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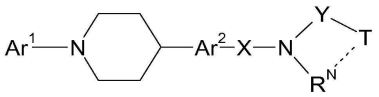
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(54) 발명의 명칭 **피페리딘 유도체 및 대사 장애의 치료를 위한 이의 용도**

(57) 요 약

본 발명은 하기 화학식 I의 신규 피페리딘 유도체, 약제로서의 이의 용도, 이의 치료적 사용을 위한 방법, 및 이를 함유하는 약제학적 조성물에 관한 것이다.

화학식 I



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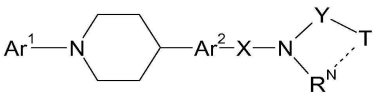
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특허청구의 범위

청구항 1

모든 토우토머 및 입체이성체를 포함하는 화학식 I의 화합물 또는 이의 염.

[화학식 I]



상기 화학식 I에서,

Ar^1은 아릴 및 헤테로아릴(이들 모두는, 하나 이상의 치환체 R^A에 의해 임의로 치환될 수 있다)로 이루어진 그룹 Ar^1-G1로부터 선택되고, 여기서, Ar^1의 인접한 C-원자들에 링크된(linked) 2개의 치환체 R^A는 서로 연결되어, 함께 C_{3-5}-알킬렌 브릿지 그룹을 형성할 수 있고, 여기서, 1, 2 또는 3개의 CH_2-그룹은 O, C(=O), S, S(=O), $S(=O)_2$, NH 또는 N(C_{1-4}-알킬)-에 의해 대체될 수 있고, 여기서, 상기 알킬렌 브릿지는 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환될 수 있고,

R^A는 H, F, Cl, Br, I, CN, OH, $-NO_2$, C_{1-6}-알킬, C_{2-6}-알케닐, C_{2-6}-알키닐, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{1-6}-알킬-O-, C_{3-6}-알케닐-O-, C_{3-6}-알키닐-O-, C_{3-10}-카보사이클릴-O-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-O-, C_{1-6}-알킬-S-, C_{1-6}-알킬-S(=O)-, C_{1-6}-알킬-$S(=O)_2$-, C_{3-10}-카보사이클릴-S-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-S-, C_{1-4}-알킬-C(=O)-, C_{3-10}-카보사이클릴-C(=O)-, $R^{N1}R^{N2}N$-, $R^{N1}R^{N2}N$-C_{2-3}-알킬-O-, $R^{N1}R^{N2}N$-C(=O)-, $R^{N1}R^{N2}N$-$S(=O)_2$-, C_{1-6}-알킬-C(=O)-NR^{N1}-, C_{1-6}-알킬-$S(=O)_2$-NR^{N1}-, C_{1-6}-알킬-C(=O)-NR^{N1}-C_{1-3}-알킬-, HO-C(=O)-, C_{1-6}-알킬-O-C(=O)-, 헤테로사이클릴, 헤테로사이클릴-O-, 헤테로사이클릴-C_{1-3}-알킬, 헤테로사이클릴-C_{1-3}-알킬-O-, 헤테로사이클릴-C(=O)-, 아릴, 아릴-C_{1-3}-알킬, 아릴-O-, 아릴-C_{1-3}-알킬-O-, 헤테로아릴, 헤테로아릴-C_{1-3}-알킬, 헤테로아릴-O-, 헤테로아릴-C_{1-3}-알킬-O- 및 헤테로아릴-C(=O)-로 이루어진 그룹 R^A-G1로부터 선택되고,

여기서, 각각의 카보사이클릴 및 헤테로사이클릴에서, CH_2-그룹은 -C(=O)- 또는 -C(=CR^{Alk}_2)-에 의해 임의로 대체될 수 있고,

여기서, 각각의 카보사이클릴 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬(이는 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있다)에 의해 임의로 치환될 수 있고,

여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있고,

여기서, 각각의 헤테로사이클릴은 아릴 또는 헤테로아릴에 의해 임의로 치환될 수 있고,

여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고,

R^C는 F, Cl, Br, CN, OH, C_{1-4}-알킬-O-, C_{3-7}-사이클로알킬-O-, C_{3-7}-사이클로알킬-C_{1-3}-알킬-O-, H_2N-, (C_{1-4}-알킬)NH-, (C_{1-4}-알킬)$_2$N-, H_2N-C(=O)-, (C_{1-4}-알킬)NH-C(=O)-, (C_{1-4}-알킬)$_2$N-C(=O)-, C_{1-4}-알킬-C(=O)-, C_{1-4}-알킬-$S(=O)_2$-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로 이루어진 그룹 R^C-G1로부터 선택되고, 여기서, 각각의 알킬 또는 사이클로알킬은 F 및 OH로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고,

R^{N1}은 H, C_{1-6}-알킬, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{3-6}-알케닐, C_{3-6}-알키닐, 헤테로사이클릴, 헤테로사이클릴-C_{1-3}-알킬, 아릴, 아릴-C_{1-3}-알킬, 헤테로아릴 및 헤테로아릴-C_{1-3}-알킬로 이루어진 그룹 R^{N1}-G1로부터 선택되고,

여기서, 각각의 카보사이클릴 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬, 아릴 또는 아릴-C_{1-3}-알킬에 의해 임의로 치환될 수 있고,

여기서, 각각의 카보사이클릴 및 헤테로사이클릴에서, CH_2-그룹은 -C(=O)-에 의해 임의로 대체될 수 있고,

여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있고,

여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고,

R^{N2}는 H 및 C_{1-6}-알킬로 이루어진 그룹 R^{N2}-G1로부터 선택되고,

R^{Alk}는 H 및 C_{1-6}-알킬(이는 하나 이상의 F 원자에 의해 치환될 수 있다)로 이루어진 그룹 R^{Alk}-G1로부터 선택되고,

Ar^2는 페닐, 및 N, O 또는 S로부터 선택된 1, 2 또는 3개의 헤테로 원자를 함유하는 5- 또는 6-원 모노사이클릭 방향족 카보사이클릭 환 시스템으로 이루어진 그룹 Ar^2-G1로부터 선택되고, 여기서, 위에서 언급한 그룹들은 모두 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고,

L은 F, Cl, Br, CN, OH, C_{1-4}-알킬-, C_{1-4}-알킬-O-, C_{1-4}-알킬-S-, C_{1-4}-알킬-S(=O)$_2$-, C_{1-4}-알킬-NR^{N2}-S(=O)$_2$-, H_2N-, (C_{1-4}-알킬)NH-, (C_{1-4}-알킬)$_2$N-, H_2N-C_{1-4}-알킬-, (C_{1-4}-알킬)NH-C_{1-4}-알킬-, (C_{1-4}-알킬)$_2$N-C_{1-4}-알킬-, C_{3-7}-사이클로알킬-, C_{3-7}-사이클로알킬-C_{1-3}-알킬-O- 및 헤테로사이클릴로 이루어진 그룹 L-G1로부터 선택되고, 여기서, 각각의 알킬은 하나 이상의 F-원자에 의해 및/또는 OH, C_{1-3}-알킬-O- 및 CN으로부터 선택되는 치환체에 의해 임의로 치환될 수 있고; 여기서, 아릴 또는 헤테로아릴 그룹에 부착된 2개의 치환체 L은 서로 링크되어 C_{2-5}-알킬렌 브릿지 그룹을 형성할 수 있고, 여기서, 1 또는 2개의 -CH_2-그룹은 O, S, NH 및 N(C_{1-4}-알킬)-로부터 서로 독립적으로 선택된 그룹에 의해 대체될 수 있고, 여기서, 상기 C_{2-5}-알킬렌 브릿지 그룹은 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환되고;

X는 하나 이상의 C_{1-3}-알킬 및 C_{1-3}-알킬-O-C_{1-3}-알킬에 의해 임의로 치환될 수 있는 직쇄형 C_{1-3}-알킬렌 그룹으로 이루어진 그룹 X-G1로부터 선택되고, 여기서, 2개의 알킬 치환체는 서로 연결되어, 함께 C_{1-5}-알킬렌 브릿지 그룹을 형성할 수 있고, 여기서, 1 또는 2개의 -CH_2-그룹은 O, S, NH 또는 N(C_{1-4}-알킬)-로부터 서로 독립적으로 선택된 그룹에 의해 대체될 수 있고, 여기서, 상기 C_{1-5}-알킬렌 브릿지는 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환되고;

Y는 -C(=O)-, -C(=S)- 및 -S(=O)$_2$-로 이루어진 그룹 Y-G1로부터 선택되고;

R^N은 H 및 C_{1-3}-알킬로 이루어진 그룹 R^N-G1로부터 선택되고,

T는 C_{1-6}-알킬, C_{2-6}-알케닐, C_{2-6}-알키닐, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C-$_{1-3}$-알킬-, C_{1-6}-알킬-O-, C_{3-10}-카보사이클릴-O-, C_{3-10}-카보사이클릴-C-$_{1-3}$-알킬-O-, C_{1-6}-알킬-S-, C_{3-10}-카보사이클릴-S-, C_{3-10}-카보사이클릴-C-$_{1-3}$-알킬-S-, C_{1-4}-알킬-C(=O)-, C_{1-4}-알킬-S(=O)$_2$-, $R^{N1}R^{N2}$-N-, $R^{N1}R^{N2}$-N-C_{1-3}-알킬-, $R^{N1}R^{N2}$-N-CO-, C_{1-4}-알킬-C(=O)-R^{N2}N-C_{1-3}-알킬-, C_{1-3}-알킬-O-N=CH-, C_{1-4}-알킬-O-C(=O)-R^{N2}N-C_{1-3}-알킬-, 헤테로사이클릴, 아릴, 헤테로아릴 및 헤테로아릴-C_{1-3}-알킬-로 이루어진 그룹 T-G1로부터 선택되고,

여기서, 각각의 카보사이클릴 및 헤테로사이클릴에서, CH_2-그룹은 -C(=O)-에 의해 임의로 대체될 수 있고,

여기서, 각각의 카보사이클릴 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬(이는 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있다)에 의해 임의로 치환될 수 있고,

여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있고,

여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있거나, 또는

그룹 T 및 R^N은 서로 연결되어, 함께, F, Cl, Br, OH, CN, C_{1-4}-알킬, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{1-4}-알킬-O-, C_{3-7}-사이클로알킬-O-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-O-, H_2N-, (C_{1-4}-알킬)NH-, (C_{1-4}-알킬)$_2$N-, C_{1-4}-알킬-C(=O)-, C_{1-4}-알킬-S(=O)$_2$-, HO-C(=O)-, C_{1-4}-알킬-O-C(=O)-로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있는 C_{2-5}-알킬렌으로 이루어진 그룹 (T-R^N)-G1로부터 선택되는 그룹을 형성할 수 있고, 여기서, 각각의 알킬 또는 카보사이클릴은 R^C로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있다.

청구항 2

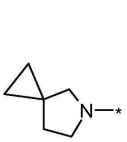
제1항에 있어서, Ar^1이 페닐, 디하이드로나프틸, 테트라하이드로나프틸, 나프틸 및 N, O, S 또는 S(O)$_r$(여기서, r은 0, 1 또는 2이다)로부터 선택되는 1, 2 또는 3개의 헤테로 원자를 함유하는 5- 또는 6-원 모노사이클릭 또는 9- 또는 10-원 비사이클릭-환 시스템으로 이루어진 그룹으로부터 선택되고, 여기서, 상기 헤테로 원자들 중의 적어도 하나는 방향족 환의 일부이고, 위에서 언급한 그룹은 모두 하나 이상의 치환체 R^A에 의해 임의로 치환될 수 있고, Ar^1의 인접한 C-원자들에 링크된 2개의 치환체 R^A는 서로 연결되어, 함께 C_{3-5}-알킬렌 브릿지 그룹을 형성할 수 있고, 여기서, 1, 2 또는 3개의 CH_2-그룹은 O, C(=O), S, S(=O), S(=O)$_2$, NH 또는 N(C_{1-4}-알킬)-에 의해 대체될 수 있고, 여기서, 상기 알킬렌 브릿지는 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환되고, 여기서, R^A는 제1항에 따라 정의되는, 화합물.

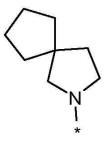
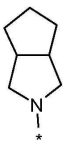
청구항 3

제1항 또는 제2항에 있어서,

그룹 R^A가 H, F, Cl, Br, I, CN, OH, NO_2, C_{1-6}-알킬, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{1-6}-알킬-O-, C_{3-6}-알케닐-O-, C_{3-6}-알키닐-O-, C_{3-10}-카보사이클릴-O-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-O-, C_{1-6}-알킬-S-, C_{3-10}-카보사이클릴-S-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-S-, C_{1-4}-알킬-C(=O)-, $R^{N1}R^{N2}N$-, $R^{N1}R^{N2}N$-C_{2-3}-알킬-O-, $R^{N1}R^{N2}N$-C(=O)-, HO-C(=O)-, C_{1-6}-알킬-O-C(=O)-, 헤테로사이클릴, 헤테로사이클릴-O-, 헤테로사이클릴-C_{1-3}-알킬, 헤테로사이클릴-C_{1-3}-알킬-O-, 헤테로사이클릴-C(=O)-, 아릴, 아릴-C_{1-3}-알킬, 아릴-O-, 아릴-C_{1-3}-알킬-O-, 헤테로아릴, 헤테로아릴-C_{1-3}-알킬, 헤테로아릴-O- 및 헤테로아릴-C_{1-3}-알킬-O-로 이루어진 그룹으로부터 선택되고,

여기서, 헤테로사이클릴은 아제티디닐, 피롤리디닐, 피페리디닐, 피페라지닐, N-C_{1-4}-알킬-피페라진-1-일, N-C_{1-4}-알킬설포닐-피페라진-1-일, 모르폴리닐, 디하이드로퀴놀리닐, 디하이드로이소퀴놀리닐, 디하이드로인돌릴, 디하이드로이소인돌릴, 옥세타닐, 테트라하이드로푸라닐 및 테트라하이드로피라닐로 이루어진 그룹으로부터, 또는


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및

으로 이루어진 그룹으로부터 선택되고,

여기서, 카보사이클릴은 C_{3-7}-사이클로알킬, 인다닐 및 테트라하이드로나프틸로부터 선택되고,

여기서, 헤테로아릴은 피롤릴, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 옥사졸릴, 이속사졸릴, 피라졸릴, 티아졸릴, 트리아졸릴, 테트라졸릴, 벤조푸라닐, 인돌릴, 퀴놀리닐 및 인다졸릴로 이루어진 그룹으로부터 선택되고;

여기서, 각각의 헤테로사이클릴 및/또는 카보사이클릴 그룹에서, $-CH_2-$그룹은 -C(=O)- 또는 $-C(=CR^{Alk}{}_2)-$에 의해 임의로 대체되고,

여기서, 각각의 카보사이클릴 및/또는 헤테로사이클릴 그룹은 하나 이상의 C_{1-3}-알킬에 의해 임의로 치환되고,

여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환되고,

여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 1, 2 또는 3개의 치환체 R^C에 의해 임의로 치환되고,

여기서, 각각의 카보사이클릴 또는 헤테로사이클릴은 아릴 또는 헤테로아릴 그룹, 특히 페닐 또는 피리딜에 의해 임의로 치환되고,

여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환되고,

여기서, 각각의 L, R^c, R^{N1}, R^{N2}는 제1항에 따라 정의되는, 화합물.

청구항 4

제1항 내지 제3항 중의 어느 한 항에 있어서, Ar^2가 페닐, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 티에닐, 피롤릴, 이미다졸릴, 트리아졸릴, 옥사졸릴, 이속사졸릴, 피라졸릴 및 티아졸릴로 이루어진 그룹으로부터 선택되고, 여기서, 위에서 언급한 그룹들은 모두 제1항에 따라 정의되는 하나 이상의 치환체 L에 의해 임의로 치환될 수 있는, 화합물.

청구항 5

제1항 내지 제4항 중의 어느 한 항에 있어서, X가, C_{1-3}-알킬로부터 선택되는 1, 2 또는 3개의 그룹에 의해 임의로 치환되는 직쇄 C_{1-3}-알킬렌 그룹이고; 여기서, 2개의 알킬 치환체는 서로 연결되어, 함께 C_{1-5}-알킬렌 브릿지 그룹을 형성할 수 있고, 여기서, 상기 C_{1-5}-알킬렌 브릿지 그룹은 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환될 수 있는, 화합물.

청구항 6

제1항 내지 제5항 중의 어느 한 항에 있어서, T가 C_{1-6}-알킬, C_{2-6}-알케닐, C_{2-6}-알키닐, C_{3-7}-사이클로알킬, C_{3-7}-사이클로알킬-C_{1-3}-알킬, C_{1-6}-알킬-O-, C_{3-7}-사이클로알킬-O-, C_{3-7}-사이클로알킬-C_{1-3}-알킬-O-, C_{1-6}-알킬-S-, C_{3-7}-사이클로알킬-S-, C_{3-7}-사이클로알킬-C_{1-3}-알킬-S-, C_{1-4}-알킬-C(=O)-, C_{1-4}-알킬-$S(=O)_2$-, $R^{T1}R^{T2}$-N-, $R^{T1}R^{T2}$-N-C_{1-3}-알킬-, $R^{T1}R^{T2}$-N-CO-, C_{1-4}-알킬-C(=O)-R^{T2}N-C_{1-3}-알킬, 헤테로사이클릴, 페닐 및 헤테로아릴로 이루어진 그룹으로부터 선택되고,

여기서, 각각의 사이클로알킬 및 헤테로사이클릴에서, CH_2-그룹은 -C(=O)-에 의해 임의로 대체될 수 있고;

여기서, 각각의 사이클로알킬 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬(이는 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있다)에 의해 임의로 치환될 수 있고,

여기서, 각각의 알킬, 사이클로알킬 및 헤테로사이클릴은 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있고,

여기서, R^{T1}은 H, C_{1-6}-알킬, C_{3-6}-사이클로알킬, C_{3-6}-사이클로알킬-C_{1-3}-알킬, 페닐 및 피리딜로 이루어진 그룹으로부터 선택되고, 여기서, 각각의 사이클로알킬은 하나 이상의 C_{1-4}-알킬에 의해 임의로 치환될 수 있고, 여기서, 각각의 알킬 및 사이클로알킬은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고, 여기서, 각각의 알킬 및 사이클로알킬은 OH, C_{1-3}-알킬-O-, C_{1-3}-알킬-C(=O)-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택되는 치환체에 의해 임의로 치환될 수 있고, 여기서, 각각의 페닐 및 피리딜 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고,

여기서, R^{T2}는 그룹 H 및 C_{1-4}-알킬로부터 선택되고,

여기서, 헤테로사이클릴은 아제티디닐, 피롤리디닐, 피페리디닐, 옥세타닐, 테트라하드로푸라닐 또는 테트라하이드로피라닐이고;

여기서, 헤테로아릴은 페닐, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 티에닐, 피롤릴, 이미다졸릴, 피라졸릴, 트리아졸릴, 옥사졸릴, 이속사졸릴, 티아졸릴 및 이소티아졸릴로 이루어진 그룹으로부터 선택되고,

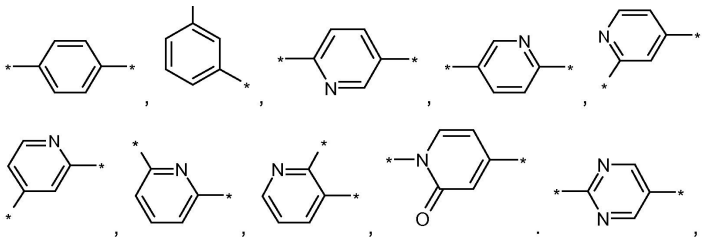
여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고,

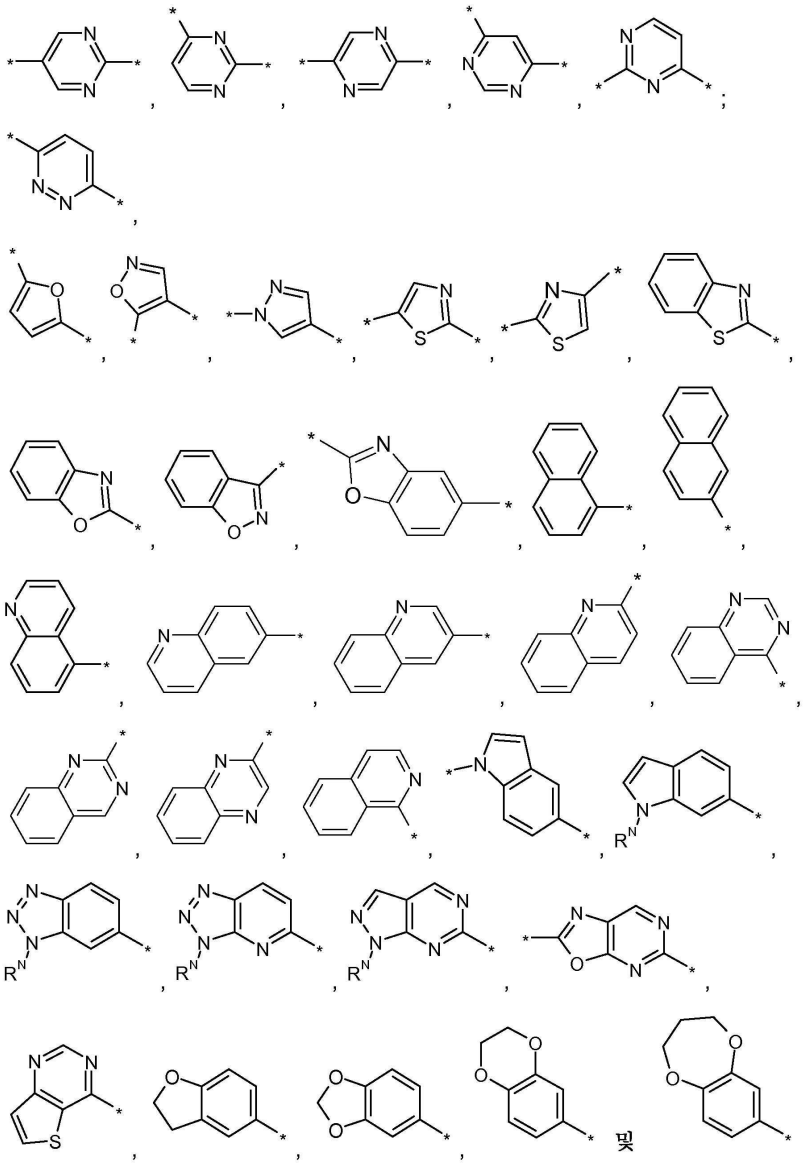
여기서, L, R^c는 제1항에 따라 정의되는, 화합물.

청구항 7

제1항 내지 제6항 중의 어느 한 항에 있어서,

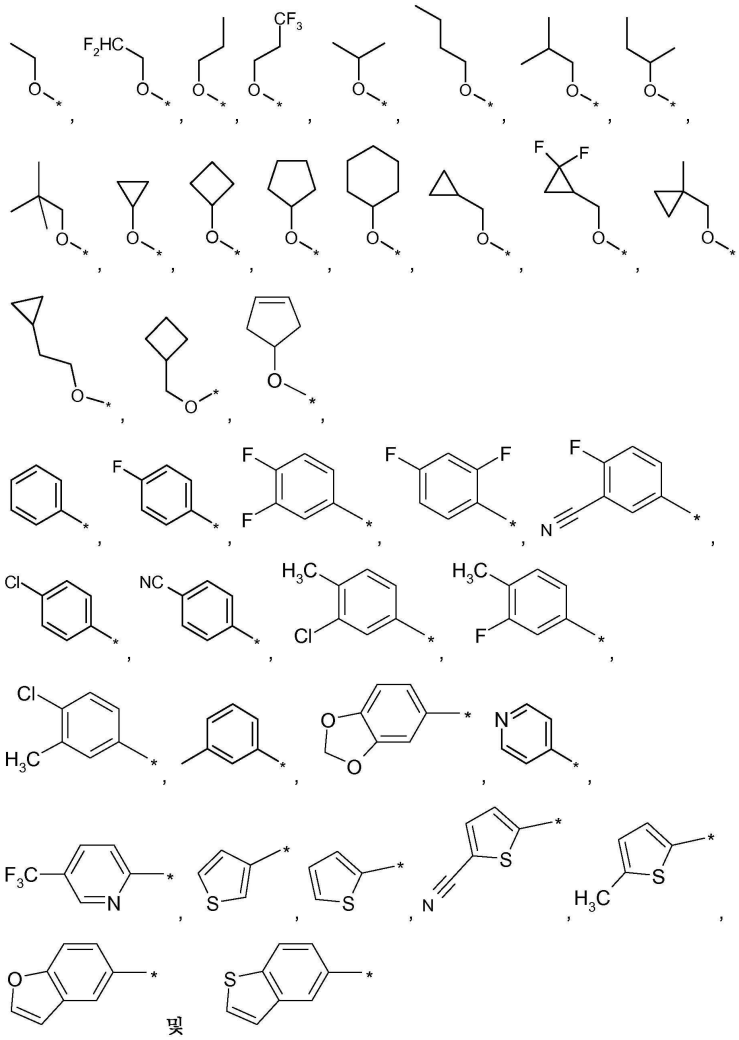
Ar^1이





(여기서, 각각의 사이클릭 그룹의 우측면에 대한 별표는, 화학식 I의 코어 구조의 피페리딘 환에 연결되는 결합을 나타내며, 각각의 사이클릭 그룹의 좌측면에 별표가 존재하는 경우, 치환체 R^A 또는 H에 연결되는 결합을 나타내고, 또한 위에서 언급한 사이클릭 그룹은 각각 하나 이상의 추가의 치환체 R^A에 의해 임의로 치환된다)로 이루어진 그룹으로부터 선택되고:

R^A가 F, Cl, Br, CN, F_3C-,



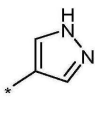
로 이루어진 그룹 R^A-G7로부터 선택되고,

Ar^2가  이고,

X가 -CH(CH_3)-이고,

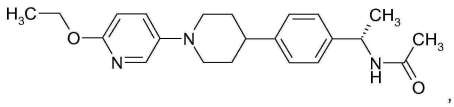
R^N이 H 또는 CH_3이고,

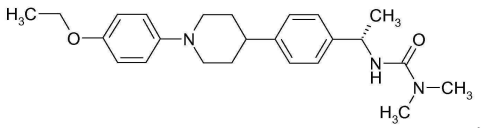
Y가 -C(=O)-이고,

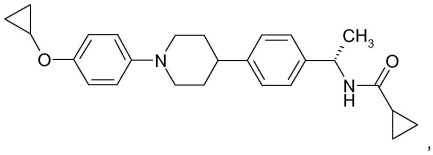
T가 H_3C-, F_3C-, H_3C-CH_2-, H_3C-O-, $(H_3C)_2N$-, ,  및  로 이루어진 그룹으로부터 선택되는, 화합물 또는 이의 염.

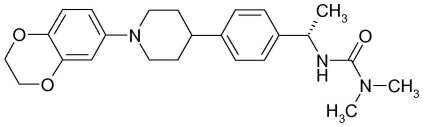
청구항 8

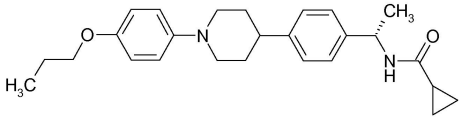
제1항에 있어서, 다음과 같은 화합물 또는 약제학적으로 허용되는 이들의 염:

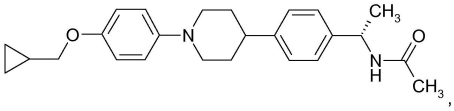
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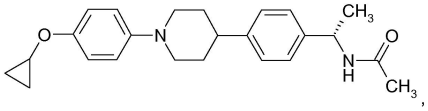
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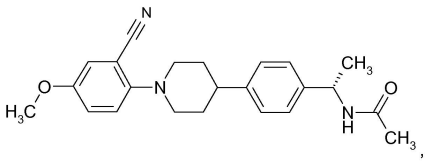
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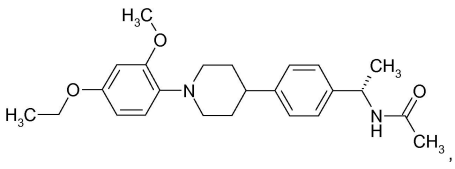
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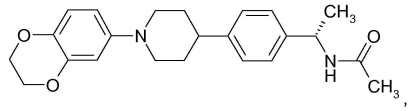
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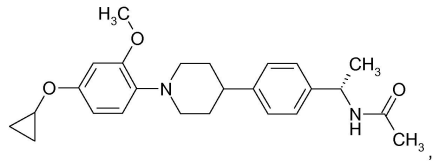
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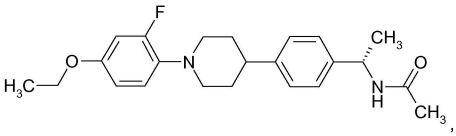
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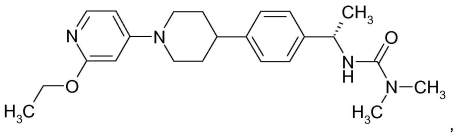
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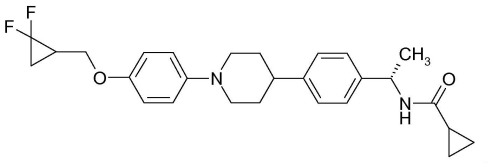
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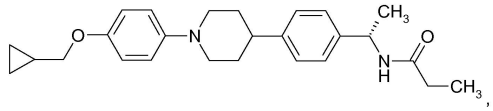


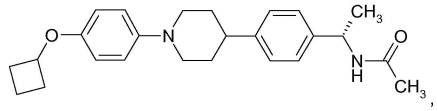


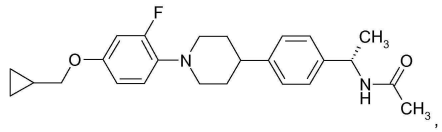


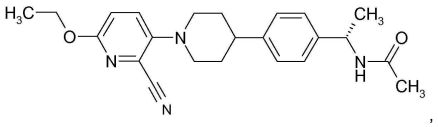


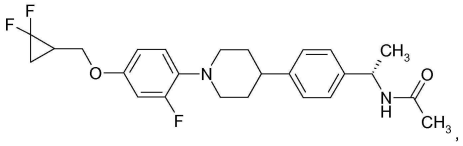


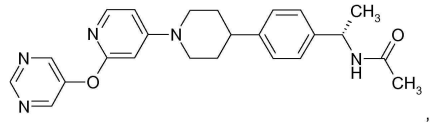


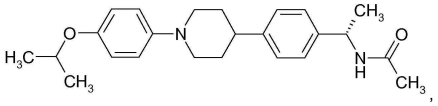


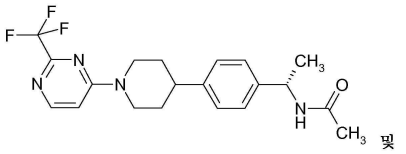
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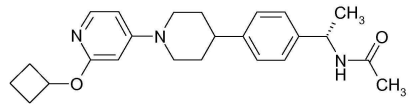
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청구항 9

제1항 내지 제8항 중의 어느 한 항에 따르는 화합물의 약제학적으로 허용되는 염.

청구항 10

약제로서의, 제1항 내지 제9항 중의 어느 한 항에 따르는 화합물, 또는 이의 약제학적으로 허용되는 염.

청구항 11

비만 또는 당뇨병의 치료를 위한, 제1항 내지 제10항 중의 어느 한 항에 따르는 화합물, 또는 이의 약제학적으로 허용되는 염.

청구항 12

제1항 내지 제8항 중의 어느 한 항에 따르는 하나 이상의 화합물 또는 하나 이상의 이의 약제학적으로 허용되는 염을, 임의로 하나 이상의 불활성 담체 및/또는 희석제와 함께 포함하는 약제학적 조성물.

청구항 13

아세틸-CoA 카복실라제 효소(들)의 활성을 억제함으로써 매개되는 질환 또는 상태의 치료를 필요로 하는 환자에게서 아세틸-CoA 카복실라제 효소(들)의 활성을 억제함으로써 매개되는 질환 또는 상태를 치료하는 방법으로서, 제1항 내지 제8항 중의 어느 한 항에 따르는 화합물 또는 이의 약제학적으로 허용되는 염을 상기 환자에게 투여함을 특징으로 하는, 방법.

청구항 14

비만 및/또는 당뇨병의 치료를 필요로 하는 환자에게서 비만 및/또는 당뇨병을 치료하는 방법으로서, 제1항 내지 제8항 중의 어느 한 항에 따르는 화합물 또는 이의 약제학적으로 허용되는 염을 상기 환자에게 투여함을 특징으로 하는, 방법.

청구항 15

제1항 내지 제8항 중의 어느 한 항에 따르는 하나 이상의 화합물 또는 하나 이상의 이의 약제학적으로 허용되는 염 및 하나 이상의 추가의 치료제를, 임의로 하나 이상의 불활성 담체 및/또는 희석제와 함께 포함하는 약제학적 조성물.

명 세 서

기 술 분 야

[0001] 본 발명은 신규 화합물, 특히 피페리딘 유도체; 상기 화합물의 제조 방법; 아세틸-CoA 카복실라제의 억제제로서의 이의 용도; 특히 아세틸-CoA 카복실라제 효소(들)의 억제에 의해 매개되는 질환 및 상태에 있어서의 상기 화합물의 치료적 사용을 위한 방법; 및 상기 화합물을 포함하는 약학 조성물에 관한 것이다.

배 경 기 술

[0002] 일반적으로 비만은 EU, USA, 일본의 경우 뿐만 아니라 세계적으로 주요 공중보건 이슈이다. 비만은 당뇨병, 이상지질혈증, 고혈압, 심혈관 및 뇌혈관 질환을 포함한 수많은 심각한 질환과 관련된다. 근본적인 메카니즘이 아직 완전히 이해되지는 못했지만, 지나친 지질의 축적에 의한 표적 조직의 인슐린 작용의 손상이 일반적으로 2차 병리학에 비만을 연결하는 주요 메카니즘으로서 간주된다(G. Wolf, Nutrition Reviews Vol. 66(10):597-600; DB Savage, KF Petersen, GI Shulman, Physiol Rev. 2007;87:507-520). 따라서, 인슐린 표적 조직에서 세포 지질 대사의 이해는, 비만과 관련된 질환의 발병을 설명하기 위해 결정적이다.

[0003] 지질 대사에서의 중심 사건은, 2개의 포유동물 ACC 이소형태(isoform) ACC1(ACC-알파, ACCA로서도 언급됨) 및 ACC2(ACC-베타, ACCB로서도 언급됨)에 의한 아세틸-CoA의 카복실화를 통한 말로닐-CoA의 생성이다(D Saggerson, Annu Rev Nutr. 2008;28:253-72). 생성된 말로닐-CoA는 데 노보 지방산 합성을 위해 사용되며, CPT-1의 억제제로서 작용함으로써, 미토콘드리아 지방산 산화를 조절한다. 더욱이, 말로닐-CoA는 또한 음식 섭취를 조절하는데 중추적인 작용을 하는 것으로 기술되어 있고, 췌장으로부터 인슐린 분비를 조절하는데 중요한 역할을 할 수 있고(GD Lopaschuk, JR Ussher, JS Jaswal. Pharmacol Rev. 2010;62:237-64; D Saggerson Annu Rev Nutr. 2008;28:253-72), 또한 중간 대사의 조절을 조정하는데 중요한 역할을 할 수 있다.

[0004] 따라서, ACC1 및 ACC2는 지방산 대사의 주요 조절제로서 제시되어 왔고, 현재 비만, 당뇨병 및 심혈관 합병증의 인간 질환을 조절하는데 관심 있는 표적으로서 고려되고 있다(SJ Wakil and LA Abu-Elheiga, J. Lipid Res. 2009. 50: S138-S143; L. Tong, HJ Harwood Jr. Journal of Cellular Biochemistry 99:1476-1488, 2006).

[0005] 중간 대사에서의 이의 독특한 위치로 인해, ACC의 억제는, 지질합성 조직(간 및 지방질)에서 데 노보 지방산 생성을 억제하는 능력을 제공하는 동시에 산화 조직(간, 심장 및 골격근)에서 지방산 산화를 촉진하며, 이에 따라, 비만, 당뇨병, 인슐린 저항성, 비알코올성 지방간(NASH) 및 대사 증후군과 관련된 많은 심혈관 위험 인자들에 일치된 방법으로 유용하게 영향을 끼치기 위한 관심 있는 양상을 제공한다(L. Tong, HJ Harwood Jr. Journal of Cellular Biochemistry 99:1476-1488, 2006; JW Corbett, JH Jr.Harwood, Recent Pat Cardiovasc Drug Discov. 2007 Nov;2(3):162-80).

[0006] 더욱이, 최근의 데이터는, 지질에 의해 매개된 세포 독성(지질독성)이 당뇨병 관련 신장병에 대한 감수성의 원인을 나타냄을 보여준다(검토를 위한 참조: M Murea, BI Freedmann, JS Parks, PA Antinozzi, SC Elbein, LM Ma; Clin J Am Soc Nephrol. 2010; 5:2373-9). 일본 특허에서 대규모 전장유전체연관분석 연구(genome-wide association study)는 9개의 독립적인 코호트(cohort)에서 복제된 당뇨성 신장병 위험과 관련되는 ACC2 유전자(ACACB) 중에서의 단일 뉴클레오티드 다형성을 확인하였다. 신장에서, 증가된 지방산 수준을 유도하는 지방산 대사의 조절곤란은 사구체 및 관 기능이상을 유도할 것으로 사료된다(M Murea, BI Freedmann, JS Parks, PA Antinozzi, SC Elbein, LM Ma; Clin J Am Soc Nephrol. 2010; 5:2373-9). 따라서, 지질 산화에 관여하는 주요 분자로서 ACC를 표적으로 하는 억제제는 당뇨성 신장병에 유리하게 영향을 주는데 유용한 잠재력을 갖는다.

[0007] 또한, 인슐린 저항성, 탈조절 지질대사, 지질독성 및 증가된 근육내 지질이 또한 1형 당뇨병에서 역할을 하는 것으로 기술되어 왔다(IE Schauer, JK Snell-Bergeon, BC Bergman, DM Maahs, A Kretowski, RH Eckel, M Rewers Diabetes 2011;60:306-14; P Ebeling, B Essen-Gustavsson, JA Tuominen and VA Koivisto Diabetologia 41: 111-115; KJ Nadeau, JG Regensteiner, TA Bauer, MS Brown, JL Dorosz, A Hull, P Zeitler, B Draznin, JEB. Reusch J Clin Endocrinol Metab, 2010, 95:513-521). 따라서, ACC 억제제는 또한

1형 당뇨병 치료를 위한 관심 있는 약제로서 여겨진다.

[0008] 또한, ACC 억제제는, 악성 세포 또는 침입 유기체의 신속한 증식을 유지하기 위한 내인성 지질 합성에 좌우되는 악성 세포 또는 침입 유기체의 신속한 성장으로부터 야기되는 질환의 진행에 개입하는 잠재력을 갖는다. 데 노보 지방질합성(de novo lipogenesis)은 다수의 종양 세포의 성장에 필요한 것으로 공지되어 있으며, ACC 상향-조절은, 신속한 성장 및 증식을 위한 암세포의 요구에 부합되는 지방생성을 촉진하는, 다수의 인간 암에서 인지되어 왔다(C Wang, S Rajput, K Watabe, DF Liao, D Cao Front Biosci 2010; 2:515-26). 이는, 암세포에서 성장 정지 및 선택적 세포독성을 유도하는 ACC 억제제를 사용하고, 상이한 형태의 암세포들에서 성장을 억제하고 아폽토시스를 유도하는 ACC의 RNA 간섭-매개된 넉다운(knock-down)에 의한 연구에서 추가로 설명된다. 더욱이, ACC1은 유방암 감수성 유전자 1(BRCA1)과 관련이 있으며 상기 유전자 1에 의해 조절된다. 통상 발생되는 BRCA1 돌연변이는 ACC1 활성화 및 유방암 감수성을 유도한다(C Wang, S Rajput, K Watabe, DF Liao, D Cao Front Biosci 2010; 2:515-26).

[0009] 더욱이, 알츠하이머병, 파킨슨병 및 간질을 포함하지만 이에 한정되지 않는 중추신경계 질환에서, 신경세포 에너지 대사의 손상이 기술되어 왔다(Ogawa M, Fukuyama H, Ouchi Y, Yamauchi H, Kimura J, J Neurol Sci. 1996;139(1):78-82). 이 대사 결함을 표적으로 하는 개입은 환자에 유용한 것으로 입증될 수 있다. 따라서, 하나의 유망한 개입은, 대체 기질로서 글루코즈-절충된 뇌신경 뇌 뉴론에 케톤체를 제공하는 것이다(ST Henderson Neurotherapeutics, 2008, 5:470-480; LC Costantini, LJ Barr, JL Vogel, ST Henderson BMC Neurosci. 2008, 9 Suppl 2:S16; KW Baranano, AL Hartman. Curr Treat Options Neurol. 2008;10:410-9). 증가된 지방산 산화를 유도하는 ACC 억제는, 이에 의해 케톤체의 혈액 수준의 증가를 야기함으로써, 뇌에 대한 대체 에너지 기질을 제공할 수 있다.

[0010] 전임상적 및 임상적 증거는, 케톤체가 파킨슨병, AD, 저산소증, 허혈, 근위축성 측삭경화증 및 신경교종의 모델에서 신경보호 효과를 제공할 수 있고(LC Costantini, LJ Barr, JL Vogel, ST Henderson BMC Neurosci. 2008, 9 Suppl 2:S16) 및 알츠하이머병 환자의 개선된 인지 등급을 제공할 수 있다(MA Reger, ST Henderson, C Hale, B Cholerton, LD Baker, GS Watson, K Hydea, D Chapmana, S Craft Neurobiology of Aging 25 (2004) 311-314)고 제시하고 있다. 증가된 케톤 수준의 최종 결과는 미토콘드리아 효율의 개선 및 반응성 산소 그룹 생성의 감소이다(검토를 위한 참조: LC Costantini, LJ Barr, JL Vogel, ST Henderson BMC Neurosci. 2008, 9 Suppl 2:S16; KW Baranano, AL Hartman. Curr Treat Options Neurol. 2008;10:410-9).

[0011] 더욱이, 항진균제로서 및 항균제로서의 ACC 억제제의 잠재력이 잘 기록되어 있다(L. Tong, HJ Harwood Jr. Journal of Cellular Biochemistry 99:1476-1488, 2006). 또한, ACC 억제제는 바이러스 감염을 퇴치하는데 사용할 수 있다. 최근에 바이러스는 바이러스 복제용 에너지 및 빌딩 블록을 제공하기 위한 이의 세포 숙주의 대사 네트워크에 따라 좌우되는 것으로 밝혀졌다(Munger J, BD Bennett, A Parikh, XJ Feng, J McArdle, HA Rabitz, T Shenk, JD Rabinowitz. Nat Biotechnol. 2008;26:1179-86). 인간 거대세포 바이러스(HCMV)에 의해 유도되는 대사활성의 변화를 정량화하는 플럭스(flux) 측정 접근법은, HCMV에 의한 감염이, 해당과정, 트리카복실산 사이클 및 지방산 생합성을 포함하는 다수의 중심 탄소 대사를 통해 플럭스를 현저히 변화시킨다고 설명하였다. 지방산 생합성의 약물학적 억제는 지방산 합성이 복제에 필수적임을 나타내는 2개의 상이한 피막 바이러스(HCMV 및 인플루엔자 A)의 복제를 억제한다. 이들 예는, 새로이 합성된 지방산 및 인지질이 바이러스 피막 형성에 중요한 것과 같이, 아세틸-CoA 플럭스 및 데 노보 지방산 생합성이 바이러스 생존 및 전파에 중요함을 나타낸다. 대사 플럭스의 변화는 유용한 인지질의 절대량에 영향을 주며, 상기 피막의 화학적 조성 및 물리적 특성은 바이러스 성장 및 복제에 부정적인 영향을 준다. 따라서, 지방산 대사에서 주요 효소들에 작용하는 ACC 억제제는 항바이러스 약제에 대한 잠재력을 갖는다.

발명의 내용

[0012] **발명의 목적**

[0013] 본 발명의 목적은 아세틸-CoA 카복실라제 효소(들)에 대해 활성인 신규 화합물, 특히 신규 피페리딘 유도체를 제공하는 것이다.

[0014] 본 발명의 또 다른 목적은 ACC2에 대해 활성인 신규 화합물, 특히 신규 피페리딘 유도체를 제공하는 것이다.

[0015] 본 발명의 추가 목적은 시험관 내 및/또는 생체 내에서 효소 아세틸-CoA 카복실라제 효소(들)에 대해 억제 효과를 가지며 약제로서 사용하기에 적합한 약물학적 및 약동학적 특성을 갖는 신규 화합물, 특히 신규 피페리딘 유

도체를 제공하는 것이다.

[0016] 본 발명의 추가 목적은 시험관 내 및/또는 생체 내에서 효소 ACC2에 대해 억제 효과를 가지며 약제로서 사용하기에 적합한 약물학적 및 약동학적 특성을 갖는 신규 화합물, 특히 신규 피페리딘 유도체를 제공하는 것이다.

[0017] 본 발명의 추가 목적은 특히 대사 장애, 예를 들면 비만 및/또는 당뇨병의 치료를 위한, 효과적인 ACC 억제제를 제공하는 것이다.

[0018] 본 발명의 추가 목적은 환자에게서 아세틸-CoA 카복실라제 효소(들)의 억제에 의해 매개되는 질환 또는 상태를 치료하는 방법을 제공하는 것이다.

[0019] 본 발명의 추가 목적은 본 발명에 따르는 적어도 하나의 화합물을 포함하는 약제학적 조성물을 제공하는 것이다.

[0020] 본 발명의 추가 목적은 하나 이상의 추가의 치료제를 갖는 본 발명에 따르는 적어도 하나의 화합물의 혼합물을 제공하는 것이다.

[0021] 본 발명의 추가 목적은 신규 화합물, 특히 피페리딘 유도체의 합성 방법을 제공하는 것이다.

[0022] 본 발명의 추가 목적은 신규 화합물의 합성을 위한 방법에 적합한 출발 및/또는 중간체 화합물을 제공하는 것이다.

[0023] 본 발명의 추가 목적은 상기 및 이어지는 기술에 의해 및 실시예에 의해 당해 분야의 숙련가에게 명확해진다.

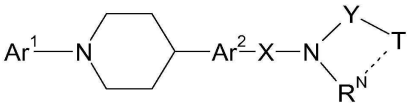
[0024] **본 발명의 목표**

[0025] 본 발명의 범위 내에서, 본 발명에 이르러 놀랍게도 아래에 기술되는 화학식 I의 신규 화합물이 아세틸-CoA 카복실라제 효소(들)에 대해 억제 활성을 나타내는 것으로 밝혀졌다.

[0026] 본 발명의 또 다른 측면에 따르면, 아래에 기술되는 화학식 I의 신규 화합물이 ACC2에 대해 억제 활성을 나타내는 것으로 밝혀졌다.

[0027] 따라서, 제1 측면에서, 본 발명은, 모든 토우토머 및 입체이성체를 포함하는 화학식 I의 화합물 또는 이의 염 또는 이의 용매화물 또는 수화물을 제공한다.

[0028] [화학식 I]

[0029] 

[0030] 상기 화학식 I에서,

[0031] Ar^1은 아릴 및 헤테로아릴(이들 모두는, 하나 이상의 치환체 R^A에 의해 임의로 치환될 수 있다)로 이루어진 그룹 Ar^1-G1로부터 선택되고, 여기서, Ar^1의 인접한 C-원자들에 링크된(linked) 2개의 치환체 R^A는 서로 연결되어, 함께 C_{3-5}-알킬렌 브릿지 그룹을 형성할 수 있고, 여기서, 1, 2 또는 3개의 CH_2-그룹은 O, C(=O), S, S(=O), $S(=O)_2$, NH 또는 N(C_{1-4}-알킬)-에 의해 대체될 수 있고, 여기서, 상기 알킬렌 브릿지는 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환될 수 있고,

[0032] R^A는 H, F, Cl, Br, I, CN, OH, $-NO_2$, C_{1-6}-알킬, C_{2-6}-알케닐, C_{2-6}-알키닐, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{1-6}-알킬-O-, C_{3-6}-알케닐-O-, C_{3-6}-알키닐-O-, C_{3-10}-카보사이클릴-O-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-O-, C_{1-6}-알킬-S-, C_{1-6}-알킬-S(=O)-, C_{1-6}-알킬-$S(=O)_2$-, C_{3-10}-카보사이클릴-S-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-S-, C_{1-4}-알킬-C(=O)-, C_{3-10}-카보사이클릴-C(=O)-, $R^{N1}R^{N2}N$-, $R^{N1}R^{N2}N$-C_{2-3}-알킬-O-, $R^{N1}R^{N2}N$-C(=O)-, $R^{N1}R^{N2}N$-$S(=O)_2$-, C_{1-6}-알킬-C(=O)-NR^{N1}-, C_{1-6}-알킬-$S(=O)_2$-NR^{N1}-, C_{1-6}-알킬-C(=O)-NR^{N1}-C_{1-3}-알킬-, HO-C(=O)-, C_{1-6}-알킬-O-C(=O)-, 헤테로사이클릴, 헤테로사이클릴-O-, 헤테로사이클릴-C_{1-3}-알킬, 헤테로사이클릴-C_{1-3}-알킬-O-, 헤테로사이클릴-C(=O)-, 아릴, 아릴-C_{1-3}-알킬, 아릴-O-, 아릴-C_{1-3}-알킬-O-, 헤테로아릴, 헤테로아릴-C_{1-3}-알킬, 헤테로아릴-O-,

헤테로아릴-C_{1-3}-알킬-O- 및 헤테로아릴-C(=O)-로 이루어진 그룹 R^{A}-G1로부터 선택되고,

[0033] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴에서, CH_2-그룹은 -C(=O)- 또는 -C(=CR^{Alk}_2)-에 의해 임의로 대체될 수 있고,

[0034] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬(이는 하나 이상의 치환체 R^{C}에 의해 임의로 치환될 수 있다)에 의해 임의로 치환될 수 있고,

[0035] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 하나 이상의 치환체 R^{C}에 의해 임의로 치환될 수 있고,

[0036] 여기서, 각각의 헤테로사이클릴은 아릴 또는 헤테로아릴에 의해 임의로 치환될 수 있고,

[0037] 여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고,

[0038] R^{C}는 F, Cl, Br, CN, OH, C_{1-4}-알킬-O-, C_{3-7}-사이클로알킬-O-, C_{3-7}-사이클로알킬-C_{1-3}-알킬-O-, H_2N-, (C_{1-4}-알킬)NH-, (C_{1-4}-알킬)$_2$N-, H_2N-C(=O)-, (C_{1-4}-알킬)NH-C(=O)-, (C_{1-4}-알킬)$_2$N-C(=O)-, C_{1-4}-알킬-C(=O)-, C_{1-4}-알킬-S(=O)$_2$-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로 이루어진 그룹 R^{C}-G1로부터 선택되고, 여기서, 각각의 알킬 또는 사이클로알킬은 F 및 OH로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고,

[0039] R^{N1}은 H, C_{1-6}-알킬, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{3-6}-알케닐, C_{3-6}-알키닐, 헤테로사이클릴, 헤테로사이클릴-C_{1-3}-알킬, 아릴, 아릴-C_{1-3}-알킬, 헤테로아릴 및 헤테로아릴-C_{1-3}-알킬로 이루어진 그룹 R^{N1}-G1로부터 선택되고,

[0040] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬, 아릴 또는 아릴-C_{1-3}-알킬에 의해 임의로 치환될 수 있고,

[0041] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴에서, CH_2-그룹은 -C(=O)-에 의해 임의로 대체될 수 있고,

[0042] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 하나 이상의 치환체 R^{C}에 의해 임의로 치환될 수 있고,

[0043] 여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고,

[0044] R^{N2}는 H 및 C_{1-6}-알킬로 이루어진 그룹 R^{N2}-G1로부터 선택되고,

[0045] R^{Alk}는 H 및 C_{1-6}-알킬(이는 하나 이상의 F 원자에 의해 치환될 수 있다)로 이루어진 그룹 R^{Alk}-G1로부터 선택되고,

[0046] Ar^{2}는 페닐, 및 N, O 또는 S로부터 선택된 1, 2 또는 3개의 헤테로 원자를 함유하는 5- 또는 6-원 모노사이클릭 방향족 카보사이클릭 환 시스템으로 이루어진 그룹 Ar^{2}-G1로부터 선택되고, 여기서, 위에서 언급한 그룹들은 모두 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고,

[0047] L은 F, Cl, Br, CN, OH, C_{1-4}-알킬-, C_{1-4}-알킬-O-, C_{1-4}-알킬-S-, C_{1-4}-알킬-S(=O)$_2$-, C_{1-4}-알킬-NR^{N2}-S(=O)$_2$-, H_2N-, (C_{1-4}-알킬)NH-, (C_{1-4}-알킬)$_2$N-, H_2N-C_{1-4}-알킬-, (C_{1-4}-알킬)NH-C_{1-4}-알킬-, (C_{1-4}-알킬)$_2$N-C_{1-4}-알킬-, C_{3-7}-사이클로알킬-, C_{3-7}-사이클로알킬-C_{1-3}-알킬-O- 및 헤테로사이클릴로 이루어진 그룹 L-G1로부터 선택되고, 여기서, 각각의 알킬은 하나 이상의 F-원자에 의해 및/또는 OH, C_{1-3}-알킬-O- 및 CN으로부터 선택되는 치환체에 의해 임의로 치환될 수 있고; 여기서, 아릴 또는 헤테로아릴 그룹에 부착된 2개의 치환체 L은 서로 링크되어 C_{2-5}-알킬렌 브릿지 그룹을 형성할 수 있고, 여기서, 1 또는 2개의 -CH_2-그룹은 O, S, NH 및 N(C_{1-4}-알킬)-로부터 서로 독립적으로 선택된 그룹에 의해 대체될 수 있고, 여기서, 상기 C_{2-5}-알킬렌 브릿지 그룹은 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환되고;

[0048] X는 하나 이상의 C_{1-3}-알킬 및 C_{1-3}-알킬-O-C_{1-3}-알킬에 의해 임의로 치환될 수 있는 직쇄형 C_{1-3}-알킬렌 그룹으로 이루어진 그룹 X-G1로부터 선택되고, 여기서, 2개의 알킬 치환체는 서로 연결되어, 함께 C_{1-5}-알킬렌 브릿지 그룹을 형성할 수 있고, 여기서, 1 또는 2개의 $-CH_2-$그룹은 O, S, NH 또는 N(C_{1-4}-알킬)-로부터 서로 독립적으로 선택된 그룹에 의해 대체될 수 있고, 여기서, 상기 C_{1-5}-알킬렌 브릿지 그룹은 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환되고;

[0049] Y는 -C(=O)-, -C(=S)- 및 $-S(=O)_2-$로 이루어진 그룹 Y-G1로부터 선택되고;

[0050] R^N은 H 및 C_{1-3}-알킬로 이루어진 그룹 R^N-G1로부터 선택되고,

[0051] T는 C_{1-6}-알킬, C_{2-6}-알케닐, C_{2-6}-알키닐, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C_{1-3}-알킬-, C_{1-6}-알킬-O-, C_{3-10}-카보사이클릴-O-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-O-, C_{1-6}-알킬-S-, C_{3-10}-카보사이클릴-S-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-S-, C_{1-4}-알킬-C(=O)-, C_{1-4}-알킬-$S(=O)_2-$, $R^{N1}R^{N2}$-N-, $R^{N1}R^{N2}$-N-C_{1-3}-알킬-, $R^{N1}R^{N2}$-N-CO-, C_{1-4}-알킬-C(=O)-R^{N2}N-C_{1-3}-알킬-, C_{1-3}-알킬-O-N=CH-, C_{1-4}-알킬-O-C(=O)-R^{N2}N-C_{1-3}-알킬-, 헤테로사이클릴, 아릴, 헤테로아릴 및 헤테로아릴-C_{1-3}-알킬-로 이루어진 그룹 T-G1로부터 선택되고,

[0052] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴에서, CH_2-그룹은 -C(=O)-에 의해 임의로 대체될 수 있고,

[0053] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬(이는 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있다)에 의해 임의로 치환될 수 있고,

[0054] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있고,

[0055] 여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있거나, 또는

[0056] 그룹 T 및 R^N은 서로 연결되어, 함께, F, Cl, Br, OH, CN, C_{1-4}-알킬, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{1-4}-알킬-O-, C_{3-7}-사이클로알킬-O-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-O-, H_2N-, (C_{1-4}-알킬)NH-, (C_{1-4}-알킬)$_2$N-, C_{1-4}-알킬-C(=O)-, C_{1-4}-알킬-$S(=O)_2-$, HO-C(=O)-, C_{1-4}-알킬-O-C(=O)-로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있는 C_{2-5}-알킬렌으로 이루어진 그룹 (T-R^N)-G1로부터 선택되는 그룹을 형성할 수 있고, 여기서, 각각의 알킬 또는 카보사이클릴은 R^C로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있다.

[0057] 추가의 측면에서, 본 발명은, 화학식 I의 화합물의 제조 방법 및 이들 방법 중의 신규 중간체 화합물에 관한 것이다.

[0058] 추가의 측면에서, 본 발명은, 본 발명에 따르는 화학식 I의 화합물의 염, 특히 이의 약제학적으로 허용되는 염에 관한 것이다.

[0059] 추가의 측면에서, 본 발명은, 임의로 하나 이상의 불활성 담체 및/또는 희석제와 함께, 본 발명에 따르는 하나 이상의 화학식 I의 화합물 또는 하나 이상의 이의 약제학적으로 허용되는 염을 포함하는 약제학적 조성물에 관한 것이다.

[0060] 추가의 측면에서, 본 발명은, 아세틸-CoA 카복실라제 효소(들)의 활성을 억제함으로써 매개되는 질환 또는 상태의 치료를 필요로 하는 환자에게서 아세틸-CoA 카복실라제 효소(들)의 활성을 억제함으로써 매개되는 질환 또는 상태를 치료하는 방법으로서, 화학식 I의 화합물 또는 이의 약제학적으로 허용되는 염을 상기 환자에세 투여함을 특징으로 하는 방법에 관한 것이다.

[0061] 본 발명의 또 다른 측면에 따라, 대사 질환 또는 장애의 치료를 필요로 하는 환자에게서 대사 질환 또는 장애를 치료하는 방법으로서, 화학식 I의 화합물 또는 이의 약제학적으로 허용되는 염을 상기 환자에게 투여함을 특징으로 하는 방법이 제공된다.

[0062] 본 발명의 또 다른 측면에 따라, 심혈관 질환 또는 장애의 치료를 필요로 하는 환자에게서 심혈관 질환 또는 장애를 치료하는 방법으로서, 화학식 I의 화합물 또는 이의 약제학적으로 허용되는 염을 상기 환자에게 투여함을 특징으로 하는 방법이 제공된다.

[0063] 본 발명의 또 다른 측면에 따라, 신경변성 질환 또는 장애의 치료 또는 중추신경계 질환 또는 장애의 치료를 필요로 하는 환자에게서 신경변성 질환 또는 장애를 치료하거나 중추신경계 질환 또는 장애를 치료하는 방법으로서, 화학식 I의 화합물 또는 이의 약제학적으로 허용되는 염을 상기 환자에게 투여함을 특징으로 하는 방법이 제공된다.

[0064] 본 발명의 또 다른 측면에 따라, 암, 악성종양 장애 또는 종양의 치료를 필요로 하는 환자에게서 암, 악성종양 장애 또는 종양을 치료하는 방법으로서, 화학식 I의 화합물 또는 이의 약제학적으로 허용되는 염을 상기 환자에게 투여함을 특징으로 하는 방법이 제공된다.

[0065] 본 발명의 또 다른 측면에 따라, 위에서 및 아래에서 기술되는 바와 같은 치료적 방법을 위한 약제의 제조를 위한 화학식 I의 화합물 또는 생리적으로 허용되는 이의 염의 용도가 제공된다.

[0066] 본 발명의 또 다른 측면에 따라, 위에서 및 아래에서 기술되는 바와 같은 치료적 방법을 위한 화학식 I의 화합물 또는 생리적으로 허용되는 이의 염이 제공된다.

[0067] 추가의 측면에서, 본 발명은, 아세틸-CoA 카복실라제 효소(들)의 억제에 의해 매개되는 질환 또는 상태의 치료를 필요로 하는 환자에게, 치료적 유효량의 화학식 I의 화합물을 치료적 유효량의 하나 이상의 추가의 치료제와 병용하여 투여하는 단계를 포함하는, 상기 환자의, 아세틸-CoA 카복실라제 효소(들)의 억제에 의해 매개되는 질환 또는 상태의 치료 방법에 관한 것이다.

[0068] 추가의 측면에서, 본 발명은, 효소(들) 아세틸-CoA 카복실라제의 억제에 의해 매개되는 질환 또는 상태의 치료 또는 예방을 위한, 하나 이상의 추가의 치료제와 병용하는 화학식 I의 화합물의 용도에 관한 것이다.

[0069] 추가의 측면에서, 본 발명은, 임의로 하나 이상의 불활성 담체 및/또는 희석제와 함께, 화학식 I에 따르는 화합물 또는 이의 약제학적으로 허용되는 염 및 하나 이상의 추가의 치료제를 포함하는 약제학적 조성물에 관한 것이다.

[0070] 본 발명의 또 다른 측면은, 위에서 및 아래에서 기술되는 바와 같이 명세서 및 실험 부분으로부터 당해 분야의 숙련가에게 분명해질 것이다.

발명을 실시하기 위한 구체적인 내용

[0071] **상세한 설명**

[0072] 별도의 언급이 없는 한, 그룹, 잔기 및 치환체, 특히 Ar^1, Ar^2, X, Y, R^N, T, R^A, R^C, R^{N1}, R^{N2}, R^{Alk}, L, T는 위에서 및 아래에서와 같이 정의된다. 잔기, 치환체 또는 그룹들이, 예를 들면 R^C, R^{N1}, R^{N2} 또는 L과 같이, 화합물에서 여러 번 발생된다면, 이들은 동일하거나 상이한 의미를 가질 수 있다. 본 발명에 따르는 화합물의 개개 그룹 및 치환체의 몇몇 바람직한 의미는 이후에 제시될 것이다. 이들 정의중 임의의 것 및 각각은 서로 조합될 수 있다.

[0073] **Ar^1:**

[0074] **Ar^1-G1:**

[0075] 그룹 Ar^1은 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 Ar^1-G1로부터 선택된다.

[0076] **Ar^1-G2:**

[0077] 하나의 양태에서, 그룹 Ar^1은, 페닐, 디하이드로나프틸, 테트라하이드로나프틸, 나프틸, 및 N, O, S 또는 $S(O)_r$ (여기서, r은 1 또는 2이다)로부터 선택되는 1, 2 또는 3개의 헤테로 원자를 함유하는 5- 또는 6-원 모노사이클릭 또는 9- 또는 10-원 비사이클릭-환 시스템으로 이루어진 그룹 Ar^1-G2로부터 선택되고, 여기서, 상기 헤테로 원자들 중의 적어도 하나는 방향족 환의 일부이고, 위에서 언급한 그룹은 모두 하나 이상의 치환체 R^A에 의해 임

의로 치환될 수 있고, 특히, 위에서 언급한 그룹은 모두 치환체 R^A 및 임의로 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고, 여기서, Ar^1의 인접한 C-원자들에 링크된 2개의 치환체 R^A는 서로 연결되어, 함께 C_{3-5}-알킬렌 브릿지 그룹을 형성할 수 있고, 여기서, 1, 2 또는 3개의 CH_2-그룹은 O, C(=O), S, S(=O), $S(=O)_2$, NH 또는 N(C_{1-4}-알킬)-에 의해 대체될 수 있고, 여기서, 상기 알킬렌 브릿지 그룹은 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환될 수 있다.

[0078] **Ar^1-G3:**

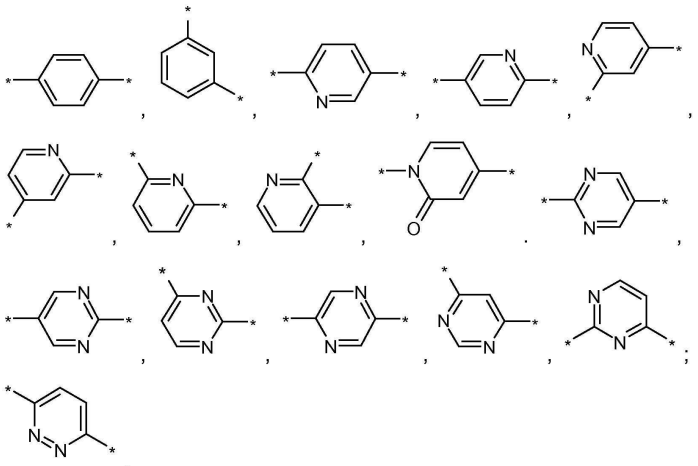
[0079] 또 다른 양태에서, 그룹 Ar^1은, 페닐, 나프틸, 피리딜, 2H-피리딘-2-오닐, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 티에닐, 피롤릴, 이미다졸릴, 트리아졸릴, 옥사졸릴, 이속사졸릴, 피라졸릴, 티아졸릴, 퀴놀리닐, 이소퀴놀리닐, 인돌릴, 벤조푸라닐, 벤조이미다졸릴, 벤조옥사졸릴, 벤조트리아졸릴, 2,3-디하이드로벤조푸라닐, 벤조[1,3]디옥솔릴 및 2,3-디하이드로벤조[1,4]디옥시닐로 이루어진 그룹 Ar^1-G3으로부터 선택되고, 여기서, 위에서 언급한 비사이클릭 그룹은 바람직하게는 상기 비사이클릭 그룹의 방향족 또는 헤테로방향족 환을 통해 화학식 I의 코어 구조의 피페리딘 환에 링크되며, 위에서 언급한 모노- 및 비사이클릭 그룹은 모두 하나 이상의 치환체 R^A에 의해 임의로 치환될 수 있고, 특히, 위에서 언급한 모노- 또는 비사이클릭 그룹은 모두 치환체 R^A 및 임의로 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0080] **Ar^1-G4:**

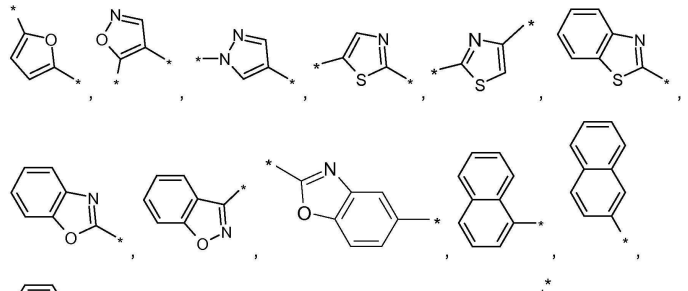
[0081] 또 다른 양태에서, 그룹 Ar^1은, 페닐, 나프틸, 피리딜, 2H-피리딘-2-오닐, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 옥사졸릴, 이속사졸릴, 피라졸릴, 티아졸릴, 퀴놀리닐, 이소퀴놀리닐, 인돌릴, 벤조푸라닐, 2,3-디하이드로벤조푸라닐, 벤조[1,3]디옥솔릴, 2,3-디하이드로-벤조[1,4]디옥시닐 및 3,4-디하이드로-2H-벤조[b][1,4]디옥세피닐로 이루어진 그룹 Ar^1-G4로부터 선택되고, 여기서, 위에서 언급한 비사이클릭 그룹은 바람직하게는 상기 비사이클릭 그룹의 방향족 또는 헤테로방향족 환을 통해 화학식 I의 코어 구조의 피페리딘 환에 링크되며, 위에서 언급한 모노- 및 비사이클릭 그룹은 모두 하나 이상의 치환체 R^A에 의해 임의로 치환될 수 있고, 특히, 위에서 언급한 모노- 또는 비사이클릭 그룹은 모두 치환체 R^A 및 임의로 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0082] **Ar^1-G5:**

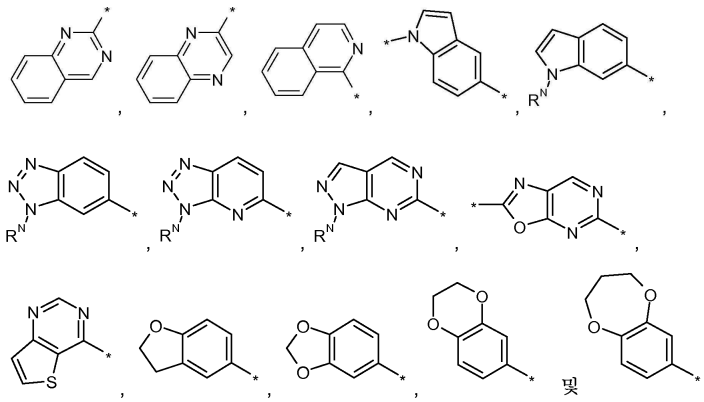
[0083] 또 다른 양태에서, 그룹 Ar^1은 하기 화학식들로 이루어진 그룹 Ar^1-G5로부터 선택되고, 여기서, 각각의 사이클릭 그룹의 우측면에 대한 별표는, 화학식 I의 코어 구조의 피페리딘 환에 연결되는 결합을 나타내며, 각각의 사이클릭 그룹의 좌측면에 별표가 존재하는 경우, 치환체 R^A 또는 H에 연결되는 결합을 나타내고, 또한 위에서 언급한 사이클릭 그룹은 각각 하나 이상의 추가의 치환체 R^A에 의해 임의로 치환되고, 특히 하나 이상의 치환체 L 및 치환체 R^N은 위에서 및 아래에서와 같이 정의된다:



[0084]

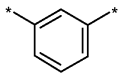
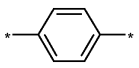


[0085]

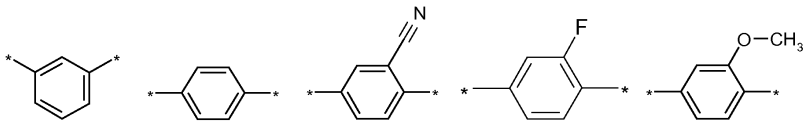


[0086]

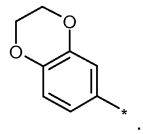
[0087] Ar^1-G6:

[0088] 또 다른 양태에서, 그룹 Ar^1은  및  으로 이루어진 그룹 Ar^1-G6으로부터 선택되고, 여기서, 상기 사이클릭 그룹의 우측면에 대한 별표는 화학식 I의 코어 구조의 피페리딘 환에 연결되는 결합을 나타내며, 사이클릭 그룹의 좌측면에 대한 별표는 치환체 R^A 또는 H에 연결되는 결합을 나타내고, 또한 위에서 언급한 사이클릭 그룹은 하나 이상의 추가의 치환체 R^A, 특히 하나 이상의 치환체 L에 의해 임의로 치환된다.

[0089] 그룹 Ar^1-G6의 멤버의 예는 다음과 같으나 이에 한정되지 않는다:

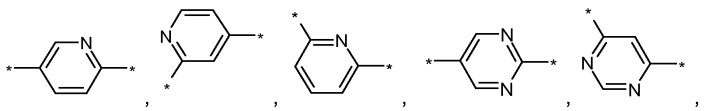


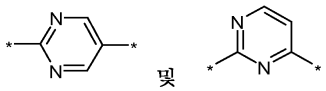
[0090] 및



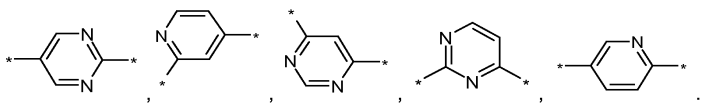
[0091] **Ar^1-G7:**

[0092] 또 다른 양태에서, 그룹 Ar^1은, 1 또는 2개의 N-원자를 함유하는 6-원 방향족 환으로 이루어진 그룹 Ar^1-G7로부터 선택되고, 여기서, 상기 환들은 하나 이상의 치환체 R^A에 의해 임의로 치환될 수 있고, 특히 상기 환들은 치환체 R^A 및 임의로 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다. 그룹 Ar^1-G7의 멤버의 예는 다음과 같으며, 여기서, 각각의 사이클릭 그룹의 우측면에 대한 별표는, 화학식 I의 코어 구조의 피페리딘 환에 연결되는 결합을 나타내며, 각각의 사이클릭 그룹의 좌측면에 대한 별표는 치환체 R^A에 연결되는 결합을 나타내고, 또한 위에서 언급한 사이클릭 그룹은 각각 하나 이상의 추가의 치환체 R^A, 특히 하나 이상의 치환체 L에 의해 임의로 치환된다:

[0093] 

[0094]  및

[0095] 그룹 Ar^1-G7의 멤버의 바람직한 예는 다음과 같으나 이에 한정되지 않는다:

[0096] 

[0097] **R^A:**

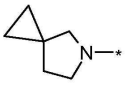
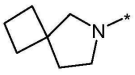
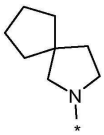
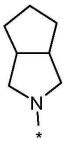
[0098] **R^A-G1:**

[0099] 그룹 R^A는 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^A-G1로부터 선택된다.

[0100] **R^A-G2:**

[0101] 또 다른 양태에서, 그룹 R^A는, H, F, Cl, Br, I, CN, OH, NO_2, C_{1-6}-알킬, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{1-6}-알킬-O-, C_{3-6}-알케닐-O-, C_{3-6}-알키닐-O-, C_{3-10}-카보사이클릴-O-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-O-, C_{1-6}-알킬-S-, C_{3-10}-카보사이클릴-S-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-S-, C_{1-4}-알킬-C(=O)-, $R^{N1}R^{N2}N$-, $R^{N1}R^{N2}N$-C_{2-3}-알킬-O-, $R^{N1}R^{N2}N$-C(=O)-, HO-C(=O)-, C_{1-6}-알킬-O-C(=O)-, 헤테로사이클릴, 헤테로사이클릴-O-, 헤테로사이클릴-C_{1-3}-알킬, 헤테로사이클릴-C_{1-3}-알킬-O-, 헤테로사이클릴-C(=O)-, 아릴, 아릴-C_{1-3}-알킬, 아릴-O-, 아릴-C_{1-3}-알킬-O-, 헤테로아릴, 헤테로아릴-C_{1-3}-알킬, 헤테로아릴-O- 및 헤테로아릴-C_{1-3}-알킬-O-로 이루어진 그룹 R^A-G2로부터 선택되고;

[0102] 여기서, 헤테로사이클릴은 위에서 및 아래에서와 같이 정의되거나, 또는 각각의 헤테로사이클릴은 아제티디닐, 피롤리디닐, 피페리디닐, 피페라지닐, N-C_{1-4}-알킬-피페라진-1-일, N-C_{1-4}-알킬설포닐-피페라진-1-일, 모르폴리닐, 디하이드로퀴놀리닐, 디하이드로이소퀴놀리닐, 디하이드로인돌릴, 디하이드로이소인돌릴, 옥세타닐, 테트라하이드로푸라닐 및 테트라하이드로피라닐로 이루어진 그룹으로부터, 또는

, ,  및  으로 이루어진 그룹으로부터 선택되고;

[0103] 여기서, 카보사이클릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 카보사이클릴은 바람직하게는 C_{3-7}-사이클로알킬, 인다닐 및 테트라하이드로나프틸로부터 선택되고;

[0104] 여기서, 헤테로아릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 헤테로아릴은 바람직하게는 피롤릴, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 옥사졸릴, 이속사졸릴, 피라졸릴, 티아졸릴, 트리아졸릴, 테트라졸릴, 벤조푸라닐, 인돌릴, 퀴놀리닐 및 인다졸릴로 이루어진 그룹으로부터 선택되고;

[0105] 여기서, 각각의 헤테로사이클릴 및 카보사이클릴에서, $-CH_2-$그룹은 -C(=O)- 또는 $-C(=CR^{Alk}{}_2)-$에 의해 임의로 대체될 수 있고;

[0106] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴은, 아래에 정의되는 바와 같이 치환될 수 있는, 하나 이상의 C_{1-3}-알킬에 의해 임의로 치환될 수 있고,

[0107] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고;

[0108] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 1, 2 또는 3개의 치환체 R^C에 의해 임의로 치환될 수 있고, 상기 치환체는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^C-G1, R^C-G2 또는 R^C-G3으로부터 선택되고; 더욱 더 바람직하게는 R^C는 Cl, Br, CN, OH, C_{1-3}-알킬-O-, C_{3-6}-사이클로알킬-O-, HO-C_{1-3}-알킬-O-, H_2N-, (C_{1-3}-알킬)NH- 및 (C_{1-3}-알킬)$_2$N-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택되고;

[0109] 여기서, 각각의 R^{N1}은 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{N1}-G1, R^{N1}-G2 또는 R^{N1}-G3으로부터 선택되고, 각각의 R^{N2}는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{N2}-G1 또는 R^{N2}-G2로부터 선택되고;

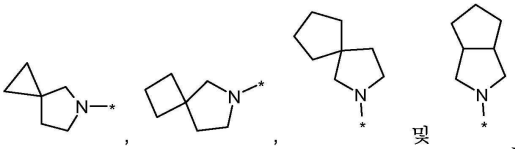
[0110] 여기서, 각각의 카보사이클릴 또는 헤테로사이클릴은 아릴 또는 헤테로아릴 그룹, 특히 페닐 또는 피리딜에 의해 임의로 치환될 수 있고;

[0111] 여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고, 여기서, L은 위에서 및 아래에서 정의되는 바와 같이 그룹 L-G1, L-G2 또는 L-G3으로부터 선택된다.

[0112] **R^A-G2a:**

[0113] 또 다른 양태에서, 그룹 R^A는, C_{1-6}-알킬-O-, C_{3-6}-알케닐-O-, C_{3-6}-알키닐-O-, C_{3-10}-카보사이클릴-O-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-O-, C_{1-6}-알킬-S-, C_{3-10}-카보사이클릴-S-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-S-, 헤테로사이클릴-O- 및 헤테로사이클릴-C_{1-3}-알킬-O-로 이루어진 그룹 R^A-G2a로부터 선택되고;

[0114] 여기서, 헤테로사이클릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 헤테로사이클릴은 바람직하게는 아제티디닐, 피롤리디닐, 피페리디닐, 피페라지닐, N-C_{1-4}-알킬-피페라진-1-일, N-C_{1-4}-알킬설포닐-피페라진-1-일, 모르폴리닐, 디하이드로퀴놀리닐, 디하이드로이소퀴놀리닐, 디하이드로인돌릴, 디하이드로이소인돌릴, 옥세타닐, 테트라하이드로푸라닐 및 테트라하이드로피라닐로 이루어진 그룹으로부터, 또는


및 으로 이루어진 그룹으로부터 선택되고;

[0115] 여기서, 카보사이클릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 카보사이클릴은 바람직하게는 C_{3-7}-사이클로알킬, 인다닐 및 테트라하이드로나프틸로부터 선택되고;

[0116] 여기서, 각각의 헤테로사이클릴 및 카보사이클릴에서, CH_2-그룹은 -C(=O)- 또는 -C(=CR^{Alk}_2)-에 의해 임의로 대체될 수 있고;

[0117] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴은, 아래에 정의되는 바와 같이 치환될 수 있는, 하나 이상의 C_{1-3}-알킬에 의해 임의로 치환될 수 있고,

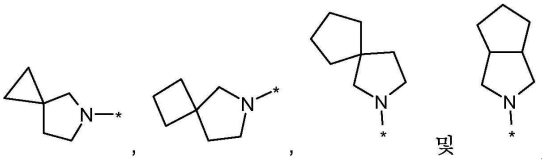
[0118] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고;

[0119] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 1, 2 또는 3개의 치환체 R^C에 의해 임의로 치환될 수 있고, 상기 치환체는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^C-G1, R^C-G2 또는 R^C-G3으로부터 선택되고; 더욱 더 바람직하게는 R^C는 Cl, Br, CN, OH, C_{1-3}-알킬-O-, C_{3-6}-사이클로알킬-O-, HO-C_{1-3}-알킬-O-, H_2N-, (C_{1-3}-알킬)NH- 및 (C_{1-3}-알킬)$_2$N-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택된다.

[0120] **R^A-G2b:**

[0121] 또 다른 양태에서, 그룹 R^A는, C_{1-6}-알킬, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C-$_{1-3}$-알킬, 헤테로사이클릴, 헤테로사이클릴-C_{1-3}-알킬, 아릴, 아릴-C_{1-3}-알킬, 헤테로아릴 및 헤테로아릴-C_{1-3}-알킬로 이루어진 그룹 R^A-G2b로부터 선택되고;

[0122] 여기서, 헤테로사이클릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 헤테로사이클릴은 바람직하게는 아제티디닐, 피롤리디닐, 피페리디닐, 피페라지닐, N-C_{1-4}-알킬-피페라진-1-일, N-C_{1-4}-알킬설포닐-피페라진-1-일, 모르폴리닐, 디하이드로퀴놀리닐, 디하이드로이소퀴놀리닐, 디하이드로인돌릴, 디하이드로이소인돌릴, 옥세타닐, 테트라하이드로푸라닐 및 테트라하이드로피라닐로 이루어진 그룹으로부터, 또는


및 으로 이루어진 그룹으로부터 선택되고;

[0123] 여기서, 카보사이클릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 카보사이클릴은 바람직하게는 C_{3-7}-사이클로알킬, 인다닐 및 테트라하이드로나프틸로부터 선택되고;

[0124] 여기서, 헤테로아릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 헤테로아릴은 바람직하게는 피롤릴, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 옥사졸릴, 이속사졸릴, 피라졸릴, 티아졸릴, 트리아졸릴, 테트라졸릴, 벤조푸라닐, 인돌릴, 퀴놀리닐 및 인다졸릴로 이루어진 그룹으로부터 선택되고;

[0125] 여기서, 각각의 헤테로사이클릴 및 카보사이클릴에서, CH_2-그룹은 -C(=O)- 또는 -C(=CR^{Alk}_2)-에 의해 임의로 대체될 수 있고;

[0126] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴은, 아래에 정의되는 바와 같이 치환될 수 있는, 하나 이상의 C_{1-3}-알킬에 의해 임의로 치환될 수 있고,

[0127] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로

치환될 수 있고;

[0128] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 1, 2 또는 3개의 치환체 R^C에 의해 임의로 치환될 수 있고, 상기 치환체는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^C-G1, R^C-G2 또는 R^C-G3으로부터 선택되고; 더욱 더 바람직하게는 R^C는 Cl, Br, CN, OH, C_{1-3}-알킬-O-, C_{3-6}-사이클로알킬-O-, HO-C_{1-3}-알킬-O-, H_2N-, (C_{1-3}-알킬)NH- 및 (C_{1-3}-알킬)$_2$N-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택되고;

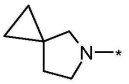
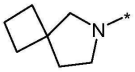
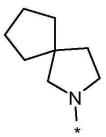
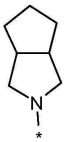
[0129] 여기서, 각각의 카보사이클릴 또는 헤테로사이클릴은 아릴 또는 헤테로아릴 그룹에 의해, 특히 페닐 또는 피리딜에 의해 임의로 치환될 수 있고;

[0130] 여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고, 여기서, L은 위에서 및 아래에서 정의되는 바와 같이 그룹 L-G1, L-G2 또는 L-G3으로부터 선택된다.

[0131] **R^A-G3:**

[0132] 또 다른 양태에서, 그룹 R^A는, F, Cl, Br, I, CN, NO_2, C_{1-6}-알킬, C_{3-10}-카보사이클릴-, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{1-6}-알킬-O-, C_{3-6}-알케닐-O-, C_{3-6}-알키닐-O-, C_{1-4}-알킬-S-, C_{3-10}-카보사이클릴-O-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-O-, C_{1-4}-알킬-C(=O)-, $R^{N1}R^{N2}$N-, $R^{N1}R^{N2}$N-C_{2-3}-알킬-O-, $R^{N1}R^{N2}$N-C(=O)-, HO-C(=O)-, C_{1-4}-알킬-O-C(=O)-, 헤테로사이클릴, 헤테로사이클릴-C_{1-3}-알킬, 헤테로사이클릴-O-, 헤테로사이클릴-C_{1-3}-알킬-O-, 헤테로사이클릴-C(=O)-, 페닐, 페닐-O-, 페닐-C_{1-3}-알킬, 페닐-C_{1-3}-알킬-O-, 헤테로아릴, 헤테로아릴-C_{1-3}-알킬, 헤테로아릴-O- 및 헤테로아릴-C_{1-3}-알킬-O-로 이루어진 그룹 R^A-G3으로부터 선택되고;

[0133] 여기서, 각각의 헤테로사이클릴은 아제티디닐, 피롤리디닐, 피페리디닐, 피페라지닐, N-C_{1-4}-알킬-피페라진-1-일, N-C_{1-4}-알킬설포닐-피페라진-1-일, 모르폴리닐, 디하이드로이소인돌릴, 옥세타닐, 테트라하이드로푸라닐 및 테트라하이드로피라닐로 이루어진 그룹으로부터, 또는


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으로 이루어진 그룹으로부터 선택되고;

[0134] 여기서, 카보사이클릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 카보사이클릴은 바람직하게는 C_{3-6}-사이클로알킬, 인다닐 및 테트라하이드로나프틸로부터 선택되고; 가장 바람직하게는 카보사이클릴은 C_{3-6}-사이클로알킬을 나타내고;

[0135] 여기서, 각각의 카보사이클릴, 피롤리디닐 및 피페리디닐에서, CH_2-그룹은 -C(=O)- 또는 -C(=CR^{Alk}_2)-에 의해 임의로 대체될 수 있고;

[0136] 여기서, 각각의 헤테로아릴은 피롤릴, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 옥사졸릴, 이속사졸릴, 피라졸릴, 티아졸릴, 트리아졸릴, 테트라졸릴, 인다졸릴, 벤조푸라닐, 인돌릴 및 퀴놀리닐로 이루어진 그룹으로부터 선택되고;

[0137] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴은, 아래에 정의되는 바와 같이 치환될 수 있는, 하나 이상의 C_{1-3}-알킬에 의해 임의로 치환될 수 있고;

[0138] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고;

[0139] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 1 또는 2개의 치환체 R^C에 의해 임의로 치환될 수 있고, 상기 치환체는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^C-G1, R^C-G2 또는 R^C-G3으로부터 선택되고;

더욱 더 바람직하게는 R^C는 Cl, Br, CN, OH, C_{1-3}-알킬-O-, C_{3-6}-사이클로알킬-O-, HO-C_{1-3}-알킬-O-, H_2N-, (C_{1-3}-알킬)NH- 및 (C_{1-3}-알킬)$_2$N-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택되고;

[0140] 여기서, 각각의 R^{N1}은 그룹 R^{N1}-G1, R^{N1}-G2 또는 R^{N1}-G3으로부터 선택되고, 각각의 R^{N2}는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{N2}-G1 또는 R^{N2}-G2로부터 선택되고; 여기서, 각각의 카보사이클릴 또는 헤테로사이클릴은 아릴 또는 헤테로아릴 그룹, 특히 페닐 또는 피리딜에 의해 임의로 치환될 수 있고;

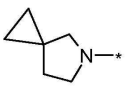
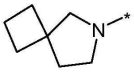
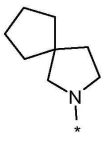
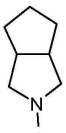
[0141] 여기서, 각각의 페닐 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고, 여기서, L은 위에서 및 아래에서 정의되는 바와 같이 그룹 L-G1, L-G2 또는 L-G3으로부터 선택된다.

[0142] **R^A-G4:**

[0143] 또 다른 양태에서, 그룹 R^A는, F, Cl, Br, I, CN, NO_2, C_{1-6}-알킬, C_{3-10}-카보사이클릴-, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{1-5}-알킬-O-, C_{3-5}-알케닐-O-, C_{3-5}-알키닐-O-, C_{3-10}-카보사이클릴-O-, C_{3-10}-카보사이클릴-C_{1-3}-알킬-O-, $R^{N1}R^{N2}$N-, $R^{N1}R^{N2}$N-C(=O)-, 헤테로사이클릴, 헤테로사이클릴-C_{1-3}-알킬, 헤테로사이클릴-O-, 헤테로사이클릴-C_{1-3}-알킬-O-, 헤테로사이클릴-C(=O)-, 페닐, 페닐-O-, 페닐-C_{1-3}-알킬, 페닐-C_{1-3}-알킬-O-, 헤테로아릴, 헤테로아릴-C_{1-3}-알킬, 헤테로아릴-O- 및 헤테로아릴-C_{1-3}-알킬-O-로 이루어진 그룹 R^A-G4로부터 선택되고;

[0144] 여기서, 카보사이클릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 카보사이클릴은 바람직하게는 C_{3-6}-사이클로알킬, 인다닐 및 테트라하이드로나프틸로부터 선택되고; 가장 바람직하게는 카보사이클릴은 C_{3-6}-사이클로알킬을 나타내며;

[0145] 여기서, 각각의 헤테로사이클릴은 아제티디닐, 피롤리디닐, 피페리디닐, 피페라지닐, N-C_{1-4}-알킬-피페라진-1-일, N-C_{1-4}-알킬설포닐-피페라진-1-일, 모르폴리닐, 디하이드로이소인돌릴, 옥세타닐, 테트라하이드로푸라닐 및 테트라하이드로피라닐로 이루어진 그룹으로부터, 또는


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으로 이루어진 그룹으로부터 선택되고;

[0146] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴에서, CH_2-그룹은 -C(=O)- 또는 -C(=CR^{Alk}_2)-에 의해 임의로 대체될 수 있고;

[0147] 여기서, 각각의 헤테로아릴은 피롤릴, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 옥사졸릴, 이속사졸릴, 피라졸릴, 티아졸릴, 트리아졸릴, 테트라졸릴, 인다졸릴, 벤조푸라닐, 인돌릴 및 퀴놀리닐로 이루어진 그룹으로부터 선택되고;

[0148] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴은, 아래에 정의되는 바와 같이 치환될 수 있는, 하나 이상의 C_{1-3}-알킬에 의해 임의로 치환될 수 있고;

[0149] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고;

[0150] 여기서, 각각의 알킬, 카보사이클릴 및 헤테로사이클릴은 1 또는 2개의 치환체 R^C에 의해 임의로 치환될 수 있고, 상기 치환체는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^C-G1, R^C-G2 또는 R^C-G3으로부터 선택되고; 더욱 더 바람직하게는 R^C는 Cl, Br, CN, OH, C_{1-3}-알킬-O-, C_{3-6}-사이클로알킬-O-, HO-C_{1-3}-알킬-O-, H_2N-, (C_{1-3}-알킬)NH-, (C_{1-3}-알킬)$_2$N-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택되고;

[0151] 여기서, 각각의 R^{N1}은 그룹 R^{N1}-G1, R^{N1}-G2 또는 R^{N1}-G3으로부터 선택되고, 각각의 R^{N2}는 위에서 및 아래에서 정의

되는 바와 같이 그룹 R^{N2}-G1 또는 R^{N2}-G2로부터 선택되고;

[0152] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴은 아릴 또는 헤테로아릴 그룹, 특히 페닐 또는 피리딜에 의해 임의로 치환될 수 있고;

[0153] 여기서, 각각의 페닐 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고, 여기서, L은 위에서 및 아래에서 정의되는 바와 같이 그룹 L-G1, L-G2 또는 L-G3으로부터 선택된다.

[0154] **R^A-G5:**

[0155] 또 다른 양태에서, 그룹 R^A는, F, Cl, Br, I, CN, C_{1-5}-알킬, C_{3-6}-사이클로알킬, C_{1-5}-알킬-O-, C_{3-5}-알케닐-O-, C_{3-5}-알키닐-O-, C_{3-6}-사이클로알킬-O-, C_{3-6}-사이클로알킬-C_{1-3}-알킬-O-, $R^{N1}R^{N2}N$-, 페닐, 페닐-O-, 페닐-C_{1-3}-알킬-O-, 헤테로아릴, 헤테로아릴-O- 및 헤테로아릴-C_{1-3}-알킬-O-로 이루어진 그룹 R^A-G5로부터 선택되고;

[0156] 여기서, 각각의 사이클로알킬은, 아래에 정의되는 바와 같이 치환될 수 있는, 하나 이상의 C_{1-3}-알킬에 의해 임의로 치환될 수 있고;

[0157] 여기서, 각각의 알킬 및 사이클로알킬은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고;

[0158] 각각의 사이클로알킬에서, CH_2-그룹은 -O-에 의해 임의로 치환될 수 있고;

[0159] 여기서, 각각의 알킬 및 사이클로알킬은 1 또는 2개의 치환체 R^C에 의해 임의로 치환될 수 있고, 여기서, R^C는 위에서 및 아래에서와 같이 정의되고; 바람직하게는 R^C는 Cl, Br, CN, OH, C_{1-3}-알킬-O-, C_{3-6}-사이클로알킬-O-, HO-C_{1-3}-알킬-O-, H_2N-, (C_{1-3}-알킬)NH-, (C_{1-3}-알킬)$_2$N-, HO-C(=O)- 및 C_{1-3}-알킬-O-C(=O)-로 이루어진 그룹으로부터 선택되고;

[0160] 여기서, 각각의 R^{N1}은 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{N1}-G1, R^{N1}-G2 또는 R^{N1}-G3으로부터 선택되고; 바람직하게는 R^{N1}은 H, C_{1-6}-알킬, C_{3-6}-사이클로알킬, C_{3-6}-사이클로알킬-CH_2-로 이루어진 그룹으로부터 선택되고, 여기서, 각각의 사이클로알킬은 하나 이상의 C_{1-4}-알킬에 의해 임의로 치환될 수 있고, 여기서, 각각의 알킬 및 사이클로알킬은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고, 여기서, 각각의 알킬 및 사이클로알킬은 OH, C_{1-3}-알킬-O- 및 H_2N-으로부터 선택된 치환체에 의해 임의로 치환될 수 있고;

[0161] 여기서, 각각의 R^{N2}는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{N2}-G1 또는 R^{N2}-G2로부터 선택되고;

[0162] 여기서, 헤테로아릴은 위에서 및 아래에서 정의되는 바와 같고; 바람직하게는 헤테로아릴은 피롤릴, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 옥사졸릴, 이속사졸릴, 피라졸릴, 티아졸릴, 트리아졸릴, 벤조푸라닐, 인돌릴 및 퀴놀리닐로 이루어진 그룹으로부터 선택되고;

[0163] 여기서, 각각의 페닐 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고, 여기서, L은 위에서 및 아래에서 정의되는 바와 같이 그룹 L-G1, L-G2 또는 L-G3으로부터 선택된다.

[0164] **R^A-G5a:**

[0165] 또 다른 양태에서, 그룹 R^A는, C_{1-5}-알킬-O-, C_{3-5}-알케닐-O-, C_{3-5}-알키닐-O-, C_{3-6}-사이클로알킬-O- 및 C_{3-6}-사이클로알킬-C_{1-3}-알킬-O-로 이루어진 그룹 R^A-G5a로부터 선택되고;

[0166] 여기서, 각각의 사이클로알킬은, 아래에 정의되는 바와 같이 치환될 수 있는, 하나 이상의 C_{1-3}-알킬에 의해 임의로 치환될 수 있고;

[0167] 여기서, 각각의 알킬 및 사이클로알킬은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고;

[0168] 각각의 사이클로알킬에서, CH_2-그룹은 -O-에 의해 임의로 치환될 수 있고;

[0169] 여기서, 각각의 알킬 및 사이클로알킬은 1 또는 2개의 치환체 R^C에 의해 임의로 치환될 수 있고, 여기서, R^C는 위에서 및 아래에서와 같이 정의되고; 바람직하게는 R^C는 Cl, Br, CN, OH, C_{1-3}-알킬-O-, C_{3-6}-사이클로알킬-O-, HO-C_{1-3}-알킬-O-, H_2N-, (C_{1-3}-알킬)NH-, (C_{1-3}-알킬)$_2$N-, HO-C(=O)- 및 C_{1-3}-알킬-O-C(=O)-로 이루어진 그룹으로부터 선택된다.

[0170] **R^A-G5b:**

[0171] 또 다른 양태에서, 그룹 R^A는, C_{1-5}-알킬, C_{3-6}-사이클로알킬, 페닐 및 헤테로아릴로 이루어진 그룹 R^A-G5b로부터 선택되고;

[0172] 여기서, 각각의 사이클로알킬은, 아래에 정의되는 바와 같이 치환될 수 있는, 하나 이상의 C_{1-3}-알킬에 의해 임의로 치환될 수 있고;

[0173] 여기서, 각각의 알킬 및 사이클로알킬은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고;

[0174] 각각의 사이클로알킬에서, CH_2-그룹은 -O-에 의해 임의로 대체될 수 있고;

[0175] 여기서, 각각의 알킬 및 사이클로알킬은 1 또는 2개의 치환체 R^C에 의해 임의로 치환될 수 있고, 여기서, R^C는 위에서 및 아래에서와 같이 정의되고; 바람직하게는 R^C는 Cl, Br, CN, OH, C_{1-3}-알킬-O-, C_{3-6}-사이클로알킬-O-, HO-C_{1-3}-알킬-O-, H_2N-, (C_{1-3}-알킬)NH-, (C_{1-3}-알킬)$_2$N-, HO-C(=O)- 및 C_{1-3}-알킬-O-C(=O)-로 이루어진 그룹으로부터 선택되고;

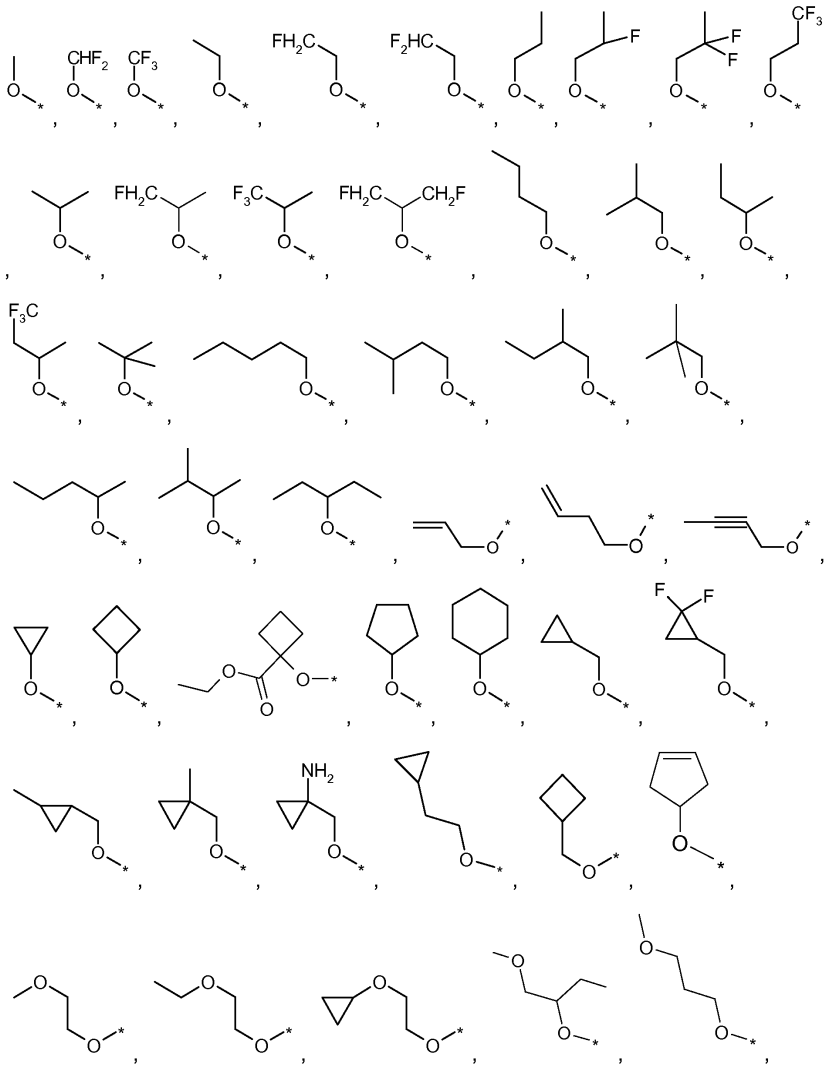
[0176] 여기서, 헤테로아릴은 위에서 및 아래에서 정의되는 바와 같고; 바람직하게는 헤테로아릴은 피롤릴, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 옥사졸릴, 이속사졸릴, 피라졸릴, 티아졸릴, 트리아졸릴, 벤조푸라닐, 인돌릴 및 퀴놀리닐로 이루어진 그룹으로부터 선택되고;

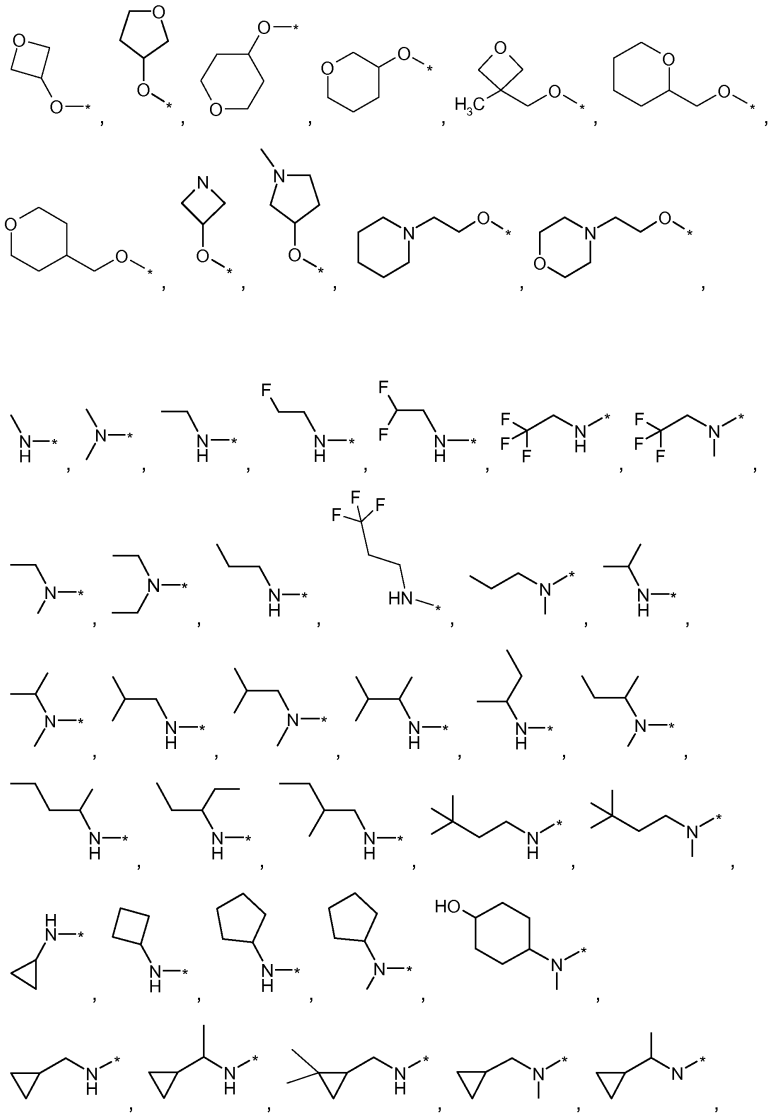
[0177] 여기서, 각각의 페닐 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있고, 여기서, L은 위에서 및 아래에서 정의되는 바와 같이 그룹 L-G1, L-G2 또는 L-G3으로부터 선택된다.

[0178] 위에서 및 아래에서 기술되는 바와 같은 R^A에 대한 양태에 있어서, 그룹 C_{3-n}-알케닐-O- 및 C_{3-n}-알키닐-O-(n은 정수이다)에서 이중 또는 삼중 결합은 바람직하게는 해당 그룹의 O-원자와 콘쥬게이트되지 않는 것으로 이해되어야 한다.

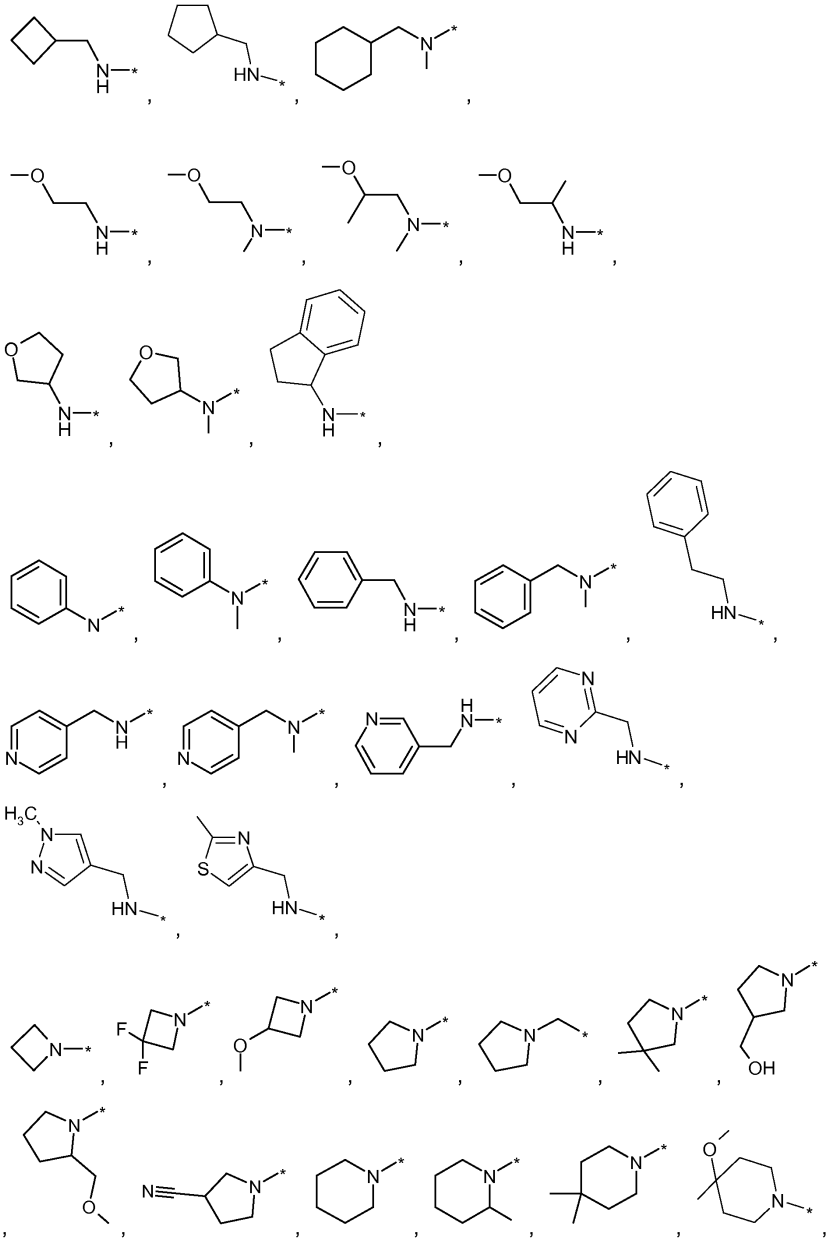
[0179] **R^A-G6:**

[0180] 또 다른 양태에서, 그룹 R^A는, F, Cl, Br, I, CN, 메틸, 에틸, n-프로필, 이소프로필, n-부틸, 2급-부틸, 3급-부틸, F_3C-, HO-CH_2CH_2-, 사이클로프로필,

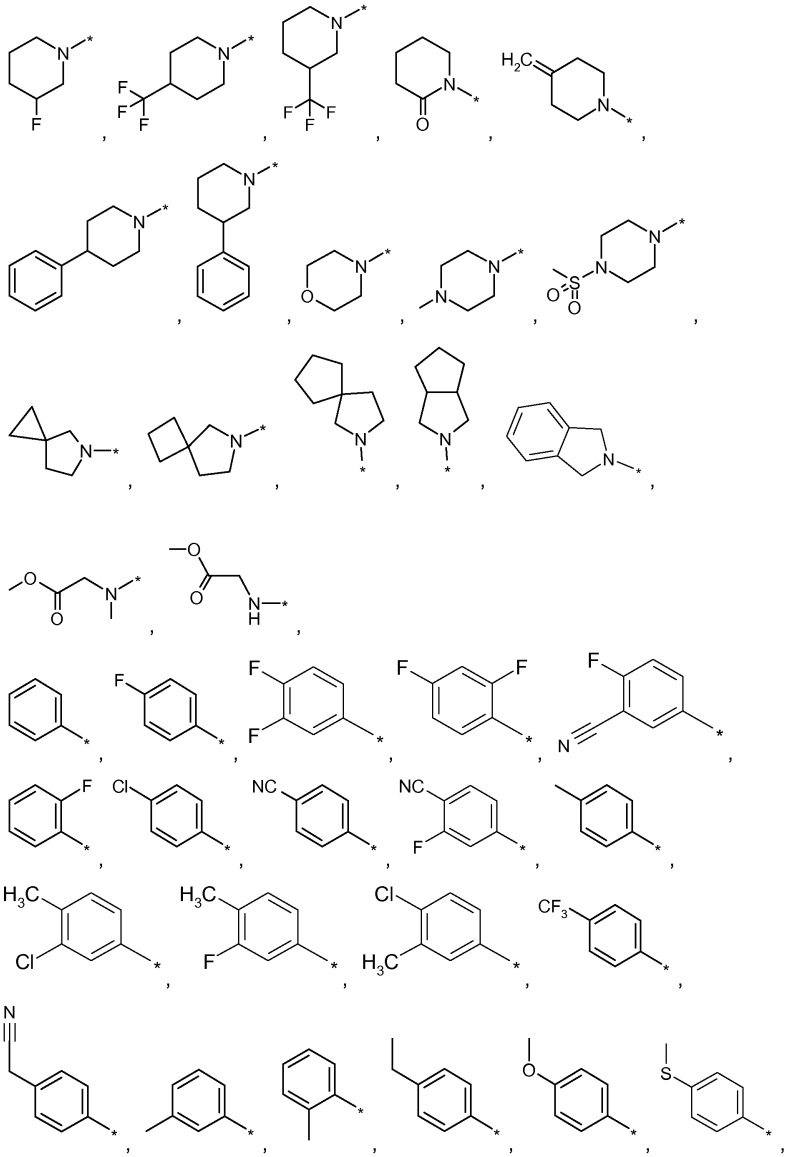
[0181] 

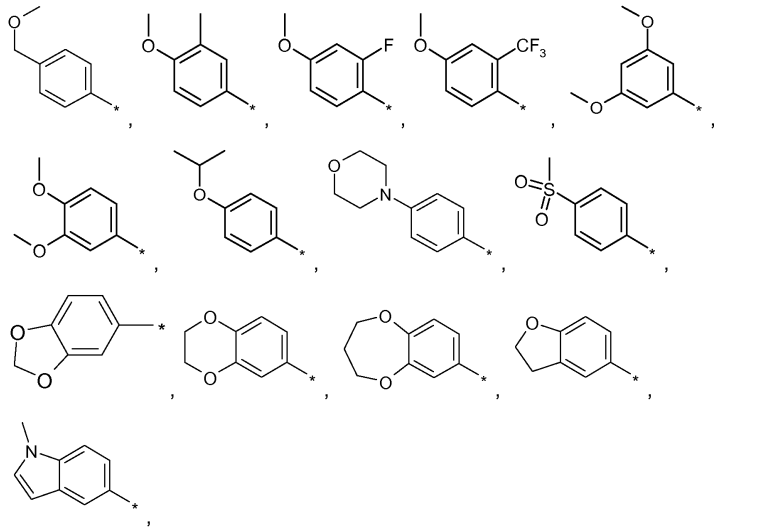


[0182]

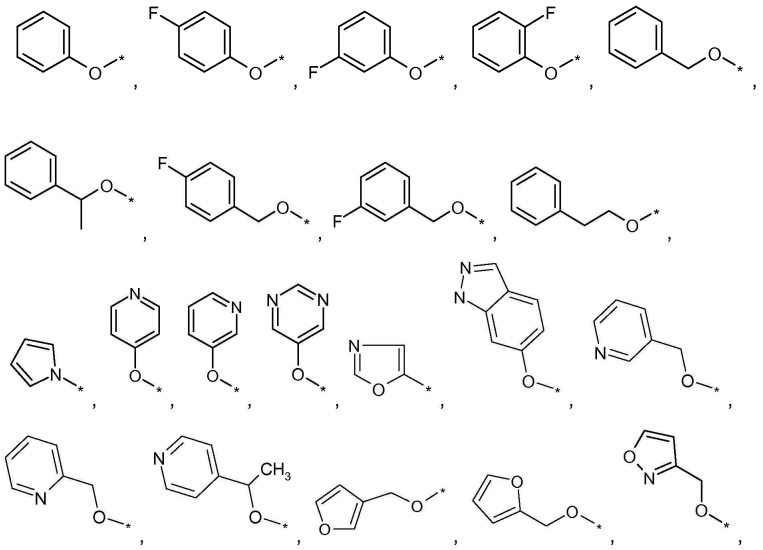


[0183]

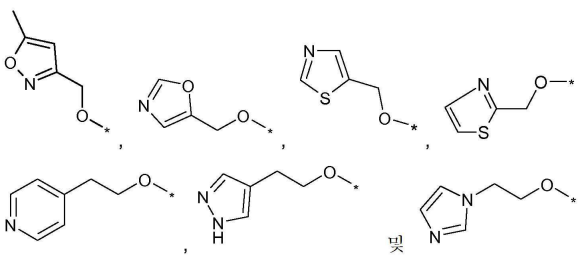
[0184] 



[0185]



[0186]



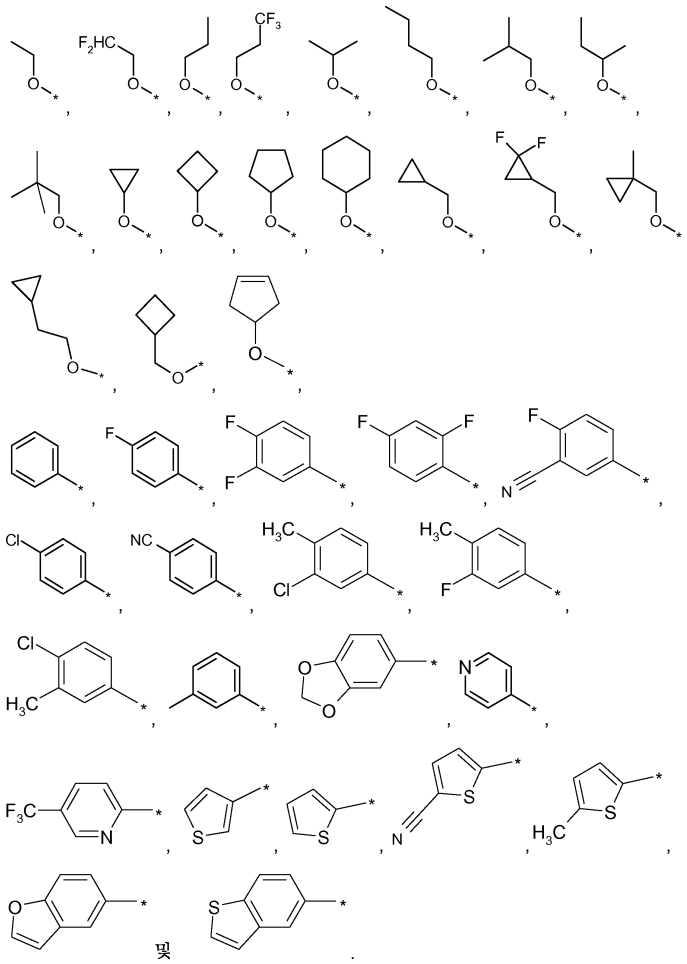
[0187] 로 이루어진 그룹 R^A-G6으로부터 선택되고;

[0188] 여기서, 각각의 알킬 그룹 및 각각의 사이클로알킬과 헤테로사이클릴 환은 하나 이상의 F 원자에 의해 임의로 치환될 수 있고;

[0189] 여기서, 각각의 페닐 및 헤테로아릴 환은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0190] **R^A-G7:**

[0191] 또 다른 양태에서, 그룹 R^A는, F, Cl, Br, CN, F_3C-,



[0192] 및 .

[0193] 로 이루어진 그룹 R^A-G7로부터 선택된다.

[0194] **R^C**

[0195] **R^C-G1:**

[0196] 그룹 R^C는 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^C-G1로부터 선택된다.

[0197] **R^C-G2:**

[0198] 또 다른 양태에서, 그룹 R^C는, F, Cl, Br, CN, OH, C_{1-4}-알킬-O-, C_{3-6}-사이클로알킬-O-, C_{3-6}-사이클로알킬-CH_2-O-, H_2N-, (C_{1-3}-알킬)NH-, (C_{1-3}-알킬)$_2$N-, C_{1-3}-알킬-C(=O)-, C_{1-3}-알킬-S(=O)$_2$-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로 이루어진 그룹 R^C-G2로부터 선택되고, 여기서, 각각의 알킬 또는 사이클로알킬은 F 및 OH로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있다.

[0199] R^C-G3:

[0200] 또 다른 양태에서, 그룹 R^C는, F, Cl, Br, CN, OH, C_{1-3}-알킬-O-, C_{3-6}-사이클로알킬-O-, H_2N-, (C_{1-3}-알킬)NH-, (C_{1-3}-알킬)$_2$N-, C_{1-3}-알킬-C(=O)-, C_{1-3}-알킬-S(=O)$_2$-, HO-C(=O)- 및 C_{1-3}-알킬-O-C(=O)-로 이루어진 그룹 R^C-G3으로부터 선택되고, 여기서, 각각의 알킬은 하나 이상의 F-원자에 의해 임의로 치환될 수 있고/있거나, OH에 의해 치환될 수 있다.

[0201] R^{N1}

[0202] R^{N1}-G1:

[0203] 그룹 R^{N1}은 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{N1}-G1로부터 선택된다.

[0204] R^{N1}-G2:

[0205] 또 다른 양태에서, 그룹 R^{N1}은, H, C_{1-6}-알킬, C_{3-10}-카보사이클릴, C_{3-10}-카보사이클릴-C_{1-3}-알킬, C_{3-6}-알키닐, 헤테로사이클릴, 헤테로사이클릴- C_{1-3}-알킬, 페닐, 페닐-C_{1-3}-알킬, 피리딜, 피리딜-C_{1-3}-알킬 및 옥사졸릴-C_{1-3}-알킬로 이루어진 그룹 R^{N1}-G2로부터 선택되고;

[0206] 여기서, 카보사이클릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 카보사이클릴은 바람직하게는 C_{3-7}-사이클로알킬, 인다닐 및 테트라하이드로푸라닐로부터 선택되고;

[0207] 여기서, 헤테로사이클릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 헤테로사이클릴은 바람직하게는 테트라하이드로푸라닐, 테트라하이드로피라닐, 피롤리디닐, 피페리디닐, 피페라지닐 및 모르폴리닐로부터 선택되고;

[0208] 여기서, 헤테로아릴은 위에서 및 아래에서와 같이 정의되거나, 헤테로아릴은 바람직하게는 피리딜, 피라졸릴 및 옥사졸릴을 나타내고;

[0209] 여기서, 각각의 카보사이클릴 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬에 의해 임의로 치환될 수 있고;

[0210] 여기서, 각각의 알킬, 카보사이클릴, 헤테로사이클릴(이는 피페라지닐 및 모르폴리닐을 포함한다)은 F로부터 선택된 하나 이상의 치환체에 의해 임의로 치환될 수 있고;

[0211] 여기서, 각각의 알킬, 카보사이클릴, 헤테로사이클릴(이는 피페라지닐 및 모르폴리닐을 포함한다)은 OH, C_{1-3}-알킬-O-, H_2N-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택된 치환체에 의해 임의로 치환될 수 있고;

[0212] 여기서, 각각의 페닐 및 헤테로아릴은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0213] 아미노-그룹의 N-원자에 부착된 알케닐 또는 알키닐 그룹, 예를 들면 R^{N1}에 있어서, 이중 또는 삼중 결합은 바람직하게는 N-원자에 콘쥬게이트되지 않는 것으로 이해되어야 한다.

[0214] R^{N1}-G3 :

[0215] 또 다른 양태에서, 그룹 R^{N1}은, H, C_{1-6}-알킬, C_{3-6}-사이클로알킬, C_{3-6}-사이클로알킬-CH_2-, 헤테로사이클릴, 헤테로사이클릴-CH_2-, 페닐, 페닐-CH_2-, 피리딜, 피리딜-CH_2-, 피라졸릴-CH_2- 및 옥사졸릴-C_{1-3}-알킬로 이루어진 그룹 R^{N1}-G3으로부터 선택되고;

[0216] 여기서, 헤테로사이클릴은 위에서 및 아래에서와 같이 정의되거나, 각각의 헤테로사이클릴은 바람직하게는 테트라하이드로푸라닐, 테트라하이드로피라닐, 피롤리디닐 및 피페리디닐로부터 선택되고;

[0217] 여기서, 각각의 사이클로알킬 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬에 의해 임의로 치환될 수 있고;

[0218] 여기서, 각각의 알킬, 사이클로알킬 및 헤테로사이클릴은 F로부터 선택된 하나 이상의 치환체에 의해 임의로 치환될 수 있고;

[0219] 여기서, 각각의 알킬, 사이클로알킬 및 헤테로사이클릴은 OH, C_{1-3}-알킬-O-, H_2N-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택된 치환체에 의해 임의로 치환될 수 있고;

[0220] 여기서, 각각의 페닐과 헤테로아릴(이는 피리딜, 피라졸릴 및 옥사졸릴을 포함한다)은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0221] 아미노-그룹의 N-원자에 부착된 알케닐 또는 알키닐 그룹, 예를 들면 R^{N1}에 있어서, 이중 또는 삼중 결합은 바람직하게는 N-원자에 콘쥬게이트되지 않는 것으로 이해되어야 한다.

[0222] R^{N2}

[0223] R^{N2}-G1:

[0224] 그룹 R^{N2}는 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{N2}-G1로부터 선택된다.

[0225] R^{N2}-G2:

[0226] 또 다른 양태에서, 그룹 R^{N2}는 H 및 C_{1-4}-알킬로 이루어진 그룹 R^{N2}-G2로부터 선택된다.

[0227] R^{Alk}:

[0228] R^{Alk}-G1:

[0229] 그룹 R^{Alk}는 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{Alk}-G1로부터 선택된다.

[0230] R^{Alk}-G2:

[0231] 또 다른 양태에서, 그룹 R^{Alk}는 H 및 C_{1-3}-알킬(이는 하나 이상의 F 원자에 의해 치환될 수 있다)로 이루어진 그룹 R^{Alk}-G2로부터 선택된다.

[0232] Ar^2:

[0233] Ar^2-G1:

[0234] 그룹 Ar^2는 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 Ar^2-G1로부터 선택된다.

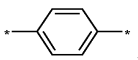
[0235] Ar^2-G2:

[0236] 또 다른 양태에서, 그룹 Ar^2는, 페닐, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 티에닐, 피롤릴, 이미다졸릴, 트리아졸릴, 옥사졸릴, 이속사졸릴, 피라졸릴 및 티아졸릴로 이루어진 그룹 Ar^2-G2로부터 선택되고, 여기서, 위에서 언급한 그룹들은 모두 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0237] Ar^2-G3:

[0238] 또 다른 양태에서, 그룹 Ar^2는 페닐 및 피리딜로 이루어진 그룹 Ar^2-G3으로부터 선택되고, 여기서, 위에서 언급한 그룹들은 모두 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0239] Ar^2-G4:

[0240] 또 다른 양태에서, 그룹 Ar^2는  으로 이루어진 그룹 Ar^2-G4로부터 선택되고, 여기서, 위에서 언급한 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0241] L:

[0242] L-G1:

[0243] 그룹 L은 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 L-G1로부터 선택된다.

[0244] L-G2:

[0245] 또 다른 양태에서, 그룹 L은, F, Cl, Br, CN, OH, C_{1-3}-알킬-, C_{1-3}-알킬-O-, C_{1-3}-알킬-S-, H_2N-, (C_{1-3}-알킬)NH-, (C_{1-3}-알킬)$_2$N- 및 헤테로사이클릴로 이루어진 그룹 L-G2로부터 선택되고;

[0246] 여기서, 각각의 알킬은 하나 이상의 F-원자에 의해 및/또는 OH, C_{1-3}-알킬-O- 및 CN으로부터 선택되는 치환체에 의해 임의로 치환될 수 있고;

[0247] 여기서, 헤테로사이클릴은 위에서 및 아래에서와 같이 정의되거나, 헤테로사이클릴은 바람직하게는 C_{3-6}-사이클로알킬 환을 나타내며, 여기서, 1 또는 2개의 -CH_2-그룹은 -O-, -NH-, -N(C_{1-3}-알킬)-로부터 선택되는 그룹에 의해 치환되고;

[0248] 여기서, 아릴 또는 헤테로아릴 그룹에 부착된 2개의 치환체 L은 서로 링크되어 C_{2-5}-알킬렌 브릿지 그룹을 형성할 수 있고, 여기서, 1 또는 2개의 -CH_2-그룹은 -O-, -NH- 및 -N(C_{1-4}-알킬)-로부터 서로 독립적으로 선택되는 그룹에 의해 대체될 수 있고, 여기서, 상기 C_{2-5}-알킬렌 브릿지 그룹은 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환된다.

[0249] L-G3:

[0250] 또 다른 양태에서, 그룹 L은, F, Cl, CN, OH, C_{1-3}-알킬-, C_{1-3}-알킬-O-, C_{1-3}-알킬-S-, H_2N-, (C_{1-3}-알킬)NH-, (C_{1-3}-알킬)$_2$N- 및 헤테로사이클릴로 이루어진 그룹 L-G3으로부터 선택되고;

[0251] 여기서, 각각의 알킬은 하나 이상의 F-원자에 의해 및/또는 OH, CH_3-O- 및 CN으로부터 선택되는 치환체에 의해 임의로 치환될 수 있고;

[0252] 여기서, 헤테로사이클릴은 위에서 및 아래에서와 같이 정의되거나, 헤테로사이클릴은 바람직하게는 C_{3-6}-사이클로알킬 환을 나타내며, 여기서, 1 또는 2개의 -CH_2-그룹은 -O-, -NH-, -N(C_{1-3}-알킬)-로부터 선택되는 그룹에 의해 치환되고;

[0253] 여기서, 아릴 또는 헤테로아릴 그룹의 인접한 C-원자들에 링크된 2개의 치환체 L은 서로 링크되어, 1 또는 2개의 CH_3-그룹에 의해 임의로 치환되는, -CH_2-CH_2-O-, -O-CH_2-CH_2-O- 또는 -O-CH_2-O- 브릿지 그룹을 형성할 수 있다.

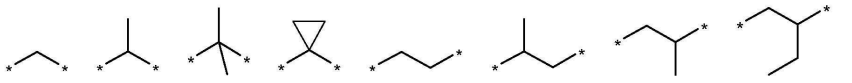
[0254] X:

[0255] X-G1:

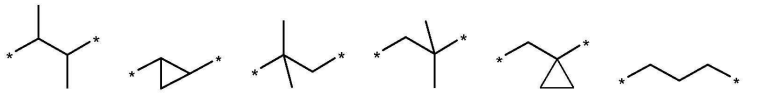
[0256] 그룹 X는 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 X-G1로부터 선택되고, 특히 C_{1-3}-알킬 및 C_{1-3}-알킬-O-C_{1-3}-알킬로부터 선택되는 1, 2 또는 3개의 그룹에 의해 임의로 치환될 수 있고, 더욱 더 바람직하게는 메틸, 에틸 또는 메톡시메틸로부터 독립적으로 선택된 1 또는 2개의 그룹에 의해 임의로 치환될 수 있는 직쇄형 C_{1-3}-알킬렌 그룹으로 이루어진 그룹으로부터 선택되고; 여기서, 2개의 알킬 치환체는 서로 연결되어, 1 또는 2개의 CH_2-그룹이 O, S, NH 또는 N(C_{1-4}-알킬)-에 의해 치환될 수 있는 C_{1-5}-알킬렌 브릿지 그룹을 함께 형성할 수 있고, 여기서, 상기 C_{1-5}-알킬렌 브릿지 그룹은 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환될 수 있다.

[0257] X-G2:

[0258] 또 다른 양태에서, 그룹 X는

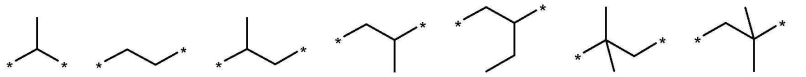


[0259]



[0260] 로 이루어진 그룹 X-G2로부터 선택되고;

[0261] 더욱 더 바람직하게는



[0262]



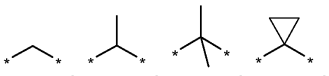
[0263] 로 이루어진 그룹 X-G3으로부터 선택된다.

[0264] **X-GC1:**

[0265] 양태 X-GC1에 따르면, 그룹 X는 1 또는 2개의 C_{1-3}-알킬 그룹에 의해, 바람직하게는 메틸 및 에틸로부터 독립적으로 선택된 1 또는 2개의 그룹에 의해 임의로 치환될 수 있는 $-CH_2-$이며, 여기서, 2개의 알킬 치환체는 서로 연결되어, 1 또는 2개의 CH_2-그룹이 O, S, NH 또는 N(C_{1-4}-알킬)-에 의해 대체될 수 있는 C_{2-5}-알킬렌 브릿지 그룹을 함께 형성할 수 있고, 여기서, 상기 C_{1-5}-알킬렌 브릿지 그룹은 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환될 수 있다.

[0266] 이 양태의 예는 다음과 같다:

[0267]



[0268] **X-GC1a:**

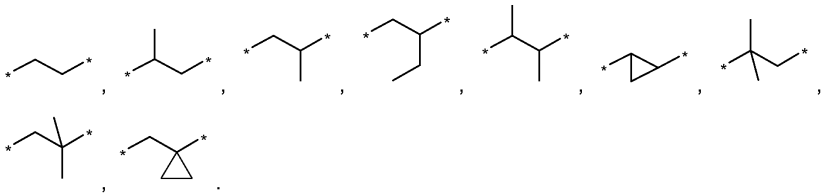
[0269] 양태 X-GC1a에 따르면, 그룹 X는  및 을 포함하는 이다. 그룹 X-GC1의 바람직한 예는 으로, 여기서, 우측면에 대한 별표는 화학식 I의 코어 구조의 N 원자에 연결되는 결합을 나타내며, 좌측면에 대한 별표는 Ar^2에 연결되는 결합을 나타낸다.

[0270] **X-GC2:**

[0271] 또 다른 양태 X-GC2에 따르면, 그룹 X는, 하나 이상의 C_{1-3}-알킬 그룹에 의해, 바람직하게는 메틸 및 에틸로부터 독립적으로 선택된 1 또는 2개의 그룹에 의해 임의로 치환될 수 있는 $-CH_2-CH_2-$이며, 여기서, 2개의 알킬 치환체는 서로 연결되어, 1 또는 2개의 CH_2-그룹이 O, S, NH 또는 N(C_{1-4}-알킬)-에 의해 치환될 수 있는 C_{1-5}-알킬렌 브릿지 그룹을 함께 형성할 수 있고, 여기서, 상기 C_{1-5}-알킬렌 브릿지 그룹은 1 또는 2개의 C_{1-3}-알킬 그룹에 의해

임의로 치환될 수 있다.

[0272] 이 양태의 예는 다음과 같다:

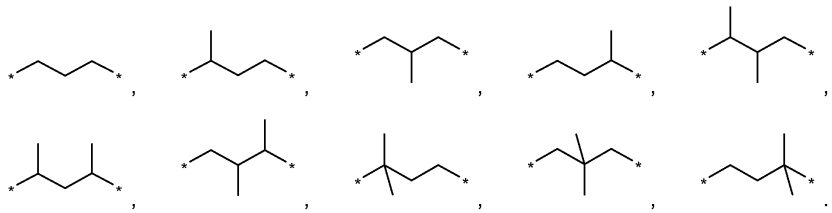


[0273]

[0274] X-GC3:

[0275] 또 다른 양태 X-GC3에 따르면, 그룹 X는, 하나 이상의 C_{1-3}-알킬 그룹에 의해, 바람직하게는 메틸 및 에틸로부터 독립적으로 선택된 1 또는 2개의 그룹에 의해 임의로 치환될 수 있는 $-CH_2-CH_2-CH_2-$이며, 여기서, 2개의 알킬 치환체는 서로 연결되어, 1 또는 2개의 CH_2-그룹이 O, S, NH 또는 N(C_{1-4}-알킬)-에 의해 치환될 수 있는 C_{1-5}-알킬렌 브릿지 그룹을 함께 형성할 수 있고, 여기서, 상기 C_{1-5}-알킬렌 브릿지 그룹은 1 또는 2개의 C_{1-3}-알킬 그룹에 의해 임의로 치환될 수 있다.

[0276] 이 양태의 예는 다음과 같다:



[0277]

[0278] Y:

[0279] Y-G1:

[0280] 그룹 Y는 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 Y-G1로부터 선택된다.

[0281] Y-G2:

[0282] 또 다른 양태에서, 그룹 Y는 -C(=O)- 및 -S(=O)-로 이루어진 그룹 Y-G2로부터 선택된다.

[0283] Y-G3:

[0284] 또 다른 양태에서, 그룹 Y는 $-S(=O)_2-$로 이루어진 그룹 Y-G3으로부터 선택된다.

[0285] Y-G4:

[0286] 또 다른 양태에서, 그룹 Y는 -C(=O)-로 이루어진 그룹 Y-G4로부터 선택된다.

[0287] R^N:

[0288] R^N-G1:

[0289] 그룹 R^N은 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^N-G1로부터 선택된다.

[0290] R^N-G2:

[0291] 또 다른 양태에서, 그룹 R^N은 H 및 메틸로 이루어진 그룹 R^N-G2로부터 선택된다.

[0292] R^N-G3:

[0293] 또 다른 양태에서, 그룹 R^N은 H로 이루어진 그룹 R^N-G3으로부터 선택된다.

[0294] T:

[0295] T-G1:

[0296] 그룹 T는 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 T-G1로부터 선택된다.

[0297] T-G2:

[0298] 또 다른 양태에서, 그룹 T는, C_{1-6}-알킬, C_{2-6}-알케닐, C_{2-6}-알키닐, C_{3-7}-사이클로알킬, C_{3-7}-사이클로알킬-C_{1-3}-알킬, C_{1-6}-알킬-O-, C_{3-7}-사이클로알킬-O-, C_{3-7}-사이클로알킬-C_{1-3}-알킬-O-, C_{1-6}-알킬-S-, C_{3-7}-사이클로알킬-S-, C_{3-7}-사이클로알킬-C_{1-3}-알킬-S-, C_{1-4}-알킬-C(=O)-, C_{1-4}-알킬-$S(=O)_2$-, $R^{T1}R^{T2}$-N-, $R^{T1}R^{T2}$-N-C_{1-3}-알킬-, $R^{T1}R^{T2}$-N-CO-, C_{1-4}-알킬-C(=O)-R^{T2}N-C_{1-3}-알킬, 헤테로사이클릴, 페닐 및 헤테로아릴로 이루어진 그룹 T-G2로부터 선택되고;

[0299] 여기서, 각각의 사이클로알킬 및 헤테로사이클릴에서, CH_2-그룹은 -C(=O)-에 의해 임의로 대체될 수 있고;

[0300] 여기서, 각각의 사이클로알킬 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬(이는 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있다)에 의해 임의로 치환될 수 있고;

[0301] 여기서, 각각의 알킬, 사이클로알킬 및 헤테로사이클릴은 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있고;

[0302] 여기서, R^C는 위에서 및 아래에서 정의되는 바와 같이 R^C-G1, R^C-G2 또는 R^C-G3으로 이루어진 그룹으로부터 선택되고;

[0303] 여기서, R^{T1}은 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{T1}-G1 또는 R^{T1}-G2로부터 선택되고;

[0304] 여기서, R^{T2}는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{T2}-G1 또는 R^{T2}-G2로부터 선택되고;

[0305] 여기서, 헤테로사이클릴은 위에서 및 아래에서와 같이 정의되며; 바람직하게는 헤테로사이클릴은 아제티디닐, 피롤리디닐, 피페리디닐, 옥세타닐, 테트라하이드로푸라닐 또는 테트라하이드로피라닐이고;

[0306] 여기서, 헤테로아릴은 페닐, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 티에닐, 피롤릴, 이미다졸릴, 피라졸릴, 트리아졸릴, 옥사졸릴, 이속사졸릴, 티아졸릴 및 이소티아졸릴로 이루어진 그룹으로부터 선택되고;

[0307] 여기서, 각각의 아릴 및 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0308] T-G3:

[0309] 또 다른 양태에서, 그룹 T는 C_{1-4}-알킬, C_{3-6}-사이클로알킬, C_{1-4}-알킬-O-, $R^{T1}R^{T2}$-N-, 헤테로사이클릴, 페닐 및 헤테로아릴로 이루어진 그룹 T-G3으로부터 선택되고;

[0310] 여기서, 각각의 사이클로알킬 및 헤테로사이클릴에서, CH_2-그룹은 -C(=O)-에 의해 임의로 대체될 수 있고;

[0311] 여기서, 각각의 사이클로알킬 및 헤테로사이클릴은 하나 이상의 C_{1-4}-알킬(이는 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있다)에 의해 임의로 치환될 수 있고;

[0312] 여기서, 각각의 알킬, 사이클로알킬 및 헤테로사이클릴은 하나 이상의 치환체 R^C에 의해 임의로 치환될 수 있고;

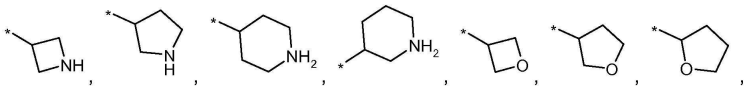
[0313] 여기서, R^C는 위에서 및 아래에서 정의되는 바와 같이 R^C-G1, R^C-G2 또는 R^C-G3으로 이루어진 그룹으로부터 선택되고;

[0314] 여기서, R^{T1}은 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{T1}-G1 또는 R^{T1}-G2로부터 선택되고; 바람직하게는 R^{T1}은 H, C_{1-4}-알킬, C_{3-6}-사이클로알킬 또는 C_{3-6}-사이클로알킬-C_{1-3}-알킬을 나타내며;

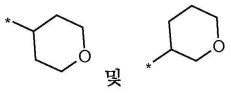
[0315] 여기서, R^{T2}는 위에서 및 아래에서 정의되는 바와 같이 그룹 R^{T2}-G1 또는 R^{T2}-G2로부터 선택되고; 바람직하게는

R^{T2}는 H 또는 C_{1-4}-알킬을 나타내며;

[0316] 여기서, 헤테로사이클릴은 위에서 및 아래에서와 같이 정의되며; 바람직하게는 헤테로사이클릴은



[0317] 및



[0318] 로 이루어진 그룹으로부터 선택되고;

[0319] 여기서, 헤테로아릴은 페닐, 피리딜, 피리미디닐, 피리다지닐, 피라지닐, 푸라닐, 티에닐, 피롤릴, 이미다졸릴, 피라졸릴, 트리아졸릴, 옥사졸릴, 이속사졸릴 및 티아졸릴로 이루어진 그룹으로부터 선택되고;

[0320] 여기서, 각각의 헤테로아릴 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0321] **T-G4:**

[0322] 또 다른 양태에서, 그룹 T는, C_{1-3}-알킬, C_{3-5}-사이클로알킬, C_{1-3}-알킬-O- 및 $R^{T1}R^{T2}$-N-으로 이루어진 그룹 T-G4로부터 선택되고;

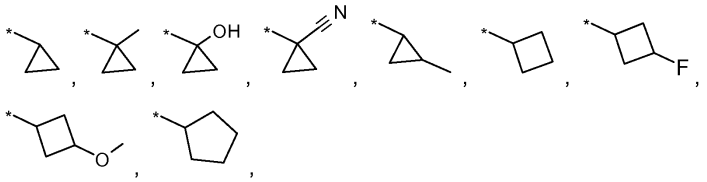
[0323] 여기서, 각각의 사이클로알킬은 하나 이상의 C_{1-3}-알킬에 의해 임의로 치환될 수 있고;

[0324] 여기서, R^{T1} 및 R^{T2}는 H 및 C_{1-3}-알킬로부터 서로 독립적으로 선택된다.

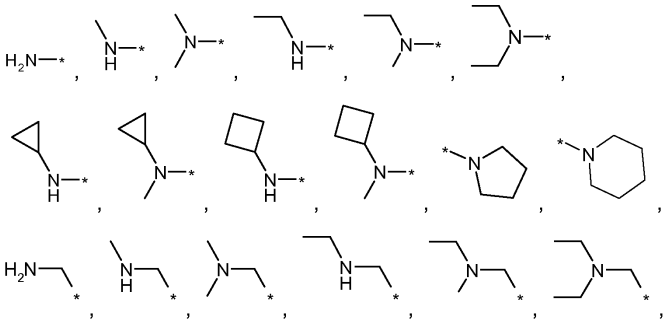
[0325] 그룹 T-G4의 바람직한 예는 H_3C-, H_3C-O-, $(H_3C)_2N$-,  및 이다.

[0326] **T-G5:**

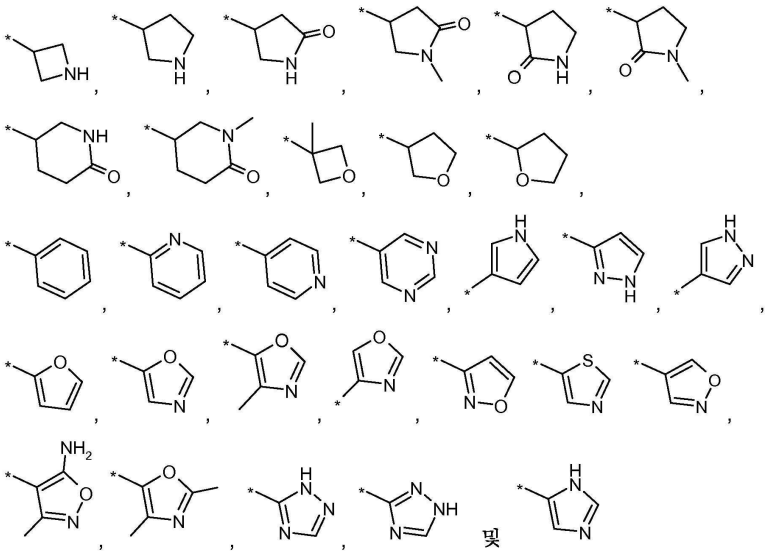
[0327] 또 다른 양태에서, 그룹 T는, H_3C-, H_2FC-, HF_2C-, F_3C-, NC-CH_2-, F_3C-CH_2-, $(H_3C)_2CF$-, H_5C_2-, n-프로필, i-프로필, n-부틸, i-부틸, H_3C-(H_3CO)CH-, H_3C-(HO)CH-, NC-CH_2-, NC-CH_2-CH_2-, 사이클로프로필, 사이클로부틸, 사이클로프로필-CH_2-,



HO-CH_2-, HO-CH_2-CH_2-, $(CH_3)_2$CH-(HO)CH-, H_3C-(HO)CH-,
H_3C-O-CH_2-, H_3C-O-CH_2-CH_2-,
H_3C-O-,

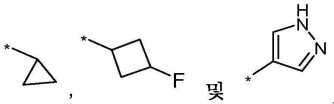


[0328]

[0329] 

[0330] 로 이루어진 그룹 T-G5로부터 선택된다.

[0331] **T-G6:**

[0332] 또 다른 양태에서, 그룹 T는 H_3C-, F_3C-, H_3C-CH_2-, H_3C-O-, $(H_3C)_2N$-,  로 이루어진 그룹 T-G6으로부터 선택된다.

[0333] **T-G7:**

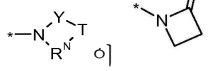
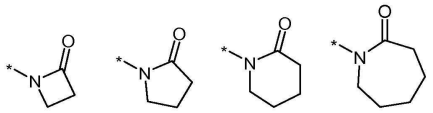
[0334] 또 다른 양태에서, 그룹 T는 H_3C-, $(H_3C)_2N$- 및 사이클로프로필로 이루어진 그룹 T-G7로부터 선택된다.

[0335] **(T-R^N):**

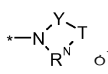
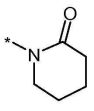
[0336] **(T- R^N)-G1:**

[0337] 하나의 양태에서, 그룹 T 및 R^N은 서로 연결되어 바람직하게는 위에서 및 아래에서 정의되는 바와 같이 그룹 (T-R^N)-G1로부터 선택되는 그룹을 함께 형성한다.

[0338] **(T- R^N)-G2:**

[0339] 또 다른 양태에서, 그룹 T 및 R^N은, 그룹  이  로 이루어진 그룹 (T-R^N)-G2로부터 선택되도록 서로 연결되며, 이들 모두는, F, Cl, Br, OH, CN, C_{1-4}-알킬, C_{3-6}-사이클로알킬, C_{3-6}-사이클로알킬-C_{1-3}-알킬, C_{1-4}-알킬-O-, C_{3-6}-사이클로알킬-O-, C_{3-6}-사이클로알킬-C-$_{1-3}$-알킬-O-, H_2N-, (C_{1-4}-알킬)NH-, (C_{1-4}-알킬)$_2$N-, C_{1-4}-알킬-C(=O)-, C_{1-4}-알킬-S(=O)$_2$-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고, 여기서, 각각의 알킬 또는 사이클로알킬은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고, 여기서, 각각의 알킬 또는 사이클로알킬은 Cl, Br, OH, CN, C_{1-3}-알킬-O-, C_{3-6}-사이클로알킬-O-, C_{3-6}-사이클로알킬-C-$_{1-3}$-알킬-O-, H_2N-, (C_{1-3}-알킬)NH-, (C_{1-3}-알킬)$_2$N-, C_{1-4}-알킬-C(=O)-, C_{1-4}-알킬-S(=O)$_2$-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택되는 치환체에 의해 임의로 치환될 수 있다.

[0340] **(T-R^N)-G3:**

[0341] 또 다른 양태에서, 그룹 T 및 R^N은, 그룹  이 , , 로 이루어진 그룹 $(T\text{-}R^N)$-G3으로부터 선택되도록 서로 연결되며, 이들 모두는 하나 이상의 F 원자 및/또는 C_{1-3}-알킬에 의해 치환될 수 있다.

[0342] R^{T1}

[0343] R^{T1}-G1:

[0344] 그룹 R^{T1}은 바람직하게는, H, C_{1-6}-알킬, C_{3-6}-사이클로알킬, C_{3-6}-사이클로알킬-C_{1-3}-알킬, 페닐 및 피리딜로 이루어진 그룹 R^{T1}-G1로부터 선택되고, 여기서, 각각의 사이클로알킬은 하나 이상의 C_{1-4}-알킬에 의해 임의로 치환될 수 있고, 여기서, 각각의 알킬 및 사이클로알킬은 F로부터 선택되는 하나 이상의 치환체에 의해 임의로 치환될 수 있고,

[0345] 여기서, 각각의 알킬 및 사이클로알킬은 OH, C_{1-3}-알킬-O-, C_{1-3}-알킬-C(=O)-, HO-C(=O)- 및 C_{1-4}-알킬-O-C(=O)-로부터 선택되는 치환체에 의해 임의로 치환될 수 있고;

[0346] 여기서, 각각의 페닐 및 피리딜 그룹은 하나 이상의 치환체 L에 의해 임의로 치환될 수 있다.

[0347] R^{T1}-G2:

[0348] 또 다른 양태에서, 그룹 R^{T1}은, 메틸, 에틸, n-프로필, 이소프로필, $HOOC\text{-}CH_2$-, $H_3C\text{-}CO$-, 페닐, 피리디닐로 이루어진 그룹 R^{T1}-G2로부터 선택되고, 여기서, 그룹 페닐 및 피리딜은 하나 이상의 치환체 L에 의해 치환될 수 있다.

[0349] R^{T2}

[0350] R^{T2}-G1:

[0351] 그룹 R^{T2}는 바람직하게는, H 및 C_{1-4}-알킬로 이루어진 그룹 R^{T2}-G1로부터 선택된다.

[0352] R^{T2}-G2:

[0353] 또 다른 양태에서, 그룹 R^{T2}는, H, 메틸, 에틸, n-프로필 및 이소프로필로 이루어진 그룹 R^{T2}-G2로부터 선택된다.

[0354] 본 발명에 따르는 바람직한 하위개념 양태의 예가 하기 표에 제시되어 있으며, 여기서, 각각의 양태의 각각의 치환체 그룹은 상기 제시된 바와 같은 정의에 따라 정의되고, 화학식 I의 모두 다른 치환체들은 상기 제시된 바와 같은 정의에 따라 정의된다:

양태	Ar^1	R^A	Ar^2	X	Y	R^N 및 T
E-1	Ar^1-G1	R^A-G1	Ar^2-G1	X-G1	Y-G1	R^N-G1, T-G1 또는 (T-R^N)-G1
E-2	Ar^1-G2	R^A-G2	Ar^2-G2	X-G1	Y-G1	R^N-G1, T-G2 또는 (T-R^N)-G2
E-3	Ar^1-G3	R^A-G3	Ar^2-G2	X-G1	Y-G1	R^N-G1, T-G2 또는 (T-R^N)-G2
E-4	Ar^1-G4	R^A-G5	Ar^2-G3	X-G1	Y-G1	R^N-G1, T-G2
E-5	Ar^1-G4	R^A-G5	Ar^2-G3	X-G1	Y-G1	(T-R^N)-G2
E-6	Ar^1-G6	R^A-G4	Ar^2-G3	X-G1	Y-G1	R^N-G1, T-G3 또는 (T-R^N)-G2
E-7	Ar^1-G7	R^A-G4	Ar^2-G3	X-G1	Y-G1	R^N-G1, T-G3 또는 (T-R^N)-G2
E-8	Ar^1-G6	R^A-G5	Ar^2-G4	X-G1	Y-G1	R^N-G1, T-G3 또는 (T-R^N)-G2
E-9	Ar^1-G7	R^A-G5	Ar^2-G4	X-G1	Y-G1	R^N-G1, T-G3 또는 (T-R^N)-G2
E-10	Ar^1-G5	R^A-G6	Ar^2-G3	X-G2	Y-G1	R^N-G1, T-G4 또는 (T-R^N)-G3
E-11	Ar^1-G1	R^A-G1	Ar^2-G1	X-GC1	-C(=O)-	R^N-G1, T-G1 또는 (T-R^N)-G1
E-12	Ar^1-G1	R^A-G1	Ar^2-G1	X-GC2	-C(=O)	R^N-G1, T-G1 또는 (T-R^N)-G1
E-13	Ar^1-G1	R^A-G1	Ar^2-G1	X-GC3	-C(=O)	R^N-G1, T-G1 또는 (T-R^N)-G1
E-14	Ar^1-G6	R^A-G4	Ar^2-G3	X-GC1	-C(=O)-	R^N-G1, T-G3 또는 (T-R^N)-G2
E-15	Ar^1-G6	R^A-G4	Ar^2-G3	X-GC2	-C(=O)	R^N-G1, T-G3 또는 (T-R^N)-G2
E-16	Ar^1-G6	R^A-G4	Ar^2-G3	X-GC3	-C(=O)	R^N-G1, T-G3 또는 (T-R^N)-G2
E-17	Ar^1-G7	R^A-G4	Ar^2-G3	X-GC1	-C(=O)-	R^N-G1, T-G3 또는 (T-R^N)-G2

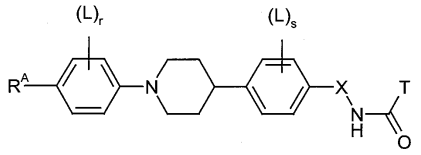
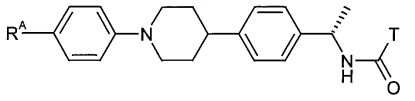
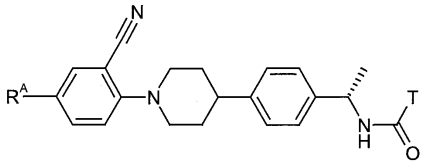
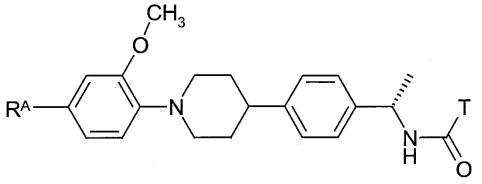
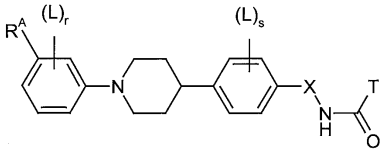
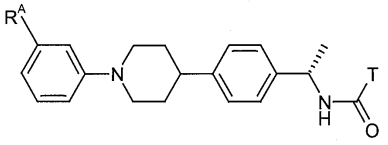
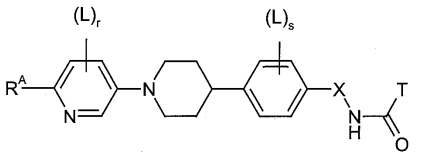
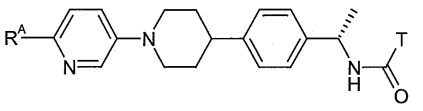
[0355]

양태	Ar^1	R^A	Ar^2	X	Y	R^N 및 T
E-18	Ar^1-G7	R^A-G4	Ar^2-G3	X-GC2	-C(=O)	R^N-G1, T-G3 또는 (T-R^N)-G2
E-19	Ar^1-G7	R^A-G4	Ar^2-G3	X-GC3	-C(=O)	R^N-G1, T-G3 또는 (T-R^N)-G2

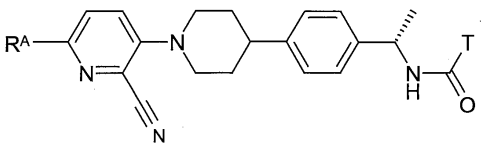
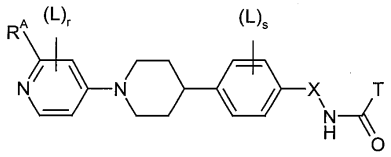
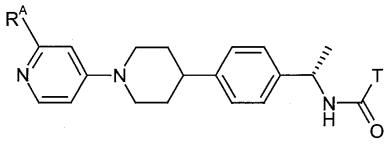
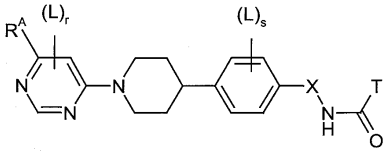
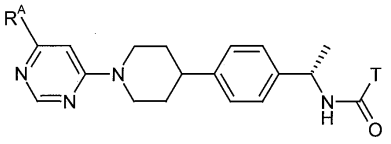
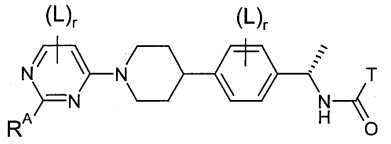
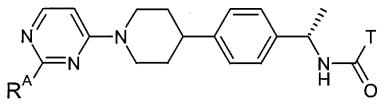
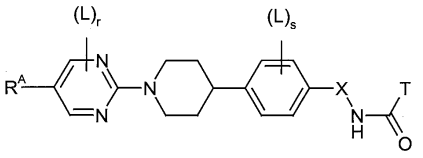
[0356]

[0357] 하기 화학식 I의 화합물의 바람직한 양태는 일반식 (I.1) 내지 (I.7a)를 사용하여 기술하였고, 여기서, 이의 모든 토우토머 및 입체이성체, 용매화물, 수화물 및 염, 특히 이의 약제학적으로 허용되는 염이 포함된다.

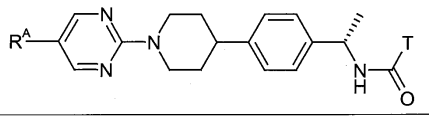
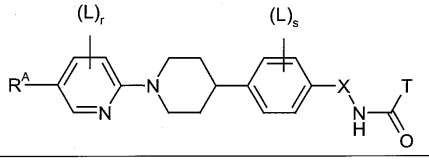
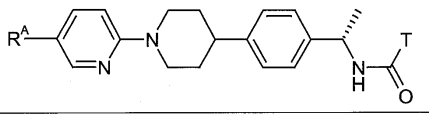
[0358]

(I.1)	
(I.1a)	
(I.1b)	
(I.1c)	
(I.2)	
(I.2a)	
(I.3)	
(I.3a)	

[0359]

(I.3b)	
(I.4)	
(I.4a)	
(I.5)	
(I.5a)	
(I.5b)	
(I.5c)	
(I.6)	

[0360]

(I.6a)	
(I.7)	
(I.7a)	

[0361] 이때, 상기 화학식 (I.1) 내지 (I.7a) 각각에서, 그룹 R^A, L, X 및 T는 위에서 및 아래에서와 같이 정의되며,

[0362] r은 0, 1 또는 2이고,

[0363] s는 0, 1 또는 2이다.

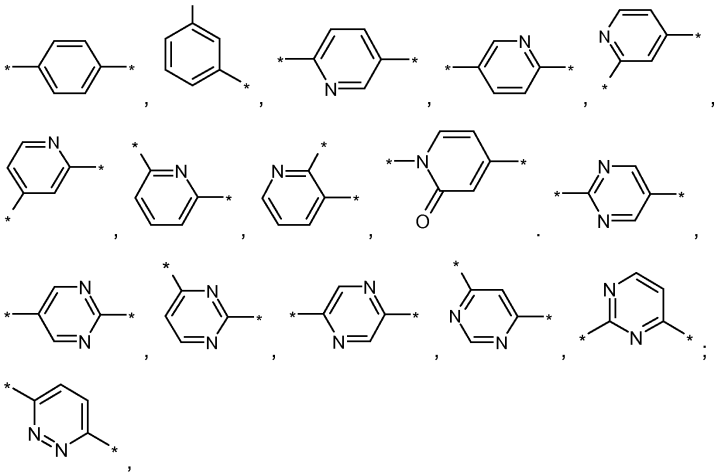
[0364] 본 발명에 따르는 상기 화학식 (I.1) 내지 (I.7a)의 바람직한 양태가 하기 표에 제시되어 있으며, 여기서, 각각의 양태의 각각의 그룹 R^A, X, T, L은 상기 제시된 정의에 따라 정의되고, 이의 모든 토우토머 및 입체이성체, 용매화물, 수화물 및 염, 특히 이의 약제학적으로 허용되는 염을 포함한 화학식 I의 모두 다른 치환체들은 상기 제시된 정의에 따라 정의되며, r은 0, 1 또는 2이고, s는 0, 1 또는 2이다:

양태	화학식	R^A	X	T	L
E-A	(I.1)	R^A-G2	X-G1	T-G2	L-G2
E-B	(I.1)	R^A-G2a	X-GC1	T-G3	L-G3
E-C	(I.1)	R^A-G5a	X-GC1	T-G4	L-G3
E-D	(I.1a)	R^A-G5a	-	T-G4	-
E-E	(I.1b)	R^A-G5a	-	T-G4	-
E-Ea	(I-1c)	R^A-G5a	-	T-G4	-
E-F	(I.2)	R^A-G2	X-G1	T-G2	L-G2
E-G	(I.2)	R^A-G2a	X-GC1	T-G3	L-G3
E-H	(I.2)	R^A-G5a	X-GC1	T-G4	L-G3
E-I	(I.2a)	R^A-G5a	-	T-G4	-
E-J	(I.3)	R^A-G2	X-G1	T-G2	L-G2
E-K	(I.3)	R^A-G2a	X-GC1	T-G3	L-G3
E-L	(I.3)	R^A-G5a	X-GC1	T-G4	L-G3
E-M	(I.3a)	R^A-G5a	-	T-G4	-
E-Ma	(I.3b)	R^A-G5a	-	T-G4	-
E-N	(I.4)	R^A-G2	X-G1	T-G2	L-G2
E-O	(I.4)	R^A-G2a	X-GC1	T-G3	L-G3
E-P	(I.4)	R^A-G5a	X-GC1	T-G4	L-G3
E-Q	(I.4a)	R^A-G5a	-	T-G4	-
E-R	(I.5)	R^A-G2	X-G1	T-G2	L-G2
E-S	(I.5)	R^A-G2a	X-GC1	T-G3	L-G3
E-T	(I.5)	R^A-G5a	X-GC1	T-G4	L-G3
E-U	(I.5a)	R^A-G5a	-	T-G4	-
E-Ua	(I.15b)	R^A-G5a	-	T-G4	L-G3
E-Ub	(I-5c)	R^A-G5a	-	T-G4	-
E-V	(I.6)	R^A-G2	X-G1	T-G2	L-G2
E-W	(I.6)	R^A-G2b	X-GC1	T-G3	L-G3
E-X	(I.6)	R^A-G5b	X-GC1	T-G4	L-G3
E-Y	(I.6a)	R^A-G5b	-	T-G4	-
E-Za	(I.7)	R^A-G2a	X-GC1	T-G3	L-G3
E-Zb	(I.7)	R^A-G5a	X-GC1	T-G4	L-G3
E-Zc	(I.7a)	R^A-G5a	-	T-G4	-

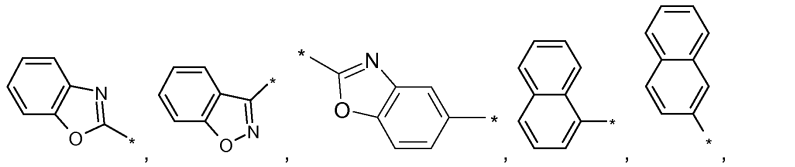
[0365]

[0366] 하나의 바람직한 양태는,

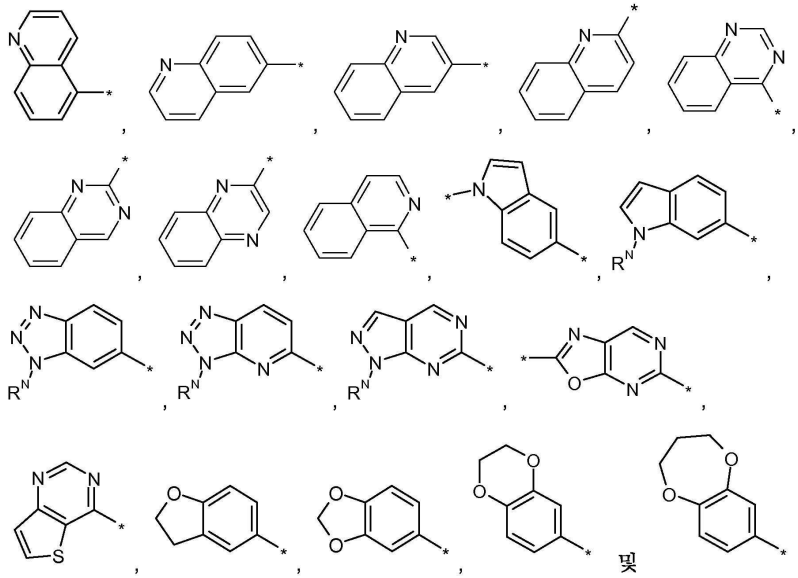
[0367] Ar^1이



[0368]

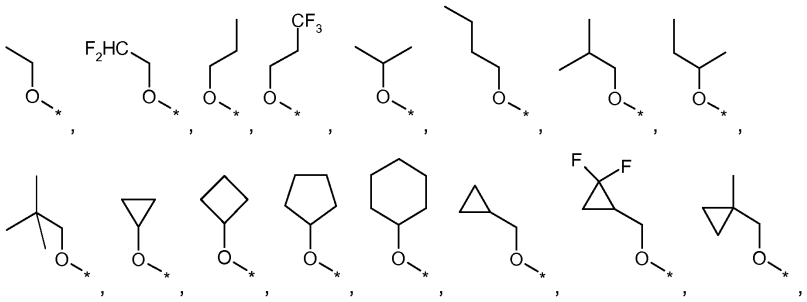


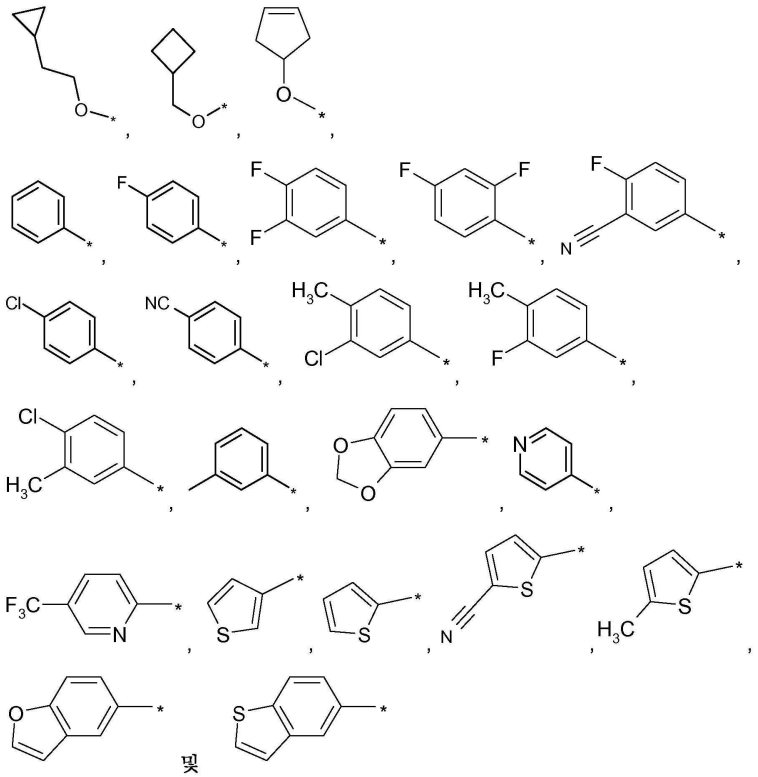
[0369]



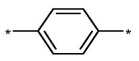
[0370] 로 이루어진 그룹으로부터 선택되고, 여기서, 각각의 사이클릭 그룹의 우측면에 대한 별표는, 화학식 I의 코어 구조의 피페리딘 환에 연결되는 결합을 나타내고, 각각의 사이클릭 그룹의 좌측면에 대한 별표가 존재하는 경우, 치환체 R^A 및 H에 연결되는 결합을 나타내며, 또한 위에서 언급한 사이클릭 그룹들은 각각 하나 이상의 추가의 치환체 R^A에 의해 임의로 치환되고,

[0371] R^A는, F, Cl, Br, CN, F_3C-,

[0372] 

[0373] 
및

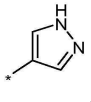
[0374] 로 이루어진 그룹 R^A-G7로부터 선택되고,

[0375] Ar^2는  이고,

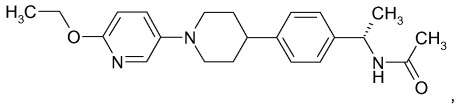
[0376] X는 -CH(CH_3)-이고,

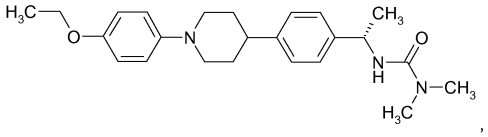
[0377] R^N은 H 또는 CH_3이고,

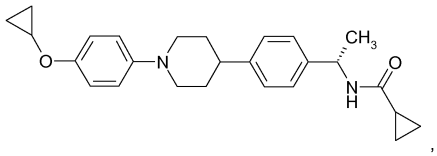
[0378] Y는 -C(=O)-이고,

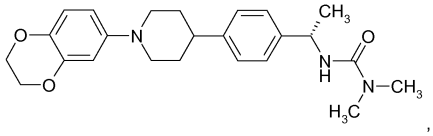
[0379] T는 H_3C-,F_3C-, H_3C-CH_2-, H_3C-O-, $(H_3C)_2N$-, , 
및

로 이루어진 그룹으로부터 선택되는 화학식 I의 화합물 또는 이의 염에 관한 것이다.

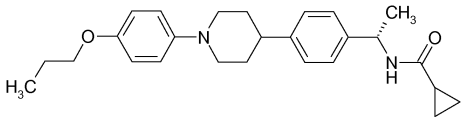
[0380] 특히 바람직한 화합물은 다음과 같다:



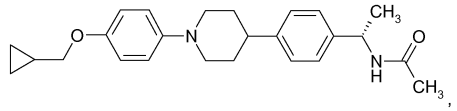


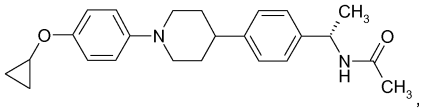


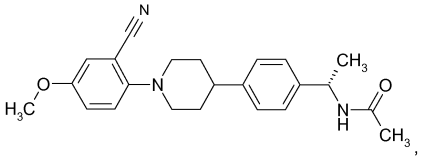


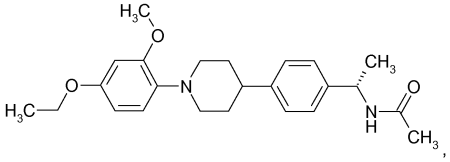


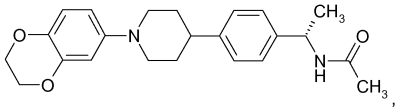
[0381]

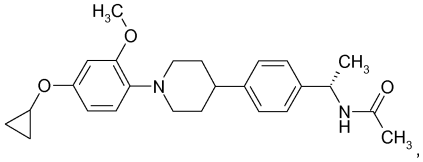


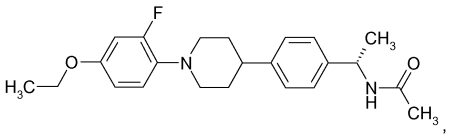




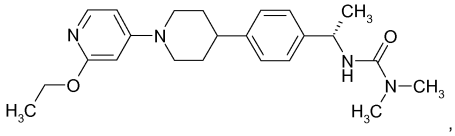




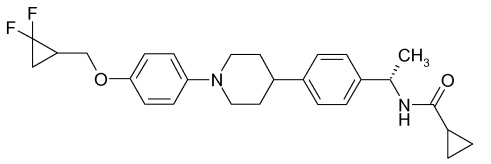




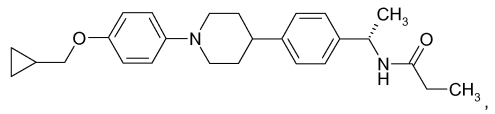
[0382]



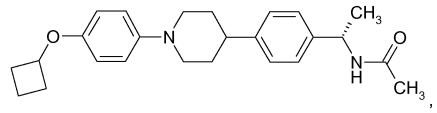
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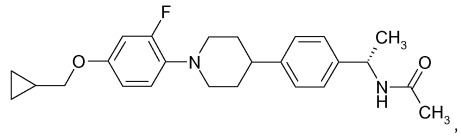
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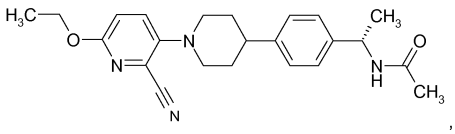
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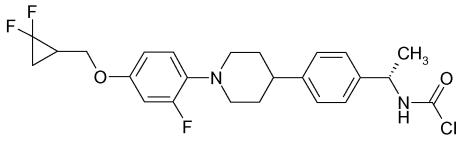
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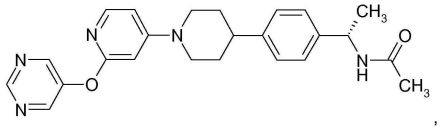
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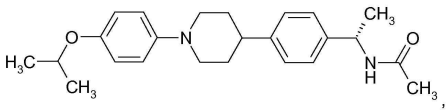
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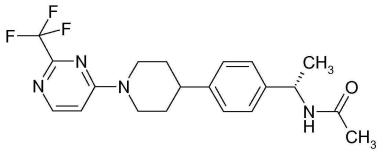
[0383]



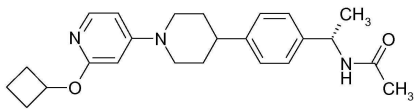
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및



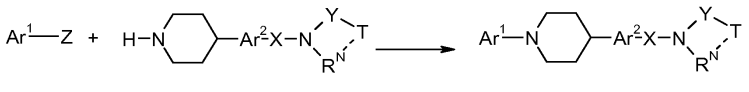
[0384]

[0385] 또는 이의 약제학적으로 허용되는 염.

[0386] 이들의 토우토머 및 입체이성체, 이의 염 또는 이의 임의의 용매화물이나 수화물을 포함하는, 특히 바람직한 화합물이 이후의 실험 섹션에 또한 기술되어 있다.

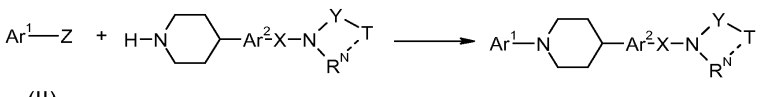
[0387] 본 발명에 따르는 화합물은 당해 분야의 숙련가에게 공지되고, 유기 합성 문헌에 기술된 합성 방법을 사용하여 수득할 수 있다. 바람직하게는, 상기 화합물은 이후에 더욱 상세히 설명되는, 특히 실험 섹션에 기술되는 바와 같은 제조 방법과 유사하게 수득한다.

[0388] 화학식 I의 화합물은 다음의 방법에 의해 제조할 수 있다:



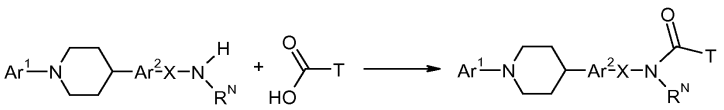
[0389] (II) (III) (I)

[0390] 화학식 I의 화합물은 아릴 할로게니드 또는 아릴 트리플레이트(II)와 피페리딘(III)의 팔라듐-매개된 부크발트(Buchwald) 반응 또는 구리-매개된 울만(Ullmann) 반응(여기서, Z는, 예를 들면, Cl, Br, I 또는 OTf(트리플레이트)를 나타내는 이탈 그룹이다)에 의해 제조할 수 있다.



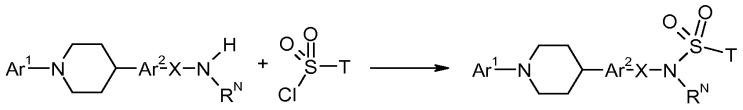
[0391] (II) (III) (I)

[0392] 또는, 화학식 I의 화합물은 아릴/헤테로아릴 할로게니드 또는 아릴/헤테로아릴 트리플레이트(II)와 피페리딘(III)의 친핵성 방향족 치환 반응(S_NAr)(여기서, Z는, 예를 들면, Cl, Br, I, $S(=O)CH_3$ 또는 트리플레이트를 나타내는 이탈 그룹이다)에 의해 제조할 수 있다.



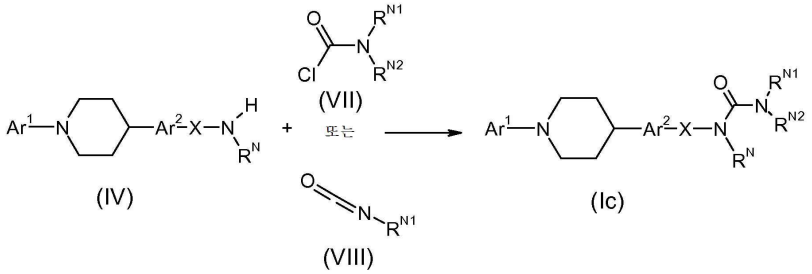
[0393] (IV) (V) (Ia)

[0394] 화학식 Ia의 화합물은 커플링 시약(예: TBTU, HOBt 또는 HATU)에 의해 매개되는 아민(IV)과 카복실산(V)의 아미드 커플링 반응에 의해 제조할 수 있다. 또는, 케텐(예: 디케텐)은 카복실산 등가물로서 사용될 수 있다.



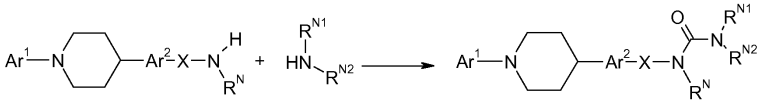
[0395] (IV) (VI) (Ib)

[0396] 화학식 Ib의 화합물은 설포닐 클로라이드(VI)에 의한 아민(IV)의 설포닐화에 의해 제조할 수 있다.



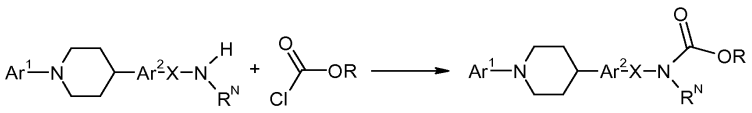
[0397] (IV) (VII) 또는 (VIII) (Ic)

[0398] 화학식 Ic의 화합물은 아민(IV)과 카바모일 클로라이드(VII) 또는 이소시아네이트(VIII)의 반응과 같은 우레아 형성 반응에 의해 제조할 수 있다.



[0399] (IV) (XX) (Ic)

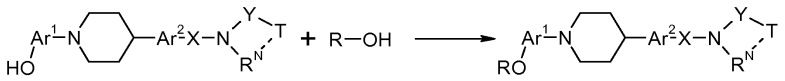
[0400] 또는, 화학식 Ic의 화합물은 시약(예: CDI 또는 CDT)과의 반응 후 아민(IV)과 아민(XX)의 반응에 의해 제조할 수 있다.



(IV) (IX) (Id)

[0401]

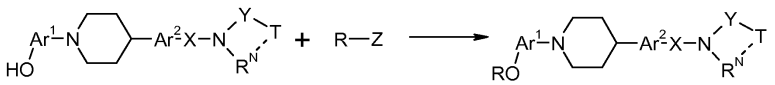
[0402] 화학식 Id의 화합물은 아민(IV)과 클로로 포르메이트(X)의 반응과 같은 우레탄 형성 반응에 의해 제조할 수 있다.



(XI) (XII) (X)

[0403]

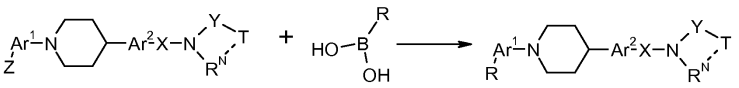
[0404] 화학식 X의 화합물은 아조디카복실레이트(예: DEAD, DIAT 등) 및 포스핀(예: 트리페닐포스핀)과 같은 커플링 시약에 의해 매개되는 방향족 알코올(XI)과 알코올(XII)의 미쓰노부(Mitsunobu) 반응에 의해 제조할 수 있다.



(XI) (XIII) (X)

[0405]

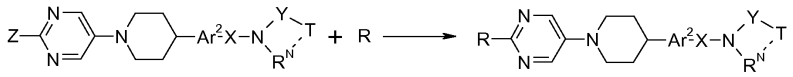
[0406] 또는, 화학식 X의 화합물은 방향족 알코올(XI)과 친전자체(XIII)의 알킬화 반응(여기서, Z는, 예를 들면, Cl, Br, I, S(=O)CH_3 또는 트리플레이트를 나타내는 이탈 그룹이다)에 의해 제조할 수 있다.



(XV) (XVI) (XIV)

[0407]

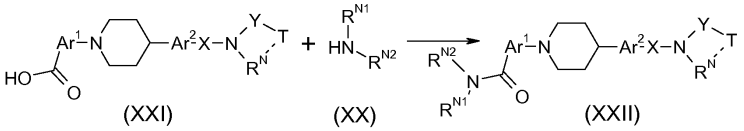
[0408] 화학식 XIV의 화합물은 아릴/헤테로아릴 할로게니드 또는 아릴/헤테로아릴 트리플레이트(XV)와 보론산(XVI) 또는 트리메틸보록신의 팔라듐-촉매화된 스즈키 커플링 반응(여기서, Z는, 예를 들면, Cl, Br, I 또는 트리플레이트를 나타내는 이탈 그룹이다)에 의해 제조할 수 있다.



(XVIII) (XIX) (XVII)

[0409]

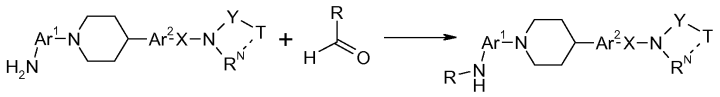
[0410] 화학식 XVII의 화합물은 피리미딘(XVIII)과 친핵체 R(XIX)의 친핵성 방향족 치환 반응(S_NAr)에 의해 제조할 수 있고, 여기서, Z는, 예를 들면, Cl, Br, I, S(=O)CH_3 또는 트리플레이트를 나타내는 이탈 그룹이고, R은 친핵체, 예를 들면, 알코올 또는 아민이며, 상기 반응은 피리미딘 또는 다른 헤테로아릴의 다른 레지오이성체를 사용하여 또한 수행할 수 있다. 알코올은 친핵체로서 사용하기 전에 적합한 염기에 의해 탈양성자화시킬 수 있다.



(XXI) (XX) (XXII)

[0411]

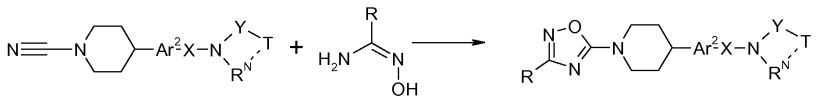
[0412] 화학식 XXII의 화합물은 커플링 시약(예: TBTU, HOBt 또는 HATU)에 의해 매개되는 아민(XX)과 카복실산(XXI)의 아미드 커플링 반응에 의해 제조할 수 있다.



(XXIII) (XXIV) (XXV)

[0413]

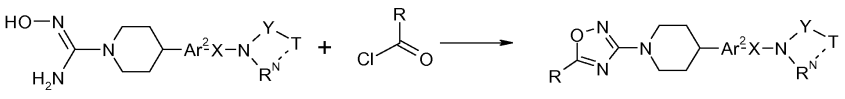
[0414] 화학식 XXV의 화합물은 환원제(예: 나트륨 보로하이드라이드, $NaB(OAc)_3H$ 또는 $NaBH_3(CN)$)를 사용하여 방향족 아민(XXIII)과 알데히드(XXIV)의 환원성 아미노화에 의해 제조할 수 있다.



(XXVI) (XXVII) (XXVIII)

[0415]

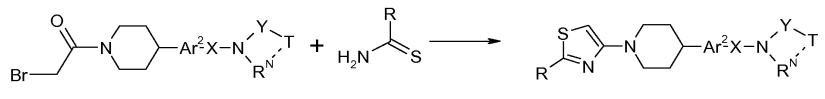
[0416] 화학식 XXVIII의 화합물은 촉매(예: 염화아연(II))를 사용하여 니트릴(XXVI)과 하이드록시아미딘(XXVII)의 축합 반응에 의해 제조할 수 있다.



(XXIX) (XXX) (XXXI)

[0417]

[0418] 화학식 XXIX의 화합물은 하이드록시아미딘(XXIX)과 카보닐 클로라이드(XXX)의 축합 반응에 의해 제조할 수 있다.



(XXXII) (XXXIII) (XXXIV)

[0419]

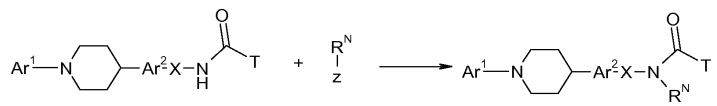
[0420] 화학식 XXXIV의 화합물은 아세틸 브로마이드(XXXII)와 티오아미드(XXXIII)의 축합 반응에 의해 제조할 수 있다.



(XXXV) (XXXVI)

[0421]

[0422] 화학식 XXXVI의 화합물은 라웨슨 시약(Lawesson's reagent) 또는 P_2S_5와 같은 시약과 아미드(XXXV)의 반응에 의해 제조할 수 있다.



(XXXVII) (XXXVIII) (XXIX)

[0423]

[0424] 화학식 XXXIX의 화합물은 염기(예: 수소화나트륨)에 의한 탈양성자화 후에 아미드(XXXVII)와 알킬화 시약 R^NZ의 반응(여기서, Z는, 예를 들면, Cl, Br, I, $S(=O)CH_3$ 또는 트리플레이트를 나타내는 이탈 그룹이다)에 의해 제조할 수 있다.

[0425] **용어 및 정의**

[0426] 본 명세서에서 특히 정의되지 않은 용어들은 기술 및 내용 면에서 당해 분야의 숙련가중 하나에 의해 이들에게 제시된 의미로 제공되어야 한다. 그러나 명세서에 사용된 바와 같이, 달리 명시되지 않으면, 다음의 용어들은 제시된 의미를 가지며, 다음의 관례를 따라야 한다.

[0427] 용어 "본 발명에 따르는 화합물(들)", "화학식 I의 화합물(들)" 및 "본 발명의 화합물(들)" 등은 이들의 토우토머, 입체이성체 및 이의 혼합물과 이의 염, 특히 이의 약제학적으로 허용되는 염을 포함한 본 발명에 따르는 화학식 I의 화합물, 및 상기 토우토머, 입체이성체 및 이의 염의 용매화물 및 수화물을 포함하는, 상기 화합물의

용매화물 및 수화물을 나타낸다.

[0428] 용어 "치료(treatment)" 및 "치료하는(treating)"은 예방적, 즉 예방학적 또는 치료적, 즉 치유력 있고/있거나 일시적인 치료를 모두 포함한다. 따라서, 용어 "치료" 및 "치료하는"은 특히 명백한 형태로, 이미 당해 상태가 발병된 환자의 치료적 치료를 포함한다. 치료적 치료는 특정 징후의 증상을 완화시키기 위한 증상적 치료 또는 징후의 상태를 반전 또는 부분적으로 반전시키거나, 질환의 진행을 멈추거나 느리게 하기 위한 원인적 치료일 수 있다. 따라서, 본 발명의 조성물 및 방법은, 예를 들면, 만성 치료를 위해 뿐만 아니라, 일정 시간에 걸친 치료적 치료(therapeutic treatment)로서 사용될 수 있다. 또한, 용어 "치료" 및 "치료하는"은 예방학적 치료, 즉 상기 언급한 상태가 발병할 위험에서 환자의 치료에 의해, 상기 위험이 감소됨을 포함한다.

[0429] 본 발명이 치료를 필요로 하는 환자를 언급할 때, 이는 주로 포유동물, 특히 인간의 치료에 관한 것이다.

[0430] 용어 "치료적 유효량"은 (i) 특별한 질환 또는 상태를 치료 또는 예방하거나, (ii) 특별한 질환 또는 상태의 하나 이상의 증상들을 약화, 개선 또는 제거하거나, (iii) 본 명세서에 기술된 특별한 질환 또는 상태의 하나 이상의 증상을 예방 또는 지연시키는 본 발명의 화합물의 양을 의미한다.

[0431] 본 명세서에 사용된 바와 같은, 용어 "조절된(modulated)" 또는 "조절하는(modulating)" 또는 "조절하다(modulate(s))"는, 달리 제시되지 않으면, 하나 이상의 본 발명의 화합물에 의한 아세틸-CoA 카복실라제(ACC) 효소(들)의 억제를 의미한다.

[0432] 본 명세서에 사용된 바와 같은, 용어 "매개된(mediated)" 또는 "매개하는(mediating)" 또는 "매개하다(mediate)"는, 달리 제시되지 않으면, (i) 특별한 질환 또는 상태의 예방을 포함한 치료, (ii) 특별한 질환 또는 상태의 하나 이상의 증상의 약화, 개선 또는 제거, 또는 (iii) 본 명세서에 기술된 특별한 질환 또는 상태의 하나 이상의 증상 개시의 예방 또는 지연을 의미한다.

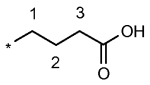
[0433] 본 명세서에 사용된 바와 같은, 용어 "치환된(substituted)"은 지정된 원자, 라디칼 또는 잔기 상의 임의의 하나 이상의 수소가 제시된 그룹으로부터의 선택에 의해 치환되지만, 단 상기 원자의 통상의 원자가는 초과하지 않으며, 치환에 의해, 허용적으로 안정한 화합물이 생성되어야 함을 의미한다.

[0434] 하기 정의되는 그룹, 라디칼 또는 잔기에서, 탄소 원자의 갯수는 종종 그룹 앞에 명시되며, 예를 들면, C_{1-6}-알킬은 탄소수가 1 내지 6인 알킬 그룹 또는 라디칼을 의미한다. 일반적으로, 2개 이상의 서브그룹을 포함하는 그룹의 경우, 마지막으로 명명된 서브그룹은 라디칼 부착 지점이며, 예를 들면, 치환체 "아릴-C_{1-3}-알킬-"은 C_{1-3}-알킬-그룹에 결합되는 아릴 그룹을 의미하며, 이들 중의 후자는 치환체가 부착되는 코어 또는 그룹에 결합된다.

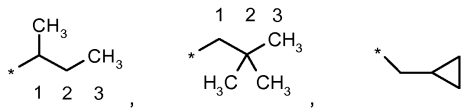
[0435] 본 발명의 화합물이 화학명의 형태로 그리고 화학식으로서 도시되는 경우, 임의의 차이의 경우에 화학식이 우세할 것이다.

[0436] 별표는 정의된 바와 같이 코어 분자에 연결되는 결합을 나타내기 위해 서브-화학식에 사용될 수 있다.

[0437] 치환체의 원자의 넘버링은 치환체가 부착되는 코어 또는 그룹에 가장 근접한 원자에서 시작한다. 예를 들면, 용어 "3-카복시프로필-그룹"은 하기 치환체를 나타낸다:

[0438] 

[0439] 여기서, 상기 카복시 그룹은 프로필 그룹의 세 번째 탄소 원자에 부착된다. 용어 "1-메틸프로필-", "2,2-디메틸프로필-" 또는 "사이클로프로필메틸-" 그룹은 하기 그룹을 나타낸다:

[0440] 

[0441] 별표는 정의된 바와 같이 코어 분자에 연결되는 결합을 나타내기 위해 서브-화학식에서 사용될 수 있다.

[0442] 그룹의 정의에서, 용어 "X, Y 및 Z는 각각 ~에 의해 임의로 치환된다" 등은, 각각의 그룹 X, 각각의 그룹 Y 및 각각의 그룹 Z가 별도의 그룹으로서 각각 또는 복합 그룹의 일부로서 각각 정의된 바와 같이 치환될 수 있음을

나타낸다. 예를 들면, 정의 "R^{ex}는 H, C_{1-3}-알킬, C_{3-6}-사이클로알킬, C_{3-6}-사이클로알킬-C_{1-3}-알킬 또는 C_{1-3}-알킬-O-를 나타내며, 여기서, 각각의 알킬 그룹은 하나 이상의 L^{ex}에 의해 임의로 치환된다" 등은 용어 알킬을 포함하는 위에서 언급한 각각의 그룹에서, 즉 그룹 C_{1-3}-알킬, C_{3-6}-사이클로알킬, C_{3-6}-사이클로알킬-C_{1-3}-알킬 또는 C_{1-3}-알킬-O- 각각에서, 알킬 잔기는 정의한 바와 같이 L^{ex}에 의해 치환될 수 있음을 의미한다.

[0443] 다음에서, 용어 비사이클릭은 스피로사이클릭을 포함한다.

[0444] 달리 제시되지 않으면, 명세서 및 첨부된 특허청구범위를 통해, 제시된 화학식 또는 화학명은 토우토머 및 이의 모든 입체, 광학 및 기하 이성체(예: 에난티오머, 디아스테레오머, E/Z 이성체 등...)와 라세메이트 및 상이한 비의 별도의 에난티오머의 혼합물, 디아스테레오머의 혼합물 또는 상기 형태 중의 임의의 것의 혼합물을 포함할 것이며, 여기서, 이의 약제학적으로 허용되는 염을 포함한 염, 및 예를 들면, 유리 화합물의 용매화물 또는 화합물의 염의 용매화물을 포함한 수화물과 같은 이의 용매화물 뿐만 아니라 상기 이성체 및 에난티오머가 존재한다.

[0445] 구문 "약제학적으로 허용됨"은, 양호한 의학적 판단의 범위 내에서, 지나친 독성, 자극, 알러지 반응 또는 다른 문제점이나 합병증 없이, 인간 및 동물의 조직과 접촉시 사용하기에 적합하고, 합당한 이익/위험 비로 균형잡힌 화합물, 물질, 조성물 및/또는 투여 형태를 의미하는 것으로 본 명세서에서 사용된다.

[0446] 본 명세서에 사용된 바와 같이, "약제학적으로 허용되는 염"은, 모 화합물이 이의 산 또는 염기 염을 만듬으로써 개질되는, 기재된 화합물의 유도체를 의미한다. 약제학적으로 허용되는 염의 예는 염기성 잔기(예: 아민)의 무기 또는 유기산 염; 산성 잔기(예: 카복실산)의 알칼리 또는 유기 염 등을 포함하지만 이에 한정되지 않는다. 예를 들면, 상기 염들은 아세테이트, 아스코르베이트, 벤젠설포네이트, 벤조에이트, 베실레이트, 비카보네이트, 비타트레이트, 브로마이드/하이드로브로마이드, Ca-에테테이트/에데테이트, 캄실레이트, 카보네이트, 클로라이드/하이드로클로라이드, 시트레이트, 에디실레이트, 에탄 디설포네이트, 에스톨레이트 에실레이트, 푸마레이트, 글루셉테이트, 글루코네이트, 글루타메이트, 글리콜레이트, 글리콜릴아르스닐레이트, 헥실레조르시네이트, 하이드라바민, 하이드록시말레에이트, 하이드록시나프토에이트, 요오다이드, 이소티오네이트, 락테이트, 락토비오네이트, 말레이트, 말레에이트, 만델레이트, 메탄설포네이트, 메실레이트, 메틸브로마이드, 메틸니트레이트, 메틸설페이트, 무케이트, 납실레이트, 니트레이트, 옥살레이트, 파모에이트, 판토테네이트, 페닐아세테이트, 포스페이트/디포스페이트, 폴리갈락투로네이트, 프로피오네이트, 살리실레이트, 스테아레이트 수바세테이트, 석시네이트, 설파미드, 설페이트, 탄네이트, 타트레이트, 테오클레이트, 톨루엔설포네이트, 트리에트요오다이드, 암모늄 벤자틴, 클로로프로카인, 콜린, 디에탄올아민, 에틸렌디아민, 메글루민 및 프로카인을 포함한다. 추가의 약제학적으로 허용되는 염은 알루미늄, 칼슘, 리튬, 마그네슘, 칼륨, 나트륨 및 아연 등과 같은 금속으로부터의 양이온에 의해 형성될 수 있다(참조: Pharmaceutical salts, Birge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19).

[0447] 본 발명의 약제학적으로 허용되는 염은, 통상적인 화학 방법에 의해, 염기성 또는 산성 잔기를 함유하는 모 화합물로부터 합성할 수 있다. 일반적으로, 상기 염들은 물 속에서, 또는 에테르, 에틸 아세테이트, 에탄올, 이소프로판올 또는 아세토니트릴과 같은 유기 희석제 또는 이들의 혼합물 속에서, 충분한 양의 적합한 염기 또는 산과 이들 화합물의 유리 산 또는 염기 형태를 반응시켜 제조할 수 있다.

[0448] 예를 들면, 본 발명의 화합물을 정제 또는 분리하는데 유용한 상기 언급한 것들과 다른 산의 염(예: 트리플루오로 아세테이트 염)이 또한 본 발명의 일부를 포함한다.

[0449] 용어 할로겐은 일반적으로 불소, 염소, 브롬 및 요오드를 나타낸다.

[0450] 단독으로 또는 다른 라디칼과 함께, 용어 "C_{1-n}-알킬"(여기서, n은 1 내지 n의 정수이다)은 탄소수가 1 내지 n개인 어사이클릭, 포화, 분지형 또는 직쇄형의 탄화수소를 나타낸다. 예를 들면, 용어 C_{1-5}-알킬은 라디칼 H_3C-, H_3C-CH_2-, $H_3C-CH_2-CH_2$-, $H_3C-CH(CH_3)$-, $H_3C-CH_2-CH_2-CH_2$-, $H_3C-CH_2-CH(CH_3)$-, $H_3C-CH(CH_3)-CH_2$-, $H_3C-C(CH_3)_2$-, $H_3C-CH_2-CH_2-CH_2-CH_2$-, $H_3C-CH_2-CH_2-CH(CH_3)$-, $H_3C-CH_2-CH(CH_3)-CH_2$-, $H_3C-CH(CH_3)-CH_2-CH_2$-, $H_3C-CH_2-C(CH_3)_2$-, $H_3C-C(CH_3)_2-CH_2$-, $H_3C-CH(CH_3)-CH(CH_3)$- 및 $H_3C-CH_2-CH(CH_2CH_3)$-를 포함한다.

[0451] 단독으로 또는 다른 라디칼과 함께, 용어 "C_{1-n}-알킬렌"(여기서, n은 1 내지 n의 정수이다)은 탄소수가 1 내지 n

개인 어사이클릭, 직쇄 또는 분지형의 2가 알킬 라디칼을 나타낸다. 예를 들면, 용어 C_{1-4}-알킬렌은 -(CH_2)-, -(CH_2-CH_2)-, -(CH(CH_3))-, -(CH_2-CH_2-CH_2)-, -(C(CH_3)$_2$)-, -(CH(CH_2CH_3))-, -(CH(CH_3)-CH_2)-, -(CH_2-CH(CH_3))-, -(CH_2-CH_2-CH_2-CH_2)-, -(CH_2-CH_2-CH(CH_3))-, -(CH(CH_3)-CH_2-CH_2)-, -(CH_2-CH(CH_3)-CH_2)-, -(CH_2-C(CH_3)$_2$)-, -(C(CH_3)$_2$-CH_2)-, -(CH(CH_3)-CH(CH_3))-, -(CH_2-CH(CH_2CH_3))-, -(CH(CH_2CH_3)-CH_2)-, -(CH($CH_2CH_2CH_3$))-, -(CHCH(CH_3)$_2$)- 및 -C(CH_3)(CH_2CH_3)-을 포함한다.

[0452] 용어 "C_{2-n}-알케닐"은 상기 그룹의 탄소 원자들 중의 적어도 2개가 이중 결합에 의해 서로 결합된다면, 적어도 2개의 탄소 원자를 갖는 "C_{1-n}-알킬"에 대한 정의에서 정의한 바와 같은 그룹에 대해 사용된다. 예를 들면, 용어 C_{2-3}-알케닐은 -CH=CH_2, -CH=CH-CH_3, -CH_2-CH=CH_2를 포함한다.

[0453] 용어 "용어 "C_{2-n}-알케닐렌"은 상기 그룹의 탄소 원자들 중의 적어도 2개가 이중 결합에 의해 서로 결합된다면, 적어도 2개의 탄소 원자를 갖는 "C_{1-n}-알킬렌"에 대한 정의에서 정의한 바와 같은 그룹에 대해 사용된다. 예를 들면, 용어 C_{2-3}-알케닐렌은 -CH=CH, -CH=CH-CH_2, -CH_2-CH=CH-를 포함한다.

[0454] 용어 "C_{2-n}-알키닐"은 상기 그룹의 탄소 원자들 중의 적어도 2개가 삼중 결합에 의해 서로 결합된다면, 적어도 2개의 탄소 원자를 갖는 "C_{1-n}-알킬"에 대한 정의에서 정의한 바와 같은 그룹에 대해 사용된다. 예를 들면, 용어 C_{2-3}-알키닐은 -C≡CH, -C≡C-CH_3, -CH_2-C≡CH를 포함한다.

[0455] 용어 "C_{2-n}-알키닐렌"은 상기 그룹의 탄소 원자들 중의 적어도 2개가 삼중 결합에 의해 서로 결합된다면, 적어도 2개의 탄소 원자를 갖는 "C_{1-n}-알킬렌"에 대한 정의에서 정의한 바와 같은 그룹에 대해 사용된다. 예를 들면, 용어 C_{2-3}-알키닐렌은 -C≡C-, -C≡C-CH_2-, -CH_2-C≡C-를 포함한다.

[0456] 단독으로 또는 다른 라디칼과 함께 사용되는 바와 같은, 용어 "C_{3-n}-카보사이클릴"은 탄소수가 3 내지 n개인 모노사이클릭, 비사이클릭 또는 트리사이클릭, 포화 또는 불포화 탄화수소를 나타낸다. 탄화수소 라디칼은 바람직하게는 비방향족이다. 바람직하게는 3 내지 n개의 C 원자는 1 또는 2개의 환을 형성한다. 비사이클릭 또는 트리사이클릭 환 시스템의 경우, 환은 단일 결합을 통해 서로 결합되거나, 융합되거나, 스피로사이클릭 또는 브릿지된 환 시스템을 형성할 수 있다. 예를 들면, 용어 C_{3-10}-카보사이클릴은 C_{3-10}-사이클로알킬, C_{3-10}-사이클로알케닐, 옥타하이드로펜탈레닐, 옥타하이드로인데닐, 데카하이드로나프틸, 인다닐, 테트라하이드로나프틸을 포함한다. 가장 바람직하게는, 용어 C_{3-n}-카보사이클릴은 C_{3-n}-사이클로알킬, 특히 C_{3-7}-사이클로알킬을 나타낸다.

[0457] 단독으로 또는 다른 라디칼과 함께, 용어 "C_{3-n}-사이클로알킬"(여기서, n은 4 내지 n의 정수이다)은 탄소수가 3 내지 n개인 사이클릭, 포화, 비분지형 탄화수소라디칼을 나타낸다. 사이클릭 그룹은 모노-, 비-, 트리- 또는 스피로사이클릭, 가장 바람직하게는 모노사이클릭일 수 있다. 상기 사이클로알킬 그룹의 예는 사이클로프로필, 사이클로부틸, 사이클로펜틸, 사이클로헥실, 사이클로헵틸, 사이클로옥틸, 사이클로노닐, 사이클로도데실, 비사이클로[3.2.1]옥틸, 스피로[4.5]데실, 노르피닐, 노르보닐, 노르카릴, 아다만틸 등을 포함한다.

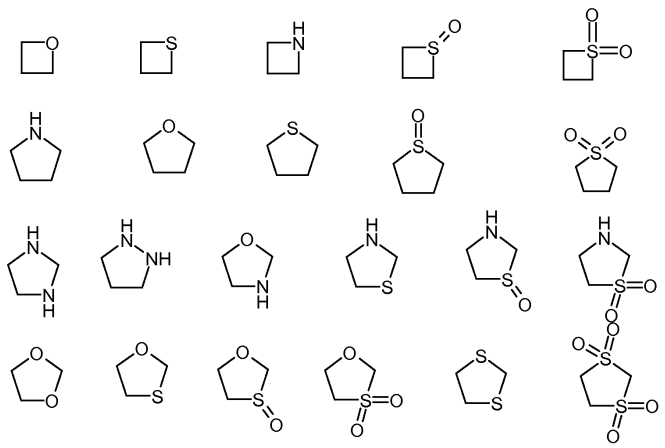
[0458] 단독으로 또는 다른 라디칼과 함께, 용어 "C_{3-n}-사이클로알케닐"(여기서, n은 3 내지 n의 정수이다)은 이들 중의 적어도 2개가 이중 결합에 의해 서로 결합되는, 탄소수가 3 내지 n개인 사이클릭, 불포화이지만 비방향족, 비분지형 탄화수소 라디칼을 나타낸다. 예를 들면, 용어 C_{3-7}-사이클로알케닐은 사이클로프로페닐, 사이클로부테닐, 사이클로펜테닐, 사이클로펜타디에닐, 사이클로헥세닐, 사이클로헥사디에닐, 사이클로헵테닐, 사이클로헵타디에닐 및 사이클로헵타트리에닐을 포함한다.

[0459] 단독으로 또는 다른 라디칼과 함께, 본 명세서에 사용된 바와 같은 용어 "아릴"은 방향족, 포화 또는 불포화일 수 있는 제2의 5- 또는 6-원 카보사이클릭 그룹에 추가로 융합될 수 있는 6개의 탄소 원자를 함유하는 카보사이클릭 방향족 모노사이클릭 그룹을 나타낸다. 아릴은, 페닐, 인다닐, 인데닐, 나프틸, 안트라세닐, 페난트레닐, 테트라하이드로나프틸 및 디하이드로나프틸을 포함하지만 이에 한정되지 않는다. 더욱 바람직하게는, 단독으로 또는 다른 라디칼과 함께, 본 명세서에 사용된 바와 같은 용어 "아릴"은 페닐 또는 나프틸, 가장 바람직하게는 페닐을 나타낸다.

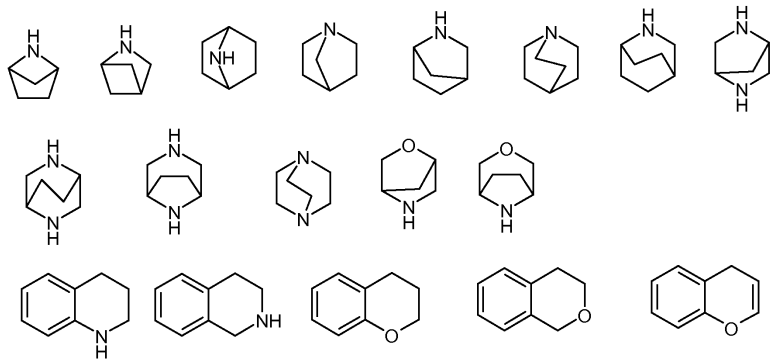
[0460] 용어 "헤테로사이클릴"은 N, O 또는 S(O)$_r$(여기서, r은 0, 1 또는 2이다)로부터 선택되는 하나 이상의 헤테로

원자를 함유하는 포화 또는 불포화 모노-, 비-, 트리- 또는 스피로카보사이클릭, 바람직하게는 모노- 또는 비사이클릭-환 시스템을 의미하며, 이는 카보닐 그룹을 또한 가질 수 있다. 더욱 바람직하게는, 단독으로 또는 다른 라디칼과 함께, 본 명세서에 사용된 바와 같은 용어 "헤테로사이클릴"은 포화 또는 불포화, 더욱 더 바람직하게는 N, O 또는 $S(O)_r$(여기서, r은 0, 1 또는 2이다)로부터 선택되는 1, 2, 3 또는 4개의 헤테로 원자를 함유하는 포화 모노- 또는 비사이클릭-환 시스템을 의미하며, 이는 카보닐 그룹을 또한 가질 수 있다. 용어 "헤테로사이클릴"은 모든 가능한 이성체 형태를 포함하고자 한다. 상기 그룹의 예는 아지리디닐, 옥시라닐, 아제티디닐, 옥세타닐, 피롤리디닐, 테트라하이드로푸라닐, 피페리디닐, 테트라하이드로피라닐, 아제파닐, 피페라지닐, 모르폴리닐, 테트라하이드로푸라노닐, 테트라하이드로피라노닐, 피롤리디노닐, 피페리디노닐, 피페라지노닐, 모르폴리노닐을 포함한다.

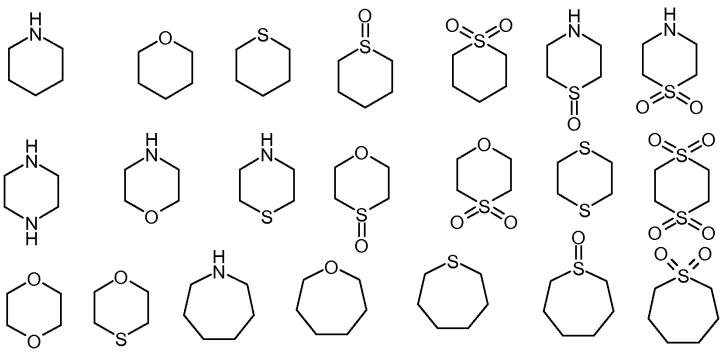
[0461] 따라서, 용어 "헤테로사이클릴"은 각각의 형태가 적합한 원자가를 유지하는 한 임의의 원자에 공유 결합을 통해 부착될 수 있는 라디칼로서 도시되지 않은 다음의 예시적 구조를 포함한다:

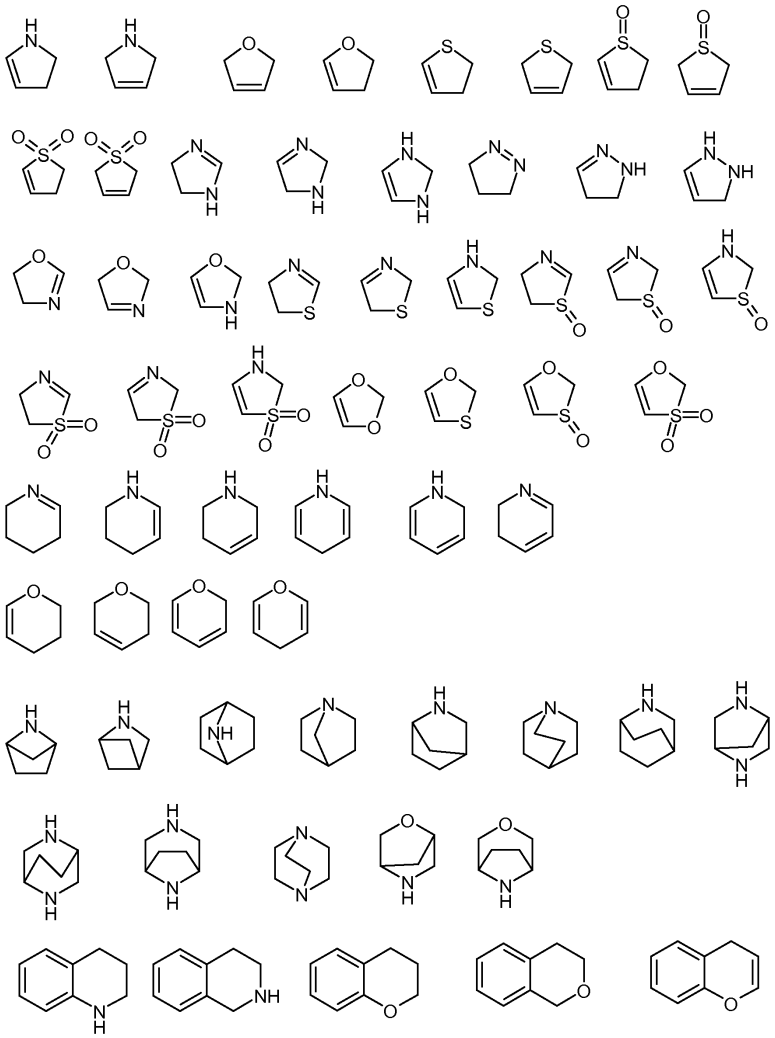


[0462]

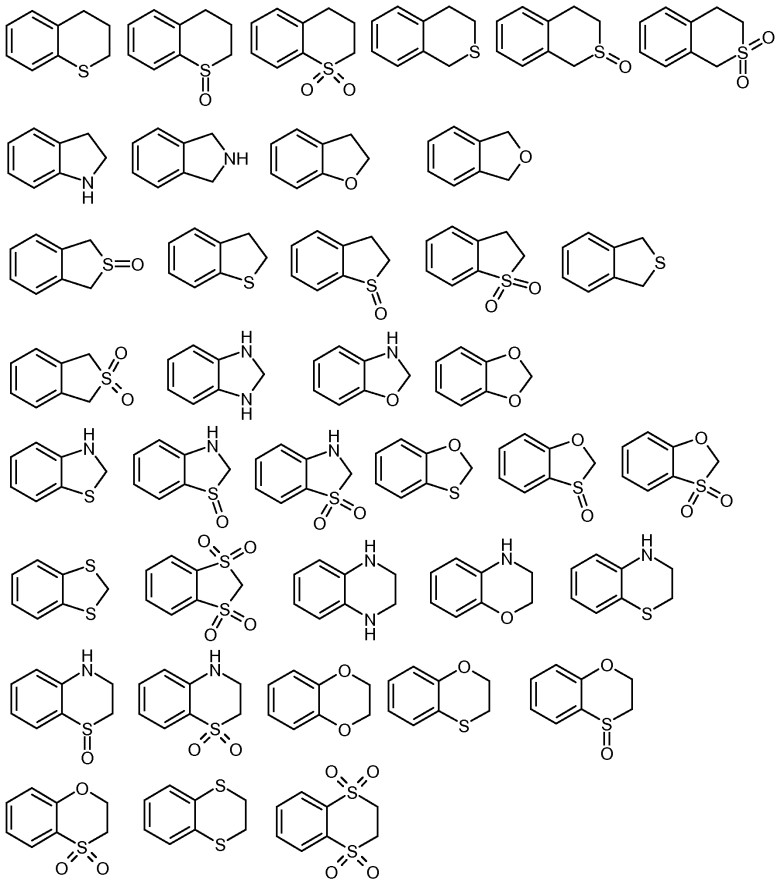


[0463]





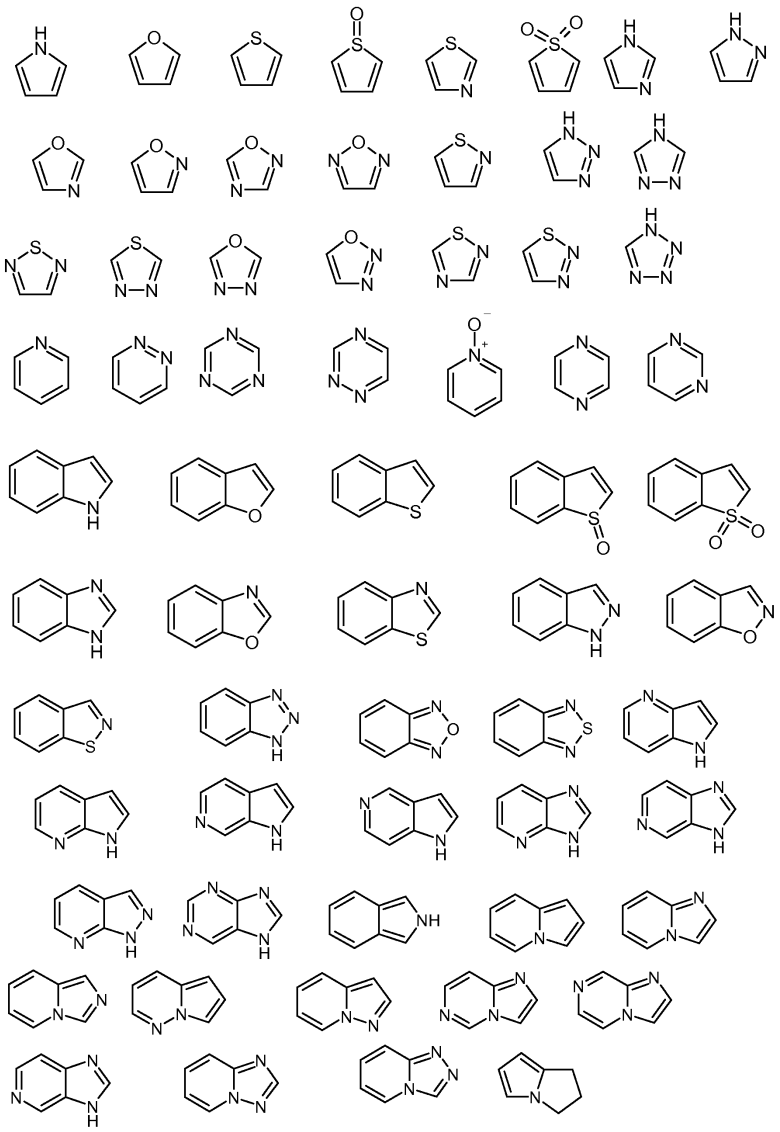
[0464]



[0465]

[0466] 용어 "헤테로아릴"은 N, O 또는 $S(O)_r$(여기서, r은 0, 1 또는 2이다)로부터 선택되는 하나 이상의 헤테로 원자를 함유하는 모노- 또는 폴리사이클릭, 바람직하게는 모노- 또는 비사이클릭-환 시스템을 의미하며, 여기서, 상기 헤테로 원자들 중의 적어도 하나는 방향족 환의 일부이고, 상기 환 시스템은 카보닐 그룹을 가질 수 있다. 더욱 바람직하게는, 단독으로 또는 다른 라디칼과 함께, 본 명세서에 사용된 바와 같은 용어 "헤테로아릴"은 N, O 또는 $S(O)_r$(여기서, r은 0, 1 또는 2이다)로부터 선택되는 1, 2, 3 또는 4개의 헤테로 원자를 함유하는 모노- 또는 비사이클릭-환 시스템을 의미하며, 여기서, 상기 헤테로 원자들 중의 적어도 하나는 방향족 환의 일부이고, 상기 환 시스템은 카보닐 그룹을 가질 수 있다. 용어 "헤테로아릴"은 모든 가능한 이성체 형태를 포함하고자 한다.

[0467] 따라서, 용어 "헤테로아릴"은 각각의 형태가 적합한 원자가를 유지하는 한 임의의 원자에 공유 결합을 통해 부착될 수 있는 라디칼로서 도시되지 않은 다음의 예시적 구조를 포함한다:



[0468]

[0469] 상기 제시된 용어들 중의 많은 것이 화학식 또는 그룹의 정의에서 반복적으로 사용될 수 있고, 각각의 경우에 서로 무관하게 상기 제시된 의미 중의 하나를 가질 수 있다.

[0470] **약물학적 활성**

[0471] 본 발명의 화합물의 활성은 하기 ACC2 검정법을 사용하여 입증될 수 있다:

[0472] **분광광도 384 웰 검정법(spectrophotometric 384 well assay)**

[0473] 아세틸 CoA 카복실라제에 의한 말로닐 CoA 형성은 ATP의 소비에 화학양론적으로 링크된다. ACC2 활성은, 결합 락테이트 데하이드로게나제/피루베이트 키나제 반응을 사용하는 ACC 반응 과정에서 생성되는 ADP를 측정하는 NADH-링크된 운동학적 방법으로 측정한다.

[0474] 생물학적 시험을 위해, 증가된 용해도를 위해 N-말단에 128개 아미노산이 결여된 인간 ACC2 작제물(nt 385-6966 in Genbank entry AJ575592)을 클론화한다. 이어서, 상기 단백질을 바큘로바이러스 발현계(baculoviral expression system)를 사용하여 곤충 세포에서 발현시킨다. 단백질 정제는 음이온 교환에 의해 수행한다. 모든 화합물은 10mM의 농도로 디메틸 설폭사이드(DMSO)에 용해시킨다.

[0475] 이어서, 검정 반응은, 적합한 희석액 중에서, 100mM Tris(pH 7.5), 10mM 트리나트륨 시트레이트, 25mM $KHCO_3$, 10mM $MgCl_2$, 0.5mg/mL BSA, 3.75mM 환원형 L-글루타티온, 15U/mL 락테이트 데하이드로게나제, 0.5mM 포스포엔올피루베이트, 15U/mL 피루베이트 키나제, 1%의 최종 DMSO 농도에서 상이한 농도인 화합물의 최종 검정 농도(f.c.)에서 hACC2를 사용하여 384-웰 플레이트에서 수행한다.

[0476] 이어서, 효소 반응은, NADH, 아세틸 코엔자임 A(모두 200μM f.c.) 및 ATP(500uM f.c.)의 혼합물을 첨가하여 개시한다. 이어서, 광학밀도의 감소(기울기 S)는 분광광도계 리더에서 15분에 걸쳐 340㎚의 파장에서 25℃에서 측정한다.

[0477] 각각의 검정 미세역가판은 억제되지 않은 효소에 대한 대조군으로서의 화합물 대신에 비히클을 갖는 웰(100% CTL; 'HIGH') 및 비-특이적 NADH 분해에 대한 대조군으로서의 아세틸-CoA 없는 웰(0% CTL; 'LOW')을 함유한다.

[0478] 기울기 S는 %CTL = (S(화합물) - S('LOW'))/(S('HIGH') - S('LOW')) * 100의 계산을 위해 사용된다. 상기 화합물은 100% CTL(억제 없음) 및 0% CTL(완전한 억제) 사이의 값을 제공할 것이다.

[0479] IC50 값 측정을 위해, 저 대조군(low controls)을 뺀 후 시험 화합물의 존재하에 샘플 기울기 (S(화합물)-S('LOW'))가 사용된다. IC50 값은, 비선형 회귀곡선 피팅 (방정식 y = (A+((B-A)/(1+((C/x)^D)))))에 의해 저 대조군을 뺀 후 상이한 용량에서의 화합물 기울기 (S(화합물)-S('LOW'))로부터 유도된다.

[0480] 본 발명에 따르는 화학식 I의 화합물은, 예를 들면, 30000nM 미만, 특히 1000nM 미만, 바람직하게는 300nM 미만의 IC_{50} 값을 갖는다.

[0481] 하기 표에, 본 발명에 따르는 화합물의 IC50(μM)으로서 표현된 활성이 제시되어 있으며, 여기서, IC50 값은 앞서 기술한 바와 같은 ACC2 검정법으로 측정한다. 용어 "Ex"는 하기 실험 섹션에 따르는 실시예 번호를 의미한다.

[0482]

Ex.	IC50 [μM]	Ex.	IC50 [μM]	Ex.	IC50 [μM]	Ex.	IC50 [μM]
1.1	0.13	1.13	0.10	1.25	0.15	1.37	0.11
1.2	0.05	1.14	0.10	1.26	0.09	1.38	0.35
1.3	0.09	1.15	0.24	1.27	5.8	1.39	0.13
1.4	0.32	1.16	0.09	1.28	0.05	1.40	0.14
1.5	0.35	1.17	0.45	1.29	0.08	1.41	0.32
1.6	0.14	1.18	0.35	1.30	0.23	1.42	0.63
1.7	0.14	1.19	0.26	1.31	0.18	1.43	4.1
1.8	0.12	1.20	0.29	1.32	0.09	1.44	0.18
1.9	0.05	1.21	0.08	1.33	0.12	1.45	0.37
1.10	0.22	1.22	0.14	1.34	0.26	1.46	0.70
1.11	0.30	1.23	0.05	1.35	0.32	1.47	2.9
1.12	0.08	1.24	0.21	1.36	0.41	1.48	11.3

1.49		1.82	0.16	1.115	0.11	1.148	0.70
1.50	0.12	1.83	0.10	1.116	0.77	1.149	0.14
1.51	0.09	1.84	0.18	1.117	0.06	1.150	0.13
1.52	0.11	1.85	0.14	1.118	0.12	1.151	0.11
1.53	0.82	1.86	0.21	1.119	0.26	1.152	0.08
1.54	0.13	1.87	1.2	1.120	0.25	1.153	0.52
1.55	0.24	1.88	0.54	1.121	8.1	1.154	0.30
1.56	0.72	1.89	0.39	1.122	0.12	1.155	0.41
1.57	0.10	1.90	0.23	1.123	0.07	1.156	0.60
1.58	0.12	1.91	0.60	1.124	0.18	1.157	0.58
1.59	0.14	1.92	0.12	1.125	0.10	1.158	1.3
1.60	0.18	1.93	0.58	1.126	0.23	1.159	2.7
1.61	0.21	1.94	0.21	1.127	0.33	1.160	2.1
1.62	0.20	1.95	1.2	1.128	0.12	1.161	0.64
1.63	1.3	1.96	0.36	1.129	3.5	1.162	3.1
1.64	0.07	1.97	0.53	1.130	0.08	1.163	0.67
1.65	20.0	1.98	0.47	1.131	0.19	1.164	0.77
1.66	0.42	1.99	0.33	1.132	0.84	1.165	0.10
1.67	0.36	1.100	0.52	1.133	0.13	1.166	4.0
1.68	23.9	1.101	0.05	1.134	0.28	1.167	0.91
1.69	4.0	1.102	0.16	1.135	0.34	1.168	0.50
1.70	7.4	1.103	0.09	1.136	0.50	1.169	1.7
1.71	0.08	1.104	0.20	1.137	16.0	1.170	0.40
1.72	23.7	1.105	0.24	1.138	0.16	1.171	16.3
1.73	3.4	1.106	0.17	1.139	0.07	1.172	0.25
1.74	0.10	1.107	0.52	1.140	0.09	1.173	0.82
1.75	2.2	1.108	0.93	1.141	0.32	1.174	7.5
1.76	1.9	1.109	3.1	1.142	0.06	1.175	1.1
1.77	0.90	1.110	4.5	1.143	0.12	1.176	0.03
1.78	3.4	1.111	0.17	1.144	0.06	1.177	0.04
1.79	0.18	1.112	0.21	1.145	0.14	1.178	0.17
1.80	0.53	1.113	0.14	1.146	1.1	1.179	0.31

[0483]

1.81	0.28	1.114	0.13	1.147	0.49	1.180	0.53
1.181	0.09	3.1	0.36	4.19	0.10	4.52	0.53
1.182	0.21	3.2	0.33	4.20	1.3	4.53	0.16
1.183	0.15	3.3	0.11	4.21	0.52	4.54	1.8
1.184	1.2	3.4	0.11	4.22	1.1	4.101	2.7
1.185	22.1	3.5	0.59	4.23	0.72	4.102	0.47
1.186	0.17	3.6	0.24	4.24	2.1	4.201	0.06
1.187	0.03	3.7	0.74	4.25	0.23	4.202	0.15
1.188	0.08	3.8	0.34	4.26	0.29	4.301	0.39
1.189	0.06	3.9	13.3	4.27	0.33	4.302	0.20
1.190	1.4	3.10	1.6	4.28	0.06	4.303	15.6
1.191	0.39	3.11	3.0	4.29	1.7	4.304	0.24
1.192	0.12	3.12	0.06	4.30	1.1	4.305	1.4
1.200	0.45	3.13	0.47	4.31	2.0	4.306	0.12
1.201	4.6	3.14	0.42	4.32	2.3	5.1	0.20
1.202	1.9	3.20	7.4	4.33	0.51	5.2	0.33
1.203	0.62	4.1	2.5	4.34	9.5	5.3	0.13
1.204	0.45	4.2	1.3	4.35	0.51	5.4	0.09
1.205	0.66	4.3	0.45	4.36	1.2	5.5	0.02
1.206	4.7	4.4	1.8	4.37	0.30	5.6	0.06
1.207	5.1	4.5	2.6	4.38	0.44	5.7	0.05
1.300	23.3	4.6	1.6	4.39	1.9	5.8	19.2
2.1	2.1	4.7	0.95	4.40	0.93	5.9	25.4
2.3	0.99	4.8	0.97	4.41	0.10	5.10	0.10
2.4	1.8	4.9	1.9	4.42	0.53	5.11	0.15
2.5	0.83	4.10	0.67	4.43	0.41	5.12	0.22
2.6	0.92	4.11	0.85	4.44	0.65	5.13	3.0
2.7	1.6	4.12	11.6	4.45	1.5	5.14	
2.8	0.96	4.13	3.2	4.46	0.21	5.15	4.9
2.9	0.46	4.14	2.4	4.47	0.08	5.16	0.26
2.10	1.6	4.15	0.22	4.48	0.13	5.17	1.2
2.11	1.3	4.16	1.1	4.49	0.21	5.18	

[0484]

2.12	0.53	4.17	0.44	4.50	0.46	5.19	1.0
2.13	1.9	4.18	0.32	4.51	0.31	5.20	1.2
5.21	0.86	5.54	9.3	6.27	4.8	8.9	0.60
5.22	2.3	5.55	7.6	6.28	1.3	8.10	0.10
5.23	0.42	5.56	1.2	6.29	3.6	8.11	1.8
5.24	0.99	5.57	0.23	6.30	1.1	8.12	2.3
5.25	2.4	5.58	0.86	6.31	2.8	8.13	0.11
5.26	9.0	5.200	7.5	6.32	0.86	8.14	0.13
5.27	5.2	5.201	0.79	6.33	3.1	8.15	0.83
5.28	8.0	6.1	0.46	6.34	0.25	8.16	5.6
5.29	0.17	6.2	2.8	6.35	7.1	8.17	0.29
5.30	0.18	6.3	2.6	6.36	9.1	8.18	2.7
5.31	1.0	6.4	2.1	6.37	0.76	8.19	6.0
5.32	3.8	6.5	0.38	6.38	0.09	8.20	12.0
5.33	0.33	6.6	0.99	6.39	1.3	8.21	1.5
5.34	3.2	6.7	0.77	6.40	1.2	8.22	14.6
5.35	2.8	6.8	0.19	6.41	4.1	8.23	0.57
5.36	3.1	6.9	0.15	6.42	2.8	8.24	12.4
5.37	2.9	6.10	0.25	6.43	1.1	8.25	0.71
5.38	0.57	6.11	0.34	6.44	25.0	8.26	0.84
5.39	0.34	6.12	1.3	6.45	2.6	8.27	2.6
5.40	0.41	6.13	1.1	6.46	10.4	8.28	0.15
5.41	5.0	6.14	0.19	6.47	0.73	8.29	0.89
5.42	0.21	6.15	1.0	6.48	3.7	8.30	0.16
5.43	0.63	6.16	0.57	6.49	8.3	8.31	1.2
5.44	0.07	6.17	1.9	7.1	0.58	8.32	3.2
5.45		6.18	1.1	7.2	0.19	8.33	3.5
5.46	1.6	6.19	1.5	8.1	0.44	8.34	0.26
5.47	0.80	6.20	0.67	8.2	0.30	8.35	0.49
5.48	0.42	6.21	1.6	8.3	0.20	8.36	2.2
5.49	2.6	6.22	0.67	8.4	0.40	8.37	0.66
5.50	0.09	6.23	0.42	8.5	0.22	8.38	1.2

[0485]

5.51	4.8	6.24	3.9	8.6	0.33	8.39	0.11
5.52	19.6	6.25	0.34	8.7	0.16	8.40	1.4
5.53	7.7	6.26	0.28	8.8	0.29	8.41	4.2
8.42	0.09	9.8	0.20	9.42	0.16	10.29	0.13
8.43	2.1	9.9	0.21	9.43	0.43	10.30	0.13
8.44	0.29	9.10	0.53	9.44	0.48	10.31	0.18
8.45	7.0	9.11	0.17	9.45	0.38	10.32	0.41
8.46	1.0	9.12	0.25	9.46	0.56	10.33	0.64
8.47	2.6	9.13	0.57	10.1	0.05	10.34	0.21
8.48	1.6	9.14	0.27	10.2	0.20	10.35	1.1
8.49	26.6	9.15	0.37	10.3	0.13	10.36	0.21
8.50	1.1	9.16	0.69	10.4	2.0	10.37	0.19
8.51	0.76	9.17	0.55	10.5	0.54	10.38	3.0
8.52	3.0	9.18	0.15	10.6	0.10	10.39	
8.53	0.30	9.19	0.14	10.7	0.04	10.40	6.9
8.54	1.5	9.20	0.09	10.8	0.20	10.41	1.9
8.55	0.30	9.21	0.10	10.9	0.02	10.42	
8.56	1.0	9.22	0.16	10.10	0.07	10.43	0.03
8.57	3.2	9.23	0.20	10.11	5.8	10.44	0.10
8.58	0.37	9.24	0.47	10.12	0.36	10.45	1.1
8.59	0.84	9.25	1.1	10.13	0.09	10.46	0.14
8.60	0.18	9.26	0.22	10.14	0.10	10.47	0.27
8.61	0.30	9.27	0.07	10.15	0.55	10.48	1.2
8.62	0.20	9.28	0.78	10.16	0.71	10.49	0.26
8.63	0.10	9.29	0.06	10.17	0.02	10.50	0.05
8.64	0.12	9.30	2.3	10.18	0.18	10.51	1.5
8.65	0.22	9.31	4.8	10.19		10.52	0.07
8.66	0.06	9.32	0.99	10.20	2.7	10.53	0.08
8.67	27.7	9.33	0.12	10.21	0.07	10.54	0.42
9.1	0.37	9.34	0.15	10.22	1.1	10.55	0.64
9.2	0.30	9.35	0.21	10.23	0.29	10.56	0.32
9.3	1.4	9.36	3.3	10.24	0.07	10.57	0.24

[0486]

9.4	0.04	9.37	0.69	10.25	0.32	10.58	0.76
9.5	0.26	9.38	0.41	10.26	0.41	10.59	
9.6	0.13	9.40	2.9	10.27	0.97	10.60	0.39
9.7	0.56	9.41	0.22	10.28		10.61	0.53
10.62	0.05	10.95	2.0	10.128	0.14	11.12	0.30
10.63	0.03	10.96	0.60	10.129	0.34	11.13	4.6
10.64	7.0	10.97	8.2	10.130	0.04	11.14	3.5
10.65	0.33	10.98	0.90	10.201	0.34	11.15	0.23
10.66	0.16	10.99	0.38	10.202	0.57	11.16	0.43
10.67	0.09	10.100	0.09	10.203	0.16	11.17	1.2
10.68	0.32	10.101	0.08	10.204	0.35	11.18	6.2
10.69	0.27	10.102	0.24	10.301	0.32	11.19	0.88
10.70	0.23	10.103	0.56	10.302	0.43	11.20	1.3
10.71	0.15	10.104	0.17	10.303	0.16	11.21	0.89
10.72	1.2	10.105	0.10	10.304	0.75	11.22	0.82
10.73	0.18	1.0106	0.38	10.305	0.46	11.23	1.5
10.74	1.2	10.107	0.11	10.306	0.31	11.24	0.37
10.75	0.05	10.108	0.09	10.307	0.31	11.25	0.24
10.76	0.11	10.109	0.09	10.308	0.08	11.26	0.38
10.77	1.6	10.110	0.43	10.309	0.08	11.27	0.30
10.78	0.20	10.111	0.17	10.310	0.04	11.28	0.35
10.79	1.1	10.112	0.12	10.311	0.18	11.29	3.8
10.80	0.14	10.113	0.53	10.312	0.16	11.30	8.4
10.81	10.4	10.114	0.41	10.313	0.12	11.31	0.69
10.82	0.15	10.115	0.41	10.314	0.28	11.32	1.1
10.83	1.9	10.116	0.46	10.315	0.12	11.33	0.59
10.84	1.3	10.117	0.68	11.1	0.18	11.34	23.2
10.85	2.6	10.118	0.15	11.2	0.08	11.35	0.71
10.86	5.9	10.119	0.31	11.3	0.25	11.36	0.58
10.87	0.07	10.120	0.74	11.4	0.45	11.37	0.93
10.88	0.03	10.121	0.11	11.5	0.20	11.38	0.56
1.089	0.79	10.122	0.15	11.6	0.18	11.39	6.6

[0487]

10.90	0.35	10.123	0.42	11.7	0.17	11.40	8.1
10.91	0.17	10.124	0.09	11.8	0.49	11.41	3.1
10.92	0.37	10.125	0.64	11.9	0.38	11.42	7.1
10.93	4.3	10.126	1.3	11.10	0.27	11.43	3.3
10.94	2.3	10.127	1.6	11.11	0.82	11.44	5.0
11.45	1.5	11.78	0.61	11.111	0.64	14.52	
11.46	2.8	11.79	4.0	11.112	1.1	14.53	4.9
11.47	0.54	11.80	2.3	11.113	0.20	14.54	1.1
11.48	0.58	11.81	2.3	11.114	0.18	14.55	1.7
11.49	0.35	11.82	0.87	11.115	1.5	14.56	14.7
11.50	4.2	11.83	0.41	11.116	14.5	14.57	14.2
11.51	7.8	11.84	6.5	11.117	4.3	14.58	7.1
11.52	18.5	11.85	13.9	11.118	0.29	14.59	1.5
11.53	6.0	11.86	0.77	11.119	0.24	14.60	2.1
11.54	3.7	11.87	0.79	11.120	0.28	14.61	0.53
11.55	3.7	11.88	1.6	11.121	0.47	14.62	13.3
11.56	2.3	11.89	0.76	11.122	1.4	14.63	1.6
11.57	0.42	11.90	0.23	11.123	0.20	14.64	3.8
11.58	0.26	11.91	0.44	11.124	0.88	14.65	3.7
11.59	6.1	11.92	0.32	11.125	0.34	14.66	2.2
11.60	5.3	11.93	0.55	11.126	0.81	14.67	1.9
11.61	1.3	11.94	1.7	11.127	3.5	14.68	7.8
11.62	3.3	11.95	2.0	11.128	0.41	14.69	12.1
11.63	2.0	11.96	0.35	11.129	1.3	14.70	0.79
11.64	17.9	11.97	0.33	11.130	0.37	15.1	2.8
11.65	4.7	11.98	0.66	11.131	1.1	15.2	0.35
11.66	2.2	11.99	2.5	11.132	3.0	15.3	0.20
11.67	26.4	11.100	5.2	12.1	0.61	15.4	
11.68	0.61	11.101	4.0	13.1	0.09	15.5	17.7
11.69	0.20	11.102	3.2	13.2	0.13	15.6	0.26
11.70	4.5	11.103	2.6	13.3	0.17	15.7	1.5
11.71	2.3	11.104	0.60	14.1	0.47	15.8	8.4

[0488]

11.72	10.5	11.105	1.7	14.2	2.7	15.9	19.9
11.73	15.6	11.106	1.6	14.3	1.4	15.10	3.2
11.74	8.3	11.107	2.4	14.4		15.11	0.16
11.75	3.8	11.108	0.11	14.5	1.7	15.12	2.2
11.76	6.0	11.109	0.08	14.50	3.8	15.13	0.97
11.77	0.28	11.110	0.23	14.51	0.61	15.14	0.88
15.15	0.99	18.10	11.5	18.43	16.8	18.76	4.0
15.16		18.11	0.74	18.44	18.3	18.77	1.7
15.17	0.30	18.12	0.42	18.45	17.2	18.78	12.7
15.18	0.33	18.13	6.1	18.46	6.0	18.79	16.7
15.19	3.9	18.14	10.2	18.47	29.1	18.80	27.2
15.20	3.9	18.15	7.2	18.48	3.6	18.81	16.5
15.21	1.2	18.16	5.1	18.49	1.3	18.82	6.2
15.22	13.2	18.17	7.9	18.50	13.3	18.83	8.7
15.23	6.4	18.18	1.1	18.51	13.8	18.84	18.1
16.1	1.4	18.19	20.5	18.52	13.6	18.85	
16.2	4.8	18.20	0.53	18.53	15.1	18.86	11.3
16.3		18.21	2.6	18.54	2.1	18.87	
16.4	0.62	18.22	11.4	18.55	8.8	18.88	16.6
16.5	2.5	18.23	3.1	18.56	14.9	18.89	1.2
16.6	0.45	18.24	5.2	18.57	22.4	18.90	1.2
16.7	1.4	18.25	7.1	18.58	18.1	18.91	0.91
16.8	3.9	18.26	2.5	18.59	18.5	18.92	2.2
16.9	6.7	18.27	10.4	18.60	15.5	18.93	0.80
16.10	0.93	18.28	16.9	18.61	18.9	18.94	2.2
16.11	1.3	18.29	6.5	18.62	11.8	18.95	0.19
17.1	2.9	18.30	5.2	18.63	23.1	19.1	0.11
17.2	4.2	18.31	9.3	18.64	25.4	19.2	0.04
17.3	7.5	18.32	5.3	18.65	10.2	19.3	0.70
17.4	11.3	18.33	1.5	18.66	15.8	19.4	0.07
18.1	9.8	18.34	3.5	18.67	23.7	19.5	0.08
18.2	1.4	18.35	7.3	18.68	19.0	19.6	0.08

[0489]

18.3	0.18	18.36	13.2	18.69	20.8	19.7	0.59
18.4	1.8	18.37	6.4	18.70	17.4	19.8	1.5
18.5	1.9	18.38	3.1	18.71	14.8	19.9	1.3
18.6	0.26	18.39	15.2	18.72	8.9	19.10	0.10
18.7	3.6	18.40	6.6	18.73	17.9	19.11	0.14
18.8	0.26	18.41	21.4	18.74	24.5	19.12	0.18
18.9	1.6	18.42	14.0	18.75	17.8	19.13	0.09
19.14	0.40	19.35	27.4	22.11	0.39	29.3	6.7
19.15	0.08	19.36		22.12	3.3	29.4	
19.16	0.27	19.37	1.2	22.13	0.44	30.1	2.7
19.17	0.33	19.38	1.2	23.1	0.29	31.1	1.6
19.18	0.34	20.1	0.60	24.1	1.0	32.1	7.2
19.19	0.11	20.2	0.22	24.2	1.9	33.1	1.7
19.20	0.13	20.3	0.18	24.3	1.1	33.2	8.9
19.21	0.22	20.4	0.19	24.4	1.3	34.1	0.42
19.22		21.1	0.26	25.1	2.7	34.2	0.04
19.23	0.12	21.2	0.15	25.2	10.3	35.1	5.4
19.24	0.24	21.3	0.32	25.3	0.95	36.1	1.6
19.25	0.07	22.1	1.1	26.1	1.9	37.1	23.1
19.26	0.15	22.2	2.5	26.2	4.1	38.1	0.43
19.27	0.41	22.3	1.0	26.3	0.71	38.2	0.29
19.28	0.23	22.4	0.39	26.4	9.1	39.1	12.0
19.29	0.92	22.5	0.94	27.1	0.15	39.2	1.5
19.30	0.54	22.6	1.2	27.2	2.7	40.1	0.29
19.31	0.75	22.7	4.1	27.3	0.86	40.2	0.08
19.32	0.27	22.8	2.9	28.1	9.3		
19.33	0.40	22.9	3.1	29.1	1.6		
19.34	0.52	22.10	0.24	29.2	1.7		

[0490]

[0491] 효소(들) 아세틸-CoA 카복실라제를 억제하는 이들의 능력 면에서, 본 발명에 따르는 화학식 I의 화합물 및 상응하는 이의 염은, 효소(들) 아세틸-CoA 카복실라제, 특히 ACC2 활성의 억제에 의해 영향을 받을 수 있거나 상기 억제에 의해 매개되는 모든 질환 또는 상태의 예방적 치료를 포함하는 치료에 이론적으로 적합하다.

[0492] 따라서, 본 발명은 약제로서의 화학식 I의 화합물에 관한 것이다.

[0493] 더욱이, 본 발명은 환자에서, 바람직하게는 인간에서, 아세틸-CoA 카복실라제 효소(들), 특히 ACC2의 억제에 의해 매개되는 질환 또는 상태의 치료 및/또는 예방을 위한 화학식 I의 화합물의 용도에 관한 것이다.

[0494] 또 다른 측면에서, 본 발명은, 아세틸-CoA 카복실라제 효소(들)의 억제에 의해 매개되는 질환 또는 상태의 예방을 포함하는 치료를 필요로 하는 환자, 바람직하게는 인간에게 치료적 유효량의 본 발명의 화합물 또는 이의 약제학적 조성물을 투여하는 단계를 포함하는, 포유동물에서 아세틸-CoA 카복실라제 효소(들)의 억제에 의해 매개되는 질환 또는 상태의 예방을 포함하는 치료 방법에 관한 것이다.

[0495] 아세틸-CoA 카복실라제 억제제에 의해 매개되는 질환 및 상태는 대사 및/또는 심혈관 및/또는 신경변성 질환 또는 상태를 포함한다.

[0496] 하나의 측면에 따르면, 본 발명의 화합물은 특히 당뇨병, 특히 2형 당뇨병, 1형 당뇨병 및 당뇨병-관련 질환, 예를 들면, 혈전증, 응고항진 상태 및 전혈전 단계(동맥 및 정맥)를 포함한 대혈관 및 미세혈관 질환, 고혈압, 관상동맥 질환 및 심부전, 증가된 복부둘레, 응고항진, 고요산혈증, 미세알부민혈증과 같은 합병증을 포함하는, 고혈당증, 대사 증후군, 내당능 장애, 당뇨성 신경병증, 당뇨성 신장병, 당뇨성 망막병증, 이상지질혈증, 고혈압, 고인슐린증 및 인슐린 저항성 증후군, 간 인슐린 저항성의 치료에 적합하다.

[0497] 또 다른 측면에 따르면, 본 발명의 화합물은 과체중, 복부 비만을 포함한 비만, 비알코올성 지방간 질환(NAFLD)

및 비만 관련 질환(예: 체중 증가 또는 체중 유지)의 치료에 특히 적합하다.

[0498] 비만 및 과체중은 일반적으로 체질량 지수(BMI)에 의해 정의되는데, 이는 총 신체 지방과 상관관계가 있고 질환의 상대 위험도를 추정하는 것이다. BMI는 체중(kg)을 키(㎡)로 나누어 계산한다(kg/㎡). 과체중은 통상 25 내지 29.9kg/㎡의 BMI로서 정의하며, 비만은 통상 30kg/㎡ 또는 그 이상의 BMI로서 정의한다.

[0499] 또 다른 측면에 따르면, 본 발명의 화합물은 1형(인슐린-의존성 당뇨병, "IDDM"으로도 언급함) 및 2형(비인슐린-의존성 당뇨병, "NIDDM"으로도 언급함) 당뇨병, 내당능 장애, 인슐린 저항성, 고혈당증, 췌장 베타 세포 변성 및 당뇨 합병증(예: 대혈관 및 미세혈관 질환, 아테롬성 동맥경화증, 관상동맥 심장 질환, 졸중, 말초 혈관 질환, 신장병, 고혈압, 신경증 및 망막병증)을 포함한 당뇨병 또는 당뇨병-관련 질환의 진행 또는 개시를 예방 또는 지연시키는 것을 포함하는 치료에 특히 적합하다.

[0500] 또한, 본 발명의 화합물은, 아테롬성 동맥경화증, 관상동맥 심장 질환, 뇌혈관 질환, 당뇨병, 대사 증후군, 비만, 인슐린 저항성 및/또는 심혈관 질환을 포함하는, 혈액 및 조직에서 일반적으로 이상지질혈증, 및 더욱 특히, 증가된 지질 농도, LDL, HDL 및 VLDL의 조절 장애, 특히, 높은 혈장 트리글리세리드 농도, 높은 식후 혈장 트리글리세리드 농도, 낮은 HDL 콜레스테롤 농도, 낮은 apoA 지질단백질 농도, 높은 LDL 콜레스테롤 농도, 높은 apoB 지질단백질 농도를 치료하는데 적합하다.

[0501] ACC 억제는 음식물 섭취에 대한 중심 자극 효과를 유도할 수 있다. 따라서, 본 발명의 화합물은 거식증과 같은 식이장애의 치료에 적합할 수 있다.

[0502] 또한, 본 발명의 화합물은 파킨슨병, 알츠하이머병, 저산소증, 허혈, 근위축성 측삭경화증 및 신경교종이 있는 환자의 신경보호 효과를 제공할 수 있고, 알츠하이머병 환자의 인지 등급을 개선할 수 있다.

[0503] 아세틸-CoA 카복실라제 억제제에 의해 매개되는 추가의 질환 및 상태는 다음을 포함하지만 이에 한정되지 않는다:

[0504] A. 지방산 대사 장애 및 글루코즈 활용 장애; 인슐린 저항성이 관여되는 질환;

[0505] B. 지방간, 알코올성 지방간, 비-알코올성 간염, 비-알코올성 지방간(NASH), 알코올성 간염, 급성 지방간, 임신성 지방간, 약물-유도 간염, 철 저장(iron storage) 질환, 간섬유증, 간경변증, 간암, 바이러스성 간염을 포함하는 간 질환 및 이와 관련된 상태;

[0506] C. 피부 질환과 상태, 및 다중불포화 지방산과 관련된 피부 질환과 상태, 예를 들면,

[0507] - 습진, 여드름, 피지선 질환, 건선, 켈로이드 반흔 형성 또는 방지, 점막 지방산 조성과 관련된 다른 질환;

[0508] D. 가족성 조직구 세망증, 지질단백질 리파제 결핍, 고지질단백혈증, 아포지단백질 결핍(예: apoCII 또는 apoE 결핍)이 이어지는 1차 고중성지방혈증 또는 2차 고중성지방혈증;

[0509] E. 종양 세포증식과 관련된 질환 또는 상태, 예를 들면, 양성 또는 악성종양, 암, 종양형성, 전이, 발암 현상;

[0510] F. 신경적, 정신적 또는 면역 장애 또는 상태와 관련된 질환 또는 상태;

[0511] G. 염증 반응, 세포 미분화 및/또는 기타 ACC-매개된 측면이 관여될 수 있는 다른 질환 또는 상태는, 예를 들면, 다음과 같다:

[0512] - 아테롬성 동맥경화증, 예를 들면, (이로써 제한되는 것은 아니지만) 협심증 또는 심근경색, 졸중, 허혈성 졸중 및 일과성 뇌허혈 발작(TIA)을 포함한 관상동맥 경화증,

[0513] - 말초 폐쇄성 질환,

[0514] - 혈관 재협착증 또는 재폐쇄,

[0515] - 만성 염증성 장 질환, 예를 들면, 크론병 및 궤양성 대장염,

[0516] - 췌장염,

[0517] - 부비동염,

[0518] - 망막병증, 허혈성 망막병증,

[0519] - 지방질 세포 종양,

[0520] - 지질성 암종, 예를 들면, 지방육종,

[0521] - 고형 종양 및 신생물, 예를 들면, (이로써 제한되는 것은 아니지만) 위장관, 간, 담관 및 췌장의 암종; 내분비 종양; 폐, 신장 및 요도, 생식기의 암종; 전립선 암종, 유방암(특히, BRCA1 돌연변이가 있는 유방암) 등,

[0522] - ACC가 상향 조절되는 종양,

[0523] - 급성 및 만성 골수증식성 장애 및 림프종, 혈관 신생

[0524] - 알츠하이머병, 다발성 경화증, 파킨슨병, 간질을 포함한 신경변성 질환,

[0525] - 전신홍반-편평상피 피부병, 예를 들면, 건선,

[0526] - 여드름,

[0527] - PPAR에 의해 조절되는 다른 피부 장애 및 피부 상태,

[0528] - 습진 및 신경피부염,

[0529] - 피부염, 예를 들면, 지루성 피부염 또는 광피부염,

[0530] - 각막염 및 각화증, 예를 들면, 지루성 각화증, 노인성 각화증, 광선 각화증, 광-유래 각화증 또는 모낭 각화증,

[0531] - 켈로이드 및 켈로이드 예방,

[0532] - 세균성 감염,

[0533] - 진균성 감염,

[0534] - 콘틸로마 또는 첨형 콘틸로마를 포함하는, 사마귀,

[0535] - 바이러스 감염, 예를 들면, 인간 간염 B 바이러스(HBV), 간염 C 바이러스(HCV), 웨스트 닐 바이러스(WNV) 또는 Dengue 바이러스, 인간 면역결핍 바이러스(HIV), 폭스바이러스 및 백신 바이러스(VV), HCMV, 인플루엔자 A, 인유두종 바이러스(HPV), 성병 유두종, 바이러스성 사마귀, 예를 들면, 전염성 연속종, 백반증,

[0536] - 구진성 피부병, 예를 들면, 편평태선,

[0537] - 피부암, 예를 들면, 기저-세포 암종, 흑색종 또는 피부 T-세포 림프종,

[0538] - 국소적 양성 상피 종양, 예를 들면, 각질피부증, 상피 모반,

[0539] - 동창,

[0540] - 고혈압,

[0541] - 다낭성 난소 증후군(PCOS),

[0542] - 천식,

[0543] - 낭포성 섬유증,

[0544] - 골관절염,

[0545] - 전신성 홍반성 낭창(LE) 또는 염증성 류마티스 질환, 예를 들면, 류마티스 관절염,

[0546] - 혈관염,

[0547] - 소모성 (악액질),

[0548] - 통풍,

[0549] - 허혈/재관류 증후군,

[0550] - 급성 호흡곤란 증후군(ARDS),

[0551] - 바이러스성 질환 및 감염,

[0552] - 또한 해로운 약물 효과를 치료하기 위한 지방이영양증 및 지방이영양 상태,

[0553] - 근육병증 및 지방근병증(예: 카르니틴 팔미토일트랜스퍼라제 I 또는 II 결핍);

[0554] H. 근육 및 제지방(lean body)의 형성 또는 근육량 형성.

[0555] 1일 투여 가능한 화학식 I의 화합물의 용량 범위는 대개 환자 체중 1kg당 0.001 내지 10mg, 예를 들면, 0.01 내지 8mg이다. 각각의 용량 단위는 편의상 0.1 내지 1000mg, 예를 들면, 0.5 내지 500mg을 함유할 수 있다.

[0556] 실제 치료적 유효량 또는 치료적 용량은 물론, 환자의 연령 및 체중, 투여 경로 및 질환의 중증도와 같은 당해 분야의 숙련가에게 공지된 인자들에 좌우될 것이다. 임의의 경우, 환자의 독특한 상태를 기준으로 하여 치료적 유효량이 전달될 수 있도록 하는 용량 및 방식으로 상기 병용물이 투여될 것이다.

[0557] **약제학적 조성물**

[0558] 화학식 I의 화합물을 투여하기에 적합한 제제는 당해 분야의 통상의 숙련가에게 명확할 것이며, 예를 들면, 정제, 환제, 캡슐제, 좌제, 함당정제, 트로키제, 액제, 시럽제, 엘릭시르제, 사셰제(sachet), 주사제, 흡입제 및 산제 등을 포함한다. 약제학적 활성 화합물(들)의 함량은 유용하게 전체적으로 상기 조성물의 0.1 내지 90중량%, 예를 들면, 1 내지 70중량%의 범위이다.

[0559] 적합한 정제는, 예를 들면, 공지된 부형제, 예를 들면, 불활성 희석제, 담체, 붕해제, 보조제, 계면활성제, 결합제 및/또는 윤활제와 화학식 I에 따르는 하나 이상의 화합물을 혼합하여 수득할 수 있다. 정제는 또한 여러 층으로 이루어질 수 있다.

[0560] **병용 요법**

[0561] 본 발명의 화합물은 하나 이상, 바람직하게는 1개의 추가의 치료제와 추가로 혼합할 수 있다. 하나의 양태에 따르면, 추가의 치료제는 대사 질환 또는 상태와 관련된 질환 또는 상태, 예를 들면, 당뇨병, 비만, 당뇨 합병증, 고혈압, 과지질혈증의 치료에 유용한 치료제의 그룹으로부터 선택된다.

[0562] 따라서, 본 발명의 화합물은 항비만제(식욕 억제제 포함), 혈당을 저하시키는 제제, 항당뇨제, 이상지질혈증 치료용 제제(예: 지질 저하제), 항고혈압제, 항아테롬성 동맥경화제, 항염증성 활성 성분, 악성종양 치료용 제제, 항혈전제, 심부전 치료용 제제, 및 당뇨병에 의해 유발되거나 당뇨병과 관련된 합병증 치료용 제제로 이루어진 그룹으로부터 선택된 하나 이상의 추가의 치료제와 병용될 수 있다.

[0563] 적합한 항비만제는 11베타-하이드록시 스테로이드 데하이드로게나제-1(11베타-HSD 1형) 억제제, 스테아로일-CoA 데사투라제-1(SCD-1) 억제제, MCR-4 효능제, 콜레시스토키닌-A(CCK-A) 효능제, 모노아민 재흡수 억제제, 교감신경 흥분제, 베타3 아드레날린 효능제, 도파민 효능제, 멜라닌 세포-자극 호르몬 동족체, 5HT2c 효능제, 멜라닌 응집 호르몬 길항제, 렙틴(OB 단백질), 렙틴 동족체, 렙틴 효능제, 갈라닌 길항제, 리파제 억제제, 식욕감퇴제, 뉴로펩티드-Y 길항제(예: NPY Y5 길항제), PY_{3-36}(이의 동족체 포함), 티로미메틱 제제(thyromimetic agent), 데하이드로에피안드로스테론 또는 이의 동족체, 글루코코르티코이드 효능제 또는 길항제, 오렉신 길항제, 글루카곤-유사 펩티드-1 효능제, 섬모 향신경성 인자, 인간 아구티-관련 단백질(AGRP) 억제제, 그렐린 길항제, GOAT(그렐린 O-아실트렌스퍼라제) 억제제, 히스타민 3 길항제 또는 역 효능제, 뉴로메딘 U 효능제, MTP/ApoB 억제제(예: 장관-선택적 MTP 억제제), 오피오이드 길항제 및 오렉신 길항제 등을 포함한다.

[0564] 본 발명의 병용 측면에서 사용하기 위한 바람직한 항비만제는 장관-선택적 MTP 억제제 CCKa 효능제, 5HT2c 효능제, MCR4 효능제, 리파제 억제제, 아편양 제제 길항제, 올레오일-에스트론, 오비네피티드, 프라믈린티드(Symlin®), 테소펜신(NS2330), 렙틴, 리라글루티드, 브로모크립틴, 오를리스타트, 엑세나티드(Byetta®) 및 AOD-9604(CAS No. 221231-10-3)를 포함한다.

[0565] 적합한 항당뇨제는 나트륨-글루코즈 코-트랜스포터(SGLT) 억제제, 11베타-하이드록시 스테로이드 데하이드로게나제-1(11베타-HSD 1형) 억제제, 포스포디에스테라제(PDE) 10 억제제, 디아실글리세롤 아실트랜스퍼라제(DGAT) 1 또는 2 억제제, 설포닐우레아(예: 아세토헥사미드, 키오르프로파미드, 디아비네스, 글리벤클라미드, 글리피지드, 글리부리드, 글리메피리드, 글리클라지드, 글리펜티드, 글리퀴돈, 글리솔라미드, 톨라자미드 및 톨부타미드), 메글리티니드, 알파-아밀라제 억제제(예: 텐다미스타트, 트레스타틴 및 AL-3688), 알파-글루코사이드 하이드롤라제 억제제(예: 아카르보스), 알파-글리코시다제 억제제(예: 아디포신, 카미글리보스, 에미글리테이트, 미글리톨, 보글리보스, 프라디미신-Q 및 살보스타틴), PPAR 감마 효능제(예: 발라글리타존, 시글리타존, 다르글리타존, 엔글리타존, 이사글리타존, 피오글리타존, 로시글리타존 및 트로글리타존), PPAR 알파/감마 효능제(예: CLX-0940, GW-1536, GW-20 1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767 및 SB-

219994), 비구아니드(예: 메트포르민), GLP-1 유도체, 글루카곤-유사 펩티드 1(GLP-1) 효능제(예: Byetta™, 엑센딘-3 및 엑센딘-4), GLP-1 수용체 및 글루카곤 수용체 공-효능제, 글루카곤 수용체 길항제, GIP 수용체 길항제, 단백질 티로신 포스파타제-1 B(PTP-1 B) 억제제(예: 트로두스퀘민, 히르티오살 반응물), SIRT-1 활성화제(예: 레제르바트롤), 디펩티딜 펩티데아제 IV(DPP-IV) 억제제(예: 시타글립틴, 빌다글립틴, 알로글립틴, 리나글립틴 및 삭사글립틴), 인슐린 세크레타고구스, GPR 119 효능제, GPR40 효능제, TGR5 효능제, MNK2 억제제, GOAT(그렐린 O-아실트렌스퍼라제) 억제제, 지방산 산화 억제제, A2 길항제, c-jun 아미노-말단 키나제(JNK) 억제제, 인슐린, 인슐린 유도체, 속작용성 인슐린, 흡입용 인슐린, 경구용 인슐린, 인슐린 유사체, 글리코겐 포스포릴라제 억제제, VPAC2 수용체 효능제 및 글루코키나제 활성화제를 포함한다.

[0566] 바람직한 항당뇨제는 메트포르민, 글루카곤-유사 펩티드 1(GLP-1) 효능제(예: Byetta™), GLP-1 수용체 및 글루카곤 수용체 공-효능제, 나트륨-글루코즈 공-트랜스포터(SGLT) 억제제, 11베타-하이드록시 스테로이드 데하이드로게나제-1(11베타-HSD 1형) 억제제 및 DPP-IV 억제제(예: 시타글립틴, 빌다글립틴, 알로글립틴, 리나글립틴 및 삭사글립틴)이다.

[0567] 바람직하게는, 본 발명의 화합물, 및/또는 임의로 하나 이상의 추가의 치료제와 병용하여 본 발명의 화합물을 포함하는 약제학적 조성물은, 운동 및/또는 식이와 함께 투여된다.

[0568] 따라서, 또 다른 측면에서, 본 발명은, 효소(들) 아세틸-CoA 카복실라제, 특히 ACC2의 억제에 의해 영향을 받을 수 있거나 상기 억제에 의해 매개되는 질환 또는 상태, 특히 위에서 및 아래에서 기술되는 바와 같은 질환 또는 상태의 치료 및/또는 예방을 위한, 위에서 및 아래에서 기술된 하나 이상의 추가의 치료제와 병용하는 본 발명에 따르는 화합물의 용도에 관한 것이다.

[0569] 또 다른 측면에서, 본 발명은, 아세틸-CoA 카복실라제 효소(들)의 억제에 의해 매개되는 질환 또는 상태의 예방을 포함하는 치료를 필요로 하는 환자, 바람직하게는 인간에게 위에서 및 아래에서 기술된 치료적 유효량의 하나 이상의 추가의 치료제와 병용하여 치료적 유효량의 본 발명의 화합물을 투여하는 단계를 포함하는, 상기 환자에서 아세틸-CoA 카복실라제 효소(들)의 억제에 의해 매개되는 질환 또는 상태의 예방을 포함하는 치료 방법에 관한 것이다.

[0570] 추가의 치료제와 병용하여 본 발명에 따르는 화합물을 사용하는 것은 동시에 또는 시차를 두어 일어날 수 있다.

[0571] 본 발명에 따르는 화합물 및 하나 이상의 추가의 치료제는 둘 다, 하나의 제형 중에, 예를 들면, 정제 또는 캡슐제에 함께 존재할 수 있거나, 또는 2개의 동일하거나 상이한 제형 중에, 예를 들면, 소위 부품들의 키트(kit-of-parts)로서 별도로 존재할 수 있다.

[0572] 결과적으로, 또 다른 측면에서, 본 발명은, 임의로 하나 이상의 불활성 담체 및/또는 희석제와 함께, 본 발명에 따르는 화합물 및 위에서 및 아래에서 기술된 하나 이상의 추가의 치료제를 포함하는 약제학적 조성물에 관한 것이다.

[0573] 본 발명의 추가의 측면은, 진균 감염을 퇴치하고/하거나 방지하기 위한, 또는 다른 충해, 예를 들면, 작물에 유해한 잡초, 곤충 또는 진드기를 방제하기 위한 작물 보호제로서의 본 발명에 따르는 화합물 또는 이의 염의 용도를 포함한다. 본 발명의 또 다른 측면은, 식물 병원성 미생물, 예를 들면, 식물 병원성 진균을 방제 및/또는 예방하기 위한, 본 발명에 따르는 화합물 또는 이의 염의 용도에 관한 것이다. 따라서, 본 발명의 하나의 측면은, 살진균제, 살충제, 살비제 및/또는 제초제로서 사용하기 위한 화학식 I에 따르는 화합물 또는 이의 염이다. 본 발명의 또 다른 측면은, 하나 이상의 적합한 담체와 함께 본 발명의 화합물을 포함하는 농업용 조성물에 관한 것이다. 본 발명의 또 다른 측면은, 하나 이상의 적합한 담체와 함께 적어도 하나의 추가의 살진균제 및/또는 조직적으로 획득한 저항성 유도체와 병용되는 본 발명의 화합물을 포함하는 농업용 조성물에 관한 것이다.

[0574] **실시예**

[0575] 이어지는 실시예는 본 발명을 한정시키지 않고 설명하고자 하는 것이다. 용어 "주위 온도" 및 "실온"은 상호교환적으로 사용되며 약 20℃의 온도이다.

[0576] 서문:

[0577] 대체로, 상기 제조된 화합물들에 대해 1H-NMR 및/또는 질량 스펙트럼이 수득되었다. R_f 값은 Merck 실리카 겔 60 F_{254} 플레이트 및 254nm의 UV 광을 사용하여 측정한다.

[0578] **실험 부분**

[0579] 다음의 약어들이 위에서 및 아래에서 사용된다:

ACN	아세토니트릴
aq.	수성
BINAP	2,2′-비스(디페닐포스피노)-1,1′-비나프탈렌
Boc	*3 급*-부톡시카보닐
CDI	1,1'-카보닐디이미다졸
CDT	1,1'-카보닐디트리아졸
CyH	사이클로헥산
DCM	디클로로메탄
DIPEA	*N,N*-디이소프로필에틸아민
DMA	*N,N*-디메틸아세트아미드
DMF	*N,N*-디메틸포름아미드
dppf	1,1'- 비스(디페닐포스피노)페로센
EI-MS	전자유도 질량 분석법
ESI	전자분무 이온화
EtOAc	에틸 아세테이트
FA	포름산
HATU	2-(7-아자-1H-벤조트리아졸-1-일)-1,1,3,3-테트라메틸우로늄 헥사플루오로포스페이트
HCl	염산
HPLC	고성능 액체 크로마토그래피
KOH	수산화칼륨
mCPBA	메타-클로로퍼옥소벤조산
MeOH	메탄올
MS	질량 스펙트럼
NaOH	소다액
n.d.	측정되지 않음
NMP	*N*-메틸-2-피롤리돈
PE	석유 에테르

[0580]

R_f	보유 인자
R_t	보유 시간
rt	실온 (약 20°C)
sat.	포화
TBME	*3 급 부틸메틸 에테르*
TBTU	2-(1H-벤조트리아졸-1-일)-1,1,3,3-테트라메틸우로늄 테트라플루오로보레이트
TEA	트리에틸아민
TFA	트리플루오로아세트산
THF	테트라하이드로푸란
TLC	박층 크로마토그래피
X-Phos	2-디사이클로헥실포스피노 2′,4′,6′-트리이소프로필페닐

[0581]

[0582] **분석 방법**

[0583] HPLC

[0584] **방법 A**

[0585]

시간 (분)	물 (용적%) (0.2% NH_4OH 포함)	메탄올 (용적%) (3% 물 포함)
0.0	95	5
0.2	95	5
2.2	5	95
2.3	5	95
2.4	0	100
2.6	0	100

[0586] 분석 칼럼: XBridge C18 (Waters) 2.5㎛; 3.0×30mm; 칼럼 온도: 40℃; 유동: 1.3mL/min.

[0587] **방법 B**

[0588]

시간(분)	물 (용적%) (0.1% TFA 포함)	메탄올 (용적%)
0.0	80	20
1.7	0	100
2.5	0	100
2.6	80	20

[0589] 분석 칼럼: Sunfire C18 (Waters) 3.5㎛; 4.6×50mm; 칼럼 온도: 60℃; 유동: 2mL/min; 검출 210 내지 500nm.

[0590] **방법 C**

[0591]

시간(분)	물 (용적%) (0.1% FA 포함)	아세토니트릴 (용적%) (0.1% FA 포함)
0.0	95	5
0.1	95	5
3.1	2	98
4.5	2	98
5.0	95	5

[0592] 분석 칼럼: X-terra MS C18 (Waters) 2.5㎛; 4.6×30mm; 칼럼 온도: 실온; 유동: 1.0mL/min; 검출 210 내지 420nm.

[0593] **방법 D**

[0594]

시간(분)	물 (용적%) (0.2% FA 포함)	메탄올 (용적%) (3% 물 포함)
0.0	95	5
0.2	95	5
2.2	5	95
2.3	5	95
2.4	0	100
2.6	0	100

[0595] 분석 칼럼: Zorbax StableBond C18 (Agilent) 1.8㎛; 3.0×30mm; 칼럼 온도: 40℃; 유동: 1.3mL/min;

[0596] **방법 E**

시간(분)	물 (용적%) (0.1% TFA 포함)	ACN (용적%) (0.08% TFA 포함)
0.0	95	5
2.0	0	100
2.5	0	100
2.6	95	5

[0597]

[0598] 분석 칼럼: Sunfire C18 (Waters) 3.5㎛; 4.6×50mm; 칼럼 온도: 60℃; 유동: 1.5mL/min; 검출 210 내지 500nm.

[0599] **방법 F**

시간(분)	물 (용적%) (0.2% NH_4OH 포함)	메탄올 (용적%) (3% 물 포함)
0.0	95	5
0.2	95	5
2.2	5	95
2.3	5	95
2.4	0	100
2.6	0	100

[0600]

[0601] 분석 칼럼: XBridge C18 (Waters) 2.5㎛; 3.0×30mm; 칼럼 온도: 60℃; 유동: 1.3mL/min;

[0602] **방법 G**

분석 칼럼:			XBridge C18, 3 x 30 mm, 2.5 µm (Waters)	
시간(분)	용적% [H_2O,0.2%NH_4OH]	용적% [메탄올]	유동[mL/min]	온도 [°C]
0.0	95	5	2.2	60
0.05	95	5	2.2	60
1.40	0	100	2.2	60
1.80	0	100	2.2	60

[0603]

[0604] **방법 H**

분석 칼럼:			XBridge C18, 3 x 30 mm, 2.5 µm (Waters)	
시간(분)	용적% [H_2O,0.2%TFA]	용적% [메탄올]	유동 [mL/min]	온도 [°C]
0.0	95	5	2.2	60
0.05	95	5	2.2	60
1.40	0	100	2.2	60
1.80	0	100	2.2	60

[0605]

[0606] **방법 I**

시간(분)	물 (용적%) (0.1% TFA 포함)	ACN (용적%) (0.1% TFA 포함)
0.0	95	5
2.0	0	100
2.49	0	100
2.50	95	5

[0607]

[0608] 분석 칼럼: Sunfire C18 (Waters) 3.5㎛; 4.6×50mm; 칼럼 온도: 40℃; 유동: 1.5mL/min.

[0609] **방법 J**

시간(분)	물 (용적%) (0.01M NH_4Oac 포함)	ACN (용적%)
0.0	50	50
6	10	90
15	10	90
15.1	40	60

[0610]

[0611] 분석 칼럼: Eclipse-XDB-C18 (Agilent) 5.0㎛; 4.6×150mm; 칼럼 온도: 실온; 유동: 1.0mL/min.

[0612] **방법 K**

시간(분)	물 (용적%) (0.01 M NH_4Oac 포함)	ACN (용적%)
0.0	70	30
8	10	90
15	10	90
15.1	70	30

[0613]

[0614] 분석 칼럼: XBridge C18 (Waters) 5.0㎛; 4.6×150mm; 칼럼 온도: 실온; 유동: 1.0mL/min;

[0615] **방법 L**

분석 칼럼:	XBridge C18, 3 x 30 mm, 2.5 µm (Waters)			
시간(분)	용적% [H_2O,0.1%NH_4OH]	용적%[메탄올]	유동 [mL/min]	온도 [°C]
0.0	95	5	2.2	60
0.30	95	5	2.2	60
1.50	0	100	2.2	60
1.55	0	100	2.9	60
1.70	0	100	2.9	60

[0616]

[0617] **방법 M**

분석 칼럼:	Sunfire C18, 3 x 30 mm, 2.5 µm (Waters)			
시간(분)	용적% [H_2O,0.1%TFA]	용적% [메탄올]	유동 [mL/min]	온도 [°C]
0.0	95	5	2.2	60
0.30	95	5	2.2	60
1.50	0	100	2.2	60
1.55	0	100	2.9	60
1.65	0	100	2.9	60

[0618]

[0619] **방법 N**

분석 칼럼:	Sunfire C18, 4,6 x 30 mm, 3.5 µm (Waters)			
시간(분)	용적% [H_2O,0.1%TFA]	메탄올 (용적%),0.1%TFA]	유동 [mL/min]	온도 [°C]
0.0	95	5	4	60
0.15	95	5	4	60
1.7	0	100	4	60
2.25	0	100	4	60

[0620]

[0621] **방법 O**

분석 칼럼:		XBridge C18, 4,6 x 30 mm, 3.5 μm (Waters)		
시간(분)	용적% [H_2O,0.1%TFA]	용적% [메탄올,0.1%TFA]	유동 [mL/min]	온도 [°C]
0.0	95	5	4	60
0.15	95	5	4	60
1.7	0	100	4	60
2.25	0	100	4	60

[0622]

[0623] **방법 P**

분석 칼럼:		Sunfire C18_4.6x50mm, 3.5μm (Waters)		
시간(분)	용적% [H_2O,0.1%TFA]	용적% [메탄올]	유동 [mL/min]	온도 [°C]
0.0	80.0	20.0	2.0	60
1.7	0.0	100.0	2.0	60
2.5	0.0	100.0	2.0	60
2.6	80.0	20.0	2.0	60

[0624]

[0625] **방법 Q**

분석 칼럼:		StableBond C18_3.0x30mm, 1.8μm (Agilent)		
시간(분)	용적% [H_2O,0.1%HCOOH]	용적% [아세토니트릴, 0.1% HCOOH]	유동 [mL/min]	온도 [°C]
0.0	95.0	5.0	1.6	-1.0
0.1	95.0	5.0	1.6	-1.0
1.75	5.0	95.0	1.6	-1.0
1.9	5.0	95.0	1.6	-1.0
1.95	95.0	5.0	1.6	-1.0
2.0	95.0	0.0	1.6	-1.0

[0626]

[0627] **방법 R**

분석 칼럼:		XBridge C18_4.6x50mm, 3.5μm (Waters)		
시간(분)	용적% [H_2O, 0.032% NH_4OH]	용적% [메탄올]	유동 [mL/min]	온도 [°C]
0.0	95.0	5.0	1.5	40
2.0	0.0	100.0	1.5	40

[0628]

[0629] **방법 S**

분석 칼럼:		XBridge C18_4.6x50mm, 3.5μm (Waters)		
시간(분)	용적% [H_2O, 0.1% NH_4OH]	용적% [메탄올]	유동 [mL/min]	온도 [°C]
0.0	95.0	5.0	1.5	40
2.0	0.0	100.0	1.5	40

[0630]

[0631] **방법 T**

분석 칼럼:		Sunfire C18_4.6x30mm, 2.5μm (Waters)		
시간(분)	용적% [H_2O, 0.1% TFA]	용적% [메탄올]	유동 [mL/min]	온도 [°C]
0.0	95.0	5.0	4	60
0.05	95.0	5.0	3	60
2.05	0	100	3	60
2.10	0	100	4.5	60
2.40	0	100	4.5	60

[0632]

[0633] **방법 U**

분석 칼럼:		Sunfire C18_4.6x30mm, 2.5μm (Waters)		
시간(분)	용적% [H_2O, 0.1% TFA]	용적% [메탄올, 0.1% TFA]	유동[mL/min]	온도 [°C]
0.0	95.0	5.0	4.0	60
0.05	95.0	5.0	3.0	60
2.05	0.0	100.0	3.0	60
2.1	0.0	100.0	4.0	60
2.35	0.0	100.0	4.0	60

[0634]

[0635] **방법 V**

분석 칼럼:		Ascentis Express C18_2.1x50mm, 2.7μm (Supelco)		
시간(분)	용적% [H_2O, 0.1% TFA]	용적% [아세토니트릴, 0.08% TFA]	유동[mL/min]	온도 [°C]
0.0	95.0	5.0	1.5	60.0
0.7	1.0	99.0	1.5	60.0
0.8	1.0	99.0	1.5	60.0
0.81	95.0	5.0	1.5	60.0

[0636]

[0637] **방법 W**

분석 칼럼:		XBridge C18_4.6x50mm, 3.5μm (Waters)		
시간(분)	용적% [H_2O, 0.1% NH_4OH]	용적% [메탄올]	유동[mL/min]	온도[°C]
0.0	80.0	20.0	2.0	60
1.7	0.0	100.0	2.0	60
2.5	0.0	100.0	2.0	60
2.6	80.0	20.0	2.0	60

[0638]

[0639] **방법 X**

분석 칼럼:		XBridge C18_4.6x50mm, 3.5μm (Waters)		
시간(분)	용적% [H_2O, 0.1% NH_4OH]	용적% [메탄올]	유동 [mL/min]	온도 [°C]
0.0	80.0	20.0	2.0	60
1.7	0.0	100.0	2.0	60
2.5	0.0	100.0	2.0	60

[0640]

[0641] **방법 Y**

분석 칼럼:		XBridge C18_2.1x50mm, 1.7μm (Waters)	
시간(분)	용적% [H_2O, 0.1% NH_4OH]	유동 [mL/min]	온도 [°C]
0.0	95.0	1.5	60
0.7	0.0	1.5	60
0.8	0.0	1.5	60
0.81	95.0	1.5	60
1.9	95.0	0.2	60
2.0	0.0	0.2	60
3.0	0.0	0.2	60

[0642]

[0643] **방법 Z**

[0644]

분석 칼럼:		Sunfire C18_4.6x50mm, 3.5μm (Waters)		
시간(분)	용적% [H_2O, 0.1% TFA]	용적% [메탄올]	유동 [mL/min]	온도 [°C]
0.0	95.0	5.0	1.5	40
1.3	0.0	100.0	1.5	40
2.5	0.0	100.0	1.5	40
2.6	95.0	5.0	1.5	40

[0645] **방법 AA**

[0646]

분석 칼럼:		XBridge C18, 4,6 x 30 mm, 3.5 μm (Waters)		
시간(분)	용적% [H_2O,0.1%NH_4OH]	용적% [ACN]	유동 [mL/min]	온도 [°C]
0.0	95	5	4	60
0.15	95	5	4	60
1.7	0	100	4	60
2.1	0	100	4	60

[0647] **방법 AB**

[0648]

분석 칼럼:		Sunfire C18, 3x30mm, 2.5μm (Waters)		
시간(분)	용적% [H_2O, 0.1% TFA]	용적% [메탄올]	유동 [mL/min]	온도 [°C]
0.0	95	5	1.8	60
0.05	95	5	1.8	60
2.05	0	100	1.8	60
2.1	0	100	2.5	60
2.35	0	100	2.5	60

[0649] **방법 AC**

[0650]

분석 칼럼:		Viridis Ethylpyridin 5μm 3x100mm		
Rate	용적% [CO_2]	용적%[메탄올]	유동 [mL/min]	온도[°C]
0	95	5	4	40
14	65	35	4	40
99	95	5	4	40

[0651] **방법 AD**

[0652]

분석 칼럼:		Sunfire C18, 3 x 30 mm, 2.5 μm		
시간(분)	용적% [H_2O,0.2%TFA]	용적%[메탄올]	유동[mL/min]	온도 [°C]
0.0	95	5	2.2	60
0.05	95	5	2.2	60
1.40	0	100	2.2	60
1.80	0	100	2.2	60

[0653] **방법 AE**

[0654]

시간(분)	물 (용적%) (0.1% FA 포함)	메탄올 (용적%) (3%물 포함)
0.0	95	5
0.2	95	5
2.2	5	95
2.3	5	95
2.4	0	100
2.6	0	100

[0655] 분석 칼럼: XBridge C18 (Waters) 2.5㎛; 3.0×30mm; 칼럼 온도: 40℃; 유동: 1.3mL/min;

[0656] **방법 AF**

[0657]

시간(분)	물 (용적%) (0.05% TFA 포함)	ACN (용적%)
0.0	40	60
6	10	90
15	10	90
15.1	40	60

[0658] 분석 칼럼: XBridge C18 (Waters) 3.5㎛; 4.6×50mm; 칼럼 온도: 실온;

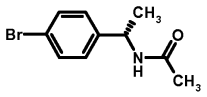
[0659] **출발 화합물의 제조**

[0660] **실시예 I**

[0661] 실시예 I.1

[0662] (S)-N-[1-(4-브로모-페닐)-에틸]-아세트아미드

[0663]



[0664] 반응 온도를 30℃ 미만으로 유지하면서, 아세트산 무수물 23.6mL(250mmol)를, 디클로로메탄 200mL 중의 (S)-1-(4-브로모페닐)-에틸아민 50.0g(250mmol)에 첨가한다. 실온에서 12시간 동안 계속 교반한다. 그 시간 후, 포화 $NaHCO_3$-용액을 첨가한다. 유기 층을 분리하고, 물로 세척하고, 황산마그네슘으로 건조시키고 용매는 증발에 의해 제거한다.

[0665] $C_{10}H_{12}BrNO$ (M = 242.1g/mol), ESI-MS: 240/242 $[M+H]^+$

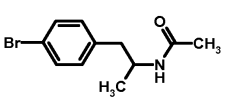
[0666] R_t (HPLC): 1.03분 (방법 L)

[0667] 하기 화합물은 실시예 I.1과 유사하게 제조한다:

[0668] 실시예 I.2

[0669] N-[2-(4-브로모-페닐)-1-메틸-에틸]-아세트아미드

[0670]



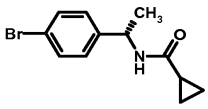
[0671] 반응물: 2-(4-브로모-페닐)-1-메틸-에틸아민(J. Org. Chem. 1985, 50, 133).

[0672] $C_{11}H_{14}BrNO$ (M = 256.1g/mol), ESI-MS: 256 $[M+H]^+$

[0673] R_t (HPLC): 2.60분 (방법 C)

[0674] 실시예 I.3

[0675] (S)-사이클로프로판카복실산 [1-(4-브로모-페닐)-에틸]-아미드

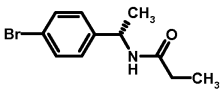
[0676] 

[0677] $C_{12}H_{14}BrNO$ (M = 268.2g/mol), ESI-MS: 268 $[M+H]^+$

[0678] R_t (HPLC): 2.76분 (방법 C)

[0679] 실시예 I.4

[0680] (S)-N-[1-(4-브로모-페닐)-에틸]-프로피온아미드

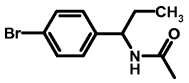
[0681] 

[0682] $C_{11}H_{14}BrNO$ (M = 256.1g/mol), EI-MS: 256 $[M+H]^+$

[0683] R_t (HPLC): 1.05분 (방법 G)

[0684] 실시예 I.5

[0685] N-[1-(4-브로모-페닐)-프로필]-아세트아미드

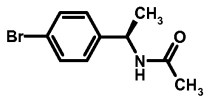
[0686] 

[0687] $C_{11}H_{14}BrNO$ (M = 256.1g/mol), ESI-MS: 256 $[M+H]^+$

[0688] R_t (HPLC): 1.08분 (방법 G)

[0689] 실시예 I.6

[0690] (R)-N-[1-(4-브로모-페닐)-에틸]-아세트아미드

[0691] 

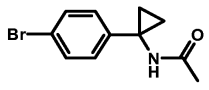
[0692] 반응물: (R)-1-(4-브로모페닐)-에틸아민

[0693] $C_{10}H_{12}BrNO$ (M = 242.1g/mol), ESI-MS: 242 $[M+H]^+$

[0694] R_t (HPLC): 1.63분 (방법 A)

[0695] 실시예 I.7

[0696] N-[1-(4-브로모-페닐)-사이클로프로필]-아세트아미드

[0697] 

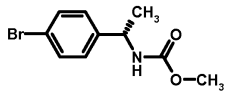
[0698] $C_{11}H_{12}BrNO$ (M = 254.1g/mol), ESI-MS: 255 $[M+H]^+$

[0699] R_t (HPLC): 1.58분 (방법 A)

[0700] **실시예 II**

[0701] 실시예 II.1

[0702] (S)-[1-(4-브로모-페닐)-에틸]-카밤산 메틸 에스테르

[0703] 

[0704] CDT 17.2g(105mmol)을 0℃에서 디클로로메탄 300mL 중의 (S)-1-(4-브로모페닐)-에틸아민 20.0g(100mmol) 및 TEA 17.6mL(125mmol)의 혼합물에 첨가한다. 5℃에서 15분 동안 계속 교반한다. 그 시간 후, 용매를 진공하에 제거하고, 메탄올 50mL에 용해시킨다. 메탄올(30%) 중의 나트륨 메톡사이드 33.4mL(180mmol)를 첨가하고, 실온에서 48시간 동안 계속 교반한다. 그 시간 후, 용매를 진공하에 제거하고, 잔사를 에틸 아세테이트에 용해시킨 다음, 포화 $KHSO_4$-용액으로 2회 세척하고 물로 세척한다. 유기 층을 황산마그네슘으로 건조시키고 용매는 증발에 의해 제거한다.

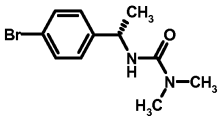
[0705] $C_{10}H_{12}BrNO_2$ (M = 258.1g/mol), ESI-MS: 258 $[M+H]^+$

[0706] R_t (HPLC): 2.60분 (방법 A)

[0707] 하기 화합물은 실시예 II.1과 유사하게 제조한다:

[0708] 실시예 II.2

[0709] (S)-3-[1-(4-브로모-페닐)-에틸]-1,1-디메틸-우레아

[0710] 

[0711] 반응물: 디메틸아민

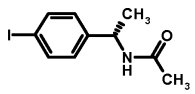
[0712] $C_{11}H_{15}BrN_2O$ (M = 271.2g/mol), ESI-MS: 271 $[M+H]^+$

[0713] R_t (HPLC): 1.68분 (방법 A)

[0714] **실시예 III**

[0715] 실시예 III.1

[0716] (S)-N-[1-(4-요오도-페닐)-에틸]-아세트아미드

[0717] 

[0718] 요오드화구리(I) 9.01g(47.3mmol)을 1.3L 1,4-디옥산 중의 (S)-N-[1-(4-브로모-페닐)-에틸]-아세트아미드(I.1) 114.6g(473.3mmol), 요오드화나트륨 283.8g(1.893mmol) 및 N,N'-디메틸에틸렌디아민 10.43g(118.3mmol)의 혼합물에 첨가한다. 상기 혼합물을 120℃에서 60시간 동안 교반한다. 그 시간 후, 용매를 증발시키고 잔사는 2L 디클로로메탄에 현탁시켜, 얼음(1kg), 암모니아(1L) 및 물(2L)의 혼합물에 붓는다. 유기 층을 분리하고, 수성층은 디클로로메탄으로 2회 세척하며, 합한 유기 층은 물로 2회 세척하고, 황산나트륨으로 건조시킨다. 용매는 증발시키고, 잔사는 디에틸 에테르로 세척한다.

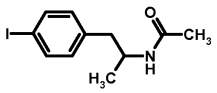
[0719] $C_{10}H_{12}INO$ (M = 289.1g/mol), ESI-MS: 290 $[M+H]^+$

[0720] R_t (TLC): 0.57 (실리카 겔, 디클로로메탄:메탄올 9:1)

[0721] 하기 화합물은 실시예 III.1과 유사하게 제조한다:

[0722] 실시예 III.2

[0723] N-[2-(4-요오도-페닐)-1-메틸-에틸]-아세트아미드

[0724] 

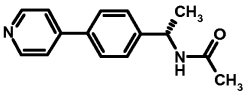
[0725] $C_{11}H_{14}INO$ (M = 303.1g/mol), ESI-MS: 304 $[M+H]^+$

[0726] R_t (HPLC): 2.85분 (방법 C)

[0727] **실시예 IV**

[0728] 실시예 IV.1

[0729] (S)-N-[1-(4-피리딘-4-일-페닐)-에틸]-아세트아미드

[0730] 

[0731] 불활성 기체 대기하에, $PdCl_2(dppf)xCH_2Cl_2$ 181mg(0.248mmol)을 1,4-디옥산 300mL 및 메탄올 100mL 중의 (S)-N-[1-(4-브로모-페닐)-에틸]-아세트아미드(I.1) 30.0g(124mmol), 2N 탄산나트륨 용액 139mL(279mmol) 및 피리딘-4-보론산 16.8g(136mmol)의 혼합물에 첨가한다. 상기 혼합물을 환류하에 5일 동안 교반한다. 그 시간 후, 잔사를 물(3L)에 붓고, 디클로로메탄으로 3회 추출한다. 합한 유기 층은 물로 세척하고, 황산마그네슘으로 건조시킨다. 용매는 증발시키고, 잔사는 아세톤 및 3급-부틸 메틸 에테르로 연마한다.

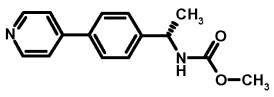
[0732] $C_{15}H_{16}N_2O$ (M = 240.3g/mol), ESI-MS: 241 $[M+H]^+$

[0733] R_t (HPLC): 1.44분 (방법 A)

[0734] 하기 화합물은 실시예 IV.1과 유사하게 제조한다:

[0735] 실시예 IV.2

[0736] (S)-[1-(4-피리딘-4-일-페닐)-에틸]-카밤산 메틸 에스테르

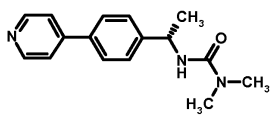
[0737] 

[0738] $C_{15}H_{16}N_2O_2$ (M = 256.3g/mol), ESI-MS: 257 $[M+H]^+$

[0739] R_t (HPLC): 1.60분 (방법 A)

[0740] 실시예 IV.3

[0741] (S)-1,1-디메틸-3-[1-(4-피리딘-4-일-페닐)-에틸]-우레아

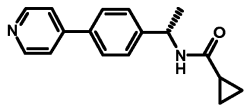
[0742] 

[0743] $C_{16}H_{19}N_3O$ (M = 269.3g/mol), ESI-MS: 270 $[M+H]^+$

[0744] R_t (HPLC): 1.49분 (방법 A)

[0745] 실시예 IV.4

[0746] (S)-사이클로프로판카복실산[1-(4-피리딘-4-일-페닐)-에틸]-아미드

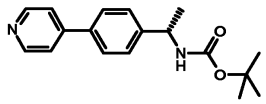
[0747] 

[0748] $C_{17}H_{18}N_2O$ (M = 266.3g/mol), ESI-MS: 267 $[M+H]^+$

[0749] R_t (HPLC): 1.56분 (방법 A)

[0750] 실시예 IV.5

[0751] (S)-[1-(4-피리딘-4-일-페닐)-에틸]-카밤산 3급-부틸 에스테르

[0752] 

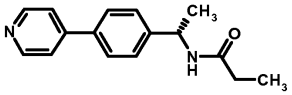
[0753] 반응물: (S)-[1-(4-브로모-페닐)-에틸]-카밤산 3급-부틸 에스테르

[0754] $C_{18}H_{22}N_2O_2$ (M = 298.4g/mol), ESI-MS: 299 $[M+H]^+$

[0755] R_t (HPLC): 1.92분 (방법 A)

[0756] 실시예 IV.6

[0757] (S)-N-[1-4-피리딘-4-일-페닐)-에틸]-프로피온아미드

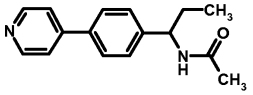
[0758] 

[0759] $C_{16}H_{18}N_2O$ (M = 254.3g/mol), ESI-MS: 255 $[M+H]^+$

[0760] R_t (HPLC): 0.94분 (방법 G)

[0761] 실시예 IV.7

[0762] N-[1-(4-피리딘-4-일-페닐)-프로필]-아세트아미드

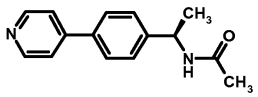
[0763] 

[0764] $C_{16}H_{18}N_2O$ (M = 254.3g/mol), ESI-MS: 255 $[M+H]^+$

[0765] R_t (HPLC): 0.84분 (방법 G)

[0766] 실시예 IV.9

[0767] (R)-N-[1-(4-피리딘-4-일-페닐)-에틸]-아세트아미드



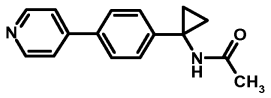
[0768]

[0769] $C_{15}H_{16}N_2O$ (M = 240.3g/mol), ESI-MS: 241 $[M+H]^+$

[0770] R_t (HPLC): 1.40분 (방법 A)

[0771] 실시예 IV.10

[0772] N-[1-(4-피리딘-4-일-페닐)-사이클로프로필]-아세트아미드



[0773]

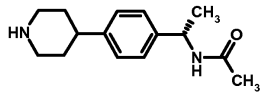
[0774] $C_{16}H_{16}N_2O$ (M = 252.3g/mol), ESI-MS: 253 $[M+H]^+$

[0775] R_t (HPLC): 1.41분 (방법 A)

[0776] **실시예 V**

[0777] 실시예 V.1

[0778] (S)-N-[1-(피페리딘-4-일-페닐)-에틸]-아세트아미드



[0779]

[0780] 1N HCl 195mL를 에탄올 500mL 중의 (S)-N-[1-(4-피리딘-4-일-페닐)-에틸]-아세트아미드(IV.1) 21.9g(91.1mmol)에 첨가한다. 상기 혼합물은 산화백금(IV) 2.00g을 사용하여 실온에서 6.5시간 동안 수소화시킨다(3bar). 그 시간 후, 촉매를 여과하고, 용매를 증발시킨다. 잔사를 물에 용해시키고, 1N NaOH로 중화시킨 다음, 에틸 아세테이트/메탄올로 추출한다. 유기 층을 황산마그네슘으로 건조시키고, 용매는 증발시킨다. 수성 층을 염화나트륨으로 포화시키고, THF로 추출한다. 유기 층을 포화 NaCl-용액으로 세척하고, 용매는 증발시킨다. 합한 잔사는 칼럼 크로마토그래피(실리카 겔; 용출제 A: THF, 용출제 B: THF/메탄올/암모니아 2:1:0.1)로 정제하여 목적 생성물을 수득한다.

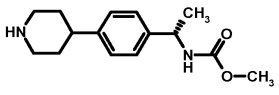
[0781] $C_{15}H_{22}N_2O$ (M = 246.3g/mol), ESI-MS: 247 $[M+H]^+$

[0782] R_t (HPLC): 1.42분 (방법 A)

[0783] 하기 화합물들은 실시예 V.1과 유사하게 제조한다:

[0784] 실시예 V.2

[0785] (S)-[1-(4-피페리딘-4-일-페닐)-에틸]-카밤산 메틸 에스테르



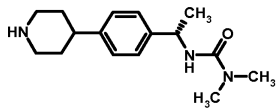
[0786]

[0787] $C_{15}H_{22}N_2O_2$ (M = 262.3g/mol), ESI-MS: 263 $[M+H]^+$

[0788] R_t (HPLC): 1.60분 (방법 A)

[0789] 실시예 V.3

[0790] (S)-1,1-디메틸-3-[1-(4-피페리딘-4-일-페닐)-에틸]-우레아



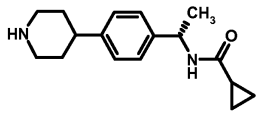
[0791]

[0792] $C_{16}H_{25}N_3O$ (M = 275.4g/mol), ESI-MS: 276 $[M+H]^+$

[0793] R_t (HPLC): 1.48분 (방법 A)

[0794] 실시예 V.4

[0795] (S)-사이클로프로판카복실산[1-(4-피페리딘-4-일-페닐)-에틸]-아미드



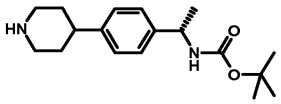
[0796]

[0797] $C_{17}H_{24}N_2O$ (M = 272.4g/mol), ESI-MS: 273 $[M+H]^+$

[0798] R_t (HPLC): 1.12분 (방법 A)

[0799] 실시예 V.5

[0800] (S)-[1-(4-피페리딘-4-일-페닐)-에틸]-카밤산 3급-부틸 에스테르



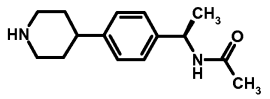
[0801]

[0802] $C_{18}H_{28}N_2O_2$ (M = 304.4g/mol), ESI-MS: 305 $[M+H]^+$

[0803] R_t (HPLC): 1.12분 (방법 A)

[0804] 실시예 V.6

[0805] (R)-N-[1-(피페리딘-4-일-페닐)-에틸]-아세트아미드



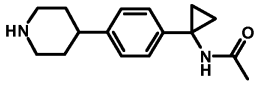
[0806]

[0807] $C_{15}H_{22}N_2O$ (M = 246.3g/mol), ESI-MS: 247 $[M+H]^+$

[0808] R_t (HPLC): 1.10분 (방법 A)

[0809] 실시예 V.7

[0810] N-(1-(4-(피페리딘-4-일)페닐)사이클로프로필)아세트아미드



[0811]

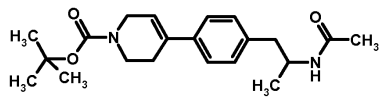
[0812] $C_{16}H_{22}N_2O$ (M = 258.4g/mol), ESI-MS: 259 $[M+H]^+$

[0813] R_t (HPLC): 1.40분 (방법 A)

[0814] **실시예 VI**

[0815] 실시예 VI.1

[0816] 4-[4-(2-아세틸아미노-프로필)-페닐]-3,6-디하이드로-2H-피리딘-1-카복실산 3급-부틸 에스테르

[0817] 

[0818] 불활성 기체 대기하에, N-[2-(4-요오도-페닐)-1-메틸-에틸]-아세트아미드(III.2) 303mg(1.00mmol)을 DMF 5mL 중의 4-(4,4,5,5-테트라메틸-[1,3,2]디옥사보롤란-2-일)-3,6-디하이드로-2H-피리딘-1-카복실산 3급-부틸 에스테르 309mg(1.00mmol), $PdCl_2(dppf)xCH_2Cl_2$ 49mg(0.060mmol) 및 K_2CO_3 415mg(3.00mmol)의 혼합물에 첨가한다. 상기 혼합물을 실온에서 48시간 동안 교반한다. 그 시간 후, 용매를 증발시키고 잔사는 에틸 아세테이트에 용해시켜, 물로 세척한다. 황산나트륨으로 건조시킨 후, 용매는 진공하에 제거하고 잔사는 칼럼 크로마토그래피(실리카 겔; 에틸 아세테이트)로 정제하여 목적 생성물을 수득한다.

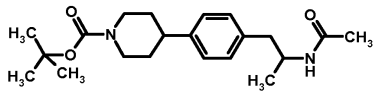
[0819] $C_{21}H_{30}N_2O_3$ (M = 358.5g/mol), ESI-MS: 376 $[M+H]^+$

[0820] R_t (TLC): 0.20 (실리카 겔, DCM/에틸 아세테이트 1:1)

[0821] **실시예 VII**

[0822] 실시예 VII.1

[0823] 4-[4-(2-아세틸아미노-프로필)-페닐]-피페리딘-1-카복실산 3급-부틸 에스테르

[0824] 

[0825] 메탄올 100mL 중의 4-[4-(2-아세틸아미노-프로필)-페닐]-3,6-디하이드로-2H-피리딘-1-카복실산 3급-부틸 에스테르(VI.1) 2.20g(6.14mmol)을 목탄상 팔라듐(10%) 250mg을 사용하여 실온에서 7.0시간 동안 수소화시킨다(50psi). 그 시간 후, 촉매를 여과하고, 용매는 증발시켜 목적 생성물을 수득한다.

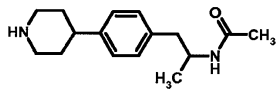
[0826] $C_{21}H_{32}N_2O_3$ (M = 360.5g/mol), ESI-MS: 361 $[M+H]^+$

[0827] R_t (TLC): 0.40 (실리카 겔, DCM/메탄올 9:1)

[0828] **실시예 VIII**

[0829] 실시예 VIII.1

[0830] N-[1-메틸-2-(4-피페리딘-4-일-페닐)-에틸]-아세트아미드

[0831] 

[0832] 디클로로메탄 50mL 중의 4-[4-(2-아세틸아미노-프로필)-페닐]-피페리딘-1-카복실산 3급-부틸 에스테르(VII.1) 2.10g(5.83mmol)에 트리플루오로아세트산 4.4mL(58.3mmol)를 첨가한다. 상기 혼합물을 실온에서 3시간 동안 교반시킨다. 그 시간 후, 용매를 증발시키고 잔사는 에틸 아세테이트에 용해시켜, 포화 $NaHCO_3$-용액으로 세척한다. 황산나트륨으로 건조시킨 후, 용매를 진공하에 제거하고 잔사는 디에틸 에테르로부터 재결정화한다.

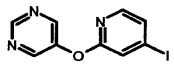
[0833] $C_{16}H_{24}N_2O$ (M = 260.4g/mol), ESI-MS: 261 $[M+H]^+$

[0834] R_t (TLC): 0.20 (실리카 겔, DCM/메탄올/NH_4OH 5:1:0.02)

[0835] **실시예 IX**

[0836] 실시예 IX.1

[0837] 5-(4-요오도-피리딘-2-일옥시)-피리미딘

[0838] 

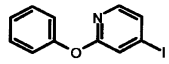
[0839] DMF 200mL 중의 피리미딘-5-올(J. Chem. Soc. 1956, 2033) 259mg(26.9mmol)에 수소화나트륨(광유 중의 60% 분산액) 108mg(26.9mmol)을 첨가한다. 상기 혼합물을 실온에서 20분 동안 교반한다. 그 시간 후, 2-플루오로-4-요오도피리딘 500mg(22.4mmol)을 첨가하고, 상기 혼합물을 80℃에서 12시간 동안 교반한다. 이어서, 상기 혼합물을 물에 붓고, 에틸 아세테이트로 3회 추출한다. 합한 유기 층을 염수로 세척한다. 황산나트륨으로 건조시킨 후, 용매를 진공하에 제거하고 잔사는 칼럼 크로마토그래피(실리카 겔; 헵탄/에틸 아세테이트, 구배 0 내지 60%)로 정제하여 목적 생성물을 수득한다.

[0840] $C_9H_6IN_3O$ (M = 299.1g/mol), ESI-MS: 300 $[M+H]^+$

[0841] 하기 화합물들은 실시예 IX.1과 유사하게 제조한다:

[0842] 실시예 IX.2

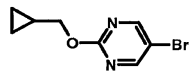
[0843] 4-요오도-2-페녹시-피리딘

[0844] 

[0845] $C_{11}H_8INO$ (M = 297.1g/mol), ESI-MS: 298 $[M+H]^+$

[0846] 실시예 IX.3

[0847] 5-브로모-2-사이클로프로필메톡시-피리미딘

[0848] 

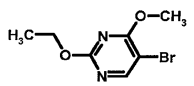
[0849] 반응물: 5-브로모-2-클로로-피리미딘/사이클로프로필메탄올

[0850] $C_8H_9BrN_2O$ (M = 229.1g/mol), ESI-MS: 229 $[M+H]^+$

[0851] R_t (HPLC): 0.98분 (방법 H)

[0852] 실시예 IX.4

[0853] 5-브로모-2-에톡시-4-메톡시-피리미딘

[0854] 

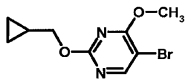
[0855] 반응물: 5-브로모-2-클로로-4-메톡시-피리미딘/에탄올

[0856] $C_7H_9BrN_2O_2$ (M = 233.1g/mol), EI-MS: 232 $[M]^+$

[0857] R_t (HPLC): 0.97분 (방법 F)

[0858] 실시예 IX.5

[0859] 5-브로모-2-사이클로프로필메톡시-4-메톡시-피리미딘

[0860] 

[0861] 반응물: 5-브로모-2-클로로-4-메톡시-피리미딘/사이클로프로필메탄올

[0862] $C_9H_{11}BrN_2O_2$ (M = 259.1g/mol), EI-MS: 258 $[M]^+$

[0863] R_t (HPLC): 1.09분 (방법 F)

[0864] 실시예 IX.6

[0865] 5-(5-브로모-피리딘-2-일옥시)-피리미딘

[0866] 

[0867] 반응물: 2,5-디브로모-피리딘/5-하이드록시피리미딘

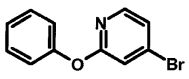
[0868] 염기로서 탄산세슘 및 용매로서 DMA를 사용함

[0869] $C_9H_6BrN_3O$ (M = 252.1g/mol), EI-MS: 252 $[M]^+$

[0870] R_t (HPLC): 1.16분 (방법 M)

[0871] 실시예 IX.7

[0872] 4-브로모-2-페녹시-피리딘

[0873] 

[0874] 반응물: 4-브로모-2-플루오로-피리딘/페놀

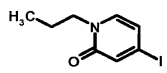
[0875] $C_{11}H_8BrNO$ (M = 250.1g/mol), ESI-MS: 250 $[M+H]^+$

[0876] R_t (HPLC): 1.12분 (방법 G)

[0877] **실시예 X**

[0878] 실시예 X.1

[0879] 4-요오도-1-프로필-1H-피리딘-2-온

[0880] 

[0881] DMF 10mL 중의 4-요오도-1H-피리딘-2-온 2.0g(9.05mmol) 및 탄산칼륨 3.13g(22.6mmol)의 혼합물에 1-요오도프로판 1.05mL(10.9mmol)를 첨가한다. 상기 혼합물을 실온에서 2시간 동안 교반한다. 이어서, 상기 혼합물을 물에 붓고, 에틸 아세테이트로 2회 추출한다. 합한 유기 층을 포화 $NaHCO_3$-용액으로 세척한다. 황산나트륨으로 건조시킨 후, 용매를 진공하에 제거하고 잔사는 HPLC(칼럼: Agilent Stablebond C18, 7 µM; 용출제 A: 물 + 0.15% HCOOH, 용출제 B: MeOH)로 정제하여 목적 생성물을 수득한다.

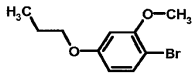
[0882] $C_8H_{10}INO$ (M = 263.1g/mol), ESI-MS: 264 $[M+H]^+$

[0883] R_t (HPLC): 1.51분 (방법 A)

[0884] 하기 화합물들은 실시예 X.1과 유사하게 제조한다:

[0885] 실시예 X.2

[0886] 1-브로모-2-메톡시-4-프로폭시-벤젠

[0887] 

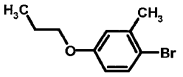
[0888] 반응물: 4-브로모-3-메톡시-페놀/1-브로모프로판

[0889] $C_{10}H_{13}BrO_2$ (M = 245.1g/mol), ESI-MS: 245 $[M+H]^+$

[0890] R_t (HPLC): 2.12분 (방법 A)

[0891] 실시예 X.3

[0892] 1-브로모-2-메틸-4-프로폭시-벤젠

[0893] 

[0894] 반응물: 4-브로모-3-메틸-페놀/1-브로모프로판

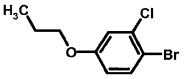
[0895] $C_{10}H_{13}BrO$ (M = 229.1g/mol)

[0896] R_t (HPLC): 2.31분 (방법 A)

[0897] R_f (TLC): 0.79 (실리카 겔, 사이클로헥산/에틸 아세테이트 9:1)

[0898] 실시예 X.4

[0899] 1-브로모-2-클로로-4-프로폭시-벤젠

[0900] 

[0901] 반응물: 4-브로모-3-클로로-페놀/1-브로모프로판

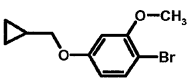
[0902] $C_9H_{10}BrClO$ (M = 249.5g/mol)

[0903] R_t (HPLC): 2.37분 (방법 A)

[0904] R_f (TLC): 0.78 (실리카 겔, 사이클로헥산/에틸 아세테이트 9:1)

[0905] 실시예 X.5

[0906] 1-브로모-4-사이클로프로필메톡시-2-메톡시-벤젠

[0907] 

[0908] 반응물: 4-브로모-3-메톡시-페놀/클로로메틸사이클로프로판

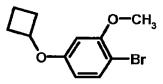
[0909] $C_{11}H_{13}BrO_2$ (M = 257.1g/mol), ESI-MS: 257 $[M+H]^+$

[0910] R_t (HPLC): 2.11분 (방법 A)

[0911] R_f (TLC): 0.79 (실리카 겔, 사이클로헥산/에틸 아세테이트 9:1)

[0912] 실시예 X.6

[0913] 1-브로모-4-사이클로부톡시-2-메톡시-벤젠

[0914] 

[0915] 반응물: 4-브로모-3-메톡시-페놀/사이클로부틸브로마이드

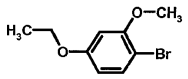
[0916] $C_{11}H_{13}BrO_2$ (M = 257.1g/mol)

[0917] ESI-MS: 257 $[M+H]^+$

[0918] R_t (HPLC): 2.18분 (방법 A)

[0919] 실시예 X.7

[0920] 1-브로모-4-에톡시-2-메톡시-벤젠

[0921] 

[0922] 반응물: 4-브로모-3-메톡시-페놀/브로모에탄

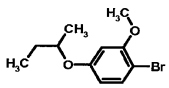
[0923] $C_9H_{11}BrO_2$ (M = 231.1g/mol)

[0924] ESI-MS: 231 $[M+H]^+$

[0925] R_t (HPLC): 2.00분 (방법 A)

[0926] 실시예 X.8

[0927] 1-브로모-4-2급-부틸옥시-2-메톡시-벤젠

[0928] 

[0929] 반응물: 4-브로모-3-메톡시-페놀/2-브로모부탄

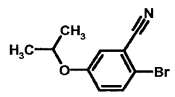
[0930] $C_{11}H_{15}BrO_2$ (M = 259.1g/mol)

[0931] ESI-MS: 259 $[M+H]^+$

[0932] R_t (HPLC): 2.21분 (방법 A)

[0933] 실시예 X.9

[0934] 2-브로모-5-이소프로폭시-벤조니트릴

[0935] 

[0936] 반응물: 2-브로모-5-하이드록시-벤조니트릴/2-브로모프로판

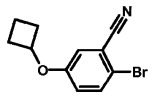
[0937] $C_{10}H_{10}BrNO$ (M = 240.1g/mol)

[0938] EI-MS: 239 $[M]^+$

[0939] R_t (HPLC): 1.98분 (방법 A)

[0940] 실시예 X.10

[0941] 2-브로모-5-사이클로부톡시-벤조니트릴

[0942] 

[0943] 반응물: 2-브로모-5-하이드록시-벤조니트릴/사이클로부틸 브로마이드

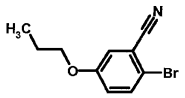
[0944] $C_{11}H_{10}BrNO$ (M = 252.1g/mol)

[0945] EI-MS: 251 $[M]^+$

[0946] R_t (HPLC): 2.07분 (방법 A)

[0947] 실시예 X.11

[0948] 2-브로모-5-프로폭시-벤조니트릴

[0949] 

[0950] 반응물: 2-브로모-5-하이드록시-벤조니트릴/1-브로모프로판

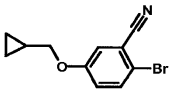
[0951] $C_{10}H_{10}BrNO$ (M = 240.1g/mol)

[0952] ESI-MS: 257 $[M+NH_4]^+$

[0953] R_t (HPLC): 2.27분 (방법 A)

[0954] 실시예 X.12

[0955] 2-브로모-5-사이클로프로필메톡시-벤조니트릴

[0956] 

[0957] 반응물: 2-브로모-5-하이드록시-벤조니트릴/클로로메틸사이클로프로판

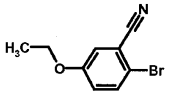
[0958] $C_{11}H_{10}BrNO$ (M = 252.1g/mol)

[0959] ESI-MS: 252 $[M+H]^+$

[0960] R_t (HPLC): 2.00분 (방법 A)

[0961] 실시예 X.13

[0962] 2-브로모-5-에톡시-벤조니트릴

[0963] 

[0964] 반응물: 2-브로모-5-하이드록시-벤조니트릴/브로모에탄

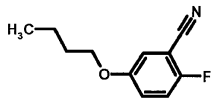
[0965] C_9H_8BrNO (M = 226.1g/mol)

[0966] ESI-MS: 226 $[M+H]^+$

[0967] R_t (HPLC): 1.82분 (방법 A)

[0968] 실시예 X.14

[0969] 5-부톡시-2-플루오로-벤조니트릴

[0970] 

[0971] 반응물: 2-플루오로-5-하이드록시-벤조니트릴/1-브로모부탄

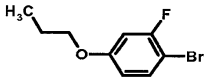
[0972] $C_{11}H_{12}FNO$ (M = 193.2g/mol)

[0973] R_t (HPLC): 2.02분 (방법 A)

[0974] R_f (TLC): 0.64 (실리카; 사이클로헥산/에틸 아세테이트 8:2)

[0975] 실시예 X.15

[0976] 1-브로모-2-플루오로-4-프로폭시-벤젠

[0977] 

[0978] 반응물: 4-브로모-3-플루오로-페놀/1-브로모프로판

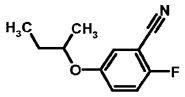
[0979] $C_9H_{10}BrFO$ (M = 233.1g/mol)

[0980] EI-MS: 232 $[M]^+$

[0981] R_t (HPLC): 2.12분 (방법 F)

[0982] 실시예 X.16

[0983] 5-2급-부톡시-2-플루오로-벤조니트릴

[0984] 

[0985] 반응물: 2-플루오로-5-하이드록시-벤조니트릴/2-브로모부탄

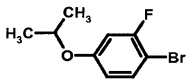
[0986] $C_{11}H_{12}FNO$ (M = 193.2g/mol)

[0987] R_t (HPLC): 1.86분 (방법 F)

[0988] R_f (TLC): 0.60 (실리카; 사이클로헥산/에틸 아세테이트 8:2)

[0989] 실시예 X.17

[0990] 1-브로모-2-플루오로-4-이소프로폭시-벤젠

[0991] 

[0992] 반응물: 4-브로모-3-플루오로-페놀/2-브로모프로판

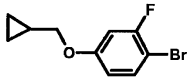
[0993] $C_9H_{10}BrFO$ (M = 233.1g/mol)

[0994] R_t (HPLC): 2.25분 (방법 F)

[0995] R_f (TLC): 0.27 (실리카; 사이클로헥산)

[0996] 실시예 X.18

[0997] 1-브로모-4-사이클로프로필메톡시-2-플루오로-벤젠

[0998] 

[0999] 반응물: 4-브로모-3-플루오로-페놀/클로로메틸사이클로프로판

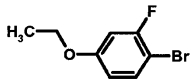
[1000] $C_{10}H_{10}BrFO$ (M = 245.1g/mol)

[1001] EI-MS: 244 $[M]^+$

[1002] R_t (HPLC): 2.08분 (방법 F)

[1003] 실시예 X.19

[1004] 1-브로모-4-에톡시-2-플루오로-벤젠

[1005] 

[1006] 반응물: 4-브로모-3-플루오로-페놀/에틸브로마이드

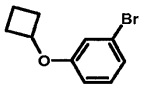
[1007] C_8H_8BrFO (M = 219.1g/mol)

[1008] R_f (TLC): 0.57분 (실리카 겔, CyH)

[1009] R_t (HPLC): 2.16분 (방법 F)

[1010] 실시예 X.20

[1011] 1-브로모-3-사이클로부톡시-벤젠

[1012] 

[1013] 반응물: 3-브로모-페놀/클로로-사이클로부탄

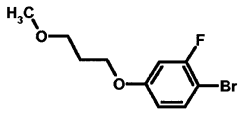
[1014] $C_{10}H_{11}BrO$ (M = 227.1g/mol)

[1015] R_f (TLC): 0.58 (실리카 겔, CyH)

[1016] R_t (HPLC): 1.40분 (방법 L)

[1017] 실시예 X.21

[1018] 1-브로모-2-플루오로-4-(3-메톡시-프로폭시)-벤젠

[1019] 

[1020] 반응물: 4-브로모-3-플루오로-페놀/1-브로모-3-메톡시프로판

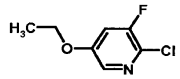
[1021] $C_{10}H_{12}BrFO_2$ (M = 263.1g/mol)

[1022] R_f (TLC): 0.49 (실리카 겔, CyH/EtOAc 9/1)

[1023] R_t (HPLC): 0.72분 (방법 H)

[1024] 실시예 X.22

[1025] 2-클로로-5-에톡시-3-플루오로-피리딘

[1026] 

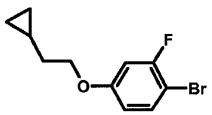
[1027] 반응물: 2-클로로-3-플루오로-5-하이드록시-피리딘/에틸브로마이드

[1028] C_7H_7ClFNO (M = 175.6g/mol), ESI-MS: 176 $[M+H]^+$

[1029] R_t (HPLC): 1.07분 (방법 L)

[1030] 실시예 X.23

[1031] 1-브로모-4-(2-사이클로프로필-에톡시)-2-플루오로-벤젠

[1032] 

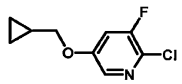
[1033] 반응물: 4-브로모-3-플루오로-페놀/(2-요오도-에틸)-사이클로프로판

[1034] $C_{11}H_{12}BrFO$ (M = 259.1g/mol)

[1035] R_f (TLC): 0.71 (실리카 겔, Cy/EtOAc 9/1), R_t (HPLC): 1.43분 (방법 L)

[1036] 실시예 X.24

[1037] 2-클로로-5-사이클로프로필메톡시-3-플루오로-피리딘

[1038] 

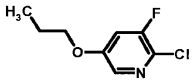
[1039] 반응물: 2-클로로-3-플루오로-5-하이드록시-피리딘/(브로모메틸)사이클로프로판

[1040] C_9H_9ClFNO (M = 201.6g/mol), ESI-MS: 202 $[M+H]^+$

[1041] R_t (HPLC): 1.20분 (방법 L)

[1042] 실시예 X.25

[1043] 2-클로로-3-플루오로-5-프로폭시-피리딘

[1044] 

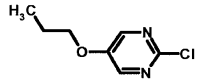
[1045] 반응물: 2-클로로-3-플루오로-5-하이드록시-피리딘/1-브로모프로판

[1046] C_8H_9ClFNO (M = 189.6g/mol), ESI-MS: 190 $[M+H]^+$

[1047] R_t (HPLC): 1.19분 (방법 L)

[1048] 실시예 X.26

[1049] 2-클로로-5-프로폭시-피리미딘

[1050] 

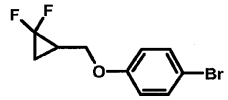
[1051] 반응물: 2-클로로-5-하이드록시-피리미딘/1-브로모프로판

[1052] $C_7H_9ClN_2O$ (M = 172.6g/mol), ESI-MS: 173 $[M+H]^+$

[1053] R_t (HPLC): 1.53분 (방법 A)

[1054] 실시예 X.27

[1055] 1-브로모-4-(2,2-디플루오로-사이클로프로필메톡시)-벤젠

[1056] 

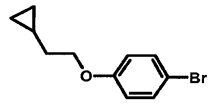
[1057] 반응물: 4-브로모-3-페놀/2-브로모메틸-1,1-디플루오로-사이클로프로판

[1058] $C_{10}H_9BrF_2O$ (M = 263.1g/mol), EI-MS: 262 $[M]^+$

[1059] R_t (HPLC): 1.15분 (방법 G)

[1060] 실시예 X.28

[1061] 1-브로모-4-(2-사이클로프로필-에톡시)-벤젠

[1062] 

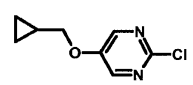
[1063] 반응물: 4-브로모-페놀/(2-요오도-에틸)-사이클로프로판

[1064] $C_{11}H_{13}BrO$ (M = 241.1g/mol), EI-MS: 240 $[M]^+$

[1065] R_t (HPLC): 1.30분 (방법 G)

[1066] 실시예 X.29

[1067] 2-클로로-5-사이클로프로필메톡시-피리미딘

[1068] 

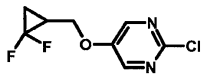
[1069] 반응물: 2-클로로-5-하이드록시-피리미딘/(브로모메틸)사이클로프로판

[1070] $C_8H_9ClN_2O$ (M = 184.6g/mol), ESI-MS: 185 $[M+H]^+$

[1071] R_t (HPLC): 1.23분 (방법 N)

[1072] 실시예 X.30

[1073] 2-클로로-5-(2,2-디플루오로사이클로프로필메톡시)-피리미딘

[1074] 

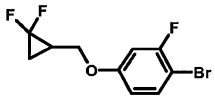
[1075] 반응물: 2-클로로-5-하이드록시-피리미딘/2-브로모메틸-1,1-디플루오로-사이클로프로판

[1076] $C_8H_7ClF_2N_2O$ (M = 220.6g/mol), ESI-MS: 221 $[M+H]^+$

[1077] R_t (HPLC): 1.21분 (방법 N)

[1078] 실시예 X.31

[1079] 1-브로모-4-(2,2-디플루오로-사이클로프로필메톡시)-2-플루오로-벤젠

[1080] 

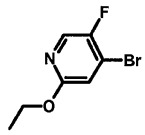
[1081] 반응물: 4-브로모-3-플루오로-페놀/2-브로모메틸-1,1-디플루오로-사이클로프로판

[1082] $C_{10}H_8BrF_3O$ (M = 281.1g/mol), EI-MS: 282 $[M+H]^+$

[1083] R_t (HPLC): 1.31분 (방법 L)

[1084] 실시예 X.32

[1085] 4-브로모-2-에톡시-5-플루오로-피리딘

[1086] 

[1087] 반응물: 4-브로모-5-플루오로-피리딘-2-올/에틸 요오다이드

[1088] 염기로서 메틸렌 클로라이드 중의 탄산은을 사용함

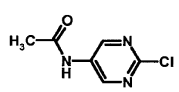
[1089] C_7H_7BrFNO (M = 220.0g/mol), EI-MS: 220 $[M+H]^+$

[1090] R_t (HPLC): 1.27분 (방법 M)

[1091] **실시예 XI**

[1092] 실시예 XI.1

[1093] N-(2-클로로-피리미딘-5-일)-아세트아미드

[1094] 

[1095] 아세트산 무수물 78㎕(0.83mmol)를 0℃에서 디클로로메탄 20mL 중의 2-클로로-피리미딘-5-일아민 100mg (0.77mmol)에 첨가한다. 이어서, TEA 115㎕를 첨가하고, 실온에서 12시간 동안 계속 교반한다. 그 시간 후, 용매를 증발에 의해 제거하고 잔사는 물로 세척한다.

[1096] $C_6H_6ClN_3O$ (M = 171.6g/mol)

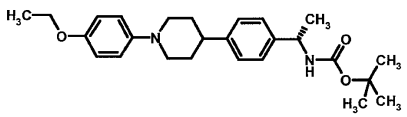
[1097] ESI-MS: 172 $[M+H]^+$

[1098] R_t (HPLC): 0.86분 (방법 A)

[1099] **실시예 XII**

[1100] 실시예 XII.1

[1101] (S)-(1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸)-카밤산 3급-부틸 에스테르

[1102] 

[1103] 탄산세슘 6.21g(19.1mmol)을 톨루엔 50mL/3급-부탄올 10mL 중의 (S)-[1-(4-피페리딘-4-일-페닐)-에틸]-카밤산 3급-부틸 에스테르(V.5) 5.80mg(19.1mmol), 1-브로모-4-에톡시-벤젠 4.21g(21.0mmol), X-Phos 454mg (0.953mmol) 및 팔라듐(II) 아세테이트 214mg(0.953mmol)의 혼합물에 첨가한다. 상기 혼합물을, 불활성 기체 대기하에, 120℃에서 3시간 동안 교반한다. 그 시간 후, 상기 혼합물을 물로 붓고, 에틸 아세테이트로 추출한다. 유기 층을 물로 세척하고, 황산마그네슘으로 건조시킨다. 용매를 진공하에 제거하고 잔사는 아세토니트릴로부터 재결정화한다.

[1104] $C_{26}H_{36}N_2O_3$ (M = 424.6g/mol)

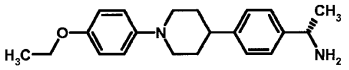
[1105] ESI-MS: 425 $[M+H]^+$

[1106] R_t (HPLC): 2.10분 (방법 A)

[1107] **실시예 XIII**

[1108] 실시예 XIII.1

[1109] (S)-1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸아민 디하이드로클로라이드

[1110] 

[1111] 메탄올 중의 1.25N HCl 11.3mL(14.1mmol)를 디클로로메탄 25mL 중의 (S)-(1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸)-카밤산 3급-부틸 에스테르(XII.1) 900mg(2.12mmol)에 첨가한다. 상기 혼합물을 실온에서 14시간 동안 및 5℃에서 1시간 동안 교반한다. 그 시간 후, 용매를 진공하에 제거하여 목적 생성물을 수득한다.

[1112] $C_{21}H_{28}N_2O \cdot 2HCl$ (M = 397.4g/mol)

[1113] ESI-MS: 325 $[M+H]^+$

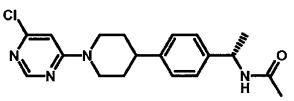
[1114] R_t (HPLC): 1.11분 (방법 D)

[1115] 상응하는 유리 염기는 NaOH(물 중의 10%)의 첨가 및 디클로로메탄에 의한 즉시 추출에 의해 합성된다. 유기 층을 물로 2회 세척하고, 황산마그네슘으로 건조시킨 다음, 용매는 증발시켜 목적 생성물을 수득한다.

[1116] **실시예 XIV**

[1117] 실시예 XIV.1

[1118] (S)-N-(1-{4-[1-(6-클로로-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1119] 

[1120] TEA 0.34mL(2.43mmol)를 THF 3mL 중의 4,6-디클로로피리미딘 181mg(1.22mmol) 및 (S)-N-[1-(4-피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 300mg(1.22mmol)의 혼합물에 첨가한다. 상기 혼합물을 80℃에서 5분 동안 및 실온에서 2시간 동안 교반한다. 그 시간 후, 물을 첨가하고, 상기 혼합물은 디클로로메탄으로 2회 추출한다.

합한 유기 층을 황산나트륨으로 건조시킨다. 용매를 증발시키고 잔사는 칼럼 크로마토그래피(실리카 겔; 디클로로메탄/메탄올, 구배 98:2 내지 95:5)로 정제하여 목적 생성물을 수득한다.

[1121] $C_{19}H_{23}ClN_4O$ (M = 358.9g/mol)

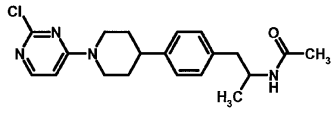
[1122] ESI-MS: 359 $[M+H]^+$

[1123] R_t (HPLC): 2.00분 (방법 B)

[1124] 하기 화합물들은 실시예 XIV.1과 유사하게 제조한다:

[1125] 실시예 XIV.2

[1126] N-(2-{4-[1-(2-클로로-피리미딘-4-일)-피페리딘-4-일]-페닐}-1-메틸-에틸)-아세트아미드

[1127] 

[1128] 반응물: VIII.1/2,4-디클로로피리미딘

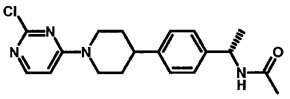
[1129] (염기로서 K_2CO_3 및 용매로서 아세톤을 사용함)

[1130] $C_{20}H_{25}ClN_4O$ (M = 372.9g/mol)

[1131] ESI-MS: 373 $[M+H]^+$

[1132] 실시예 XIV.3

[1133] (S)-N-(1-{4-[1-(2-클로로-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1134] 

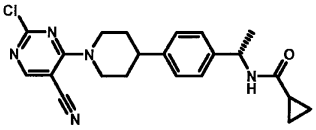
[1135] 반응물: V.1/4,6-디클로로피리미딘

[1136] $C_{19}H_{23}ClN_4O$ (M = 358.9g/mol); ESI-MS: 359 $[M+H]^+$

[1137] R_t (HPLC): 2.00분 (방법 P)

[1138] 실시예 XIV.4

[1139] (S)-사이클로프로판카복실산(1-{4-[1-(2-클로로-5-시아노-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아미드

[1140] 

[1141] 반응물: V.4/2,4-디클로로-5-시아노피리미딘

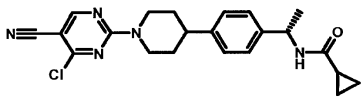
[1142] (염기로서 K_2CO_3 및 용매로서 아세톤을 사용함)

[1143] $C_{22}H_{24}ClN_5O$ (M = 409.9g/mol); ESI-MS: 410 $[M+H]^+$

[1144] R_t (HPLC): 1.97분 (방법 T)

[1145] 실시예 XIV.5

[1146] (S)-사이클로프로판카복실산(1-{4-[1-(4-클로로-5-시아노-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아미드



[1147]

[1148] 반응물: V.4/2,4-디클로로-5-시아노피리미딘

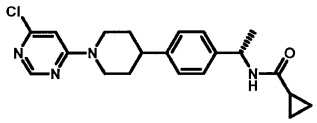
[1149] (염기로서 K_2CO_3 및 용매로서 아세톤을 사용함)

[1150] $C_{22}H_{24}ClN_5O$ (M = 409.9g/mol); ESI-MS: 410 $[M+H]^+$

[1151] R_t (HPLC): 2.07분 (방법 T)

[1152] 실시예 XIV.6

[1153] (S)-사이클로프로판카복실산(1-{4-[1-(6-클로로-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드



[1154]

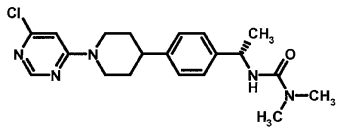
[1155] 반응물: V.4/4,6-디클로로피리미딘

[1156] $C_{21}H_{25}ClN_4O$ (M = 384.9g/mol); ESI-MS: 385 $[M+H]^+$

[1157] R_t (HPLC): 1.19분 (방법 L)

[1158] 실시예 XIV.7

[1159] (S)-3-(1-{4-[1-(6-클로로-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-1,1-디메틸-우레아



[1160]

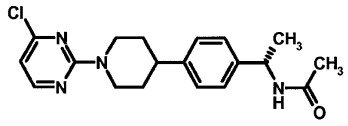
[1161] 반응물: V.3/4,6-디클로로피리미딘

[1162] $C_{20}H_{26}ClN_5O$ (M = 387.9g/mol); ESI-MS: 388 $[M+H]^+$

[1163] R_t (HPLC): 1.17분 (방법 L)

[1164] 실시예 XIV.8

[1165] (S)-N-(1-{4-[1-(4-클로로-피리미딘-2-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드



[1166]

[1167] 반응물: V.1/4,6-디클로로피리미딘, 용매 DMF; 화합물 XIV.3은 제2 생성물로서 수득된다.

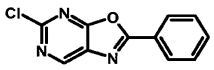
[1168] $C_{19}H_{23}ClN_4O$ (M = 358.9g/mol); ESI-MS: 359 $[M+H]^+$

[1169] R_t (HPLC): 1.34분 (방법 L)

[1170] **실시예 XV**

[1171] 실시예 XV.1

[1172] 5-클로로-2-페닐옥사졸로[5,4-d]피리미딘

[1173] 

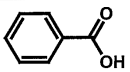
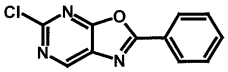
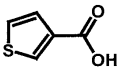
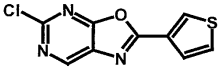
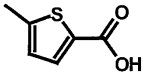
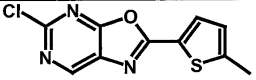
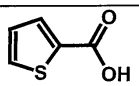
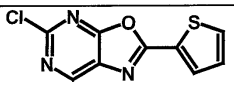
[1174] 벤조산 7.82g(64.0mmol) 및 $POCl_3$ 20mL를 30분 동안 100℃에서 함께 교반한다. 45분 이내에, 2,6-디클로로-5-아미노피리미딘 7.00g(42.7mmol)을 몇 개의 분획으로 첨가한다. 상기 반응 혼합물을 동일한 온도에서 다시 2시간 동안 교반한다. 그 시간 후, 상기 혼합물을 빙냉 NaOH 수용액에 주의해서 첨가한다. 생성된 침전을 여과하고, 물로 세척하여 건조시킨다.

[1175] $C_{11}H_6ClN_3O$ (M = 231.6g/mol); ESI-MS: 232 $[M+H]^+$

[1176] R_t (HPLC): 2.22분 (방법 I)

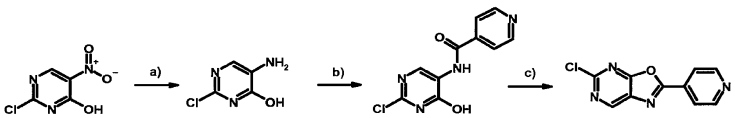
[1177] 하기 화합물들은 실시예 XV.1과 유사하게 제조한다:

[1178]

실시예	출발 물질	생성물 구조	질량 스펙트럼 결과	R_t (HPLC) [분] (방법)
XV.1			232 $[M+H]^+$	2.22 (I)
XV.2			238 $[M+H]^+$	1.43 (I)
XV.3			252 $[M+H]^+$	n.d.
XV.4			238 $[M+H]^+$	n.d.

[1179] 실시예 XV.5

[1180] 5-클로로-2-피리딘-4-일-옥사졸로[5,4-d]피리미딘

[1181] 

[1182] a) 2-클로로-5-니트로-피리미딘-4-올 25g(126mmol), PtO_2 2.0g 및 MeOH 2.5L를 1시간 동안 수소화시킨다 (50psi). 상기 혼합물을 여과하고 농축시킨 다음 건조시켜, 5-아미노-2-클로로-피리미딘-4-올을 수득한다.

[1183] b) DMF 30mL 중의 이소니코틴산 5.88g(47.7mmol) 및 1,1'-카보닐디이미다졸 7.74g(47.7mmol)을 5-아미노-2-클로로-피리미딘-4-올 8.0g(47.7mmol)의 첨가 전에 45℃에서 30분 동안 교반한다. 상기 혼합물을 실온에서 12시간 동안 교반하고, 농축시킨 다음, HPLC(역상, 물(+0.1% TFA)/MeOH)로 정제하여 N-(2-클로로-4-하이드록시-피리미딘-5-일)-이소니코틴아미드를 수득한다.

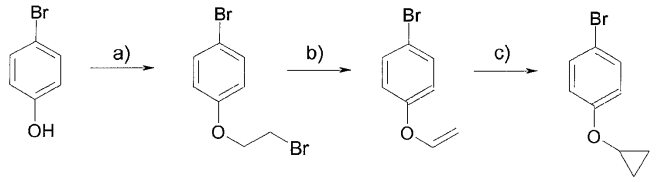
[1184] c) 중합체 결합된 트리페닐포스핀 12.0g(35.9mmol) 및 트리에틸아민 5.03mL(35.9mmol)를 1,2-디클로로메탄 40mL 중의 헥사클로로에탄 4.77g(20.0mmol)에 첨가한다. 상기 혼합물을 실온에서 5분 동안 교반한다. 1,2-디클로로에탄 20mL 중의 N-(2-클로로-4-하이드록시-피리미딘-5-일)-이소니코틴아미드 1.00g(4.0mmol)을 첨가하고, 상기 혼합물을 실온에서 12시간 동안 교반한다. 이어서, 상기 혼합물을 진공하에 농축시키고, 디에틸 에테르로 처리하여, 여과하고 다시 농축시킨다. 상기 잔사는 HPLC(역상; 물(+0.1% TFA)/MeOH)로 정제하여 목적 생성물을 수득한다.

[1185] $C_{10}H_5ClN_4O$ (M = 232.6g/mol); ESI-MS: 233 $[M+H]^+$

[1186] **실시예 XVI**

[1187] 실시예 XVI.1

[1188] 1-브로모-4-(2-브로모에톡시)벤젠

[1189] 

[1190] a) 4-브로모페놀 55.0g(318mmol) 및 NaOH 14.1g(352mmol)를 물 110mL에 첨가한다. 디브로모에탄 41.1mL(477mmol)를 서서히 첨가하고, 반응 혼합물은 환류하에 16시간 동안 교반한다. 이어서, 상기 반응 혼합물은 디클로로메탄으로 추출하고, 용매는 진공하에 제거한다. 조 생성물은 칼럼 크로마토그래피(실리카 겔, 사이클로헥산/EtOAc 4/1)로 정제한다.

[1191] b) 1-브로모-4-(2-브로모에톡시)벤젠 52.0g(186mmol)을 THF 300mL에 첨가하고, 0℃로 냉각시킨다. 30분 이내에, KOtBu 25.0g(223mmol)을 상기 혼합물에 몇 개의 분획으로 첨가한다. 냉각을 제거하고, 반응 혼합물은 실온에서 밤새 교반한다. 반응은 물의 첨가에 의해 급냉시킨다. 생성된 혼합물은 EtOAc로 2회 추출한다. 유기상을 합하고, 염수로 세척한 다음, $MgSO_4$으로 건조시키고, 용매는 진공하에 제거한다. 생성된 생성물은 추가의 정제 없이 사용한다.

[1192] c) 1-브로모-4-비닐옥시벤젠 39.0g(176mmol) 및 클로로요오도메탄 32.4mL(441mmol)를 디클로로메탄 500mL에 첨가하고, 0℃로 냉각시킨다. 1시간 동안, 디에틸아연 용액(헥산 중의 c = 1mol/ℓ) 200mL를 첨가하고, 0℃에서 2시간 동안 계속 교반한다. 반응은 포화 수성 NH_4Cl 용액 200mL의 첨가에 의해 급냉시키고, TBME로 2회 추출한다. 유기상을 합하고, 염수로 세척한 다음, $MgSO_4$으로 건조시키고, 용매는 진공하에 제거한다. 조 생성물은 칼럼 크로마토그래피(실리카 겔, PE)로 정제한다.

[1193] C_9H_9BrO (M = 213.1g/mol)

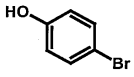
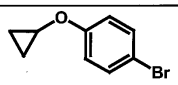
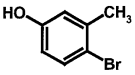
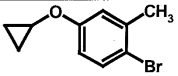
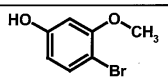
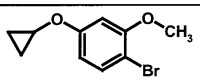
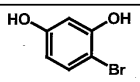
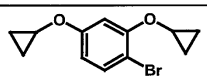
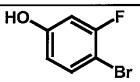
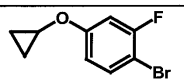
[1194] EI-MS: 212/214 $[M]^+$

[1195] R_f (TLC): 0.4 (실리카 겔, PE)

[1196] 하기 화합물들은 실시예 XVI.1과 유사하게 제조한다.

[1197] 실시예 XVI.2/XVI.3의 경우, 단계 a)의 펜올레이트는 1시간 동안 실온에서 MeOH/물(1/1) 혼합물에서 적합한 페놀과 NaOH를 반응시켜 수행한다. 이어서, 용매는 진공하에 제거하고, 생성된 나트륨 염은 24시간 동안 100℃에서 디브로모에탄(5eq.)과 반응시킨다. 상기 반응 혼합물은 물의 첨가에 의해 급냉시키고, DCM으로 추출한다.

[1198] 실시예 XVI.4 단계 a의 경우: 아세톤 중의 디페놀 및 디브로모에탄(8eq.)에 Cs_2CO_3(5eq.)을 첨가하고, 반응 혼합물은 45시간 동안 90℃에서 교반한다. 상기 반응 혼합물은 물의 첨가에 의해 급냉시키고, EtOAc로 추출한다.

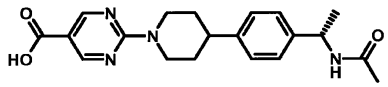
실시예	출발 물질	생성물 구조	질량 스펙트럼 결과	R_t (HPLC) [분] (방법)
XVI.1			212/214 $[M]^+$	n.d.
XVI.2			n.d.	5.89 (AF)
XVI.3			n.d.	5.30 (J)
XVI.4			n.d.	8.50 (K)
XVI.5			230/232 $[M]^+$	n.d.

[1199]

[1200] **실시예 XVII**

[1201] 실시예 XVII.1

[1202] (S)-2-{4-[4-(1-아세틸아미노-에틸)-페닐]-피페리딘-1-일}-피리미딘-5-카복실산

[1203] 

[1204] NMP 80mL 중의 2-클로로피리미딘-5-카복실산 메틸 에스테르 1.52g(8.5mmol)에 (S)-N-[1-(4-피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 2.1g(8.5mmol) 및 DIPEA 2.9mL(17.1mmol)를 첨가하고, 상기 혼합물을 100℃에서 4시간 동안 교반한다. 용매는 진공하에 제거한다. 잔사를 MeOH 100mL로 처리하고, 4N 수산화나트륨 용액 10mL를 첨가한다. 상기 혼합물을 60℃에서 1시간 동안 교반한다. 실온으로 냉각시킨 후, pH가 산성이 될 때 까지 4N HCl 용액을 첨가한다. 침전을 수거하고 건조시켜, 목적 생성물을 수득한다.

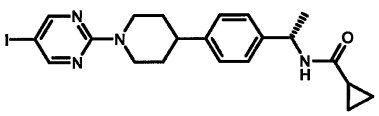
[1205] $C_{20}H_{24}N_4O_3$ (M = 368.4g/mol); ESI-MS: 369 $[M+H]^+$

[1206] R_t (HPLC): 2.04분 (방법 P)

[1207] **실시예 XVIII**

[1208] 실시예 XVIII.1

[1209] (S)-사이클로프로판카복실산(1-{4-[1-(5-요오도-피리미딘-2-일)-피페리딘-4-일]-페닐}-에틸)-아미드

[1210] 

[1211] NMP 10mL 중의 2-클로로-5-요오도피리미딘 633mg(2.5mmol), (S)-사이클로프로판카복실산[1-(4-피페리딘-4-일-페닐)-에틸]-아미드(V.4) 757mg(2.5mmol) 및 DIPEA 0.855mL(5.0mmol)를 130℃에서 2시간 동안 교반한다. 실온으로 냉각시킨 후, 혼합물을 물로 처리하고, 침전을 여과에 의해 수거한 다음, 에테르로 연마시켜, 목적 화합물을 수득한다.

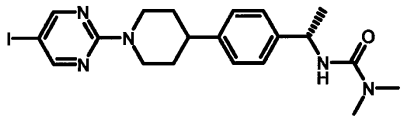
[1212] $C_{21}H_{25}IN_4O$ (M = 476.4g/mol); ESI-MS: 477 $[M+H]^+$

[1213] R_t (HPLC): 2.25분 (방법 P)

[1214] 하기 화합물들은 실시예 XVIII.1과 유사하게 제조한다:

[1215] 실시예 XVIII.2

[1216] (S)-3-(1-{4-[1-(5-요오도-피리미딘-2-일)-피페리딘-4-일]-페닐}-에틸)-1,1-디메틸-우레아



[1217]

[1218] 반응물: V.3/2-클로로-5-요오도피리미딘

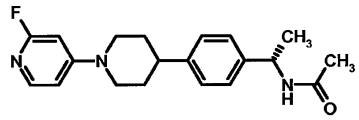
[1219] $C_{20}H_{26}IN_5O$ (M = 479.4g/mol); ESI-MS: 480 $[M+H]^+$

[1220] R_t (HPLC): 2.22분 (방법 P)

[1221] **실시예 XIX**

[1222] 실시예 XIX.1

[1223] (S)-N-{1-[4-(2'-플루오로-3,4,5,6-테트라하이드로-2H-[1,4']비피리디닐-4-일)-페닐]-에틸}-아세트아미드



[1224]

[1225] THF 10mL 및 DMF 10mL 중의 (S)-N-[1-(피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 1.41g(5.74mmol)에 트리에틸아민 0.80mL(5.74mmol) 및 2,4-디플루오로피리딘 0.60g(5.21mmol)을 첨가한다. 상기 혼합물을 0℃에서 12시간 동안 교반한다. 이어서, 상기 혼합물을 진공하에 농축시키고, 잔사는 HPLC(C18 RP Sunfire; 물(+0.1% TFA)/MeOH))에 의해 정제하여 목적 생성물을 수득한다.

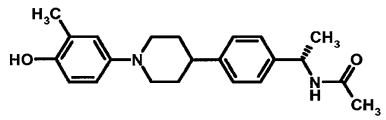
[1226] $C_{20}H_{24}FN_3O$ (M = 341.4g/mol); ESI-MS: 342 $[M+H]^+$

[1227] R_t (HPLC): 1.59분 (방법 T)

[1228] **실시예 XX**

[1229] 실시예 XX.1

[1230] (S)-N-(1-{4-[1-(4-하이드록시-3-메틸-페닐)-피페리딘-4-일]-페닐}-에틸)-아세트아미드



[1231]

[1232] 디옥산 40mL 중의 4-브로모-2-메틸페놀 760mg(4.06mmol), 나트륨 3급-부틸레이트 1.7g(16.24mmol) 및 2-(디-3급-부틸포스피노)비페닐 484mg(1.62mmol)의 혼합물에 (S)-N-[1-(피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 1.0g(4.06mmol)을 첨가한다. 이어서, 트리스-(디벤질리덴아세톤)-팔라듐(0) 371.7mg(0.41mmol)을 아르곤 대기하에 첨가하고, 상기 혼합물을 45℃에서 12시간 동안 교반한다. 이어서, 상기 혼합물을 물로 붓고, 1N HCl 용액을 사용하여 산성화시킨 다음, 디클로로메탄으로 추출한다. DCM 용액은 이어서, 1N HCl 용액으로 2회 추출하고, 합한 수성 층은 고체 $NaHPO_4$를 사용하여 중성 pH로 만든다. 이어서, 침전을 DCM/MeOH로 처리하고, 용매는 진공하에 제거한다. 상기 잔사는 HPLC(C18 RP Sunfire; 용출제 A: 물 +0.1% TFA, 용출제 B: MeOH)에 의해 정제하여 목적 생성물을 수득한다.

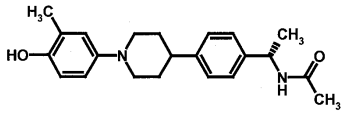
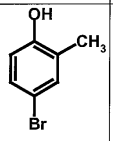
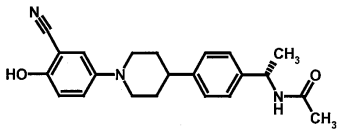
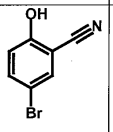
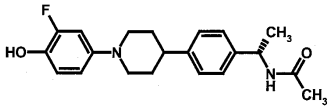
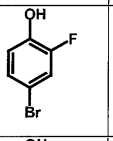
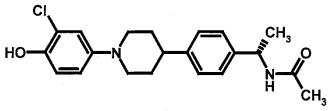
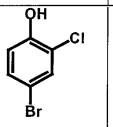
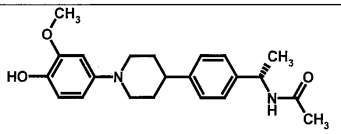
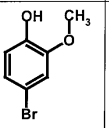
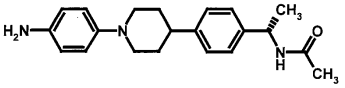
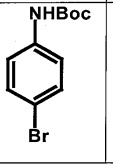
[1233] $C_{20}H_{28}N_2O_2$ (M = 352.5g/mol); ESI-MS: 353 $[M+H]^+$

[1234] R_t (HPLC): 1.14분 (방법 P)

[1235] 하기 화합물들은 실시예 XX.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼에 제시되어

있다.

[1236] 실시예 XX.6의 경우, 반응의 끝에서, 용매는 진공하에 제거하고, 잔사에 2N HCl을 첨가한다. 수성 층은 EtOAc로 추출하고, 여과하고, 4N NaOH로 염기성화시킨다. 생성된 침전을 여과하여, 진공하에 건조시킨다.

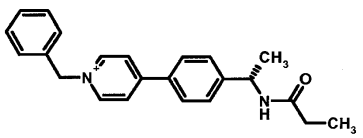
실시예	생성물	E 1	E 2	ESI-MS [m/z]	R_t (HPLC) [분] (방법)
XX.1			V.1	353 $[M+H]^+$	1.14 (P)
XX.2			V.1	364 $[M+H]^+$	1.20 (P)
XX.3			V.1	357 $[M+H]^+$	1.12 (P)
XX.4			V.1	373 $[M+H]^+$	1.21 (P)
XX.5			V.1	369 $[M+H]^+$	1.09 (P)
XX.6			V.1	338 $[M+H]^+$	0.81 (N)

[1237]

[1238] **실시예 XXI**

[1239] 실시예 XXI.1

[1240] (S)-1-벤질-4-[4-(1-프로피오닐아미노-에틸)-페닐]-피리디늄 브로마이드

[1241] 

[1242] 아세톤 120mL 중의 (S)-N-[1-(4-피리딘-4-일-페닐)-에틸]-프로피온아미드(IV.6) 9.60g(37.7mmol)에 벤질 브로마이드 4.91mL(41.5mmol)를 첨가한다. 상기 혼합물을 12시간 동안 환류시킨다. 그 시간 후, 침전을 여과하고, 아세톤으로 세척한 다음, 50℃에서 건조시켜 목적 생성물을 수득한다.

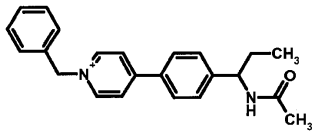
[1243] $C_{23}H_{25}N_2O*Br$ (M = 425.4g/mol); EI-MS: 345 $[M]^+$

[1244] R_t (HPLC): 1.03분 (방법 O)

[1245] 하기 화합물들은 실시예 XXI.1과 유사하게 제조한다.

[1246] 실시예 XXI.2

[1247] 1-벤질-4-[4-(1-아세틸아미노-프로필)-페닐]-피리디늄 브로마이드

[1248] 

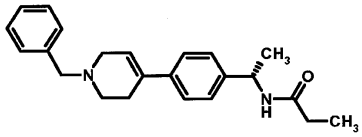
[1249] $C_{23}H_{25}N_2O*Br$ (M = 425.4g/mol); EI-MS: 345 $[M]^+$

[1250] R_t (HPLC): 0.93분 (방법 N)

[1251] **실시예 XXII**

[1252] 실시예 XXII.1

[1253] (S)-N-{1-[4-(1-벤질-1,2,3,6-테트라하이드로-피리딘-4-일)-페닐]-에틸}-프로피온아미드

[1254] 

[1255] 에탄올 270mL 중의 (S)-1-벤질-4-[4-(1-프로피오닐아미노-에틸)-페닐]-피리디늄 브로마이드(XXI.1) 13.60g(32.0mmol)에 0℃에서 나트륨 보로하이드라이드 2.42g(64.1mmol)을 서서히 첨가한다. 상기 혼합물을 실온에서 48시간 동안 교반한다. 그 시간 후, 용매를 진공하에 제거하고, 에틸 아세테이트를 첨가한다. 상기 혼합물을 1N HCl로 추출한다. 수성상을 4N NaOH로 중화시키고, 침전을 여과하여, 45℃에서 건조시켜 목적 생성물을 수득한다.

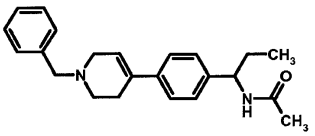
[1256] $C_{23}H_{28}N_2O$ (M = 348.5g/mol); ESI-MS: 349 $[M+H]^+$

[1257] R_t (HPLC): 0.91분 (방법 N)

[1258] 하기 화합물들은 실시예 XXII.1과 유사하게 제조한다.

[1259] 실시예 XXII.2

[1260] (N-{1-[4-(1-벤질-1,2,3,6-테트라하이드로-피리딘-4-일)-페닐]-프로필}-아세트아미드

[1261] 

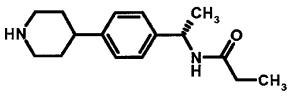
[1262] $C_{23}H_{28}N_2O$ (M = 348.5g/mol); ESI-MS: 349 $[M+H]^+$

[1263] R_t (HPLC): 0.93분 (방법 N)

[1264] **실시예 XXIII**

[1265] 실시예 XXIII.1

[1266] (S)-N-[1-(4-피페리딘-4-일-페닐)-에틸]-프로피온아미드

[1267] 

[1268] 에탄올 130mL 중의 ((S)-N-{1-[4-(1-벤질-1,2,3,6-테트라하이드로-피리딘-4-일)-페닐]-에틸}-프로피온아미드(XXII.1) 9.58g(27.5mmol)은 Pd/C(10%) 0.80g을 사용하여 50℃에서 7시간 동안 수소화시킨다(3bar). 그 시간

후, 촉매를 여과하고, 용매를 증발시킨다. 상기 잔사는 HPLC(칼럼: Gemini Phenomenex, 10μM; 용출제 A: 물 +0.30% NH_4OH, 용출제 B: 아세톤)에 의해 정제하여 목적 생성물을 수득한다.

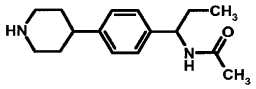
[1269] $C_{16}H_{24}N_2O$ (M = 260.4g/mol); ESI-MS: 261 $[M+H]^+$

[1270] R_t (HPLC): 0.69분 (방법 N)

[1271] 하기 화합물들은 실시예 XXIII.1과 유사하게 제조한다.

[1272] 실시예 XXIII.2

[1273] N-[1-(4-피페리딘-4-일-페닐)-프로필]-아세트아미드

[1274] 

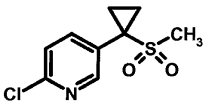
[1275] $C_{16}H_{24}N_2O$ (M = 260.4g/mol); ESI-MS: 261 $[M+H]^+$

[1276] R_t (HPLC): 0.72분 (방법 N)

[1277] **실시예 XXIV**

[1278] 실시예 XXIV.1

[1279] 2-클로로-5-(1-메탄설포닐-사이클로프로필)-피리딘

[1280] 

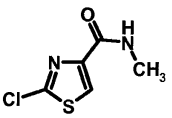
[1281] 9mL NaOH 용액(물 중의 50%) 및 9mL 디클로로메탄을 실온에서 혼합하고, 테트라부틸암모늄 브로마이드 137mg (0.42mmol) 및 2-클로로-5-[(메틸설포닐)메틸]피리딘 0.87g(4.25mmol)에 이어서, 디브로모메탄 1.83mL(21.2mmol)를 첨가한다. 상기 혼합물을 35℃에서 12시간 동안 교반한다. 이어서, 상기 혼합물을 디클로로메탄으로 추출하고, 합한 유기상은 물 및 염수로 세척한다. 용매는 진공하에 제거하고 잔사는 HPLC(실리카겔, 사이클로헥산/에틸 아세테이트)에 의해 정제하여 목적 생성물을 수득한다.

[1282] $C_9H_{10}ClNO_2S$ (M = 231.7g/mol); ESI-MS: 232 $[M+H]^+$

[1283] **실시예 XXV**

[1284] 실시예 XXV.1

[1285] 2-클로로-티아졸-4-카복실산 메틸아미드

[1286] 

[1287] 디클로로메탄 8.0mL 중의 2-클로로-티아졸-4-카보닐 클로라이드 445mg(2.44mmol)에 THF 중의 트리에틸아민 0.38mL(2.69mmol) 및 메틸아민의 2 molare 용액 1.35mL(2.69mmol)의 혼합물을 첨가한다. 상기 혼합물을 밤새 교반하고, 농축시킨 다음, 잔사는 물 및 $NaHCO_3$ 용액으로 처리한다. 에틸 아세테이트로 추출한 후에, 유기상을 합하고, 건조(Na_2SO_4) 및 농축시켜 목적 생성물을 수득한다.

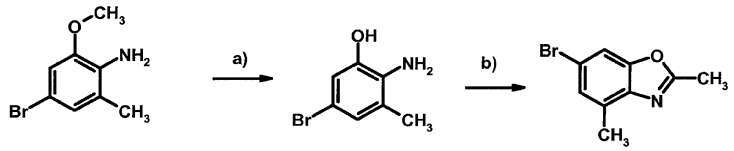
[1288] $C_5H_5ClN_2OS$ (M = 176.6g/mol), ESI-MS: 177 $[M+H]^+$

[1289] R_f (사이클로헥산/에틸 아세테이트 = 1:1) = 0.3

[1290] **실시예 XXVI**

[1291] 실시예 XXVI.1

[1292] 6-브로모-2,4-디메틸-벤조옥사졸



[1293]

[1294] a) 디클로로메탄 5mL 중의 4-브로모-2-메톡시-6-메틸-페닐아민 0.50g(2.31mmol)을 얼음/에탄올로 냉각시키고, 디클로로메탄 5mL 중의 삼브롬화붕소 0.24mL(2.49mmol)를 서서히 첨가한다. 냉각하에 30 및 실온에서 2시간 동안 계속 교반한다. 상기 혼합물을 얼음으로 붓고, 30분 동안 방치시킨 다음, 수성 층을 디클로로메탄으로 추출한다. 수성상은 혼합물이 염기성 pH를 나타낼 때까지 $NaHCO_3$으로 처리한 다음, 디클로로메탄으로 추출한다. 합한 유기상을 건조시키고 농축시켜 추가의 정제 없이 사용되는 목적 생성물을 수득한다.

[1295] b) 크실렌 30mL 중의 2-아미노-5-브로모-3-메틸-페놀 1.5g(7.42mmol)에 트리에틸아민 1.15mL(8.19mmol), 피리디늄 p-톨루엔설포네이트 0.68g(2.70mmol) 및 아세틸 클로라이드 0.55mL(7.74mmol)를 첨가한다. 상기 혼합물을 3일 동안 환류시킨다. 이어서, 용매는 진공하에 제거하고 잔사는 에틸아세테이트 50mL로 처리한다. 상기 혼합물을 물로 2회 추출한다. 합한 유기 층을 에틸아세테이트로 추출한다. 합한 유기 층은 건조 및 농축시켜 목적 생성물을 수득한다.

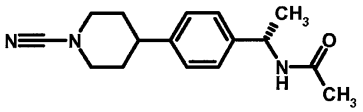
[1296] C_9H_8BrNO (M = 226.1g/mol), ESI-MS: 226 $[M+H]^+$

[1297] R_f (HPLC): 1.55분 (방법 Q)

[1298] **실시예 XXVII**

[1299] 실시예 XXVII.1

[1300] (S)-N-{1-[4-(1-시아노-피페리딘-4-일)-페닐]-에틸}-아세트아미드



[1301]

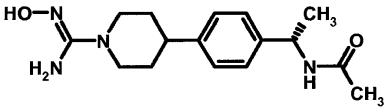
[1302] 시아노겐 브로마이드 1.37g(13.0mmol)을 THF 15mL 및 디클로로메탄 15mL 중의 (S)-N-[1-(4-피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 2.0g(8.12mmol) 및 DIPEA 4.86mL(28.4mmol)의 혼합물에 첨가한다. 상기 혼합물을 실온에서 4시간 동안 교반한다. 그 시간 후, 용매를 진공하에 제거한다. 잔사를 에틸아세테이트에 용해시키고, 상기 혼합물은 물로 세척하며, 유기 층은 농축시킨다. 디에틸 에테르의 첨가 후, 침전을 여과하여 수거한 다음, 디에틸에테르로 세척하여 목적 생성물을 수득한다.

[1303] $C_{16}H_{21}N_3O$ (M = 271.4g/mol), ESI-MS: 272 $[M+H]^+$

[1304] R_f (HPLC): 2.10분 (방법 R)

[1305] 실시예 XXVII.2

[1306] (S)-N-(1-{4-[1-(N-하이드록시카바미미도일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드



[1307]

[1308] 하이드록실아민 하이드로클로라이드 256.4mg(3.69mmol)을 에탄올 20mL 중의 (S)-N-{1-[4-(1-시아노-피페리딘-4-일)-페닐]-에틸}-아세트아미드(XXVII.1) 1.0g(3.69mmol) 및 DIPEA 0.63mL(3.69mmol)의 혼합물에 첨가한다. 상

기 혼합물을 4시간 동안 환류시키고, 하이드록실아민 하이드로클로라이드의 첨가량 50mg을 첨가하여, 2시간 동안 계속해서 환류시킨다. 용매를 진공하에 제거하고, 물을 첨가한다. 이어서, 상기 혼합물을 HPLC(RP C18 Xbridge, 물(+0.1% 암모니아)/MeOH)에 의해 정제하여 목적 생성물을 수득한다.

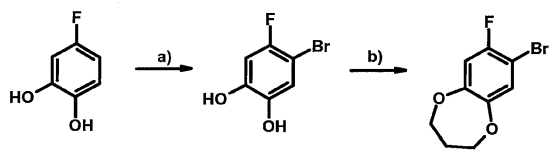
[1309] $C_{16}H_{24}N_4O_2$ (M = 304.4g/mol), ESI-MS: 305 $[M+H]^+$

[1310] R_f (HPLC): 1.89분 (방법 S)

[1311] **실시예 XXVIII**

[1312] 실시예 XXVIII.1

[1313] 7-브로모-8-플루오로-3,4-디하이드로-2H-벤조-[1,4]-디옥세핀

[1314] 

[1315] a) DCM 50mL 중의 4-플루오로카테콜 1.00g(7.57mmol)에 DCM 10mL 중의 브롬 0.58mL(11.4mmol)를 첨가한다. 상기 반응 혼합물을 실온에서 3시간 동안 교반한다. 이어서, 용매를 진공하에 제거하고, 조 생성물은 칼럼 크로마토그래피(실리카 겔, DCM/MeOH 9/1)로 정제한다.

[1316] b) DMF 25mL 중의 4-브로모-5-플루오로벤젠-1,2-디올 1.50g(7.25mmol)에 Cs_2CO_3 5.90g(18.1mmol) 및 1,3-디브로모프로판 0.89mL(8.70mmol)를 첨가한다. 상기 반응 혼합물을 밤새 120℃에서 교반한다. 용매를 진공하에 제거하고, 잔사에 물을 첨가한다. EtOAc로 몇 번 추출한 후, 유기상을 합하고, 포화 수성 NaCl 용액으로 세척하여, $MgSO_4$으로 건조시킨다. 용매를 진공하에 제거하고, 생성된 잔사는 칼럼 크로마토그래피(실리카 겔, PE/EtOAc 9/1 → 7/3)로 정제한다.

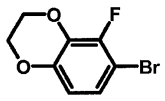
[1317] $C_9H_8BrFO_2$ (M = 247.1g/mol), EI-MS: 246/248 $[M]^+$

[1318] R_f (TLC): 0.50 (실리카 겔, PE/EtOAc 4/1)

[1319] 하기 화합물은 실시예 XXVIII.1과 유사하게 제조한다:

[1320] 실시예 XXVIII.2

[1321] 6-브로모-5-플루오로-2,3-디하이드로-벤조[1,4]디옥신

[1322] 

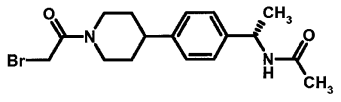
[1323] 반응물: 3-플루오로카테콜(단계 a)/디브로모에탄(단계 b), 단계 b에서 K_2CO_3가 염기로서, ACN이 용매로서 사용된다.

[1324] $C_8H_6BrFO_2$ (M = 233.0g/mol), EI-MS: 232 $[M]^+$

[1325] **실시예 XXIX**

[1326] 실시예 XXIX.1

[1327] (S)-N-{1-[4-(1-(2-브로모아세틸)피페리딘-4-일)-페닐]-에틸}-아세트아미드

[1328] 

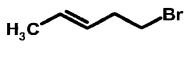
[1329] 브로모아세틸브로마이드 530㎕(6.09mmol)를, 디클로로메탄 20mL 중의 (S)-N-[1-(4-피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 1.50g(6.09mmol) 및 TEA 1.03mL(7.31mmol)의 빙냉 혼합물에 적가한다. 이어서, 냉각을 제거하고, 상기 혼합물은 실온으로 가온한 다음, 물의 첨가에 의해 급냉시킨다. 상기 혼합물을 DCM으로 추출하고, 유기 층을 합하여, 물로 세척하고, $MgSO_4$으로 건조시킨다. 용매를 진공하에 제거하고, 조 생성물은 추가의 정제 없이 사용한다.

[1330] $C_{17}H_{23}BrN_2O_2$ (M = 367.3g/mol); ESI-MS: 367 $[M+H]^+$

[1331] R_t (HPLC): 0.83분 (방법 G)

[1332] **실시예 XXX**

[1333] (E)-5-브로모펜트-2-엔

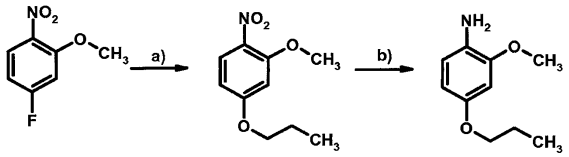
[1334] 

[1335] 0℃에서 1-사이클로프로필에탄올 1.00g(11.6mmol)에 PBr_3 364㎕(3.83mmol)를 주의해서 첨가하고, 상기 혼합물을 실온으로 가온한다. 이어서, 물 1방울을 첨가하고, 상기 혼합물을 염기성 산화알루미늄을 통해 여과한다.

[1336] C_5H_9Br (M = 149.0g/mol); EI-MS: 148 $[M]^+$

[1337] **실시예 XXXI**

[1338] 2-메톡시-4-프로폭시아닐린

[1339] 

[1340] a) 0℃에서 DMF 23mL 중의 4-플루오로-2-메톡시-1-니트로-벤젠 1.80g(10.5mmol) 및 1-프로판올 0.87mL(11.6mmol)에 NaH 278mg(11.6mmol)을 첨가한다. 상기 반응 혼합물을 0℃에서 30분 동안 교반한 다음, 실온으로 가온한다. 반응은 물의 첨가에 의해 급냉시킨다. 생성된 혼합물은 EtOAc로 추출한다. 유기 층을 물로 2회 세척하고, $MgSO_4$으로 건조시킨다. 용매를 진공하에 제거하고 잔사는 HPLC(RP C18 Xbridge, 물(+0.3% 암모니아)/MeOH)에 의해 정제한다.

[1341] b) 20mL EtOAc 중의 2-메톡시-1-니트로-4-프로폭시벤젠 1.40g(6.63mmol)을 Pd/C(5%) 100mg으로 충전시키고, 실온에서 50psi의 수소 압력으로 수소화시킨다. 상기 혼합물을 여과하고, 용매를 진공하에 제거한다. 조 생성물은 추가의 정제 없이 사용한다.

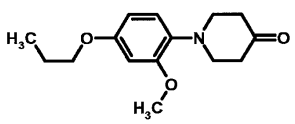
[1342] $C_{10}H_{15}NO_2$ (M = 181.2g/mol); EI-MS: 182 $[M]^+$

[1343] R_t (HPLC): 1.50분 (방법 F)

[1344] **실시예 XXXII**

[1345] 실시예 XXXII.1

[1346] 1-(2-메톡시-4-프로폭시페닐)피페리딘-4-온

[1347] 

[1348] 8.5mL EtOH 및 1.8mL 물 중의 2-메톡시-4-프로폭시아닐린(실시예 XXXI) 1.20g(6.62mmol)을 환류하에 교반한다.

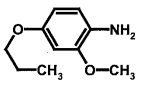
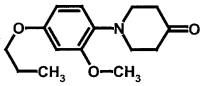
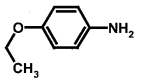
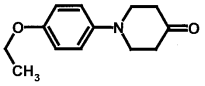
30분 동안, N-메틸-N-벤질-4-옥소피페리디늄 요오다이드(Org. Lett. 1999, 1, 1261-1262) 2.19g(6.62mmol)을 몇 개의 분획으로 첨가한다. 환류하에 교반을 1시간 동안 계속한다. 이어서, 상기 반응 혼합물은 물 및 DCM을 첨가하기 전에 실온으로 냉각시킨다. 층을 분리하고, 유기 층은 $MgSO_4$으로 건조시키며, 여과하여, 용매를 진공하에 제거한다. 생성된 잔사는 칼럼 크로마토그래피(실리카 겔, PE/EtOAc 8/2)로 정제한다.

[1349] $C_{15}H_{21}NO_3$ (M = 263.3g/mol); ESI-MS: 264 $[M+H]^+$

[1350] R_t (HPLC): 1.80분 (방법 F)

[1351] 하기 화합물들은 실시예 XXXII.1과 유사하게 제조한다.

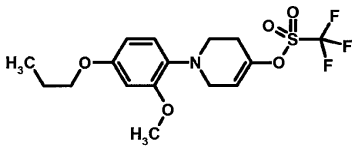
[1352]

실시예	출발 물질	생성물 구조	질량 스펙트럼 결과	R_t (HPLC) [분] (방법)
XXXII.1			264 $[M+H]^+$	1.80 (F)
XXXII.2			220 $[M+H]^+$	1.63 (A)

[1353] **실시예 XXXIII**

[1354] 실시예 XXXIII.1

[1355] 1-(2-메톡시-4-프로폭시페닐)-1,2,3,6-테트라하이드로피리딘-4-일 트리플루오로메탄설포네이트

[1356] 

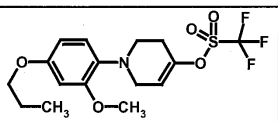
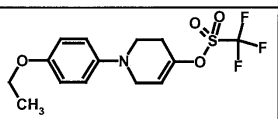
[1357] -70℃에서 THF 6mL 중의 실시예 XXXII.1 0.60g(2.28mmol) 및 N,N-비스-(트리플루오로메탄설포닐)-아닐린 0.85g(2.39mmol)에 1시간에 걸쳐 나트륨 비스(트리메틸실릴)아미드(c = 1.0mol/ℓ) 2.51mL(2.51mmol)를 첨가한다. 냉각을 제거하고, 상기 혼합물을 실온으로 가온한다. 수성 반-포화 $NaHCO_3$ 용액을 첨가하고, 생성된 혼합물을 DCM으로 2회 추출한다. 유기 층을 합하고, $MgSO_4$으로 건조시키며, 용매를 진공하에 제거한다. 생성된 잔사는 칼럼 크로마토그래피(실리카 겔, PE/EtOAc 8/2)로 정제한다.

[1358] $C_{16}H_{20}F_3NO_5S$ (M = 395.4g/mol); ESI-MS: 396 $[M+H]^+$

[1359] R_t (HPLC): 1.68분 (방법 F)

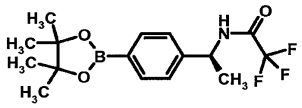
[1360] 하기 화합물들은 실시예 XXXIII.1과 유사하게 제조한다.

[1361]

실시예	출발 물질	생성물 구조	질량 스펙트럼 결과	R_t (HPLC) [분] (방법)
XXXIII.1	XXXII.1		396 $[M+H]^+$	1.68 (F)
XXXIII.2	XXXII.2		352 $[M+H]^+$	2.20 (A)

[1362] **실시예 XXXIV**

[1363] (S)-2,2,2-트리플루오로-N-{1-[4-(4,4,5,5-테트라메틸-1,3,2-디옥사보롤란-2-일)페닐]-에틸}-아세트아미드

[1364] 

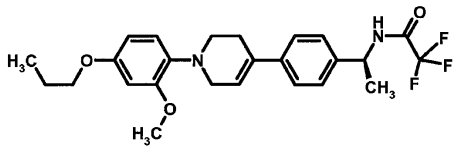
[1365] DMSO 130mL에, (S)-N-(1-(4-브로모페닐)에틸)-2,2,2-트리플루오로아세트아미드 13.0g(43.9mmol) 및 KOAc 14.5g(148mmol)을 첨가한다. 상기 혼합물을 탈기시킨 후, 비스(피나콜라토)디보론 13.7g(52.9mmol) 및 $PdCl_2(dppf)*CH_2Cl_2$ 1.10mg(1.35mmol)을 첨가하고, 상기 혼합물을 3시간 동안 90℃에서 교반한다. EtOAc 350mL 및 물 100mL를 첨가하고, 생성된 혼합물을 셀라이트 상에서 여과한다. 유기 층을 분리하고, 물로 2회 및 포화 수성 NaCl 용액으로 2회 세척한다. 유기상을 $MgSO_4$으로 건조시키고, 용매는 진공하에 제거한다. 조 생성물은 칼럼 크로마토그래피(실리카 겔, CyH/EtOAc 95/5 → 1/1)로 정제한다.

[1366] $C_{16}H_{21}BF_3NO_3$ (M = 343.2g/mol); ESI-MS: 361 $[M+NH_4]^+$

[1367] **실시예 XXXV**

[1368] 실시예 XXXV.1

[1369] (S)-2,2,2-트리플루오로-N-{1-[4-(1-(2-메톡시-4-프로폭시페닐)-1,2,3,6-테트라하이드로피리딘-4-일)페닐]-에틸}-아세트아미드

[1370] 

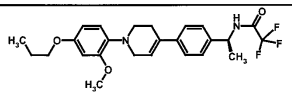
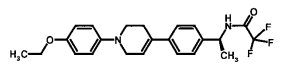
[1371] 디옥산 6mL 및 MeOH 6mL 중의 실시예 XXXIII.1 0.30g(0.76mmol) 및 실시예 XXXIV 260mg(0.76mmol)에 수성 Na_2CO_3 용액(c = 2mol/L) 0.76mL(1.52mmol) 및 $Pd(PPh_3)Cl_2$ 21.3mg(0.03mmol)을 첨가한다. 상기 반응 혼합물을 3시간 동안 95℃에서 교반한다. 물 및 DCM을 첨가하고, 층을 분리한다. 유기 층을 $MgSO_4$으로 건조시키고, 용매는 진공하에 제거한다. 생성된 잔사는 HPLC(RP C18 Xbridge, 물(+0.3% 암모니아)/MeOH)로 정제한다.

[1372] $C_{25}H_{29}F_3N_2O_3$ (M = 462.5g/mol); ESI-MS: 463 $[M+H]^+$

[1373] R_t (HPLC): 2.20 (방법 F)

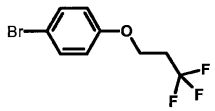
[1374] 하기 화합물들은 실시예 XXXV.1과 유사하게 제조한다.

[1375]

실시예	출발 물질	생성물 구조	질량 스펙트럼 결과	R_t (HPLC) [분] (방법)
XXXV.1	XXXIII.1		463 $[M+H]^+$	2.20 (F)
XXXV.2	XXXIII.2		419 $[M+H]^+$	2.16 (A)

[1376] **실시예 XXXVI**

[1377] 1-브로모-4-(3,3,3-트리플루오로프로폭시)벤젠

[1378] 

[1379] 4-브로모페놀 3.81g(22.0mmol), 3,3,3-트리플루오로-1-프로판올 2.76g(24.2mmol) 및 트리페닐포스핀 5.77g(22.0mmol)을 DCM 50mL에 첨가하고, 0℃로 냉각시킨다. 이어서, 디-이소-프로필 아조디카복실레이트 4.55mL(22.0mmol)를 첨가하고, 상기 혼합물을 실온으로 가온시킨 다음, 밤새 계속 교반한다. 이어서, 상기 반응 혼합물을 물로 붓고, DCM으로 추출한다. 유기 층을 합하고, Na_2SO_4으로 건조시키고, 여과하고, 용매는 진공하에 제거한다. 상기 잔사는 플래시 크로마토그래피(실리카 겔, PE/EtOAc 8/2)를 사용하여 정제한다.

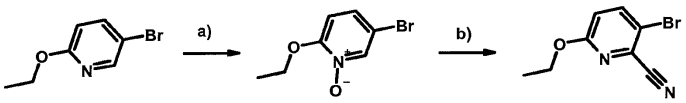
[1380] $C_9H_8BrF_3O$ (M = 269.1g/mol); ESI-MS: 301 $[M+MeOH+H]^+$

[1381] R_t (HPLC): 1.90분 (방법 A)

[1382] **실시예 XXXVII**

[1383] 실시예 XXXVII.1

[1384] 3-브로모-6-에톡시-피리딘-2-카보니트릴

[1385] 

[1386] a) DCM 100mL 중의 3-브로모-6-에톡시-피리딘 4.50g(22.3mmol)에 mCPBA 20.5g(89.1mmol)을 여러 개의 분획으로 첨가한다. 상기 반응 혼합물을 밤새 실온에서 교반하고, $MgSO_4$으로 충전하여, 염기성 산화알루미늄 100g 상에서 여과한다. 용매는 DCM 및 수성 $NaHCO_3$ 용액을 첨가하기 전에 진공하에 제거하고, 층을 분리한다. 수성 층을 NaCl로 포화시키고, DCM으로 몇 회 추출한다. 유기 층을 합하고, 용매는 진공하에 제거한다. 상기 잔사는 실리카 겔의 플러그를 통해 여과한다.

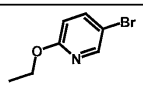
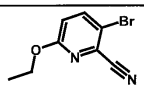
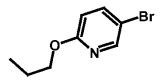
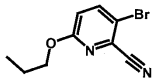
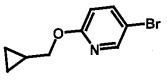
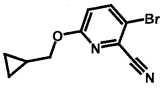
[1387] b) 10mL ACN 중의 5-브로모-2-에톡시-피리딘-1-옥사이드 1.00g(4.59mmol), 트리메틸실릴 시아니드 2.46mL(18.3mmol) 및 TEA 1.92mL(13.8mmol)를 24시간 동안 100℃에서 함께 교반한다. 이어서, 휘발성 성분을 진공하에 제거하고 잔사는 DCM에 용해시켜, 수성 $NaHCO_3$ 용액으로 세척하고, $MgSO_4$으로 건조시켜, 실리카 겔의 플러그를 통해 여과한다. 이어서, 용매를 진공하에 제거한다.

[1388] $C_8H_7BrN_2O$ (M = 227.1g/mol), ESI-MS: 227 $[M+H]^+$

[1389] R_f (TLC): 0.85 (실리카 겔, PE/EtOAc 7/3)

[1390] 하기 화합물들은 실시예 XXXVII.1과 유사하게 제조한다.

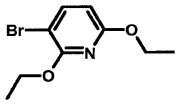
[1391] 실시예 XXXVII.2 및 XXXVII.3의 경우, 단계 a로부터의 중간체는 염기성 산화알루미늄 상에서 여과한 후 HPLC로 정제한다.

실시예	출발 물질	생성물 구조	질량 스펙트럼 결과	R_t (HPLC) [분] (방법)
XXXVII.1			227 $[M+H]^+$	n.d.
XXXVII.2			241 $[M+H]^+$	1.09 (G)
XXXVII.3			253 $[M+H]^+$	1.08 (G)

[1392]

[1393] **실시예 XXXVIII**

[1394] 3-브로모-2,6-디에톡시-피리딘

[1395] 

[1396] DMF 1mL 중의 에탄올 59.1㎕(1.00mmol)에 NaH 25.3mg(1.00mmol)에 이어서, 3-브로모-6-클로로-피리딘-2-카보니트릴 109mg(0.50mmol)을 첨가한다. 생성된 혼합물을 1시간 동안 50℃에서 교반한다. 이어서, 상기 반응 혼합물을 물로 붓고, TBME로 추출한다. 유기 층을 합하고, $MgSO_4$으로 건조시키고, 여과하고, 용매를 진공하에 제거한다.

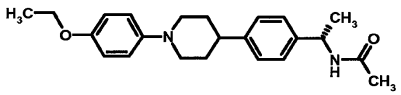
[1397] $C_9H_{12}BrNO_2$ (M = 246.1g/mol), ESI-MS: 246 $[M+H]^+$

[1398] **최종 화합물의 제조**

[1399] **실시예 1**

[1400] 실시예 1.1

[1401] (S)-N-(1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1402] 

[1403] (S)-N-[1-(피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 147mg(0.60mmol)을, 1,4-디옥산 2.0mL 중의 1-브로모-4-에톡시-벤젠 100mg(0.50mmol), 나트륨 3급-부티레이트 197mg(2.00mmol), 2-(디-3급-부틸포스피노)비페닐 59mg(0.20mmol) 및 트리스-(디벤질리덴아세톤)-디팔라듐(0) 46mg(0.05mmol)의 혼합물에 첨가한다. 상기 혼합물을 4시간 동안 45℃에서 교반한다. 그 시간 후, 상기 혼합물을 셀라이트 상에서 여과한다. 용매를 여액으로부터 진공하에 제거한다. 상기 잔사는 HPLC(칼럼: Waters XBridge 5μM; 용출제 A: 물 + 0.3% NH_4OH, 용출제 B: MeOH)로 정제하여 목적 생성물을 수득한다.

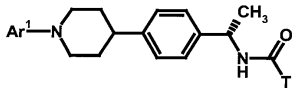
[1404] $C_{23}H_{30}N_2O_2$ (M = 366.5g/mol)

[1405] ESI-MS: 367 $[M+H]^+$

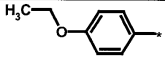
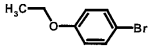
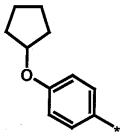
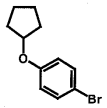
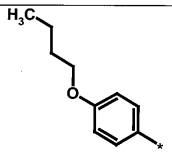
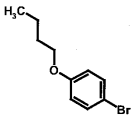
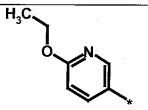
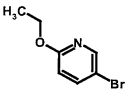
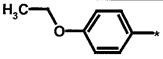
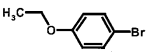
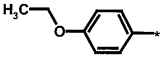
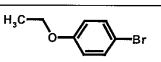
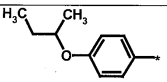
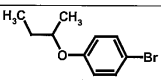
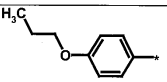
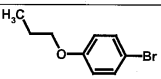
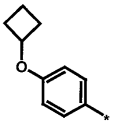
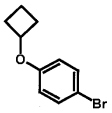
[1406] R_t (HPLC): 2.11분 (방법 A)

[1407] 하기 화학식 1-1의 화합물은 실시예 1.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다. 또는, 120℃ 이하의 반응 온도 및 120℃ 이하의 마이크로웨이브 오븐에서의 가열이 하기 실시예에서 반응 조건으로서 사용된다. 예를 들면, 실시예 1.177의 경우, 반응 온도는 110℃이고; 실시예 1.184 및 1.185의 경우, 반응 조건은 마이크로웨이브 오븐에서 80℃에서 45분이다.

[1408] [화학식 1-1]

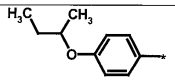
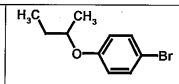
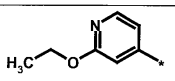
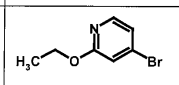
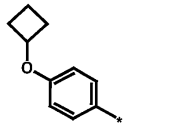
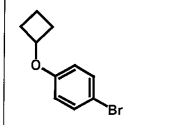
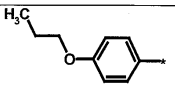
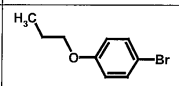
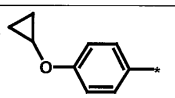
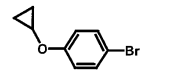
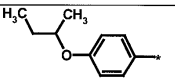
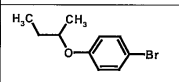
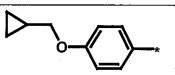
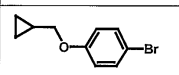
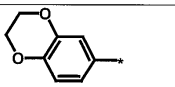
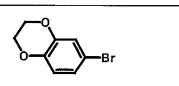
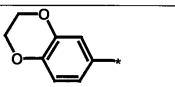
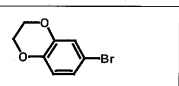
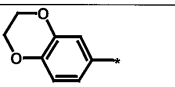
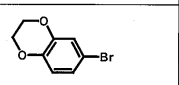
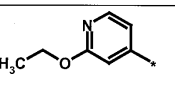
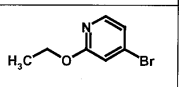
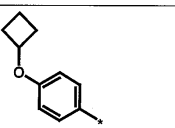
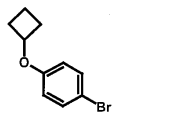
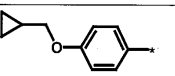
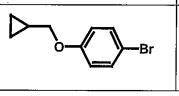


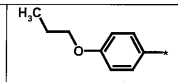
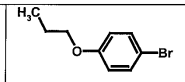
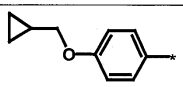
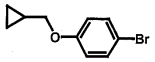
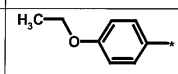
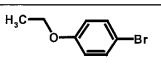
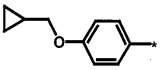
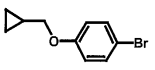
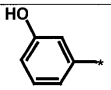
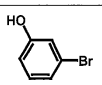
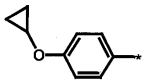
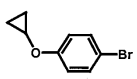
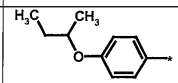
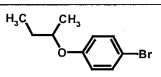
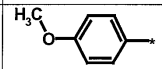
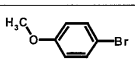
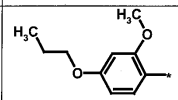
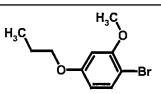
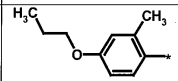
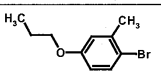
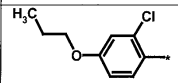
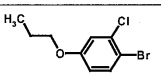
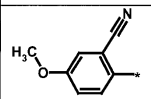
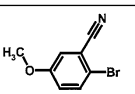
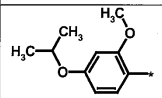
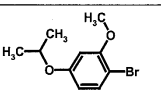
[1409]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t (HPLC) [분] (방법)
1.1				V.1	367 $[M+H]^+$	2.11 (A)
1.2				V.1	407 $[M+H]^+$	2.30 (A)
1.3				V.1	395 $[M+H]^+$	2.30 (A)
1.4				V.1	368 $[M+H]^+$	2.03 (A)
1.5				V.2	383 $[M+H]^+$	2.18 (A)
1.6				V.3	396 $[M+H]^+$	2.13 (A)
1.7				V.3	424 $[M+H]^+$	2.26 (A)
1.8				V.3	410 $[M+H]^+$	2.22 (A)
1.9				V.4	419 $[M+H]^+$	2.26 (A)

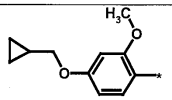
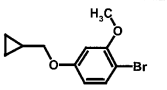
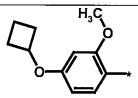
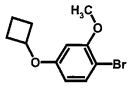
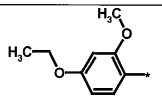
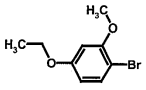
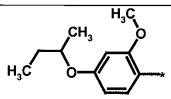
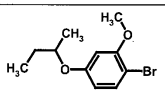
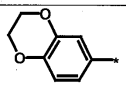
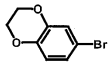
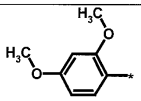
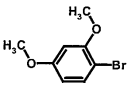
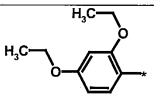
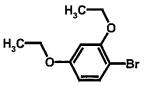
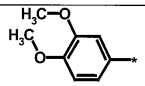
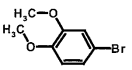
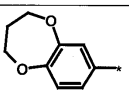
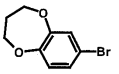
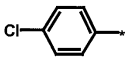
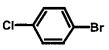
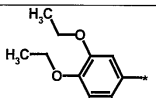
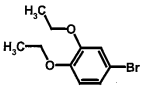
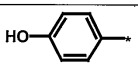
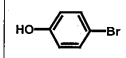
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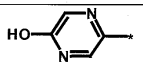
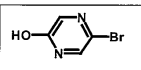
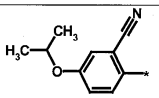
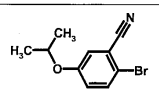
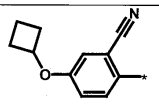
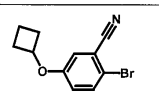
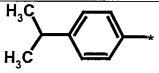
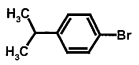
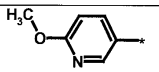
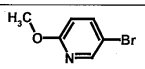
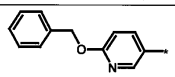
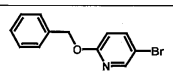
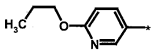
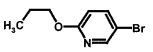
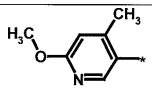
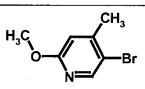
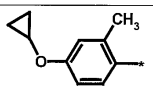
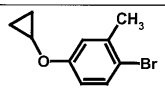
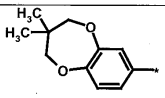
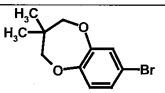
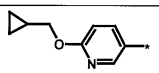
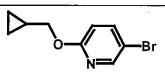
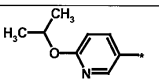
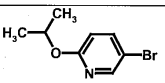
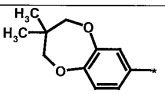
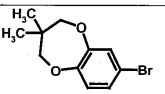
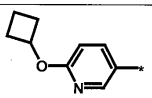
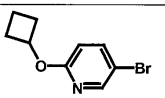
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1.11				V.2	384 [M+H]+	2.06 (A)
1.12				V.2	409 [M+H]+	2.27 (A)
1.13				V.2	397 [M+H]+	2.26 (A)
1.14				V.4	405 [M+H]+	2.18 (A)
1.15				V.2	411 [M+H]+	2.29 (A)
1.16				V.4	419 [M+H]+	2.22 (A)
1.17				V.2	397 [M+H]+	2.07 (A)
1.18				V.3	410 [M+H]+	2.01 (A)
1.19				V.4	407 [M+H]+	2.04 (A)
1.20				V.4	394 [M+H]+	2.04 (A)
1.21				V.3	422 [M+H]+	2.24 (A)
1.22				V.2	409 [M+H]+	2.24 (A)

1.23				V.4	407 $[M+H]^+$	2.25 (A)
1.24				V.3	422 $[M+H]^+$	2.20 (A)
1.25				V.4	393 $[M+H]^+$	2.16 (A)
1.26				V.1	393 $[M+H]^+$	2.16 (A)
1.27				V.1	339 $[M+H]^+$	1.79 (A)
1.28				V.1	379 $[M+H]^+$	2.19 (A)
1.29				V.1	395 $[M+H]^+$	2.25 (A)
1.30				V.1	353 $[M+H]^+$	2.03 (A)
1.31				V.1	411 $[M+H]^+$	2.21 (A)
1.32				V.1	395 $[M+H]^+$	2.46 (A)
1.33				V.1	415 $[M+H]^+$	2.39 (A)
1.34				V.1	378 $[M+H]^+$	2.10 (A)
1.35				V.1	411 $[M+H]^+$	2.20 (A)

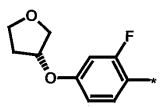
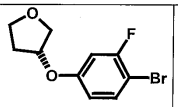
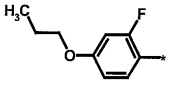
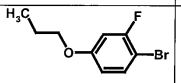
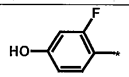
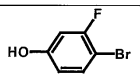
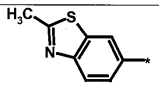
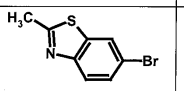
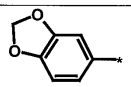
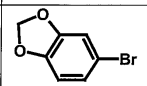
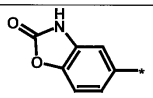
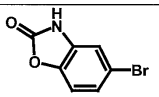
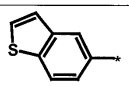
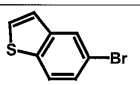
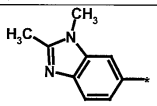
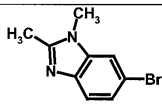
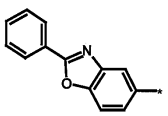
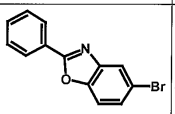
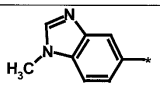
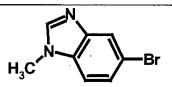
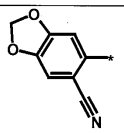
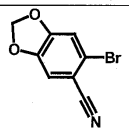
[1412]

1.36		*—CH_3		V.1	423 $[M+H]^+$	2.22 (A)
1.37		*—CH_3		V.1	423 $[M+H]^+$	2.26 (A)
1.38		*—CH_3		V.1	397 $[M+H]^+$	2.15 (A)
1.39		*—CH_3		V.1	425 $[M+H]^+$	2.28 (A)
1.40		*—CH_3		V.1	381 $[M+H]^+$	1.99 (A)
1.41		*—CH_3		V.1	383 $[M+H]^+$	2.06 (A)
1.42		*—CH_3		V.1	411 $[M+H]^+$	2.23 (A)
1.43		*—CH_3		V.1	383 $[M+H]^+$	1.85 (A)
1.44		*—CH_3		V.1	395 $[M+H]^+$	2.00 (A)
1.45		*—CH_3		V.1	323 $[M+H]^+$	2.08 (A)
1.46		*—CH_3		V.1	357 $[M+H]^+$	2.21 (A)
1.47		*—CH_3		V.1	411 $[M+H]^+$	2.14 (A)
1.48		*—CH_3		V.1	339 $[M+H]^+$	1.70 (A)

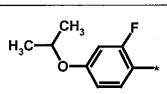
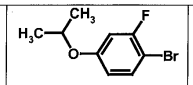
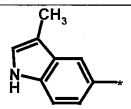
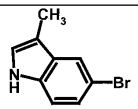
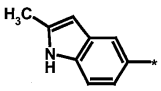
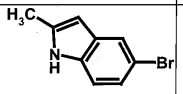
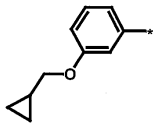
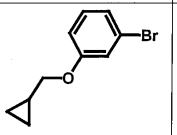
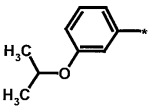
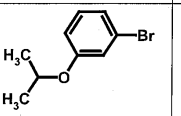
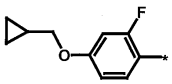
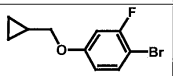
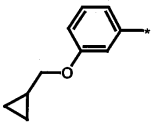
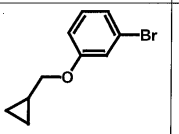
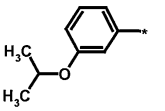
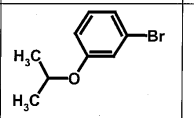
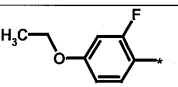
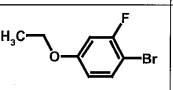
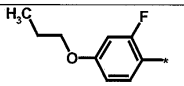
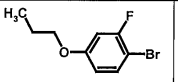
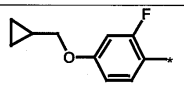
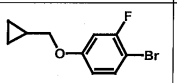
[1413]

1.49		*—CH_3		V.1	341 $[M+H]^+$	1.15 (A)
1.50		*—CH_3		V.1	406 $[M+H]^+$	2.18 (A)
1.51		*—CH_3		V.1	418 $[M+H]^+$	2.25 (A)
1.52		*—CH_3		V.1	365 $[M+H]^+$	2.32 (A)
1.53		*—CH_3		V.1	354 $[M+H]^+$	1.90 (A)
1.54		*—CH_3		V.1	430 $[M+H]^+$	2.21 (A)
1.55		*—CH_3		V.1	382 $[M+H]^+$	2.11 (A)
1.56		*—CH_3		V.1	368 $[M+H]^+$	2.09 (A)
1.57		*—$N(CH_3)_2$		V.3	422 $[M+H]^+$	2.30 (A)
1.58		*—$N(CH_3)_2$		V.3	452 $[M+H]^+$	2.21 (A)
1.59		*—CH_3		V.1	394 $[M+H]^+$	2.08 (A)
1.60		*—CH_3		V.1	382 $[M+H]^+$	2.06 (A)
1.61		*—CH_3		V.1	423 $[M+H]^+$	2.19 (A)
1.62		*—CH_3		V.1	394 $[M+H]^+$	2.03 (F)

[1414]

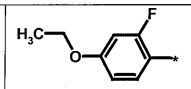
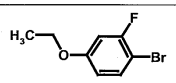
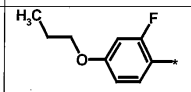
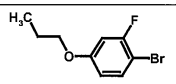
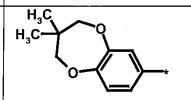
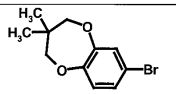
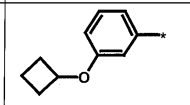
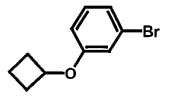
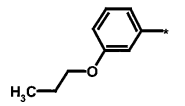
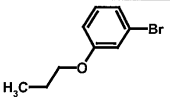
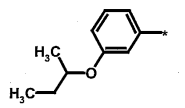
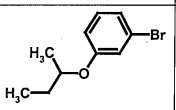
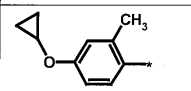
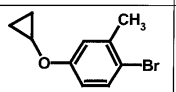
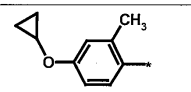
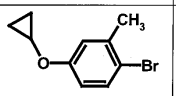
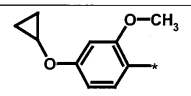
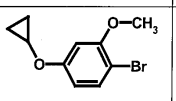
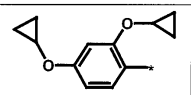
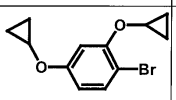
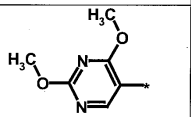
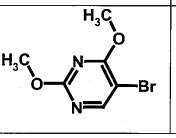
1.63		*—CH_3		V.1	427 $[M+H]^+$	1.90 (F)
1.64		*—CH_3		V.1	399 $[M+H]^+$	2.18 (F)
1.65		*—CH_3		V.1	357 $[M+H]^+$	1.02 (F)
1.66		*—CH_3		V.1	394 $[M+H]^+$	1.93 (F)
1.67		*—CH_3		V.1	367 $[M+H]^+$	1.90 (F)
1.68		*—CH_3		V.1	380 $[M+H]^+$	1.37 (F)
1.69		*—CH_3		V.1	379 $[M+H]^+$	2.08 (F)
1.70		*—CH_3		V.1	391 $[M+H]^+$	1.70 (F)
1.71		*—CH_3		V.1	440 $[M+H]^+$	2.21 (F)
1.72		*—CH_3		V.1	377 $[M+H]^+$	1.65 (F)
1.73		*—CH_3		V.1	392 $[M+H]^+$	1.88 (F)

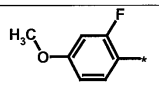
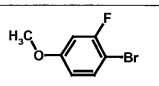
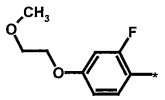
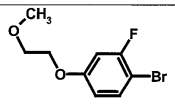
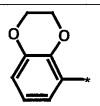
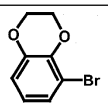
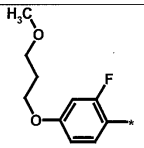
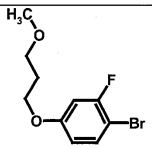
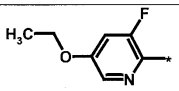
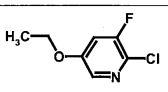
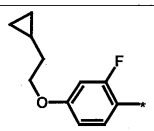
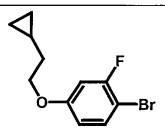
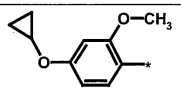
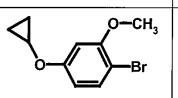
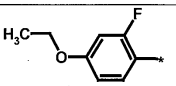
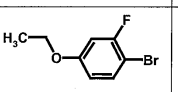
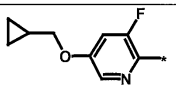
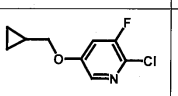
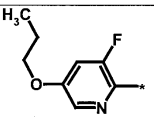
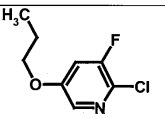
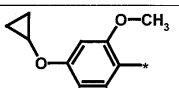
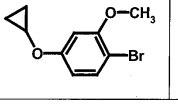
[1415]

1.74				V.1	399 $[M+H]^+$	2.14 (A)
1.75				V.1	376 $[M+H]^+$	1.23 (G)
1.76				V.1	376 $[M+H]^+$	1.23 (G)
1.77				V.4	419 $[M+H]^+$	1.28 (G)
1.78				V.4	407 $[M+H]^+$	1.26 (G)
1.79				V.4	437 $[M+H]^+$	1.30 (G)
1.80				V.3	422 $[M+H]^+$	1.27 (G)
1.81				V.3	410 $[M+H]^+$	1.26 (G)
1.82				V.4	411 $[M+H]^+$	1.25 (G)
1.83				V.4	425 $[M+H]^+$	1.31 (G)
1.84				V.3	440 $[M+H]^+$	1.28 (G)

[1416]

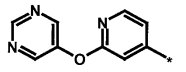
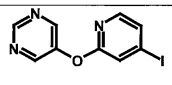
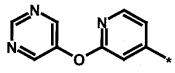
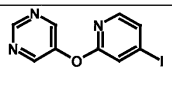
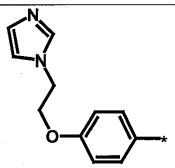
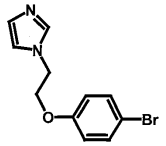
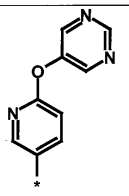
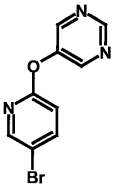
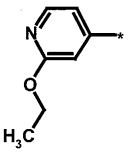
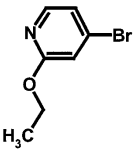
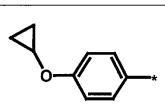
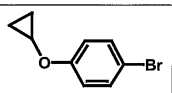
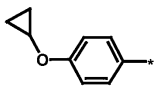
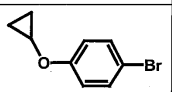
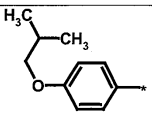
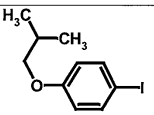
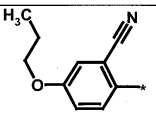
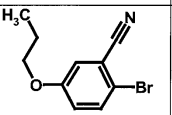
[1417]

1.85				V.3	414 [M+H]+	1.24 (G)
1.86				V.3	428 [M+H]+	1.33 (G)
1.87				V.4	449 [M+H]+	1.30 (G)
1.88				V.1	393 [M+H]+	1.29 (G)
1.89				V.1	381 [M+H]+	1.30 (G)
1.90				V.1	395 [M+H]+	1.29 (G)
1.91				V.4	419 [M+H]+	1.36 (G)
1.92				V.1	393 [M+H]+	1.29 (G)
1.93				V.4	435 [M+H]+	1.26 (G)
1.94				V.1	435 [M+H]+	1.01 (G)
1.95				V.1	385 [M+H]+	1.03 (G)

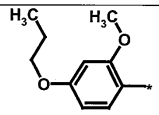
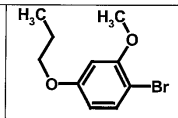
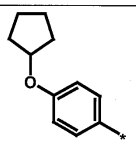
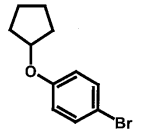
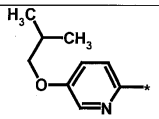
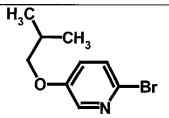
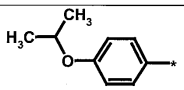
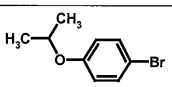
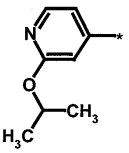
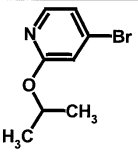
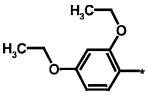
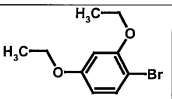
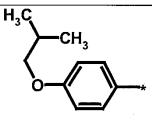
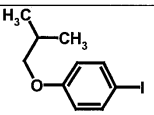
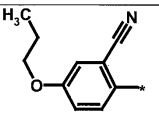
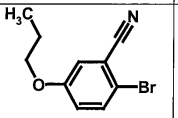
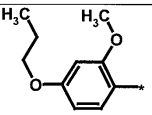
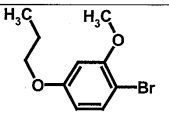
1.96		*—CH_3		V.1	371 $[M+H]^+$	1.99 (A)
1.97		*—CH_3		V.1	415 $[M+H]^+$	2.10 (F)
1.98		*—CH_3		V.1	381 $[M+H]^+$	2.13 (F)
1.99		*—CH_3		V.1	429 $[M+H]^+$	1.30 (L)
1.100		*—CH_3		V.1	386 $[M+H]^+$	1.31 (L)
1.101		*—CH_3		V.1	425 $[M+H]^+$	1.45 (L)
1.102		*—CH_3		V.1	409 $[M+H]^+$	2.06 (F)
1.103		*—CH_3		V.1	385 $[M+H]^+$	2.17 (F)
1.104		*—CH_3		V.1	412 $[M+H]^+$	1.36 (L)
1.105		*—CH_3		V.1	400 $[M+H]^+$	1.37 (L)
1.106				V.3	438 $[M+H]^+$	1.37 (L)

[1418]

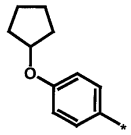
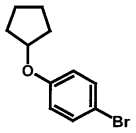
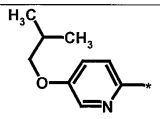
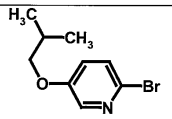
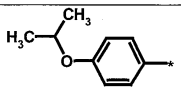
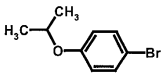
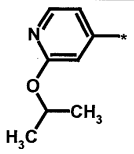
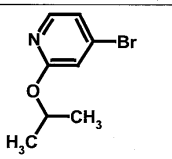
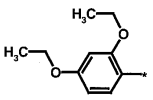
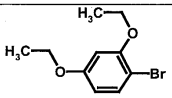
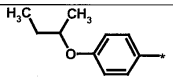
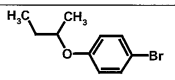
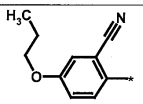
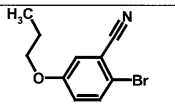
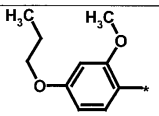
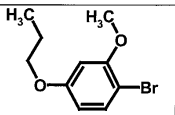
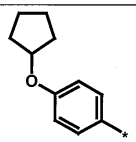
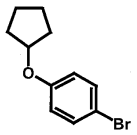
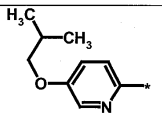
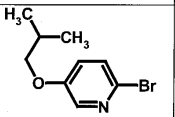
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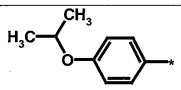
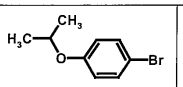
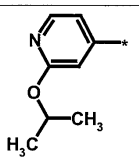
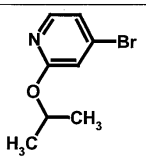
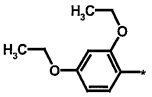
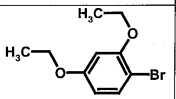
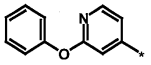
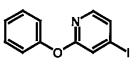
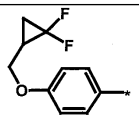
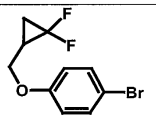
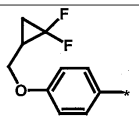
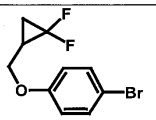
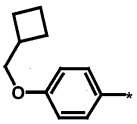
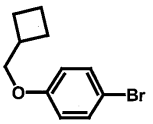
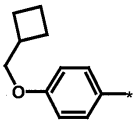
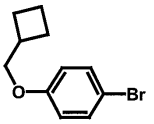
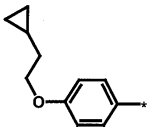
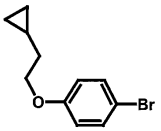
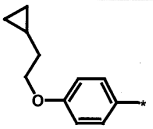
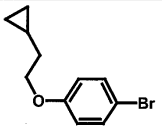
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1.108				V.4	444 $[M+H]^+$	1.19 (L)
1.109				V.1	433 $[M+H]^+$	1.17 (L)
1.110				V.1	418 $[M+H]^+$	1.16 (L)
1.111				V.3	397 $[M+H]^+$	1.99 (A)
1.112				V.3	408 $[M+H]^+$	2.14 (A)
1.113				V.2	395 $[M+H]^+$	2.20 (A)
1.114				V.4	421 $[M+H]^+$	2.30 (L)
1.115				V.4	432 $[M+H]^+$	2.15 (F)

[1420]

1.116				V.4	437 $[M+H]^+$	2.17 (F)
1.117				V.4	433 $[M+H]^+$	1.33 (G)
1.118				V.4	422 $[M+H]^+$	2.22 (A)
1.119				V.4	407 $[M+H]^+$	2.18 (A)
1.120				V.4	408 $[M+H]^+$	2.09 (A)
1.121				V.4	437 $[M+H]^+$	2.12 (A)
1.122				V.3	424 $[M+H]^+$	2.28 (A)
1.123				V.3	435 $[M+H]^+$	2.15 (F)
1.124				V.3	440 $[M+H]^+$	2.15 (F)

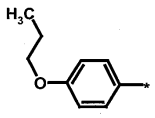
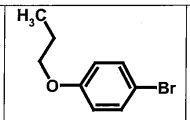
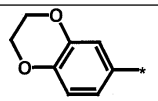
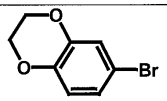
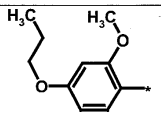
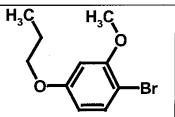
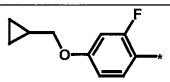
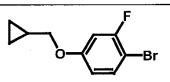
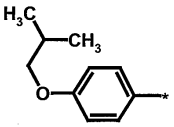
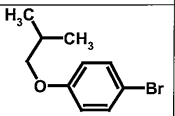
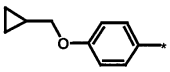
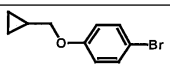
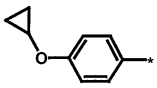
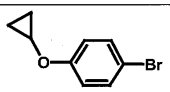
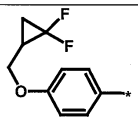
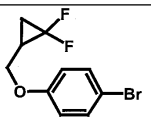
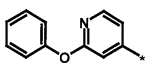
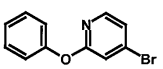
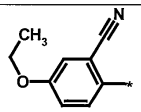
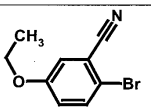
[1421]

1.125				V.3	436 $[M+H]^+$	1.82 (G)
1.126				V.3	425 $[M+H]^+$	2.20 (A)
1.127				V.3	410 $[M+H]^+$	2.15 (A)
1.128				V.3	411 $[M+H]^+$	2.06 (A)
1.129				V.3	440 $[M+H]^+$	2.09 (A)
1.130				V.2	411 $[M+H]^+$	2.31 (A)
1.131				V.2	422 $[M+H]^+$	2.16 (F)
1.132				V.2	427 $[M+H]^+$	2.22 (F)
1.133				V.2	423 $[M+H]^+$	2.31 (A)
1.134				V.2	412 $[M+H]^+$	2.23 (A)

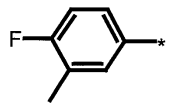
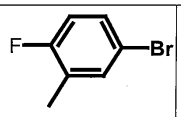
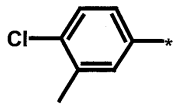
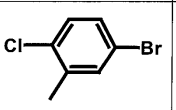
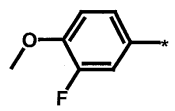
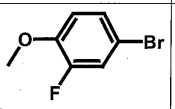
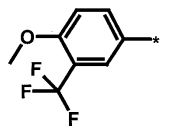
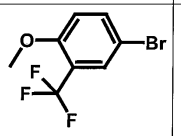
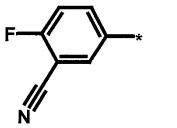
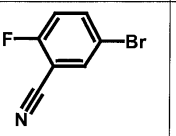
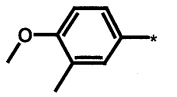
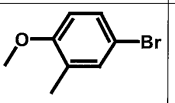
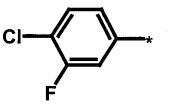
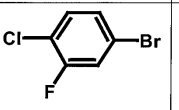
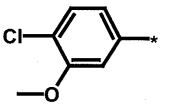
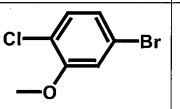
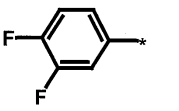
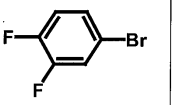
1.135				V.2	397 $[M+H]^+$	2.19 (A)
1.136				V.2	398 $[M+H]^+$	2.11 (A)
1.137				V.2	427 $[M+H]^+$	2.07 (F)
1.138				V.3	445 $[M+H]^+$	1.30 (G)
1.139				V.4	455 $[M+H]^+$	1.23 (G)
1.140				V.3	458 $[M+H]^+$	1.21 (G)
1.141				V.4	433 $[M+H]^+$	1.35 (G)
1.142				V.3	436 $[M+H]^+$	1.34 (G)
1.143				V.4	433 $[M+H]^+$	1.34 (G)
1.144				V.3	436 $[M+H]^+$	1.32 (G)

[1422]

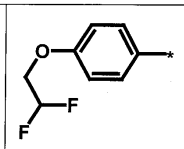
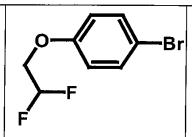
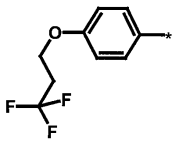
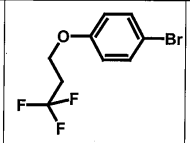
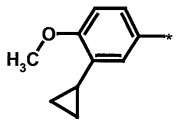
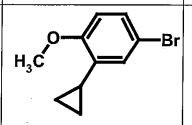
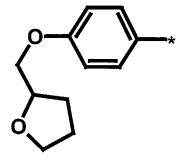
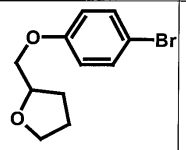
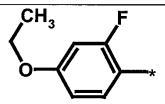
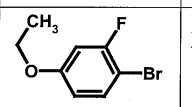
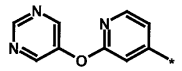
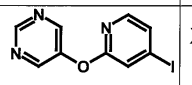
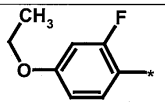
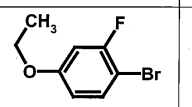
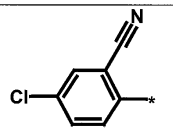
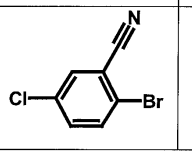
[1423]

1.145				XXIII.1	395 $[M+H]^+$	1.18 (N)
1.146				XXIII.1	395 $[M+H]^+$	1.04 (N)
1.147				XXIII.1	425 $[M+H]^+$	1.19 (N)
1.148				XXIII.1	425 $[M+H]^+$	1.40 (O)
1.149				XXIII.1	409 $[M+H]^+$	1.29 (O)
1.150				XXIII.1	407 $[M+H]^+$	1.16 (N)
1.151				XXIII.1	393 $[M+H]^+$	1.12 (N)
1.152				XXIII.1	443 $[M+H]^+$	1.16 (N)
1.153				XXIII.1	430 $[M+H]^+$	1.18 (N)
1.154				XXIII.1	406 $[M+H]^+$	1.64 (N)

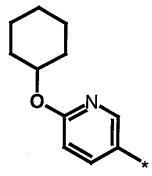
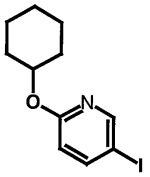
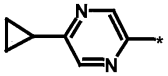
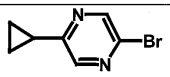
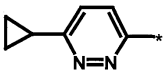
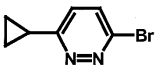
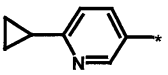
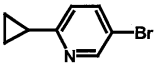
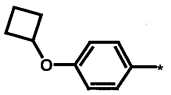
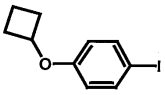
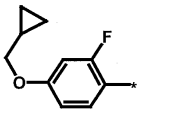
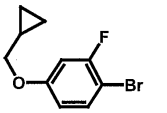
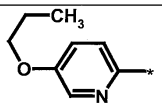
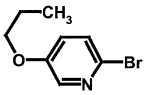
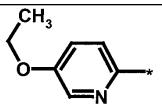
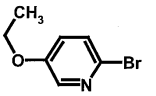
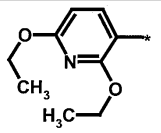
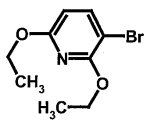
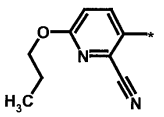
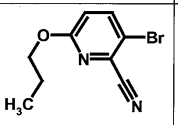
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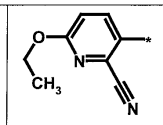
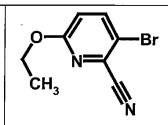
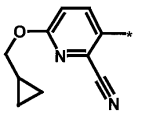
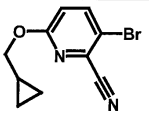
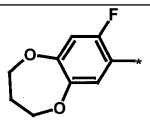
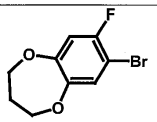
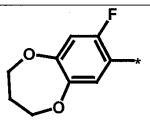
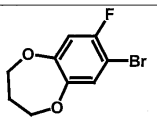
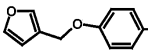
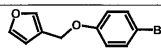
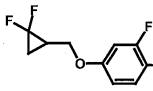
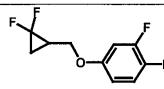
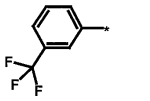
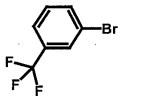
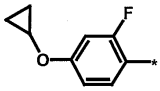
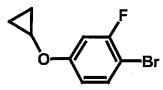
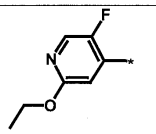
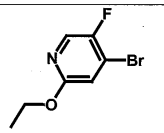
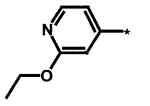
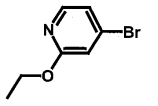
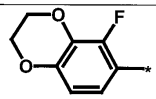
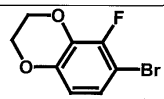
1.155				V.1	355 $[M+H]^+$	1.43 (AA)
1.156				V.1	371 $[M+H]^+$	1.51 (AA)
1.157				V.1	371 $[M+H]^+$	1.31 (AA)
1.158				V.1	841 $[2M+H]^+$	1.41 (AA)
1.159				V.1	366 $[M+H]^+$	1.31 (AA)
1.160				V.1	367 $[M+H]^+$	1.36 (AA)
1.161				V.1	375 $[M+H]^+$	1.45 (AA)
1.162				V.1	387 $[M+H]^+$	1.39 (AA)
1.163				V.1	359 $[M+H]^+$	1.38 (AA)

[1425]

1.164				V.1	403 $[M+H]^+$	1.33 (AA)
1.165				V.1	435 $[M+H]^+$	1.40 (AA)
1.166				V.1	393 $[M+H]^+$	1.13 (N)
1.167				V.1	423 $[M+H]^+$	1.05 (N)
1.168				XXIII. 1	399 $[M+H]^+$	1.32 (N)
1.169				XXIII. 1	432 $[M+H]^+$	1.10 (N)
1.170				V.2	401 $[M+H]^+$	1.36 (N)
1.171				V.1	382 $[M+H]^+$	1.20 (G)

[1426]

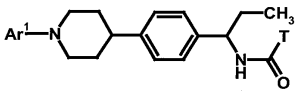
1.172		*—CH_3		V.1	422 $[M+H]^+$	1.35 (G)
1.173		*—CH_3		V.1	365 $[M+H]^+$	1.51 (N)
1.174		*—CH_3		V.1	365 $[M+H]^+$	0.99 (N)
1.175		*—CH_3		V.1	364 $[M+H]^+$	1.06 (N)
1.176		*—CH_3		V.1	393 $[M+H]^+$	1.65 (D)
1.177		*—CH_3		V.1	411 $[M+H]^+$	1.28 (G)
1.178				V.3	411 $[M+H]^+$	1.19 (G)
1.179				V.3	397 $[M+H]^+$	1.12 (G)
1.180		*—CH_3		V.1	412 $[M+H]^+$	1.25 (G)
1.181		*—CH_3		V.1	407 $[M+H]^+$	1.24 (G)

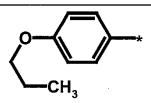
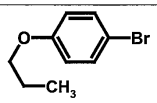
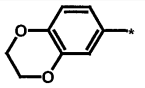
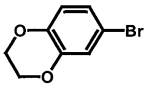
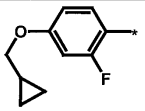
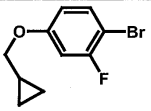
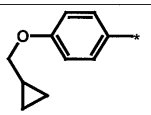
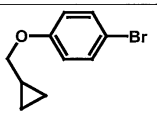
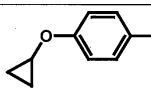
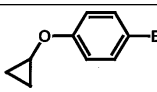
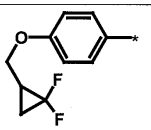
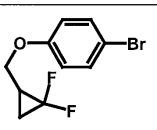
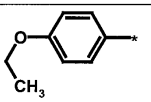
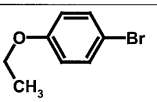
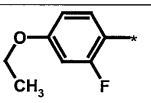
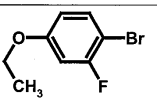
1.182		*—CH_3		V.1	393 $[M+H]^+$	1.16 (G)
1.183		*—CH_3		V.1	419 $[M+H]^+$	1.21 (G)
1.184		*—CH_3		V.1	413 $[M+H]^+$	1.15 (G)
1.185		*		V.4	439 $[M+H]^+$	1.19 (G)
1.186		*—CH_3		V.1	419 $[M+H]^+$	1.40 (AE)
1.187		*—CH_3		V.1	447 $[M+H]^+$	1.43 (L)
1.188		*—CH_3		V.1	391 $[M+H]^+$	1.39 (L)
1.189		*—CH_3		V.1	397 $[M+H]^+$	1.37 (L)
1.190		*—CH_3		V.1	386 $[M+H]^+$	1.32 (L)
1.191		*—CH_3		V.1	368 $[M+H]^+$	1.05 (N)
1.192		*—CH_3		V.1	399 $[M+H]^+$	1.10 (G)

[1427]

[1428] 하기 화학식 1-2의 화합물은 실시예 1.1과 유사하게 제조하며, 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다:

[1429] [화학식 1-2]

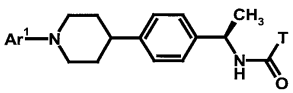
[1430] 

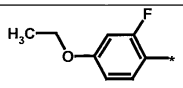
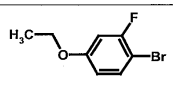
실시예	Ar^1	T	추출물 1	추출물 2	ESI-MS [m/z]	R_t(HPLC)[분] (방법)
1.200				XXIII.2	395 $[M+H]^+$	1.19 (N)
1.201				XXIII.2	395 $[M+H]^+$	0.94 (N)
1.202				XXIII.2	425 $[M+H]^+$	1.46 (N)
1.203				XXIII.2	407 $[M+H]^+$	1.18 (N)
1.204				XXIII.2	393 $[M+H]^+$	1.14 (N)
1.205				XXIII.2	443 $[M+H]^+$	1.18 (N)
1.206				XXIII.2	381 $[M+H]^+$	1.11 (N)
1.207				XXIII.2	399 $[M+H]^+$	1.34 (N)

[1431]

[1432] 하기 화학식 1-3의 화합물은 실시예 1.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다:

[1433] [화학식 1-3]

[1434] 

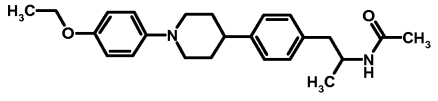
실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
1.300				V.6	385 $[M+H]^+$	1.21 (G)

[1435]

[1436] **실시예 2**

[1437] 실시예 2.1

[1438] N-(2-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-1-메틸-에틸)-아세트아미드

[1439] 

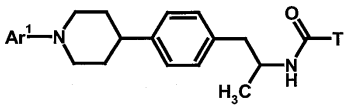
[1440] 톨루엔/3급-부탄올(5:1) 3.0mL를, N-[1-메틸-2-(4-피페리딘-4-일-페닐)-에틸]-아세트아미드(VIII.1) 130mg (0.50mmol), 1-브로모-4-에톡시-벤젠 100mg(0.50mmol), 나트륨 3급-부티레이트 80mg(0.83mmol), X-Phos 20mg (0.040mmol) 및 팔라듐(II) 아세테이트 10mg(0.040mmol)의 혼합물에 첨가한다. 상기 혼합물을 밀봉된 튜브에서 마이크로웨이브 조사하에 10분 동안 150℃에서 교반한다. 그 시간 후, 상기 혼합물을 0.1N HCl 1mL에 붓는다. 진한 암모니아 1mL를 첨가하고, 상기 혼합물을 에틸 아세테이트로 3회 추출한다. 합한 유기 층을 황산나트륨으로 건조시키고 용매를 진공하에 제거한다. 상기 잔사는 칼럼 크로마토그래피(실리카 겔; DCM/MeOH 19:1)로 정제하여 목적 생성물을 수득한다.

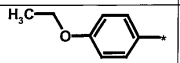
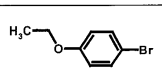
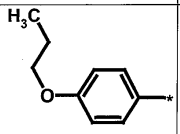
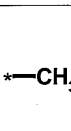
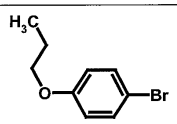
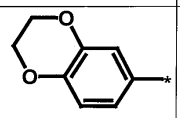
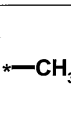
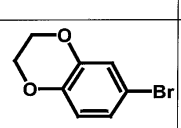
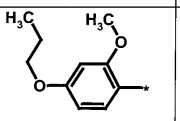
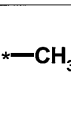
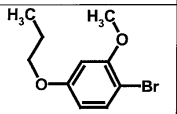
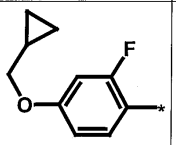
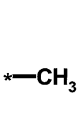
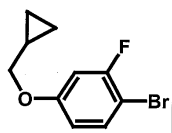
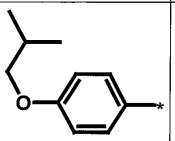
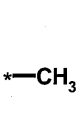
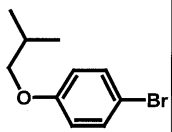
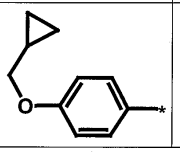
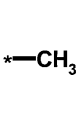
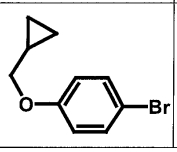
[1441] $C_{24}H_{32}N_2O_2$ (M = 380.5g/mol), ESI-MS: 381 $[M+H]^+$

[1442] R_t (HPLC): 2.15분 (방법 C)

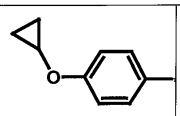
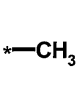
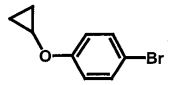
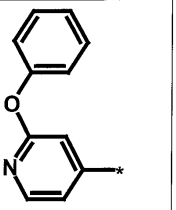
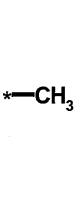
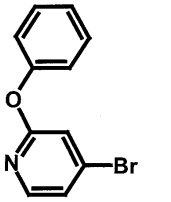
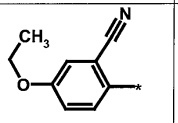
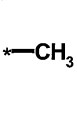
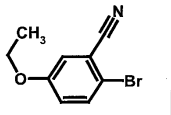
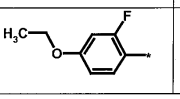
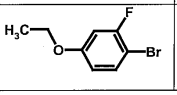
[1443] 하기 화학식 2-1의 화합물은 실시예 2.1과 유사하게 제조하며, 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다. 실시예 2.3 내지 2.12의 경우, 피페리딘 빌딩 블록을 1,4-디옥산 중의 적합한 아릴 브로마이드 (1당량), 나트륨 3급-부티레이트(4당량), 2-(디-3급-부틸포스피노)비페닐(0.4당량) 및 트리스-(디벤질리덴아세톤)-디팔라듐(0)(0.1당량)의 혼합물에 첨가한다. 상기 반응 혼합물을 밤새 45℃에서 교반한 다음 HPLC로 정제한다.

[1444] [화학식 2-1]

[1445] 

실시예	Ar^1	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC)[분] (방법)
2.1				VIII.1	381 $[M+H]^+$	2.15 (C)
2.3				VIII.1	395 $[M+H]^+$	1.28 (G)
2.4				VIII.1	395 $[M+H]^+$	1.16 (G)
2.5				VIII.1	425 $[M+H]^+$	1.31 (G)
2.6				VIII.1	425 $[M+H]^+$	1.30 (G)
2.7				VIII.1	409 $[M+H]^+$	1.34 (G)
2.8				VIII.1	407 $[M+H]^+$	1.27 (G)

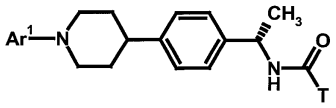
[1446]

2.9				VIII.1	393 $[M+H]^+$	1.03 (N)
2.10				VIII.1	393 $[M+H]^+$	1.03 (N)
2.11				VIII.1	406 $[M+H]^+$	1.64 (N)
2.12				VIII.1	399 $[M+H]^+$	1.33 (N)

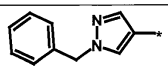
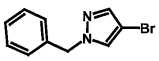
[1447]

[1448] 하기 화학식 2-2의 화합물은 실시예 2.1과 유사하게 제조하며, 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다:

[1449] [화학식 2-2]

[1450] 

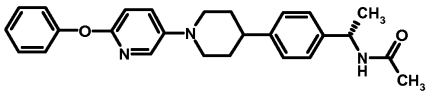
[1451]

실시예	Ar¹	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC)[분] (방법)
2.13				V.1	403 $[M+H]^+$	1.91 (A)

[1452] **실시예 3**

[1453] 실시예 3.1

[1454] (S)-N-{1-[4-(6'-페녹시-3,4,5,6-테트라하이드로-2H-[1,3']비피리디닐-4-일)-페닐]-에틸}-아세트아미드

[1455] 

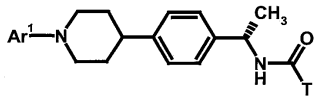
[1456] 불활성 기체 대기하에, (S)-N-[1-(피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 123mg(0.50mmol)을 2-프로판올 5.0mL 중의 5-요오도-2-페녹시-피리딘(J. Organomet. Chem. 2003, 677, 57) 149mg(0.50mmol), K_3PO_4 212mg (1.00mmol), 에틸렌글리콜 62mg(1.00mmol) 및 요오드화구리(I) 5mg(0.025mmol)의 혼합물에 첨가한다. 상기 혼합물을 밀봉된 튜브에서 12시간 동안 80℃에서 교반한다. 냉각시킨 후, 침전을 여과하고 아세토니트릴로 세척한다. 침전은 HPLC(칼럼: Agilent Zorbax Stablebond C18, 8μM; 용출제 A: 물 + 0.3% NH_4OH, 용출제 B: MeOH)로 정제하여 목적 생성물을 수득한다.

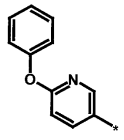
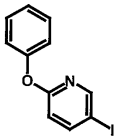
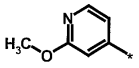
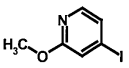
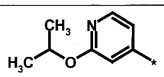
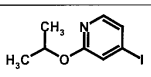
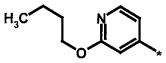
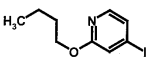
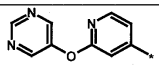
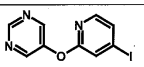
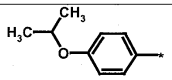
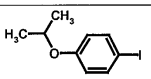
[1457] $C_{26}H_{29}N_3O_2$ (M = 415.5g/mol), ESI-MS: 416 $[M+H]^+$

[1458] R_t (HPLC): 2.08분 (방법 A)

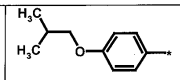
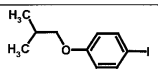
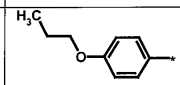
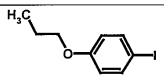
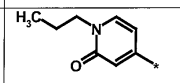
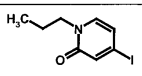
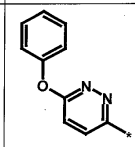
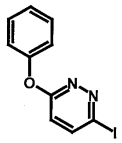
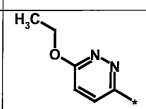
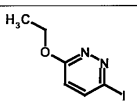
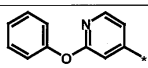
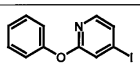
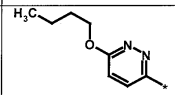
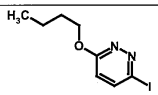
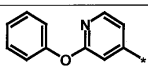
[1459] 하기 화학식 3-1의 화합물은 실시예 3.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1460] [화학식 3-1]

[1461] 

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC)[분] (방법)
3.1				V.1	416 $[M+H]^+$	2.08 (A)
3.2				V.1	354 $[M+H]^+$	1.90 (A)
3.3				V.1	382 $[M+H]^+$	2.06 (A)
3.4				V.1	396 $[M+H]^+$	2.18 (A)
3.5				V.1	418 $[M+H]^+$	1.82 (A)
3.6				V.1	381 $[M+H]^+$	2.15 (A)

[1462]

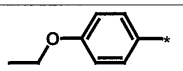
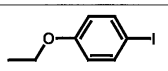
3.7				V.1	395 $[M+H]^+$	2.29 (A)
3.8				V.1	381 $[M+H]^+$	2.21 (A)
3.9				V.1	382 $[M+H]^+$	1.74 (A)
3.10				V.1	417 $[M+H]^+$	1.91 (A)
3.11				V.1	369 $[M+H]^+$	1.88 (A)
3.12				V.1	416 $[M+H]^+$	2.06 (A)
3.13				V.1	397 $[M+H]^+$	2.09 (A)
3.14				V.4	442 $[M+H]^+$	1.32 (G)

[1463]

[1464] 하기 화학식 3-2의 화합물은 실시예 3.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1465] [화학식 3-2]

[1466]

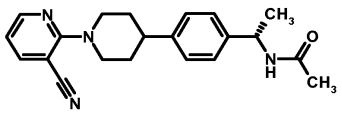
실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
3.20				V.7	379 $[M+H]^+$	2.01 (F)

[1467]

[1468] **실시예 4**

[1469] 실시예 4.1

[1470] (S)-N-(1-{4-[1-(3-시아노피리딘-2-일)피페리딘-4-일]-페닐}-에틸)아세트아미드

[1471] 

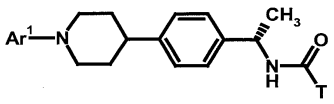
[1472] DIPEA 50㎕(0.29mmol)를 NMP 1.45mL 중의 2-클로로니코틴니트릴 14mg(0.10mmol) 및 (S)-N-[1-(4-피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 29mg(0.11mmol)의 혼합물에 첨가한다. 상기 혼합물을 밤새 130℃에서 교반한다. 이어서, 용매를 진공하에 제거하고 잔사는 DMF에 용해시키고, 상기 혼합물은 역상 HPLC(물/MeOH, 0.1% TFA)를 사용하여 정제하여 목적 생성물을 수득한다.

[1473] $C_{10}H_{11}NO$ (M = 348.4g/mol), ESI-MS: 349 $[M+H]^+$

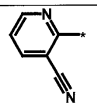
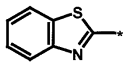
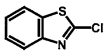
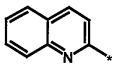
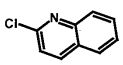
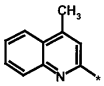
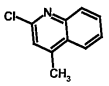
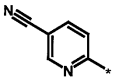
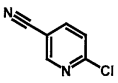
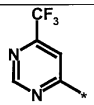
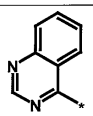
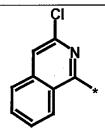
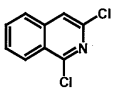
[1474] R_t (HPLC): 1.89분 (방법 B)

[1475] 하기 화학식 4-1의 화합물은 실시예 4.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다. 실시예 4.52 및 4.53의 경우, 반응 혼합물은 마이크로웨이브 오븐에서 2시간 동안 130℃에서 교반한다.

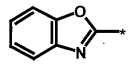
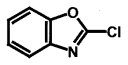
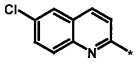
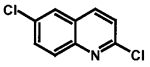
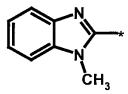
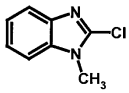
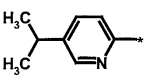
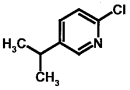
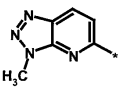
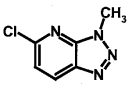
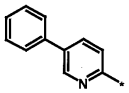
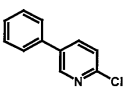
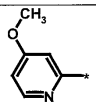
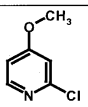
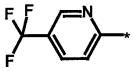
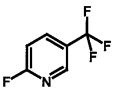
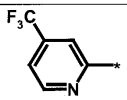
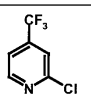
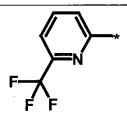
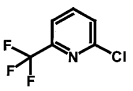
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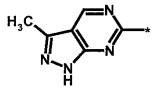
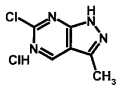
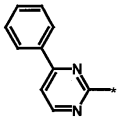
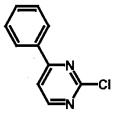
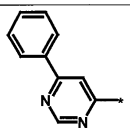
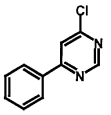
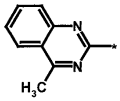
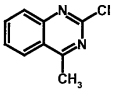
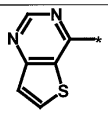
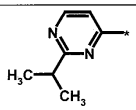
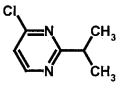
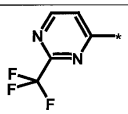
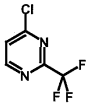
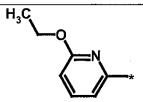
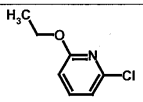
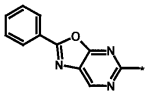
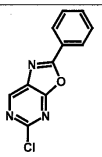
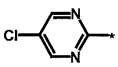
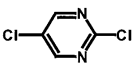
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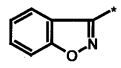
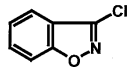
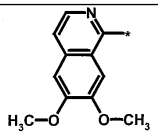
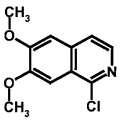
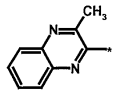
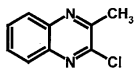
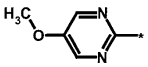
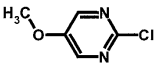
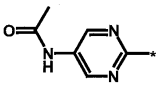
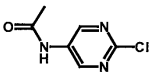
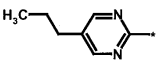
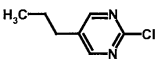
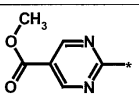
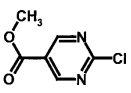
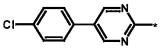
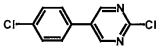
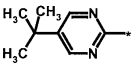
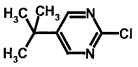
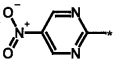
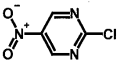
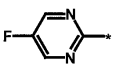
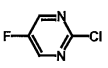
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4.1				V.1	349 $[M+H]^+$	1.89 (B)
4.2				V.1	380 $[M+H]^+$	1.78 (B)
4.3				V.1	374 $[M+H]^+$	1.24 (B)
4.4				V.1	388 $[M+H]^+$	1.32 (B)
4.5				V.1	349 $[M+H]^+$	1.86 (B)
4.6				V.1	393 $[M+H]^+$	1.93 (B)
4.7				V.1	375 $[M+H]^+$	1.20 (B)
4.8				V.1	408 $[M+H]^+$	2.29 (B)

[1479]

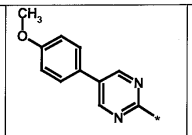
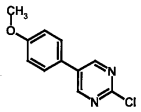
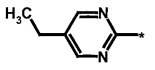
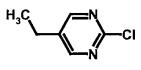
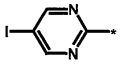
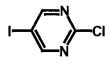
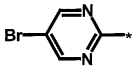
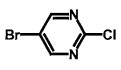
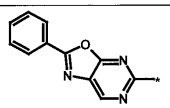
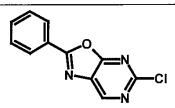
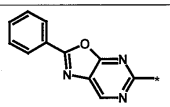
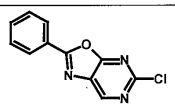
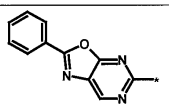
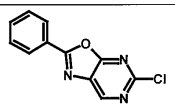
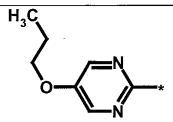
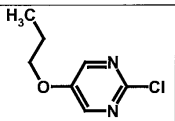
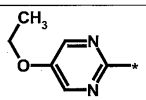
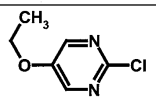
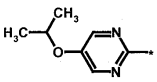
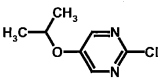
4.9				V.1	364 $[M+H]^+$	1.91 (B)
4.10				V.1	408 $[M+H]^+$	1.39 (B)
4.11				V.1	393 $[M+H]^+$	2.17 (B)
4.12				V.1	377 $[M+H]^+$	1.22 (B)
4.13				V.1	366 $[M+H]^+$	1.37 (B)
4.14				V.1	379 $[M+H]^+$	1.86 (B)
4.15				V.1	400 $[M+H]^+$	1.43 (B)
4.16				V.1	354 $[M+H]^+$	1.16 (B)
4.17				V.1	392 $[M+H]^+$	2.07 (B)
4.18				V.1	392 $[M+H]^+$	2.03 (B)
4.19				V.1	392 $[M+H]^+$	2.15 (B)

[1480]

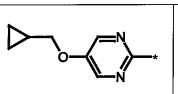
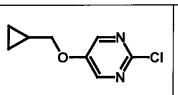
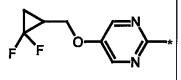
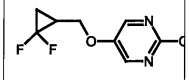
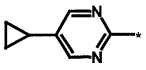
4.20		*—CH_3		V.1	379 $[M+H]^+$	1.72 (B)
4.21		*—CH_3		V.1	401 $[M+H]^+$	2.04 (B)
4.22		*—CH_3		V.1	401 $[M+H]^+$	1.33 (B)
4.23		*—CH_3		V.1	389 $[M+H]^+$	1.39 (B)
4.24		*—CH_3		V.1	381 $[M+H]^+$	1.22 (B)
4.25		*—CH_3		V.1	367 $[M+H]^+$	1.36 (B)
4.26		*—CH_3		V.1	393 $[M+H]^+$	1.95 (B)
4.27		*—CH_3		V.1	368 $[M+H]^+$	2.04 (B)
4.28		*—CH_3		V.1	442 $[M+H]^+$	2.28 (B)
4.29		*—CH_3		V.1	359 $[M+H]^+$	2.18 (B)

4.30		*—CH_3		V.1	364 $[M+H]^+$	1.83 (B)
4.31		*—CH_3		V.1	434 $[M+H]^+$	1.76 (B)
4.32		*—CH_3		V.1	389 $[M+H]^+$	2.15 (B)
4.33		*—CH_3		V.1	355 $[M+H]^+$	2.05 (B)
4.34		*—CH_3		V.1	382 $[M+H]^+$	1.67 (A)
4.35		*—CH_3		V.1	367 $[M+H]^+$	2.15 (A)
4.36		*—CH_3		V.1	383 $[M+H]^+$	1.99 (A)
4.37		*—CH_3		V.1	435 $[M+H]^+$	2.32 (A)
4.38		*—CH_3		V.1	381 $[M+H]^+$	2.20 (A)
4.39		*—CH_3		V.1	370 $[M+H]^+$	1.98 (A)
4.40		*—CH_3		V.1	343 $[M+H]^+$	2.01 (A)

[1481]

4.41				V.1	431 $[M+H]^+$	2.20 (A)
4.42				V.1	353 $[M+H]^+$	2.05 (A)
4.43				V.1	451 $[M+H]^+$	2.21 (A)
4.44				V.1	403 $[M+H]^+$	2.19 (A)
4.45				V.1	325 $[M+H]^+$	1.83 (A)
4.46				V.4	468 $[M+H]^+$	2.31 (A)
4.47				V.3	471 $[M+H]^+$	2.29 (A)
4.48				V.2	458 $[M+H]^+$	2.32 (A)
4.49				V.1	383 $[M+H]^+$	2.04 (F)
4.50				V.1	369 $[M+H]^+$	1.92 (F)
4.51				V.1	383 $[M+H]^+$	1.99 (F)

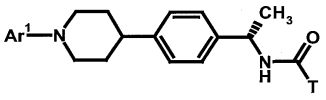
[1482]

4.52				V.1	395 $[M+H]^+$	1.56 (N)
4.53				V.1	431 $[M+H]^+$	1.53 (N)
4.54				XXIII.1	379 $[M+H]^+$	1.46 (N)

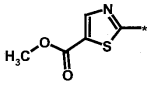
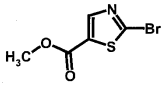
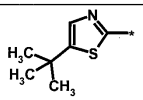
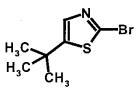
[1483]

[1484] 하기 화학식 4-1의 화합물은 용매로서 환류하는 에탄올을 사용하여 실시예 4.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1485] [화학식 4-1]



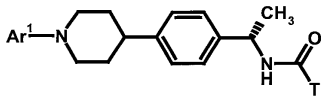
[1486]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
4.101				V.1	388 $[M+H]^+$	1.87 (A)
4.102				V.1	386 $[M+H]^+$	2.02 (A)

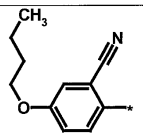
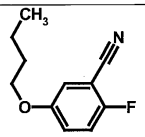
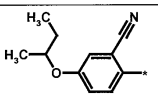
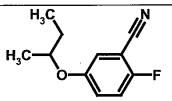
[1487]

[1488] 하기 화학식 4-1의 화합물은 용매로서 마이크로웨이브 조사하에 환류하는 DMA를 사용하고 염기로서 탄산칼륨을 사용하여 실시예 4.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1489] [화학식 4-1]



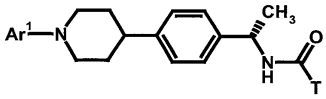
[1490]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
4.201				V.1	420 $[M+H]^+$	2.21 (F)
4.202				V.1	420 $[M+H]^+$	2.15 (F)

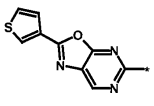
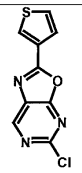
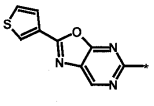
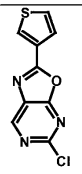
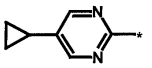
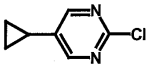
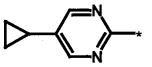
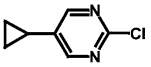
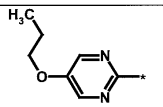
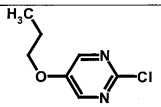
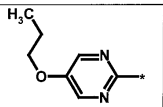
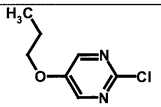
[1491]

[1492] 하기 화학식 4-1의 화합물은 용매로서 환류하는 DMSO를 사용하고 염기로서 N,N-디이소프로필에틸아민을 사용하여 실시예 4.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1493] [화학식 4-1]



[1494]

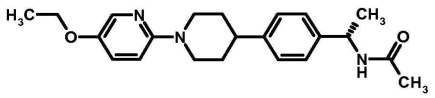
실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
4.301				V.4	474 $[M+H]^+$	1.28 (G)
4.302				V.3	477 $[M+H]^+$	1.27 (G)
4.303				V.4	391 $[M+H]^+$	1.33 (G)
4.304				V.3	394 $[M+H]^+$	1.31 (G)
4.305				V.4	409 $[M+H]^+$	1.36 (G)
4.306				V.3	412 $[M+H]^+$	1.34 (G)

[1495]

[1496] **실시예 5**

[1497] 실시예 5.1

[1498] (S)-N-{1-[4-(5'-에톡시-3,4,5,6-테트라하이드로-2H-[1,2']비피리디닐-4-일)-페닐]-에틸}-아세트아미드



[1499]

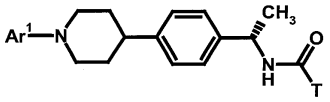
[1500] 2-브로모-5-에톡시-피리딘 250mg(1.24mmol)를 (S)-N-[1-(4-피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 250 mg(1.02mmol)에 첨가한다. 상기 혼합물을 1시간 동안 180℃에서 가열한다. 이어서, 잔사는 DMF/메탄올로 취하고, 상기 혼합물은 역상 HPLC(칼럼: Waters XBridge 5μM; 용출제 A: 물 + 0.30% NH_4OH, 용출제 B: MeOH + 0.3% NH_4OH)를 사용하여 정제하여 목적 생성물을 수득한다.

[1501] $C_{22}H_{29}N_3O_2$ (M = 367.5g/mol), ESI-MS: 368 $[M+H]^+$

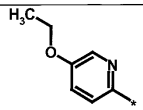
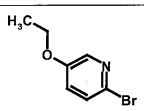
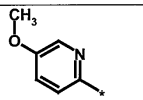
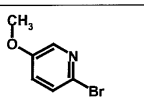
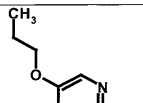
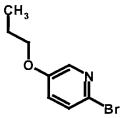
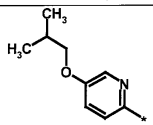
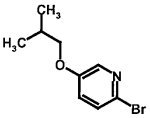
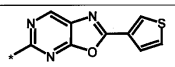
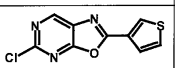
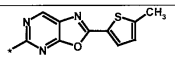
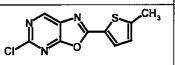
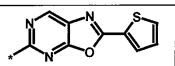
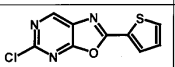
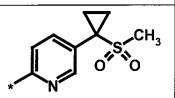
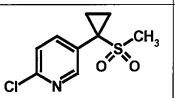
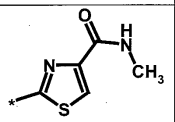
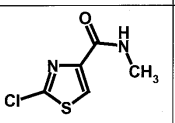
[1502] R_t (HPLC): 2.20분 (방법 A)

[1503] 하기 화학식 5-1의 화합물은 실시예 5.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다. 화합물 5.5 내지 5.35 및 5.38 내지 5.56의 제조의 경우, DIPEA(3.0당량)를 첨가하고, NMP는 용매로서 사용하며 반응 혼합물은 밤새 130℃에서 교반한다. 화합물 5.36 및 5.37의 제조의 경우, 탄산칼륨(2.0당량)을 염기로서 사용하고 아세톤을 용매로서 사용하고 상기 반응 혼합물은 0℃에서 2시간 동안 교반한다.

[1504] [화학식 5-1]

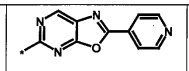
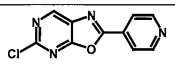
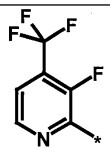
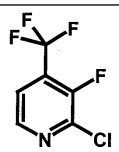
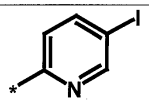
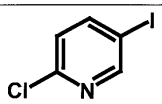
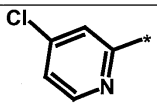
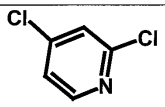
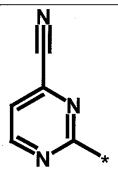
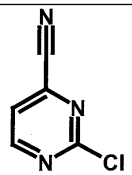
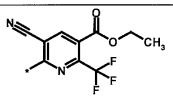
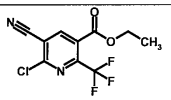
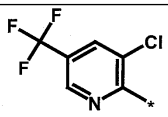
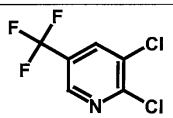
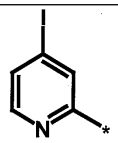
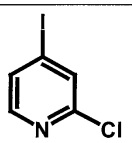
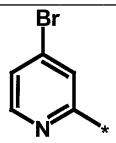
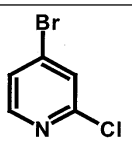


[1505]

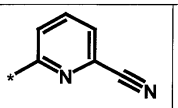
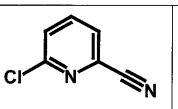
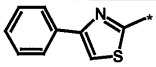
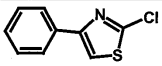
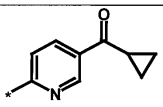
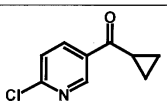
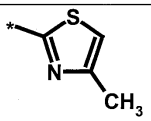
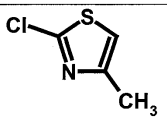
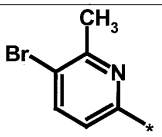
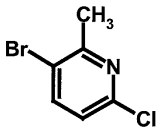
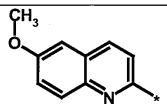
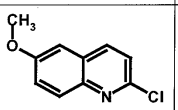
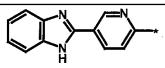
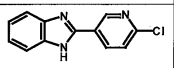
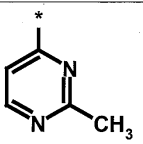
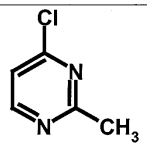
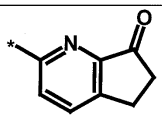
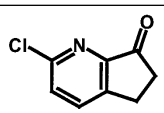
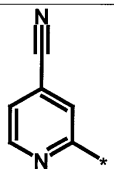
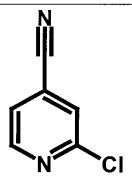
실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
5.1				V.1	368 $[M+H]^+$	2.20 (A)
5.2				V.1	354 $[M+H]^+$	2.10 (A)
5.3				V.1	382 $[M+H]^+$	2.30 (A)
5.4				V.1	396 $[M+H]^+$	2.40 (A)
5.5				V.1	448 $[M+H]^+$	0.58 (V)
5.6				V.1	462 $[M+H]^+$	0.62 (V)
5.7				V.1	448 $[M+H]^+$	2.21 (W)
5.8				V.1	442 $[M+H]^+$	0.32 (V)
5.9				V.1	387 $[M+H]^+$	0.41 (V)

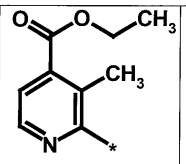
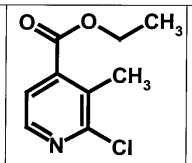
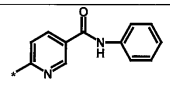
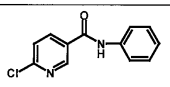
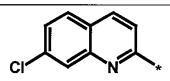
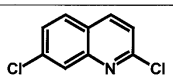
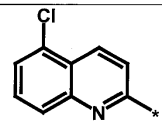
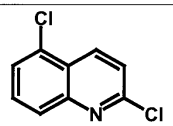
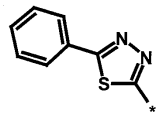
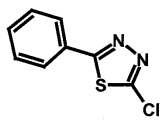
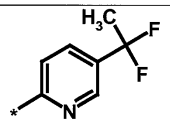
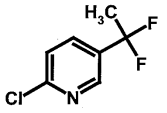
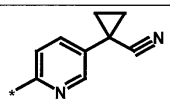
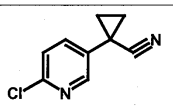
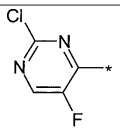
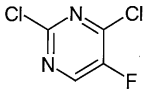
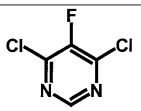
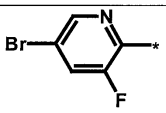
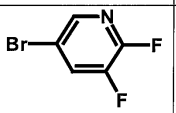
[1506]

[1507]

5.10		*—CH_3		V.1	443 $[M+H]^+$	1.95 (W)
5.11		*—CH_3		V.1	410 $[M+H]^+$	0.61 (V)
5.12		*—CH_3		V.1	450 $[M+H]^+$	0.4 (V)
5.13		*—CH_3		V.1	358 $[M+H]^+$	1.7 (W)
5.14		*—CH_3		V.1	350 $[M+H]^+$	0.52 (V)
5.15		*—CH_3		V.1	489 $[M+H]^+$	0.61 (V)
5.16		*—CH_3		V.1	426 $[M+H]^+$	2.14 (W)
5.17		*—CH_3		V.1	450 $[M+H]^+$	1.99 (W)
5.18		*—CH_3		V.1	402 $[M+H]^+$	0.36 (V)

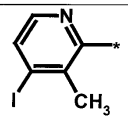
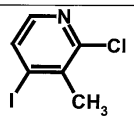
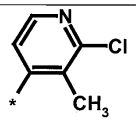
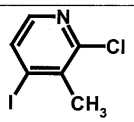
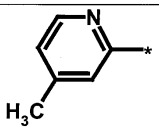
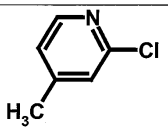
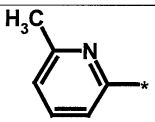
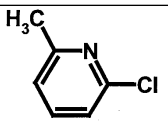
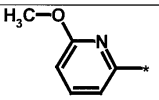
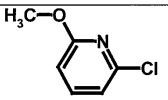
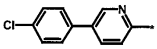
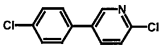
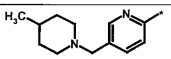
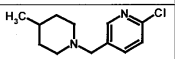
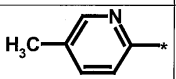
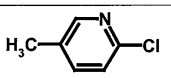
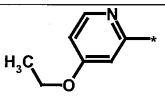
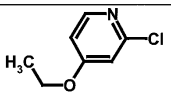
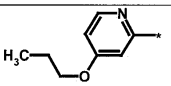
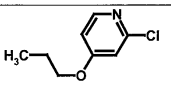
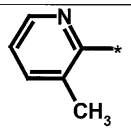
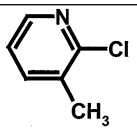
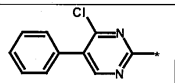
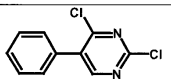
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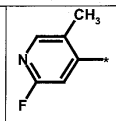
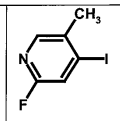
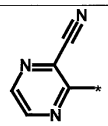
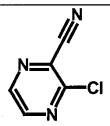
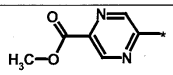
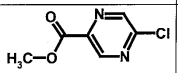
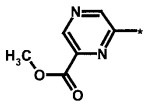
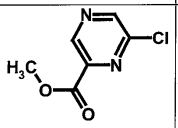
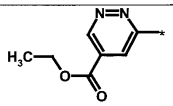
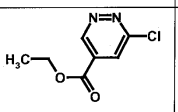
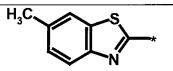
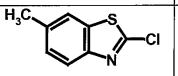
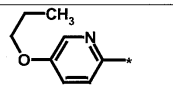
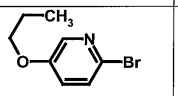
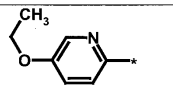
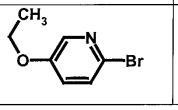
5.19		*—CH_3		V.1	349 $[M+H]^+$	0.52 (V)
5.20		*—CH_3		V.1	406 $[M+H]^+$	1.88 (W)
5.21		*—CH_3		V.1	392 $[M+H]^+$	0.36 (V)
5.22		*—CH_3		V.1	344 $[M+H]^+$	0.32 (V)
5.23		*—CH_3		V.1	416 $[M+H]^+$	0.42 (V)
5.24		*—CH_3		V.1	404 $[M+H]^+$	0.37 (V)
5.25		*—CH_3		V.1	440 $[M+H]^+$	0.37 (V)
5.26		*—CH_3		V.1	339 $[M+H]^+$	1.64 (W)
5.27		*—CH_3		V.1	378 $[M+H]^+$	1.6 (W)
5.28		*—CH_3		V.1	349 $[M+H]^+$	0.41 (V)

5.29		*—CH_3		V.1	410 $[M+H]^+$	1.93 (W)
5.30		*—CH_3		V.1	443 $[M+H]^+$	1.73 (W)
5.31		*—CH_3		V.1	408 $[M+H]^+$	2.07 (W)
5.32		*—CH_3		V.1	408 $[M+H]^+$	2.12 (W)
5.33		*—CH_3		V.1	407 $[M+H]^+$	1.84 (W)
5.34		*—CH_3		V.1	388 $[M+H]^+$	1.91 (W)
5.35		*—CH_3		V.1	389 $[M+H]^+$	0.33 (V)
5.36		*		V.4	403 $[M+H]^+$	2.42 (S)
5.37		*		V.4	403 $[M+H]^+$	2.65 (S)
5.38		*—CH_3		*V.1*	420 $[M+H]^+$	2.20 (B)

[1509]

[1510]

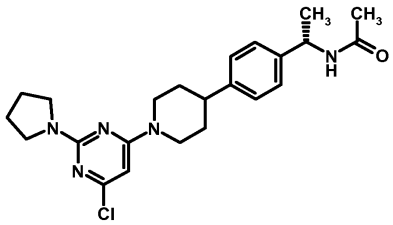
5.39		*—CH_3		V.1	464 $[M+H]^+$	2.28 (R)
5.40		*—CH_3		V.1	372 $[M+H]^+$	2.61 (R)
5.41		*—CH_3		V.1	338 $[M+H]^+$	1.40 (P)
5.42		*—CH_3		V.1	338 $[M+H]^+$	1.35 (P)
5.43		*—CH_3		V.1	354 $[M+H]^+$	2.10 (P)
5.44		*—CH_3		V.1	434 $[M+H]^+$	1.79 (P)
5.45		*—CH_3		V.1	435 $[M+H]^+$	1.26 (P)
5.46		*—CH_3		V.1	338 $[M+H]^+$	1.39 (P)
5.47		*—CH_3		V.1	368 $[M+H]^+$	1.50 (P)
5.48		*—CH_3		V.1	382 $[M+H]^+$	1.60 (P)
5.49		*—CH_3		V.1	338 $[M+H]^+$	1.42 (P)
5.50		*—CH_3		V.1	435 $[M+H]^+$	2.49 (P)

5.51				V.1	356 $[M+H]^+$	2.53 (R)
5.52				V.1	325 $[M+H]^+$	1.86 (U)
5.53				V.1	383 $[M+H]^+$	1.84 (U)
5.54				V.1	383 $[M+H]^+$	1.83 (U)
5.55				V.1	397 $[M+H]^+$	1.51 (U)
5.56				V.1	394 $[M+H]^+$	1.76 (U)
5.57				V.4	408 $[M+H]^+$	1.21 (G)
5.58				V.4	394 $[M+H]^+$	1.14 (G)

[1511]

[1512] 실시예 5.200

[1513] (S)-N-(1-{4-[1-(6-클로로-2-피롤리딘-1-일-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1514] 

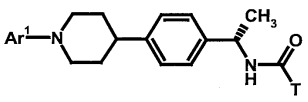
[1515] THF 1mL 중의 4,6-디클로로-2-피롤리딘-1-일-피리미딘 22mg(0.1mmol)에 DIPEA 17㎕(0.1mol) 및 (S)-N-[1-(4-피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 25mg(0.1mmol)에 첨가한다. 상기 혼합물을 밤새 실온에서 교반한다. 용매를 진공하에 제거하고 잔사는 역상 HPLC(용출제 A: 물 + 0.1% TFA, 용출제 B: MeOH)를 사용하여 정제하여 목적 생성물을 수득한다.

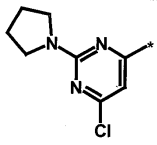
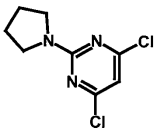
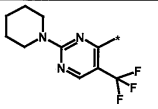
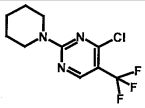
[1516] $C_{23}H_{30}N_5O$ (M = 427.97g/mol), ESI-MS: 428 $[M+H]^+$

[1517] R_t (HPLC): 1.91분 (방법 T)

[1518] 하기 화학식 5-2의 화합물은 실시예 5.200과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1519] [화학식 5-2]

[1520] 

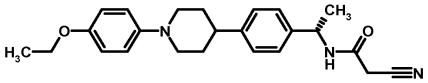
실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
5.200				V.1	428 $[M+H]^+$	1.91 (T)
5.201				V.1	476 $[M+H]^+$	1.91 (T)

[1521]

[1522] **실시예 6**

[1523] 실시예 6.1

[1524] (S)-2-시아노-N-(1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1525] 

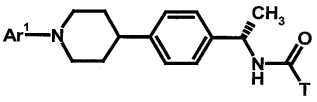
[1526] DMF 1mL 중의 시아노아세트산 7.0mg(0.08mmol)에 DIPEA 35㎕(0.20mol) 및 TBTU 29mg(0.08mmol)을 첨가하고, 상기 혼합물을 실온에서 10분 동안 교반한다. 이어서, DMF 1mL 중의 (S)-1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸아민(XIII.1) 29mg(0.09mmol)을 첨가하고 밤새 계속 교반한다. 상기 혼합물은 염기성 산화알루미늄을 통해 여과하고, DMF/MeOH(9:1)로 세척하고, 진공하에 농축시킨다. 상기 잔사는 역상 칼럼 크로마토그래피(물/MeOH, 0.1% TFA)를 사용하여 정제하고, 상응하는 분획은 농축시켜 목적 생성물을 수득한다.

[1527] $C_{10}H_{11}NO$ (M = 391.5g/mol), ESI-MS: 392 $[M+H]^+$

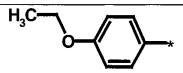
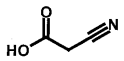
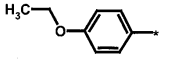
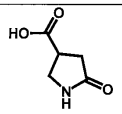
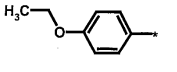
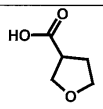
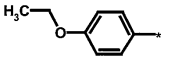
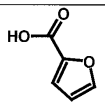
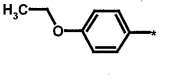
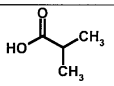
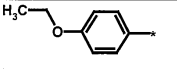
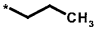
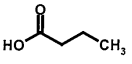
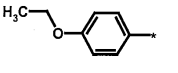
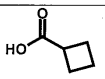
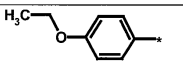
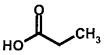
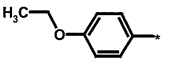
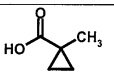
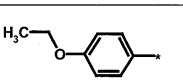
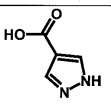
[1528] R_t (HPLC): 1.18분 (방법 B)

[1529] 하기 화학식 6-1의 화합물은 실시예 6.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

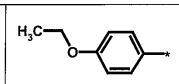
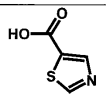
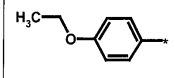
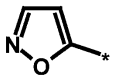
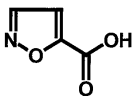
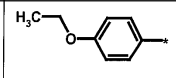
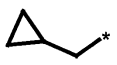
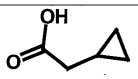
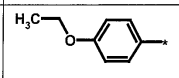
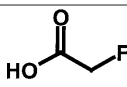
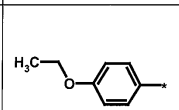
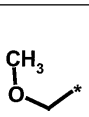
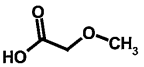
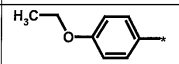
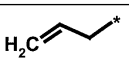
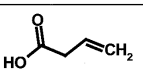
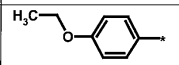
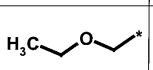
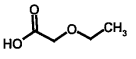
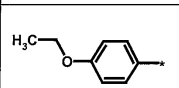
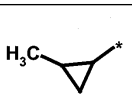
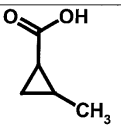
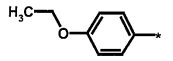
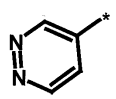
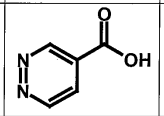
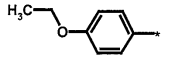
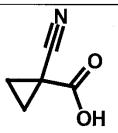
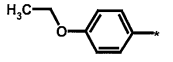
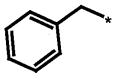
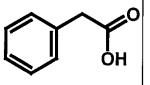
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[1531] 

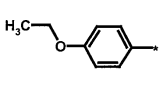
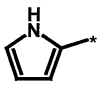
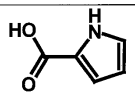
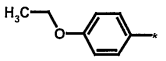
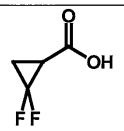
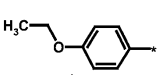
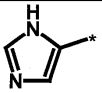
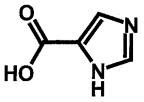
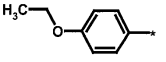
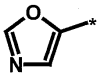
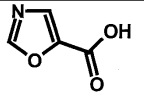
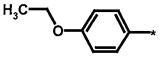
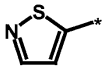
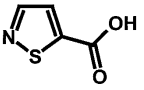
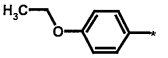
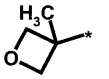
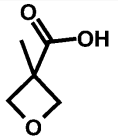
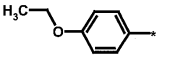
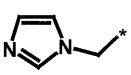
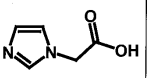
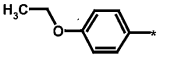
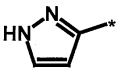
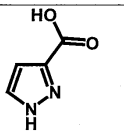
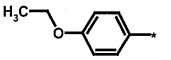
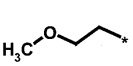
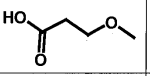
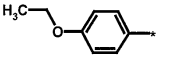
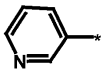
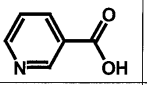
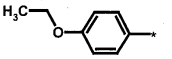
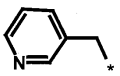
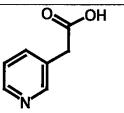
[1532]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t (HPLC) [분] (방법)
6.1			XIII.1		392 $[M+H]^+$	1.18 (B)
6.2			XIII.1		354 $[M+H]^+$	2.10 (B)
6.3			XIII.1		423 $[M+H]^+$	1.23 (B)
6.4			XIII.1		419 $[M+H]^+$	1.28 (B)
6.5			XIII.1		495 $[M+H]^+$	1.30 (B)
6.6			XIII.1		495 $[M+H]^+$	1.30 (B)
6.7			XIII.1		407 $[M+H]^+$	1.33 (B)
6.8			XIII.1		381 $[M+H]^+$	1.25 (B)
6.9			XIII.1		407 $[M+H]^+$	1.33 (B)
6.10			XIII.1		419 $[M+H]^+$	1.20 (B)

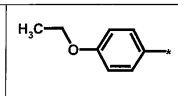
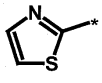
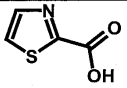
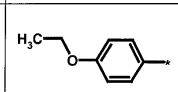
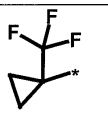
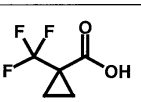
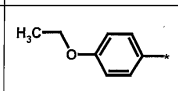
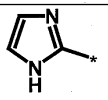
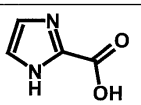
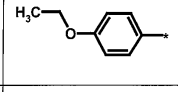
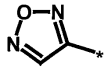
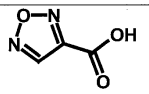
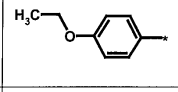
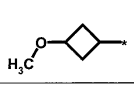
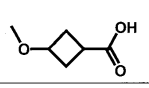
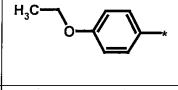
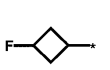
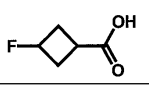
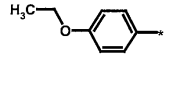
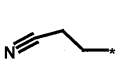
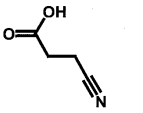
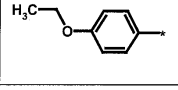
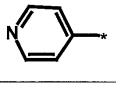
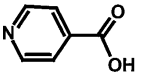
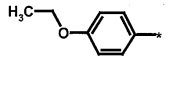
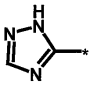
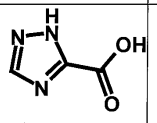
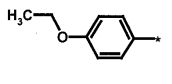
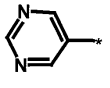
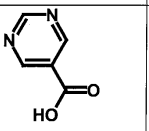
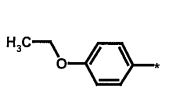
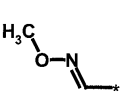
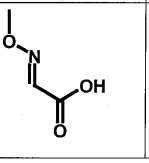
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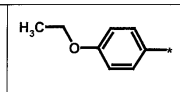
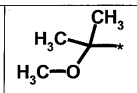
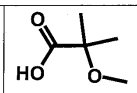
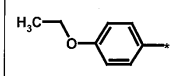
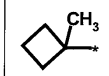
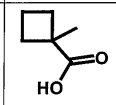
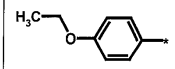
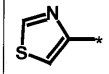
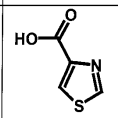
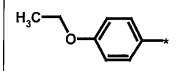
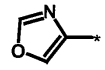
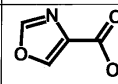
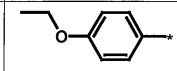
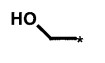
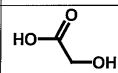
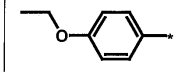
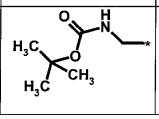
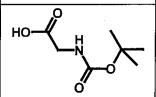
6.11			XIII.1		436 $[M+H]^+$	1.27 (B)
6.12			XIII.1		420 $[M+H]^+$	0.39 (V)
6.13			XIII.1		407 $[M+H]^+$	0.58 (Y)
6.14			XIII.1		385 $[M+H]^+$	0.55 (Y)
6.15			XIII.1		397 $[M+H]^+$	0.55 (Y)
6.16			XIII.1		393 $[M+H]^+$	0.57 (Y)
6.17			XIII.1		411 $[M+H]^+$	0.58 (Y)
6.18			XIII.1		407 $[M+H]^+$	0.59 (Y)
6.19			XIII.1		431 $[M+H]^+$	0.52 (Y)
6.20			XIII.1		418 $[M+H]^+$	0.59 (Y)
6.21			XIII.1		443 $[M+H]^+$	0.6 (Y)

[1534]

6.22			XIII.1		418 [M+H]+	0.57 (Y)
6.23			XIII.1		429 [M+H]+	0.58 (Y)
6.24			XIII.1		419 [M+H]+	0.5 (Y)
6.25			XIII.1		420 [M+H]+	0.53 (Y)
6.26			XIII.1		436 [M+H]+	0.58 (Y)
6.27			XIII.1		423 [M+H]+	0.54 (Y)
6.28			XIII.1		433 [M+H]+	0.5 (Y)
6.29			XIII.1		419 [M+H]+	0.52 (Y)
6.30			XIII.1		411 [M+H]+	0.54 (Y)
6.31			XIII.1		430 [M+H]+	0.54 (Y)
6.32			XIII.1		444 [M+H]+	0.53 (Y)

[1535]

6.33			XIII.1		436 $[M+H]^+$	0.61 (Y)
6.34			XIII.1		461 $[M+H]^+$	0.63 (Y)
6.35			XIII.1		419 $[M+H]^+$	0.54 (Y)
6.36			XIII.1		421 $[M+H]^+$	0.33 (Y)
6.37			XIII.1		437 $[M+H]^+$	0.56 (Y)
6.38			XIII.1		425 $[M+H]^+$	0.58 (Y)
6.39			XIII.1		406 $[M+H]^+$	0.53 (Y)
6.40			XIII.1		430 $[M+H]^+$	0.54 (Y)
6.41			XIII.1		420 $[M+H]^+$	0.33 (Y)
6.42			XIII.1		431 $[M+H]^+$	0.53 (Y)
6.43			XIII.1		410 $[M+H]^+$	0.58 (Y)

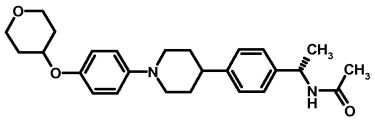
6.44			XIII.1		425 [M+H]+	0.61 (Y)
6.45			XIII.1		421 [M+H]+	0.61 (Y)
6.46			XIII.1		436 [M+H]+	1.30 (B)
6.47			XIII.1		420 [M+H]+	1.57 (P)
6.48			XIII.1		383 [M+H]+	1.15 (G)
6.49			XIII.1		482 [M+H]+	1.26 (G)

[1536]

[1537] **실시예 7**

[1538] 실시예 7.1

[1539] (S)-N-[1-(4-{1-[4-(테트라하이드로-2H-피란-4-일옥시)-페닐]-피페리딘-4-일}-페닐)-에틸]-아세트아미드

[1540] 

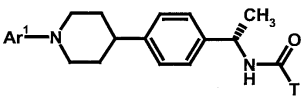
[1541] 고체 지지체 상의 (S)-N-{1-(4-[1-(4-하이드록시페닐)-피페리딘-4-일]-페닐}-에틸)-아세트아미드(화합물 1.48) 34㎎(0.10mmol), 테트라하이드로-4H-피란-4-올 15㎎(0.15mmol) 및 트리페닐포스핀 39㎎(0.15mmol)을 0℃에서 무수 THF 2mL에 현탁시킨다. 디-3급-부틸 아조디카복실레이트 35㎎(0.15mmol)을 첨가하고, 상기 혼합물을 실온으로 가온한다. 교반을 밤새 계속한 다음, 고체 지지체 상의 트리페닐포스핀 0.5당량 및 디-3급-부틸 아조디카복실레이트 0.5당량을 첨가한다. 실온에서 2시간 동안 교반한 후에, 상기 혼합물은 염기성 산화알루미늄 상에서 여과하고, DMF/MeOH(9:1)로 세척한다. 증발 후, 상기 잔사는 역상 HPLC(물/MeOH, 0.1% TFA)를 사용하여 정제하여 목적 생성물을 수득한다.

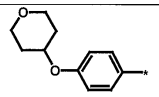
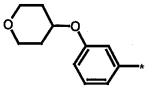
[1542] $C_{26}H_{34}N_2O_3$ (M = 422.5g/mol), ESI-MS: 423 $[M+H]^+$

[1543] R_t (HPLC): 1.26분 (방법 B)

[1544] 하기 화학식 7-1의 화합물은 실시예 7.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1545] [화학식 7-1]

[1546] 

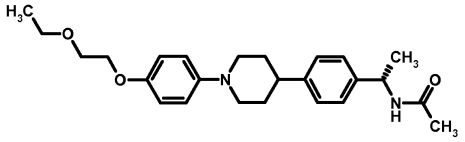
실시예	Ar¹	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
7.1				1.48	423 $[M+H]^+$	1.26 (B)
7.2				1.27	423 $[M+H]^+$	1.56 (B)

[1547]

[1548] **실시예 8**

[1549] 실시예 8.1

[1550] (S)-N-[1-(4-{1-[4-(테트라하이드로-2H-피란-4-일옥시)-페닐]-피페리딘-4-일}-페닐)-에틸]-아세트아미드

[1551] 

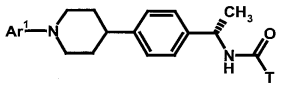
[1552] 1-브로모-2-에톡시-에탄 17㎕(0.15mmol) 및 K_2CO_3 35mg(0.25mmol)을 ACN 2mL 중의 (S)-N-{1-(4-[1-(4-하이드록시페닐)-피페리딘-4-일]-페닐}-에틸)-아세트아미드(화합물 1.48) 34mg(0.10mmol)에 첨가한다. 상기 혼합물을 90℃에서 4시간 동안 교반한 다음, 1-브로모-2-에톡시-에탄 11㎕(0.10mmol)를 첨가한다. 90℃에서 밤새 계속 교반한다. 용매를 진공하에 제거하고 잔사는 역상 HPLC(물/MeOH, 0.1% TFA)를 사용하여 정제하여 목적 생성물을 수득한다.

[1553] $C_{10}H_{11}NO$ (M = 410.5g/mol), ESI-MS: 411 $[M+H]^+$

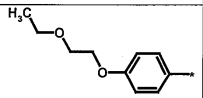
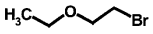
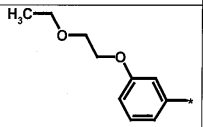
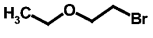
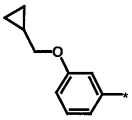
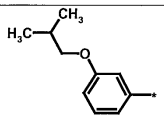
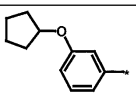
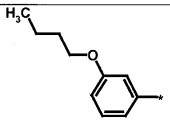
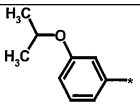
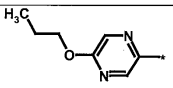
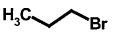
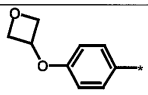
[1554] R_t (HPLC): 1.40분 (방법 B)

[1555] 하기 화학식 8-1의 화합물은 실시예 8.1과 유사하게 제조한다. 실시예 8.63 내지 8.67의 경우, DMF를 용매로서 사용하고 상기 반응 혼합물은 밤새 60℃에서 교반한다. 실시예 8.67의 경우, Boc 보호 그룹은 이후에 HCl(MeOH 중의 1.25mol/L)과 반응시켜 제거한다. 실시예 8.68의 경우, DMSO를 용매로서 사용하고 상기 반응 혼합물은 5시간 동안 100℃에서 교반한다. 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

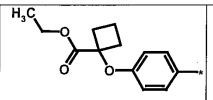
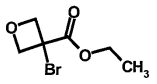
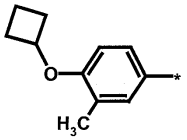
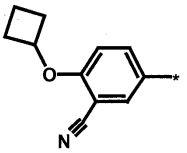
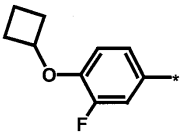
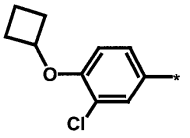
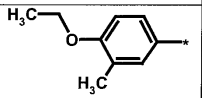
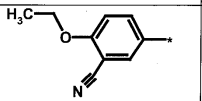
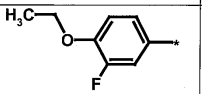
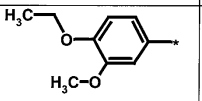
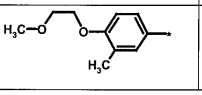
[1556] [화학식 8-1]

[1557] 

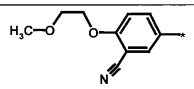
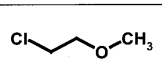
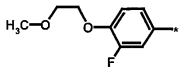
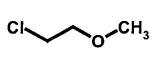
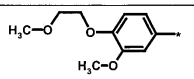
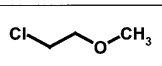
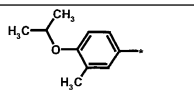
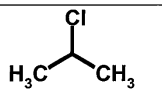
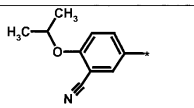
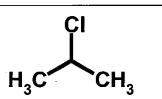
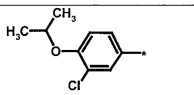
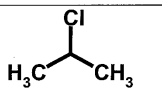
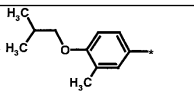
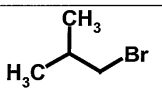
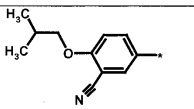
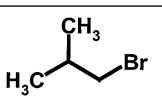
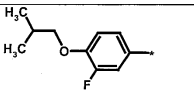
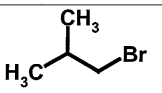
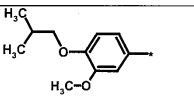
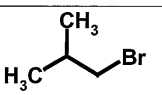
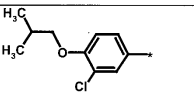
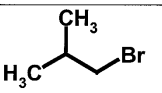
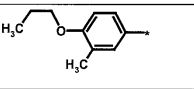
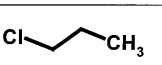
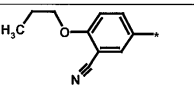
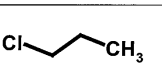
[1558]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC)[분] (방법)
8.1		*—CH_3		1.48	411 $[M+H]^+$	1.40 (B)
8.2		*—CH_3		1.27	411 $[M+H]^+$	1.51 (B)
8.3		*—CH_3		1.27	393 $[M+H]^+$	1.74 (B)
8.4		*—CH_3		1.27	395 $[M+H]^+$	1.81 (B)
8.5		*—CH_3		1.27	407 $[M+H]^+$	1.79 (B)
8.6		*—CH_3		1.27	395 $[M+H]^+$	1.68 (B)
8.7		*—CH_3		1.27	381 $[M+H]^+$	2.30 (B)
8.8		*—CH_3		1.49	383 $[M+H]^+$	2.18 (A)
8.9		*—CH_3		1.49	395 $[M+H]^+$	1.94 (A)

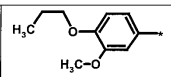
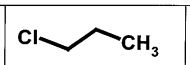
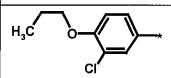
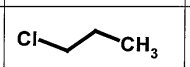
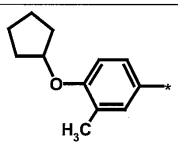
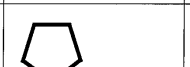
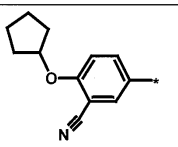
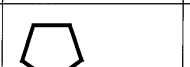
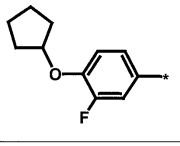
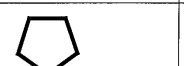
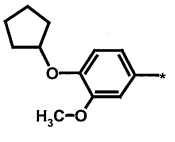
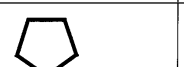
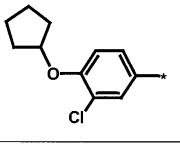
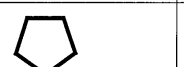
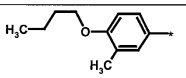
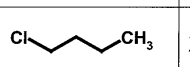
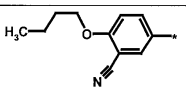
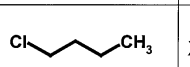
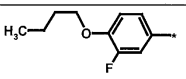
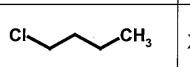
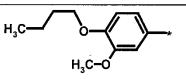
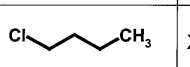
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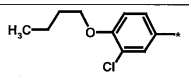
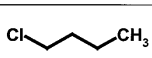
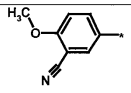
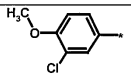
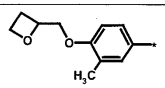
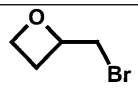
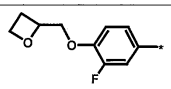
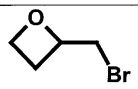
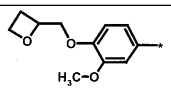
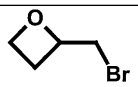
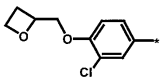
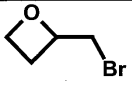
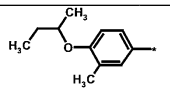
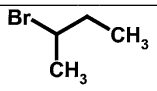
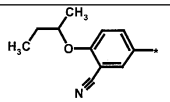
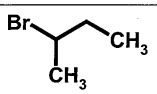
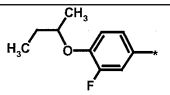
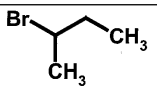
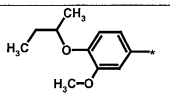
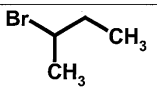
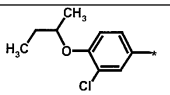
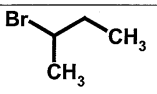
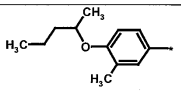
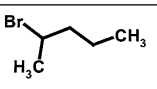
8.10		*—CH_3		1.49	465 $[M+H]^+$	2.20 (A)
8.11		*—CH_3		XX.1	407 $[M+H]^+$	1.31 (B)
8.12		*—CH_3		XX.2	418 $[M+H]^+$	1.54 (B)
8.13		*—CH_3		XX.3	411 $[M+H]^+$	1.37 (B)
8.14		*—CH_3		XX.4	427 $[M+H]^+$	1.46 (B)
8.15		*—CH_3		XX.1	381 $[M+H]^+$	1.2 (B)
8.16		*—CH_3		XX.2	392 $[M+H]^+$	1.35 (B)
8.17		*—CH_3		XX.3	385 $[M+H]^+$	1.21 (B)
8.18		*—CH_3		XX.5	397 $[M+H]^+$	1.06 (B)
8.19		*—CH_3		XX.1	411 $[M+H]^+$	1.1 (B)

[1560]

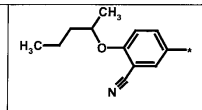
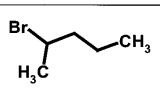
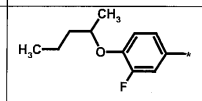
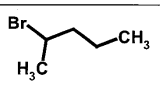
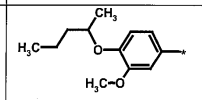
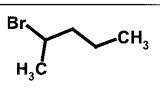
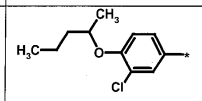
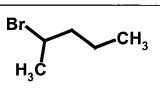
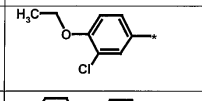
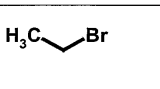
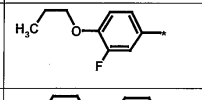
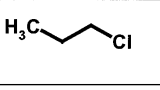
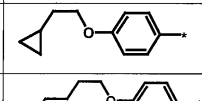
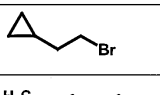
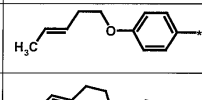
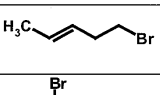
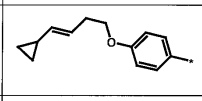
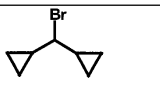
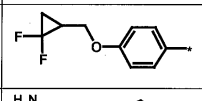
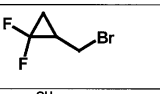
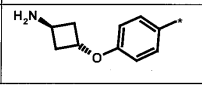
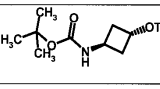
8.20				XX.2	422 $[M+H]^+$	1.26 (B)
8.21				XX.3	415 $[M+H]^+$	1.11 (B)
8.22				XX.5	427 $[M+H]^+$	1.01 (B)
8.23				XX.1	395 $[M+H]^+$	1.26 (B)
8.24				XX.2	406 $[M+H]^+$	1.44 (B)
8.25				XX.4	415 $[M+H]^+$	2.07 (W)
8.26				XX.1	409 $[M+H]^+$	1.37 (B)
8.27				XX.2	420 $[M+H]^+$	1.61 (B)
8.28				XX.3	413 $[M+H]^+$	1.46 (B)
8.29				XX.5	425 $[M+H]^+$	1.27 (B)
8.30				XX.4	429 $[M+H]^+$	1.55 (B)
8.31				XX.1	395 $[M+H]^+$	1.29 (B)
8.32				XX.2	406 $[M+H]^+$	1.48 (B)

[1561]

8.33				XX.5	411 $[M+H]^+$	1.17 (B)
8.34				XX.4	415 $[M+H]^+$	1.44 (B)
8.35				XX.1	421 $[M+H]^+$	1.38 (B)
8.36				XX.2	432 $[M+H]^+$	1.6 (B)
8.37				XX.3	425 $[M+H]^+$	1.46 (B)
8.38				XX.5	437 $[M+H]^+$	1.26 (B)
8.39				XX.4	441 $[M+H]^+$	1.55 (B)
8.40				XX.1	409 $[M+H]^+$	1.38 (B)
8.41				XX.2	420 $[M+H]^+$	1.61 (B)
8.42				XX.3	413 $[M+H]^+$	1.46 (B)
8.43				XX.5	425 $[M+H]^+$	1.27 (B)

8.44		*—CH_3		XX.4	429 $[M+H]^+$	1.55 (B)
8.45		*—CH_3		XX.2	378 $[M+H]^+$	1.23 (B)
8.46		*—CH_3		XX.4	387 $[M+H]^+$	1.19 (B)
8.47		*—CH_3		XX.1	423 $[M+H]^+$	1.08 (B)
8.48		*—CH_3		XX.3	427 $[M+H]^+$	1.11 (B)
8.49		*—CH_3		XX.5	439 $[M+H]^+$	1.01 (B)
8.50		*—CH_3		XX.4	443 $[M+H]^+$	1.2 (B)
8.51		*—CH_3		XX.1	409 $[M+H]^+$	1.34 (B)
8.52		*—CH_3		XX.2	420 $[M+H]^+$	1.55 (B)
8.53		*—CH_3		XX.3	413 $[M+H]^+$	1.44 (B)
8.54		*—CH_3		XX.5	425 $[M+H]^+$	1.23 (B)
8.55		*—CH_3		XX.4	429 $[M+H]^+$	1.51 (B)
8.56		*—CH_3		XX.1	423 $[M+H]^+$	1.42 (B)

[1562]

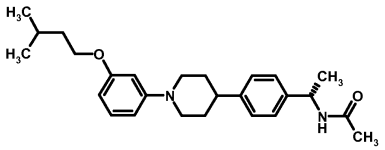
8.57		*—CH_3		XX.2	434 $[M+H]^+$	1.67 (B)
8.58		*—CH_3		XX.3	427 $[M+H]^+$	1.55 (B)
8.59		*—CH_3		XX.5	439 $[M+H]^+$	1.32 (B)
8.60		*—CH_3		XX.4	443 $[M+H]^+$	1.61 (B)
8.61		*—CH_3		XX.4	401 $[M+H]^+$	1.31 (B)
8.62		*—CH_3		XX.3	399 $[M+H]^+$	1.59 (B)
8.63		*—CH_3		1.48	407 $[M+H]^+$	1.62 (A)
8.64		*—CH_3		1.48	407 $[M+H]^+$	2.23 (A)
8.65		*—CH_3		1.48	433 $[M+H]^+$	1.58 (A)
8.66		*—CH_3		1.48	429 $[M+H]^+$	2.02 (A)
8.67		*—CH_3		1.48	445 $[M+H]^+$	1.79 (A)

[1563]

[1564] **실시예 9**

[1565] 실시예 9.1

[1566] (S)-N-[1-(4-{1-[3-(이소펜틸옥시)-페닐]-피페리딘-4-일}-페닐)-에틸]-아세트아미드

[1567] 

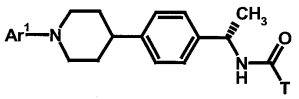
[1568] NaH(광유 중의 60%) 8mg(0.2mmol)을 0℃에서 DMF 2mL 중의 (S)-N-{1-(4-[1-(3-하이드록시페닐)-피페리딘-4-일]-페닐}-에틸)-아세트아미드(화합물 1.27) 34mg(0.10mmol) 및 1-브로모-3-메틸부탄 23mg(0.15mmol)의 혼합물에 첨가한다. 상기 혼합물을 70℃에서 3일 동안 교반한다. 상기 반응 혼합물을 물로 급냉시키고, 여과하고, 용매는 증발시킨다. 상기 잔사는 역상 HPLC(물/MeOH, 0.1% TFA)를 사용하여 정제하여 목적 생성물을 수득한다.

[1569] $C_{10}H_{11}NO$ (M = 408.6g/mol), ESI-MS: 409 $[M+H]^+$

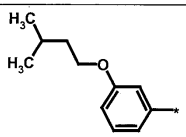
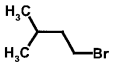
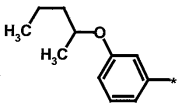
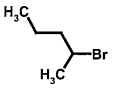
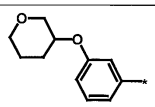
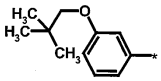
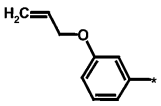
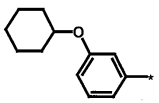
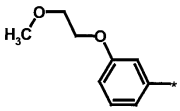
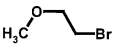
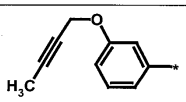
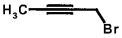
[1570] R_t (HPLC): 1.60분 (방법 B)

[1571] 하기 화학식 9-1의 화합물은 실시예 9.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1572] [화학식 9-1]

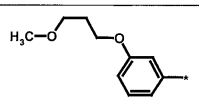
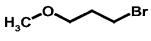
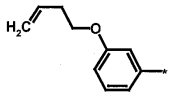
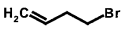
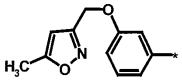
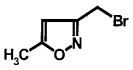
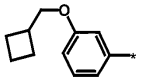
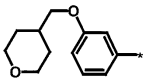
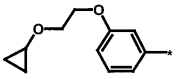
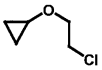
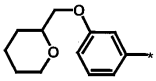
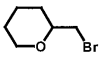
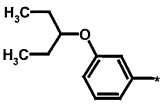
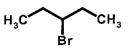
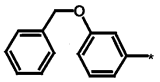
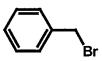
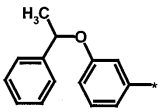
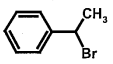
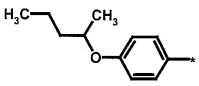
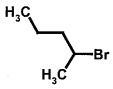


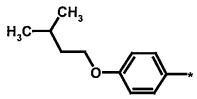
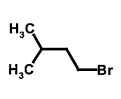
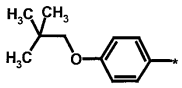
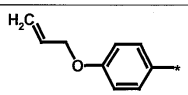
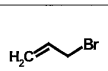
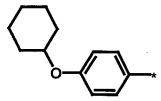
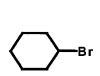
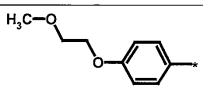
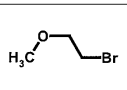
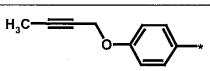
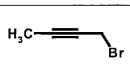
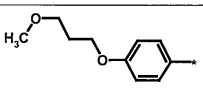
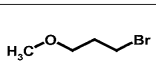
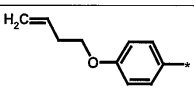
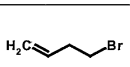
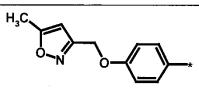
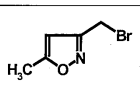
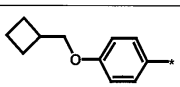
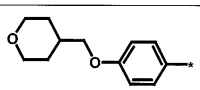
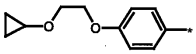
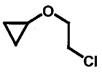
[1573]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC)[분] (방법)
9.1				1.27	409 $[M+H]^+$	1.60 (B)
9.2				1.27	409 $[M+H]^+$	1.55 (B)
9.3				1.27	423 $[M+H]^+$	1.37 (E)
9.4				1.27	409 $[M+H]^+$	1.60 (B)
9.5				1.27	379 $[M+H]^+$	1.32 (B)
9.6				1.27	421 $[M+H]^+$	1.57 (B)
9.7				1.27	397 $[M+H]^+$	1.13 (B)
9.8				1.27	391 $[M+H]^+$	1.33 (B)

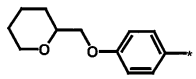
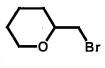
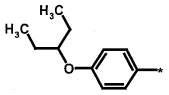
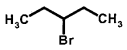
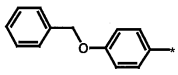
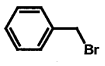
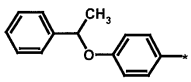
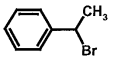
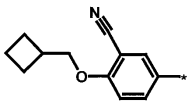
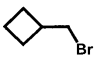
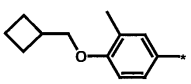
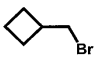
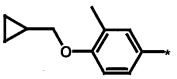
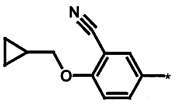
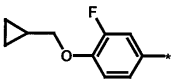
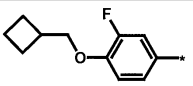
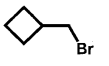
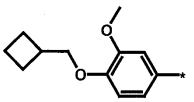
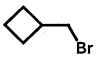
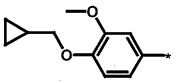
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[1575]

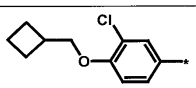
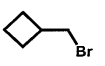
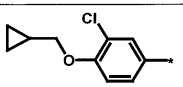
9.9		*—CH_3		1.27	411 $[M+H]^+$	1.26 (B)
9.10		*—CH_3		1.27	393 $[M+H]^+$	1.51 (E)
9.11		*—CH_3		1.27	434 $[M+H]^+$	1.29 (B)
9.12		*—CH_3		1.27	407 $[M+H]^+$	1.54 (B)
9.13		*—CH_3		1.27	437 $[M+H]^+$	1.32 (B)
9.14		*—CH_3		1.27	423 $[M+H]^+$	1.30 (B)
9.15		*—CH_3		1.27	437 $[M+H]^+$	1.35 (B)
9.16		*—CH_3		1.27	409 $[M+H]^+$	1.54 (B)
9.17		*—CH_3		1.27	429 $[M+H]^+$	1.49 (B)
9.18		*—CH_3		1.27	443 $[M+H]^+$	1.89 (B)
9.19		*—CH_3		1.48	409 $[M+H]^+$	1.40 (B)

9.20		*—CH_3		1.48	409 $[M+H]^+$	1.43 (B)
9.21		*—CH_3		1.48	409 $[M+H]^+$	1.44 (B)
9.22		*—CH_3		1.48	379 $[M+H]^+$	1.19 (B)
9.23		*—CH_3		1.48	421 $[M+H]^+$	1.54 (E)
9.24		*—CH_3		1.48	397 $[M+H]^+$	1.05 (B)
9.25		*—CH_3		1.48	391 $[M+H]^+$	1.18 (B)
9.26		*—CH_3		1.48	411 $[M+H]^+$	1.16 (B)
9.27		*—CH_3		1.48	393 $[M+H]^+$	1.28 (B)
9.28		*—CH_3		1.48	434 $[M+H]^+$	1.15 (B)
9.29		*—CH_3		1.48	407 $[M+H]^+$	1.38 (B)
9.30		*—CH_3		1.48	437 $[M+H]^+$	1.19 (B)
9.31		*—CH_3		1.48	423 $[M+H]^+$	1.18 (B)

[1576]

9.32		*—CH_3		1.48	437 $[M+H]^+$	1.23 (B)
9.33		*—CH_3		1.48	409 $[M+H]^+$	1.39 (B)
9.34		*—CH_3		1.48	429 $[M+H]^+$	1.34 (B)
9.35		*—CH_3		1.48	443 $[M+H]^+$	1.38 (B)
9.36		*—CH_3		XX.2	432 $[M+H]^+$	1.43 (AB)
9.37		*—CH_3		XX.1	421 $[M+H]^+$	1.63 (P)
9.38		*—CH_3		XX.1	407 $[M+H]^+$	1.52 (P)
9.40		*—CH_3		XX.2	418 $[M+H]^+$	1.74 (P)
9.41		*—CH_3		XX.3	411 $[M+H]^+$	1.58 (P)
9.42		*—CH_3		XX.3	425 $[M+H]^+$	1.78 (P)
9.43		*—CH_3		XX.5	437 $[M+H]^+$	1.52 (P)
9.44		*—CH_3		XX.5	423 $[M+H]^+$	1.38 (P)

[1577]

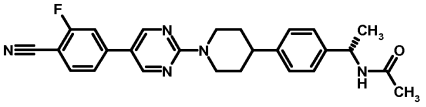
9.45		*—CH_3		XX.4	441 $[M+H]^+$	1.87 (P)
9.46		*—CH_3		XX.4	427 $[M+H]^+$	1.69 (P)

[1578]

[1579] **실시예 10**

[1580] 실시예 10.1

[1581] (S)-N-[1-(4-{1-[5-(4-시아노-3-플루오로페닐)-피리미딘-2-일]-피페리딘-4-일}-페닐)-에틸]-아세트아미드

[1582] 

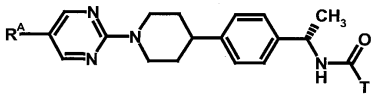
[1583] 아르곤 대기하에, 포화 Na_2CO_3-용액 0.1mL 및 비스(트리페닐포스핀)-팔라듐(II) 클로라이드 3mg(0.004mmol)을, 디옥산 2mL/MeOH 1mL 중의 4-시아노-3-플루오로페닐보론산 16mg(0.10mmol) 및 (S)-N-(1-{4-[1-(5-요오도피리미딘-2-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드(화합물 4.43) 45mg(0.10mmol)의 혼합물에 첨가한다. 상기 혼합물을 70℃에서 6시간 동안 교반한다. 그 시간 후, 상기 혼합물을 DMF로 희석하고 여과한다. 상기 여액은 역상 HPLC(물/MeOH, 0.1% TFA)를 사용하여 정제하여 목적 생성물을 수득한다.

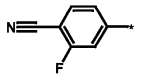
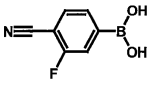
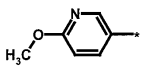
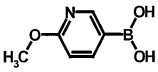
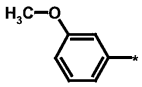
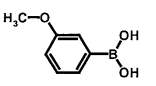
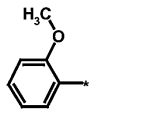
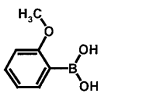
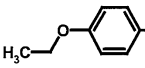
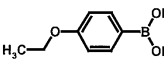
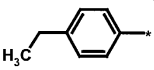
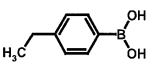
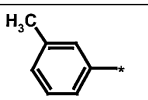
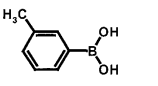
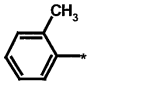
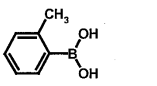
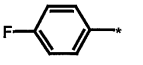
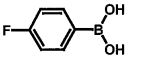
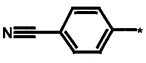
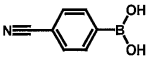
[1584] $C_{10}H_{11}NO$ (M = 443.5g/mol), ESI-MS: 444 $[M+H]^+$

[1585] R_t (HPLC): 2.28분 (방법 B)

[1586] 하기 화학식 10-1의 화합물은 실시예 10.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다. Boc-보호된 아미노 보론산이 사용되는 경우, Boc 그룹은 최종적으로 TFA/CH_2Cl_2 = 1:1(5% H_2O)를 사용하여 제거한다.

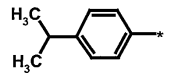
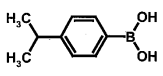
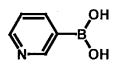
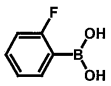
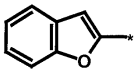
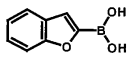
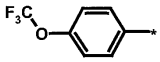
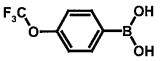
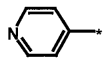
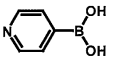
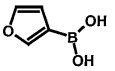
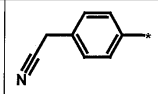
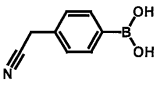
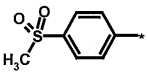
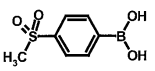
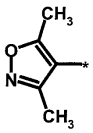
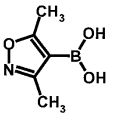
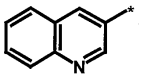
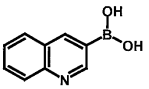
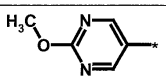
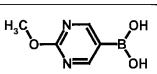
[1587] [화학식 10-1]

[1588] 

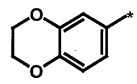
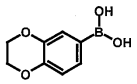
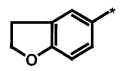
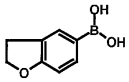
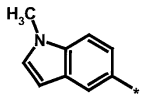
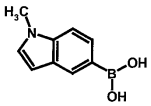
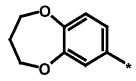
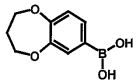
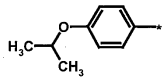
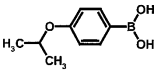
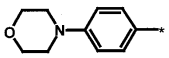
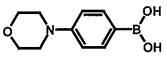
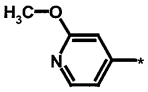
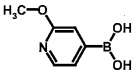
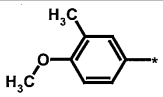
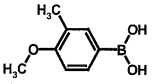
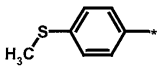
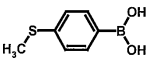
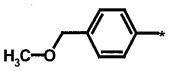
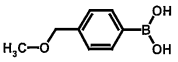
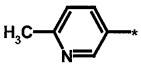
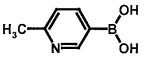
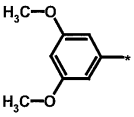
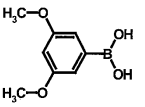
실시예	R^A	T	E 1	E 2	ESI-MS [m/z]	R_tHPLC)[분] (방법)
10.1				4.43	432 $[M+H]^+$	2.28 (B)
10.2				4.43	432 $[M+H]^+$	2.28 (B)
10.3				4.43	431 $[M+H]^+$	2.35 (B)
10.4				4.43	431 $[M+H]^+$	2.29 (B)
10.5				4.43	445 $[M+H]^+$	2.28 (B)
10.6				4.43	429 $[M+H]^+$	2.17 (B)
10.7				4.43	415 $[M+H]^+$	2.12 (B)
10.8				4.43	415 $[M+H]^+$	2.09 (B)
10.9				4.43	419 $[M+H]^+$	2.05 (B)
10.10				4.43	426 $[M+H]^+$	1.92 (B)

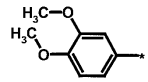
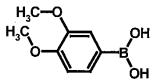
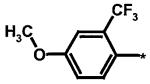
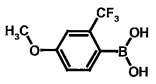
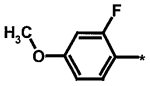
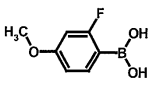
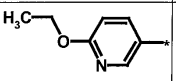
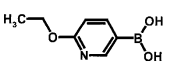
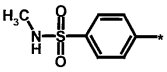
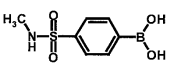
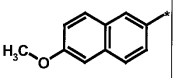
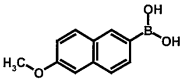
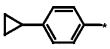
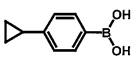
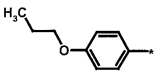
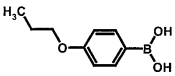
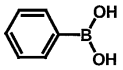
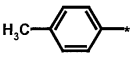
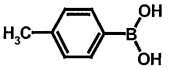
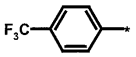
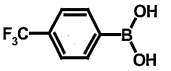
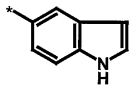
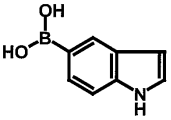
[1589]

[1590]

10.11				4.43	443 [M+H]+	2.21 (B)
10.12				4.43	402 [M+H]+	1.34 (B)
10.13				4.43	419 [M+H]+	2.07 (B)
10.14				4.43	441 [M+H]+	2.20 (B)
10.15				4.43	485 [M+H]+	2.13 (B)
10.16				4.43	402 [M+H]+	1.24 (B)
10.17				4.43	390 [M+H]+	1.90 (B)
10.18				4.43	440 [M+H]+	1.84 (B)
10.19				4.43	479 [M+H]+	1.74 (B)
10.20				4.43	420 [M+H]+	1.84 (B)
10.21				4.43	452 [M+H]+	1.77 (B)
10.22				4.43	433 [M+H]+	1.81 (B)

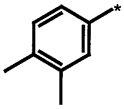
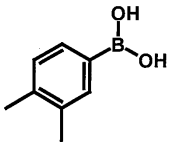
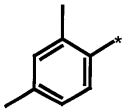
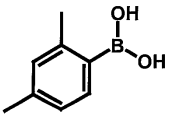
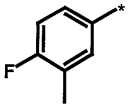
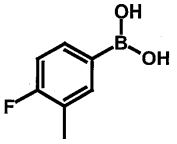
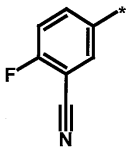
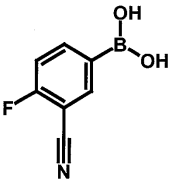
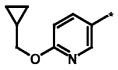
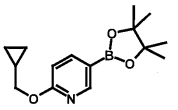
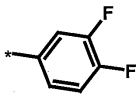
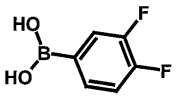
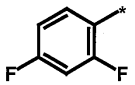
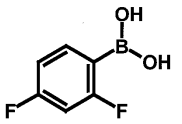
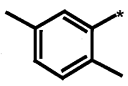
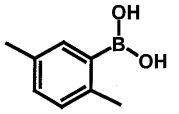
[1591]

10.23		*—CH_3		4.43	459 $[M+H]^+$	2.01 (B)
10.24		*—CH_3		4.43	443 $[M+H]^+$	2.01 (B)
10.25		*—CH_3		4.43	454 $[M+H]^+$	2.01 (B)
10.26		*—CH_3		4.43	473 $[M+H]^+$	2.03 (B)
10.27		*—CH_3		4.43	459 $[M+H]^+$	2.10 (B)
10.28		*—CH_3		4.43	486 $[M+H]^+$	1.92 (B)
10.29		*—CH_3		4.43	432 $[M+H]^+$	1.91 (B)
10.30		*—CH_3		4.43	445 $[M+H]^+$	2.10 (B)
10.31		*—CH_3		4.43	447 $[M+H]^+$	2.12 (B)
10.32		*—CH_3		4.43	445 $[M+H]^+$	1.99 (B)
10.33		*—CH_3		4.43	416 $[M+H]^+$	1.28 (B)
10.34		*—CH_3		4.43	461 $[M+H]^+$	2.06 (B)

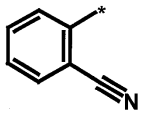
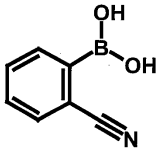
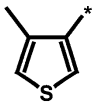
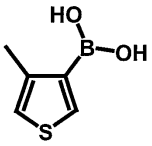
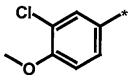
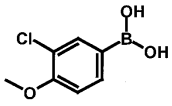
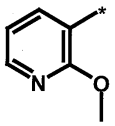
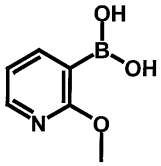
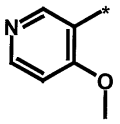
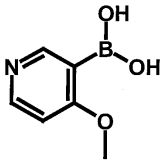
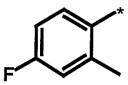
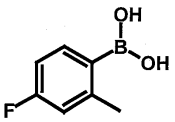
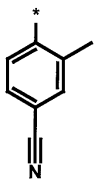
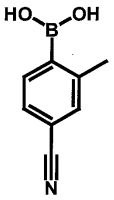
10.35		*—CH_3		4.43	461 $[M+H]^+$	1.90 (B)
10.36		*—CH_3		4.43	499 $[M+H]^+$	2.08 (B)
10.37		*—CH_3		4.43	449 $[M+H]^+$	2.07 (B)
10.38		*—CH_3		4.43	446 $[M+H]^+$	2.02 (B)
10.39		*—CH_3		4.43	494 $[M+H]^+$	1.75 (B)
10.40		*—CH_3		4.43	481 $[M+H]^+$	2.16 (B)
10.41		*—CH_3		4.43	441 $[M+H]^+$	2.17 (B)
10.42		*—CH_3		4.43	459 $[M+H]^+$	2.14 (B)
10.43		*—CH_3		4.43	401 $[M+H]^+$	2.05 (B)
10.44		*—CH_3		4.43	415 $[M+H]^+$	2.12 (B)
10.45		*—CH_3		4.43	469 $[M+H]^+$	2.13 (B)
10.46		*—CH_3		4.43	440 $[M+H]^+$	1.96 (W)

[1592]

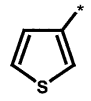
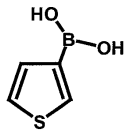
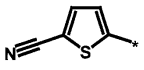
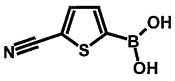
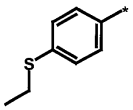
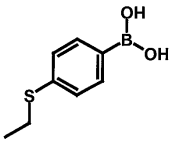
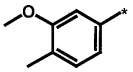
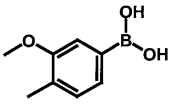
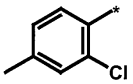
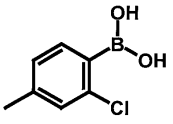
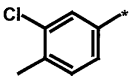
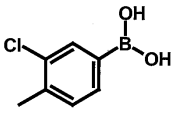
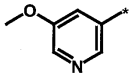
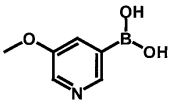
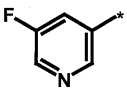
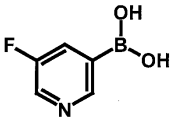
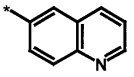
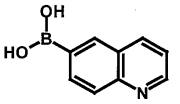
[1593]

10.47				4.43	429 $[M+H]^+$	2.28 (W)
10.48				4.43	429 $[M+H]^+$	2.25 (W)
10.49				4.43	433 $[M+H]^+$	2.21 (W)
10.50				4.43	444 $[M+H]^+$	1.97 (W)
10.51				4.43	472 $[M+H]^+$	2.16 (W)
10.52				4.43	437 $[M+H]^+$	2.12 (W)
10.53				4.43	437 $[M+H]^+$	2.13 (W)
10.54				4.43	429 $[M+H]^+$	2.25 (W)

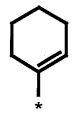
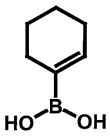
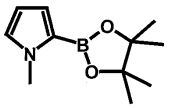
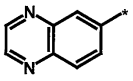
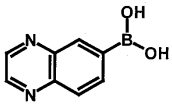
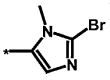
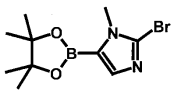
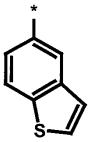
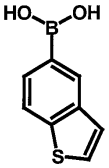
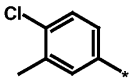
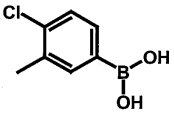
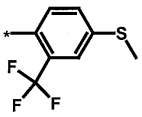
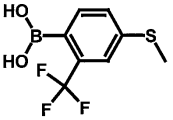
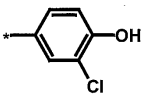
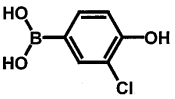
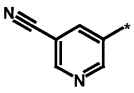
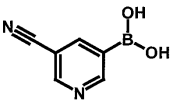
[1594]

10.55		*—CH_3		4.43	426 $[M+H]^+$	1.92 (W)
10.56		*—CH_3		4.43	421 $[M+H]^+$	2.13 (W)
10.57		*—CH_3		4.43	465 $[M+H]^+$	2.15 (W)
10.58		*—CH_3		4.43	432 $[M+H]^+$	2.01 (W)
10.59		*—CH_3		4.43	432 $[M+H]^+$	2.01 (W)
10.60		*—CH_3		4.43	433 $[M+H]^+$	2.16 (W)
10.61		*—CH_3		4.43	440 $[M+H]^+$	2.01 (W)

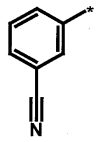
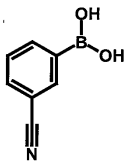
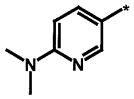
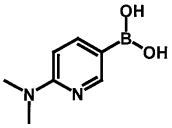
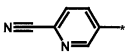
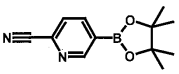
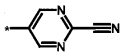
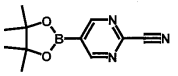
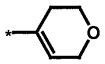
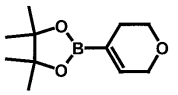
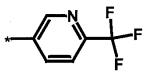
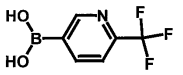
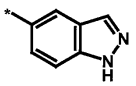
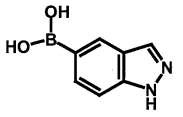
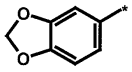
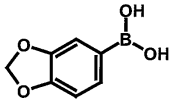
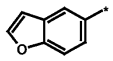
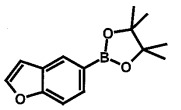
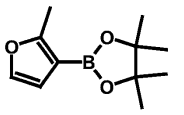
[1595]

10.62		*—CH_3		4.43	407 $[M+H]^+$	2.07 (W)
10.63		*—CH_3		4.43	432 $[M+H]^+$	2.01 (W)
10.64		*—CH_3		4.43	461 $[M+H]^+$	2.25 (W)
10.65		*—CH_3		4.43	445 $[M+H]^+$	2.22 (W)
10.66		*—CH_3		4.43	449 $[M+H]^+$	2.26 (W)
10.67		*—CH_3		4.43	449 $[M+H]^+$	2.35 (W)
10.68		*—CH_3		4.43	432 $[M+H]^+$	1.88 (W)
10.69		*—CH_3		4.43	420 $[M+H]^+$	1.9 (W)
10.70		*—CH_3		4.43	452 $[M+H]^+$	1.99 (W)

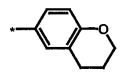
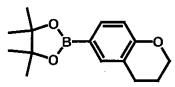
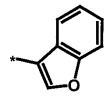
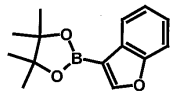
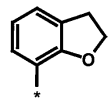
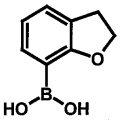
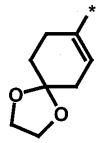
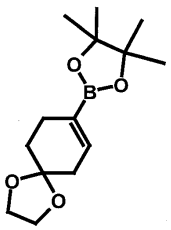
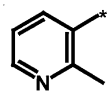
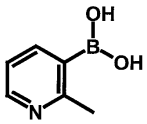
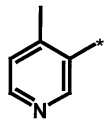
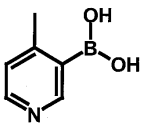
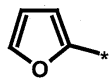
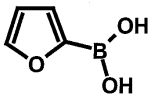
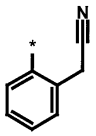
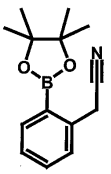
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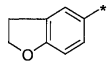
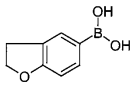
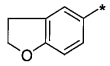
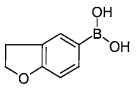
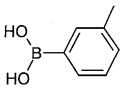
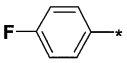
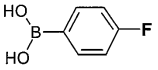
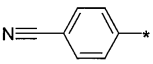
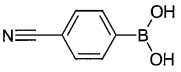
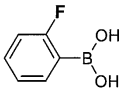
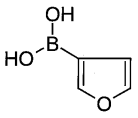
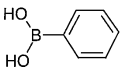
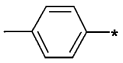
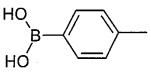
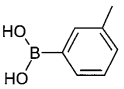
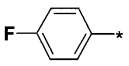
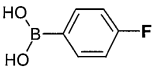
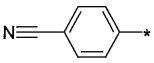
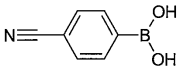
10.71		*—CH_3		4.43	405 $[M+H]^+$	2.26 (W)
10.72		*—CH_3		4.43	404 $[M+H]^+$	1.99 (W)
10.73		*—CH_3		4.43	453 $[M+H]^+$	1.95 (W)
10.74		*—CH_3		4.43	483 $[M+H]^+$	1.82 (W)
10.75		*—CH_3		4.43	457 $[M+H]^+$	2.22 (W)
10.76		*—CH_3		4.43	449 $[M+H]^+$	2.31 (W)
10.77		*—CH_3		4.43	515 $[M+H]^+$	2.21 (W)
10.78		*—CH_3		4.43	451 $[M+H]^+$	1.5 (W)
10.79		*—CH_3		4.43	427 $[M+H]^+$	1.8 (W)

[1597]

10.80		*—CH_3		4.43	426 $[M+H]^+$	1.94 (W)
10.81		*—CH_3		4.43	445 $[M+H]^+$	2 (W)
10.82		*—CH_3		4.43	427 $[M+H]^+$	1.79 (W)
10.83		*—CH_3		4.43	428 $[M+H]^+$	0.51 (V)
10.84		*—CH_3		4.43	407 $[M+H]^+$	1.88 (W)
10.85		*—CH_3		4.43	470 $[M+H]^+$	1.98 (W)
10.86		*—CH_3		4.43	441 $[M+H]^+$	1.88 (W)
10.87		*—CH_3		4.43	445 $[M+H]^+$	2.09 (W)
10.88		*—CH_3		4.43	441 $[M+H]^+$	2.14 (W)
10.89		*—CH_3		4.43	405 $[M+H]^+$	2.08 (W)

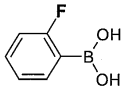
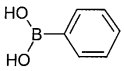
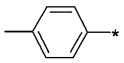
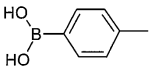
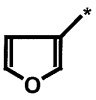
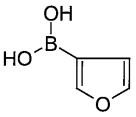
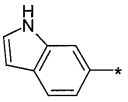
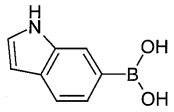
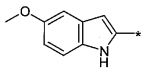
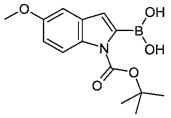
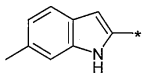
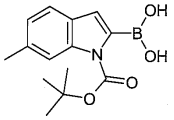
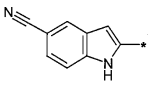
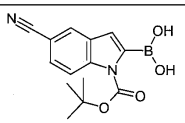
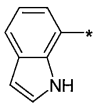
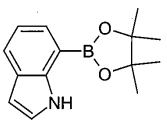
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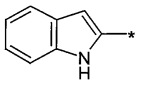
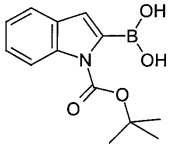
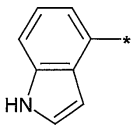
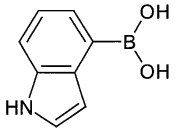
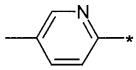
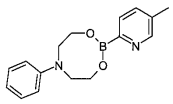
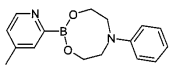
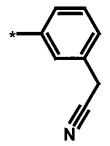
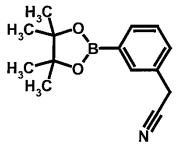
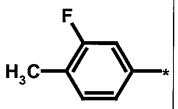
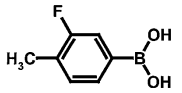
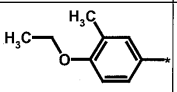
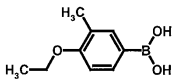
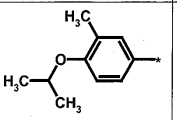
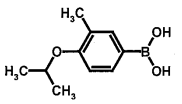
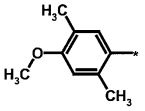
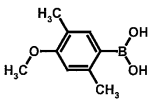
10.90				4.43	457 $[M+H]^+$	2.14 (B)
10.91				4.43	441 $[M+H]^+$	2.21 (W)
10.92				4.43	443 $[M+H]^+$	2.15 (W)
10.93				4.43	463 $[M+H]^+$	1.96 (W)
10.94				4.43	416 $[M+H]^+$	1.87 (W)
10.95				4.43	416 $[M+H]^+$	1.87 (W)
10.96				4.43	391 $[M+H]^+$	0.54 (V)
10.97				4.43	440 $[M+H]^+$	1.9 (W)

10.98				XVII I.1	469 $[M+H]^+$	2.13 (Z)
10.99				XVII I.2	472 $[M+H]^+$	2.08 (Z)
10.100				XVII I.1	441 $[M+H]^+$	2.20 (Z)
10.101				XVII I.1	445 $[M+H]^+$	2.14 (Z)
10.102				XVII I.1	452 $[M+H]^+$	2.05 (Z)
10.103				XVII I.1	445 $[M+H]^+$	2.19 (Z)
10.104				XVII I.1	417 $[M+H]^+$	2.02 (Z)
10.105				XVII I.1	427 $[M+H]^+$	2.17 (Z)
10.106				XVII I.1	441 $[M+H]^+$	2.21 (Z)
10.107				XVII I.2	444 $[M+H]^+$	2.21 (Z)
10.108				XVII I.1	448 $[M+H]^+$	2.14 (Z)
10.109				XVII I.2	455 $[M+H]^+$	2.01 (Z)

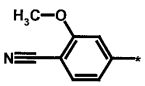
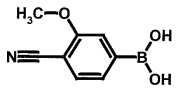
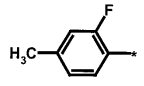
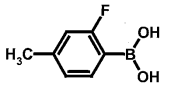
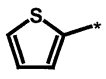
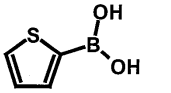
[1599]

[1600]

10.110				XVII I.2	448 $[M+H]^+$	2.14 (Z)
10.111				XVII I.2	430 $[M+H]^+$	2.15 (Z)
10.112				XVII I.1	444 $[M+H]^+$	2.27 (Z)
10.113				XVII I.2	420 $[M+H]^+$	1.98 (Z)
10.114				4.43	440 $[M+H]^+$	2.69 (R)
10.115				4.43	470 $[M+H]^+$	2.70 (R)
10.116				4.43	454 $[M+H]^+$	2.81 (R)
10.117				4.43	465 $[M+H]^+$	2.66 (R)
10.118				4.43	440 $[M+H]^+$	2.74 (R)

10.119		*—CH_3		4.43	440 $[M+H]^+$	2.75 (R)
10.120		*—CH_3		4.43	440 $[M+H]^+$	2.64 (R)
10.121		*—CH_3		4.43	416 $[M+H]^+$	2.64 (R)
10.122		*—CH_3		4.43	416 $[M+H]^+$	2.64 (R)
10.123		*—CH_3		4.43	440 $[M+H]^+$	2.17 (P)
10.124		*—CH_3		4.43	443 $[M+H]^+$	2.46 (P)
10.125		*—CH_3		4.43	459 $[M+H]^+$	2.47 (P)
10.126		*—CH_3		4.43	473 $[M+H]^+$	2.49 (P)
10.127		*—CH_3		4.43	459 $[M+H]^+$	2.43 (P)

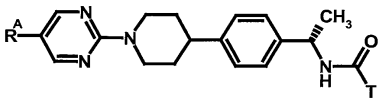
[1601]

10.128		*—CH_3		4.43	456 $[M+H]^+$	2.24 (P)
10.129		*—CH_3		4.43	433 $[M+H]^+$	2.45 (P)
10.130		*—CH_3		4.43	407 $[M+H]^+$	2.39 (P)

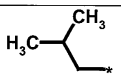
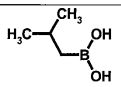
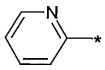
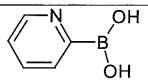
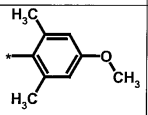
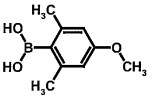
[1602]

[1603] 하기 화학식 10-2의 화합물은, 비스(트리페닐포스핀)-팔라듐(II) 클로라이드/Na_2CO_3 대신에, 톨루엔/물 중의 팔라듐(II) 아세테이트/트리사이클로헥실포스핀/인산삼칼륨 수화물을 사용하여 실시예 10.1과 유사하게 제조한다. 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1604] [화학식 10-2]



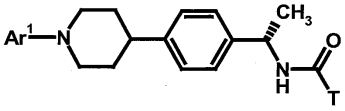
[1605]

실시예	R^A	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
10.201				4.43	381 $[M+H]^+$	2.19 (B)
10.202				4.43	365 $[M+H]^+$	2.09 (A)
10.203				4.43	402 $[M+H]^+$	2.56 (R)
10.204				4.43	459 $[M+H]^+$	2.82 (R)

[1606]

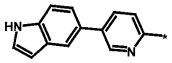
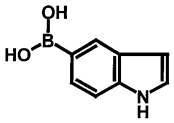
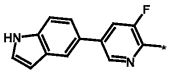
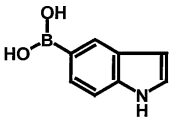
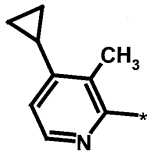
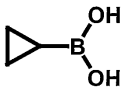
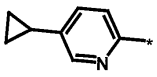
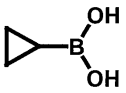
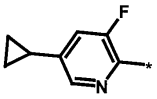
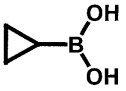
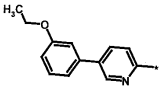
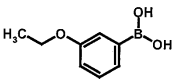
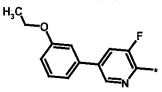
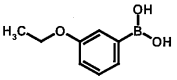
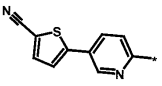
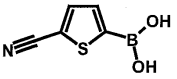
[1607] 하기 화학식 10-3의 화합물은 실시예 10.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

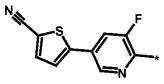
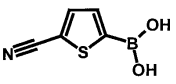
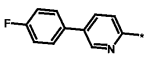
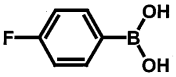
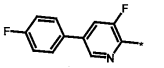
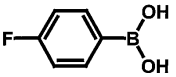
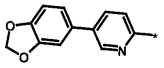
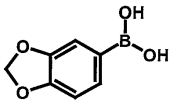
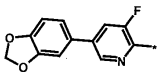
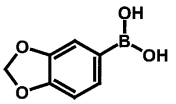
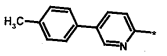
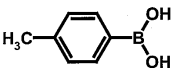
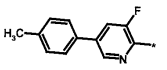
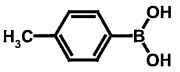
[1608] [화학식 10-3]



[1609]

[1610]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
10.301				5.12	439 $[M+H]^+$	1.74 (W)
10.302				5.38	457 $[M+H]^+$	1.84 (W)
10.303				5.39	378 $[M+H]^+$	1.87 (W)
10.304				5.12	364 $[M+H]^+$	1.1 (B)
10.305				5.38	382 $[M+H]^+$	1.89 (W)
10.306				5.12	444 $[M+H]^+$	1.94 (W)
10.307				5.38	462 $[M+H]^+$	2.04 (W)
10.308				5.12	431 $[M+H]^+$	1.78 (W)

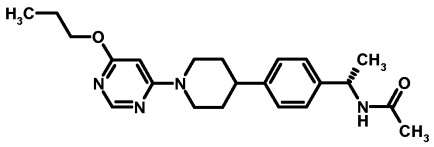
10.309		*—CH_3		5.38	449 $[M+H]^+$	1.88 (W)
10.310		*—CH_3		5.12	418 $[M+H]^+$	1.89 (W)
10.311		*—CH_3		5.38	436 $[M+H]^+$	1.98 (W)
10.312		*—CH_3		5.12	444 $[M+H]^+$	1.87 (W)
10.313		*—CH_3		5.38	462 $[M+H]^+$	1.97 (W)
10.314		*—CH_3		5.12	414 $[M+H]^+$	1.98 (W)
10.315		*—CH_3		5.38	432 $[M+H]^+$	2.08 (W)

[1611]

[1612] **실시예 11**

[1613] 실시예 11.1

[1614] (S)-N-(1-{4-[1-(6-프로폭시-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1615] 

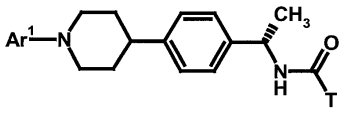
[1616] 나트륨 n-프로폭사이드(n-프로판올 중의 20%) 1.33mL(2.79mmol)를, 아세토니트릴 0.5mL 중의 (S)-N-(1-{4-[1-(6-클로로-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드(XIV.1) 200mg(0.56mmol)에 첨가한다. 상기 혼합물을 마이크로웨이브 조사하에 140℃에서 1분 동안 가열한다. 그 시간 후, 물을 첨가하고, 상기 혼합물은 디클로로메탄으로 추출한다. 용매를 증발시키고 잔사는 역상 HPLC(칼럼: Waters XBridge 5μM; 용출제 A: 물 + 0.3% NH_4OH, 용출제 B: MeOH)를 사용하여 정제하여 목적 생성물을 수득한다.

[1617] $C_{22}H_{30}N_4O_2$ (M = 382.5g/mol), ESI-MS: 383 $[M+H]^+$

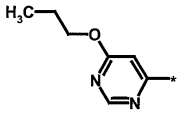
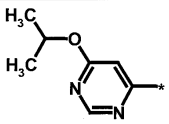
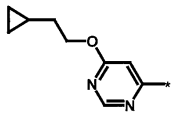
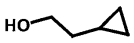
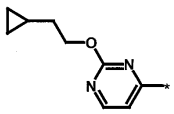
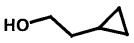
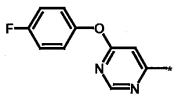
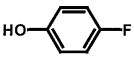
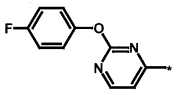
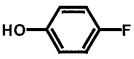
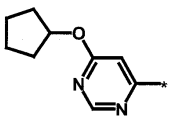
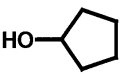
[1618] R_t (HPLC): 2.04분 (방법 A)

[1619] 하기 화학식 11-1의 화합물은 실시예 11.1과 유사하게 제조한다. 유리 알코올이 사용되는 경우, 상응하는 알코올(5.0당량)은 NMP, XIV.1 또는 XIV.3에 각각 용해시키고, 칼륨 3급-부톡사이드(2.5당량)를 첨가한 다음, 상기 혼합물은 밤새 130℃에서 교반한다. 아민이 친핵체로서 사용되는 경우, 상응하는 아민(5.0당량)은 DMSO에 용해시킨다. DIPEA(5.0 내지 10.0당량) 및 XIV.1 또는 XIV.3을 각각 첨가하고, 상기 혼합물은 밤새 130℃에서 교반한다. 화합물 11.116이 제2 생성물로서 수득된다. 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

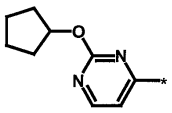
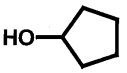
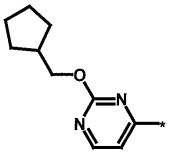
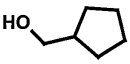
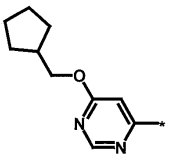
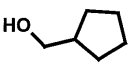
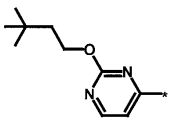
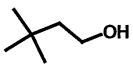
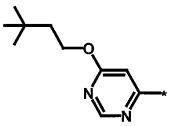
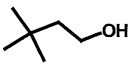
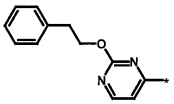
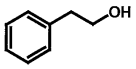
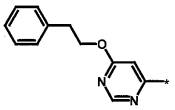
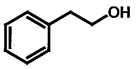
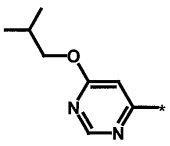
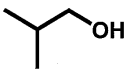
[1620] [화학식 11-1]



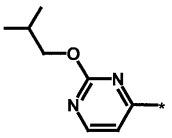
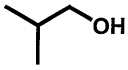
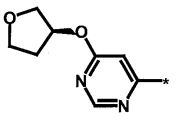
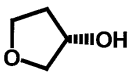
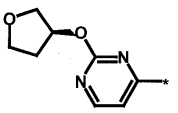
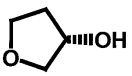
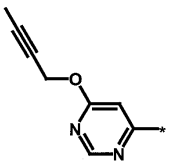
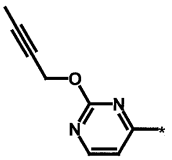
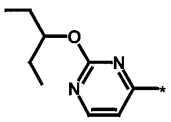
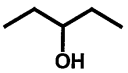
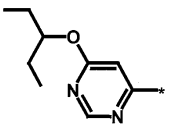
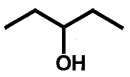
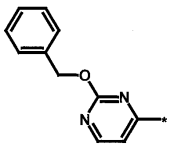
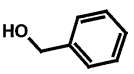
[1621]

실시예	Ar¹	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
11.1			나트륨 n-프로폭시드	XIV.1	383 $[M+H]^+$	2.04 (A)
11.2			나트륨 2급 프로폭시드	XIV.1	383 $[M+H]^+$	2.01 (A)
11.3				XIV.1	409 $[M+H]^+$	2.01 (W)
11.4				XIV.3	409 $[M+H]^+$	1.98 (W)
11.5				XIV.1	435 $[M+H]^+$	1.9 (W)
11.6				XIV.3	435 $[M+H]^+$	1.88 (W)
11.7				XIV.1	409 $[M+H]^+$	2.01 (W)

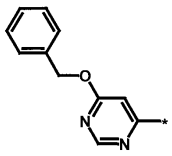
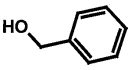
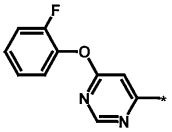
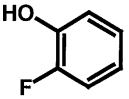
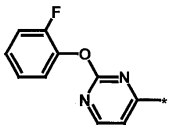
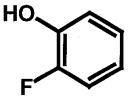
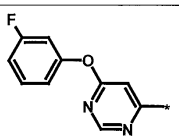
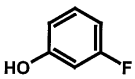
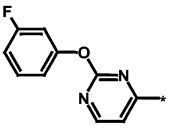
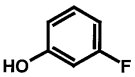
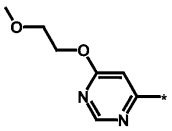
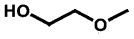
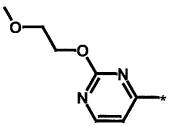
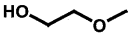
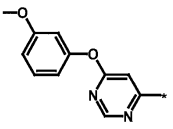
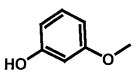
[1622]

11.8		*—CH_3		XIV.3	409 $[M+H]^+$	1.99 (W)
11.9		*—CH_3		XIV.3	423 $[M+H]^+$	2.07 (W)
11.10		*—CH_3		XIV.1	423 $[M+H]^+$	2.13 (W)
11.11		*—CH_3		XIV.3	425 $[M+H]^+$	2.09 (W)
11.12		*—CH_3		XIV.1	425 $[M+H]^+$	2.16 (W)
11.13		*—CH_3		XIV.3	445 $[M+H]^+$	2.01 (W)
11.14		*—CH_3		XIV.1	445 $[M+H]^+$	2.06 (W)
11.15		*—CH_3		XIV.1	397 $[M+H]^+$	2.00 (W)

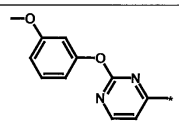
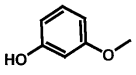
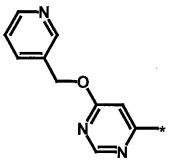
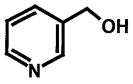
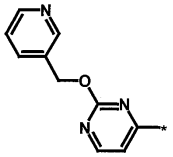
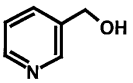
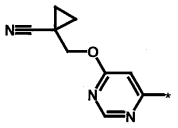
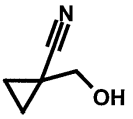
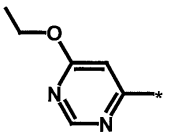
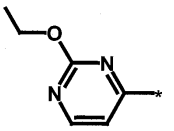
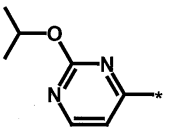
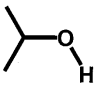
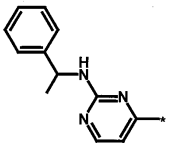
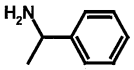
[1623]

11.16		*—CH_3		XIV.3	397 $[M+H]^+$	1.97 (W)
11.17		*—CH_3		XIV.1	411 $[M+H]^+$	1.76 (W)
11.18		*—CH_3		XIV.3	411 $[M+H]^+$	1.7 (W)
11.19		*—CH_3		XIV.1	393 $[M+H]^+$	1.86 (W)
11.20		*—CH_3		XIV.3	393 $[M+H]^+$	1.82 (W)
11.21		*—CH_3		XIV.3	411 $[M+H]^+$	2.01 (W)
11.22		*—CH_3		XIV.1	411 $[M+H]^+$	0.43 (V)
11.23		*—CH_3		XIV.3	431 $[M+H]^+$	1.95 (W)

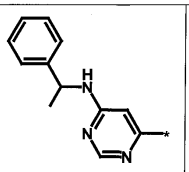
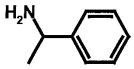
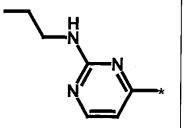
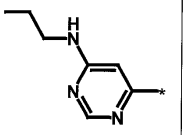
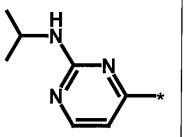
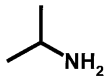
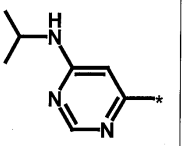
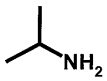
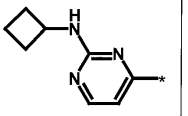
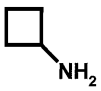
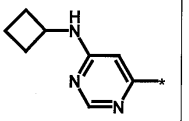
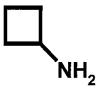
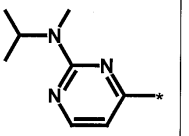
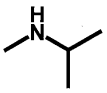
[1624]

11.24		*—CH_3		XIV.1	431 $[M+H]^+$	2.02 (W)
11.25		*—CH_3		XIV.1	435 $[M+H]^+$	1.9 (W)
11.26		*—CH_3		XIV.3	435 $[M+H]^+$	1.84 (W)
11.27		*—CH_3		XIV.1	435 $[M+H]^+$	1.92 (W)
11.28		*—CH_3		XIV.3	435 $[M+H]^+$	1.89 (W)
11.29		*—CH_3		XIV.1	399 $[M+H]^+$	1.74 (W)
11.30		*—CH_3		XIV.3	399 $[M+H]^+$	1.7 (W)
11.31		*—CH_3		XIV.1	447 $[M+H]^+$	1.9 (W)

[1625]

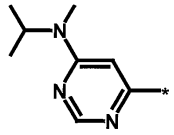
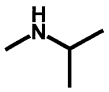
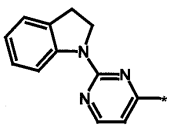
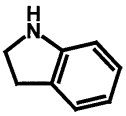
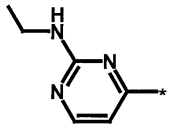
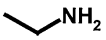
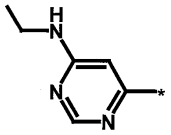
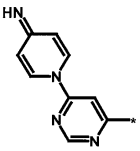
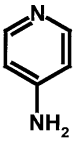
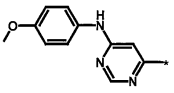
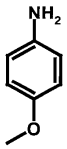
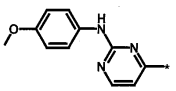
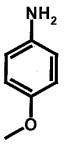
11.32		*—CH_3		XIV.3	447 $[M+H]^+$	1.87 (W)
11.33		*—CH_3		XIV.1	432 $[M+H]^+$	1.77 (W)
11.34		*—CH_3		XIV.3	432 $[M+H]^+$	1.7 (W)
11.35		*—CH_3		XIV.1	420 $[M+H]^+$	1.74 (W)
11.36		*—CH_3		XIV.1	369 $[M+H]^+$	1.83 (W)
11.37		*—CH_3		XIV.3	369 $[M+H]^+$	1.81 (W)
11.38		*—CH_3		XIV.3	383 $[M+H]^+$	1.88 (W)
11.39		*—CH_3		XIV.3	444 $[M+H]^+$	1.92 (W)

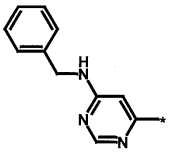
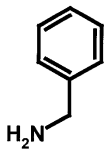
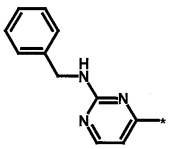
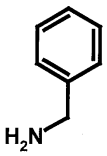
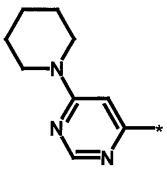
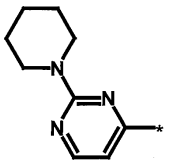
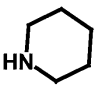
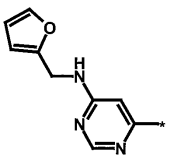
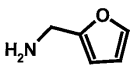
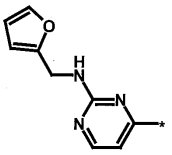
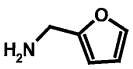
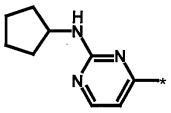
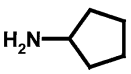
[1626]

11.40		*—CH_3		XIV.1	444 $[M+H]^+$	1.8 (W)
11.41		*—CH_3		XIV.3	382 $[M+H]^+$	1.81 (W)
11.42		*—CH_3		XIV.1	382 $[M+H]^+$	1.68 (W)
11.43		*—CH_3		XIV.3	382 $[M+H]^+$	1.82 (W)
11.44		*—CH_3		XIV.1	382 $[M+H]^+$	1.68 (W)
11.45		*—CH_3		XIV.3	394 $[M+H]^+$	1.85 (W)
11.46		*—CH_3		XIV.1	394 $[M+H]^+$	1.73 (W)
11.47		*—CH_3		XIV.3	396 $[M+H]^+$	1.94 (W)

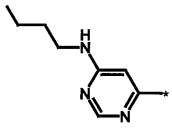
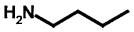
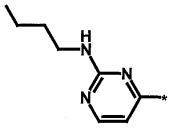
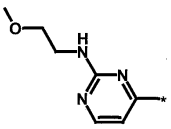
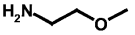
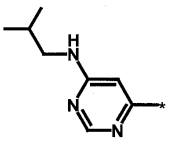
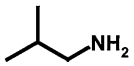
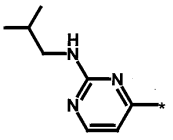
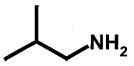
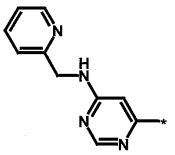
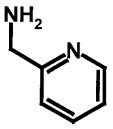
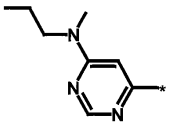
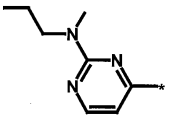
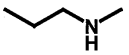
[1627]

[1628]

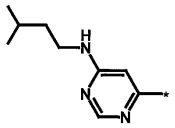
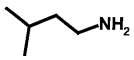
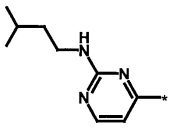
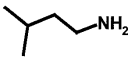
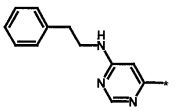
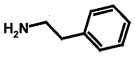
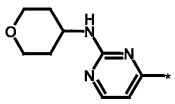
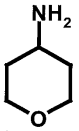
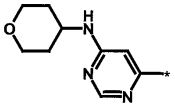
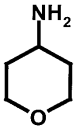
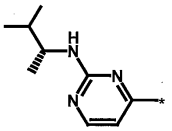
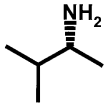
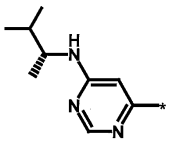
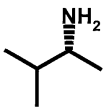
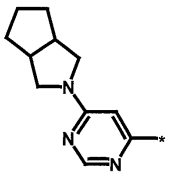
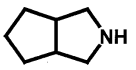
11.48		*—CH_3		XIV.1	396 $[M+H]^+$	1.79 (W)
11.49		*—CH_3		XIV.3	442 $[M+H]^+$	2.07 (W)
11.50		*—CH_3		XIV.3	368 $[M+H]^+$	1.73 (W)
11.51		*—CH_3		XIV.1	368 $[M+H]^+$	1.6 (W)
11.52		*—CH_3		XIV.1	417 $[M+H]^+$	1.21 (B)
11.53		*—CH_3		XIV.1	446 $[M+H]^+$	1.74 (W)
11.54		*—CH_3		XIV.3	446 $[M+H]^+$	1.81 (W)

11.55		*—CH_3		XIV.1	430 $[M+H]^+$	1.75 (W)
11.56		*—CH_3		XIV.3	430 $[M+H]^+$	1.87 (W)
11.57		*—CH_3		XIV.1	408 $[M+H]^+$	1.83 (W)
11.58		*—CH_3		XIV.3	408 $[M+H]^+$	1.97 (W)
11.59		*—CH_3		XIV.1	420 $[M+H]^+$	1.65 (W)
11.60		*—CH_3		XIV.3	420 $[M+H]^+$	1.77 (W)
11.61		*—CH_3		XIV.3	408 $[M+H]^+$	1.92 (W)

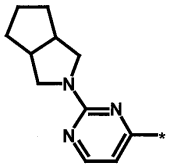
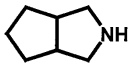
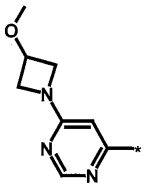
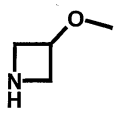
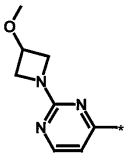
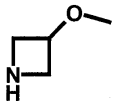
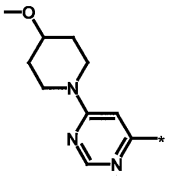
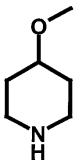
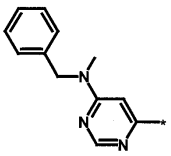
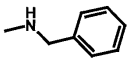
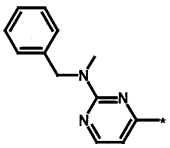
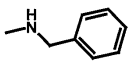
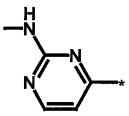
[1629]

11.62		*—CH_3		XIV.1	396 $[M+H]^+$	1.78 (W)
11.63		*—CH_3		XIV.3	396 $[M+H]^+$	1.9 (W)
11.64		*—CH_3		XIV.3	398 $[M+H]^+$	1.66 (W)
11.65		*—CH_3		XIV.1	396 $[M+H]^+$	1.76 (W)
11.66		*—CH_3		XIV.3	396 $[M+H]^+$	1.89 (W)
11.67		*—CH_3		XIV.1	431 $[M+H]^+$	1.55 (W)
11.68		*—CH_3		XIV.1	396 $[M+H]^+$	1.8 (W)
11.69		*—CH_3		XIV.3	396 $[M+H]^+$	1.95 (W)

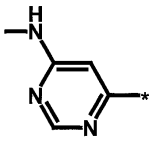
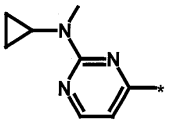
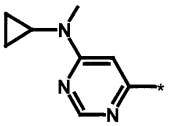
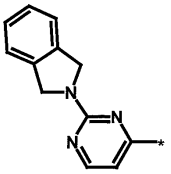
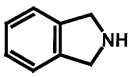
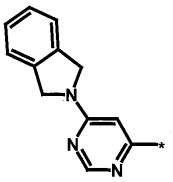
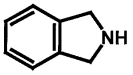
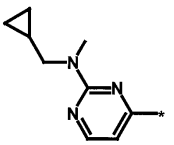
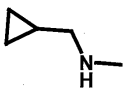
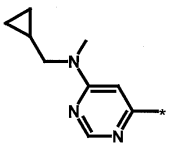
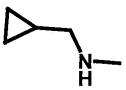
[1630]

11.70		*—CH_3		XIV.1	410 $[M+H]^+$	1.86 (W)
11.71		*—CH_3		XIV.3	410 $[M+H]^+$	1.97 (W)
11.72		*—CH_3		XIV.1	444 $[M+H]^+$	1.82 (W)
11.73		*—CH_3		XIV.3	424 $[M+H]^+$	1.68 (W)
11.74		*—CH_3		XIV.1	424 $[M+H]^+$	1.56 (W)
11.75		*—CH_3		XIV.3	410 $[M+H]^+$	1.96 (W)
11.76		*—CH_3		XIV.1	410 $[M+H]^+$	1.82 (W)
11.77		*—CH_3		XIV.1	434 $[M+H]^+$	1.93 (W)

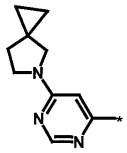
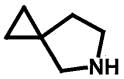
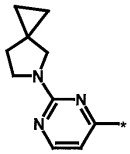
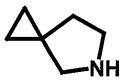
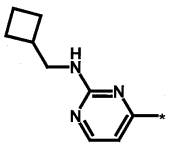
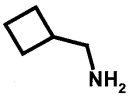
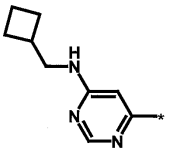
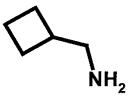
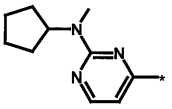
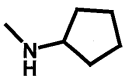
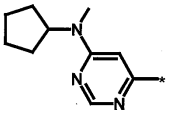
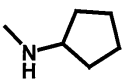
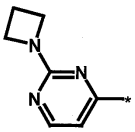
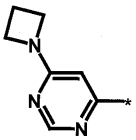
[1631]

11.78		*—CH_3		XIV.3	434 $[M+H]^+$	2.07 (W)
11.79		*—CH_3		XIV.1	410 $[M+H]^+$	1.6 (W)
11.80		*—CH_3		XIV.3	410 $[M+H]^+$	1.7 (W)
11.81		*—CH_3		XIV.1	438 $[M+H]^+$	1.69 (W)
11.82		*—CH_3		XIV.1	444 $[M+H]^+$	1.88 (W)
11.83		*—CH_3		XIV.3	444 $[M+H]^+$	2.00 (W)
11.84		*—CH_3	H_2N—	XIV.3	354 $[M+H]^+$	1.63 (W)

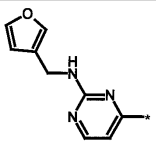
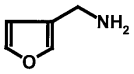
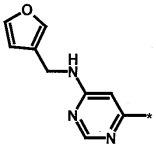
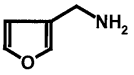
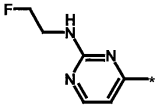
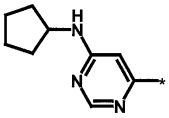
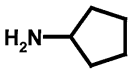
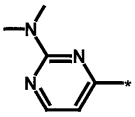
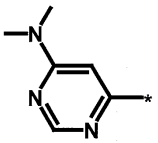
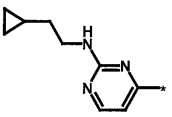
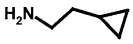
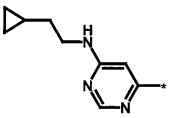
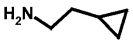
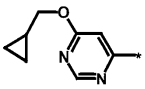
[1632]

11.85				XIV.1	354 $[M+H]^+$	1.51 (W)
11.86				XIV.3	394 $[M+H]^+$	1.90 (W)
11.87				XIV.1	394 $[M+H]^+$	1.75 (W)
11.88				XIV.3	442 $[M+H]^+$	2.06 (W)
11.89				XIV.1	442 $[M+H]^+$	1.91 (W)
11.90				XIV.3	408 $[M+H]^+$	1.96 (W)
11.91				XIV.1	408 $[M+H]^+$	1.82 (W)

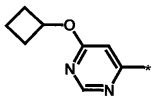
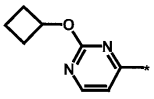
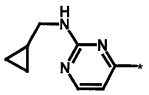
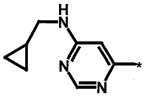
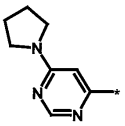
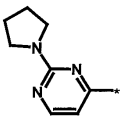
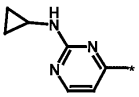
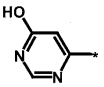
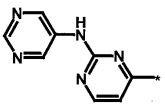
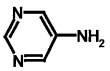
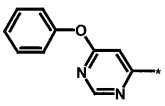
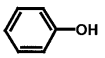
[1633]

11.92		*—CH_3		XIV.1	420 $[M+H]^+$	1.84 (W)
11.93		*—CH_3		XIV.3	420 $[M+H]^+$	1.99 (W)
11.94		*—CH_3		XIV.3	408 $[M+H]^+$	1.93 (W)
11.95		*—CH_3		XIV.1	408 $[M+H]^+$	1.80 (W)
11.96		*—CH_3		XIV.3	422 $[M+H]^+$	2.05 (W)
11.97		*—CH_3		XIV.1	422 $[M+H]^+$	1.92 (W)
11.98		*—CH_3		XIV.3	380 $[M+H]^+$	1.77 (W)
11.99		*—CH_3		XIV.1	380 $[M+H]^+$	1.65 (W)

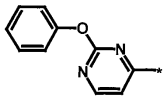
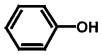
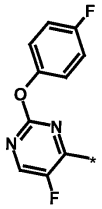
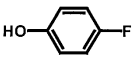
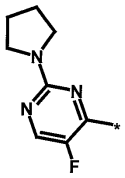
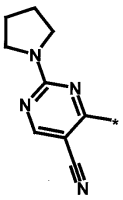
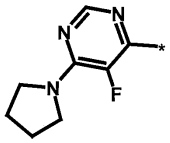
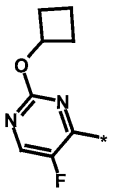
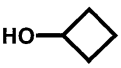
[1634]

11.100		*—CH_3		XIV.3	420 $[M+H]^+$	1.76 (W)
11.101		*—CH_3		XIV.1	420 $[M+H]^+$	1.64 (W)
11.102		*—CH_3		XIV.3	386 $[M+H]^+$	1.65 (W)
11.103		*—CH_3		XIV.1	408 $[M+H]^+$	1.79 (W)
11.104		*—CH_3		XIV.3	368 $[M+H]^+$	1.80 (W)
11.105		*—CH_3		XIV.1	368 $[M+H]^+$	1.63 (W)
11.106		*—CH_3		XIV.3	408 $[M+H]^+$	1.91 (W)
11.107		*—CH_3		XIV.1	408 $[M+H]^+$	1.78 (W)
11.108		*—CH_3		XIV.1	395 $[M+H]^+$	1.79 (P)

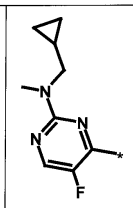
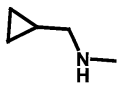
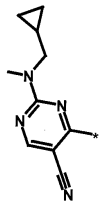
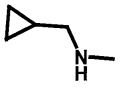
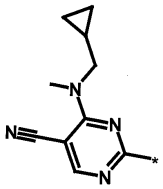
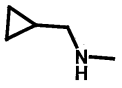
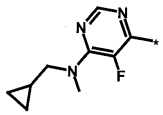
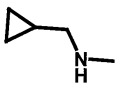
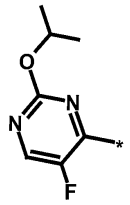
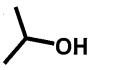
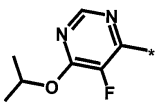
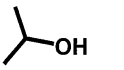
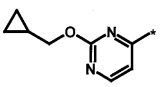
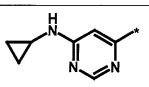
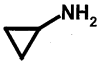
[1635]

11.109		*—CH_3		XIV.1	395 $[M+H]^+$	1.81 (P)
11.110		*—CH_3		XIV.3	395 $[M+H]^+$	1.63 (P)
11.111		*—CH_3		XIV.3	394 $[M+H]^+$	1.40 (P)
11.112		*—CH_3		XIV.1	394 $[M+H]^+$	1.65 (P)
11.113		*—CH_3		XIV.1	394 $[M+H]^+$	1.54 (P)
11.114		*—CH_3		XIV.3	394 $[M+H]^+$	1.68 (P)
11.115		*—CH_3		XIV.3	380 $[M+H]^+$	1.32 (P)
11.116		*—CH_3		XIV.1	341 $[M+H]^+$	1.40 (P)
11.117		*—CH_3		XIV.3	418 $[M+H]^+$	1.18 (P)
11.118		*—CH_3		XIV.1	417 $[M+H]^+$	2.09 (P)

[1636]

11.119				XIV.3	417 $[M+H]^+$	1.65 (P)
11.120				5.36	479 $[M+H]^+$	1.11 (AC)
11.121				5.36	438 $[M+H]^+$	1.11 (AC)
11.122				XIV.4	445 $[M+H]^+$	1.23 (AC)
11.123				5.37	438 $[M+H]^+$	1.15 (AC)
11.124				5.36	439 $[M+H]^+$	1.12 (AC)

[1637]

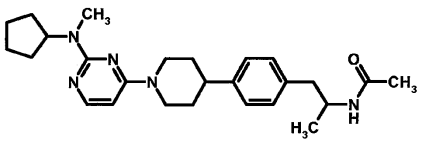
11.125				5.36	452 $[M+H]^+$	1.07 (AC)
11.126				XIV.4	459 $[M+H]^+$	1.16 (AC)
11.127				XIV.5	459 $[M+H]^+$	1.18 (AC)
11.128				5.37	452 $[M+H]^+$	1.08 (AC)
11.129				5.36	427 $[M+H]^+$	0.99 (AC)
11.130				5.37	427 $[M+H]^+$	0.97 (AC)
11.131				XIV.3	395 $[M+H]^+$	1.60 (P)
11.132				XIV.!	380 $[M+H]^+$	1.54 (P)

[1638]

[1639] **실시예 12**

[1640] 실시예 12.1

[1641] N-[2-(4-{1-[2-(사이클로펜틸-메틸-아미노)-피리미딘-4-일]-피페리딘-4-일}-페닐)-1-메틸-에틸]-아세트아미드

[1642] 

[1643] N-메틸-사이클로펜틸아민 181㎕(1.61mmol)를 아세토니트릴 3mL 중의 N-(2-{4-[1-(2-클로로-피리미딘-4-일)-피페리딘-4-일]-페닐}-1-메틸-에틸)-아세트아미드(XIV.2) 120mg(0.32mmol)에 첨가한다. 상기 혼합물을 마이크로웨이브 조사하에 150℃에서 30분 동안 가열한다. 그 시간 후, 용매를 증발시키고 잔사는 역상 HPLC(용출제 A: 물

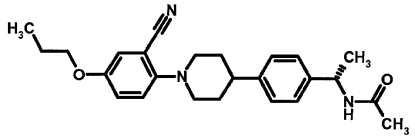
+ 0.1% TFA, 용출제 B: 아세토니트릴 + 0.1% TFA)를 사용하여 정제하여 목적 생성물을 수득한다.

[1644] $C_{26}H_{37}N_5O$ (M = 435.6g/mol), ESI-MS: 436 $[M+H]^+$

[1645] **실시예 13**

[1646] 실시예 13.1

[1647] (S)-N-(1-{4-[1-(2-시아노-4-프로폭시-페닐)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1648] 

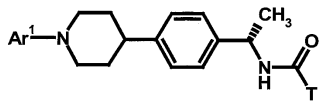
[1649] DMSO 2mL 중의 (S)-N-[1-(피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 100mg(0.41mmol)을, 불활성 기체 대기하에, 2-브로모-5-프로폭시-벤조니트릴 97mg(0.41mmol), 탄산칼륨 112mg(0.82mmol), 요오드화구리(I) 7.7mg (0.041mmol) 및 (L)-프롤린 9mg(0.08mmol)의 혼합물에 첨가한다. 상기 혼합물을 90℃에서 7일 동안 교반한다. 그 시간 후, 물을 첨가하고, 상기 혼합물은 에틸 아세테이트로 추출한다. 유기 층을 황산나트륨으로 건조시키고 용매는 진공하에 제거한다. 상기 잔사는 HPLC(칼럼: Waters XBridge 5μM; 용출제 A: 물 + 0.3% NH_4OH, 용출제 B: MeOH)로 정제하여 목적 생성물을 수득한다.

[1650] $C_{25}H_{31}N_3O_2$ (M = 405.5g/mol), ESI-MS: 406 $[M+H]^+$

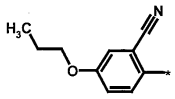
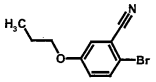
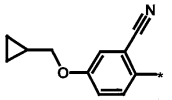
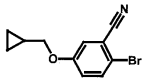
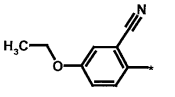
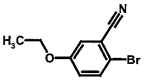
[1651] R_t (HPLC): 2.23분 (방법 A)

[1652] 하기 화학식 13-1의 화합물은 실시예 13.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1653] [화학식 13-1]

[1654] 

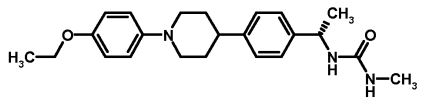
[1655]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
13.1				V.1	406 $[M+H]^+$	2.23 (A)
13.2				V.1	418 $[M+H]^+$	2.21 (A)
13.3				V.1	392 $[M+H]^+$	2.13 (A)

[1656] **실시예 14**

[1657] 실시예 14.1

[1658] (S)-1-(1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸)-3-메틸-우레아



[1659]

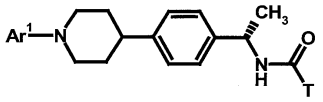
[1660] DMF 2mL 중의 (S)-1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸아민(XIII.1) 100mg(0.31mmol)에 TEA 87 μl(0.62mmol) 및 CDI 52mg(0.32mmol)을 0℃에서 첨가하고, 상기 혼합물을 0℃에서 30분 동안 교반한다. 이어서, 메틸아민 48mg(1.54mmol)을 첨가하고, 50℃에서 1시간 동안 계속 교반한다. 상기 혼합물은 염기성 산화알루미늄을 통해 여과하고 진공하에 농축시킨다. 상기 잔사는 역상 칼럼 크로마토그래피(물 + 0.15% NH_4OH; 아세톤)를 사용하여 정제하고, 상응하는 분획은 농축시켜 목적 생성물을 수득한다.

[1661] $C_{23}H_{31}N_3O_2$ (M = 381.5g/mol), ESI-MS: 382 $[M+H]^+$

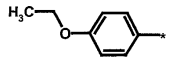
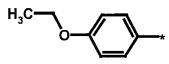
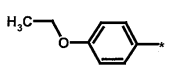
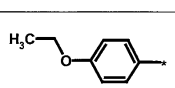
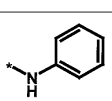
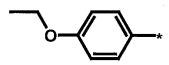
[1662] R_t (HPLC): 2.10분 (방법 A)

[1663] 하기 화학식 14-1의 화합물은 실시예 14.1과 유사하게 제조한다. 실시예 14.5의 경우, CDT가 CDI 대신에 사용된다. 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1664] [화학식 14-1]



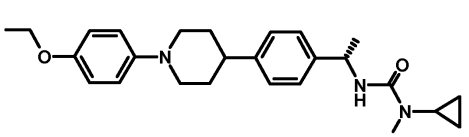
[1665]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC)[분] (방법)
14.1			XIII.1	메틸아민	382 $[M+H]^+$	2.10 (A)
14.2			XIII.1	에틸아민	396 $[M+H]^+$	2.14 (A)
14.3			XIII.1	사이클로프로필아민	408 $[M+H]^+$	2.19 (A)
14.4			XIII.1	아닐린	444 $[M+H]^+$	1.94 (A)
14.5			XIII.1	암모니아	368 $[M+H]^+$	1.13 (G)

[1666]

[1667] 실시예 14.50

[1668] (S)-1-사이클로프로필-3-(1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸)-1-메틸-우레아



[1669]

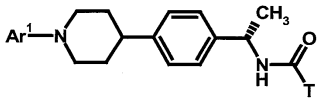
[1670] 디옥산 1.5mL 중의 (S)-1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸아민(XIII.1) 32.5mg(0.10mmol)에, DBU 30μl(0.20mmol) 및 CDT 33mg(0.20mmol)을 실온에서 첨가하고, 상기 혼합물을 5분 동안 교반한다. 이어서, 사이클로프로필-메틸-아민 8.5mg(0.15mmol)을 첨가하고 밤새 계속 교반한다. 상기 혼합물을 진공하에 농축시킨다. 상기 잔사는 역상 칼럼 크로마토그래피(물 + 0.1% TFA: MeOH)를 사용하여 정제하고, 상응하는 분획은 농축시켜 목적 생성물을 수득한다.

[1671] $C_{26}H_{35}N_3O_2$ (M = 421.6g/mol), ESI-MS: 422 $[M+H]^+$

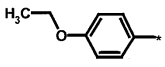
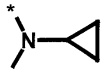
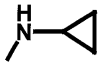
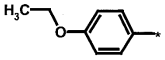
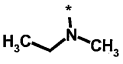
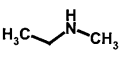
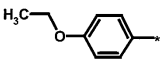
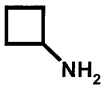
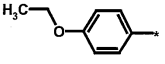
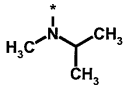
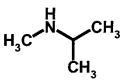
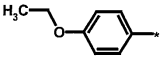
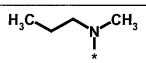
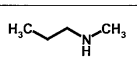
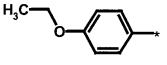
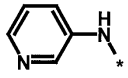
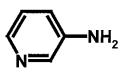
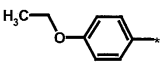
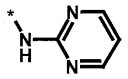
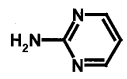
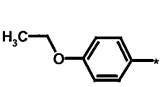
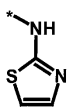
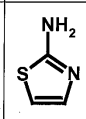
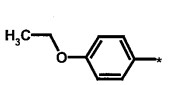
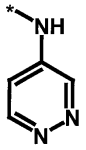
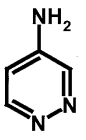
[1672] R_t (HPLC): 1.24분 (방법 B)

[1673] 하기 화학식 14-1의 화합물은 실시예 14.50과 유사하게 제조한다. 방향족 아민이 시약으로서 사용되는 경우, 활성화 단계는 반전되고, 방향족 아민은 XIII.1에 첨가하기 전에 CDT로 먼저 처리한다. 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

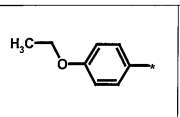
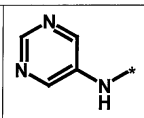
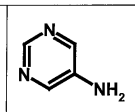
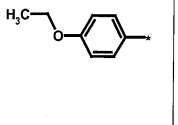
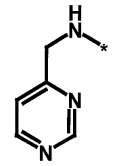
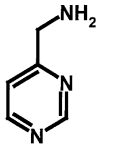
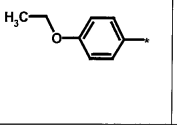
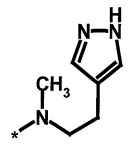
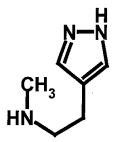
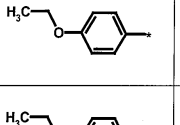
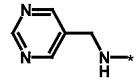
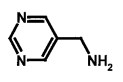
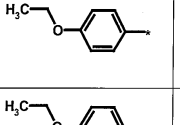
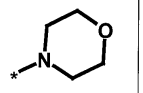
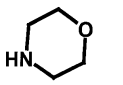
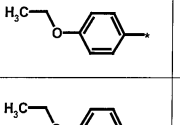
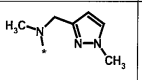
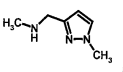
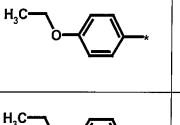
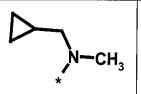
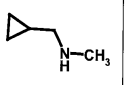
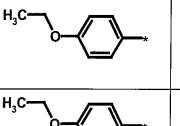
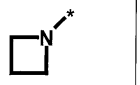
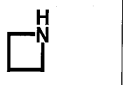
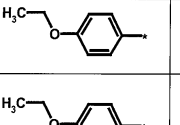
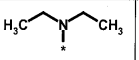
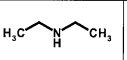
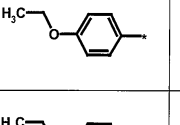
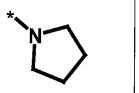
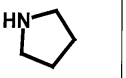
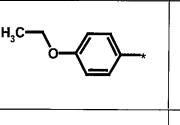
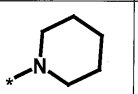
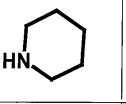
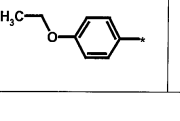
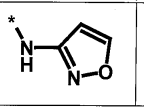
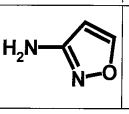
[1674] [화학식 14-1]



[1675]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t (HPLC) [분] (방법)
14.50			XIII.1		422 $[M+H]^+$	2.13 (W)
14.51			XIII.1		410 $[M+H]^+$	2.06 (W)
14.52			XIII.1		422 $[M+H]^+$	2.1 (W)
14.53			XIII.1		424 $[M+H]^+$	2.1 (W)
14.54			XIII.1		424 $[M+H]^+$	2.12 (W)
14.55			XIII.1		445 $[M+H]^+$	2.07 (W)
14.56			XIII.1		446 $[M+H]^+$	2.11 (W)
14.57			XIII.1		451 $[M+H]^+$	1.56 (U)
14.58			XIII.1		446 $[M+H]^+$	2.03 (W)

[1676]

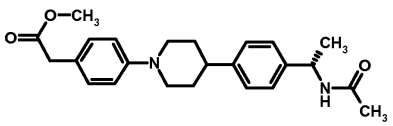
14.59			XIII.1		446 $[M+H]^+$	2.03 (W)
14.60			XIII.1		460 $[M+H]^+$	1.99 (W)
14.61			XIII.1		476 $[M+H]^+$	2.01 (W)
14.62			XIII.1		460 $[M+H]^+$	1.99 (W)
14.63			XIII.1		438 $[M+H]^+$	2.04 (W)
14.64			XIII.1		476 $[M+H]^+$	2.04 (W)
14.65			XIII.1		436 $[M+H]^+$	2.12 (W)
14.66			XIII.1		408 $[M+H]^+$	2.04 (W)
14.67			XIII.1		424 $[M+H]^+$	2.14 (W)
14.68			XIII.1		422 $[M+H]^+$	2.09 (W)
14.69			XIII.1		436 $[M+H]^+$	2.12 (W)
14.70			XIII.1		435 $[M+H]^+$	1.01 (L)

[1677]

[1678] **실시예 15**

[1679] 실시예 15.1

[1680] (S)-(4-{4-[4-(1-아세틸아미노-에틸)-페닐]-피페리딘-1-일}-페닐)-아세트산 메틸 에스테르



[1681]

[1682] 톨루엔/3급-부탄올(5:1) 1.2mL를, (S)-N-[1-(피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 100mg(0.41mmol), 4-브로모-페닐-아세트산 메틸 에스테르 93mg(0.41mmol), X-Phos 10mg(0.020mmol) 및 팔라듐(II) 아세테이트 4.5mg(0.020mmol)의 혼합물에 첨가한다. 마지막으로, 탄산세슘 132mg(0.41mmol)을, 불활성 기체 대기하에, 첨가한다. 상기 혼합물을, 불활성 기체 대기하에, 밀봉된 튜브에서 90℃에서 12시간 동안 교반한다. 그 시간

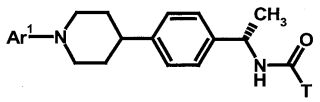
후, 상기 혼합물을 메탄올 1mL로 희석하고, 잔사는 HPLC(칼럼: Waters XBridge 5μM; 용출제 A: 물 + 0.10% NH_4OH, 용출제 B: MeOH)로 정제하여 목적 생성물을 수득한다.

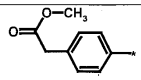
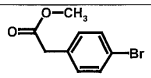
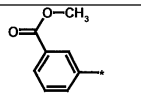
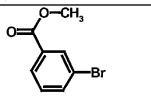
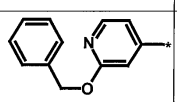
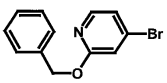
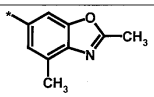
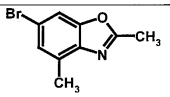
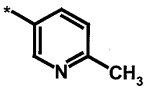
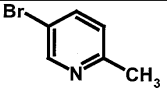
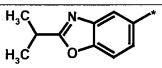
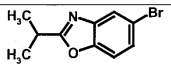
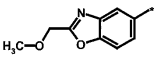
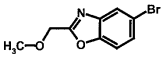
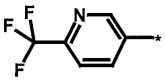
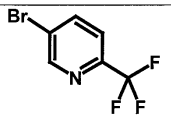
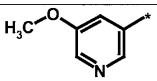
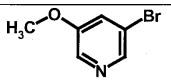
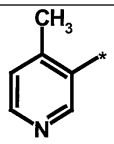
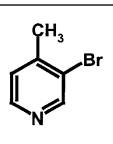
[1683] $C_{24}H_{30}N_2O_3$ (M = 394.5g/mol), ESI-MS: 395 $[M+H]^+$

[1684] R_t (HPLC): 1.10분 (방법 F)

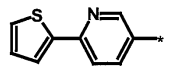
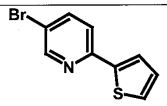
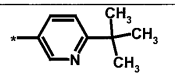
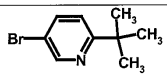
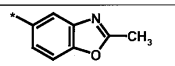
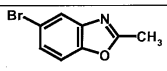
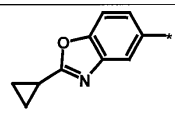
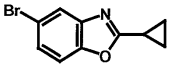
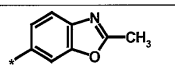
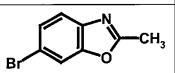
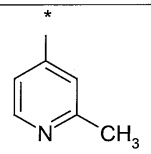
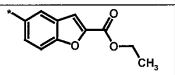
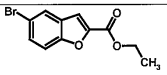
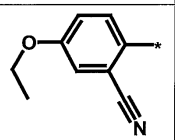
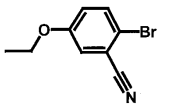
[1685] 하기 화학식 15-1의 화합물은 실시예 15.1과 유사하게 제조하며, 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다.

[1686] [화학식 15-1]

[1687] 

실시예	Ar^1	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC)[분] (방법)
15.1		*—CH_3		V.1	395 $[M+H]^+$	1.10 (G)
15.2		*—CH_3		V.1	381 $[M+H]^+$	1.15 (G)
15.3		*—CH_3		V.1	430 $[M+H]^+$	1.12 (AB)
15.4		*—CH_3		V.1	392 $[M+H]^+$	1.19 (B)
15.5		*—CH_3		V.1	338 $[M+H]^+$	1.02 (B)
15.6		*—CH_3		V.1	406 $[M+H]^+$	1.26 (B)
15.7		*—CH_3		V.1	408 $[M+H]^+$	1.07 (B)
15.8		*—CH_3		V.1	392 $[M+H]^+$	1.76 (B)
15.9		*—CH_3		V.1	354 $[M+H]^+$	1.07 (B)
15.10		*—CH_3		V.1	338 $[M+H]^+$	1.05 (B)

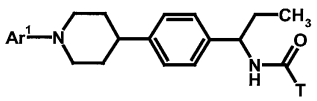
[1688]

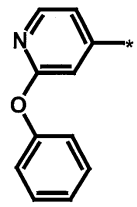
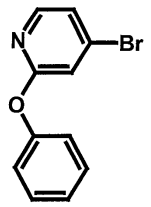
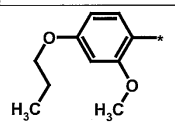
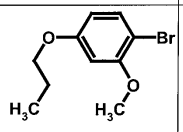
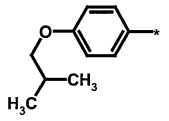
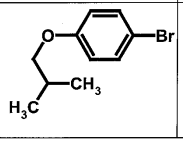
15.11		*—CH_3		V.1	406 $[M+H]^+$	1.44 (B)
15.12		*—CH_3		V.1	380 $[M+H]^+$	1.18 (B)
15.13		*—CH_3		V.1	378 $[M+H]^+$	1.05 (B)
15.14		*—CH_3		V.1	404 $[M+H]^+$	1.20 (B)
15.15		*—CH_3		V.1	378 $[M+H]^+$	1.05 (B)
15.16		*—CH_3		V.1	338 $[M+H]^+$	0.98 (B)
15.17		*—CH_3		V.1	435 $[M+H]^+$	1.27 (B)
15.18		*—O—CH_3		V.2	408 $[M+H]^+$	1.65 (N)

[1689]

[1690] 하기 화학식 15-2의 화합물은 실시예 15.1과 유사하게 제조하며, 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다.

[1691] [화학식 15-2]

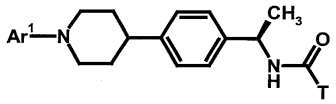
[1692] 

실시예	Ar^1	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
15.19		*—CH_3		XXIII.2	430 $[M+H]^+$	1.20 (N)
15.20		*—CH_3		XXIII.2	425 $[M+H]^+$	1.20 (N)
15.21		*—CH_3		XXIII.2	409 $[M+H]^+$	1.26 (N)

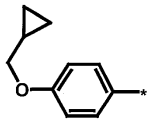
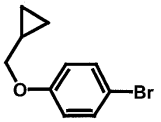
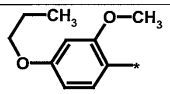
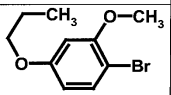
[1693]

[1694] 하기 화학식 15-3의 화합물은 실시예 15.1과 유사하게 제조하며, 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다.

[1695] [화학식 15-3]

[1696] 

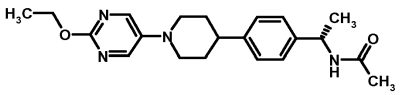
[1697]

실시예	Ar^1	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
15.22				V.6	393 $[M+H]^+$	2.10 (A)
15.23				V.6	411 $[M+H]^+$	2.21 (A)

[1698] **실시예 16**

[1699] 실시예 16.1

[1700] (S)-N-(1-{4-[1-(2-에톡시-피리미딘-5-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1701] 

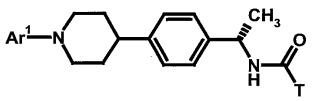
[1702] 톨루엔 3.0mL를, (S)-N-[1-(피페리딘-4-일-페닐)-에틸]-아세트아미드(V.1) 100mg(0.41mmol), 5-브로모-2-에톡시-피리미딘 82mg(0.41mmol), BINAP 24mg(0.082mmol) 및 팔라듐(II) 아세테이트 9.1mg(0.041mmol)의 혼합물에 첨가한다. 마지막으로, 탄산세슘 200mg(0.61mmol)을, 불활성 기체 대기하에, 첨가한다. 상기 혼합물을, 불활성 기체 대기하에, 밀봉된 튜브에서 120℃에서 12시간 동안 교반한다. 그 시간 후, 물 1mL를 첨가하고, 상기 혼합물은 에틸 아세테이트로 추출하고, 유기 층을 분리하여 물로 세척한다. 유기 층을 황산나트륨으로 건조시키고 용매는 진공하에 제거한다. 상기 잔사는 HPLC(칼럼: Waters XBridge 5μM; 용출제 A: 물 + 0.30% NH_4OH, 용출제 B: MeOH)로 정제하여 목적 생성물을 수득한다.

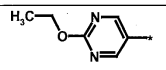
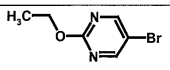
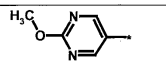
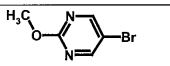
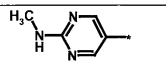
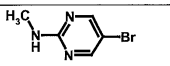
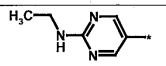
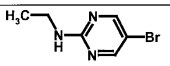
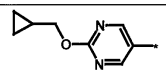
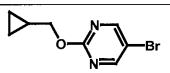
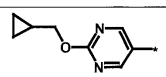
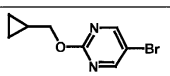
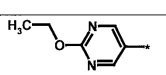
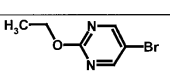
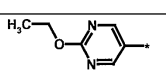
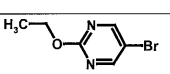
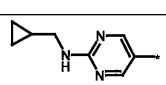
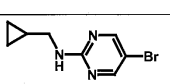
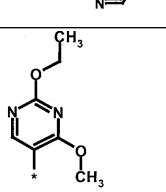
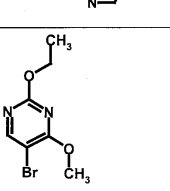
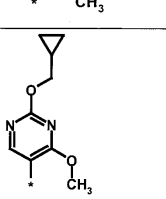
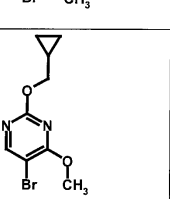
[1703] $C_{21}H_{28}N_4O_2$ (M = 368.5g/mol), ESI-MS: 369 $[M+H]^+$

[1704] R_t (HPLC): 1.02분 (방법 G)

[1705] 하기 화학식 16-1의 화합물은 실시예 16.1과 유사하게 제조하며, 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다.

[1706] [화학식 16-1]

[1707] 

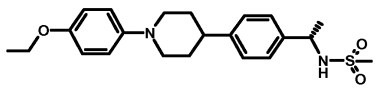
실시예	Ar^1	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
16.1				V.1	369 $[M+H]^+$	1.02 (G)
16.2				V.1	355 $[M+H]^+$	0.87 (H)
16.3				V.1	354 $[M+H]^+$	0.91 (G)
16.4				V.1	368 $[M+H]^+$	0.97 (G)
16.5				V.1	395 $[M+H]^+$	1.12 (H)
16.6				V.3	424 $[M+H]^+$	1.13 (G)
16.7				V.3	398 $[M+H]^+$	1.07 (G)
16.8				V.4	395 $[M+H]^+$	1.09 (G)
16.9				V.4	420 $[M+H]^+$	1.12 (G)
16.10				V.1	399 $[M+H]^+$	1.25 (L)
16.11				V.1	425 $[M+H]^+$	2.16 (F)

[1708]

[1709] **실시예 17**

[1710] 실시예 17.1

[1711] (S)-N-(1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸)-메탄설폰아미드

[1712] 

[1713] 메탄설포닐 클로라이드 17mg(0.15mmol)에, 디클로로메탄 2mL 중의 (S)-1-{4-[1-(4-에톡시-페닐)-피페리딘-4-일]-페닐}-에틸아민(XIII.1) 32mg(0.1mmol) 및 트리에틸 아민 42㎕의 용액을 첨가한다. 상기 혼합물을 실온에서 2일 동안 교반한다. 용매를 감압하에 제거하고 잔사는 역상 칼럼 크로마토그래피(물/MeOH, 0.1% TFA)를 사용하여 정제하고, 상응하는 분획은 농축시켜 목적 생성물을 수득한다.

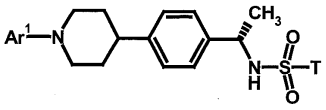
[1714] $C_{22}H_{30}N_2O_3S$ (M = 402.6g/mol), ESI-MS: 403 $[M+H]^+$

[1715] R_t (HPLC): 0.37분 (방법 B)

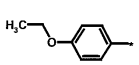
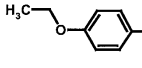
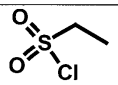
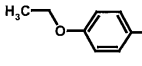
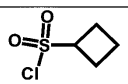
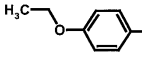
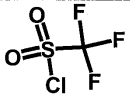
[1716] 하기 화학식 17-1의 화합물은 실시예 17.1과 유사하게 제조하며, 사용된 반응물은 "반응물"이란 제목의 칼럼으

로 제시되고 있다.

[1717] [화학식 17-1]

[1718] 

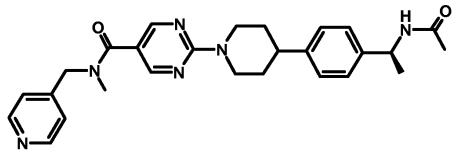
[1719]

실시예	Ar¹	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
17.1				XIII.1	403 $[M+H]^+$	0.37 (B)
17.2				XIII.1	417 $[M+H]^+$	0.39 (B)
17.3				XIII.1	443 $[M+H]^+$	0.42 (B)
17.4				XIII.1	457 $[M+H]^+$	0.46 (B)

[1720] **실시예 18**

[1721] 실시예 18.1

[1722] (S)-2-{4-[4-(1-아세틸아미노-에틸)-페닐]-피페리딘-1-일}-피리미딘-5-카복실산 메틸-피리딘-4-일메틸-아미드

[1723] 

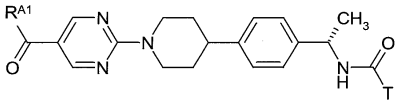
[1724] DMF 2mL 중의 (S)-2-{4-[4-(1-아세틸아미노-에틸)-페닐]-피페리딘-1-일}-피리미딘-5-카복실산(XVII.1) 36.8mg (0.1mmol) 및 DIPEA 51㎕(0.3mmol)에 HATU 38.0mg(0.1mmol)을 첨가하고, 상기 혼합물을 실온에서 15분 동안 교반한다. 이어서, 상기 혼합물을 메틸피리딘-4-일메틸아민 12.2mg(0.1mmol)에 첨가하고, 12시간 동안 계속 교반한다. 용매를 진공하에 제거하고 잔사는 역상 칼럼 크로마토그래피(물 + 0.1% NH_4OH/MeOH)를 사용하여 정제하고, 상응하는 분획은 농축시켜 목적 생성물을 수득한다.

[1725] $C_{27}H_{32}N_6O_2$ (M = 472.6g/mol), ESI-MS: 473 $[M+H]^+$

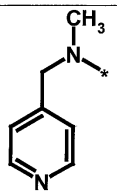
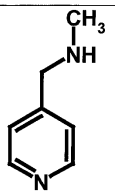
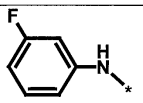
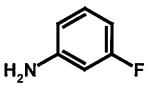
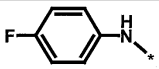
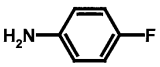
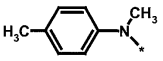
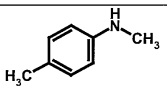
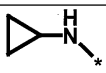
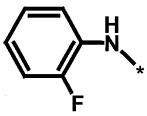
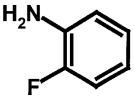
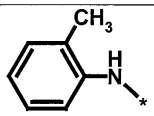
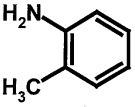
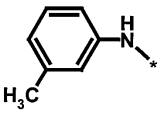
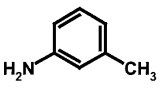
[1726] R_t (HPLC): 1.56 (방법 W)

[1727] 하기 화학식 18-1의 화합물 18.1 내지 18.40은 실시예 18.1과 유사하게 제조하며, 화합물 18.41 내지 18.89는 실시예 18.1과 유사하게 제조하지만, 배치 크기는 0.01mmol 산 XVII.1로 감소시킨다. 이들 화합물은 염기성 산 화알루미늄을 통해 여과하고, DMF/MeOH(9:1)로 세척하고, 진공하에 농축시켜 정제하여 목적 생성물을 수득한다. Boc-보호된 디아민이 사용되는 경우, Boc 보호 그룹은 최종적으로 DCM/TFA = 1/1(5% H_2O)을 사용하여 제거한다. 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다.

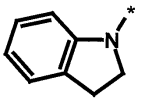
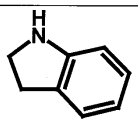
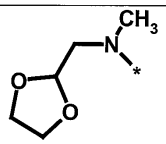
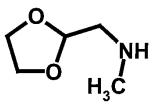
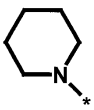
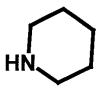
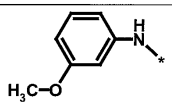
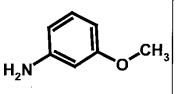
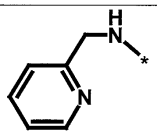
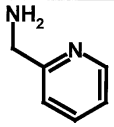
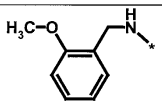
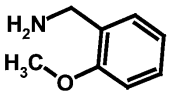
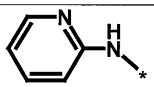
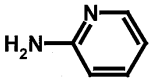
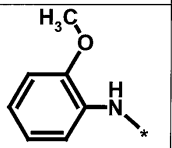
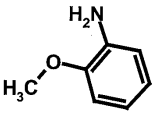
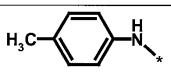
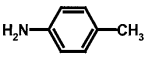
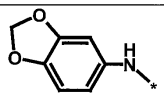
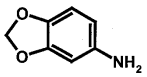
[1728] [화학식 18-1]



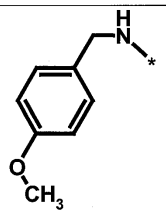
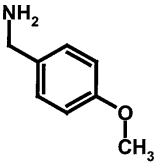
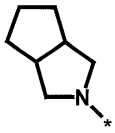
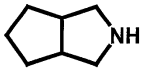
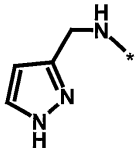
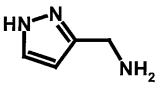
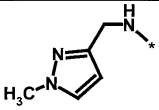
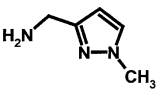
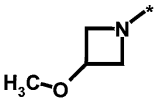
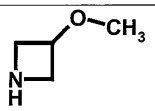
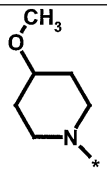
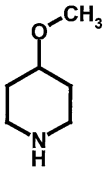
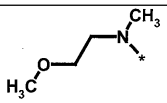
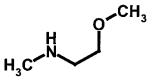
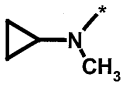
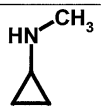
[1729]

실시예	R^{A1}	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC) [분](방법)
18.1				XVII.1	473 $[M+H]^+$	1.56 (W)
18.2				XVII.1	462 $[M+H]^+$	1.82 (B)
18.3				XVII.1	462 $[M+H]^+$	1.81 (W)
18.4				XVII.1	472 $[M+H]^+$	1.87 (W)
18.5				XVII.1	408 $[M+H]^+$	1.57 (B)
18.6				XVII.1	462 $[M+H]^+$	1.72 (B)
18.7				XVII.1	458 $[M+H]^+$	1.76 (W)
18.8				XVII.1	458 $[M+H]^+$	1.86 (W)

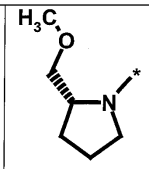
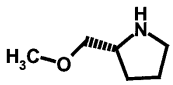
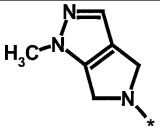
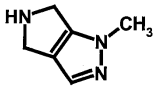
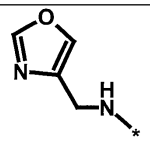
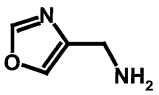
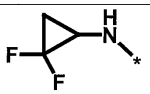
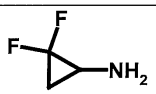
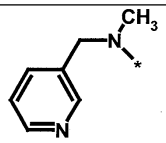
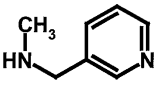
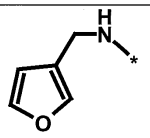
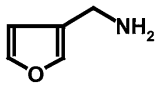
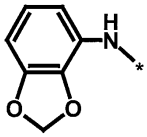
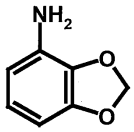
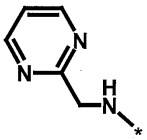
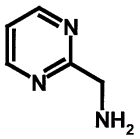
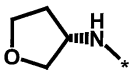
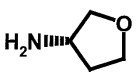
[1730]

18.9		*—CH_3		XVII.1	470 $[M+H]^+$	1.88 (W)
18.10		*—CH_3		XVII.1	468 $[M+H]^+$	1.60 (W)
18.11		*—CH_3		XVII.1	436 $[M+H]^+$	1.77 (W)
18.12		*—CH_3		XVII.1	474 $[M+H]^+$	1.80(W)
18.13		*—CH_3		XVII.1	459 $[M+H]^+$	1.59 (W)
18.14		*—CH_3		XVII.1	488 $[M+H]^+$	1.78 (W)
18.15		*—CH_3		XVII.1	445 $[M+H]^+$	1.43 (B)
18.16		*—CH_3		XVII.1	474 $[M+H]^+$	1.82 (W)
18.17		*—CH_3		XVII.1	458 $[M+H]^+$	1.82 (B)
18.18		*—CH_3		XVII.1	488 $[M+H]^+$	1.76 (W)

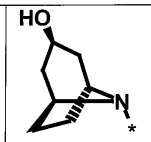
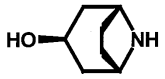
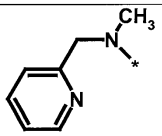
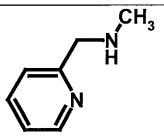
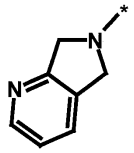
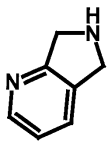
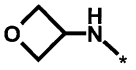
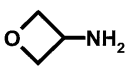
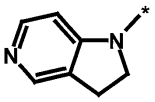
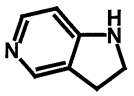
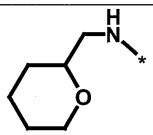
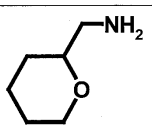
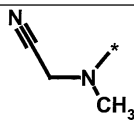
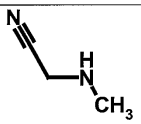
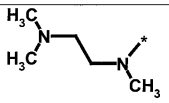
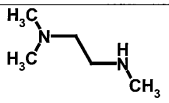
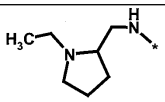
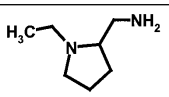
[1731]

18.19		*—CH_3		XVII.1	488 $[M+H]^+$	1.7 (W)
18.20		*—CH_3		XVII.1	462 $[M+H]^+$	1.88 (W)
18.21		*—CH_3		XVII.1	448 $[M+H]^+$	1.52 (W)
18.22		*—CH_3		XVII.1	462 $[M+H]^+$	1.54 (W)
18.23		*—CH_3		XVII.1	438 $[M+H]^+$	1.56 (B)
18.24		*—CH_3		XVII.1	466 $[M+H]^+$	1.65 (W)
18.25		*—CH_3		XVII.1	440 $[M+H]^+$	1.60 (W)
18.26		*—CH_3		XVII.1	422 $[M+H]^+$	1.60 (B)

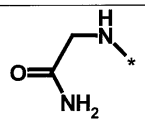
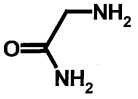
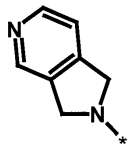
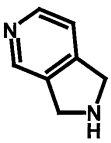
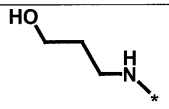
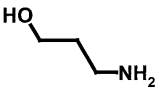
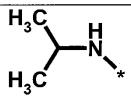
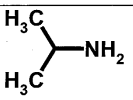
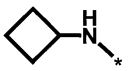
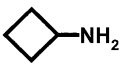
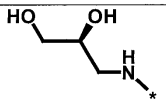
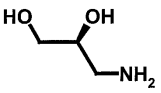
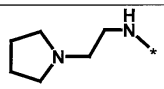
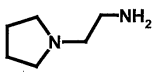
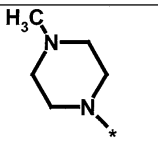
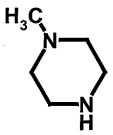
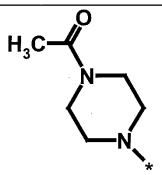
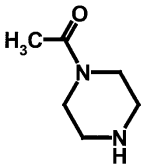
[1732]

18.27		*—CH_3		XVII.1	466 $[M+H]^+$	1.71 (W)
18.28		*—CH_3		XVII.1	474 $[M+H]^+$	1.55 (B)
18.29		*—CH_3		XVII.1	449 $[M+H]^+$	1.49 (B)
18.30		*—CH_3		XVII.1	444 $[M+H]^+$	1.46 (W)
18.31		*—CH_3		XVII.1	473 $[M+H]^+$	1.58 (W)
18.32		*—CH_3		XVII.1	448 $[M+H]^+$	1.66 (W)
18.33		*—CH_3		XVII.1	488 $[M+H]^+$	1.72 (W)
18.34		*—CH_3		XVII.1	460 $[M+H]^+$	1.49 (W)
18.35		*—CH_3		XVII.1	438 $[M+H]^+$	1.55 (W)

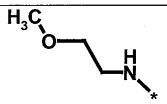
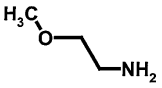
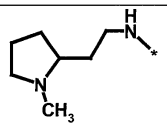
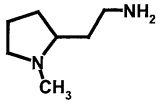
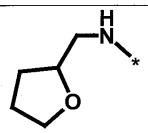
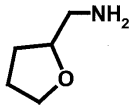
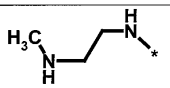
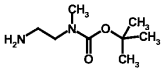
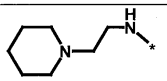
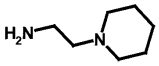
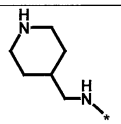
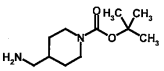
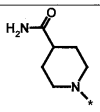
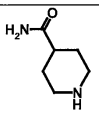
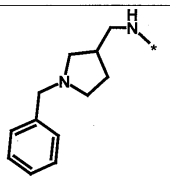
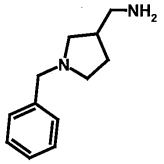
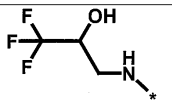
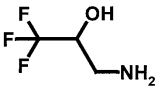
[1733]

18.36		*—CH_3		XVII.1	478 $[M+H]^+$	1.61 (W)
18.37		*—CH_3		XVII.1	473 $[M+H]^+$	1.62 (W)
18.38		*—CH_3		XVII.1	471 $[M+H]^+$	1.53 (B)
18.39		*—CH_3		XVII.1	424 $[M+H]^+$	1.49 (B)
18.40		*—CH_3		XVII.1	471 $[M+H]^+$	1.2 (B)
18.41		*—CH_3		XVII.1	466 $[M+H]^+$	1.58 (B)
18.42		*—CH_3		XVII.1	421 $[M+H]^+$	1.46 (B)
18.43		*—CH_3		XVII.1	453 $[M+H]^+$	1.13 (B)
18.44		*—CH_3		XVII.1	479 $[M+H]^+$	1.2 (B)

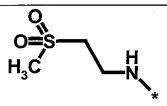
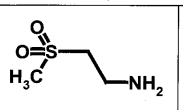
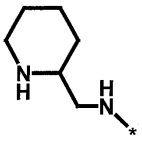
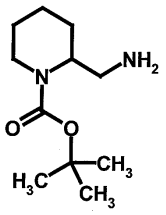
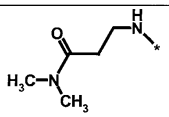
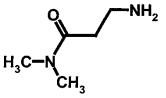
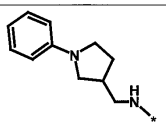
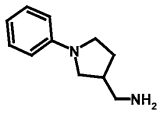
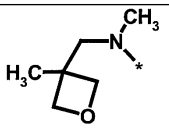
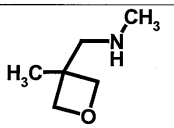
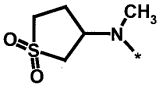
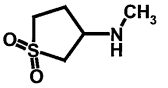
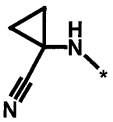
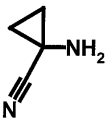
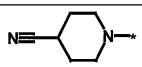
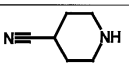
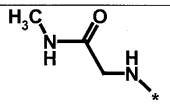
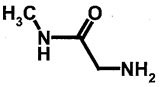
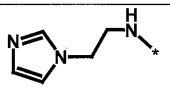
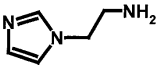
[1734]

18.45		*—CH_3		XVII.1	425 $[M+H]^+$	1.33 (B)
18.46		*—CH_3		XVII.1	471 $[M+H]^+$	1.17 (B)
18.47		*—CH_3		XVII.1	426 $[M+H]^+$	1.44 (B)
18.48		*—CH_3		XVII.1	410 $[M+H]^+$	1.61 (B)
18.49		*—CH_3		XVII.1	422 $[M+H]^+$	1.66 (B)
18.50		*—CH_3		XVII.1	442 $[M+H]^+$	1.36 (B)
18.51		*—CH_3		XVII.1	465 $[M+H]^+$	1.17 (B)
18.52		*—CH_3		XVII.1	451 $[M+H]^+$	1.10 (B)
18.53		*—CH_3		XVII.1	479 $[M+H]^+$	1.42 (B)

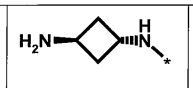
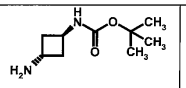
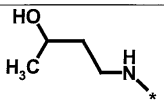
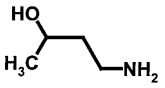
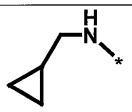
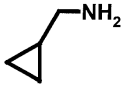
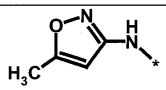
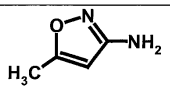
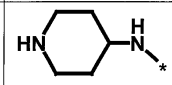
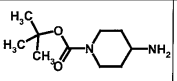
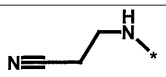
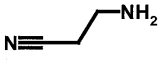
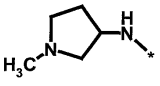
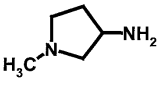
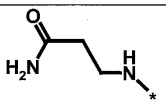
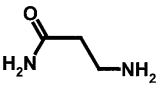
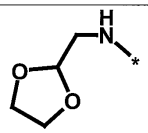
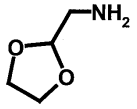
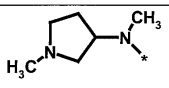
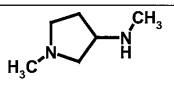
[1735]

18.54		*—CH_3		XVII.1	422 $[M+H]^+$	1.6 (B)
18.55		*—CH_3		XVII.1	426 $[M+H]^+$	1.51 (B)
18.56		*—CH_3		XVII.1	479 $[M+H]^+$	1.19 (B)
18.57		*—CH_3		XVII.1	452 $[M+H]^+$	1.57 (B)
18.58		*—CH_3		XVII.1	425 $[M+H]^+$	1.14 (B)
18.59		*—CH_3		XVII.1	479 $[M+H]^+$	1.20 (B)
18.60		*—CH_3		XVII.1	465 $[M+H]^+$	1.18 (B)
18.61		*—CH_3		XVII.1	479 $[M+H]^+$	1.39 (B)
18.62		*—CH_3		XVII.1	541 $[M+H]^+$	1.28 (B)
18.63		*—CH_3		XVII.1	480 $[M+H]^+$	1.57 (B)

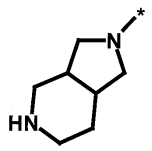
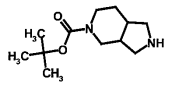
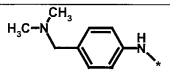
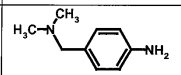
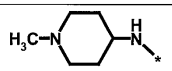
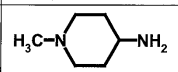
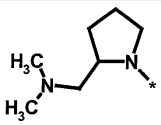
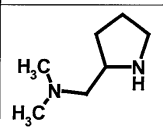
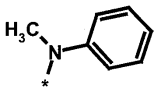
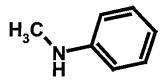
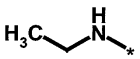
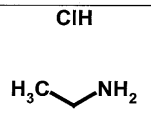
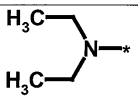
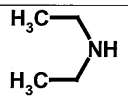
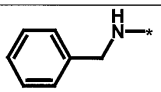
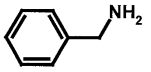
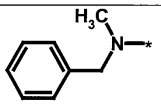
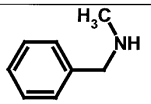
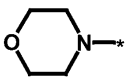
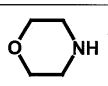
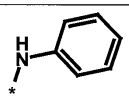
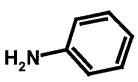
[1736]

18.64		*—CH_3		XVII.1	474 $[M+H]^+$	1.4 (B)
18.65		*—CH_3		XVII.1	465 $[M+H]^+$	1.19 (B)
18.66		*—CH_3		XVII.1	467 $[M+H]^+$	1.48 (B)
18.67		*—CH_3		XVII.1	527 $[M+H]^+$	1.82 (B)
18.68		*—CH_3		XVII.1	466 $[M+H]^+$	1.53 (B)
18.69		*—CH_3		XVII.1	500 $[M+H]^+$	1.40 (B)
18.70		*—CH_3		XVII.1	433 $[M+H]^+$	1.50 (B)
18.71		*—CH_3		XVII.1	461 $[M+H]^+$	1.50 (B)
18.72		*—CH_3		XVII.1	439 $[M+H]^+$	1.38 (B)
18.73		*—CH_3		XVII.1	462 $[M+H]^+$	1.15 (B)

[1737]

18.74		*—CH_3		XVII.1	437 $[M+H]^+$	1.17 (B)
18.75		*—CH_3		XVII.1	440 $[M+H]^+$	1.50 (B)
18.76		*—CH_3		XVII.1	408 $[M+H]^+$	1.55 (B)
18.77		*—CH_3		XVII.1	422 $[M+H]^+$	1.64 (B)
18.78		*—CH_3		XVII.1	449 $[M+H]^+$	1.66 (B)
18.79		*—CH_3		XVII.1	451 $[M+H]^+$	1.17 (B)
18.80		*—CH_3		XVII.1	421 $[M+H]^+$	1.45 (B)
18.81		*—CH_3		XVII.1	451 $[M+H]^+$	1.16 (B)
18.82		*—CH_3		XVII.1	439 $[M+H]^+$	1.38 (B)
18.83		*—CH_3		XVII.1	454 $[M+H]^+$	1.49 (B)
18.84		*—CH_3		XVII.1	465 $[M+H]^+$	1.13 (B)

[1738]

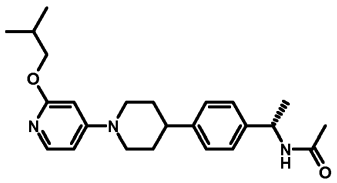
18.85		*—CH_3		XVII.1	477 $[M+H]^+$	1.13 (B)
18.86		*—CH_3		XVII.1	501 $[M+H]^+$	1.27 (B)
18.87		*—CH_3		XVII.1	465 $[M+H]^+$	1.17 (B)
18.88		*—CH_3		XVII.1	479 $[M+H]^+$	1.18 (B)
18.89		*—CH_3		XVII.1	458 $[M+H]^+$	2.14 (P)
18.90		*—CH_3		XVII.1	396 $[M+H]^+$	1.98 (P)
18.91		*—CH_3		XVII.1	424 $[M+H]^+$	2.08 (P)
18.92		*—CH_3		XVII.1	458 $[M+H]^+$	2.14 (P)
18.93		*—CH_3		XVII.1	472 $[M+H]^+$	2.19 (P)
18.94		*—CH_3		XVII.1	438 $[M+H]^+$	1.90 (P)
18.95		*—CH_3		XVII.1	444 $[M+H]^+$	2.18 (P)

[1739]

[1740] **실시예 19**

[1741] 실시예 19.1

[1742] (S)-N-{1-[4-(2'-이소부톡시-3,4,5,6-테트라하이드로-2H-[1,4']비피리디닐-4-일)-페닐]-에틸}-아세트아미드



[1743]

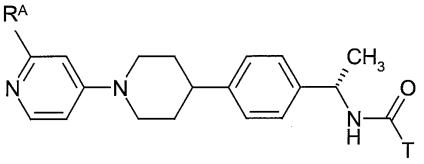
[1744] 디옥산 2mL 중의 (S)-N-{1-[4-(2'-플루오로-3,4,5,6-테트라하이드로-2H-[1,4']비피리디닐-4-일)-페닐]-에틸}-아세트아미드(XIX.1) 34mg(0.10mmol) 및 이소부틸 알코올 74mg(1.0mmol)의 혼합물에 NaH(광유 중의 60%) 20mg(0.50mmol)을 첨가한다. 상기 혼합물을 130℃에서 12시간 동안 교반한다. 용매를 진공하에 제거하고 잔사는 HPLC(RP X-Bridge; 물(+0.1% TFA)/MeOH)로 정제하여 목적 생성물을 수득한다.

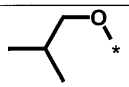
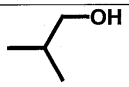
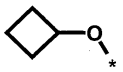
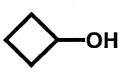
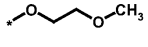
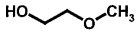
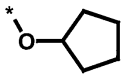
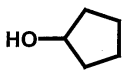
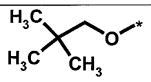
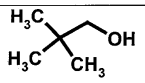
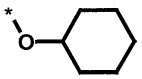
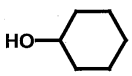
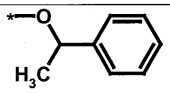
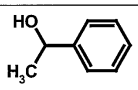
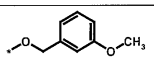
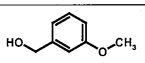
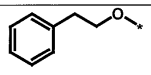
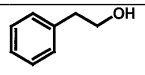
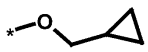
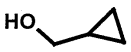
[1745] $C_{24}H_{33}N_3O_2$ (M = 395.5g/mol), ESI-MS: 396 $[M+H]^+$

[1746] R_t (HPLC): 1.35분 (방법 L)

[1747] 하기 화학식 19-1의 화합물은 실시예 19.1과 유사하게 제조하며, 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다.

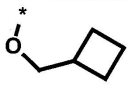
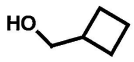
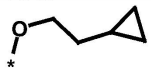
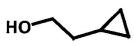
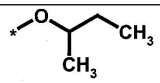
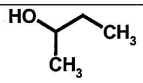
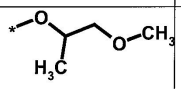
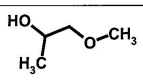
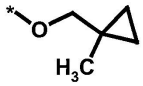
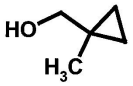
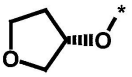
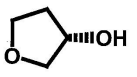
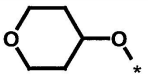
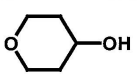
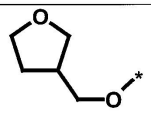
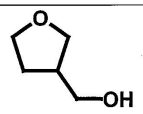
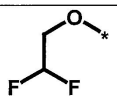
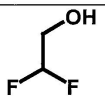
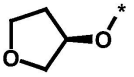
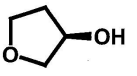
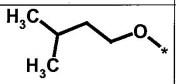
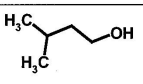
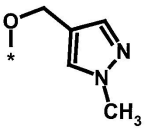
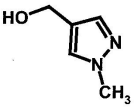
[1748] [화학식 19-1]

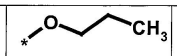
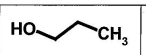
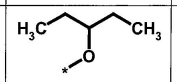
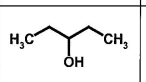
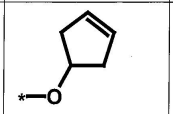
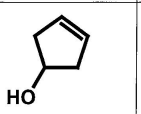
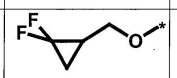
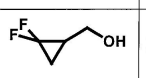
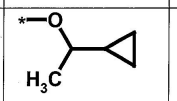
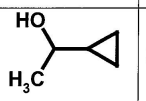
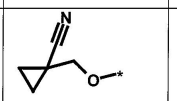
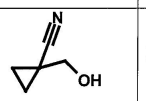
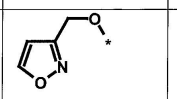
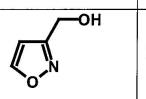
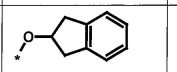
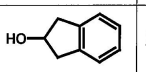
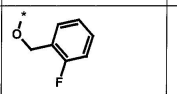
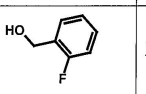
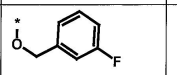
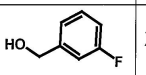
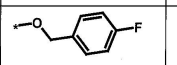
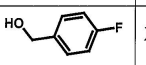
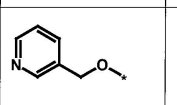
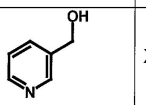
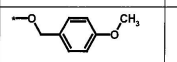
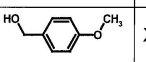
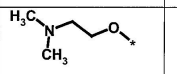
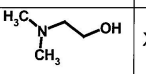
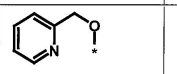
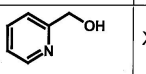
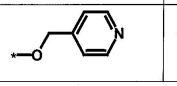
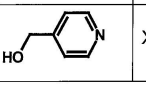


실시예	R^A	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
19.1				XIX.1	396 $[M+H]^+$	1.35 (L)
19.2				XIX.1	394 $[M+H]^+$	1.08 (AB)
19.3				XIX.1	398 $[M+H]^+$	1.54 (X)
19.4				XIX.1	408 $[M+H]^+$	1.85 (X)
19.5				XIX.1	410 $[M+H]^+$	1.90 (X)
19.6				XIX.1	422 $[M+H]^+$	1.92 (X)
19.7				XIX.1	444 $[M+H]^+$	1.84 (X)
19.8				XIX.1	460 $[M+H]^+$	1.81 (X)
19.9				XIX.1	444 $[M+H]^+$	1.87 (X)
19.10				XIX.1	394 $[M+H]^+$	1.76 (X)

[1749]

[1750]

19.11				XIX.1	408 $[M+H]^+$	1.87 (X)
19.12				XIX.1	408 $[M+H]^+$	1.85 (X)
19.13				XIX.1	396 $[M+H]^+$	1.82 (X)
19.14				XIX.1	412 $[M+H]^+$	1.65 (X)
19.15				XIX.1	408 $[M+H]^+$	1.84 (X)
19.16				XIX.1	410 $[M+H]^+$	1.58 (X)
19.17				XIX.1	424 $[M+H]^+$	1.64 (X)
19.18				XIX.1	424 $[M+H]^+$	1.62 (X)
19.19				XIX.1	404 $[M+H]^+$	1.67 (X)
19.20				XIX.1	410 $[M+H]^+$	1.58 (X)
19.21				XIX.1	410 $[M+H]^+$	1.91 (X)
19.22				XIX.1	434 $[M+H]^+$	1.53 (X)

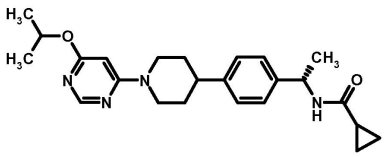
19.23		*—CH_3		XIX.1	382 $[M+H]^+$	1.77 (X)
19.24		*—CH_3		XIX.1	410 $[M+H]^+$	1.90 (X)
19.25		*—CH_3		XIX.1	406 $[M+H]^+$	1.80 (X)
19.26		*—CH_3		XIX.1	430 $[M+H]^+$	1.72 (X)
19.27		*—CH_3		XIX.1	408 $[M+H]^+$	1.81 (X)
19.28		*—CH_3		XIX.1	419 $[M+H]^+$	1.57 (X)
19.29		*—CH_3		XIX.1	421 $[M+H]^+$	1.49 (X)
19.30		*—CH_3		XIX.1	456 $[M+H]^+$	1.91 (X)
19.31		*—CH_3		XIX.1	448 $[M+H]^+$	1.84 (X)
19.32		*—CH_3		XIX.1	448 $[M+H]^+$	1.85 (X)
19.33		*—CH_3		XIX.1	448 $[M+H]^+$	1.84 (X)
19.34		*—CH_3		XIX.1	431 $[M+H]^+$	1.60 (X)
19.35		*—CH_3		XIX.1	460 $[M+H]^+$	1.8 (X)
19.36		*—CH_3		XIX.1	411 $[M+H]^+$	1.61 (X)
19.37		*—CH_3		XIX.1	431 $[M+H]^+$	1.61 (X)
19.38		*—CH_3		XIX.1	431 $[M+H]^+$	1.61 (X)

[1751]

[1752] **실시예 20**

[1753] 실시예 20.1

[1754] (S)-사이클로프로판카복실산 (1-{4-[1-(6-이소프로폭시-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아미드



[1755]

[1756] 수소화나트륨 25mg(1.04mmol)을 2-프로판올 2mL에 첨가하고, 10분 동안 80℃에서 가열한다. 그 시간 후, (S)-사이클로프로판카복실산 (1-{4-[1-(6-클로로-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아미드(XIV.6) 80mg (0.21mmol)을 첨가한다. 상기 혼합물을 80℃에서 12시간 동안 가열한다. 그 시간 후, 물을 첨가하고, 상기 혼

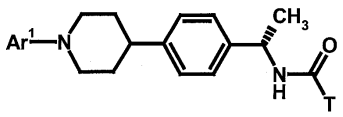
합물을 디클로로메탄으로 추출한다. 용매를 증발시키고 잔사는 역상 HPLC(칼럼: Waters XBridge 5μM; 용출제 A: 물 + 0.3% NH_4OH, 용출제 B: MeOH)를 사용하여 정제하여 목적 생성물을 수득한다.

[1757] $C_{22}H_{32}N_4O_2$ (M = 408.5g/mol), ESI-MS: 409 $[M+H]^+$

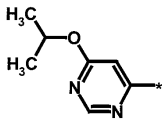
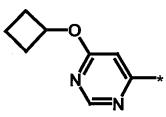
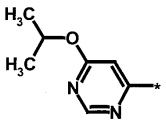
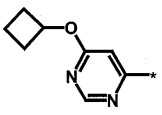
[1758] R_t (HPLC): 1.31분 (방법 L)

[1759] 하기 화학식 20-1의 화합물은 실시예 20.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1760] [화학식 20-1]



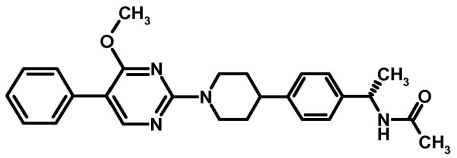
[1761]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
20.1			2-프로판올	XIV.6	409 $[M+H]^+$	1.31 (L)
20.2			사이클로부탄올	XIV.6	421 $[M+H]^+$	1.32 (L)
20.3			2-프로판올	XIV.7	412 $[M+H]^+$	1.32 (L)
20.4			2-프로판올	XIV.7	424 $[M+H]^+$	1.30 (L)

[1762] **실시예 21**

[1763] 실시예 21.1

[1764] (S)-N-(1-{4-[1-(4-메톡시-5-페닐-피리미딘-2-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1765] 

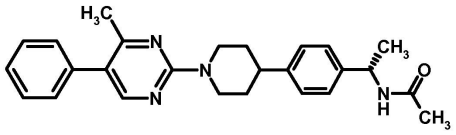
[1766] MeOH 4mL 중의 (S)-N-(1-{4-[1-(4-클로로-5-페닐-피리미딘-2-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드 (5.50mmol) 43.5mg(0.10mmol)에 나트륨 메톡사이드 0.074mL(0.40mmol)를 첨가하고, 상기 혼합물을 80℃에서 3시간 동안 교반한다. 냉각시킨 후, 조악한 혼합물을 HPLC(C18 RP Sunfire; 물(+0.1% TFA)/MeOH)로 정제하여 목적 생성물을 수득한다.

[1767] $C_{26}H_{30}N_4O_2$ (M = 430.5g/mol), ESI-MS: 431 $[M+H]^+$

[1768] R_t (HPLC): 1.88분 (방법 P)

[1769] 실시예 21.2

[1770] (S)-N-(1-{4-[1-(4-메틸-5-페닐-피리미딘-2-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1771] 

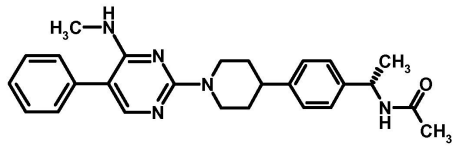
[1772] MeOH 1mL 및 디옥산 2mL 중의 (S)-N-(1-{4-[1-(4-클로로-5-페닐-피리미딘-2-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드(5.50mmol) 43.5mg(0.10mmol)에, 아르곤 대기하에서 트리메틸보록신 0.042mL(0.30mmol), $NaHCO_3$ 용액(2mmol/mL) 0.1mL 및 비스(트리페닐포스핀)-팔라듐(II) 클로라이드 2.9mg(0.0042mmol)를 첨가한다. 그 시간 후, 또 다른 트리메틸보록신 100㎕(0.7mmol) 및 비스(트리페닐포스핀)-팔라듐(II) 클로라이드 2.9mg(0.0042mmol)를 첨가하고, 80℃에서 12시간 동안 계속 교반한다. 상기 혼합물을 DMF로 희석하고, 여과하고, HPLC(C18 RP Sunfire; 물(+0.1% TFA)/MeOH)로 정제하여 목적 생성물을 수득한다.

[1773] $C_{26}H_{30}N_4O$ (M = 414.5g/mol), ESI-MS: 415 $[M+H]^+$

[1774] R_t (HPLC): 2.28분 (방법 P)

[1775] 실시예 21.3

[1776] (S)-N-(1-{4-[1-(4-메틸아미노-5-페닐-피리미딘-2-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1777] 

[1778] 디메틸아세트아미드 2mL 중의 (S)-N-(1-{4-[1-(4-클로로-5-페닐-피리미딘-2-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드(5.50mmol) 34.0mg(0.078mmol)에, DIPEA 0.027mL(0.16mmol) 및 메틸아민 1.15mL(2.3mmol)를 첨가한다. 상기 혼합물을 100℃에서 16시간 동안 교반한다. 이어서, 상기 조악한 혼합물은 HPLC(C18 RP Sunfire; 물(+0.1% TFA)/MeOH)로 정제하여 목적 생성물을 수득한다.

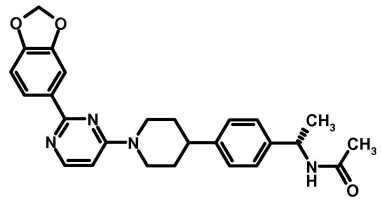
[1779] $C_{26}H_{31}N_5O$ (M = 429.6g/mol), ESI-MS: 430 $[M+H]^+$

[1780] R_t (HPLC): 1.66분 (방법 P)

[1781] **실시예 22**

[1782] 실시예 22.1

[1783] (S)-N-(1-{4-[1-(2-벤조[1,3]디옥솔-5-일-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1784] 

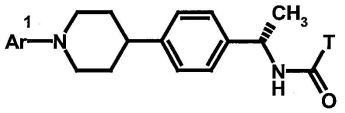
[1785] 아르곤 대기하에서, Na_2CO_3-용액(2mol/L) 0.2mL 및 비스(트리페닐포스핀)-팔라듐(II) 클로라이드 3mg(0.004mmol)를, 디옥산 2mL/MeOH 1mL 중의 3,4-(메틸렌디옥시)페닐보론산 50mg(0.30mmol) 및 (S)-N-(1-{4-[1-(2-클로로-피리미딘-4-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드(화합물 XIV.3) 36mg(0.10mmol)의 혼합물에 첨가한다. 상기 혼합물을 90℃에서 3시간 동안 교반한다. 그 시간 후, 상기 혼합물을 DMF/물로 희석하고 여과한다. 상기 여액은 역상 HPLC(물(+0.1% TFA)/MeOH)를 사용하여 정제하여 목적 생성물을 수득한다.

[1786] $C_{26}H_{28}N_4O_3$ (M = 444.5g/mol), ESI-MS: 445 $[M+H]^+$

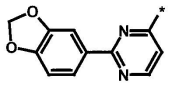
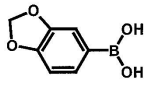
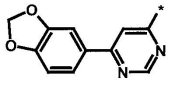
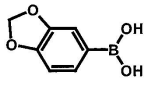
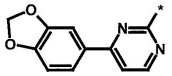
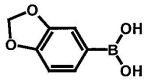
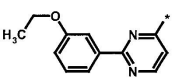
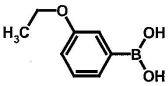
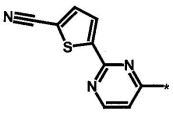
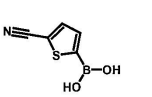
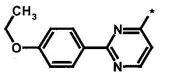
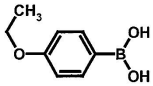
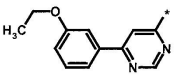
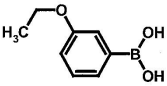
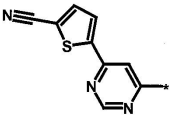
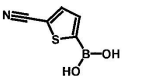
[1787] R_t (HPLC): 1.38분 (방법 E)

[1788] 하기 화학식 22-1의 화합물은 실시예 10.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

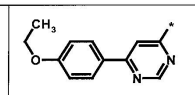
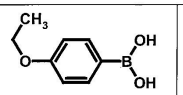
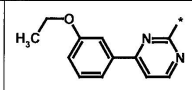
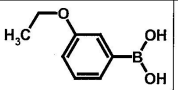
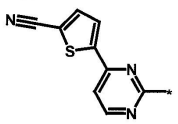
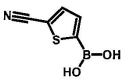
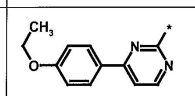
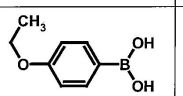
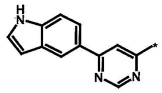
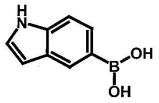
[1789] [화학식 22-1]



(22-1)

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
22.1		*—CH_3		XIV.3	445 $[M+H]^+$	1.38 (E)
22.2		*—CH_3		XIV.1	445 $[M+H]^+$	1.39 (E)
22.3		*—CH_3		XIV.8	445 $[M+H]^+$	1.54 (E)
22.4		*—CH_3		XIV.3	445 $[M+H]^+$	2.71 (S)
22.5		*—CH_3		XIV.3	432 $[M+H]^+$	2.60 (S)
22.6		*—CH_3		XIV.3	445 $[M+H]^+$	2.72 (S)
22.7		*—CH_3		XIV.1	445 $[M+H]^+$	2.67 (S)
22.8		*—CH_3		XIV.1	432 $[M+H]^+$	2.56 (S)

[1790]

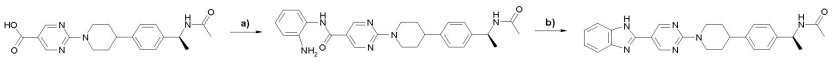
22.9		*—CH_3		XIV.1	445 $[M+H]^+$	2.65 (S)
22.10		*—CH_3		XIV.8	445 $[M+H]^+$	1.74 (E)
22.11		*—CH_3		XIV.8	432 $[M+H]^+$	1.94 (E)
22.12		*—CH_3		XIV.8	445 $[M+H]^+$	1.61 (E)
22.13		*—CH_3		XIV.1	440 $[M+H]^+$	1.39 (E)

[1791]

[1792] **실시예 23**

[1793] 실시예 23.1

[1794] (S)-N-[1-(4-{1-[5-(1H-벤조이미다졸-2-일)-피리미딘-2-일]-피페리딘-4-일}-페닐)-에틸]-아세트아미드

[1795] 

[1796] a)

[1797] DMF 4mL 중의 (S)-2-{4-[4-(1-아세틸아미노-에틸)-페닐]-피페리딘-1-일}-피리미딘-5-카복실산(XVII.1) 74.0mg (0.2mmol) 및 DIPEA 42㎕(0.24mmol)에 TBTU 77.0mg(0.2mmol)을 첨가하고, 상기 혼합물을 실온에서 10분 동안 교반한다. 이어서, o-페닐렌디아민 40.0mg(0.37mmol)을 첨가하고, 5시간 동안 계속 교반한다. 상기 혼합물은 염기성 산화알루미늄을 통해 여과하고, DMF/MeOH(9:1)로 세척한다. 용매를 진공하에 제거하고, 조 생성물은 다음 단계를 위해 직접 사용한다.

[1798] $C_{26}H_{30}N_6O_2$ (M = 458.6g/mol), ESI-MS: 459 $[M+H]^+$

[1799] R_t (HPLC): 1.79 (방법 P)

[1800] b)

[1801] HOAc 2mL 중의 (S)-2-{4-[4-(1-아세틸아미노-에틸)-페닐]-피페리딘-1-일}-피리미딘-5-카복실산 (2-아미노-페닐)-아미드 92mg의 혼합물을 110℃에서 12시간 동안 환류시킨다. 진공에서 농축시킨 후, 물을 첨가하고, 침전을 여과하여 수거하여 목적 생성물을 수득한다.

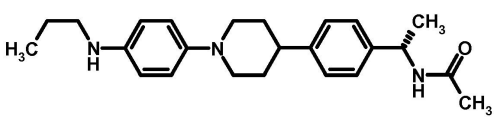
[1802] $C_{26}H_{28}N_6O$ (M = 440.5g/mol), ESI-MS: 441 $[M+H]^+$

[1803] R_t (HPLC): 1.69분 (방법 P)

[1804] **실시예 24**

[1805] 실시예 24.1

[1806] (S)-N-(1-{4-[1-(4-(프로필아미노)페닐)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1807] 

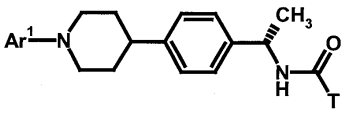
[1808] DCM 1mL 중의 아닐린 XX.6 75.0mg(0.22mmol)에 프로피온알데히드 16.2㎕(0.22mmol)를 첨가하고, 생성된 혼합물을 실온에서 30분 동안 교반한다. 이어서, $NaB(OAc)_3H$ 51.8mg(0.24mmol)을 첨가하고, 상기 혼합물을 밤새 실온에서 교반한다. 그 후, 상기 혼합물은 HPLC(물/MeOH/TFA)로 직접 정제한다.

[1809] $C_{24}H_{33}N_3O$ (M = 379.5g/mol), ESI-MS: 380 $[M+H]^+$

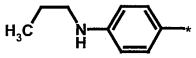
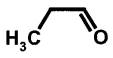
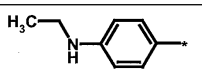
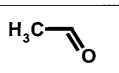
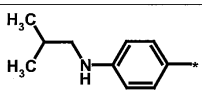
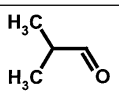
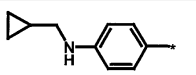
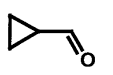
[1810] R_t (HPLC): 1.08분 (방법 N)

[1811] 하기 화학식 24-1의 화합물은 실시예 24.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1812] [화학식 24-1]



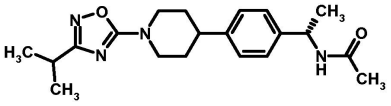
[1813]

실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t (HPLC) [분] 방법
24.1				XX.6	380 $[M+H]^+$	1.08 (N)
24.2				XX.6	366 $[M+H]^+$	0.98 (N)
24.3				XX.6	394 $[M+H]^+$	1.16 (N)
24.4				XX.6	392 $[M+H]^+$	1.16 (N)

[1814] **실시예 25**

[1815] 실시예 25.1

[1816] (S)-N-(1-{4-[1-(3-이소프로필-[1,2,4]옥사디아졸-5-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1817] 

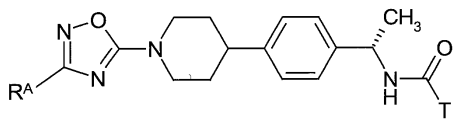
[1818] 염화아연(II)(THF 중의 0.5M 용액) 0.9mL(0.45mmol)를, 에틸아세테이트 12mL 중의 (S)-N-{1-[4-(1-시아노-피페리딘-4-일)-페닐]-에틸}-아세트아미드(XXVII.1) 40.7mg(0.15mmol) 및 N'-하이드록시-2-메틸프로판이미드아미드 30.6mg(0.30mmol)의 혼합물에 적가한다. 상기 혼합물을 실온에서 12시간 동안 교반한다. 그 후, 용매를 진공하에 제거하고, 에탄올 15mL 및 진한 HCl 용액 2mL를 첨가한다. 상기 혼합물을 3시간 동안 환류시킨다. 이어서, 상기 혼합물을 농축시키고, 물을 첨가한 다음, 침전을 수거하고 물로 세척하여 목적 생성물을 수득한다.

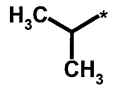
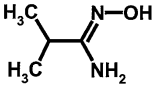
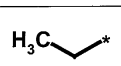
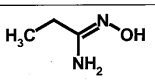
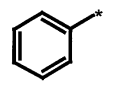
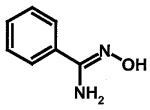
[1819] $C_{20}H_{28}N_4O_2$ (M = 356.5g/mol), ESI-MS: 357 $[M+H]^+$

[1820] R_t (HPLC): 2.06분 (방법 S)

[1821] 하기 화학식 25-1의 화합물은 실시예 25.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1822] [화학식 25-1]



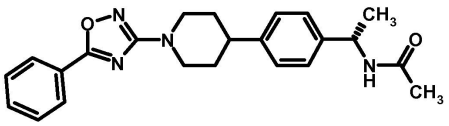
실시예	R^A	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
25.1				XXVII.1	357 $[M+H]^+$	2.06 (S)
25.2				XXVII.1	343 $[M+H]^+$	2.39 (S)
25.3				XXVII.1	391 $[M+H]^+$	2.63 (S)

[1823]

[1824] **실시예 26**

[1825] 실시예 26.1

[1826] (S)-N-(1-{4-[1-(5-페닐-[1,2,4]옥사디아졸-3-일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드

[1827] 

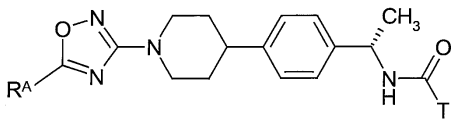
[1828] 벤조일 클로라이드 0.019mL(0.16mmol)를, THF 4mL 중의 (S)-N-(1-{4-[1-(N-하이드록시카밤이미도일)-피페리딘-4-일]-페닐}-에틸)-아세트아미드(XXVII.2) 45.7mg(0.15mmol) 및 트리에틸아민 0.063mL(0.45mmol)의 혼합물에 첨가한다. 상기 혼합물을 80℃에서 12시간 동안 교반하고, 이어서, HPLC(RP C18 Sunfire; 물(+0.1% TFA)/MeOH)로 정제하여 목적 생성물을 수득한다.

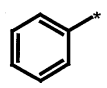
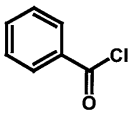
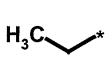
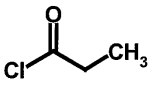
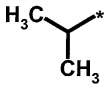
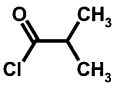
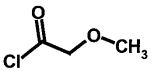
[1829] $C_{23}H_{26}N_4O_2$ (M = 390.5g/mol), ESI-MS: 391 $[M+H]^+$

[1830] R_t (HPLC): 2.12분 (방법 T)

[1831] 하기 화학식 26-1의 화합물은 실시예 26.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1832] [화학식 26-1]



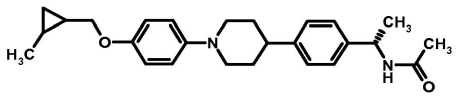
실시예	R^A	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
26.1				XXVII.2	391 $[M+H]^+$	2.12 (T)
26.2				XXVII.2	343 $[M+H]^+$	2.50 (S)
26.3				XXVII.2	357 $[M+H]^+$	2.58 (S)
26.4				XXVII.2	359 $[M+H]^+$	2.34 (S)

[1833]

[1834] **실시예 27**

[1835] 실시예 27.1

[1836] N-((1S)-1-(4-(1-(4-((2-메틸사이클로프로필)메톡시)페닐)-피페리딘-4-일)-페닐)-에틸)-아세트아미드

[1837] 

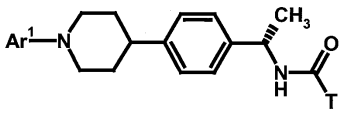
[1838] (S)-N-{1-(4-[1-(4-하이드록시페닐)-피페리딘-4-일]-페닐}-에틸)-아세트아미드(화합물 1.48) 50㎎(0.15mmol), 2-메틸사이클로프로판메탄올 14㎎(0.16mmol) 및 트리페닐포스핀 38.8㎎(0.15mmol)을 0℃에서 2-메틸-테트라하이드로푸란 2mL에 첨가한다. 디-이소프로필 아조디카복실레이트 30.5㎕(0.15mmol)를 첨가하고 상기 혼합물을 실온으로 가온한다. 밤새 계속 교반한 다음, 트리페닐포스핀 0.5당량 및 디-이소프로필 아조디카복실레이트 0.5당량을 첨가한다. 1일 동안 교반을 계속하고, 다시 추가의 트리페닐포스핀 및 디-이소프로필 아조디카복실레이트를 첨가하여, 50℃에서 16시간 동안 계속 교반한다. 이어서, 상기 혼합물을 여과하고 역상 HPLC(물/MeOH, 0.1% FA)를 사용하여 정제하여 목적 생성물을 수득한다.

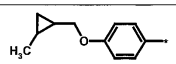
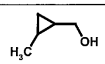
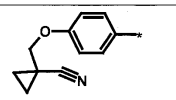
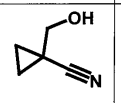
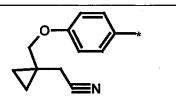
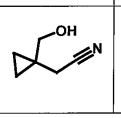
[1839] $C_{26}H_{34}N_2O_2$ (M = 406.6g/mol), ESI-MS: 407 $[M+H]^+$

[1840] R_t (HPLC): 1.58분 (방법 A)

[1841] 하기 화학식 27-1의 화합물은 실시예 27.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1842] [화학식 27-1]



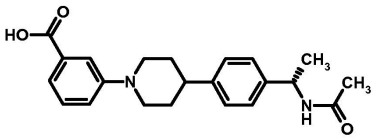
실시예	Ar1	T	E 1	E 2	ESI-MS [m/z]	Rt(HPLC) [분] (방법)
27.1				1.48	407 $[M+H]^+$	1.58 (A)
27.2				1.48	417 $[M+H]^+$	2.04 (A)
27.3				1.48	432 $[M+H]^+$	2.11 (A)

[1843]

[1844] **실시예 28**

[1845] 실시예 28.1

[1846] (S)-3-(4-(4-(1-아세트아미도에틸)페닐)피페리딘-1-일)벤조산



[1847]

[1848] 에스테르 15.02 2.90g(7.62mmol)을 MeOH 50mL 및 1N NaOH 수용액 8mL에 첨가한다. 상기 반응 혼합물을 1시간 동안 70℃에서 교반한다. 실온으로 냉각시킨 후, 용액을 묽은 수성 HCl 용액에 의해 산성화시키고, 생성된 침전을 여과하여 물로 세척하고 50℃에서 진공하에 건조시킨다.

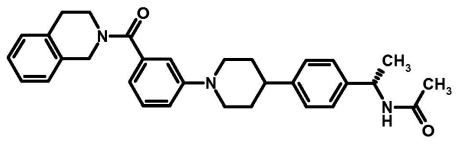
[1849] $C_{22}H_{26}N_2O_3$ (M = 366.5g/mol), ESI-MS: 367 $[M+H]^+$

[1850] R_t (HPLC): 1.11분 (방법 H)

[1851] **실시예 29**

[1852] 실시예 29.1

[1853] (S)-N-(1-(4-(1-(3-(1,2,3,4-테트라하이드로이소퀴놀린-2-카보닐))페닐)피페리딘-4-일)페닐)에틸)아세트아미드



[1854]

[1855] DMF 2mL 중의 실시예 28.1 73.3mg(0.20mmol)에, TBTU 64.2mg(0.20mmol) 및 TEA 41.8㎕(0.20mmol)를 첨가하고, 상기 혼합물을 15분 동안 실온에서 교반한다. 이어서, 1,2,3,4-테트라하이드로이소퀴놀린 26.6mg(0.20mmol)을 첨가하고, 1시간 동안 계속 교반한다. 상기 반응 혼합물은 HPLC(물 + 0.1% NH_4OH/MeOH)로 직접 정제한다.

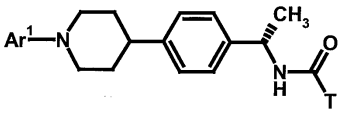
[1856] $C_{31}H_{35}N_3O_2$ (M = 481.6g/mol), ESI-MS: 482 $[M+H]^+$

[1857] R_t (HPLC): 1.39분 (방법 O)

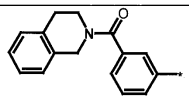
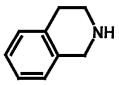
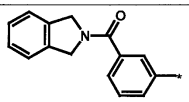
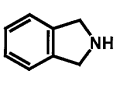
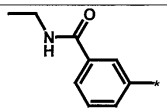
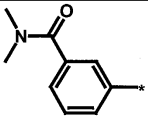
[1858] 하기 화학식 29-1의 화합물은 실시예 29.1과 유사하게 제조한다. 사용된 반응물은 "반응물"이란 제목의 칼럼으

로 제시되고 있다.

[1859] [화학식 29-1]



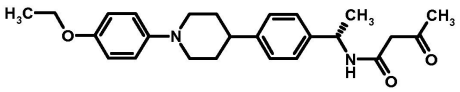
[1860]

실시예	Ar^1	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
29.1				28.1	482 $[M+H]^+$	1.39 (O)
29.2				28.1	468 $[M+H]^+$	1.35 (O)
29.3				28.1	394 $[M+H]^+$	1.02 (W)
29.4				28.1	394 $[M+H]^+$	1.00 (W)

[1861] **실시예 30**

[1862] 실시예 30.1

[1863] (S)-N-1-(4-(1-(4-에톡시페닐)피페리딘-4-일)페닐)에틸)-3-옥소부탄아미드



[1864]

[1865] 아민 XIII.1 150mg(0.46mmol)을 THF 1.5mL 및 DMAP 5.65mg(0.05mmol)에 첨가하고 0℃로 냉각시킨다. 이어서, 디케텐 42.8mg(0.51mmol)을 첨가하고, 생성된 혼합물은 1시간 동안 0℃에서 교반한다. 용매를 진공에서 제거하고 잔사는 칼럼 크로마토그래피(실리카 겔; PE/에틸 아세테이트, 구배 80:20 내지 50:50)로 정제한다.

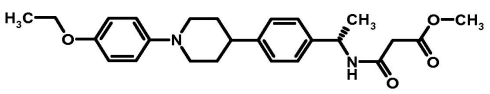
[1866] $C_{25}H_{32}N_2O_3$ (M = 408.5g/mol), ESI-MS: 409 $[M+H]^+$

[1867] R_t (HPLC): 0.88분 (방법 AD)

[1868] **실시예 31**

[1869] 실시예 31.1

[1870] (S)-메틸 3-(1-(4-(1-(4-에톡시페닐)피페리딘-4-일)페닐)에틸아미노)-3-옥소프로파노에이트



[1871]

[1872] 아민 XIII.1 324mg(1.00mmol)을 THF 10mL 및 TEA 154㎕(1.10mmol)에 첨가한다. 상기 혼합물을 냉각시키면서, 메틸 말로닐 클로라이드 108㎕(1.00mmol)를 적가한다. 생성된 혼합물을 실온에서 밤새 교반한다. 상기 혼합물을 여과하고, 용매는 진공하에 제거하고 잔사는 HPLC(물 + 0.15% FA/아세톤)로 정제한다.

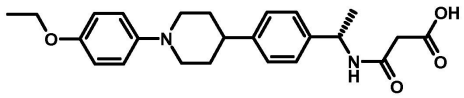
[1873] $C_{25}H_{32}N_2O_4$ (M = 424.5g/mol), ESI-MS: 425 $[M+H]^+$

[1874] R_t (HPLC): 0.73분 (방법 AD)

[1875] **실시예 32**

[1876] 실시예 32.1

[1877] (S)-3-(1-(4-(1-(4-에톡시페닐)피페리딘-4-일)페닐)에틸아모이노)-3-옥소프로파노산

[1878] 

[1879] 에스테르 31.1 250mg(0.59mmol)을 EtOH 5mL 및 1N NaOH 수용액 0.6mL에 첨가하고, 실온에서 교반한다. 용매를 진공하에 제거하고 잔사는 DCM과 수성 pH 7 완충액 사이에 분배시킨다. 유기 층을 분리하고 물로 세척하고 $MgSO_4$으로 건조시키고, 용매는 진공하에 제거한다.

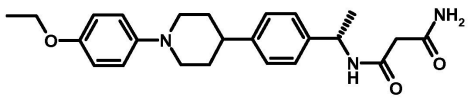
[1880] $C_{24}H_{30}N_2O_4$ (M = 410.5g/mol), ESI-MS: 411 $[M+H]^+$

[1881] R_t (HPLC): 0.90분 (방법 G)

[1882] **실시예 33**

[1883] 실시예 33.1

[1884] (S)-N-(1-{4-[1-(4-에톡시페닐)피페리딘-4-일]페닐}에틸)말론아미드

[1885] 

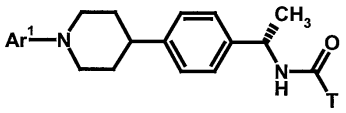
[1886] DMF 1mL 중의 카복실산 32.1 50.0mg(0.12mmol)에 TEA 25.3㎕(0.18mmol), TBTU 41.1mg(0.13mmol) 및 수성 암모니아 용액(32%) 200㎕를 첨가한다. 이어서, 상기 혼합물을 HPLC(물/MeOH, 0.15% NH_4OH)로 여과 정제한다.

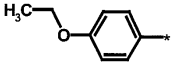
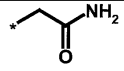
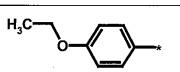
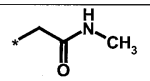
[1887] $C_{24}H_{31}N_3O_3$ (M = 409.5g/mol), ESI-MS: 410 $[M+H]^+$

[1888] R_t (HPLC): 1.10분 (방법 G)

[1889] 하기 화학식 33-1의 화합물은 실시예 33.1과 유사하게 제조하며, 사용된 반응물은 "E1" 및 "E2"란 제목의 칼럼으로 제시되고 있다.

[1890] [화학식 33-1]



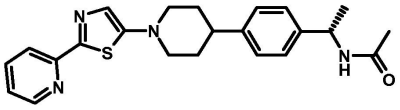
실시예	Ar^1	T	E 1	E 2	ESI-MS [m/z]	R_t(HPLC) [분] 방법
33.1			32.1	암모니아	410 $[M+H]^+$	1.10 (G)
33.2			32.1	메틸아민	424 $[M+H]^+$	1.15 (G)

[1891]

[1892] **실시예 34**

[1893] 실시예 34.1

[1894] (S)-N-(1-(4-(1-(2-(피리딘-2-일)티아졸-5-일)피페리딘-4-일)페닐)에틸)아세트아미드

[1895] 

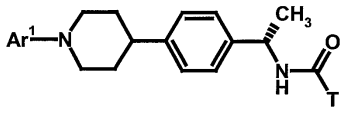
[1896] 아세틸브로마이드 XXIX.1 90.0mg(0.25mmol) 및 피리딘-2-카보티오산 아미드 33.9mg(0.25mmol)을 에탄올 2mL에 첨가하고, 80℃에서 4시간 동안 교반한다. 이어서, 상기 반응 혼합물을 HPLC(물 + 0.3% NH_4OH/MeOH)로 직접 정제한다.

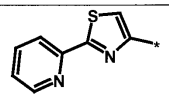
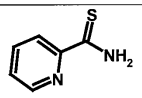
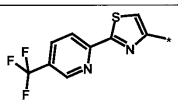
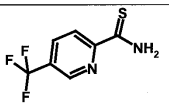
[1897] $C_{23}H_{26}N_4OS$ (M = 406.5g/mol), ESI-MS: 407 $[M+H]^+$

[1898] R_t (HPLC): 1.16분 (방법 G)

[1899] 하기 화합물은 실시예 34.1과 유사하게 제조한다. 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다.

[1900] [화학식 34-1]

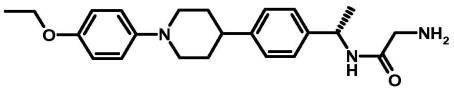
[1901] 

실시예	Ar^1	T	반응물 1	반응물 2	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
34.1		*—CH_3		XXIX.1	407 $[M+H]^+$	1.16 (G)
34.2		*—CH_3		XXIX.1	475 $[M+H]^+$	1.32 (G)

[1902] **실시예 35**

[1903] 실시예 35.1

[1904] (S)-2-아미노-N-(1-{4-[1-(4-에톡시페닐)피페리딘-4-일]페닐}에틸)아세트아미드

[1905] 

[1906] 디클로로메탄 중의 실시예 6.49 250mg(0.50mmol)에 메탄올성 HCl 용액(c = 1.25mol/ℓ) 2.02mL를 충전한다. 상기 혼합물을 밤새 환류시키고, 용매는 진공하에 제거하고, 잔사에 물을 첨가한다. 이어서, 상기 혼합물은 묽은 NaOH 수용액으로 염기성화시키고, 생성된 침전은 수거하여, DCM에 용해시키며, 물로 세척하고, $MgSO_4$으로 건조시킨다. 용매를 진공하에 제거한다.

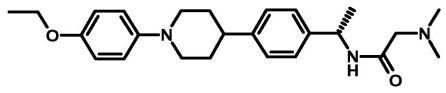
[1907] $C_{24}H_{33}N_3O_2$ (M = 395.5g/mol), ESI-MS: 396 $[M+H]^+$

[1908] R_t (HPLC): 1.16분 (방법 G)

[1909] **실시예 36**

[1910] 실시예 36.1

[1911] (S)-2-(디메틸아미노)-N-(1-{4-[1-(4-에톡시페닐)피페리딘-4-일]페닐}에틸)아세트아미드

[1912] 

[1913] THF 5mL 중의 실시예 35.1 59.3mg(0.15mmol)에 포르말린 36.5㎕(0.45mmol), 수성 pH 5 완충액 1mL 및 나트륨 트리아세톡시보로하이드라이드 95.4mg을 첨가한다. 생성된 혼합물을 실온에서 2시간 동안 교반하고, HPLC(물 + 0.15% NH_4OH/MeOH)로 직접 정제한다.

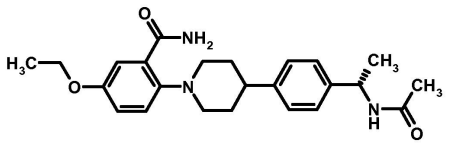
[1914] $C_{26}H_{37}N_3O_2$ (M = 423.6g/mol), ESI-MS: 424 $[M+H]^+$

[1915] R_t (HPLC): 1.22분 (방법 G)

[1916] **실시예 37**

[1917] 실시예 37.1

[1918] (S)-2-(4-(4-(1-아세트아미도에틸)페닐)피페리딘-1-일)-5-에톡시벤즈아미드

[1919] 

[1920] DMSO 2mL 중의 실시예 13.3 50.0mg(0.13mmol)을 0℃로 냉각시키고, K_2CO_3 19.5mg(0.14mmol)을 충전한다. 이어서, H_2O_2(물 중의 30%) 113㎕를 첨가하고, 상기 혼합물을 실온으로 가온시킨 다음 밤새 교반한다. 추가의 H_2O_2(물 중의 30%) 113㎕를 첨가하고, 45℃에서 2시간 동안 계속 교반한다. 상기 반응 혼합물을 여과하고, HPLC(물 + 0.15% FA/MeOH)로 직접 정제한다.

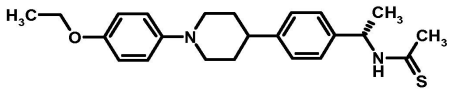
[1921] $C_{23}H_{29}N_3O_3$ (M = 409.5g/mol), ESI-MS: 410 $[M+H]^+$

[1922] R_t (HPLC): 1.09분 (방법 G)

[1923] **실시예 38**

[1924] 실시예 38.1

[1925] (S)-N-(1-(4-(1-(4-에톡시페닐)피페리딘-4-일)페닐)에틸)에탄티오아미드

[1926] 

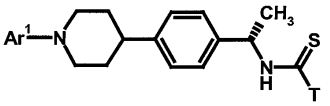
[1927] 톨루엔 3mL 중의 실시예 1.1 50.0mg(0.14mmol) 및 라웨슨 시약 55.1mg(0.14mmol)을 2시간 동안 환류시킨다. 이어서, 용매를 진공하에 제거하고 잔사는 HPLC(물 + 0.3% NH_4OH/MeOH)로 정제한다.

[1928] $C_{23}H_{30}N_2OS$ (M = 382.6g/mol), ESI-MS: 383 $[M+H]^+$

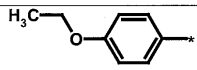
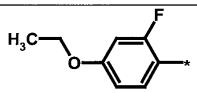
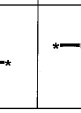
[1929] R_t (HPLC): 1.22분 (방법 G)

[1930] 하기 화합물은 실시예 38.1과 유사하게 제조한다. 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다.

[1931] [화학식 38-1]



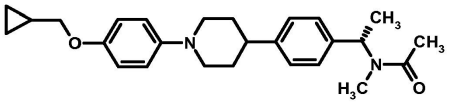
[1932]

실시예	Ar¹	T	반응물	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
38.1			1.1	383 $[M+H]^+$	1.22 (G)
38.2			1.103	401 $[M+H]^+$	1.26 (G)

[1933] **실시예 39**

[1934] 실시예 39.1

[1935] (S)-N-(1-(4-(1-(4-사이클로프로필메톡시페닐)피페리딘-4-일)페닐)에틸)-N-메틸아세트아미드

[1936] 

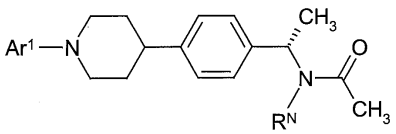
[1937] 0℃에서 THF 2.5mL 중의 NaH 32.2mg(1.27mmol)에 실시예 1.26 50.0mg(0.13mmol)을 첨가한다. 상기 혼합물은 메틸 요오다이드 15.9㎕(0.26mmol)를 첨가하기 전에 0℃에서 10분 동안 교반하고, 상기 혼합물은 2시간 동안 실온에서 교반한다. 상기 반응은 물 및 포화 수성 NH_4Cl 용액의 첨가에 의해 급냉시킨다. 생성된 혼합물은 DCM으로 추출하고, 유기 층은 합하여 $MgSO_4$으로 건조시킨다. 용매를 진공하에 제거하고 잔사는 ACN 및 일부 물에 용해시켜 동결건조시킨다.

[1938] $C_{26}H_{34}N_2O_2$ (M = 406.6g/mol), ESI-MS: 407 $[M+H]^+$

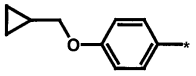
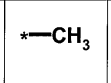
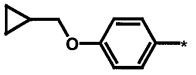
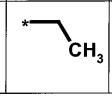
[1939] R_t (HPLC): 2.36분 (방법 F)

[1940] 하기 화합물은 실시예 39.1과 유사하게 제조한다. 사용된 반응물은 "반응물"이란 제목의 칼럼으로 제시되고 있다.

[1941] [화학식 39-1]



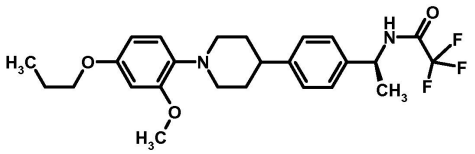
[1942]

실시예	Ar¹	R^N	반응물	ESI-MS [m/z]	R_t(HPLC) [분] (방법)
39.1			1.26	407 $[M+H]^+$	2.36 (F)
39.2			1.26	421 $[M+H]^+$	2.41 (F)

[1943] **실시예 40**

[1944] 실시예 40.1

[1945] (S)-2,2,2-트리플루오로-N-{1-[4-(1-(2-메톡시-4-프로폭시페닐)피페리딘-4-일)페닐]에틸}아세트아미드

[1946] 

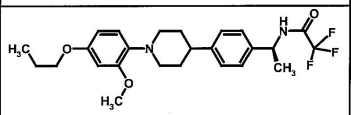
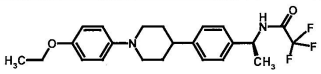
[1947] MeOH 5mL 중의 실시예 XXXV.1 100mg(0.22mmol)에 Pd/C 10mg을 충전시키고, 밤새 실온에서 수소 대기(50psi)하에 교반한다. 이어서, 상기 반응 혼합물을 여과하고 용매는 진공하에 제거하고 생성된 잔사는 HPLC(RP C18 Xbridge, 물(+0.3% 암모니아)/MeOH)로 정제한다.

[1948] $C_{25}H_{31}F_3N_2O_3$ (M = 464.5g/mol), EI-MS: 465 $[M+H]^+$

[1949] R_t (HPLC): 2.40분 (방법 F)

[1950] 하기 화합물은 실시예 XXXIII.1과 유사하게 제조한다.

[1951]

실시예	출발 물질	생성물 구조	질량 스펙트럼 결과	R_t(HPLC) [분] (방법)
40.1	XXXV.1		465 $[M+H]^+$	2.40 (F)
40.2	XXXV.2		421 $[M+H]^+$	2.11 (F)

[1952] **제형 실시예**

[1953] 당해 분야에 공지된 방법과 유사하게 수득될 수 있는, 하기 제형 실시예는 이를 이들 실시예의 내용으로 제한하지 않으면서 본 발명을 더욱 상세히 설명하기 위한 것이다. 용어 "활성 물질"은 본 발명에 따르는 하나 이상의 화합물(이의 염을 포함한다)을 나타낸다.

[1954] 실시예 1: 활성 물질 50mg을 함유하는 정제

[1955] 조성:

[1956] (1) 활성 물질 50.0mg

[1957] (2) 락토스 98.0mg

[1958] (3) 옥수수 전분 50.0mg

[1959] (4) 폴리비닐피롤리돈 15.0mg

[1960] (5) 마그네슘 스테아레이트 2.0mg

[1961] 215.0mg

[1962] 제조:

[1963] (1), (2) 및 (3)을 함께 혼합하고, (4)의 수용액과 함께 과립화한다. (5)를 건조된 과립 물질에 첨가한다. 상기 혼합물로부터, 정제를, 양면에 이중면(biplanar)의, 면체(faceted)가 있고, 한 면에는 분할 노치(dividing notch)가 있도록 압착시킨다. 정제의 직경: 9㎜.

[1964] 실시예 2: 활성 물질 350mg을 함유하는 정제

[1965] 제조:

[1966] (1) 활성 물질 350.0mg

[1967] (2) 락토스 136.0mg

[1968] (3) 옥수수 전분 80.0mg

[1969] (4) 폴리비닐피롤리돈 30.0mg

[1970] (5) 마그네슘 스테아레이트 4.0mg

[1971] 600.0mg

[1972] (1), (2) 및 (3)을 함께 혼합하고, (4)의 수용액과 함께 과립화한다. (5)를 건조된 과립 물질에 첨가한다. 상기 혼합물로부터, 정제를, 양면에 이중면의, 면체가 있고, 한 면에는 분할 노치가 있도록 압착시킨다. 정제의 직경: 12㎜.

[1973] 실시예 3: 활성 물질 50㎎을 함유하는 캡슐제

[1974] 조성:

[1975] (1) 활성 물질 50.0mg

[1976] (2) 건조된 옥수수 전분 58.0mg

[1977] (3) 분말 락토스 50.0mg

[1978] (4) 마그네슘 스테아레이트 2.0mg

[1979] 160.0mg

[1980] 제조:

[1981] (1)을 (3)으로 연마한다. 상기 연마물을 강력한 혼합과 함께 (2) 및 (4)의 혼합물에 첨가한다. 상기 분말 혼합물은 캡슐제 충전기에서 사이즈 3 경질 젤라틴 캡슐로 충전시킨다.

[1982] 실시예 4: 활성 물질 350㎎을 함유하는 캡슐제

[1983] 조성:

[1984] (1) 활성 물질 350.0mg

[1985] (2) 건조된 옥수수 전분 46.0mg

[1986] (3) 분말 락토스 30.0mg

[1987] (4) 마그네슘 스테아레이트 4.0mg

[1988] 430.0mg

[1989] 제조:

[1990] (1)을 (3)으로 연마한다. 상기 연마물을 강력한 혼합과 함께 (2) 및 (4)의 혼합물에 첨가한다. 상기 분말 혼합물은 캡슐제 충전기에서 사이즈 0 경질 젤라틴 캡슐로 충전시킨다.

[1991] 실시예 5: 2mL 당 활성 물질 35㎎을 함유하는 무수 앰풀

[1992] 조성:

[1993] 활성 물질 35.0mg

[1994] 만니톨 100.0mg

[1995] 주사용수 2.0mL를 첨가함

[1996] 제조:

[1997] 활성 물질 및 만니톨을 물에 용해시킨다. 충전 후, 상기 용액을 동결-건조시킨다. 즉시 사용하기 위한 용액을 제조하기 위해, 상기 생성물을 주사용수에 용해시킨다.