATTTGTTATTGGGACTG	78	5-8-5	2083
613412	73879	73898	GTGATCTTCCATCACTTCGA	89	5-8-5	25
623811	122370	122387	CAGTGGAGCCACTCAACG	41	5-8-5	2084
623812	122380	122397	CACCTGTCCACAGTGGAG	58	5-8-5	2085
623813	122391	122408	AACAAACGGGTCACCTGT	63	5-8-5	2086
623814	122445	122462	CGTGTAGGAGCAGCAGCT	81	5-8-5	2087
623815	122538	122555	CTTTGGTTTGGCTCTTTG	64	5-8-5	2088
623816	123104	123121	GCTGGTGGGAGAGGAGCC	9	5-8-5	2089
623817	123288	123305	ATGCGGGTGGCTGCCTCA	65	5-8-5	2090
623818	123293	123310	GCTGGATGCGGGTGGCTG	24	5-8-5	2091
623819	123341	123358	GTGCTCAGGGCAGGAAGC	45	5-8-5	2092
623820	123590	123607	CAAAGCTCAAACAGCTGA	56	5-8-5	2093
623821	123601	123618	AGAACCAGGATCAAAGCT	41	5-8-5	2094
623822	123704	123721	GCTCCGCCTCAGCAGCAC	71	5-8-5	2095
623823	123722	123739	GTGTGCACTCTCTCCCCA	45	5-8-5	2096
623824	123877	123894	GGCTAGCCCGCAGACGAG	31	5-8-5	2097
623825	123976	123993	CCTGTGAAGGTGCTCAGA	58	5-8-5	2098
623826	124033	124050	GATCCAGTGCCCCCAGAT	54	5-8-5	2099
623827	124057	124074	GGAGAGGCTAGGGCTCAG	68	5-8-5	2100
623828	124223	124240	AGAGGAGTGGATGGCAGT	37	5-8-5	2101
623829	124293	124310	TGGCCTGGGTGAGGTAAC	23	5-8-5	2102
623830	124296	124313	CTCTGGCCTGGGTGAGGT	28	5-8-5	2103
623831	124596	124613	AGGGCAGGTGGTGGTTTC	8	5-8-5	2104
623832	124780	124797	GACATTCCTGGAGTCCCC	83	5-8-5	2105
623833	124859	124876	TGGCAGACAGACAGGTCC	87	5-8-5	2106
623834	124909	124926	AGTCAAAGAACCAGCTCC	68	5-8-5	2107
623835	124949	124966	TCCCTCTGGGAATGATGA	41	5-8-5	2108
623836	124965	124982	GCCTCCAGGGCACCGCTC	76	5-8-5	2109
623837	124972	124989	GCCTGTGGCCTCCAGGGC	43	5-8-5	2110
623838	124977	124994	AGGAGGCCTGTGGCCTCC	11	5-8-5	2111
623839	125075	125092	AATAGGAACAAAGCAACA	25	5-8-5	2112
623840	125086	125103	CTGTCTTTAGCAATAGGA	84	5-8-5	2113
623841	125100	125117	TGTCCTGGACATTCCTGT	66	5-8-5	2114
623842	125291	125308	TGGAAAGGCAGGAGTGGG	0	5-8-5	2115
623843	125306	125323	TCTGAAAAATCTTGCTGG	51	5-8-5	2116
623844	125310	125327	AGCATCTGAAAAATCTTG	82	5-8-5	2117
623845	125322	125339	ATGAGTATGCACAGCATC	68	5-8-5	2118
623846	125337	125354	AAAGTGATCAATATGATG	33	5-8-5	2119
623847	125390	125407	GTCACTCCCTTTCCTGAC	68	5-8-5	2120
623848	125408	125425	ACGCTTAAGTGTAAAAAT	38	5-8-5	2121
623849	125557	125574	AAATGTGTTGTCGAAATT	19	5-8-5	2122
623850	125567	125584	CAGGGTGGAAAAATGTGT	33	5-8-5	2123

[0668]

623851	125598	125615	TTCCCAGCTGCCATGAGG	33	5-8-5	2124
623852	125743	125760	TGGAGATGAGAGAGGAGG	0	5-8-5	2125

[0669]

[0670] 표 39

[0671] 서열 번호: 1을 표적화하는 5-8-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	억제율%	모티프	서열 번호:
623661	6196	6213	GCGCTTACCTGATAGTCG	36	5-8-5	2126
613412	73879	73898	GTGATCTTCCATCACTTCGA	87	5-8-5	25
623662	73981	73998	TCCACTAACCTTTCAGGC	30	5-8-5	2127
623663	83368	83385	GGGAGATTCTGGAACACA	72	5-8-5	2128
623664	83455	83472	GGGCCCACCTTCCGCTGT	22	5-8-5	2129
623665	85895	85912	CTGTCACATCTAGAAACC	21	5-8-5	2130
623666	85982	85999	TACCCTCACCTGTGGTTC	0	5-8-5	2131
623667	89885	89902	CTTCTTCAGCTGGTGTAT	22	5-8-5	2132
623668	89951	89968	TTCACTGACCTTGGGTCA	0	5-8-5	2133
623669	94688	94705	TTTCAGGCTCTGTGTGGA	61	5-8-5	2134
623670	95441	95458	GACACAGACCTTTGAGTT	53	5-8-5	2135
623671	98550	98567	CCATGCGAGCTGATAAAA	39	5-8-5	2136
621344	98607	98624	GTCAGCTTACCTTGGCTT	34	5-8-5	814
620887	98891	98908	GTTTTCAAACACACCTTC	94	5-8-5	665
	98928	98945				
623672	101387	101404	GTGGATGTCTTAAACATA	89	5-8-5	2137
623673	101586	101603	TTTCCTTACCTTGAGTTT	0	5-8-5	2138
623674	102970	102987	ATCAGCCCCCTGTAAATG	7	5-8-5	2139
623675	103097	103114	TCTTCTTACCAGAGCTGG	0	5-8-5	2140
623676	107909	107926	GAGGTTCACCTGGGAAGG	0	5-8-5	2141
623677	108175	108192	CACTCTCACCTTCCCGCC	6	5-8-5	2142
623712	108255	108272	CCTCCAGGCGCAGCCCTA	92	5-8-5	2143
623713	108413	108430	CCTGAGGAGGGCACTCAC	28	5-8-5	2144
623714	108530	108547	GGAACCGCTGTGGGTGCC	60	5-8-5	2145
623715	108565	108582	TGGGTGGCAGTGTATTCT	63	5-8-5	2146
623716	108690	108707	GGAGAGCTCGCGAGCACC	69	5-8-5	2147
623717	108896	108913	GAGGTGGCTACCCACGGC	59	5-8-5	2148
623718	109561	109578	CCAGAAGGCCCAGCACAT	51	5-8-5	2149
623719	109574	109591	CGAGGCCCAGTGCCCAGA	59	5-8-5	2150
623720	109607	109624	AGGCCCAGGGTTCCAGAA	55	5-8-5	2151
623721	109623	109640	AGGCAAGCTGACACGCAG	73	5-8-5	2152
623722	110101	110118	CAGGAAAAGGCCGGACCT	37	5-8-5	2153
623723	110103	110120	AGCAGGAAAAGGCCGGAC	78	5-8-5	2154
623724	110182	110199	TTCCCCAAGGTCTCTAAC	14	5-8-5	2155
623725	110413	110430	AGGAAAGGCCAGTGAGGG	8	5-8-5	2156
623726	110500	110517	TTGTTATGTGACTTGAGG	74	5-8-5	2157

[0672]

623727	110630	110647	ATTCCCCACCATGGGACA	17	5-8-5	2158
623728	110635	110652	AGGACATTCCCCACCATG	9	5-8-5	2159
623729	110648	110665	AGATAAGGAGAGAAGGAC	15	5-8-5	2160
623730	110755	110772	ATGCTCAGTGTGGTCAGA	73	5-8-5	2161
623731	110852	110869	AGGGCCGGCCACCTGCAC	56	5-8-5	2162
623732	110919	110936	TCTGTCTCTGGCAACCTG	85	5-8-5	2163
623733	110954	110971	AACAGGGAAGCTACTTCC	6	5-8-5	2164
623734	111077	111094	GGGCCTTCAATGGAAAGT	21	5-8-5	2165
623735	111153	111170	GGTCGCCTGACTCTCACC	66	5-8-5	2166
623736	111174	111191	CCCTTTCTACACTTGGCA	81	5-8-5	2167
623678	121820	121837	TATCTGCACCTTTGGTAG	30	5-8-5	2168
623685	121830	121847	TCTTATTAATTATCTGCA	81	5-8-5	2169
623686	121831	121848	TTCTTATTAATTATCTGC	74	5-8-5	2170
623687	121834	121851	AGCTTCTTATTAATTATC	46	5-8-5	2171
623688	121835	121852	CAGCTTCTTATTAATTAT	6	5-8-5	2172
623689	121837	121854	TCCAGCTTCTTATTAATT	4	5-8-5	2173
623690	121838	121855	ATCCAGCTTCTTATTAAT	2	5-8-5	2174
623691	121840	121857	AGATCCAGCTTCTTATTA	2	5-8-5	2175
623692	121841	121858	AAGATCCAGCTTCTTATT	17	5-8-5	2176
623693	121843	121860	CTAAGATCCAGCTTCTTA	41	5-8-5	2177
623694	121844	121861	GCTAAGATCCAGCTTCTT	75	5-8-5	2178
623695	121846	121863	TTGCTAAGATCCAGCTTC	50	5-8-5	2179
623696	121847	121864	GTTGCTAAGATCCAGCTT	52	5-8-5	2180
623697	121865	121882	GCCACACTTGGACTGGAC	88	5-8-5	2181
623698	121866	121883	AGCCACACTTGGACTGGA	89	5-8-5	2182
623699	121868	121885	TGAGCCACACTTGGACTG	59	5-8-5	2183
623700	121869	121886	TTGAGCCACACTTGGACT	62	5-8-5	2184
623701	121872	121889	CCTTTGAGCCACACTTGG	69	5-8-5	2185
623702	121874	121891	ATCCTTTGAGCCACACTT	64	5-8-5	2186
623703	121875	121892	TATCCTTTGAGCCACACT	69	5-8-5	2187
623704	121877	121894	ATTATCCTTTGAGCCACA	76	5-8-5	2188
623705	121878	121895	TATTATCCTTTGAGCCAC	76	5-8-5	2189
623706	121880	121897	GATATTATCCTTTGAGCC	54	5-8-5	2190
623707	121881	121898	TGATATTATCCTTTGAGC	65	5-8-5	2191
623708	121884	121901	GTTTGATATTATCCTTTG	94	5-8-5	2192
623709	121886	121903	GTGTTTGATATTATCCTT	85	5-8-5	2193
623710	121887	121904	CGTGTTTGATATTATCCT	78	5-8-5	2194
623711	121904	121921	ACTGCCGCCTCCCGGGAC	50	5-8-5	2195
623679	121913	121930	GGTACTCACACTGCCGCC	72	5-8-5	1654
623680	125753	125770	TATTTGCACCTGGAGATG	0	5-8-5	2196
623681	125835	125852	CAGGGCTACCTGGTTTAT	26	5-8-5	2197
623682	130128	130145	GGCCACCTCCTAGAACAC	8	5-8-5	2198
623683	130241	130258	CCCCTTTACCTTTTTATT	0	5-8-5	2199

[0673]

623684	135466	135483	GGTTTCAATCTGCAAGAA	39	5-8-5	2200

[0674]

[0675] **실시예 11: SH-SY5Y 세포에서 인간 타우의 용량-의존적 안티센스 억제**

[0676] 타우 mRNA의 뚜렷한 *시험관내* 억제를 나타내는 상기 기술된 연구로부터의 갭머는 SH-SY5Y 세포에서의 다양한 용량에서 선택 및 시험되었다. 안티센스 올리고뉴클레오타이드는 유사한 배양 조건을 갖는 일련의 실험에서 시험되었다. 각 실험에 대한 결과는 하기 나타낸 개별 표에서 제시된다. 세포를 웰당 20,000 세포의 밀도로 플레이팅하고, 하기 표에 명시된 바와 같이 전기천공을 사용하여 0.938 μM, 0.1.875 μM, 3.750 μM, 7.500 μM, 및 15.00 μM 농도의 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 16 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한, 타우의 억제율로서 표현된다. 타우 mRNA 수준은 안티센스 올리고뉴클레오타이드 처리된 세포에서 용량-의존적 방식으로 뚜렷하게 감소되었다.

[0677] 표 40

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613369	57	67	81	91	96
613370	83	91	96	98	97
613371	68	78	95	95	97
613412	41	55	73	86	96
620887	53	76	90	93	95
621238	58	80	76	93	96
621251	68	77	87	89	90
621263	57	69	81	92	95
621302	46	66	80	78	87
621309	56	64	84	86	90
621311	38	54	69	77	86
621312	42	36	57	83	90
621318	40	54	71	87	87
621346	42	46	60	64	78
621870	42	62	76	85	92

[0678]

[0679] 표 41

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	14	45	68	84	92
620887	57	74	87	93	95
620888	63	78	76	94	96
620890	76	86	92	96	97
620891	67	79	91	96	96
620918	38	55	65	81	88
620940	38	52	73	89	96
620947	26	47	58	78	87
620958	32	38	61	79	93
621013	49	75	86	92	94
621049	38	45	68	78	80
621056	40	45	70	81	90
621078	23	28	48	67	84
621082	22	32	53	62	90
621088	26	43	59	80	92

[0680]

[0681] 표 42

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	17	45	62	84	89
620887	52	71	91	96	95
621147	28	37	59	69	84
621181	39	61	78	85	83
621183	31	43	64	72	87
621836	24	39	64	81	93
621838	33	59	70	91	97
621844	20	38	64	80	91
621845	30	37	62	72	90
621861	19	35	59	80	92
621869	30	56	64	83	91
622125	14	28	52	73	85
622129	26	36	60	71	84
622170	18	42	72	77	91
622196	11	39	59	74	89

[0682]

[0683] 표 43

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	21	42	64	82	95
620887	60	79	92	95	95
623746	19	43	54	81	91
623750	50	63	75	83	90
623758	37	54	72	80	82
623805	25	33	48	74	86
623807	15	29	44	75	88
623833	16	60	65	86	89
623860	51	71	80	85	85
623867	9	51	48	74	86
623874	24	28	72	84	94
623875	38	62	80	93	95
623876	40	63	83	93	95
623877	59	76	92	97	96
623878	50	73	90	94	95

[0684]

[0685] 표 44

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	8	25	58	77	87
620887	49	77	87	95	86
621360	27	46	68	83	90
621361	52	73	89	92	94
621363	28	45	71	76	77
621364	39	58	77	90	95
621407	38	60	75	82	78
621414	41	66	80	90	83
621424	54	72	87	94	90
621425	8	22	52	74	84
621426	33	46	63	84	91
621740	0	1	6	33	65
621793	4	15	30	41	52
621794	29	38	57	78	85
621810	15	39	45	73	79

[0686]

[0687] 표 45

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	40	72	78	92	94
620887	58	79	92	96	97
621431	62	63	79	85	87
621441	71	80	84	95	95
621446	53	70	82	89	94
621448	46	60	85	89	93
621454	63	70	81	89	94
621484	60	65	75	88	93
621570	26	55	81	79	90
621576	23	34	71	75	80
621578	30	45	67	81	90
621579	14	28	49	69	88
621598	38	55	73	88	94
621670	37	57	79	82	92
621675	31	35	51	79	87

[0688]

[0689] **표 46**

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	21	38	70	84	92
620887	50	63	83	91	96
621894	35	16	32	54	70
621895	23	48	61	82	89
621961	8	14	47	57	75
621983	33	52	63	72	83
621991	36	56	68	86	92
622001	8	33	60	77	90
622080	29	53	69	67	93
622088	20	45	66	84	91
622091	14	33	47	70	82
622110	25	24	64	80	90
622111	17	41	74	86	92
623747	12	47	53	82	87

[0690]

[0691] **표 47**

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	22	34	49	77	77
620887	51	68	83	94	95
623672	33	43	64	82	88
623697	37	53	59	80	90
623698	32	57	63	84	92
623708	47	68	82	88	95
623709	14	37	62	76	89
623712	22	45	70	86	92
623732	18	37	54	76	87
623756	23	38	68	86	94
623782	50	72	83	90	93
623791	58	71	87	93	95
623796	44	57	74	79	85
623808	30	55	73	84	91
623809	31	42	66	82	93

[0692]

[0693] **실시예 12: HepG2 세포에서의, 5-10-5 MOE, 5-8-5 MOE, 4-8-6 MOE, 또는 6-8-4 MOE 갭머에 의한 인간 타우 안티센스 억제**

[0694] 안티센스 올리고뉴클레오타이드는 타우 핵산을 표적화하도록 설계되었으며, 시험관내에서 타우 mRNA에 대한 그들의 효과에 대해서 시험되었다. 안티센스 올리고뉴클레오타이드는 유사한 배양 조건을 갖는 일련의 실험에서 시험되었다. ISIS 613412는 또한 검정에 포함되었다. 각 실험에 대한 결과는 하기 나타낸 개별 표에서 제시된다. 웰당 20,000 세포의 밀도로 배양된 HepG2 세포를 전기천공을 사용하여 8,000 nM 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 24 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한, 타우의 억제율로서 표현된다.

[0695] 하기 표에서 새롭게 설계된 키메라 안티센스 올리고뉴클레오타이드는 5-8-5 MOE, 4-8-6 MOE, 또는 6-8-4 MOE 갭머로서 설계되었다. 5-8-5 MOE 갭머는 길이가 18개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 8개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 4-8-6 MOE 갭머는 길이가 18개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 8개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 4개 및 6개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의

윙 분절에 의하여 플랭킹된다. 6-8-4 MOE 갭머는 길이가 18개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 8개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 6개 및 4개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 5' 윙 분절 내의 각각의 뉴클레오사이드 및 3' 윙 분절 내의 각각의 뉴클레오사이드는 2'-MOE 변형을 갖는다. 하기 표에서의 각각의 갭머에 대한 뉴클레오사이드간 연결 모티프는, ISIS 613412를 제외하고, 5'-sooosssssssssooss-3' 이며, 여기서 각 "s"는 포스포로티오에이트 뉴클레오사이드간 연결을 나타내고, 각 "o"는 포스포디에스테르 뉴클레오사이드간 연결을 나타낸다. ISIS 613412에 대한 뉴클레오사이드간 연결 모티프는 5'-soooosssssssssssooss-3' 이며, 여기서 각 "s"는 포스포로티오에이트 뉴클레오사이드간 연결을 나타내고, 각 "o"는 포스포디에스테르 뉴클레오사이드간 연결을 나타낸다. 각각의 갭머에서의 모든 시토신 잔기는 5-메틸시토신이다. "개시 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 5'-모스트(most) 뉴클레오사이드를 나타낸다. "정지 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 3'-모스트(most) 뉴클레오사이드를 나타낸다. 하기 표에 열거된 각각의 갭머는 본원에 개시된 서열 번호: 1과 같이 지정된 인간 타우 게놈 서열 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자 은행 수탁 번호 NT_010783.15)을 표적화한다.

[0696] **표 48**

[0697] 서열 번호: 1을 표적화하는 5-10-5 MOE 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	모티프	억제율%	서열 번호
613412	73879	73898	GTGATCTTCCATCACTTCGA	5-10-5	90	25
620887	98891	98908	GTTTTCAAACACACCTTC	5-10-5	93	665
	98928	98945				
623888	20951	20968	TTCGATTTGTTATTGGGA	5-10-5	79	2201
623889	20953	20970	ACTTCGATTTGTTATTGG	5-10-5	61	2202
623890	20954	20971	GACTTCGATTTGTTATTG	5-10-5	30	2203
623891	20955	20972	TGACTTCGATTTGTTATT	5-10-5	62	2204
623892	20956	20973	CTGACTTCGATTTGTTAT	5-10-5	60	2205
623893	20957	20974	GCTGACTTCGATTTGTTA	5-10-5	43	2206
623894	20958	20975	AGCTGACTTCGATTTGTT	5-10-5	83	2207
623895	20959	20976	CAGCTGACTTCGATTTGT	5-10-5	68	2208
623896	20961	20978	CCCAGCTGACTTCGATTT	5-10-5	11	2209
623897	20964	20981	ACGCCCAGCTGACTTCGA	5-10-5	65	2210
623898	27148	27165	TGCCTTATATATGCTGAA	5-10-5	82	2211
623899	27153	27170	TTACATGCCTTATATATG	5-10-5	31	2212
623900	27156	27173	CAGTTACATGCCTTATAT	5-10-5	33	2213
623901	27158	27175	TTCAGTTACATGCCTTAT	5-10-5	72	2214
623902	27159	27176	GTTCAGTTACATGCCTTA	5-10-5	92	2215
623903	27169	27186	AAAGTGCTGTGTTCAGTT	5-10-5	71	2216
623904	27174	27191	CCTCTAAAGTGCTGTGTT	5-10-5	35	2217
623905	28215	28232	GACTTTTCTCAATGTAAC	5-10-5	43	2218
623906	28220	28237	CTGCAGACTTTTCTCAAT	5-10-5	61	2219
623907	28226	28243	ACCTCTCTGCAGACTTTT	5-10-5	79	2220
623908	28227	28244	CACCTCTCTGCAGACTTT	5-10-5	81	2221
623909	28228	28245	GCACCTCTCTGCAGACTT	5-10-5	82	2222
623910	28229	28246	GGCACCTCTCTGCAGACT	5-10-5	81	2223
623911	28230	28247	TGGCACCTCTCTGCAGAC	5-10-5	36	2224
623912	28231	28248	CTGGCACCTCTCTGCAGA	5-10-5	11	2225
623913	28233	28250	TGCTGGCACCTCTCTGCA	5-10-5	51	2226
623914	28236	28253	TGATGCTGGCACCTCTCT	5-10-5	63	2227
623915	28241	28258	CCTTGTGATGCTGGCACC	5-10-5	79	2228
623916	75133	75150	TTTTTAGCATTAAAAGAG	5-10-5	0	2229
623917	75144	75161	GTGTTTTCTTATTTTTAG	5-10-5	80	2230
623918	75149	75166	GCAAGGTGTTTTCTTATT	5-10-5	55	2231
623919	86762	86779	TAGGCCTCTTCTGCATTT	5-10-5	27	2232

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623920	86767	86784	CTGGCTAGGCCTCTTCTG	5-10-5	54	2233
623921	86770	86787	ATCCTGGCTAGGCCTCTT	5-10-5	69	2234
623922	86772	86789	AAATCCTGGCTAGGCCTC	5-10-5	67	2235
623923	86773	86790	GAAATCCTGGCTAGGCCT	5-10-5	55	2236
623924	86774	86791	TGAAATCCTGGCTAGGCC	5-10-5	64	2237
623925	86775	86792	GTGAAATCCTGGCTAGGC	5-10-5	77	2238
623926	86776	86793	GGTGAAATCCTGGCTAGG	5-10-5	57	2239
623927	86777	86794	TGGTGAAATCCTGGCTAG	5-10-5	8	2240
623928	86778	86795	CTGGTGAAATCCTGGCTA	5-10-5	45	2241
623929	86780	86797	TGCTGGTGAAATCCTGGC	5-10-5	63	2242
623930	86783	86800	CACTGCTGGTGAAATCCT	5-10-5	70	2243
623931	121716	121733	ACCCTGGACCCGCCTACT	5-10-5	49	2244
623932	121721	121738	GCGCCACCCTGGACCCGC	5-10-5	84	2245
623933	121724	121741	CATGCGCCACCCTGGACC	5-10-5	52	2246
623934	121726	121743	GACATGCGCCACCCTGGA	5-10-5	80	2247
623935	121727	121744	TGACATGCGCCACCCTGG	5-10-5	74	2248
623936	121728	121745	GTGACATGCGCCACCCTG	5-10-5	90	2249
623937	121729	121746	AGTGACATGCGCCACCCT	5-10-5	84	2250
623938	121730	121747	GAGTGACATGCGCCACCC	5-10-5	92	2251
623939	121731	121748	TGAGTGACATGCGCCACC	5-10-5	86	2252
623940	121732	121749	ATGAGTGACATGCGCCAC	5-10-5	64	2253
623941	121734	121751	CGATGAGTGACATGCGCC	5-10-5	76	2254
623942	121737	121754	TTTCGATGAGTGACATGC	5-10-5	60	2255
623943	121742	121759	TCCACTTTCGATGAGTGA	5-10-5	34	2256
623944	121938	121955	CAGCACGGCGCATGGGAC	5-10-5	26	2257
623945	121939	121956	ACAGCACGGCGCATGGGA	5-10-5	62	2258
623946	121940	121957	CACAGCACGGCGCATGGG	5-10-5	57	2259
621455	121941	121958	CCACAGCACGGCGCATGG	5-10-5	44	1232
623804	121942	121959	GCCACAGCACGGCGCATG	5-10-5	85	1657
623947	121943	121960	AGCCACAGCACGGCGCAT	5-10-5	83	2260
623948	121944	121961	AAGCCACAGCACGGCGCA	5-10-5	56	2261
623949	121946	121963	TCAAGCCACAGCACGGCG	5-10-5	58	2262
623950	121949	121966	AATTCAAGCCACAGCACG	5-10-5	52	2263
623951	121954	121971	CTAATAATTCAAGCCACA	5-10-5	56	2264
623952	125424	125441	GACATTTGCTCAGCAAAC	5-10-5	74	2265
623953	125426	125443	CAGACATTTGCTCAGCAA	5-10-5	62	2266
623954	125427	125444	CCAGACATTTGCTCAGCA	5-10-5	75	2267
623955	125428	125445	CCCAGACATTTGCTCAGC	5-10-5	65	2268
623956	125429	125446	ACCCAGACATTTGCTCAG	5-10-5	30	2269
623957	125430	125447	GACCCAGACATTTGCTCA	5-10-5	30	2270
623958	125431	125448	AGACCCAGACATTTGCTC	5-10-5	41	2271
623959	125432	125449	AAGACCCAGACATTTGCT	5-10-5	69	2272
623960	125434	125451	GCAAGACCCAGACATTTG	5-10-5	73	2273

[0699]

623961	125437	125454	TGTGCAAGACCCAGACAT	5-10-5	62	2274
623962	125442	125459	GTCATTGTGCAAGACCCA	5-10-5	87	2275

[0700]

[0701] **표 49**

[0702] 서열 번호: 1을 표적화하는 5-10-5 MOE, 5-8-5 MOE, 4-8-6 MOE, 및 6-8-4 갭머에 의한 타우 mRNA의 억제

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	모티프	억제율%	서열 번호
613412	73879	73898	GTGATCTTCCATCACTTCGA	5-10-5	87	25
620887	98891	98908	GTTTTCAAACACACCTTC	5-8-5	96	665
	98928	98945				
620888	98881	98898	ACACCTTCATTTACTGTC	5-8-5	96	897
	98918	98935				
620889	98890	98907	TTTTCAAACACACCTTCA	5-8-5	85	898
	98927	98944				
620890	98892	98909	GGTTTTCAAACACACCTT	5-8-5	95	899
	98929	98946				
620891	98893	98910	TGGTTTTCAAACACACCT	5-8-5	96	900
	98930	98947				
623963	73877	73894	TCTTCCATCACTTCGAAC	5-8-5	58	2276
623964	73878	73895	ATCTTCCATCACTTCGAA	5-8-5	44	2277
623965	73880	73897	TGATCTTCCATCACTTCG	5-8-5	51	2278
623966	73881	73898	GTGATCTTCCATCACTTC	5-8-5	45	2279
623967	73931	73948	ATGGTGTAGCCCCCCTGA	5-8-5	66	2280
623968	73932	73949	CATGGTGTAGCCCCCCTG	5-8-5	87	2281
623969	73934	73951	TGCATGGTGTAGCCCCCC	5-8-5	94	2282
623970	73935	73952	GTGCATGGTGTAGCCCCC	5-8-5	90	2283
623971	73957	73974	CCGTGTCACCCTCTTGGT	5-8-5	83	2284
623972	73958	73975	TCCGTGTCACCCTCTTGG	5-8-5	79	2285
623973	73960	73977	CGTCCGTGTCACCCTCTT	5-8-5	92	2286
623974	83429	83446	TCTTAGCATCAGAGGTTT	5-8-5	70	2287
623975	83430	83447	CTCTTAGCATCAGAGGTT	5-8-5	76	2288
623976	83432	83449	TGCTCTTAGCATCAGAGG	5-8-5	72	2289
623977	83433	83450	GTGCTCTTAGCATCAGAG	5-8-5	86	2290
623978	95266	95283	CTCCTCCGAGTGCGCCTG	5-8-5	24	2291
623979	95267	95284	GCTCCTCCGAGTGCGCCT	5-8-5	77	2292
623980	95269	95286	ATGCTCCTCCGAGTGCGC	5-8-5	58	2293
623981	95270	95287	AATGCTCCTCCGAGTGCG	5-8-5	79	2294
623982	95272	95289	CAAATGCTCCTCCGAGTG	5-8-5	34	2295

[0703]

623983	98557	98574	TTACTGACCATGCGAGCT	5-8-5	79	2296
623984	98558	98575	TTTACTGACCATGCGAGC	5-8-5	73	2297
623985	98560	98577	CTTTTACTGACCATGCGA	5-8-5	85	2298
623986	98561	98578	GCTTTTACTGACCATGCG	5-8-5	91	2299
623987	98563	98580	TTGCTTTTACTGACCATG	5-8-5	96	2300
623988	135784	135801	ACTGCGAGGAGCAGCTGG	5-8-5	43	2301
623989	135785	135802	AACTGCGAGGAGCAGCTG	5-8-5	31	2302
623990	135787	135804	CGAACTGCGAGGAGCAGC	5-8-5	62	2303
623991	135788	135805	CCGAACTGCGAGGAGCAG	5-8-5	73	2304
623992	135790	135807	AACCGAACTGCGAGGAGC	5-8-5	73	2305
623993	135868	135885	TGCTCTTACTCCCATCAC	5-8-5	59	2306
623994	135869	135886	TTGCTCTTACTCCCATCA	5-8-5	85	2307
623995	135871	135888	ATTTGCTCTTACTCCCAT	5-8-5	77	2308
623996	135872	135889	AATTTGCTCTTACTCCCA	5-8-5	80	2309
625423	98879	98896	ACCTTCATTTACTGTCAG	5-8-5	90	2310
625424	98880	98897	CACCTTCATTTACTGTCA	5-8-5	94	2311
625425	98882	98899	CACACCTTCATTTACTGT	5-8-5	89	2312
	98919	98936		5-8-5		
625426	98883	98900	ACACACCTTCATTTACTG	5-8-5	87	2313
	98920	98937				
625427	98884	98901	AACACACCTTCATTTACT	5-8-5	86	2314
	98921	98938				
625428	98885	98902	AAACACACCTTCATTTAC	5-8-5	49	2315
	98922	98939				
625429	98886	98903	CAAACACACCTTCATTTA	5-8-5	66	2316
	98923	98940				
625430	98887	98904	TCAAACACACCTTCATTT	5-8-5	70	2317
	98924	98941				
625431	98888	98905	TTCAAACACACCTTCATT	5-8-5	74	2318
	98925	98942				
625432	98889	98906	TTTCAAACACACCTTCAT	5-8-5	81	2319
	98926	98943				
625433	98894	98911	TTGGTTTTCAAACACACC	5-8-5	92	2320
625434	75128	75145	AGCATTAAAAGAGAAAAG	5-8-5	13	2321
625435	75136	75153	TTATTTTTAGCATTAAAA	5-8-5	0	2322
625436	75138	75155	TCTTATTTTTAGCATTAA	5-8-5	52	2323
625437	75139	75156	TTCTTATTTTTAGCATTA	5-8-5	86	2324
625438	75140	75157	TTTCTTATTTTTAGCATT	5-8-5	40	2325

[0704]

625439	75141	75158	TTTTCTTATTTTTAGCAT	5-8-5	0	2326
625440	75142	75159	GTTTTCTTATTTTTAGCA	5-8-5	82	2327
625441	75143	75160	TGTTTTCTTATTTTTAGC	5-8-5	68	2328
625442	75146	75163	AGGTGTTTTCTTATTTTT	5-8-5	83	2329
625443	75154	75171	GGGCTGCAAGGTGTTTTC	5-8-5	69	2330
625444	98881	98898	ACACCTTCATTTACTGTC	4-8-6	90	897
	98918	98935				
625445	98882	98899	CACACCTTCATTTACTGT	4-8-6	82	2312
	98919	98936				
625446	98883	98900	ACACACCTTCATTTACTG	4-8-6	84	2313
	98920	98937				
625447	98884	98901	AACACACCTTCATTTACT	4-8-6	40	2314
	98921	98938				
625448	98889	98906	TTTCAAACACACCTTCAT	4-8-6	83	2319
	98926	98943				
625449	98890	98907	TTTTCAAACACACCTTCA	4-8-6	0	898
	98927	98944				
625450	98891	98908	GTTTTCAAACACACCTTC	4-8-6	94	665
	98928	98945				
625451	98892	98909	GGTTTTCAAACACACCTT	4-8-6	94	899
	98929	98946				
625452	98893	98910	TGGTTTTCAAACACACCT	4-8-6	94	900
	98930	98947				
625453	98881	98898	ACACCTTCATTTACTGTC	6-8-4	96	897
	98918	98935				
625454	98882	98899	CACACCTTCATTTACTGT	6-8-4	96	2312
	98919	98936				
625455	98883	98900	ACACACCTTCATTTACTG	6-8-4	93	2313
	98920	98937				
625456	98884	98901	AACACACCTTCATTTACT	6-8-4	88	2314
	98921	98938				
625457	98889	98906	TTTCAAACACACCTTCAT	6-8-4	85	2319
	98926	98943				
625458	98890	98907	TTTTCAAACACACCTTCA	6-8-4	90	898
	98927	98944				
625459	98891	98908	GTTTTCAAACACACCTTC	6-8-4	97	665
	98928	98945				
625460	98892	98909	GGTTTTCAAACACACCTT	6-8-4	97	899

[0705]

	98929	98946				
625461	98893	98910	TGGTTTTCAAACACACCT	6-8-4	96	900
	98930	98947				

[0706]

[0707] **실시예 13: SH-SY5Y MOE 갭머에 의한 인간 타우의 용량-의존적 안티센스 억제**

[0708] 타우 mRNA의 뚜렷한 *시험관내* 억제를 나타내는 상기 기술된 연구로부터의 갭머는 SH-SY5Y 세포에서의 다양한 용량에서 선택 및 시험되었다. 안티센스 올리고뉴클레오타이드는 유사한 배양 조건을 갖는 일련의 실험에서 시험되었다. 각 실험에 대한 결과는 하기 나타낸 개별 표에서 제시된다. 세포를 웰당 20,000 세포의 밀도로 플레이팅하고, 하기 표에 명시된 바와 같이 전기천공을 사용하여 0.938 μM, 0.1.875 μM, 3.750 μM, 7.500 μM, 및 15.00 μM 농도의 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 16 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와

같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한, 타우의 억제율로서 표현된다. 타우 mRNA 수준은 안티센스 올리고뉴클레오타이드 처리된 세포에서 용량-의존적 방식으로 뚜렷하게 감소되었다.

[0709] **표 50**

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	57	53	49	83	91
620887	68	84	95	95	97
620919	35	54	76	95	96
620930	32	49	76	86	92
620946	41	61	73	90	92
620971	61	63	75	88	96
620976	40	68	80	91	96
620978	49	49	78	93	94
620988	64	58	76	92	95
621031	51	72	90	89	92
621032	35	55	81	89	96
621041	48	73	80	88	95
621236	62	59	78	86	88
621239	46	62	63	94	94
621254	63	67	88	84	87

[0710]

[0711] **표 51**

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	33	54	63	89	95
620887	72	90	95	96	96
620889	20	45	72	87	95
621417	52	68	81	88	92
621434	45	64	69	84	76
621440	58	72	77	88	87
621492	40	60	80	78	83
621599	43	73	83	91	95
621615	36	67	74	81	87
621620	48	74	88	95	98
621644	4	28	33	55	65
623685	30	48	73	87	93
623872	31	61	80	90	94
623879	22	50	74	88	95
623932	39	62	80	91	95

[0712]

[0713] 표 52

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	23	51	50	87	94
620887	64	82	92	95	96
620891	79	89	93	96	96
623757	38	58	73	85	95
623783	30	40	67	78	91
623804	51	70	81	87	92
623902	62	77	90	87	95
623936	46	70	84	91	94
623937	48	58	79	91	93
623938	39	63	76	90	93
623939	29	57	77	91	93
623962	44	68	78	87	91
625442	32	57	66	82	88
625459	74	87	95	96	98
625460	88	94	97	97	98

[0714]

[0715] 표 53

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	6	11	20	0	35
620887	71	86	92	95	96
620888	73	89	93	95	96
620890	82	90	94	95	96
623969	41	62	84	94	n.d.
623987	46	71	89	96	97
625424	50	73	88	94	96
625433	64	83	90	95	95
625450	69	84	91	96	97
625451	85	91	95	93	95
625452	67	83	91	93	95
625453	72	85	91	94	96
625454	73	86	93	95	96
625455	44	68	86	92	94
625461	75	84	94	95	97

[0716]

[0717] 표 54

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	11	30	65	82	83
620887	59	77	66	95	79
623968	43	57	72	86	93
623970	29	54	77	88	94
623973	48	65	80	93	94
623977	38	60	72	82	89
623986	45	53	80	91	96
625423	43	57	75	77	95
625425	39	49	78	88	93
625426	15	43	61	82	92
625427	16	35	64	81	93
625437	30	45	64	84	91
625444	28	45	67	84	92
625446	16	33	58	76	92
625456	27	43	57	86	91
625458	19	45	61	85	93

[0718]

[0719] 표 55

ISIS 번호	0.938 μM	1.875 μM	3.750 μM	7.500 μM	15.00 μM
613412	0	10	31	71	77
620887	33	58	74	82	92
621842	7	31	45	72	87
621846	0	0	28	62	90
623903	0	0	25	71	83
623985	0	17	41	74	84
623994	19	42	67	81	83
625457	0	5	57	69	80

[0720]

[0721] **실시예 14: 인간 타우 빈발 영역에서의 포스포로티오에이트 및 포스포디에스테르 뉴클레오사이드간 연결을 갖는 5-7-6 MOE, 5-8-5 MOE, 5-9-5 MOE, 및 5-10-5 MOE 갭머의 설계**

[0722] 안티센스 올리고뉴클레오타이드는 상기 연구에서 '빈발(hotspot)'로 식별된 영역에서 인간 타우 핵산을 표적화하도록 설계되었다.

[0723] 하기 표에서 새롭게 설계된 키메라 안티센스 올리고뉴클레오타이드는 5-7-6 MOE, 5-8-5 MOE, 5-9-5 MOE, 또는 5-10-5 MOE로서 설계되었다. 5-7-6 MOE 갭머는 길이가 18개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 7개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5개 및 6개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 5-8-5 MOE 갭머는 길이가 18개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 8개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 5-9-5 MOE 갭머는 길이가 19개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 9개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 5-10-5 MOE 갭머는 길이가 20개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 10개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 5' 윙 분절 내의 각각의 뉴클레오사이드 및 3' 윙 분절 내의 각각의 뉴클레오사이드는 2'-MOE 변형을 갖는다. 각각의 갭머에서의 뉴클레오사이드간 연결은 포스포로티오에이트 연결 또는 포스포디에스테르 연결이다. '화학' 칼럼은 각 올리고뉴클로타이드의 뉴클레오사이드간 연결을 개시한다. 's'는 포스포로티오에이트 연결을 , 'o'는 포스포디에스테르 연결을 나타낸다. 각각의 갭머에서의 모든 시토신 잔기는 5-메틸시토신이다.

[0724] "개시 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 5'-모스트(most) 뉴클레오사이드를 나타낸다. "정지 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 3'-모스트 뉴클레오사이드를 나타낸다. 하기 표에

열거된 각각의 갭머는 본원에 개시된 서열 번호: 1과 같이 지정된 인간 타우 게놈 서열 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자은행 수탁 번호 NT_010783.15) 또는 서열 번호: 2와 같이 지정된 인간 타우 mRNA 서열 (유전자은행 수탁 번호 NM_001123066.3)에 표적화된다. 'n/a'는 안티센스 올리고뉴클레오타이드가 100% 상보성을 갖는 특정 유전자 서열을 표적화하지 않는다는 것이다.

[0725] **표 56**

[0726] 서열 번호: 1 및 2를 표적화하는 MOE 갭머

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	결합 화학성질	모티프	서열 번호
664511	135820	135837	GACAAAAGCAGGTTAAGT	2783	2800	sooossssssssssooss	5-8-5	2331
664714	135820	135838	TGACAAAAGCAGGTTAAGT	2783	2801	sooossssssssssooss	5-9-5	2332

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664661	135820	135839	GTGACAAAAGCAGGTTAAGT	2783	2802	sooossssssssssooss	5-10-5	2333
664767	135820	135837	GACAAAAGCAGGTTAAGT	2783	2800	sooossssssssooss	5-7-6	2331
664512	135821	135838	TGACAAAAGCAGGTTAAG	2784	2801	sooossssssssooss	5-8-5	2334
664715	135821	135839	GTGACAAAAGCAGGTTAAG	2784	2802	sooossssssssooss	5-9-5	2335
664662	135821	135840	AGTGACAAAAGCAGGTTAAG	2784	2803	sooossssssssssooss	5-10-5	2336
664768	135821	135838	TGACAAAAGCAGGTTAAG	2784	2801	sooossssssssooss	5-7-6	2334
622109	135822	135839	GTGACAAAAGCAGGTTAA	2785	2802	sooossssssssooss	5-8-5	2038
664716	135822	135840	AGTGACAAAAGCAGGTTAA	2785	2803	sooossssssssooss	5-9-5	2337
664663	135822	135841	GAGTGACAAAAGCAGGTTAA	2785	2804	sooossssssssssooss	5-10-5	2338
664769	135822	135839	GTGACAAAAGCAGGTTAA	2785	2802	sooossssssssooss	5-7-6	2038
664513	135823	135840	AGTGACAAAAGCAGGTTA	2786	2803	sooossssssssooss	5-8-5	2339
664717	135823	135841	GAGTGACAAAAGCAGGTTA	2786	2804	sooossssssssooss	5-9-5	2340
664664	135823	135842	CGAGTGACAAAAGCAGGTTA	2786	2805	sooossssssssssooss	5-10-5	2341
664770	135823	135840	AGTGACAAAAGCAGGTTA	2786	2803	sooossssssssooss	5-7-6	2339
664514	135824	135841	GAGTGACAAAAGCAGGTT	2787	2804	sooossssssssooss	5-8-5	2342
664718	135824	135842	CGAGTGACAAAAGCAGGTT	2787	2805	sooossssssssooss	5-9-5	2343
664665	135824	135843	CCGAGTGACAAAAGCAGGTT	2787	2806	sooossssssssssooss	5-10-5	2344
664771	135824	135841	GAGTGACAAAAGCAGGTT	2787	2804	sooossssssssooss	5-7-6	2342
622110	135825	135842	CGAGTGACAAAAGCAGGT	2788	2805	sooossssssssooss	5-8-5	2039
664719	135825	135843	CCGAGTGACAAAAGCAGGT	2788	2806	sooossssssssooss	5-9-5	2345
664666	135825	135844	GCCGAGTGACAAAAGCAGGT	2788	2807	sooossssssssssooss	5-10-5	2346
664772	135825	135842	CGAGTGACAAAAGCAGGT	2788	2805	sooossssssssooss	5-7-6	2039
664515	135826	135843	CCGAGTGACAAAAGCAGG	2789	2806	sooossssssssooss	5-8-5	2347
664720	135826	135844	GCCGAGTGACAAAAGCAGG	2789	2807	sooossssssssooss	5-9-5	2348
664667	135826	135845	AGCCGAGTGACAAAAGCAGG	2789	2808	sooossssssssssooss	5-10-5	2349
664773	135826	135843	CCGAGTGACAAAAGCAGG	2789	2806	sooossssssssooss	5-7-6	2347
664516	135827	135844	GCCGAGTGACAAAAGCAG	2790	2807	sooossssssssooss	5-8-5	2350
664721	135827	135845	AGCCGAGTGACAAAAGCAG	2790	2808	sooossssssssooss	5-9-5	2351
664668	135827	135846	AAGCCGAGTGACAAAAGCAG	2790	2809	sooossssssssssooss	5-10-5	2352
664774	135827	135844	GCCGAGTGACAAAAGCAG	2790	2807	sooossssssssooss	5-7-6	2350
622111	135828	135845	AGCCGAGTGACAAAAGCA	2791	2808	sooossssssssooss	5-8-5	2040
664722	135828	135846	AAGCCGAGTGACAAAAGCA	2791	2809	sooossssssssooss	5-9-5	2353
664669	135828	135847	AAAGCCGAGTGACAAAAGCA	2791	2810	sooossssssssssooss	5-10-5	2354
664775	135828	135845	AGCCGAGTGACAAAAGCA	2791	2808	sooossssssssooss	5-7-6	2040
664517	135829	135846	AAGCCGAGTGACAAAAGC	2792	2809	sooossssssssooss	5-8-5	2355
664723	135829	135847	AAAGCCGAGTGACAAAAGC	2792	2810	sooossssssssooss	5-9-5	2356
664670	135829	135848	CAAAGCCGAGTGACAAAAGC	2792	2811	sooossssssssssooss	5-10-5	2357

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664776	135829	135846	AAGCCGAGTGACAAAAGC	2792	2809	sooossssssssoooss	5-7-6	2355
664518	135830	135847	AAAGCCGAGTGACAAAAG	2793	2810	sooossssssssooss	5-8-5	2358
664724	135830	135848	CAAAGCCGAGTGACAAAAG	2793	2811	sooossssssssooss	5-9-5	2359
664671	135830	135849	CCAAAGCCGAGTGACAAAAG	2793	2812	sooossssssssssooss	5-10-5	2360
664777	135830	135847	AAAGCCGAGTGACAAAAG	2793	2810	sooossssssssooss	5-7-6	2358
622112	135831	135848	CAAAGCCGAGTGACAAAA	2794	2811	sooossssssssooss	5-8-5	2041
664725	135831	135849	CCAAAGCCGAGTGACAAAA	2794	2812	sooossssssssooss	5-9-5	2361
664672	135831	135850	GCCAAAGCCGAGTGACAAAA	2794	2813	sooossssssssssooss	5-10-5	2362
664778	135831	135848	CAAAGCCGAGTGACAAAA	2794	2811	sooossssssssooss	5-7-6	2041
664519	135832	135849	CCAAAGCCGAGTGACAAA	2795	2812	sooossssssssooss	5-8-5	2363
664726	135832	135850	GCCAAAGCCGAGTGACAAA	2795	2813	sooossssssssooss	5-9-5	2364
664673	135832	135851	AGCCAAAGCCGAGTGACAAA	2795	2814	sooossssssssssooss	5-10-5	2365
664779	135832	135849	CCAAAGCCGAGTGACAAA	2795	2812	sooossssssssooss	5-7-6	2363
664520	135833	135850	GCCAAAGCCGAGTGACAA	2796	2813	sooossssssssooss	5-8-5	2366
664727	135833	135851	AGCCAAAGCCGAGTGACAA	2796	2814	sooossssssssooss	5-9-5	2367
664674	135833	135852	GAGCCAAAGCCGAGTGACAA	2796	2815	sooossssssssssooss	5-10-5	2368
664780	135833	135850	GCCAAAGCCGAGTGACAA	2796	2813	sooossssssssooss	5-7-6	2366
622113	135834	135851	AGCCAAAGCCGAGTGACA	2797	2814	sooossssssssooss	5-8-5	2042
664728	135834	135852	GAGCCAAAGCCGAGTGACA	2797	2815	sooossssssssooss	5-9-5	2369
664675	135834	135853	CGAGCCAAAGCCGAGTGACA	2797	2816	sooossssssssssooss	5-10-5	2419
664781	135834	135851	AGCCAAAGCCGAGTGACA	2797	2814	sooossssssssooss	5-7-6	2042
664521	135835	135852	GAGCCAAAGCCGAGTGAC	2798	2815	sooossssssssooss	5-8-5	2420
664729	135835	135853	CGAGCCAAAGCCGAGTGAC	2798	2816	sooossssssssooss	5-9-5	2421
664676	135835	135854	CCGAGCCAAAGCCGAGTGAC	2798	2817	sooossssssssssooss	5-10-5	2422
664782	135835	135852	GAGCCAAAGCCGAGTGAC	2798	2815	sooossssssssooss	5-7-6	2420
664522	135836	135853	CGAGCCAAAGCCGAGTGA	2799	2816	sooossssssssooss	5-8-5	2423
664730	135836	135854	CCGAGCCAAAGCCGAGTGA	2799	2817	sooossssssssooss	5-9-5	2424
664677	135836	135855	CCCGAGCCAAAGCCGAGTGA	2799	2818	sooossssssssssooss	5-10-5	2425
664783	135836	135853	CGAGCCAAAGCCGAGTGA	2799	2816	sooossssssssooss	5-7-6	2423
622114	135837	135854	CCGAGCCAAAGCCGAGTG	2800	2817	sooossssssssooss	5-8-5	2043
664731	135837	135855	CCCGAGCCAAAGCCGAGTG	2800	2818	sooossssssssooss	5-9-5	2426
664678	135837	135856	TCCCGAGCCAAAGCCGAGTG	2800	2819	sooossssssssssooss	5-10-5	2427
664784	135837	135854	CCGAGCCAAAGCCGAGTG	2800	2817	sooossssssssooss	5-7-6	2043
664523	135838	135855	CCCGAGCCAAAGCCGAGT	2801	2818	sooossssssssooss	5-8-5	2428
664732	135838	135856	TCCCGAGCCAAAGCCGAGT	2801	2819	sooossssssssooss	5-9-5	2429
664679	135838	135857	GTCCCGAGCCAAAGCCGAGT	2801	2820	sooossssssssssooss	5-10-5	2430
664785	135838	135855	CCCGAGCCAAAGCCGAGT	2801	2818	sooossssssssooss	5-7-6	2428

[0729]

664524	135839	135856	TCCCGAGCCAAAGCCGAG	2802	2819	sooossssssssooss	5-8-5	2431
664733	135839	135857	GTCCCGAGCCAAAGCCGAG	2802	2820	sooossssssssooss	5-9-5	2432
664680	135839	135858	AGTCCCGAGCCAAAGCCGAG	2802	2821	sooossssssssooss	5-10-5	2433
664786	135839	135856	TCCCGAGCCAAAGCCGAG	2802	2819	sooossssssssooss	5-7-6	2431
622115	135840	135857	GTCCCGAGCCAAAGCCGA	2803	2820	sooossssssssooss	5-8-5	2044
664734	135840	135858	AGTCCCGAGCCAAAGCCGA	2803	2821	sooossssssssooss	5-9-5	2434
664681	135840	135859	AAGTCCCGAGCCAAAGCCGA	2803	2822	sooossssssssooss	5-10-5	2435
664787	135840	135857	GTCCCGAGCCAAAGCCGA	2803	2820	sooossssssssooss	5-7-6	2044
664525	135841	135858	AGTCCCGAGCCAAAGCCG	2804	2821	sooossssssssooss	5-8-5	2436
664735	135841	135859	AAGTCCCGAGCCAAAGCCG	2804	2822	sooossssssssooss	5-9-5	2437
664682	135841	135860	GAAGTCCCGAGCCAAAGCCG	2804	2823	sooossssssssooss	5-10-5	2438
664788	135841	135858	AGTCCCGAGCCAAAGCCG	2804	2821	sooossssssssooss	5-7-6	2436
664526	135842	135859	AAGTCCCGAGCCAAAGCC	2805	2822	sooossssssssooss	5-8-5	2439
664736	135842	135860	GAAGTCCCGAGCCAAAGCC	2805	2823	sooossssssssooss	5-9-5	2440
664683	135842	135861	TGAAGTCCCGAGCCAAAGCC	2805	2824	sooossssssssooss	5-10-5	2441
664789	135842	135859	AAGTCCCGAGCCAAAGCC	2805	2822	sooossssssssooss	5-7-6	2439
622116	135843	135860	GAAGTCCCGAGCCAAAGC	2806	2823	sooossssssssooss	5-8-5	2045
664737	135843	135861	TGAAGTCCCGAGCCAAAGC	2806	2824	sooossssssssooss	5-9-5	2442
664684	135843	135862	TTGAAGTCCCGAGCCAAAGC	2806	2825	sooossssssssooss	5-10-5	2443
664790	135843	135860	GAAGTCCCGAGCCAAAGC	2806	2823	sooossssssssooss	5-7-6	2045
664527	135844	135861	TGAAGTCCCGAGCCAAAG	2807	2824	sooossssssssooss	5-8-5	2478
664738	135844	135862	TTGAAGTCCCGAGCCAAAG	2807	2825	sooossssssssooss	5-9-5	2532
664685	135844	135863	TTTGAAGTCCCGAGCCAAAG	2807	2826	sooossssssssooss	5-10-5	2533
664791	135844	135861	TGAAGTCCCGAGCCAAAG	2807	2824	sooossssssssooss	5-7-6	2478
664528	135845	135862	TTGAAGTCCCGAGCCAAA	2808	2825	sooossssssssooss	5-8-5	2479
664739	135845	135863	TTTGAAGTCCCGAGCCAAA	2808	2826	sooossssssssooss	5-9-5	2534
664686	135845	135864	TTTTGAAGTCCCGAGCCAAA	2808	2827	sooossssssssooss	5-10-5	2535
664792	135845	135862	TTGAAGTCCCGAGCCAAA	2808	2825	sooossssssssooss	5-7-6	2479
622117	135846	135863	TTTGAAGTCCCGAGCCAA	2809	2826	sooossssssssooss	5-8-5	2046
664740	135846	135864	TTTTGAAGTCCCGAGCCAA	2809	2827	sooossssssssooss	5-9-5	2536
664687	135846	135865	ATTTTGAAGTCCCGAGCCAA	2809	2828	sooossssssssooss	5-10-5	2537
664793	135846	135863	TTTGAAGTCCCGAGCCAA	2809	2826	sooossssssssooss	5-7-6	2538
664529	135847	135864	TTTTGAAGTCCCGAGCCA	2810	2827	sooossssssssooss	5-8-5	2480
664741	135847	135865	ATTTTGAAGTCCCGAGCCA	2810	2828	sooossssssssooss	5-9-5	2539
664688	135847	135866	GATTTTGAAGTCCCGAGCCA	2810	2829	sooossssssssooss	5-10-5	2540
664794	135847	135864	TTTTGAAGTCCCGAGCCA	2810	2827	sooossssssssooss	5-7-6	2480
664530	135848	135865	ATTTTGAAGTCCCGAGCC	2811	2828	sooossssssssooss	5-8-5	2481

[0730]

664742	135848	135866	GATTTTGAAGTCCCGAGCC	2811	2829	sooossssssssssooss	5-9-5	2541
664689	135848	135867	TGATTTTGAAGTCCCGAGCC	1644	1663	sooossssssssssooss	5-10-5	56
664795	135848	135865	ATTTTGAAGTCCCGAGCC	2811	2828	sooossssssssooss	5-7-6	2481
622118	135849	135866	GATTTTGAAGTCCCGAGC	2812	2829	sooossssssssooss	5-8-5	2047
664743	135849	135867	TGATTTTGAAGTCCCGAGC	2812	2830	sooossssssssssooss	5-9-5	2542
664690	135849	135868	CTGATTTTGAAGTCCCGAGC	2812	2831	sooossssssssssooss	5-10-5	464
664796	135849	135866	GATTTTGAAGTCCCGAGC	2812	2829	sooossssssssooss	5-7-6	2047
664531	135850	135867	TGATTTTGAAGTCCCGAG	2813	2830	sooossssssssooss	5-8-5	2482
664744	135850	135868	CTGATTTTGAAGTCCCGAG	2813	2831	sooossssssssssooss	5-9-5	2543
664691	135850	135869	ACTGATTTTGAAGTCCCGAG	2813	2832	sooossssssssssooss	5-10-5	2544
664797	135850	135867	TGATTTTGAAGTCCCGAG	2813	2830	sooossssssssooss	5-7-6	2482
664532	135851	135868	CTGATTTTGAAGTCCCGA	2814	2831	sooossssssssooss	5-8-5	2483
664745	135851	135869	ACTGATTTTGAAGTCCCGA	2814	2832	sooossssssssooss	5-9-5	2545
664692	135851	135870	CACTGATTTTGAAGTCCCGA	2814	2833	sooossssssssssooss	5-10-5	2546
664798	135851	135868	CTGATTTTGAAGTCCCGA	2814	2831	sooossssssssooss	5-7-6	2483
622119	135852	135869	ACTGATTTTGAAGTCCCG	2815	2832	sooossssssssooss	5-8-5	2048
664746	135852	135870	CACTGATTTTGAAGTCCCG	2815	2833	sooossssssssooss	5-9-5	2547
664693	135852	135871	TCACTGATTTTGAAGTCCCG	2815	2834	sooossssssssssooss	5-10-5	2548
664799	135852	135869	ACTGATTTTGAAGTCCCG	2815	2832	sooossssssssooss	5-7-6	2549
664533	135853	135870	CACTGATTTTGAAGTCCC	2816	2833	sooossssssssooss	5-8-5	2370
664747	135853	135871	TCACTGATTTTGAAGTCCC	2816	2834	sooossssssssooss	5-9-5	2371
664694	135853	135872	ATCACTGATTTTGAAGTCCC	1649	1668	sooossssssssssooss	5-10-5	57
664800	135853	135870	CACTGATTTTGAAGTCCC	2816	2833	sooossssssssooss	5-7-6	2370
664534	135854	135871	TCACTGATTTTGAAGTCC	2817	2834	sooossssssssooss	5-8-5	2372
664748	135854	135872	ATCACTGATTTTGAAGTCC	2817	2835	sooossssssssooss	5-9-5	2373
664695	135854	135873	CATCACTGATTTTGAAGTCC	2817	2836	sooossssssssssooss	5-10-5	2374
664801	135854	135871	TCACTGATTTTGAAGTCC	2817	2834	sooossssssssooss	5-7-6	2372
622120	135855	135872	ATCACTGATTTTGAAGTC	2818	2835	sooossssssssooss	5-8-5	1668
664749	135855	135873	CATCACTGATTTTGAAGTC	2818	2836	sooossssssssooss	5-9-5	2375
664696	135855	135874	CCATCACTGATTTTGAAGTC	2818	2837	sooossssssssssooss	5-10-5	2376
664802	135855	135872	ATCACTGATTTTGAAGTC	2818	2835	sooossssssssooss	5-7-6	1668
664535	135856	135873	CATCACTGATTTTGAAGT	2819	2836	sooossssssssooss	5-8-5	2377
664750	135856	135874	CCATCACTGATTTTGAAGT	2819	2837	sooossssssssooss	5-9-5	2378
664697	135856	135875	CCCATCACTGATTTTGAAGT	2819	2838	sooossssssssssooss	5-10-5	2379
664803	135856	135873	CATCACTGATTTTGAAGT	2819	2836	sooossssssssooss	5-7-6	2377
664536	135857	135874	CCATCACTGATTTTGAAG	2820	2837	sooossssssssooss	5-8-5	2380
664751	135857	135875	CCCATCACTGATTTTGAAG	2820	2838	sooossssssssooss	5-9-5	2381

[0731]

664698	135857	135876	TCCCATCACTGATTTTGAAG	2820	2839	sooossssssssssooss	5-10-5	2382
664804	135857	135874	CCATCACTGATTTTGAAG	2820	2837	sooossssssssoooss	5-7-6	2380
622121	135858	135875	CCCATCACTGATTTTGAA	2821	2838	sooossssssssooss	5-8-5	1669
664752	135858	135876	TCCCATCACTGATTTTGAA	2821	2839	sooossssssssooss	5-9-5	2383
664699	135858	135877	CTCCCATCACTGATTTTGAA	2821	2840	sooossssssssssooss	5-10-5	2384
664805	135858	135875	CCCATCACTGATTTTGAA	2821	2838	sooossssssssoooss	5-7-6	1669
664537	135859	135876	TCCCATCACTGATTTTGA	2822	2839	sooossssssssooss	5-8-5	2385
664753	135859	135877	CTCCCATCACTGATTTTGA	2822	2840	sooossssssssooss	5-9-5	2386
664700	135859	135878	ACTCCCATCACTGATTTTGA	2822	2841	sooossssssssssooss	5-10-5	2387
664806	135859	135876	TCCCATCACTGATTTTGA	2822	2839	sooossssssssooooss	5-7-6	2385
664538	135860	135877	CTCCCATCACTGATTTTG	2823	2840	sooossssssssooss	5-8-5	2388
664754	135860	135878	ACTCCCATCACTGATTTTG	2823	2841	sooossssssssooss	5-9-5	2389
664701	135860	135879	TACTCCCATCACTGATTTTG	2823	2842	sooossssssssssooss	5-10-5	2390
664807	135860	135877	CTCCCATCACTGATTTTG	2823	2840	sooossssssssooooss	5-7-6	2388
622122	135861	135878	ACTCCCATCACTGATTTT	2824	2841	sooossssssssooss	5-8-5	1670
664755	135861	135879	TACTCCCATCACTGATTTT	2824	2842	sooossssssssooss	5-9-5	2391
664702	135861	135880	TTACTCCCATCACTGATTTT	2824	2843	sooossssssssssooss	5-10-5	2392
664808	135861	135878	ACTCCCATCACTGATTTT	2824	2841	sooossssssssooooss	5-7-6	1670
664539	135862	135879	TACTCCCATCACTGATTT	2825	2842	sooossssssssooss	5-8-5	2393
664756	135862	135880	TTACTCCCATCACTGATTT	2825	2843	sooossssssssooss	5-9-5	2394
664703	135862	135881	CTTACTCCCATCACTGATTT	2825	2844	sooossssssssssooss	5-10-5	2395
664809	135862	135879	TACTCCCATCACTGATTT	2825	2842	sooossssssssooooss	5-7-6	2393
664540	135863	135880	TTACTCCCATCACTGATT	2826	2843	sooossssssssooss	5-8-5	2396
664757	135863	135881	CTTACTCCCATCACTGATT	2826	2844	sooossssssssooss	5-9-5	2397
664704	135863	135882	TCTTACTCCCATCACTGATT	2826	2845	sooossssssssssooss	5-10-5	2398
664810	135863	135880	TTACTCCCATCACTGATT	2826	2843	sooossssssssooooss	5-7-6	2396
622123	135864	135881	CTTACTCCCATCACTGAT	2827	2844	sooossssssssooss	5-8-5	1671
664758	135864	135882	TCTTACTCCCATCACTGAT	2827	2845	sooossssssssooss	5-9-5	2399
664705	135864	135883	CTCTTACTCCCATCACTGAT	2827	2846	sooossssssssssooss	5-10-5	2400
664811	135864	135881	CTTACTCCCATCACTGAT	2827	2844	sooossssssssooooss	5-7-6	1671
664541	135865	135882	TCTTACTCCCATCACTGA	2828	2845	sooossssssssooss	5-8-5	2401
664759	135865	135883	CTCTTACTCCCATCACTGA	2828	2846	sooossssssssooss	5-9-5	2402
664706	135865	135884	GCTCTTACTCCCATCACTGA	2828	2847	sooossssssssssooss	5-10-5	2403
664812	135865	135882	TCTTACTCCCATCACTGA	2828	2845	sooossssssssooooss	5-7-6	2401
664542	135866	135883	CTCTTACTCCCATCACTG	2829	2846	sooossssssssooss	5-8-5	2404
664760	135866	135884	GCTCTTACTCCCATCACTG	2829	2847	sooossssssssooss	5-9-5	2405
664707	135866	135885	TGCTCTTACTCCCATCACTG	2829	2848	sooossssssssssooss	5-10-5	2406

[0732]

664813	135866	135883	CTCTTACTCCCATCACTG	2829	2846	sooossssssssoooss	5-7-6	2404
622124	135867	135884	GCTCTTACTCCCATCACT	2830	2847	sooossssssssooss	5-8-5	1672
664761	135867	135885	TGCTCTTACTCCCATCACT	2830	2848	sooossssssssooss	5-9-5	2407
664708	135867	135886	TTGCTCTTACTCCCATCACT	2830	2849	sooossssssssssooss	5-10-5	2408
664814	135867	135884	GCTCTTACTCCCATCACT	2830	2847	sooossssssssooss	5-7-6	1672
623993	135868	135885	TGCTCTTACTCCCATCAC	2831	2848	sooossssssssooss	5-8-5	2306
664762	135868	135886	TTGCTCTTACTCCCATCAC	2831	2849	sooossssssssooss	5-9-5	2409
664709	135868	135887	TTTGCTCTTACTCCCATCAC	2831	2850	sooossssssssssooss	5-10-5	2410
664815	135868	135885	TGCTCTTACTCCCATCAC	2831	2848	sooossssssssooss	5-7-6	2306
623994	135869	135886	TTGCTCTTACTCCCATCA	2832	2849	sooossssssssooss	5-8-5	2307
664763	135869	135887	TTTGCTCTTACTCCCATCA	2832	2850	sooossssssssooss	5-9-5	2411
664710	135869	135888	ATTTGCTCTTACTCCCATCA	2832	2851	sooossssssssssooss	5-10-5	2412
664816	135869	135886	TTGCTCTTACTCCCATCA	2832	2849	sooossssssssooss	5-7-6	2307
622125	135870	135887	TTTGCTCTTACTCCCATC	2833	2850	sooossssssssooss	5-8-5	1673
664764	135870	135888	ATTTGCTCTTACTCCCATC	2833	2851	sooossssssssooss	5-9-5	2413
664711	135870	135889	AATTTGCTCTTACTCCCATC	2833	2852	sooossssssssssooss	5-10-5	2414
664817	135870	135887	TTTGCTCTTACTCCCATC	2833	2850	sooossssssssooss	5-7-6	1673
623995	135871	135888	ATTTGCTCTTACTCCCAT	2834	2851	sooossssssssooss	5-8-5	2308
664765	135871	135889	AATTTGCTCTTACTCCCAT	2834	2852	sooossssssssooss	5-9-5	2415
664712	135871	135890	AAATTTGCTCTTACTCCCAT	2834	2853	sooossssssssssooss	5-10-5	2416
664818	135871	135888	ATTTGCTCTTACTCCCAT	2834	2851	sooossssssssooss	5-7-6	2308
623996	135872	135889	AATTTGCTCTTACTCCCA	2835	2852	sooossssssssooss	5-8-5	2309
664766	135872	135890	AAATTTGCTCTTACTCCCA	2835	2853	sooossssssssooss	5-9-5	2417
664713	135872	135891	GAAATTTGCTCTTACTCCCA	2835	2854	sooossssssssssooss	5-10-5	2418
664819	135872	135889	AATTTGCTCTTACTCCCA	2835	2852	sooossssssssooss	5-7-6	2309

[0733]

[0734] **실시예 15: htau 마우스에서의 인간 타우 mRNA에 대한 안티센스 올리고뉴클레오타이드의 뇌실내 투여**

[0735] 선택된 화합물을 인간 타우 형질전환 마우스에서의 ICV 투여에 의한 효능에 대하여 시험하였다 (Duff et al., Neurobiology of Disease 7:87-98, 2000).

[0736] *치료 및 수술*

[0737] 4 마리 마우스의 그룹 각각에게 200 g의 ISIS 613255, ISIS 613329, ISIS 613344, ISIS 613361, ISIS 613369, ISIS 613370, ISIS 613397, ISIS 613045, ISIS 613099, ISIS 613118, ISIS 613136을 ICV 볼러스 주사로 투여하였다. 2마리 마우스의 대조군은 ISIS 424880로 유사하게 처리되었고 4마리 마우스의 대조군은 PBS로 유사하게 처리되었다. 모든 절차는 이소플로란 안락사 하에서, 그리고 IACUC(Institutional Animal Care and Use Committee) 규정에 따라 수행되었다 마우스 ICV 볼러스 주사에 대하여, 안티센스 올리고뉴클레오타이드는 인간 타우 형질전환 마우스의 우측 뇌실에 주사되었다. PBS 중 300 μg의 올리고뉴클레오타이드를 함유하는 10 마이크로리터의 용액이 약 10초 초과동안 주사되었다. 올리고뉴클레오타이드 투여 이후 14일간 조직을 수집하였다.

[0738] *RNA 분석*

[0739] 올리고뉴클레오타이드 투여 이후 14일째에, 타우 mRNA 수준의 실시간 PCR 분석을 위하여 RNA를 해마, 척수, 및 피질로부터 추출하였다. 인간 프라이머 프로브 세트 RTS3104를 사용하여 인간 타우 mRNA 수준을 측정하였다. 결과는 대조군과 비교된 인간 타우 mRNA 발현의 억제%로서 산출되었다. 모든 안티센스 올리고뉴클레오타이드는 뚜렷한 인간 타우 mRNA 수준의 억제에 영향을 미친다.

[0740] **표 57**

[0741] **hTau 마우스에서의 인간 타우 mRNA 수준의 백분율 감소**

ISIS 번호	Cortex	Hippocampus	Spinal Cord
613255	30	46	36
613329	20	69	67
613344	41	42	34
613361	69	57	72
613369	17	48	46
613370	42	61	63
613397	33	41	57
613045	12	38	47
613099	42	55	54
613118	64	73	58
613136	26	39	27
424880	50	53	55

[0742]

[0743] **실시예 16: SH-SY5Y 세포에서의, 5-7-6 MOE, 5-8-5 MOE, 5-9-5 MOE, 및 5-10-5 MOE 갭머에 의한 인간 타우 안티센스 억제**

[0744] 상기 실시예에 기술된 안티센스 올리고뉴클레오타이드, 뿐만 아니라 인간 타우 핵산을 표적화하는 새롭게 설계된 안티센스 올리고뉴클레오타이드를 유사한 배양 조건을 갖는 일련의 실험에서 시험하였다. 각 실험에 대한 결과는 하기 나타낸 개별 표에서 제시된다. 배양된 SH-SY5Y 세포를 전기천공을 사용하여 8,000 nM 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 24 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한, 타우의 억제율로서 표현된다.

[0745] 하기 표에서 새롭게 설계된 키메라 안티센스 올리고뉴클레오타이드는 5-7-6 MOE, 5-8-5 MOE, 5-9-5 MOE, 또는 5-10-5 MOE 갭머로서 설계되었다. 5-7-6 MOE 갭머는 길이가 18개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 7개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5개 및 6개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 5-8-5 MOE 갭머는 길이가 18개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 8개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 5-9-5 MOE 갭머는 길이가 19개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 9개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 5-10-5 MOE 갭머는 길이가 20개의 뉴클레오사이드이고, 여기서 중앙 갭 분절은 10개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5개의 뉴클레오사이드를 포함하는 5' 방향 및 3' 방향 상에서의 윙 분절에 의하여 플랭킹된다. 5' 윙 분절 내의 각각의 뉴클레오사이드 및 3' 윙 분절 내의 각각의 뉴클레오사이드는 2'-MOE 변형을 갖는다. 각각의 갭머에서의 뉴클레오사이드간 연결은 포스포로티오에이트 연결 또는 포스포디에스테르 연결이다. '연결 화학' 칼럼은 각 올리고뉴클로타이드의 뉴클레오사이드간 연결을 개시한다. 's'는 포스포로티오에이트 연결을 , 'o'는 포스포디에스테르 연결을 나타낸다. 각각의 갭머에서의 모든 시토신 잔기는 5-메틸시토신이다.

[0746] "개시 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 5'-모스트(most) 뉴클레오사이드를 나타낸다. "정지 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 3'-모스트 뉴클레오사이드를 나타낸다. 하기 표에 열거된 각각의 갭머는 본원에 개시된 서열 번호: 1과 같이 지정된 인간 타우 게놈 서열 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자은행 수탁 번호 NT_010783.15) 또는 서열 번호: 2와 같이 지정된 인간 타우 mRNA 서열 (유전자은행 수탁 번호 NM_001123066.3)에 표적화된다. 'n/a'는 안티센스 올리고뉴클레오타이드가 100% 상보성을 갖는 특정 유전자 서열을 표적화하지 않는다는 것이다.

[0747] 표 58

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	결합 화학성질	모티프	억제율%	서열 번호
623965	73880	73897	TGATCTTCCATCACTTCG	n/a	n/a	sooossssssssooss	5-8-5	52	2278
620887	98891	98908	GTTTTCAAACACACCTTC	n/a	n/a	sooossssssssooss	5-8-5	91	665
	98928	98945							
664511	135820	135837	GACAAAAGCAGGTTAAGT	2783	2800	sooossssssssooss	5-8-5	65	2331
664767	135820	135837	GACAAAAGCAGGTTAAGT	2783	2800	sooossssssssooss	5-7-6	21	2331
664512	135821	135838	TGACAAAAGCAGGTTAAG	2784	2801	sooossssssssooss	5-8-5	60	2334

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664768	135821	135838	TGACAAAAGCAGGTTAAG	2784	2801	sooossssssssooss	5-7-6	30	2334
622109	135822	135839	GTGACAAAAGCAGGTTAA	2785	2802	sooossssssssooss	5-8-5	72	2038
664769	135822	135839	GTGACAAAAGCAGGTTAA	2785	2802	sooossssssssooss	5-7-6	49	2038
664513	135823	135840	AGTGACAAAAGCAGGTTA	2786	2803	sooossssssssooss	5-8-5	56	2339
664770	135823	135840	AGTGACAAAAGCAGGTTA	2786	2803	sooossssssssooss	5-7-6	45	2339
664514	135824	135841	GAGTGACAAAAGCAGGTT	2787	2804	sooossssssssooss	5-8-5	84	2342
664771	135824	135841	GAGTGACAAAAGCAGGTT	2787	2804	sooossssssssooss	5-7-6	63	2342
622110	135825	135842	CGAGTGACAAAAGCAGGT	2788	2805	sooossssssssooss	5-8-5	77	2039
664772	135825	135842	CGAGTGACAAAAGCAGGT	2788	2805	sooossssssssooss	5-7-6	37	2039
664515	135826	135843	CCGAGTGACAAAAGCAGG	2789	2806	sooossssssssooss	5-8-5	70	2347
664773	135826	135843	CCGAGTGACAAAAGCAGG	2789	2806	sooossssssssooss	5-7-6	62	2347
664516	135827	135844	GCCGAGTGACAAAAGCAG	2790	2807	sooossssssssooss	5-8-5	79	2350
664774	135827	135844	GCCGAGTGACAAAAGCAG	2790	2807	sooossssssssooss	5-7-6	70	2350
622111	135828	135845	AGCCGAGTGACAAAAGCA	2791	2808	sooossssssssooss	5-8-5	75	2040
664775	135828	135845	AGCCGAGTGACAAAAGCA	2791	2808	sooossssssssooss	5-7-6	78	2040
664517	135829	135846	AAGCCGAGTGACAAAAGC	2792	2809	sooossssssssooss	5-8-5	67	2355
664776	135829	135846	AAGCCGAGTGACAAAAGC	2792	2809	sooossssssssooss	5-7-6	50	2355
664518	135830	135847	AAAGCCGAGTGACAAAAG	2793	2810	sooossssssssooss	5-8-5	47	2358
664777	135830	135847	AAAGCCGAGTGACAAAAG	2793	2810	sooossssssssooss	5-7-6	42	2358
622112	135831	135848	CAAAGCCGAGTGACAAAA	2794	2811	sooossssssssooss	5-8-5	46	2041
664778	135831	135848	CAAAGCCGAGTGACAAAA	2794	2811	sooossssssssooss	5-7-6	34	2041
664519	135832	135849	CCAAAGCCGAGTGACAAA	2795	2812	sooossssssssooss	5-8-5	57	2363
664779	135832	135849	CCAAAGCCGAGTGACAAA	2795	2812	sooossssssssooss	5-7-6	34	2363
664520	135833	135850	GCCAAAGCCGAGTGACAA	2796	2813	sooossssssssooss	5-8-5	63	2366
664780	135833	135850	GCCAAAGCCGAGTGACAA	2796	2813	sooossssssssooss	5-7-6	66	2366
622113	135834	135851	AGCCAAAGCCGAGTGACA	2797	2814	sooossssssssooss	5-8-5	70	2042
664781	135834	135851	AGCCAAAGCCGAGTGACA	2797	2814	sooossssssssooss	5-7-6	74	2042
664521	135835	135852	GAGCCAAAGCCGAGTGAC	2798	2815	sooossssssssooss	5-8-5	71	2420
664782	135835	135852	GAGCCAAAGCCGAGTGAC	2798	2815	sooossssssssooss	5-7-6	31	2420
664522	135836	135853	CGAGCCAAAGCCGAGTGA	2799	2816	sooossssssssooss	5-8-5	50	2423
664783	135836	135853	CGAGCCAAAGCCGAGTGA	2799	2816	sooossssssssooss	5-7-6	30	2423
622114	135837	135854	CCGAGCCAAAGCCGAGTG	2800	2817	sooossssssssooss	5-8-5	72	2043
664784	135837	135854	CCGAGCCAAAGCCGAGTG	2800	2817	sooossssssssooss	5-7-6	76	2043
664523	135838	135855	CCCGAGCCAAAGCCGAGT	2801	2818	sooossssssssooss	5-8-5	70	2428
664785	135838	135855	CCCGAGCCAAAGCCGAGT	2801	2818	sooossssssssooss	5-7-6	56	2428
664524	135839	135856	TCCCGAGCCAAAGCCGAG	2802	2819	sooossssssssooss	5-8-5	55	2431
664786	135839	135856	TCCCGAGCCAAAGCCGAG	2802	2819	sooossssssssooss	5-7-6	36	2431
622115	135840	135857	GTCCCGAGCCAAAGCCGA	2803	2820	sooossssssssooss	5-8-5	59	2044
664787	135840	135857	GTCCCGAGCCAAAGCCGA	2803	2820	sooossssssssooss	5-7-6	54	2044
664525	135841	135858	AGTCCCGAGCCAAAGCCG	2804	2821	sooossssssssooss	5-8-5	74	2436
664788	135841	135858	AGTCCCGAGCCAAAGCCG	2804	2821	sooossssssssooss	5-7-6	77	2436
664789	135842	135859	AAGTCCCGAGCCAAAGCC	2805	2822	sooossssssssooss	5-7-6	42	2439
664790	135843	135860	GAAGTCCCGAGCCAAAGC	2806	2823	sooossssssssooss	5-7-6	38	2045
664791	135844	135861	TGAAGTCCCGAGCCAAAG	2807	2824	sooossssssssooss	5-7-6	44	2478
664792	135845	135862	TTGAAGTCCCGAGCCAAA	2808	2825	sooossssssssooss	5-7-6	44	2479
664793	135846	135863	TTTGAAGTCCCGAGCCAA	2809	2826	sooossssssssooss	5-7-6	29	2046

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664794	135847	135864	TTTTGAAGTCCCGAGCCA	2810	2827	sooossssssssoooss	5-7-6	32	2480
664795	135848	135865	ATTTTGAAGTCCCGAGCC	2811	2828	sooossssssssoooss	5-7-6	15	2481
664796	135849	135866	GATTTTGAAGTCCCGAGC	2812	2829	sooossssssssoooss	5-7-6	76	2047
664797	135850	135867	TGATTTTGAAGTCCCGAG	2813	2830	sooossssssssoooss	5-7-6	70	2482
664798	135851	135868	CTGATTTTGAAGTCCCGA	2814	2831	sooossssssssoooss	5-7-6	75	2483
664799	135852	135869	ACTGATTTTGAAGTCCCG	2815	2832	sooossssssssoooss	5-7-6	79	2048
664800	135853	135870	CACTGATTTTGAAGTCCC	2816	2833	sooossssssssoooss	5-7-6	82	2370
664534	135854	135871	TCACTGATTTTGAAGTCC	2817	2834	sooossssssssooss	5-8-5	78	2372
664801	135854	135871	TCACTGATTTTGAAGTCC	2817	2834	sooossssssssoooss	5-7-6	29	2372
664802	135855	135872	ATCACTGATTTTGAAGTC	2818	2835	sooossssssssoooss	5-7-6	52	1668
664803	135856	135873	CATCACTGATTTTGAAGT	2819	2836	sooossssssssoooss	5-7-6	55	2377
664804	135857	135874	CCATCACTGATTTTGAAG	2820	2837	sooossssssssoooss	5-7-6	38	2380
664805	135858	135875	CCCATCACTGATTTTGAA	2821	2838	sooossssssssoooss	5-7-6	62	1669
664806	135859	135876	TCCCATCACTGATTTTGA	2822	2839	sooossssssssoooss	5-7-6	72	2385
664807	135860	135877	CTCCCATCACTGATTTTG	2823	2840	sooossssssssoooss	5-7-6	55	2388
664808	135861	135878	ACTCCCATCACTGATTTT	2824	2841	sooossssssssoooss	5-7-6	38	1670
664809	135862	135879	TACTCCCATCACTGATTT	2825	2842	sooossssssssoooss	5-7-6	54	2393
664810	135863	135880	TTACTCCCATCACTGATT	2826	2843	sooossssssssoooss	5-7-6	39	2396
664811	135864	135881	CTTACTCCCATCACTGAT	2827	2844	sooossssssssoooss	5-7-6	39	1671
664812	135865	135882	TCTTACTCCCATCACTGA	2828	2845	sooossssssssoooss	5-7-6	45	2401
664813	135866	135883	CTCTTACTCCCATCACTG	2829	2846	sooossssssssoooss	5-7-6	61	2404
664814	135867	135884	GCTCTTACTCCCATCACT	2830	2847	sooossssssssoooss	5-7-6	14	1672
664815	135868	135885	TGCTCTTACTCCCATCAC	2831	2848	sooossssssssoooss	5-7-6	70	2306
664816	135869	135886	TTGCTCTTACTCCCATCA	2832	2849	sooossssssssoooss	5-7-6	72	2307
664817	135870	135887	TTTGCTCTTACTCCCATC	2833	2850	sooossssssssoooss	5-7-6	62	1673
664818	135871	135888	ATTTGCTCTTACTCCCAT	2834	2851	sooossssssssoooss	5-7-6	69	2308
664819	135872	135889	AATTTGCTCTTACTCCCA	2835	2852	sooossssssssoooss	5-7-6	67	2309

[0750]

[0751] 표 59

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	결합 화학성질	모티프	억제율%	서열 번호
665045	21592	21609	ACATCCAAATAACAATAT	n/a	n/a	sooossssssssooss	5-8-5	1	2444
665046	21617	21634	TCCTGTCTCAAACACCTA	n/a	n/a	sooossssssssooss	5-8-5	44	2445
665047	30083	30100	AGCTTATCACAGTAGGTG	n/a	n/a	sooossssssssooss	5-8-5	94	2446
665048	30108	30125	CCTTTGCTTCACACACCA	n/a	n/a	sooossssssssooss	5-8-5	67	2447
621013	30133	30150	AGCTCACTACAGCAGGCA	n/a	n/a	sooossssssssooss	5-8-5	90	868
665049	30158	30175	TGGTTCTACAACCTGCCC	n/a	n/a	sooossssssssooss	5-8-5	57	2448
665050	30183	30200	CCTTTGTAACCTTGGAAC	n/a	n/a	sooossssssssooss	5-8-5	25	2449
665051	33838	33855	AGTTAAAAGATGGCAACC	n/a	n/a	sooossssssssooss	5-8-5	32	2450
665052	33863	33880	CTGGGCATTTTGATAAAA	n/a	n/a	sooossssssssooss	5-8-5	28	2451
621031	33888	33905	GGTATAATTTGTTTGGAC	n/a	n/a	sooossssssssooss	5-8-5	85	886
665053	33913	33930	AGTGCCAGACATTTTCAA	n/a	n/a	sooossssssssooss	5-8-5	20	2452

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665054	33938	33955	CTGGCACAACAGGCATTG	n/a	n/a	sooossssssssooss	5-8-5	25	2453
621041	35721	35738	TTGCCATCTTGGACAGGG	n/a	n/a	sooossssssssooss	5-8-5	70	896
665055	35746	35763	GTGGTACAGAGGCTGTGT	n/a	n/a	sooossssssssooss	5-8-5	47	2454
665056	35771	35788	TTGCAGATTCTGAATACC	n/a	n/a	sooossssssssooss	5-8-5	78	2455
665057	64499	64516	TATGATTCCCAGGAGTCT	n/a	n/a	sooossssssssooss	5-8-5	0	2456
621181	64543	64560	GTAGGTGTCATCATCATC	n/a	n/a	sooossssssssooss	5-8-5	77	1113
665058	64568	64585	GTGACCCTTCAGGGCAAT	n/a	n/a	sooossssssssooss	5-8-5	35	2457
665059	64593	64610	ATGCAGGTGCCTTGCAGG	n/a	n/a	sooossssssssooss	5-8-5	36	2458
623965	73880	73897	TGATCTTCCATCACTTCG	n/a	n/a	sooossssssssooss	5-8-5	48	2278
665060	77364	77381	CCTGCTGCCAACAGTAGA	n/a	n/a	sooossssssssooss	5-8-5	51	2459
665061	77389	77406	CCCTCACGGGCTGTTGTG	n/a	n/a	sooossssssssooss	5-8-5	20	2460
621236	77414	77431	TCATCTGTGAAGCGGACG	73377	73394	sooossssssssooss	5-8-5	79	706
665062	77439	77456	ACGGTCTGAGCATGAGGC	n/a	n/a	sooossssssssooss	5-8-5	77	2461
665063	77464	77481	AGCCATGGACCTGCTCTG	n/a	n/a	sooossssssssooss	5-8-5	48	2462
665064	77731	77748	GACAGTATACCCCACATC	n/a	n/a	sooossssssssooss	5-8-5	48	2463
621238	77781	77798	GTTATTTTGGAACAGTTT	73744	73761	sooossssssssooss	5-8-5	89	708
665065	78142	78159	AAGAGTGGTAAAACCTAC	n/a	n/a	sooossssssssooss	5-8-5	51	2464
665066	80259	80276	GCTCACCAGCAGGAACTT	n/a	n/a	sooossssssssooss	5-8-5	56	2465
665067	80284	80301	AAGGGCCCAGTGTAGCAC	n/a	n/a	sooossssssssooss	5-8-5	66	2466
621251	80309	80326	AGTCATTATCATGTCACC	76272	76289	sooossssssssooss	5-8-5	73	721
665068	80334	80351	CCAATAAGTGGCAGTGAT	n/a	n/a	sooossssssssooss	5-8-5	49	2467
665069	80359	80376	ACCATGCCTGGCAGATGA	n/a	n/a	sooossssssssooss	5-8-5	66	2468
665070	80799	80816	CTTAGTCATCTTCCCTCA	n/a	n/a	sooossssssssooss	5-8-5	64	2469
665071	80824	80841	ATTTCTGAATTCTTTGCC	n/a	n/a	sooossssssssooss	5-8-5	69	2470
621254	80849	80866	GGTAACATGTAAAGCTTC	76812	76829	sooossssssssooss	5-8-5	76	724
665072	82508	82525	CTTACACTCTGGAAGGTT	n/a	n/a	sooossssssssooss	5-8-5	74	2471
665073	82533	82550	TATCCAGGGCTGAGCAGG	n/a	n/a	sooossssssssooss	5-8-5	38	2472
621263	82558	82575	ATGGGCTTATCAATGCAT	78521	78538	sooossssssssooss	5-8-5	80	733
665074	82583	82600	GGAGTCAATCTGCCCTGG	n/a	n/a	sooossssssssooss	5-8-5	54	2473
665075	82608	82625	CTTCCCTGTGGCACTTTG	n/a	n/a	sooossssssssooss	5-8-5	29	2474
665076	89600	89617	ATGCCTCACTCAACAAGG	n/a	n/a	sooossssssssooss	5-8-5	26	2475
665077	89625	89642	CTCCACTTTGGGACCAGG	n/a	n/a	sooossssssssooss	5-8-5	87	2476
621302	89650	89667	GCTATGACCTAGTAGGAA	n/a	n/a	sooossssssssooss	5-8-5	68	772
665078	89675	89692	GGCACAGCACCCACATGC	n/a	n/a	sooossssssssooss	5-8-5	66	2477
665079	89700	89717	GGTGATAAAAGTTCACTA	n/a	n/a	sooossssssssooss	5-8-5	63	2531
620887	98891	98908	GTTTTCAAACACACCTTC	n/a	n/a	sooossssssssooss	5-8-5	91	665
	98928	98945							
664526	135842	135859	AAGTCCCGAGCCAAAGCC	2805	2822	sooossssssssooss	5-8-5	55	2439
622116	135843	135860	GAAGTCCCGAGCCAAAGC	2806	2823	sooossssssssooss	5-8-5	63	2045
664527	135844	135861	TGAAGTCCCGAGCCAAAG	2807	2824	sooossssssssooss	5-8-5	40	2478
664528	135845	135862	TTGAAGTCCCGAGCCAAA	2808	2825	sooossssssssooss	5-8-5	61	2479
622117	135846	135863	TTTGAAGTCCCGAGCCAA	2809	2826	sooossssssssooss	5-8-5	55	2046
664529	135847	135864	TTTTGAAGTCCCGAGCCA	2810	2827	sooossssssssooss	5-8-5	25	2480

[0753]

664530	135848	135865	ATTTTGAAGTCCCGAGCC	2811	2828	sooossssssssooss	5-8-5	38	2481
622118	135849	135866	GATTTTGAAGTCCCGAGC	2812	2829	sooossssssssooss	5-8-5	63	2047
664531	135850	135867	TGATTTTGAAGTCCCGAG	2813	2830	sooossssssssooss	5-8-5	66	2482
664532	135851	135868	CTGATTTTGAAGTCCCGA	2814	2831	sooossssssssooss	5-8-5	73	2483
622119	135852	135869	ACTGATTTTGAAGTCCCG	2815	2832	sooossssssssooss	5-8-5	66	2048
664533	135853	135870	CACTGATTTTGAAGTCCC	2816	2833	sooossssssssooss	5-8-5	72	2370
664534	135854	135871	TCACTGATTTTGAAGTCC	2817	2834	sooossssssssooss	5-8-5	61	2372
622120	135855	135872	ATCACTGATTTTGAAGTC	2818	2835	sooossssssssooss	5-8-5	47	1668
664535	135856	135873	CATCACTGATTTTGAAGT	2819	2836	sooossssssssooss	5-8-5	59	2377
664536	135857	135874	CCATCACTGATTTTGAAG	2820	2837	sooossssssssooss	5-8-5	34	2380
622121	135858	135875	CCCATCACTGATTTTGAA	2821	2838	sooossssssssooss	5-8-5	49	1669
664537	135859	135876	TCCCATCACTGATTTTGA	2822	2839	sooossssssssooss	5-8-5	61	2385
664538	135860	135877	CTCCCATCACTGATTTTG	2823	2840	sooossssssssooss	5-8-5	76	2388
622122	135861	135878	ACTCCCATCACTGATTTT	2824	2841	sooossssssssooss	5-8-5	38	1670
664539	135862	135879	TACTCCCATCACTGATTT	2825	2842	sooossssssssooss	5-8-5	57	2393
664540	135863	135880	TTACTCCCATCACTGATT	2826	2843	sooossssssssooss	5-8-5	32	2396
622123	135864	135881	CTTACTCCCATCACTGAT	2827	2844	sooossssssssooss	5-8-5	33	1671
664541	135865	135882	TCTTACTCCCATCACTGA	2828	2845	sooossssssssooss	5-8-5	50	2401
664542	135866	135883	CTCTTACTCCCATCACTG	2829	2846	sooossssssssooss	5-8-5	58	2404
622124	135867	135884	GCTCTTACTCCCATCACT	2830	2847	sooossssssssooss	5-8-5	64	1672
623993	135868	135885	TGCTCTTACTCCCATCAC	n/a	n/a	sooossssssssooss	5-8-5	65	2306
623994	135869	135886	TTGCTCTTACTCCCATCA	n/a	n/a	sooossssssssooss	5-8-5	63	2307
622125	135870	135887	TTTGCTCTTACTCCCATC	2833	2850	sooossssssssooss	5-8-5	75	1673
623995	135871	135888	ATTTGCTCTTACTCCCAT	n/a	n/a	sooossssssssooss	5-8-5	60	2308
623996	135872	135889	AATTTGCTCTTACTCCCA	n/a	n/a	sooossssssssooss	5-8-5	72	2309

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[0755] **표 60**

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	결합 화학성질	모티프	억제율%	서열 번호
665043	73879	73897	TGATCTTCCATCACTTCGA	345	364	sooossssssssooss	5-9-5	67	2484
665044	98890	98908	GTTTTCAAACACACCTTCA	n/a	n/a	sooossssssssooss	5-9-5	90	2485
	98927	98945							
665081	120039	120057	TTTTCTTACCACCCTAACA	n/a	n/a	sooossssssssooss	5-9-5	28	2486
665082	120041	120059	CGTTTTCTTACCACCCTAA	n/a	n/a	sooossssssssooss	5-9-5	86	2487
665083	120045	120063	AAACCGTTTTCTTACCACC	n/a	n/a	sooossssssssooss	5-9-5	86	2488
665084	120047	120065	AAAAACCGTTTTCTTACCA	n/a	n/a	sooossssssssooss	5-9-5	65	2489
665085	120060	120078	AGCTCATCAAAGCAAAAAC	n/a	n/a	sooossssssssooss	5-9-5	65	2490
665086	120110	120128	TCAAAAGACTATGTATTTT	n/a	n/a	sooossssssssooss	5-9-5	54	2491
665087	120389	120407	TGTAAATAATTGCCAAGTG	n/a	n/a	sooossssssssooss	5-9-5	61	2492
665088	120439	120457	TAAGCCACCATGCCTGTAA	n/a	n/a	sooossssssssooss	5-9-5	61	2493
665089	121711	121729	TGGACCCGCCTACTTGCTC	n/a	n/a	sooossssssssooss	5-9-5	85	2494

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665090	121736	121754	TTTCGATGAGTGACATGCG	n/a	n/a	sooossssssssssooss	5-9-5	50	2495
665091	121761	121779	TGCTTGCTCGCAAGGACGC	n/a	n/a	sooossssssssssooss	5-9-5	80	2496
665092	121765	121783	CGCCTGCTTGCTCGCAAGG	n/a	n/a	sooossssssssssooss	5-9-5	82	2497
665093	121767	121785	CCCGCCTGCTTGCTCGCAA	n/a	n/a	sooossssssssssooss	5-9-5	92	2498
665094	121769	121787	GACCCGCCTGCTTGCTCGC	n/a	n/a	sooossssssssssooss	5-9-5	91	2499
665095	121771	121789	TGGACCCGCCTGCTTGCTC	n/a	n/a	sooossssssssssooss	5-9-5	83	2500
665096	121773	121791	CCTGGACCCGCCTGCTTGC	n/a	n/a	sooossssssssssooss	5-9-5	88	2501
665097	121775	121793	ACCCTGGACCCGCCTGCTT	n/a	n/a	sooossssssssssooss	5-9-5	60	2502
665098	121786	121804	AGTGACACGCCACCCTGGA	n/a	n/a	sooossssssssssooss	5-9-5	62	2503
665099	121811	121829	CCTTTGGTAGCCAGAAAAA	n/a	n/a	sooossssssssssooss	5-9-5	53	2504
665100	121817	121835	TCTGCACCTTTGGTAGCCA	n/a	n/a	sooossssssssssooss	5-9-5	84	2505
665101	121938	121956	ACAGCACGGCGCATGGGAC	n/a	n/a	sooossssssssssooss	5-9-5	54	2506
665102	121940	121958	CCACAGCACGGCGCATGGG	n/a	n/a	sooossssssssssooss	5-9-5	84	2507
665103	121942	121960	AGCCACAGCACGGCGCATG	n/a	n/a	sooossssssssssooss	5-9-5	85	2508
664714	135820	135838	TGACAAAAGCAGGTTAAGT	2783	2801	sooossssssssssooss	5-9-5	54	2332
664715	135821	135839	GTGACAAAAGCAGGTTAAG	2784	2802	sooossssssssssooss	5-9-5	65	2335
664716	135822	135840	AGTGACAAAAGCAGGTTAA	2785	2803	sooossssssssssooss	5-9-5	79	2337
664717	135823	135841	GAGTGACAAAAGCAGGTTA	2786	2804	sooossssssssssooss	5-9-5	70	2340
664718	135824	135842	CGAGTGACAAAAGCAGGTT	2787	2805	sooossssssssssooss	5-9-5	89	2343
664719	135825	135843	CCGAGTGACAAAAGCAGGT	2788	2806	sooossssssssssooss	5-9-5	84	2345
664720	135826	135844	GCCGAGTGACAAAAGCAGG	2789	2807	sooossssssssssooss	5-9-5	71	2348
664721	135827	135845	AGCCGAGTGACAAAAGCAG	2790	2808	sooossssssssssooss	5-9-5	81	2351
664722	135828	135846	AAGCCGAGTGACAAAAGCA	2791	2809	sooossssssssssooss	5-9-5	68	2353
664723	135829	135847	AAAGCCGAGTGACAAAAGC	2792	2810	sooossssssssssooss	5-9-5	51	2356
664724	135830	135848	CAAAGCCGAGTGACAAAAG	2793	2811	sooossssssssssooss	5-9-5	47	2359
664725	135831	135849	CCAAAGCCGAGTGACAAAA	2794	2812	sooossssssssssooss	5-9-5	69	2361
664726	135832	135850	GCCAAAGCCGAGTGACAAA	2795	2813	sooossssssssssooss	5-9-5	76	2364
664727	135833	135851	AGCCAAAGCCGAGTGACAA	2796	2814	sooossssssssssooss	5-9-5	64	2367
664728	135834	135852	GAGCCAAAGCCGAGTGACA	2797	2815	sooossssssssssooss	5-9-5	78	2369
664729	135835	135853	CGAGCCAAAGCCGAGTGAC	2798	2816	sooossssssssssooss	5-9-5	74	2421
664730	135836	135854	CCGAGCCAAAGCCGAGTGA	2799	2817	sooossssssssssooss	5-9-5	76	2424
664731	135837	135855	CCCGAGCCAAAGCCGAGTG	2800	2818	sooossssssssssooss	5-9-5	75	2426
664732	135838	135856	TCCCGAGCCAAAGCCGAGT	2801	2819	sooossssssssssooss	5-9-5	80	2429
664733	135839	135857	GTCCCGAGCCAAAGCCGAG	2802	2820	sooossssssssssooss	5-9-5	70	2432
664734	135840	135858	AGTCCCGAGCCAAAGCCGA	2803	2821	sooossssssssssooss	5-9-5	59	2434
664735	135841	135859	AAGTCCCGAGCCAAAGCCG	2804	2822	sooossssssssssooss	5-9-5	58	2437
664736	135842	135860	GAAGTCCCGAGCCAAAGCC	2805	2823	sooossssssssssooss	5-9-5	76	2440
664737	135843	135861	TGAAGTCCCGAGCCAAAGC	2806	2824	sooossssssssssooss	5-9-5	46	2442
664738	135844	135862	TTGAAGTCCCGAGCCAAAG	2807	2825	sooossssssssssooss	5-9-5	46	2550
664739	135845	135863	TTTGAAGTCCCGAGCCAAA	2808	2826	sooossssssssssooss	5-9-5	56	2551
664740	135846	135864	TTTTGAAGTCCCGAGCCAA	2809	2827	sooossssssssssooss	5-9-5	44	2552
664741	135847	135865	ATTTTGAAGTCCCGAGCCA	2810	2828	sooossssssssssooss	5-9-5	61	2553
664742	135848	135866	GATTTTGAAGTCCCGAGCC	2811	2829	sooossssssssssooss	5-9-5	59	2554

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664743	135849	135867	TGATTTTGAAGTCCCGAGC	2812	2830	sooossssssssssooss	5-9-5	64	2555
664744	135850	135868	CTGATTTTGAAGTCCCGAG	2813	2831	sooossssssssssooss	5-9-5	67	2556
664745	135851	135869	ACTGATTTTGAAGTCCCGA	2814	2832	sooossssssssssooss	5-9-5	73	2557
664746	135852	135870	CACTGATTTTGAAGTCCCG	2815	2833	sooossssssssssooss	5-9-5	86	2558
664747	135853	135871	TCACTGATTTTGAAGTCCC	2816	2834	sooossssssssssooss	5-9-5	76	2371
664748	135854	135872	ATCACTGATTTTGAAGTCC	2817	2835	sooossssssssssooss	5-9-5	74	2373
664749	135855	135873	CATCACTGATTTTGAAGTC	2818	2836	sooossssssssssooss	5-9-5	50	2375
664750	135856	135874	CCATCACTGATTTTGAAGT	2819	2837	sooossssssssssooss	5-9-5	57	2378
664751	135857	135875	CCCATCACTGATTTTGAAG	2820	2838	sooossssssssssooss	5-9-5	64	2381
664752	135858	135876	TCCCATCACTGATTTTGAA	2821	2839	sooossssssssssooss	5-9-5	59	2383
664753	135859	135877	CTCCCATCACTGATTTTGA	2822	2840	sooossssssssssooss	5-9-5	73	2386
664754	135860	135878	ACTCCCATCACTGATTTTG	2823	2841	sooossssssssssooss	5-9-5	75	2389
664755	135861	135879	TACTCCCATCACTGATTTT	2824	2842	sooossssssssssooss	5-9-5	40	2391
664756	135862	135880	TTACTCCCATCACTGATTT	2825	2843	sooossssssssssooss	5-9-5	43	2394
664757	135863	135881	CTTACTCCCATCACTGATT	2826	2844	sooossssssssssooss	5-9-5	70	2397
664758	135864	135882	TCTTACTCCCATCACTGAT	2827	2845	sooossssssssssooss	5-9-5	61	2399
664759	135865	135883	CTCTTACTCCCATCACTGA	2828	2846	sooossssssssssooss	5-9-5	68	2402
664760	135866	135884	GCTCTTACTCCCATCACTG	2829	2847	sooossssssssssooss	5-9-5	82	2405
664761	135867	135885	TGCTCTTACTCCCATCACT	2830	2848	sooossssssssssooss	5-9-5	76	2407
664762	135868	135886	TTGCTCTTACTCCCATCAC	2831	2849	sooossssssssssooss	5-9-5	77	2409
664763	135869	135887	TTTGCTCTTACTCCCATCA	2832	2850	sooossssssssssooss	5-9-5	83	2411
664764	135870	135888	ATTTGCTCTTACTCCCATC	2833	2851	sooossssssssssooss	5-9-5	82	2413
664765	135871	135889	AATTTGCTCTTACTCCCAT	2834	2852	sooossssssssssooss	5-9-5	77	2415
664766	135872	135890	AAATTTGCTCTTACTCCCA	2835	2853	sooossssssssssooss	5-9-5	69	2417

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[0759] **표 61**

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	결합 화학성질	모티프	억제율%	서열 번호
665041	73879	73898	GTGATCTTCCATCACTTCGA	345	364	sooossssssssssooss	5-10-5	86	25
665044	98890	98908	GTTTTCAAACACACCTTCA	n/a	n/a	sooossssssssssooss	5-9-5	90	2485
	98927	98945							
665201	102119	102138	GGTTTGTTTTTTAAACAATT	n/a	n/a	sooossssssssssooss	5-10-5	57	2509
665202	102144	102163	GAACCCAATGAGAGTAGCAA	n/a	n/a	sooossssssssssooss	5-10-5	86	2510
665203	102169	102188	TTGCCAAAATCAGGAATGGG	n/a	n/a	sooossssssssssooss	5-10-5	87	2511
665204	102194	102213	TCAGGGCAATCTGGAAGCAT	n/a	n/a	sooossssssssssooss	5-10-5	79	2512
665205	102659	102678	ACTCTCCACTCCATGTCAAT	n/a	n/a	sooossssssssssooss	5-10-5	26	2513
665206	102684	102703	CAGAGCTCACAGCAATGATC	n/a	n/a	sooossssssssssooss	5-10-5	78	2514
665207	102709	102728	TCAGCATGAGTTGTGCCAAG	n/a	n/a	sooossssssssssooss	5-10-5	91	2515
665208	102734	102753	CCAGAGGAACTGTGTGCATT	n/a	n/a	sooossssssssssooss	5-10-5	79	2516
665209	102759	102778	CCAAGTTCCCTGAGGACATT	n/a	n/a	sooossssssssssooss	5-10-5	13	2517
665210	112934	112953	GTTGTGTTTTCTGGTTTATT	n/a	n/a	sooossssssssssooss	5-10-5	96	2518

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665211	112959	112978	TTTTTTTTTAAGTTAGGAGT	n/a	n/a	soooossssssssssooss	5-10-5	20	2519
665212	112984	113003	TTTTACTGGTTGTGTTTTCT	n/a	n/a	soooossssssssssooss	5-10-5	90	2520
665213	113009	113028	CAGCTCTTAATGCTGTTATA	n/a	n/a	soooossssssssssooss	5-10-5	90	2521
665214	113498	113517	TTCAGCTCCTGCACCCAGCA	n/a	n/a	soooossssssssssooss	5-10-5	54	2522
665215	113548	113567	TTTTGCTTTTGCTCTGAAGA	n/a	n/a	soooossssssssssooss	5-10-5	57	2523
665216	115105	115124	TTGCTATTAAATATAATGTA	n/a	n/a	soooossssssssssooss	5-10-5	35	2524
665217	115130	115149	GCTTTTTAAAGTGACAACTG	n/a	n/a	soooossssssssssooss	5-10-5	78	2525
665218	115155	115174	TTCCACATAAATGTTCTACA	n/a	n/a	soooossssssssssooss	5-10-5	93	2526
665219	115205	115224	CCCTGATTGAGGAGAGGCAA	n/a	n/a	soooossssssssssooss	5-10-5	77	2527
665220	116595	116614	ATGTTTTTTTCTGGCCGGGC	n/a	n/a	soooossssssssssooss	5-10-5	85	2528
665221	116620	116639	TTCAGTATCTGCCACATACT	n/a	n/a	soooossssssssssooss	5-10-5	64	2529
665222	116645	116664	TGAATCAAAGGACATTAAGC	n/a	n/a	soooossssssssssooss	5-10-5	69	2530
664661	135820	135839	GTGACAAAAGCAGGTTAAGT	2783	2802	soooossssssssssooss	5-10-5	78	2333
664662	135821	135840	AGTGACAAAAGCAGGTTAAG	2784	2803	soooossssssssssooss	5-10-5	18	2336
664663	135822	135841	GAGTGACAAAAGCAGGTTAA	2785	2804	soooossssssssssooss	5-10-5	79	2338
664664	135823	135842	CGAGTGACAAAAGCAGGTTA	2786	2805	soooossssssssssooss	5-10-5	66	2341
664665	135824	135843	CCGAGTGACAAAAGCAGGTT	2787	2806	soooossssssssssooss	5-10-5	94	2344
664666	135825	135844	GCCGAGTGACAAAAGCAGGT	2788	2807	soooossssssssssooss	5-10-5	89	2346
664667	135826	135845	AGCCGAGTGACAAAAGCAGG	2789	2808	soooossssssssssooss	5-10-5	29	2349
664668	135827	135846	AAGCCGAGTGACAAAAGCAG	2790	2809	soooossssssssssooss	5-10-5	72	2352
664669	135828	135847	AAAGCCGAGTGACAAAAGCA	2791	2810	soooossssssssssooss	5-10-5	53	2354
664670	135829	135848	CAAAGCCGAGTGACAAAAGC	2792	2811	soooossssssssssooss	5-10-5	55	2357
664671	135830	135849	CCAAAGCCGAGTGACAAAAG	2793	2812	soooossssssssssooss	5-10-5	58	2360
664672	135831	135850	GCCAAAGCCGAGTGACAAAA	2794	2813	soooossssssssssooss	5-10-5	80	2362
664673	135832	135851	AGCCAAAGCCGAGTGACAAA	2795	2814	soooossssssssssooss	5-10-5	52	2365
664674	135833	135852	GAGCCAAAGCCGAGTGACAA	2796	2815	soooossssssssssooss	5-10-5	71	2368
664675	135834	135853	CGAGCCAAAGCCGAGTGACA	2797	2816	soooossssssssssooss	5-10-5	76	2419
664676	135835	135854	CCGAGCCAAAGCCGAGTGAC	2798	2817	soooossssssssssooss	5-10-5	78	2422
664677	135836	135855	CCCGAGCCAAAGCCGAGTGA	2799	2818	soooossssssssssooss	5-10-5	77	2425
664678	135837	135856	TCCCGAGCCAAAGCCGAGTG	2800	2819	soooossssssssssooss	5-10-5	73	2427
664679	135838	135857	GTCCCGAGCCAAAGCCGAGT	2801	2820	soooossssssssssooss	5-10-5	73	2430
664680	135839	135858	AGTCCCGAGCCAAAGCCGAG	2802	2821	soooossssssssssooss	5-10-5	20	2433
664681	135840	135859	AAGTCCCGAGCCAAAGCCGA	2803	2822	soooossssssssssooss	5-10-5	64	2435
664682	135841	135860	GAAGTCCCGAGCCAAAGCCG	2804	2823	soooossssssssssooss	5-10-5	60	2438
664683	135842	135861	TGAAGTCCCGAGCCAAAGCC	2805	2824	soooossssssssssooss	5-10-5	64	2441
664684	135843	135862	TTGAAGTCCCGAGCCAAAGC	2806	2825	soooossssssssssooss	5-10-5	52	2443
664685	135844	135863	TTTGAAGTCCCGAGCCAAAG	2807	2826	soooossssssssssooss	5-10-5	45	2559
664686	135845	135864	TTTTGAAGTCCCGAGCCAAA	2808	2827	soooossssssssssooss	5-10-5	56	2560
664687	135846	135865	ATTTTGAAGTCCCGAGCCAA	2809	2828	soooossssssssssooss	5-10-5	67	2561
664688	135847	135866	GATTTTGAAGTCCCGAGCCA	2810	2829	soooossssssssssooss	5-10-5	73	2562
664689	135848	135867	TGATTTTGAAGTCCCGAGCC	1644	1663	soooossssssssssooss	5-10-5	67	56
664690	135849	135868	CTGATTTTGAAGTCCCGAGC	2812	2831	soooossssssssssooss	5-10-5	73	464
664691	135850	135869	ACTGATTTTGAAGTCCCGAG	2813	2832	soooossssssssssooss	5-10-5	85	2563

[0761]

664692	135851	135870	CACTGATTTTGAAGTCCCGA	2814	2833	soooossssssssssooss	5-10-5	89	2564
664693	135852	135871	TCACTGATTTTGAAGTCCCG	2815	2834	soooossssssssssooss	5-10-5	75	2565
424880	135853	135872	ATCACTGATTTTGAAGTCCC	2816	2835	sssssssssssssssss	5-10-5	62	57
664694	135853	135872	ATCACTGATTTTGAAGTCCC	1649	1668	soooossssssssssooss	5-10-5	85	57
664695	135854	135873	CATCACTGATTTTGAAGTCC	2817	2836	soooossssssssssooss	5-10-5	83	2374
664696	135855	135874	CCATCACTGATTTTGAAGTC	2818	2837	soooossssssssssooss	5-10-5	66	2376
664697	135856	135875	CCCATCACTGATTTTGAAGT	2819	2838	soooossssssssssooss	5-10-5	58	2379
664698	135857	135876	TCCCATCACTGATTTTGAAG	2820	2839	soooossssssssssooss	5-10-5	71	2382
664699	135858	135877	CTCCCATCACTGATTTTGAA	2821	2840	soooossssssssssooss	5-10-5	32	2384
664700	135859	135878	ACTCCCATCACTGATTTTGA	2822	2841	soooossssssssssooss	5-10-5	71	2387
664701	135860	135879	TACTCCCATCACTGATTTTG	2823	2842	soooossssssssssooss	5-10-5	75	2390
664702	135861	135880	TTACTCCCATCACTGATTTT	2824	2843	soooossssssssssooss	5-10-5	46	2392
664703	135862	135881	CTTACTCCCATCACTGATTT	2825	2844	soooossssssssssooss	5-10-5	22	2395
664704	135863	135882	TCTTACTCCCATCACTGATT	2826	2845	soooossssssssssooss	5-10-5	72	2398
664705	135864	135883	CTCTTACTCCCATCACTGAT	2827	2846	soooossssssssssooss	5-10-5	70	2400
664706	135865	135884	GCTCTTACTCCCATCACTGA	2828	2847	soooossssssssssooss	5-10-5	77	2403
664707	135866	135885	TGCTCTTACTCCCATCACTG	2829	2848	soooossssssssssooss	5-10-5	88	2406
664708	135867	135886	TTGCTCTTACTCCCATCACT	2830	2849	soooossssssssssooss	5-10-5	86	2408
664709	135868	135887	TTTGCTCTTACTCCCATCAC	2831	2850	soooossssssssssooss	5-10-5	16	2410
664710	135869	135888	ATTTGCTCTTACTCCCATCA	2832	2851	soooossssssssssooss	5-10-5	80	2412
664711	135870	135889	AATTTGCTCTTACTCCCATC	2833	2852	soooossssssssssooss	5-10-5	65	2414
664712	135871	135890	AAATTTGCTCTTACTCCCAT	2834	2853	soooossssssssssooss	5-10-5	60	2416
664713	135872	135891	GAAATTTGCTCTTACTCCCA	2835	2854	soooossssssssssooss	5-10-5	85	2418

[0762]

[0763] **실시예 17: SH-SY5Y 세포에서 인간 타우의 용량-의존적 안티센스 억제**

[0764] 타우 mRNA의 뚜렷한 *시험관내* 억제를 나타내는 상기 기술된 연구로부터의 갭머는 SH-SY5Y 세포에서의 다양한 용량에서 선택 및 시험되었다. 안티센스 올리고뉴클레오타이드는 유사한 배양 조건을 갖는 일련의 실험에서 시험되었다. 각 실험에 대한 결과는 하기 나타낸 개별 표에서 제시된다. 세포를 웰당 20,000 세포의 밀도로 플레이팅하고, 하기 표에 명시된 바와 같이 전기천공을 사용하여 0.247 μM, 0.741 μM, 2.22 μM, 6.67 μM, 및 20.00 μM 농도의 안티센스 올리고뉴클레오타이드로 형질감염시켰다. 대략 16 시간의 처리 기간 후에, RNA를 세포로부터 분리시키고, 타우 mRNA 수준을 정량적 실시간 PCR에 의해서 측정하였다. 인간 프라이머 프로브 세트 RTS3104을 사용하여 mRNA 수준을 측정하였다. 타우 mRNA 수준은 리보그린(RIBOGREEN)®에 의해서 측정되는 바와 같은 총 RNA 함량에 따라 조정되었다. 결과는 비처리 대조군 세포와 비교한, 타우의 억제율로서 표현된다. 타우 mRNA 수준은 안티센스 올리고뉴클레오타이드 처리된 세포에서 용량-의존적 방식으로 뚜렷하게 감소되었다.

[0765] **표 62**

ISIS 번호	0.247 μM	0.741 μM	2.22 μM	6.67 μM	20.00 μM	IC_{50} (μM)
620887	18	39	71	88	95	1.2
664662	5	16	34	59	68	6.4
664665	16	41	69	89	96	1.2
664667	5	20	39	78	90	2.9
664680	7	11	21	56	81	5.9
664699	0	1	28	59	85	5.7
664709	8	16	48	66	89	3.1
665044	15	33	59	84	94	1.6
665205	0	7	35	51	86	5.3
665207	22	36	57	82	93	1.4
665210	15	47	74	94	97	1.0
665212	6	22	56	82	95	2.1
665213	0	18	57	78	93	2.5
665217	10	28	63	86	95	1.7
665218	10	31	64	85	93	1.7

[0766]

[0767] **표 63**

ISIS 번호	0.247 μM	0.741 μM	2.22 μM	6.67 μM	20.00 μM	IC_{50} (μM)
664718	26	34	60	88	86	1.3
664745	34	39	67	87	95	0.9
664746	15	37	60	87	92	1.5
664760	32	50	75	89	97	0.7
665044	21	44	75	92	97	0.9
665082	5	27	67	87	96	1.7
665083	17	34	67	85	97	1.4
665089	9	26	53	84	94	2.0
665093	11	57	81	93	95	0.9
665094	25	53	76	91	93	0.7
665095	20	33	63	89	95	1.4
665096	5	37	57	86	95	1.8
665102	8	36	61	90	96	1.6
665103	6	24	59	83	92	2.1

[0768]

[0769] **표 64**

ISIS 번호	0.247 μM	0.741 μM	2.22 μM	6.67 μM	20.00 μM	IC_{50} (μM)
620887	26	45	72	89	96	1.2
621013	26	49	82	93	97	0.7
621031	25	41	66	84	92	1.1
621041	26	55	70	89	92	0.7
621238	23	41	59	85	95	1.2
621251	33	56	74	88	92	0.5
664514	11	36	68	79	91	1.6
664516	16	36	64	82	94	1.5
664534	18	35	48	76	91	1.9
664775	24	30	59	79	92	1.6
664788	11	21	26	55	73	6.2
664799	26	37	63	79	90	1.3
664800	15	0	61	75	90	2.7
665047	43	65	82	95	98	0.2
665077	19	44	63	85	96	1.2

[0770]

[0771] **실시예 18: Htau마우스에서의 인간 타우 mRNA에 대한 안티센스 올리고뉴클레오타이드의 뇌실내 투여**

[0772] 선택된 화합물을 인간 타우 형질전환 마우스에서의 ICV 투여에 의한 효능에 대하여 시험하였다 (Duff et al., Neurobiology of Disease 7:87-98, 2000).

[0773] *치료 및 수술*

[0774] 4 마리 마우스의 그룹 각각에게 200 g의 ISIS 613099, ISIS 613361, ISIS 613370, ISIS 623782, 또는 ISIS 623996를 ICV 볼러스 주사로 투여하였다. 2마리 마우스의 대조군은 ISIS 424880로 유사하게 처리되었고 4마리 마우스의 대조군은 PBS로 유사하게 처리되었다. 모든 절차는 이소플로란 안락사 하에서, 그리고 IACUC(Institutional Animal Care and Use Committee) 규정에 따라 수행되었다 마우스 ICV 볼러스 주사에 대하여, 안티센스 올리고뉴클레오타이드는 인간 타우 형질전환 마우스의 우측 뇌실에 주사되었다. PBS 중 200 μg의 올리고뉴클레오타이드를 함유하는 10 마이크로리터의 용액이 약 10초 초과동안 주사되었다. 올리고뉴클레오타이드 투여 이후 14일간 조직을 수집하였다.

[0775] *RNA 분석*

[0776] 올리고뉴클레오타이드 투여 이후 14일째에, 타우 mRNA 수준의 실시간 PCR 분석을 위하여 RNA를 해마, 척수, 및 피질로부터 추출하였다. 인간 프라이머 프로브 세트 RTS3104를 사용하여 인간 타우 mRNA 수준을 측정하였다. 결과는 대조군과 비교된 인간 타우 mRNA 발현의 억제%로서 산출되었다. 모든 안티센스 올리고뉴클레오타이드는 여러 조직에서 뚜렷한 인간 타우 mRNA 수준의 억제에 영향을 미친다.

[0777] **표 65**

[0778] **hTau 마우스에서의 인간 타우 mRNA 수준의 백분율 감소**

ISIS 번호	Cortex	Hippocampus	Spinal Cord
613099	41.8	55.2	54.1
613361	69.4	57.3	72.5
613370	42.2	61.0	63.0
623782	62.2	79.1	70.8
623996	74.1	69.2	76.4
424880	50.3	53.1	55.2

[0779]

[0780] **실시예 19: 인간 타우를 표적화하는 안티센스 올리고뉴클레오타이드의 설계**

[0781] ISIS 번호 603054를 인간 타우를 표적화하도록 설계하였다. ISIS 번호 603054의 핵염기 서열 및 연결 화학성질은 하기 표 66에 나타낸다. ISIS No. 603054는 5-10-5 MOE 갭머이다. ISIS No. 603054는 길이가 20개의 뉴클레

오사이드이고, 여기에서 중앙 갭 분절은 10 개의 2'-데옥시뉴클레오사이드를 포함하고, 각각 5 개의 뉴클레오사이드를 포함하는, 양 측면 (5' 및 3' 방향으로) 상의 윙 분절에 의하여 플랭킹된다. 5' 윙 분절 내의 각각의 뉴클레오사이드 및 3' 윙 분절 내의 각각의 뉴클레오사이드는 2'-MOE 변형을 갖는다. 각각의 갭머에서의 모든 시토신 잔기는 5-메틸시토신이다. "개시 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 5'-모스트(most) 뉴클레오사이드를 나타낸다. "정지 부위"는 인간 유전자 서열 내에서 갭머가 표적으로 하는 3'-모스트(most) 뉴클레오사이드를 나타낸다. 하기 표 1에 열거된 각각의 갭머는 본원에 개시된 서열 번호: 1과 같이 지정된 인간 타우 게놈 서열 (뉴클레오타이드 9240000 내지 9381000로부터 절단된 유전자은행 수탁 번호 NT_010783.15) 또는 서열 번호: 2와 같이 지정된 인간 타우 mRNA 서열 (유전자은행 수탁 번호 NM_001123066.3)에 표적화된다.

[0782] **표 66**

[0783] **hTau 마우스 및 WT C57Bl6 마우스에서의 체내 연구**

ISIS 번호	서열 번호: 1 개시 부위	서열 번호: 1 정지 부위	서열	서열 번호: 2 개시 부위	서열 번호: 2 정지 부위	결합 화학성질	서열 번호
603054	135853	135872	ATCACTGATTTTGAAGTCCC	2816	2835	sooossssssssssooos	57

[0784]

[0785] **실시예 20: 인간 타우를 표적으로 하는 올리고뉴클레오타이드의 마우스내 *체내* 분석**

[0786] 하기 표에 나타난 올리고뉴클레오타이드는 타우를 표적화하도록 설계되었다. 인간 타우 형질전환 마우스 "hTau" (Duff et al., Neurobiology of Disease 7:87-98, 2000; Davies et al. J. Neurochem. (2003) 86, 582-590) 또는 야생형 WT C57Bl6 마우스인, 마우스는 3 또는 4개 마우스 그룹으로 분리되었다. 마우스의 각 그룹에서의 각 마우스에 하기 표에서의 올리고뉴클레오타이드를 각각 300ug 또는 200ug의 단일 ICV 용량으로 투여하였다. 주사후 3시간 째에서, 각 마우스를 7개의 상이한 기준에 따라 평가하였다. 7개의 기준은 (1) 마우스가 밝고, 기민하고, 그리고 반응성이 있었고; (2) 마우스가 자극 없이 서있거나 웅크리고 있었고; (3) 마우스가 자극 없이 임의의 움직임을 보였고; (4) 마우스가 들어올려진 후 정방향 움직임을 나타내고; (5) 마우스가 들어올려진 후 임의의 움직임을 나타내고; (6) 마우스가 테일 핀치(tail pinch)에 반응하고; (7) 정상 호흡이다. 상기 7개 상이한 기준에 대하여, 각 마우스는 그 기준을 만족할 경우 0의 서브스코어가 주어지고, 아닐 경우 1의 서브스코어가 주어졌다. 모든 7개의 기준을 평가한 후, 서브스코어를 각 마우스에 대하여 합하고 이후 각 그룹에 대해 평균치를 구하였다. 예를 들어, 만약 마우스가 300 μg의 ICV 용량 투여 후 3시간째에 밝고, 기민하고, 그리고 반응성이 있고, 다른 모든 기준을 만족한다면, 총계 스코어는 0이 될 것이다. 만약 다른 마우스가 300 μg의 ICV 용량 투여 후 3시간째에 밝고, 기민하고, 그리고 반응성이 있으나, 다른 모든 기준을 만족하지 못한다면, 총계 스코어는 1이 될 것이다. 염수 처리된 마우스는 일반적으로 0의 스코어가 주어진다. 결과는 각 처리 그룹에 대한 평균 스코어로서 하기 표 67에 제시된다. "ND"는 데이터없음을 의미한다. 이러한 결과는 ISIS 613099, ISIS 613361, ISIS 613370, ISIS 623782, ISIS 623996, ISIS 424880, 및 ISIS 603054가 잘 용인된다는 것을 나타낸다.

[0787] **표 67**

[0788] **hTau 마우스 및 WT C57Bl6 마우스에서의 체내 연구**

계통:	hTau		WT C57Bl6
용량:	300ug	200ug	300ug
613099	0	ND	ND
613361	0	ND	ND
613370	0	ND	ND
623782	0	ND	ND
623996	0	ND	ND
424880	ND	3	ND
603054	ND	ND	0.25

[0789]

[0790] **실시예 20: 인간 타우를 표적화하는 안티센스 올리고뉴클레오타이드의 *체내* 분석**

[0791] 스프라그 다울리(Sprague Dawley) 래트를 각각 4마리의 래트 그룹으로 분리하였다. 각 그룹의 래트에서 각 래트에 ISIS 613099, ISIS 613361, ISIS 613370, ISIS 623782, ISIS 623996, ISIS 424880, 또는 ISIS 603054를 단일 1mg 척추강내 (IT) 용량 또는 단일 3mg 척추강내 (IT) 용량으로 투여하였다. 주사 후 3시간 째에, 몸체의 7개의 상이한 부분의 움직임을 각 래트에 대해 평가하였다. 7개 몸체 부분은 (1) 래트의 꼬리; (2) 래트의 후면 자세; (3) 래트의 뒷다리; (4) 래트의 뒷발; (5) 래트의 앞발; (6) 래트의 후면 자세; 및 (7) 래트의 두부이다. 상기 7개 상이한 몸체 부분에 대하여, 각 래트는 만약 상기 몸체 부분이 움직일 경우 0의 서브스코어가 주어지고, 상기 몸체 부분이 마비될 경우 1의 서브스코어가 주어졌다. 모든 7개의 몸체 부분이 평가된 후, 서브스코어를 각 마우스에 대하여 합하고 이후 각 그룹에 대해 평균치를 구하였다. 예를 들어, 만약 3 mg의 IT 용량 투여 후 3시간째에 래트의 꼬리, 두부 및 모든 다른 평가된 몸체가 움직일 경우, 총계 스코어는 0이 될 것이다. 예를 들어, 만약 3 mg의 IT 용량 투여 후 3시간째에 다른 래트의 꼬리는 움직이지 않으나, 모든 다른 평가된 몸체가 움직일 경우, 총계 스코어는 1이 될 것이다. 염수 처리된 래트는 일반적으로 0의 스코어가 주어진다. 상기 범위의 상부 제한에서의 스코어는 독성을 의미하는 것일 수 있다. 결과는 각 처리 그룹에 대한 평균 스코어로서 하기 표 68에 제시된다.

[0792] **표 68**

[0793] **1 mg 및 3 mg IT 볼러스 *체내* 연구**

[0794]

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	용량	
	1mg	3mg
613099	0.25	3
613361	0	0.33
613370	0	0
623782	0.25	0.75
623996	0	2
424880	2.3	6
603054	1.25	2.75

서 열 목 록

SEQUENCE LISTING

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Met

1

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cgccaccaca gccaccttct cctcctccgc tgtcctctcc cgtcctcgcc tctgtcgact 300

atcaggtgaa ctttgaacca gg atg gct gag ccc cgc cag gag ttc gaa gtg 352

Met Ala Glu Pro Arg Gln Glu Phe Glu Val

1 5 10

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Met Glu Asp His Ala Gly Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln

15 20 25

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Gly Gly Tyr Thr Met His Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly

30 35 40

ctg aaa gaa tct ccc ctg cag acc ccc act gag gac gga tct gag gaa 496

Leu Lys Glu Ser Pro Leu Gln Thr Pro Thr Glu Asp Gly Ser Glu Glu

45 50 55

ccg ggc tct gaa acc tct gat gct aag agc act cca aca gcg gaa gct 544

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Pro Gly Ser Glu Thr Ser Asp Ala Lys Ser Thr Pro Thr Ala Glu Ala
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gaa gaa gca ggc att gga gac acc ccc agc ctg gaa gac gaa gct gct        592
Glu Glu Ala Gly Ile Gly Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala
75                  80                  85                  90
ggt cac gtg acc caa gct cgc atg gtc agt aaa agc aaa gac ggg act        640
Gly His Val Thr Gln Ala Arg Met Val Ser Lys Ser Lys Asp Gly Thr

                95                  100                 105
gga agc gat gac aaa aaa gcc aag ggg gct gat ggt aaa acg aag atc        688
Gly Ser Asp Asp Lys Lys Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile
            110                 115                 120
gcc aca ccg cgg gga gca gcc cct cca ggc cag aag ggc cag gcc aac        736
Ala Thr Pro Arg Gly Ala Ala Pro Pro Gly Gln Lys Gly Gln Ala Asn
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gcc acc agg att cca gca aaa acc ccg ccc gct cca aag aca cca ccc        784
Ala Thr Arg Ile Pro Ala Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro
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agc tct ggt gaa cct cca aaa tca ggg gat cgc agc ggc tac agc agc        832
Ser Ser Gly Glu Pro Pro Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser
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ccc ggc tcc cca ggc act ccc ggc agc cgc tcc cgc acc ccg tcc ctt        880

Pro Gly Ser Pro Gly Thr Pro Gly Ser Arg Ser Arg Thr Pro Ser Leu
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cca acc cca ccc acc cgg gag ccc aag aag gtg gca gtg gtc cgt act        928
Pro Thr Pro Pro Thr Arg Glu Pro Lys Lys Val Ala Val Val Arg Thr
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Pro Pro Lys Ser Pro Ser Ser Ala Lys Ser Arg Leu Gln Thr Ala Pro

        205                 210                 215
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Val Pro Met Pro Asp Leu Lys Asn Val Lys Ser Lys Ile Gly Ser Thr
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gag aac ctg aag cac cag ccg gga ggc ggg aag gtg caa ata gtc tac       1072
Glu Asn Leu Lys His Gln Pro Gly Gly Gly Lys Val Gln Ile Val Tyr
235                 240                 245                 250

aaa cca gtt gac ctg agc aag gtg acc tcc aag tgt ggc tca tta ggc       1120
Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys Cys Gly Ser Leu Gly
                255                 260                 265
aac atc cat cat aaa cca gga ggt ggc cag gtg gaa gta aaa tct gag       1168
Asn Ile His His Lys Pro Gly Gly Gly Gln Val Glu Val Lys Ser Glu
            270                 275                 280
aag ctt gac ttc aag gac aga gtc cag tcg aag att ggg tcc ctg gac       1216

Lys Leu Asp Phe Lys Asp Arg Val Gln Ser Lys Ile Gly Ser Leu Asp
        285                 290                 295
aat atc acc cac gtc cct ggc gga gga aat aaa aag att gaa acc cac       1264
Asn Ile Thr His Val Pro Gly Gly Gly Asn Lys Lys Ile Glu Thr His
    300                 305                 310
aag ctg acc ttc cgc gag aac gcc aaa gcc aag aca gac cac ggg gcg       1312
Lys Leu Thr Phe Arg Glu Asn Ala Lys Ala Lys Thr Asp His Gly Ala

315                 320                 325                 330
gag atc gtg tac aag tcg cca gtg gtg tct ggg gac acg tct cca cgg       1360
Glu Ile Val Tyr Lys Ser Pro Val Val Ser Gly Asp Thr Ser Pro Arg
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cat ctc agc aat gtc tcc tcc acc ggc agc atc gac atg gta gac tcg       1408
His Leu Ser Asn Val Ser Ser Thr Gly Ser Ile Asp Met Val Asp Ser
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ccc cag ctc gcc acg cta gct gac gag gtg tct gcc tcc ctg gcc aag       1456
Pro Gln Leu Ala Thr Leu Ala Asp Glu Val Ser Ala Ser Leu Ala Lys
        365                 370                 375
cag ggt ttg tga tcaggcccct ggggcggtca ataattgtgg agaggagaga           1508
Gln Gly Leu
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Met Ala Glu Pro Arg Gln Glu Phe Glu Val

1 5 10

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Met Glu Asp His Ala Gly Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln

15 20 25

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Pro Gly Ser Glu Thr Ser Asp Ala Lys Ser Thr Pro Thr Ala Glu Asp
    60                  65                  70
gtg aca gca ccc tta gtg gat gag gga gct ccc ggc aag cag gct gcc        592
Val Thr Ala Pro Leu Val Asp Glu Gly Ala Pro Gly Lys Gln Ala Ala

75                  80                  85                  90
gcg cag ccc cac acg gag atc cca gaa gga acc aca gct gaa gaa gca        640
Ala Gln Pro His Thr Glu Ile Pro Glu Gly Thr Thr Ala Glu Glu Ala
                95                  100                 105
ggc att gga gac acc ccc agc ctg gaa gac gaa gct gct ggt cac gtg        688
Gly Ile Gly Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val
            110                 115                 120

acc caa gag cct gaa agt ggt aag gtg gtc cag gaa ggc ttc ctc cga        736
Thr Gln Glu Pro Glu Ser Gly Lys Val Val Gln Glu Gly Phe Leu Arg
        125                 130                 135
gag cca ggc ccc cca ggt ctg agc cac cag ctc atg tcc ggc atg cct        784
Glu Pro Gly Pro Pro Gly Leu Ser His Gln Leu Met Ser Gly Met Pro
    140                 145                 150
ggg gct ccc ctc ctg cct gag ggc ccc aga gag gcc aca cgc caa cct        832

Gly Ala Pro Leu Leu Pro Glu Gly Pro Arg Glu Ala Thr Arg Gln Pro
155                 160                 165                 170
tcg ggg aca gga cct gag gac aca gag ggc ggc cgc cac gcc cct gag        880
Ser Gly Thr Gly Pro Glu Asp Thr Glu Gly Gly Arg His Ala Pro Glu
                175                 180                 185
ctg ctc aag cac cag ctt cta gga gac ctg cac cag gag ggg ccg ccg        928
Leu Leu Lys His Gln Leu Leu Gly Asp Leu His Gln Glu Gly Pro Pro

            190                 195                 200
ctg aag ggg gca ggg ggc aaa gag agg ccg ggg agc aag gag gag gtg        976
Leu Lys Gly Ala Gly Gly Lys Glu Arg Pro Gly Ser Lys Glu Glu Val
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        205                 210                 215
gat gaa gac cgc gac gtc gat gag tcc tcc ccc caa gac tcc cct ccc       1024
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    220                 225                 230

tcc aag gcc tcc cca gcc caa gat ggg cgg cct ccc cag aca gcc gcc       1072
Ser Lys Ala Ser Pro Ala Gln Asp Gly Arg Pro Pro Gln Thr Ala Ala
235                 240                 245                 250
aga gaa gcc acc agc atc cca ggc ttc cca gcg gag ggt gcc atc ccc       1120
Arg Glu Ala Thr Ser Ile Pro Gly Phe Pro Ala Glu Gly Ala Ile Pro
                255                 260                 265
ctc cct gtg gat ttc ctc tcc aaa gtt tcc aca gag atc cca gcc tca       1168

Leu Pro Val Asp Phe Leu Ser Lys Val Ser Thr Glu Ile Pro Ala Ser
            270                 275                 280
gag ccc gac ggg ccc agt gta ggg cgg gcc aaa ggg cag gat gcc ccc       1216
Glu Pro Asp Gly Pro Ser Val Gly Arg Ala Lys Gly Gln Asp Ala Pro
        285                 290                 295
ctg gag ttc acg ttt cac gtg gaa atc aca ccc aac gtg cag aag gag       1264
Leu Glu Phe Thr Phe His Val Glu Ile Thr Pro Asn Val Gln Lys Glu

    300                 305                 310
cag gcg cac tcg gag gag cat ttg gga agg gct gca ttt cca ggg gcc       1312
Gln Ala His Ser Glu Glu His Leu Gly Arg Ala Ala Phe Pro Gly Ala
315                 320                 325                 330
cct gga gag ggg cca gag gcc cgg ggc ccc tct ttg gga gag gac aca       1360
Pro Gly Glu Gly Pro Glu Ala Arg Gly Pro Ser Leu Gly Glu Asp Thr
                335                 340                 345

aaa gag gct gac ctt cca gag ccc tct gaa aag cag cct gct gct gct       1408
Lys Glu Ala Asp Leu Pro Glu Pro Ser Glu Lys Gln Pro Ala Ala Ala
            350                 355                 360
ccg cgg ggg aag ccc gtc agc cgg gtc cct caa ctc aaa gct cgc atg       1456
Pro Arg Gly Lys Pro Val Ser Arg Val Pro Gln Leu Lys Ala Arg Met
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Ser Pro Lys His Pro Thr Pro Gly Ser Ser Asp Pro Leu Ile Gln Pro

415 420 425

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460 465 470

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Ala Pro Pro Gly Gln Lys Gly Gln Ala Asn Ala Thr Arg Ile Pro Ala
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Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly Glu Pro Pro
495 500 505

aaa tca ggg gat cgc agc ggc tac agc agc ccc ggc tcc cca ggc act 1888
Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr
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Pro Gly Ser Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro Pro Thr Arg

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Glu Pro Lys Lys Val Ala Val Val Arg Thr Pro Pro Lys Ser Pro Ser
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tcc gcc aag agc cgc ctg cag aca gcc ccc gtg ccc atg cca gac ctg       2032
Ser Ala Lys Ser Arg Leu Gln Thr Ala Pro Val Pro Met Pro Asp Leu
555                 560                 565                 570

aag aat gtc aag tcc aag atc ggc tcc act gag aac ctg aag cac cag       2080
Lys Asn Val Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu Lys His Gln
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ccg gga ggc ggg aag gtg cag ata att aat aag aag ctg gat ctt agc       2128
Pro Gly Gly Gly Lys Val Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser
            590                 595                 600
aac gtc cag tcc aag tgt ggc tca aag gat aat atc aaa cac gtc ccg       2176

Asn Val Gln Ser Lys Cys Gly Ser Lys Asp Asn Ile Lys His Val Pro
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gga ggc ggc agt gtg caa ata gtc tac aaa cca gtt gac ctg agc aag       2224
Gly Gly Gly Ser Val Gln Ile Val Tyr Lys Pro Val Asp Leu Ser Lys
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gtg acc tcc aag tgt ggc tca tta ggc aac atc cat cat aaa cca gga       2272
Val Thr Ser Lys Cys Gly Ser Leu Gly Asn Ile His His Lys Pro Gly

635                 640                 645                 650
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Gly Gly Gln Val Glu Val Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg
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gtc cag tcg aag att ggg tcc ctg gac aat atc acc cac gtc cct ggc       2368
Val Gln Ser Lys Ile Gly Ser Leu Asp Asn Ile Thr His Val Pro Gly
            670                 675                 680

gga gga aat aaa aag att gaa acc cac aag ctg acc ttc cgc gag aac       2416
Gly Gly Asn Lys Lys Ile Glu Thr His Lys Leu Thr Phe Arg Glu Asn
        685                 690                 695
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gtg gtg tct ggg gac acg tct cca cgg cat ctc agc aat gtc tcc tcc 2512

Val Val Ser Gly Asp Thr Ser Pro Arg His Leu Ser Asn Val Ser Ser

715 720 725 730

acc ggc agc atc gac atg gta gac tcg ccc cag ctc gcc acg cta gct 2560

Thr Gly Ser Ile Asp Met Val Asp Ser Pro Gln Leu Ala Thr Leu Ala

735 740 745

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Asp Glu Val Ser Ala Ser Leu Ala Lys Gln Gly Leu

750 755

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