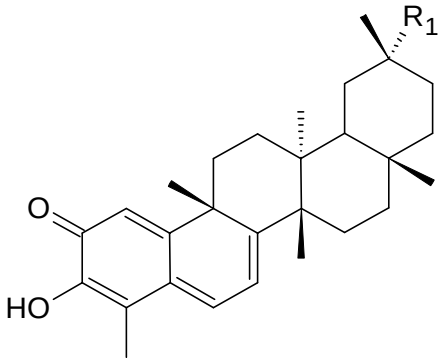
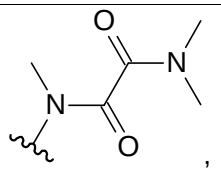
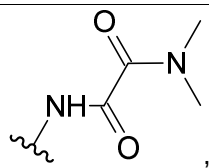
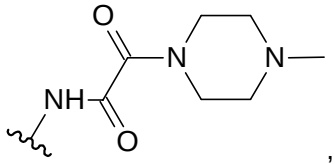
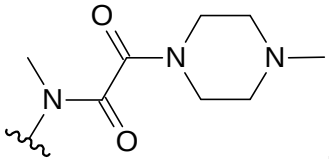
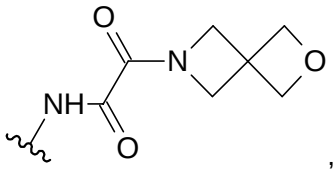
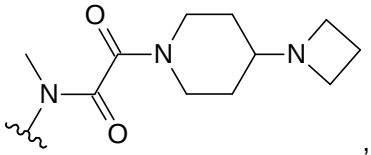
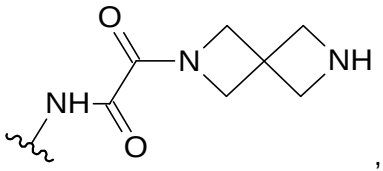
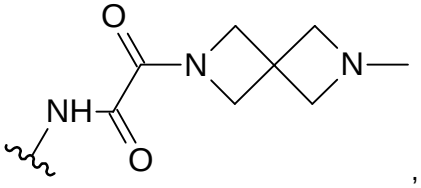
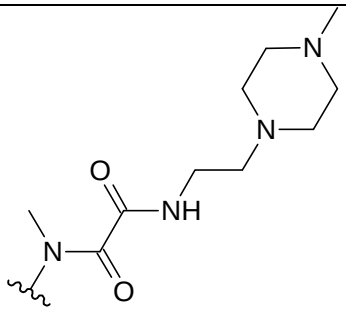
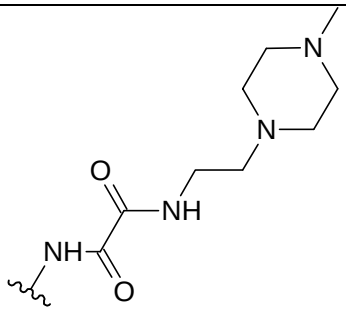
**CLAIMS**

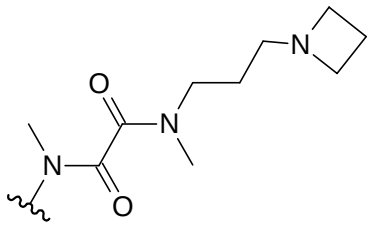
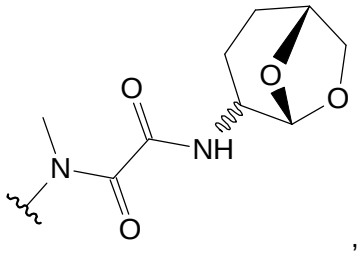
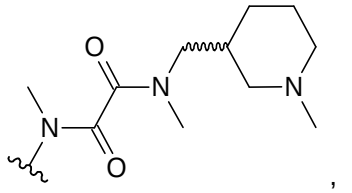
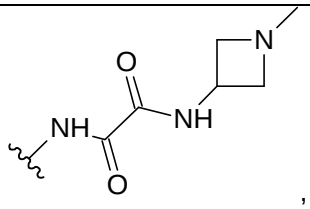
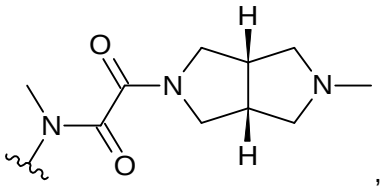
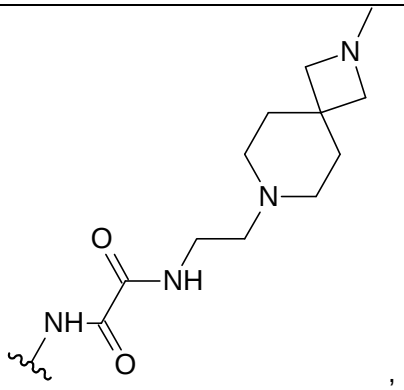
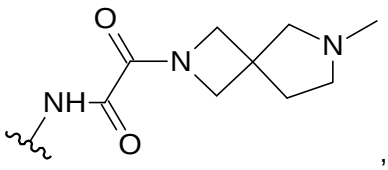
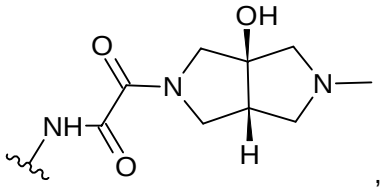
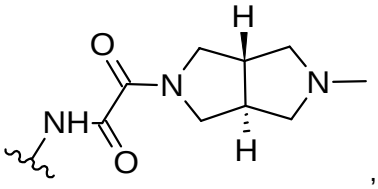
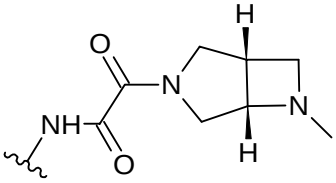
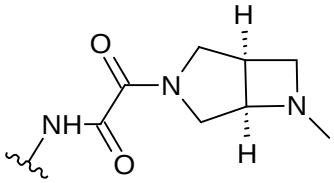
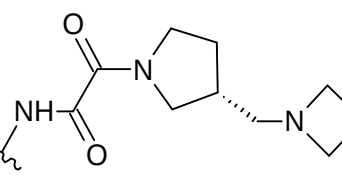
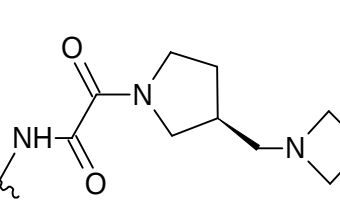
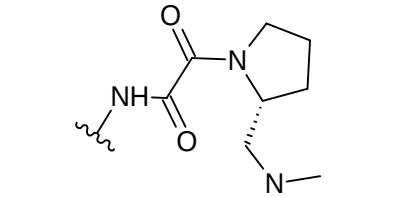
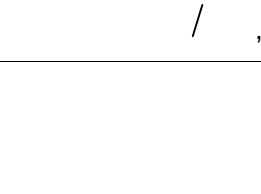
1. A compound of structural formula (**I**)

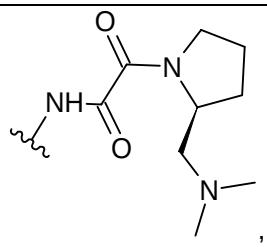
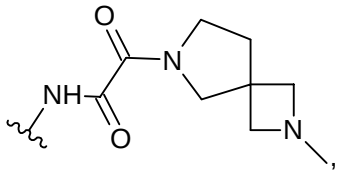
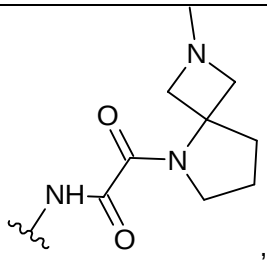
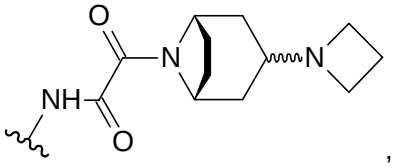
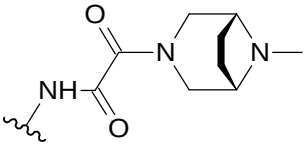
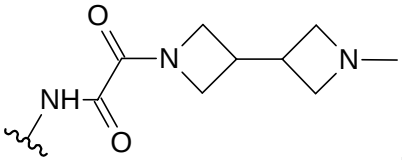
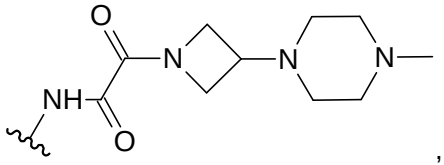
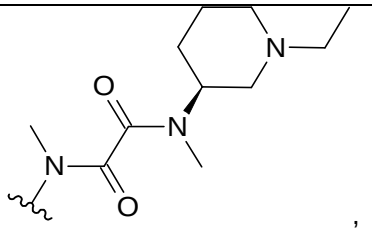
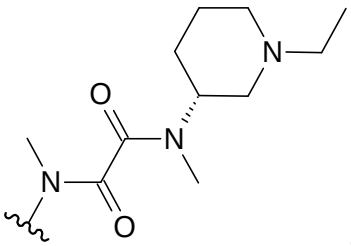
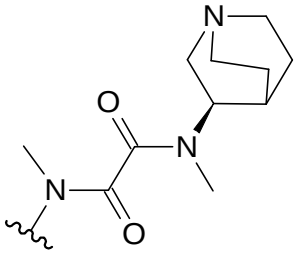
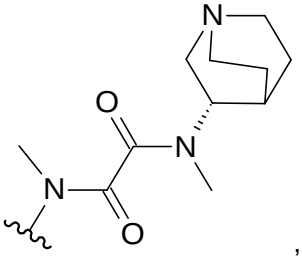
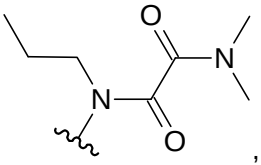
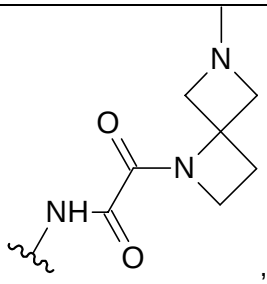
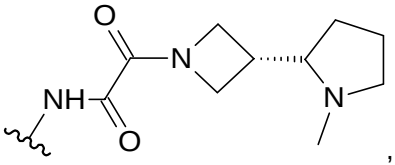


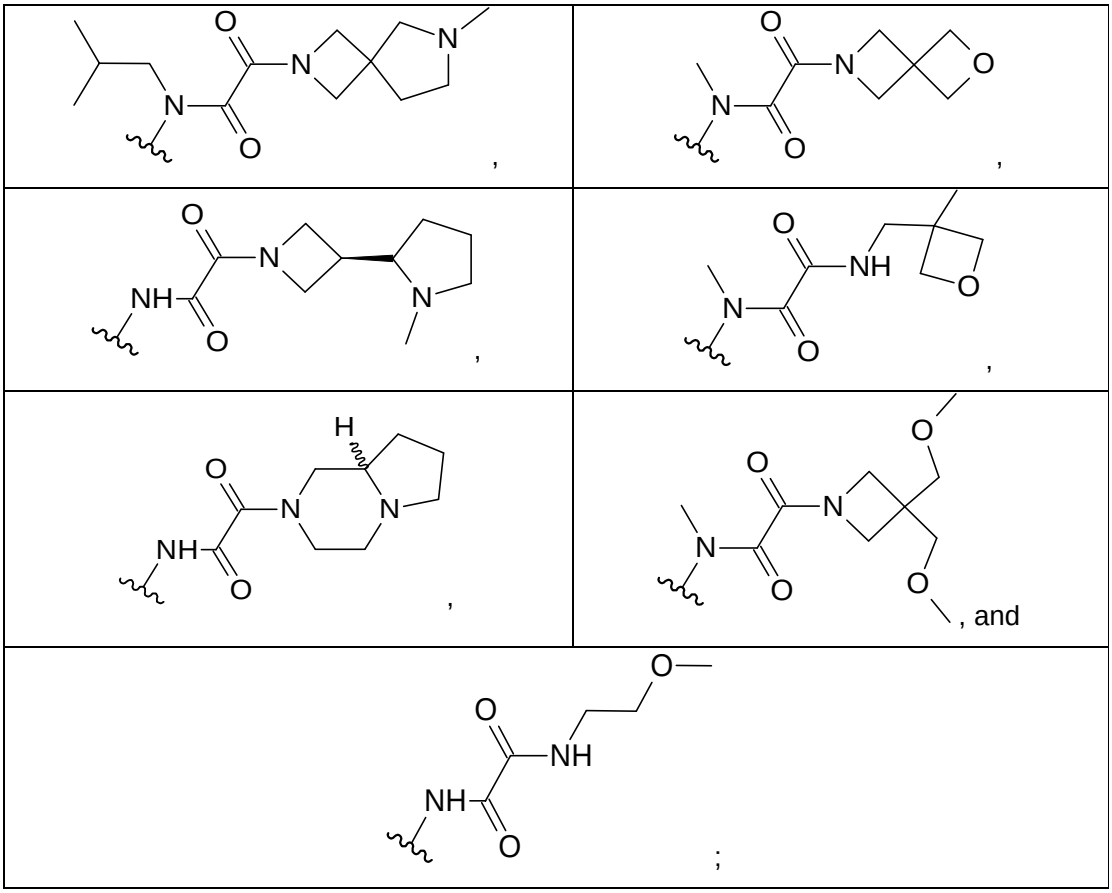
(**I**)

wherein, $R_1$ is selected from:

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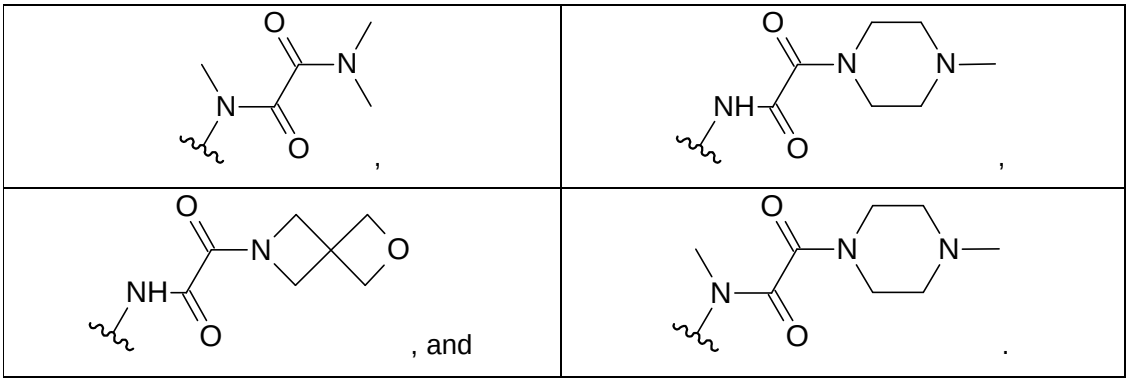
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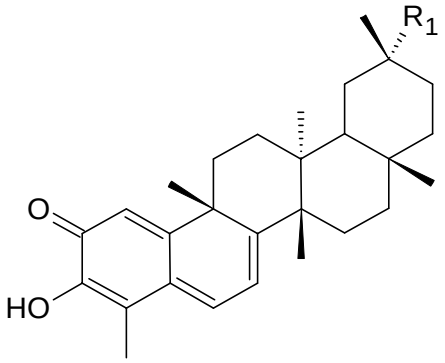


or a pharmaceutically acceptable salt, single stereoisomer, mixture of stereoisomers, tautomer, or prodrug thereof.

2. The compound of claim 1, wherein $R_1$ is selected from:



3. A compound of structural formula (**I**)




(**I**)

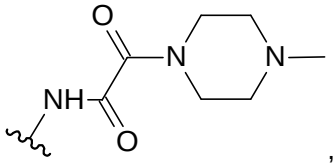
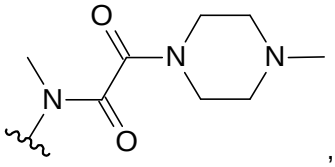
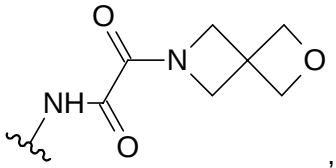
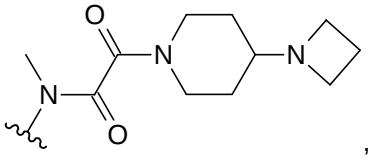
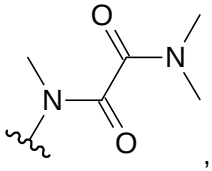
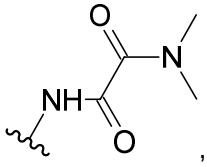
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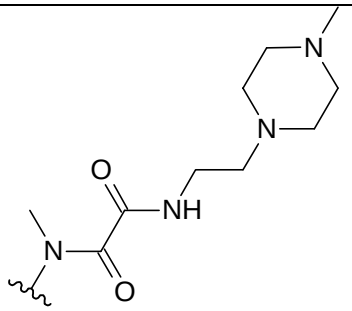
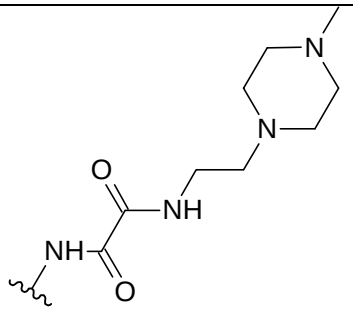
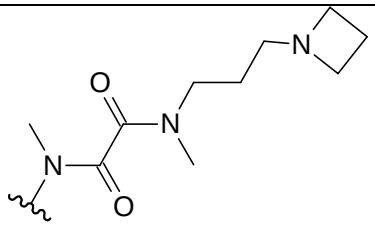
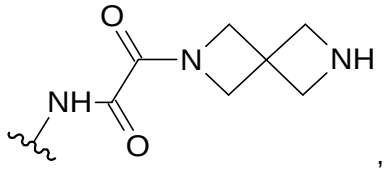
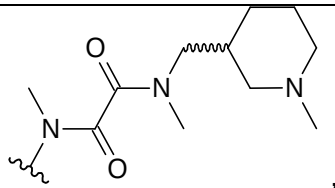
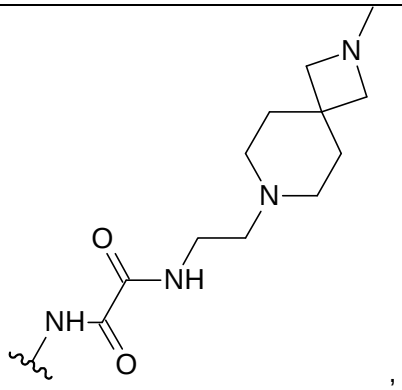
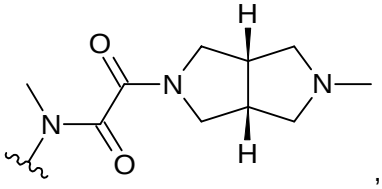
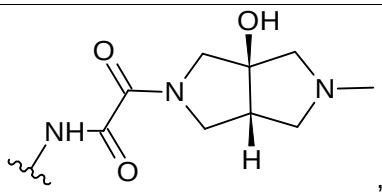
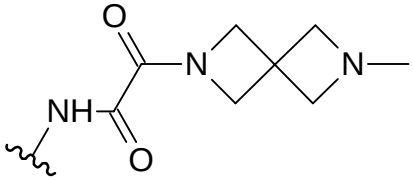
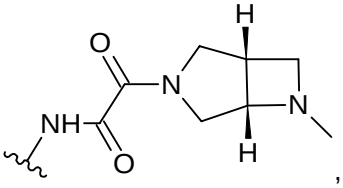
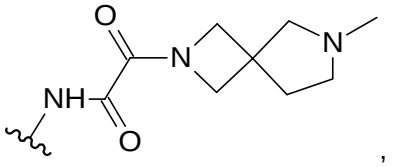
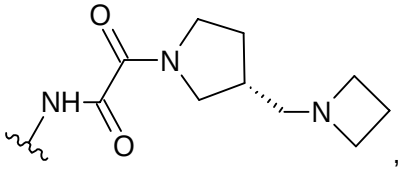
$R_1$ is –NH-$(CO)_2$-$NR_2R_3$, or –N$(CH_3)$-$(CO)_2$-$NR_2R_3$;

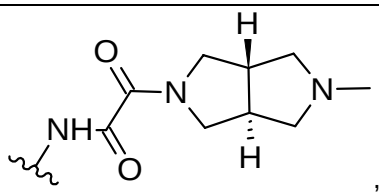
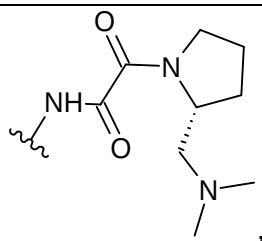
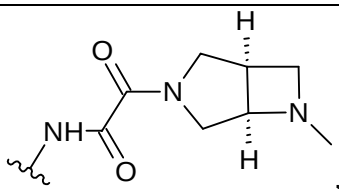
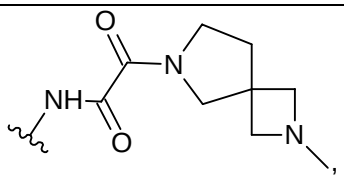
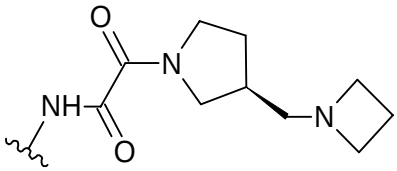
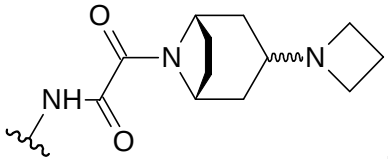
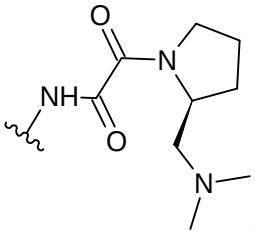
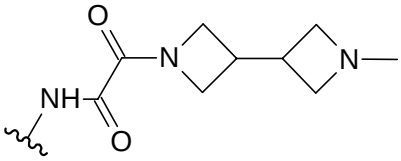
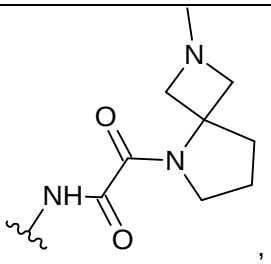
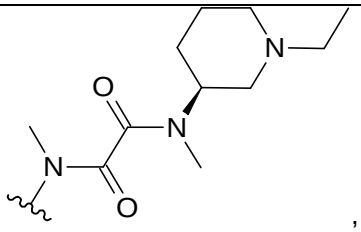
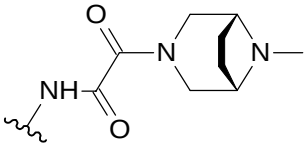
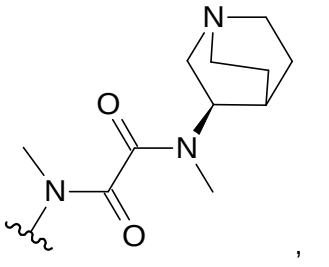
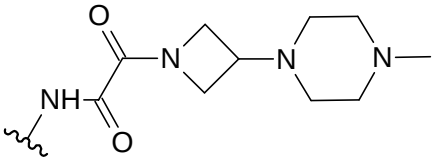
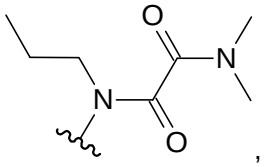
$R_2$ and $R_3$ are independently selected from hydrogen, an alkyl, cycloalkyl, alkoxy, heterocycloalkyl, alkylaryl, alkenyl, alkynyl, aryl, amine, or heteroaryl, optionally substituted with substituents individually selected from alkyl, alkoxy, cycloalkyl, ether, amine optionally substituted with one or more alkyl, halogen, hydroxyl, ether, cyano, nitrile, $CF_3$, ester, amide, cycloalkyl amide, sugar, heteroarylamide optionally substituted with alkyl and/or alkoxy, urea, carbamate, thioether, sulfate, sulfonyl, sulfonic acid carboxylic acid, and aryl; or

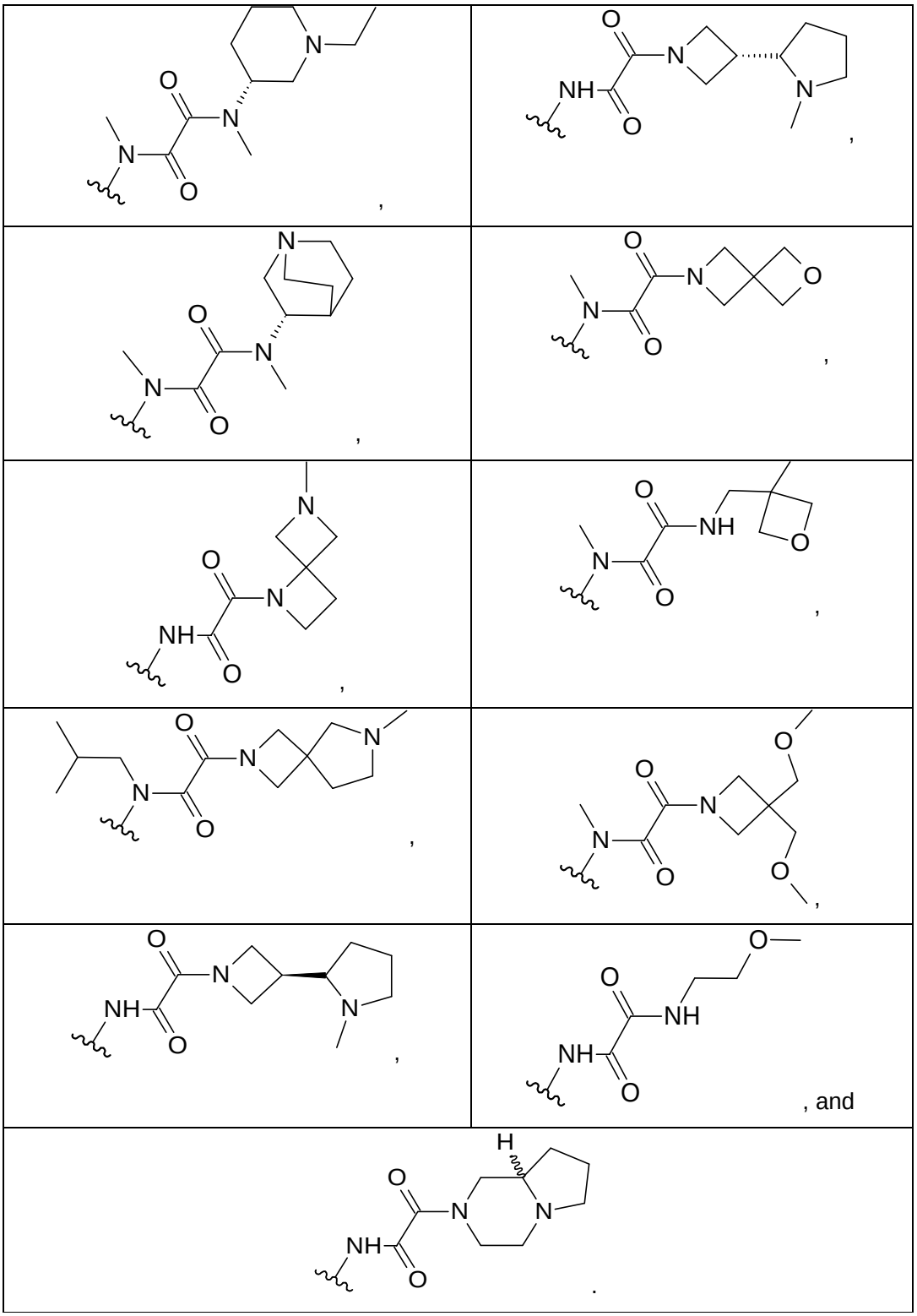
$R_2$ and $R_3$ taken together form a cycloalkyl, heterocycloalkyl, aryl or heteraryl group, optionally substituted with substituents individually selected from alkyl, cycloalkyl, alkoxy, heterocycloalkyl, alkylaryl, alkenyl, alkynyl, aryl, heteroaryl, amine, halogen, hydroxyl, ether, nitrile, cyano, nitro, $CF_3$, ester amide, urea, carbamate, thioether, or carboxylic acid group; or a pharmaceutically acceptable salt, single stereoisomer, mixture of stereoisomers, tautomer, or prodrug thereof.

4. The compound of claim 3, wherein $R_1$ is selected from:

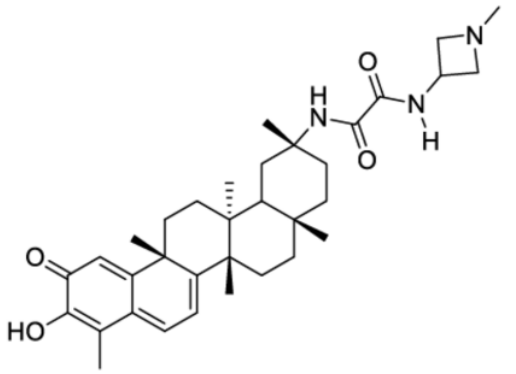
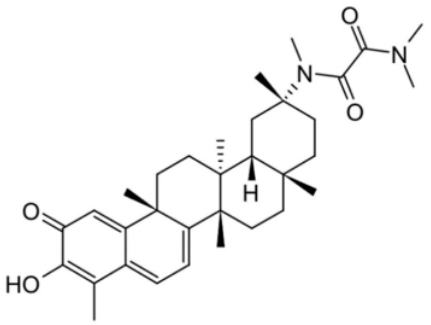
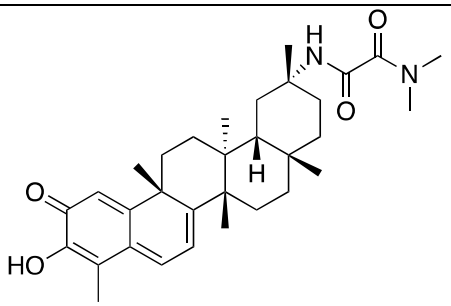
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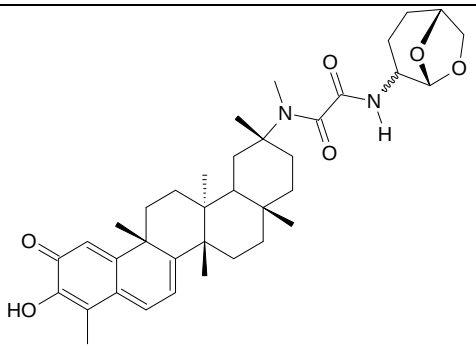


5. The compound of any one of claims 1 to 4, wherein the compound is selected from compound **14**, compound **15**, compound **16**, compound **17,** compound **22**, and compound **22-1**

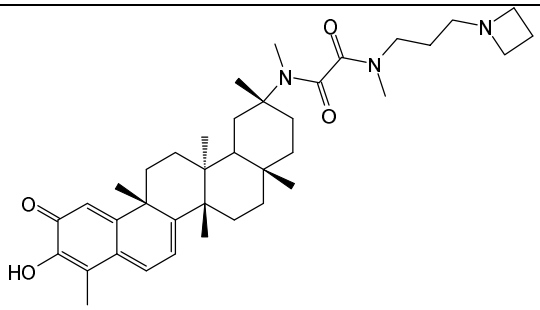
| | |
|---|---|
| **14** | **15** |
| **16** |  **17** |
|  **22** |  **22-1** |

or a pharmaceutically acceptable salt, single stereoisomer, mixture of stereoisomers, tautomer, or prodrug thereof.

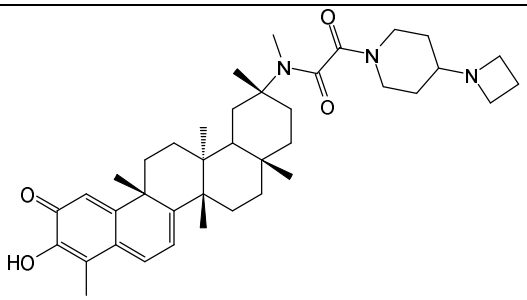
6. The compound of any one of claims 1 to 4, wherein the compound is selected from compound **42,** compound **54,** compound **55**, compound **56**, compound **57**, compound **58**, compound **59**, compound **60**, compound **61**, compound **62**, compound **63**, compound **64**, compound **65**, compound **66**, compound **67**, compound **68**, compound **69**, compound **70**, compound **71**, compound **72**, compound **73**, compound **74**, compound **75**, compound **76**, compound **77**, compound **78**, compound **79**, compound **80**, compound **81**, compound **82**, compound **83**, compound **84**, compound **85**, compound **86**, compound **87**, compound **88**, compound **89**, compound **90**, compound **91**, and compound **92**



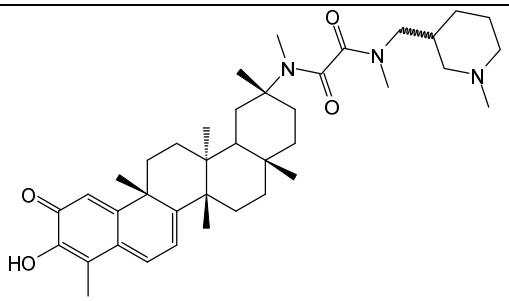
**42**



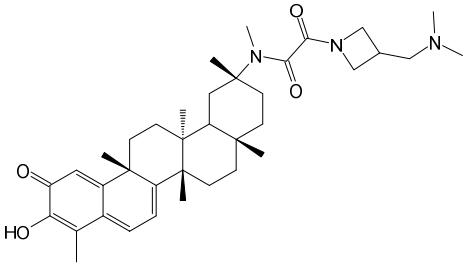
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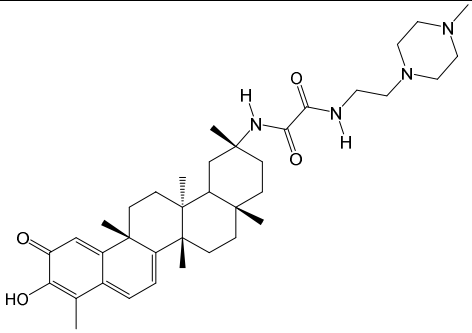
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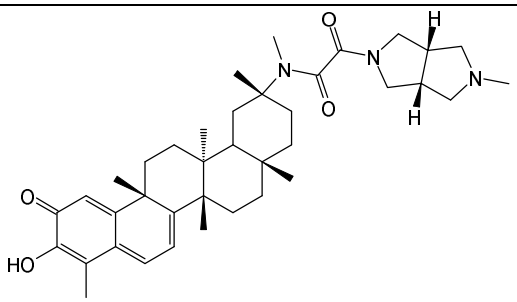
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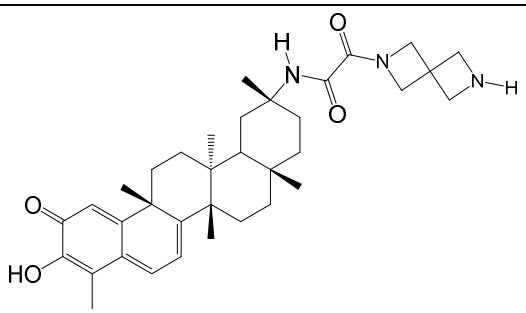
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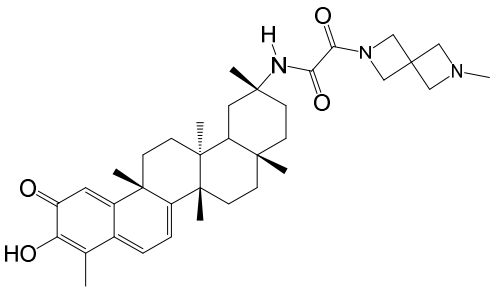
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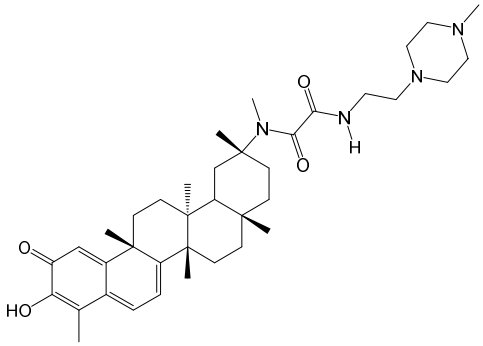
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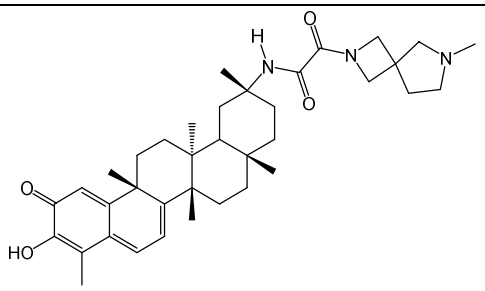
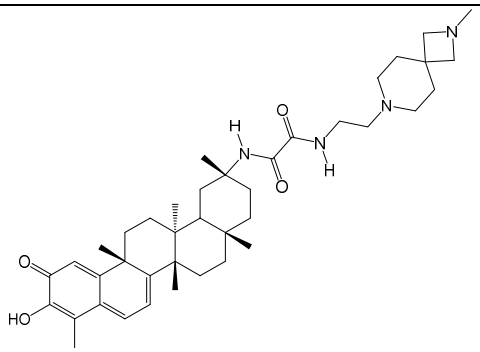
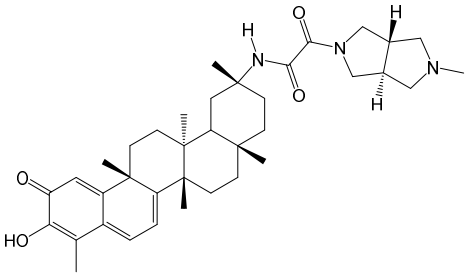
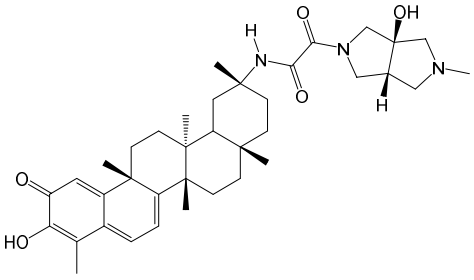
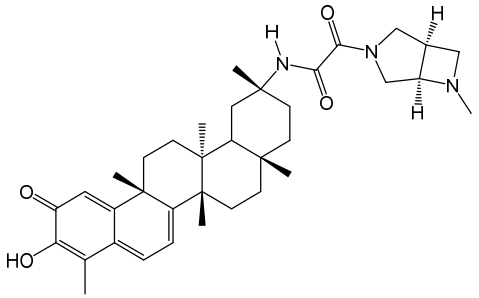
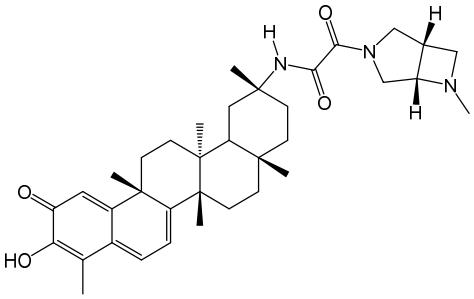
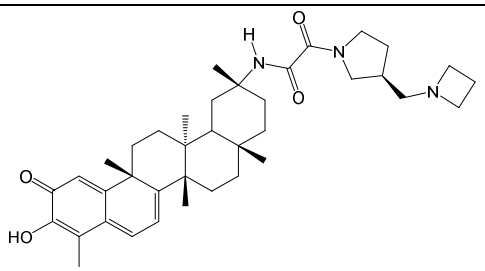
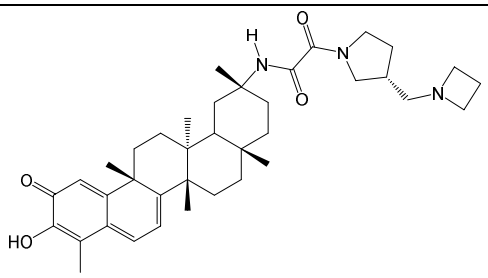
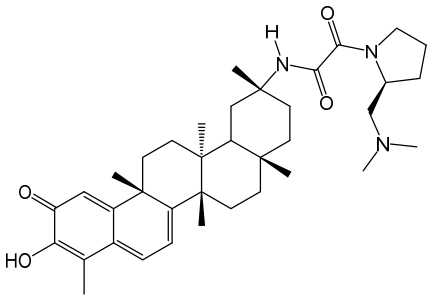
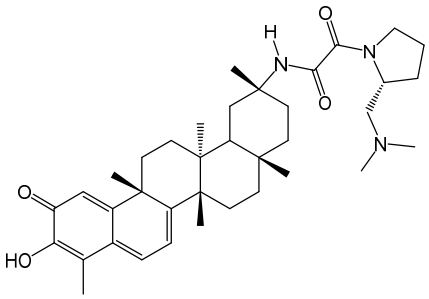
**60**

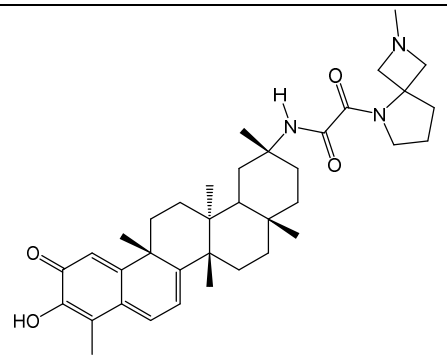
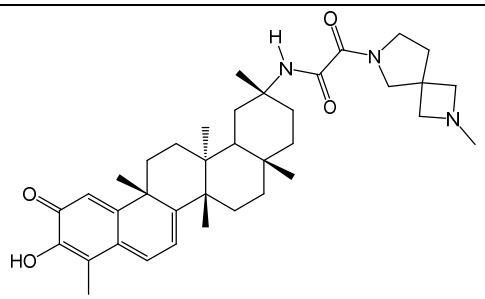
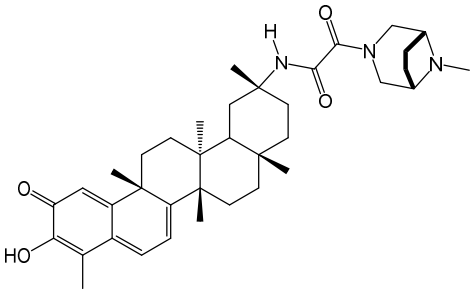
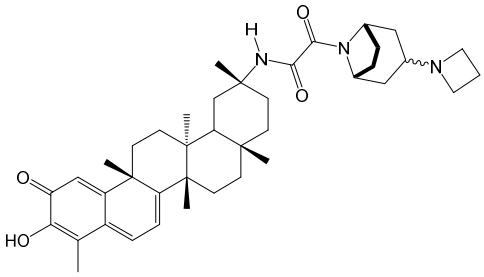
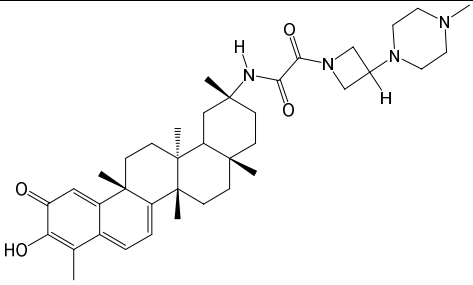
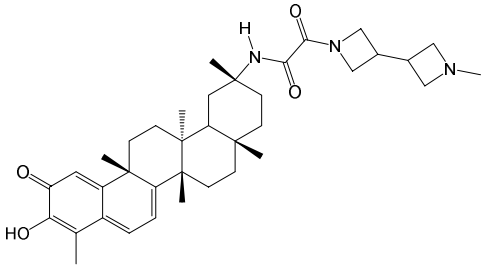
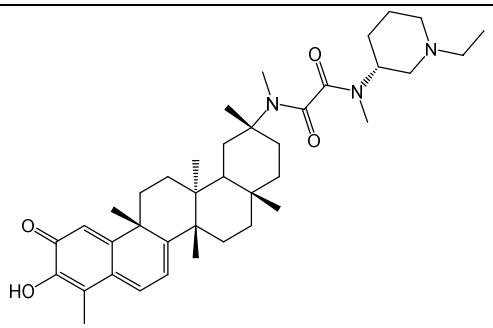
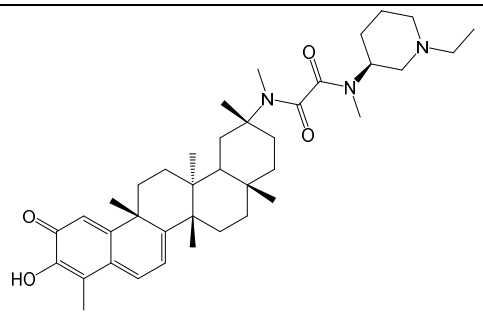
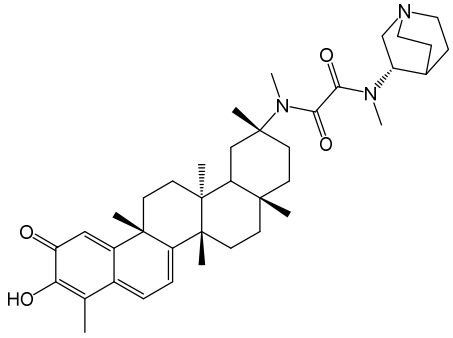
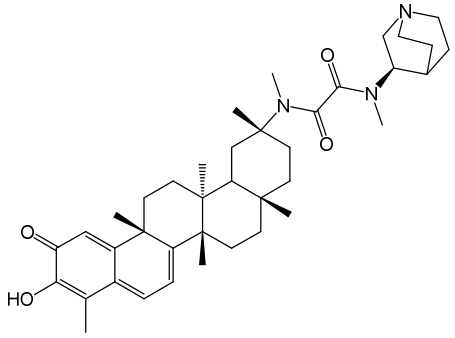


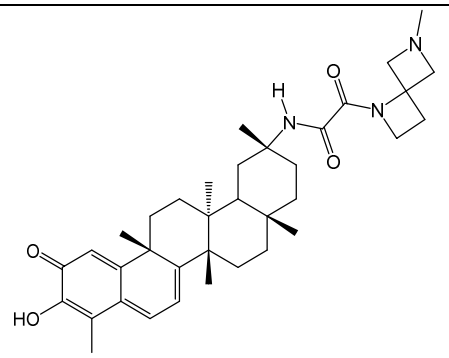
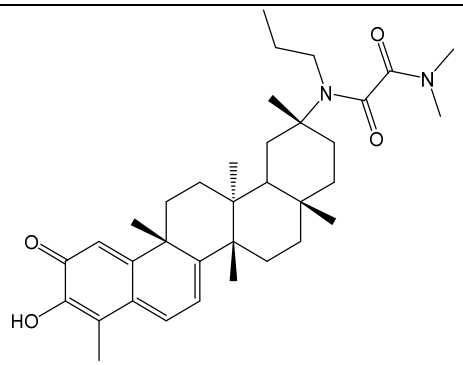
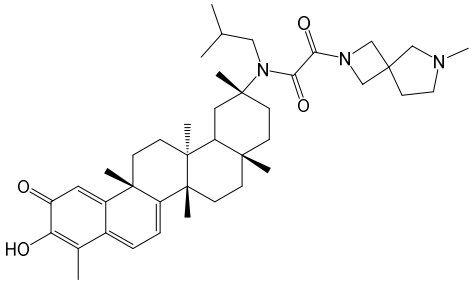
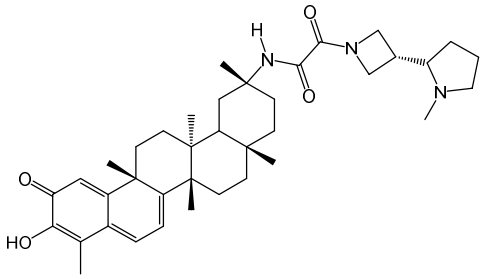
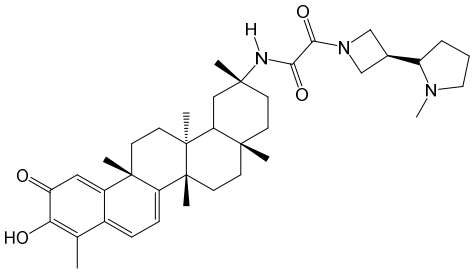
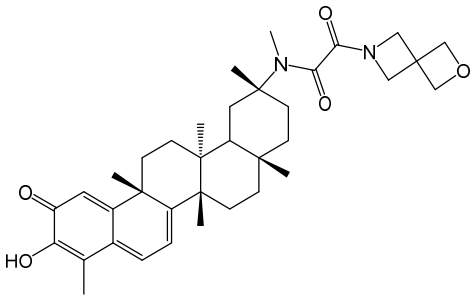
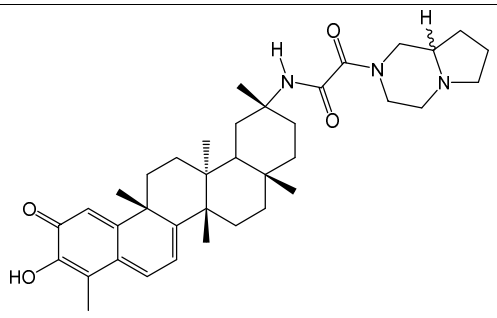
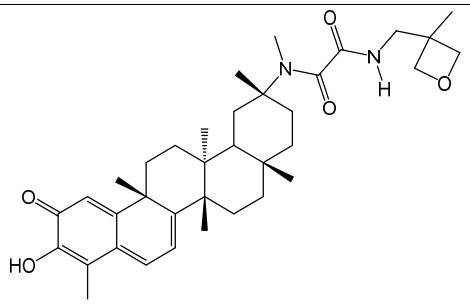
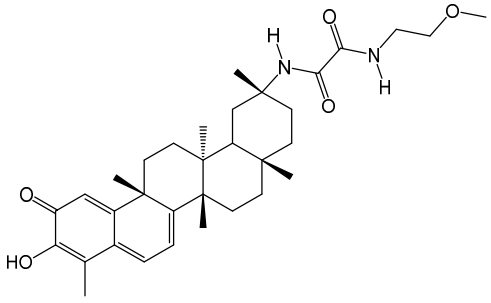
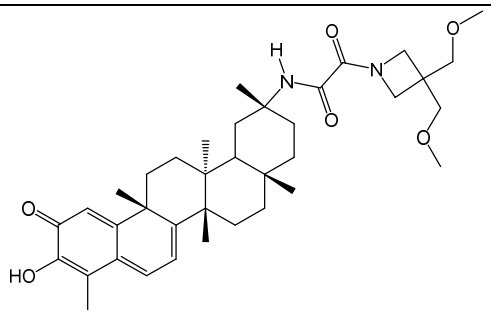
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or a pharmaceutically acceptable salt, single stereoisomer, mixture of stereoisomers, tautomer, or prodrug thereof.

7. The compound of any one of claims 1 to 6, wherein the compound is characterized by having an $IC_{50}$ in a NF-kB reporter assay of about 1200 nM or less, about 1000 nM or less, 750 nM or less, 500 nM or less, or 300 nM or less.

8. A pharmaceutical composition comprising a compound of any one of claims 1 to 7, and a pharmaceutically acceptable excipient.

9. Use of a compound of any one of claims 1 to 7, or a pharmaceutical composition of claim 8, in the manufacture of a medicament for treating a celastrol-responsive disease or disorder in a subject.

10. The use of claim 9, wherein the celastrol-responsive disease or disorder is a cancer; optionally, wherein the cancer is selected from: gastric cancer, multiple myeloma, melanoma, leukemia, lymphoma, renal cell carcinoma, hepatocellular carcinoma, breast cancer, prostate cancer, head and neck cancer, non-small cell lung carcinoma, brain cancer, and glioblastoma multiforme (GBM).

11. The use of claim 9, wherein the celastrol-responsive disease or disorder is an inflammatory and/or autoimmune disorder; optionally, wherein the inflammatory and/or autoimmune disorder is selected from rheumatoid arthritis (RA), multiple sclerosis (MS), ankylosing spondylitis, systemic lupus erythematosus (SLE), inflammatory bowel disease, osteoarthritis (OA), acute respiratory distress syndrome (ARDS), Guillain–Barré syndrome (GBS), Sickle cell disease (SCD), allergy (e.g. Asthma), psoriasis and other inflammatory skin conditions.

12. The use of claim 9, wherein the celastrol-responsive disease or disorder is a neurological disorder; optionally, wherein the neurological disorder is selected from Parkinson’s disease, Huntington disease, Alzheimer’s disease, and amyotrophic lateral sclerosis (ALS) , and Gaucher disease (GD).

13. The use of claim 9, wherein the celastrol-responsive disease or disorder is an obesity-related disease or disorder; optionally, wherein the obesity-related disease or disorder is selected from obesity, pre-obesity, morbid obesity, type 2 diabetes (T2D), atherosclerosis, diabetic nephropathy, gout, cardiac fibrosis, Prader-Willi Syndrome, Hypothalamic Injury Associated Obesity, non-alcoholic steatohepatitis, hyperlipidemia,

hypertension, diabetes, lipodystrophy, fatty liver, Bardet-Biedl Syndrome, Cohen Syndrome, cardiovascular disease, arthritis, stroke, metabolic syndrome, and MOMO (Macrosomia Obesity Macrocephaly Ocular abnormalities) Syndrome.

14. The use of claim 9, wherein the celastrol-responsive disease or disorder is a liver-related disease or disorder; optionally, wherein the liver-related disease or disorder is selected from acute-chronic liver failure (ACLF), alcoholic liver disease, cholestatic liver disease, drug-induced liver disease, hepatocellular carcinoma, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), viral hepatitis, and viral liver disease.

15. The use of claim 9, wherein the celastrol-responsive disease or disorder is a brain injury or brain disorder; optionally, wherein the brain-related injury or disorder is selected from middle cerebral artery occlusion (MCAO)-induced brain injury, cerebral ischemia/reperfusion (I/R) injury, Vascular dementia (VD), and acute ischemic stroke-induced brain injury.

16. The use of claim 9, wherein the celastrol-responsive disease or disorder is an ocular disorder or injury; optionally, wherein the ocular-related injury or disorder is selected from dry eye disease, ocular inflammation, age-related macular degeneration (AMD), subconjunctival fibrosis, ocular hypertension-induced degeneration of the retina, bright light-induced degeneration, macrophage-induced corneal neovascularization, corneal allograft survival, and optic nerve crush.

17. The use of any one of claims 9 to 16, wherein the subject is a mammal.

18. The use of any one of claims 9 to 17, wherein the subject is a human.

19. A compound according to any one of claims 1 to 7, or a pharmaceutical composition according to claim 8, for use in therapy.

20. A compound according to any one of claims 1 to 7, or a pharmaceutical composition according to claim 8, for use as a medicament.