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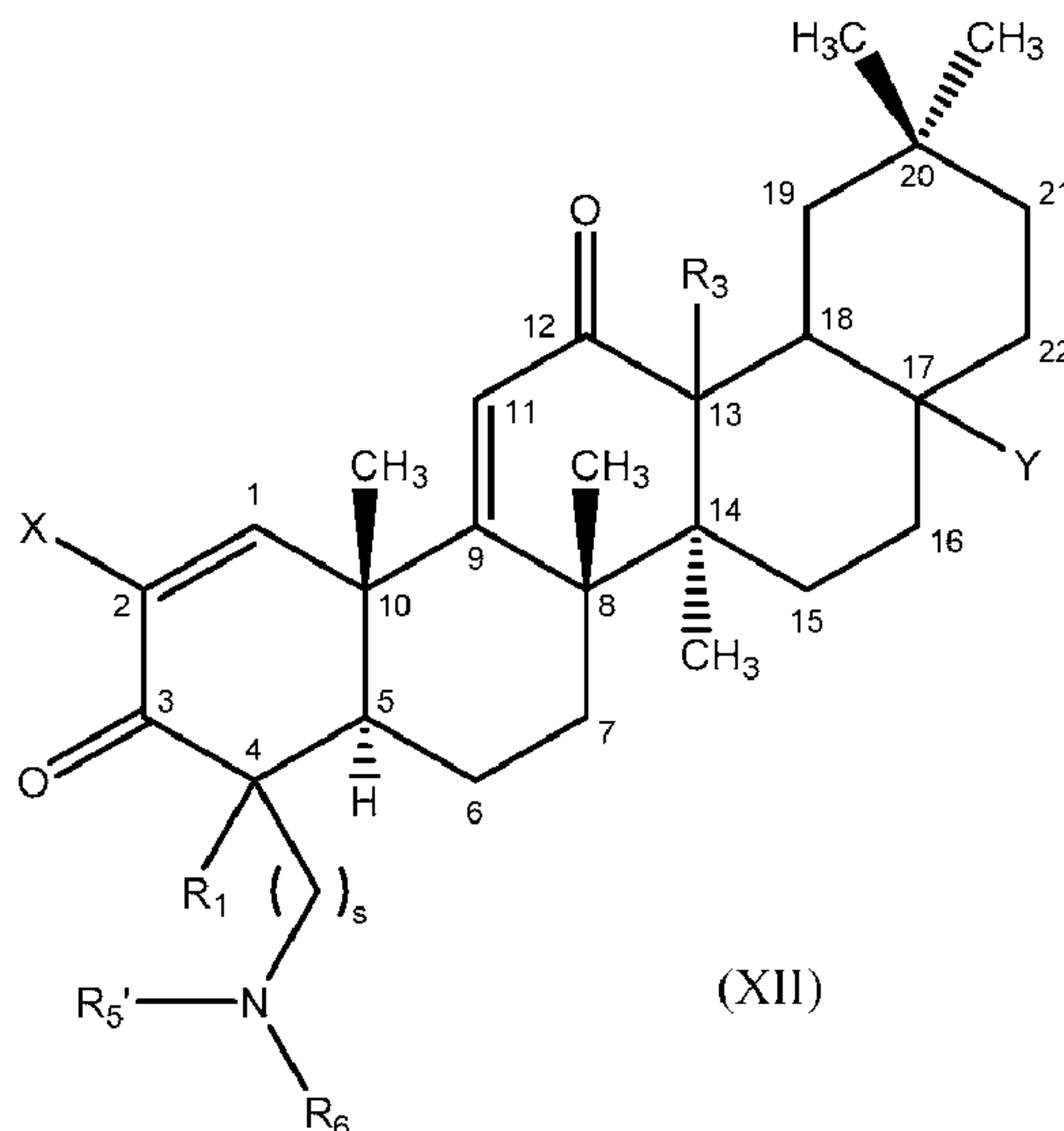
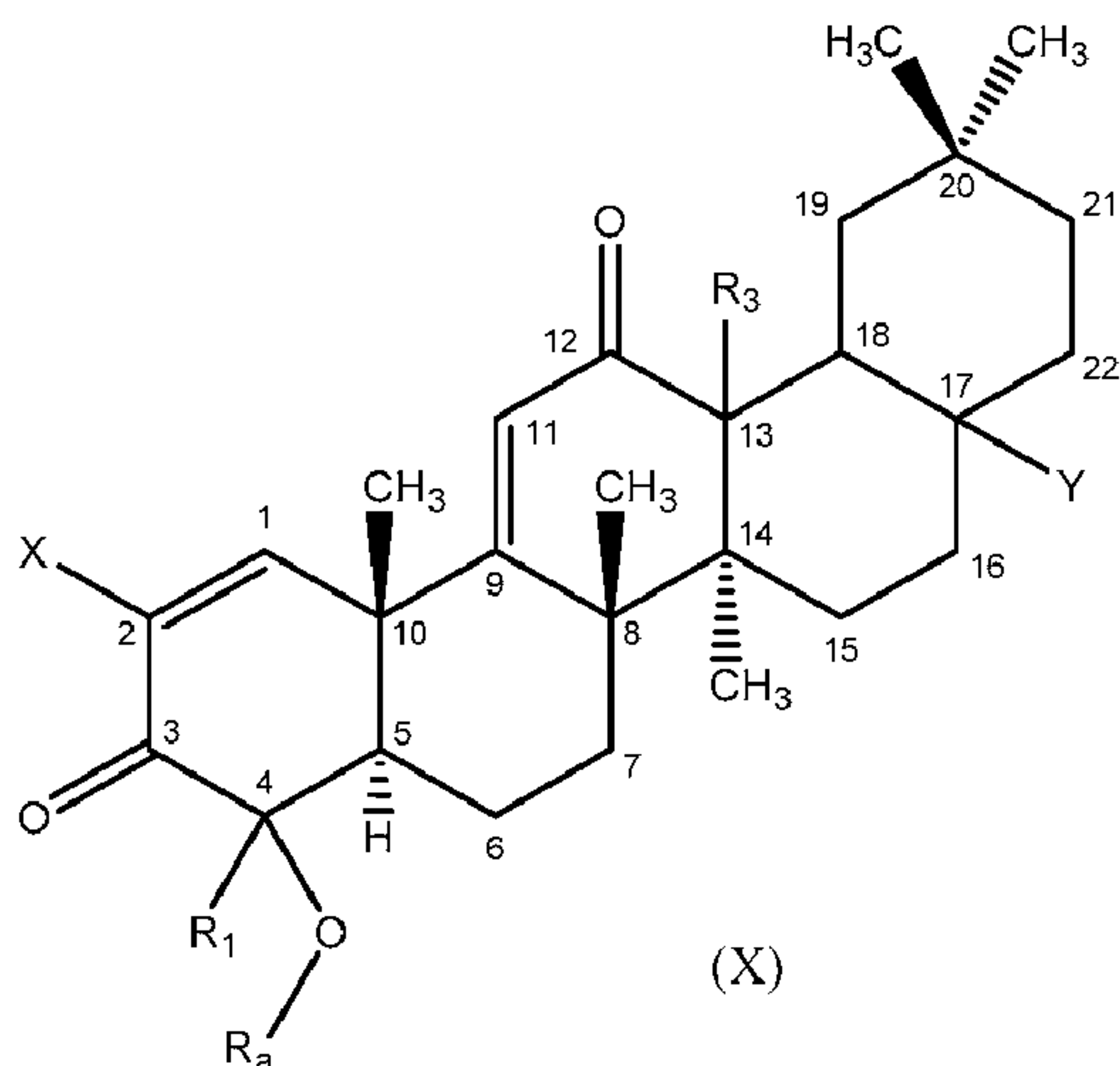
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(54) Titre : DERIVES D'ACIDE OLEANOLIQUE MODIFIE EN C4 POUR L'INHIBITION DE L'IL-17 ET D'AUTRES
UTILISATIONS

(54) Title: C4-MODIFIED OLEANOLIC ACID DERIVATIVES FOR INHIBITION OF IL-17 AND OTHER USES



(57) Abrégé/Abstract:

Disclosed herein are C4 modified oleanolic acid derivatives of the formula: Formula (X) or Formula (XII), as well as analogs thereof, wherein the variables are defined herein. In addition, disclosed herein are pharmaceutical compositions of these derivatives or analogs, methods for their manufacture, and methods for their use, including for the prevention and treatment of diseases or disorders associated with overproduction of IL-17.

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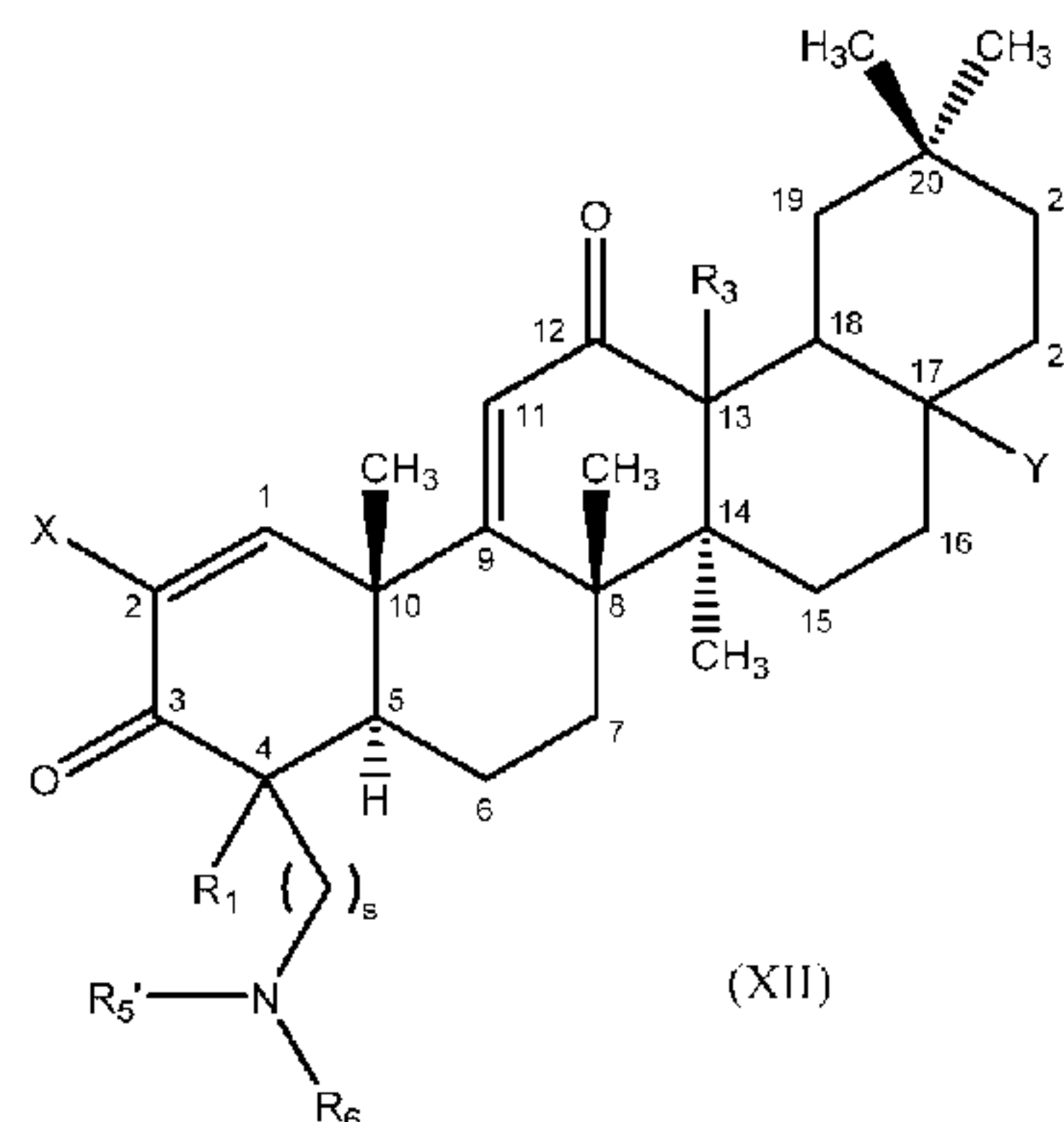
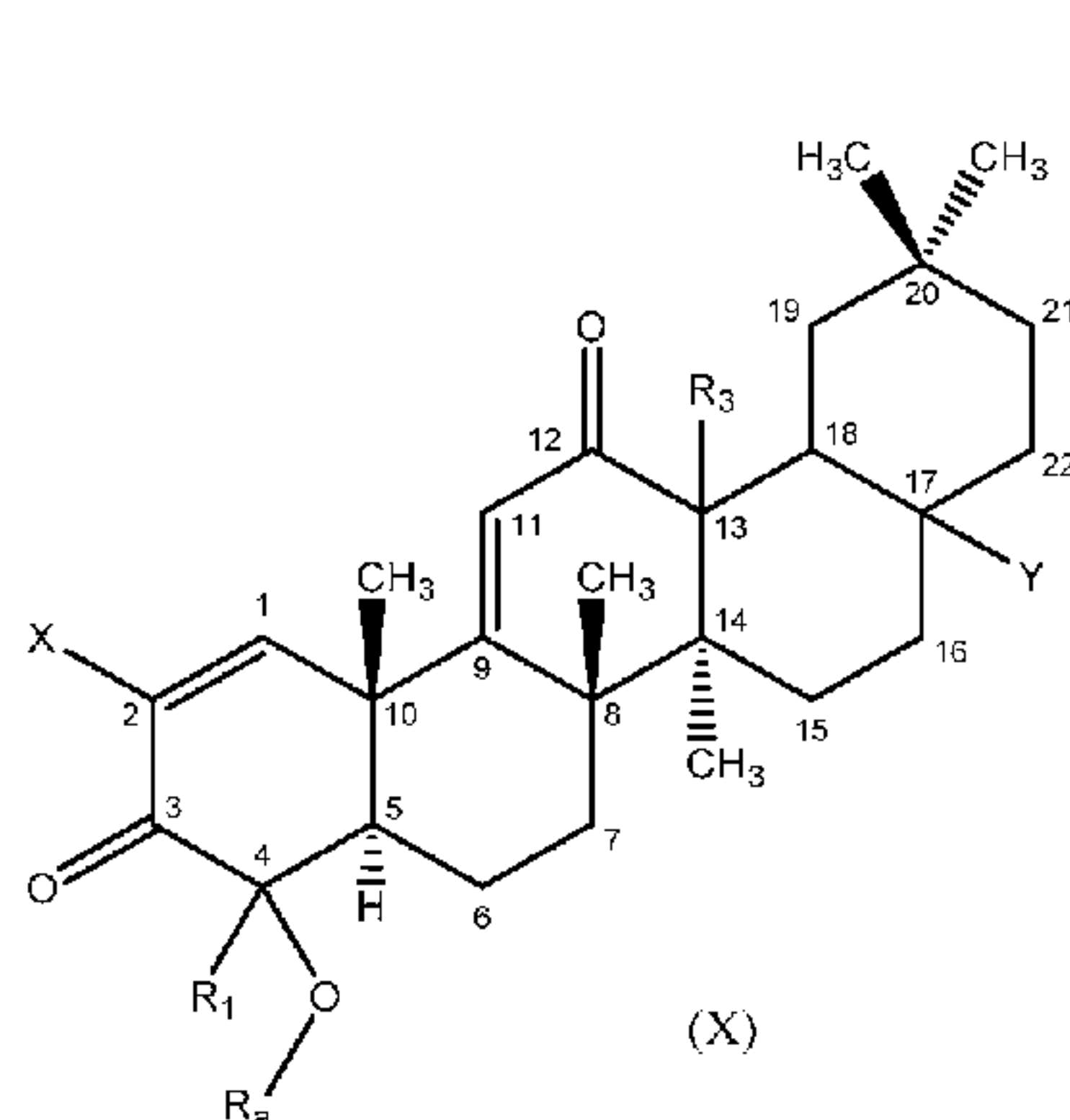
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(54) Title: C4-MODIFIED OLEANOLIC ACID DERIVATIVES FOR INHIBITION OF IL-17 AND OTHER USES



(57) Abstract: Disclosed herein are C4 modified oleanolic acid derivatives of the formula: Formula (X) or Formula (XII), as well as analogs thereof, wherein the variables are defined herein. In addition, disclosed herein are pharmaceutical compositions of these derivatives or analogs, methods for their manufacture, and methods for their use, including for the prevention and treatment of diseases or disorders associated with overproduction of IL-17.

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DESCRIPTION

C4-MODIFIED OLEANOLIC ACID DERIVATIVES FOR INHIBITION OF IL-17 AND OTHER USES

The present application claims the benefit of United States Provisional Patent
5 Application No. 62/222,632, filed on September 23, 2015, the entirety of which is
incorporated herein by reference.

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention relates generally to the fields of biology and medicine. More
10 particularly, it concerns compounds, compositions, and methods for the treatment and
prevention of diseases or disorders, such as those associated with excess production of IL-17.

II. Description of Related Art

Inflammatory diseases, particularly autoimmune diseases, such as rheumatoid
arthritis, osteoarthritis, psoriasis, and multiple sclerosis, frequently have severe and long-term
15 adverse effects on physical well-being and quality of life. In many patients these diseases
cause significant disability, and in some cases (*e.g.*, lupus and multiple sclerosis) may be life-
threatening. Recent advances in therapeutic options, such as the development of therapeutic
antibodies against tumor necrosis factor (TNF), have improved outcomes and quality of life
for many patients. However, significant numbers of patients do not achieve adequate relief of
20 symptoms from these therapies or cannot tolerate them. Even in patients who do respond,
side effects can be significant and may be life-threatening due to immune suppression or
other complications.

Recent research on chronic inflammation and autoimmunity has revealed an important
role played by a subpopulation of T lymphocytes known as Th17 cells. These cells produce
25 the inflammatory cytokine interleukin 17 (IL-17). Excessive levels of IL-17 have been
reported in a variety of autoimmune diseases including multiple sclerosis, rheumatoid
arthritis, psoriasis, inflammatory bowel diseases, vitiligo, Sjögren syndrome, and ankylosing
spondylitis (Miossec and Kolls, 2012; Yang *et al.*, 2014; Gaffen *et al.*, 2014). Evidence
suggests that IL-17 also plays a significant role in the pathology of vasculitis, atherosclerosis,
30 and inflammatory lung diseases, such as cystic fibrosis and chronic obstructive pulmonary
disorder (COPD). IL-17 is also implicated in the pathophysiology of epilepsy and

neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and ALS. Elevated levels of IL-17 or Th17 cells have been reported in patients with psychiatric and neuropsychiatric conditions including schizophrenia, obsessive-compulsive disorder, bipolar disorder, post-traumatic stress disorder, major depression, and autism. Elevations in IL-17
5 have been implicated in other conditions involving dysregulated inflammatory signaling, including obesity, insulin resistance, and fatty liver disease.

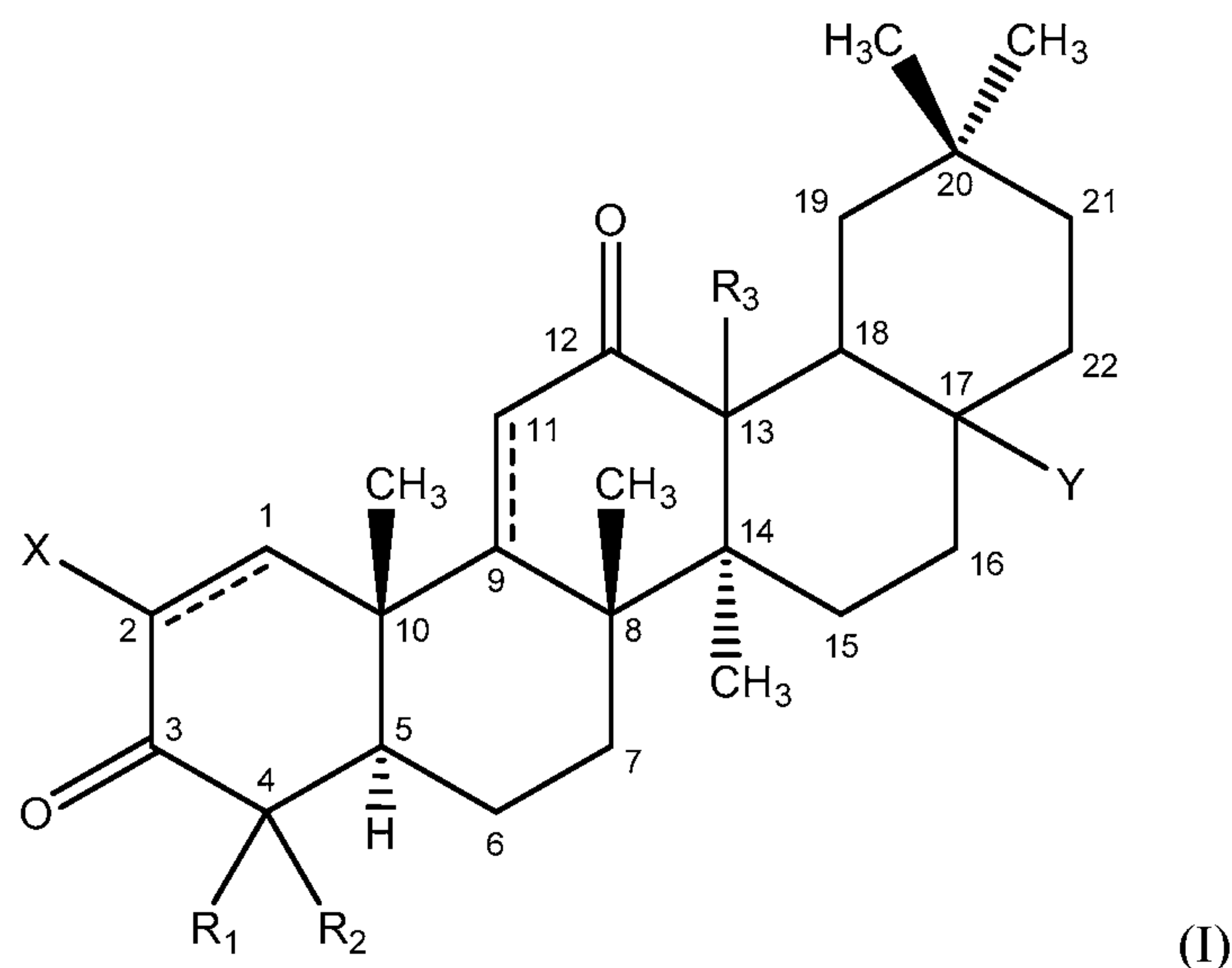
Although Th17 cells are not the only source of IL-17, it has been reported that these cells are a major source of this cytokine in tissues undergoing damage from autoimmune disease, such as arthritic joints. And elevated levels of IL-17 have been reported to promote
10 tissue degradation, *e.g.* by stimulating the production of matrix metalloproteinases (a source of damage to connective tissue and cartilage) and increasing the expression of receptor activator of NF- κ B ligand (RANKL), which stimulates osteoclast activity and promotes bone damage.

Inappropriate activity of Th17 cells, including overproduction of IL-17, has also been
15 implicated in the pathologies associated with certain viral and parasitic infections. For example, IL-17 has been implicated in the development of severe neuroinflammation associated with *Toxoplasma gondii* infection and increased severity of lesions associated with *Leishmania* infection. In these and other cases, IL-17 appears to play a role in perpetuating the infection, promoting an excessive inflammatory response, and inhibiting clearance of the
20 infectious agent (Waite and Skokos, 2012). Accordingly, therapies that prevent or inhibit excess production of IL-17, or otherwise reduce circulating levels of IL-17, would have significant potential in a wide range of diseases or disorders, including those with inflammatory and autoimmune-related components.

SUMMARY OF THE INVENTION

The present disclosure provides novel compounds, including C4 modified oleanolic acid derivatives, pharmaceutical compositions thereof, methods for their manufacture, and methods for their use, including for the prevention and treatment of diseases or disorders associated with overproduction of IL-17.

In some aspects, the present disclosure provides compounds of the formula:



wherein:

the bond between atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between atoms 9 and 11 is a single bond or a double bond;

X is cyano, heteroaryl_(C≤8), substituted heteroaryl_(C≤8), -CF₃, or -C(O)-R₄; wherein

R₄ is hydroxy, amino, or alkoxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkylsulfonylamino_(C≤8), or a substituted version of any of these groups;

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

wherein variables R₂ and Y are defined according to either Group A or B, wherein for Group

A:

R₂ is amino, cyano, halo, or hydroxy,

substituted alkyl_(C≤8), substituted cycloalkyl_(C≤8), heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted

amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8),
dialkylamino_(C≤8), or dialkylamino_(C≤8);

—OR_a, wherein:

5 R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12),
aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or
a substituted version of any of these groups;

—(CH₂)_m—(OCH₂)_n—R₅, wherein:

R₅ is hydroxy or acyl_(C≤8), alkoxy_(C≤8), acyloxy_(C≤8), alkylsilyloxy_(C≤8),
or a substituted version of any of these groups;

10 m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

—(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

15 R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8),
substituted acyl_(C≤8), —C(O)—alkoxy_(C≤8), substituted
—C(O)—alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8),
alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

—(CH₂)_q—C(O)—R_{5''}, wherein:

20 R_{5''} is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or
a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

25 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), heteroaryl_(C≤8),
heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12),
acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8),
arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8),
alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

30 —alkanediyl_(C≤8)—R_b, —alkenediyl_(C≤8)—R_b, or a substituted version of any of
these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

aryl_(C≤8), heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8),
 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8),
 alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8),
 arylamino_(C≤8), aralkylamino_(C≤8), heteroarylamino_(C≤8),
 alkylsulfonylamino_(C≤8), amido_(C≤8), $-\text{OC}(\text{O})\text{NH}-\text{alkyl}_{(C\leq 8)}$,
 $-\text{OC}(\text{O})\text{CH}_2\text{NHC}(\text{O})\text{O}-t\text{-butyl}$, $-\text{OCH}_2-\text{alkylthio}_{(C\leq 8)}$, or a
 substituted version of any of these groups;

$-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_c$, wherein p is 0–6 and R_c is:

hydrogen, halo, amino, $-\text{NHOH}$, or mercapto; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),
 aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8),
 alkylamino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), alkyl-
 sulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),
 heterocycloalkylamino_(C≤8), $-\text{NHC}(\text{NOH})-\text{alkyl}_{(C\leq 8)}$,
 $-\text{NH}-\text{amido}_{(C\leq 8)}$, or a substituted version of any of these
 groups;

$-\text{NR}_d\text{C}(\text{O})\text{R}_e$, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),
 aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8),
 cycloalkoxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8),
 acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8),
 or a substituted version of any of these groups; or

Y is taken together with R_3 and is $-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_f-$, wherein

p is 0–6; and

R_f is $-\text{O}-$ or $-\text{NR}_7-$; wherein:

R_7 is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
 acyl_(C≤8); or

for Group B:

R_2 is amino, cyano, halo, or hydroxy,

haloalkyl_(C≤8), substituted cycloalkyl_(C≤8), heteroaryl_(C≤8), substituted heteroaryl_(C≤8),
 acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8),

alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8); or

—OR_a, wherein:

5 R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or a substituted version of any of these groups;

—(CH₂)_m—R_{5'''}, wherein:

10 R_{5'''} is alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and
m is 0, 1, 2, 3, or 4;

—(CH₂)_{m2}—R_{5'''}, wherein:

R_{5'''} is hydroxy; and

m₂ is 2, 3, or 4;

—(CH₂)_sNR_{5'}(R₆), wherein:

15 s is 0, 1, 2, 3, or 4;

R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), —C(O)—alkoxy_(C≤8), substituted —C(O)—alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

20 R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

—(CH₂)_q—C(O)—R_{5''}, wherein:

R_{5''} is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and

25 q is 0, 1, 2, 3, or 4; and

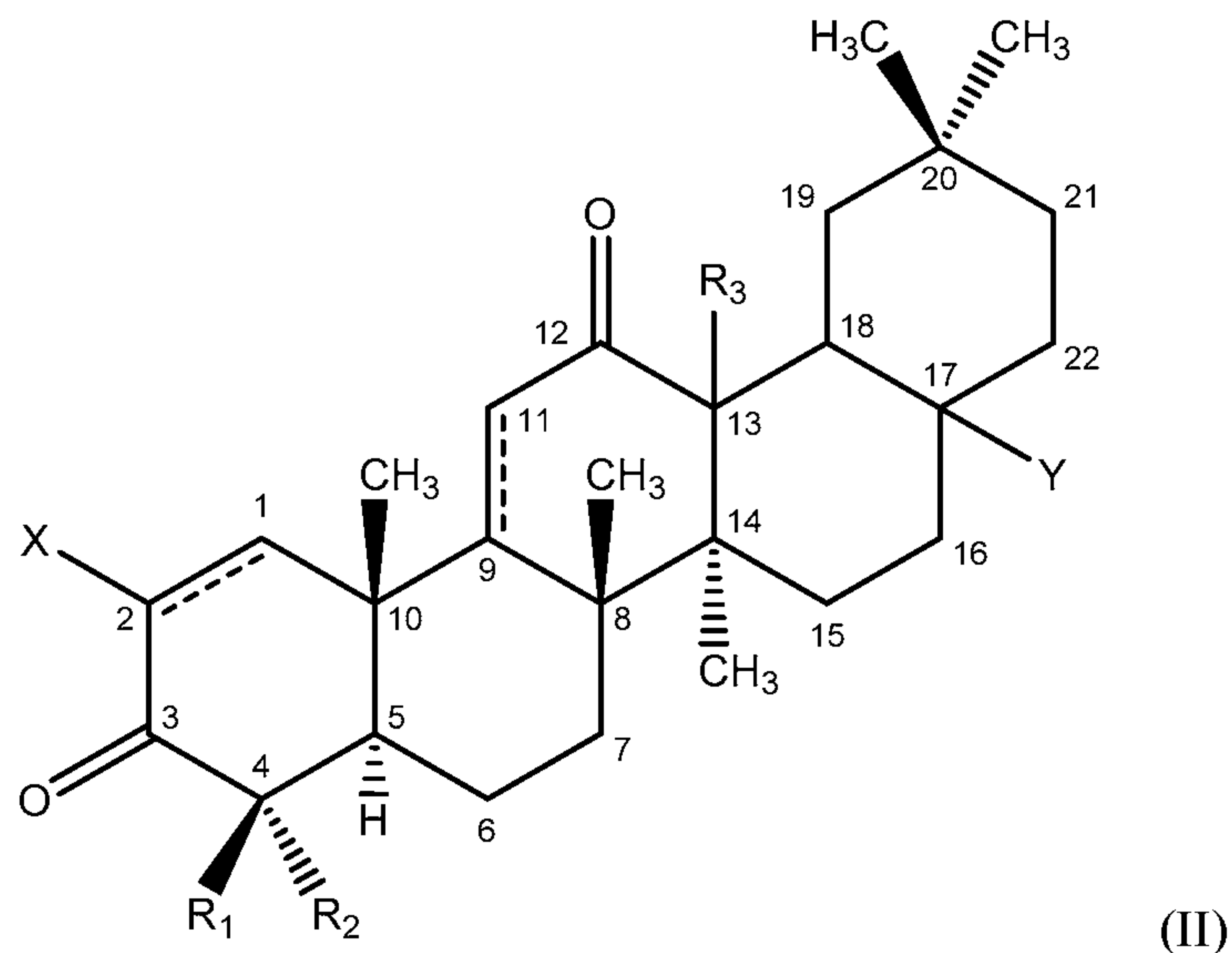
Y is —(CH₂)_oC(O)R_c, wherein o is 0–6 and R_c is:

hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these
30 groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

the bond between atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between atoms 9 and 11 is a single bond or a double bond;

X is cyano, heteroaryl_(C≤8), substituted heteroaryl_(C≤8), -CF₃, or -C(O)-R₄; wherein

R₄ is hydroxy, amino, or alkoxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkylsulfonylamino_(C≤8), or a substituted version of any of these groups;

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is amino,

heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8);

-OR_a, wherein:

R_a is hydrogen or alkyl_(C≤8), acyl_(C≤8), or a substituted version of either of these groups;

-(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), -C(O)-alkoxy_(C≤8), substituted

$-\text{C}(\text{O})-\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{acyloxy}_{(\text{C}\leq 8)}$, substituted $\text{acyloxy}_{(\text{C}\leq 8)}$,
 $\text{alkylsilyloxy}_{(\text{C}\leq 8)}$, or substituted $\text{alkylsilyloxy}_{(\text{C}\leq 8)}$; and

R_6 is hydrogen, $\text{alkyl}_{(\text{C}\leq 8)}$, or substituted $\text{alkyl}_{(\text{C}\leq 8)}$; or

$-(\text{CH}_2)_q-\text{C}(\text{O})-\text{R}_5''$, wherein:

5 R_5'' is amino, hydroxy, or mercapto; or

$\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{alkylthio}_{(\text{C}\leq 8)}$, $\text{alkylamino}_{(\text{C}\leq 8)}$, $\text{dialkylamino}_{(\text{C}\leq 8)}$, or
a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or $\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{acyloxy}_{(\text{C}\leq 8)}$, or substituted version of either
10 of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

$\text{alkyl}_{(\text{C}\leq 8)}$, $\text{cycloalkyl}_{(\text{C}\leq 8)}$, $\text{alkenyl}_{(\text{C}\leq 8)}$, $\text{alkynyl}_{(\text{C}\leq 8)}$, $\text{aryl}_{(\text{C}\leq 12)}$, $\text{heteroaryl}_{(\text{C}\leq 8)}$,
 $\text{heterocycloalkyl}_{(\text{C}\leq 12)}$, $\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{cycloalkoxy}_{(\text{C}\leq 8)}$, $\text{aryloxy}_{(\text{C}\leq 12)}$,
 $\text{acyloxy}_{(\text{C}\leq 8)}$, $\text{alkylamino}_{(\text{C}\leq 8)}$, $\text{dialkylamino}_{(\text{C}\leq 8)}$, $\text{alkenylamino}_{(\text{C}\leq 8)}$,
15 $\text{arylamino}_{(\text{C}\leq 8)}$, $\text{aralkylamino}_{(\text{C}\leq 8)}$, $\text{alkylthio}_{(\text{C}\leq 8)}$, $\text{acylthio}_{(\text{C}\leq 8)}$,
 $\text{alkylsulfonylamino}_{(\text{C}\leq 8)}$, or substituted versions of any of these groups;

$-\text{alkanediyl}_{(\text{C}\leq 8)}-\text{R}_b$, $-\text{alkenediyl}_{(\text{C}\leq 8)}-\text{R}_b$, or a substituted version of any of
these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

20 $\text{aryl}_{(\text{C}\leq 8)}$, $\text{heteroaryl}_{(\text{C}\leq 8)}$, $\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{cycloalkoxy}_{(\text{C}\leq 8)}$, $\text{alkenyloxy}_{(\text{C}\leq 8)}$,
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 $\text{arylamino}_{(\text{C}\leq 8)}$, $\text{aralkylamino}_{(\text{C}\leq 8)}$, $\text{heteroarylamino}_{(\text{C}\leq 8)}$,
 $\text{alkylsulfonylamino}_{(\text{C}\leq 8)}$, $\text{amido}_{(\text{C}\leq 8)}$, $-\text{OC}(\text{O})\text{NH}-\text{alkyl}_{(\text{C}\leq 8)}$,
25 $-\text{OC}(\text{O})\text{CH}_2\text{NHC}(\text{O})\text{O}-t\text{-butyl}$, $-\text{OCH}_2-\text{alkylthio}_{(\text{C}\leq 8)}$, or a
substituted version of any of these groups;

$-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_c$, wherein p is 0–6 and R_c is:

hydrogen, halo, hydroxy, amino, $-\text{NHOH}$, or mercapto; or

30 $\text{alkyl}_{(\text{C}\leq 8)}$, $\text{cycloalkyl}_{(\text{C}\leq 8)}$, $\text{alkenyl}_{(\text{C}\leq 8)}$, $\text{alkynyl}_{(\text{C}\leq 8)}$, $\text{aryl}_{(\text{C}\leq 8)}$,
 $\text{aralkyl}_{(\text{C}\leq 8)}$, $\text{heteroaryl}_{(\text{C}\leq 8)}$, $\text{heterocycloalkyl}_{(\text{C}\leq 8)}$,
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 $\text{aryloxy}_{(\text{C}\leq 8)}$, $\text{aralkoxy}_{(\text{C}\leq 8)}$, $\text{heteroaryloxy}_{(\text{C}\leq 8)}$,

acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
 arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),
 alkoxyamino_(C≤8), heterocycloalkylamino_(C≤8),
 -NHC(NO₂)-alkyl_(C≤8), -NH-amido_(C≤8), or a
 substituted version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),

aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8),

cycloalkoxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8),

acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8),

or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f-, wherein

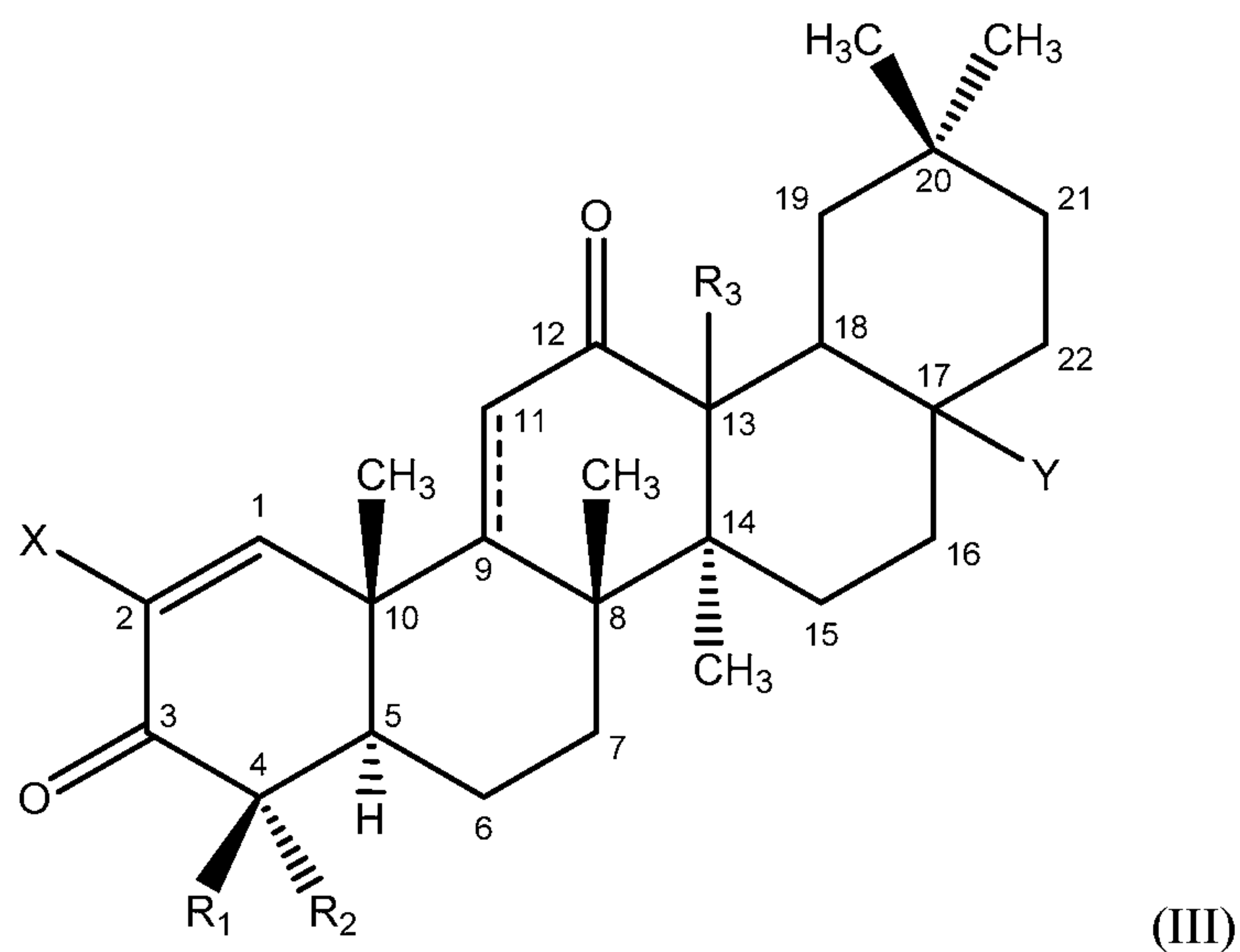
p is 0-6; and

R_f is -O- or -NR₇-; wherein:

R₇ is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
 acyl_(C≤8);

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



wherein:

the bond between atoms 9 and 11 is a single bond or a double bond;

X is cyano, heteroaryl_(C≤8), substituted heteroaryl_(C≤8), -CF₃, or -C(O)-R₄; wherein

R₄ is hydroxy, amino, or alkoxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkylsulfonylamino_(C≤8), or a substituted version of any of these groups;

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is amino,

heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8);

-OR_a, wherein:

R_a is hydrogen or alkyl_(C≤8), acyl_(C≤8), or a substituted version of either of these groups;

-(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), -C(O)-alkoxy_(C≤8), substituted -C(O)-alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

-(CH₂)_q-C(O)-R_{5''}, wherein:

R_{5''} is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

–alkanediyl_(C≤8)–R_b, –alkenediyl_(C≤8)–R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

aryl_(C≤8), heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8),

5 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8),

alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8),

arylamino_(C≤8), aralkylamino_(C≤8), heteroarylamino_(C≤8),

alkylsulfonylamino_(C≤8), amido_(C≤8), –OC(O)NH–alkyl_(C≤8),

–OC(O)CH₂NHC(O)O–*t*-butyl, –OCH₂–alkylthio_(C≤8), or a

10 substituted version of any of these groups;

–(CH₂)_pC(O)R_c, wherein p is 0–6 and R_c is:

hydrogen, halo, hydroxy, amino, –NHOH, or mercapto; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),

aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8),

15 alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8),

aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8),

acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),

alkoxyamino_(C≤8), heterocycloalkylamino_(C≤8),

20 –NHC(NO₂)–alkyl_(C≤8), –NH–amido_(C≤8), or a

substituted version of any of these groups;

–NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

25 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),

aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8),

cycloalkoxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8),

acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8),

or a substituted version of any of these groups; or

30 Y is taken together with R₃ and is –(CH₂)_pC(O)R_f–, wherein

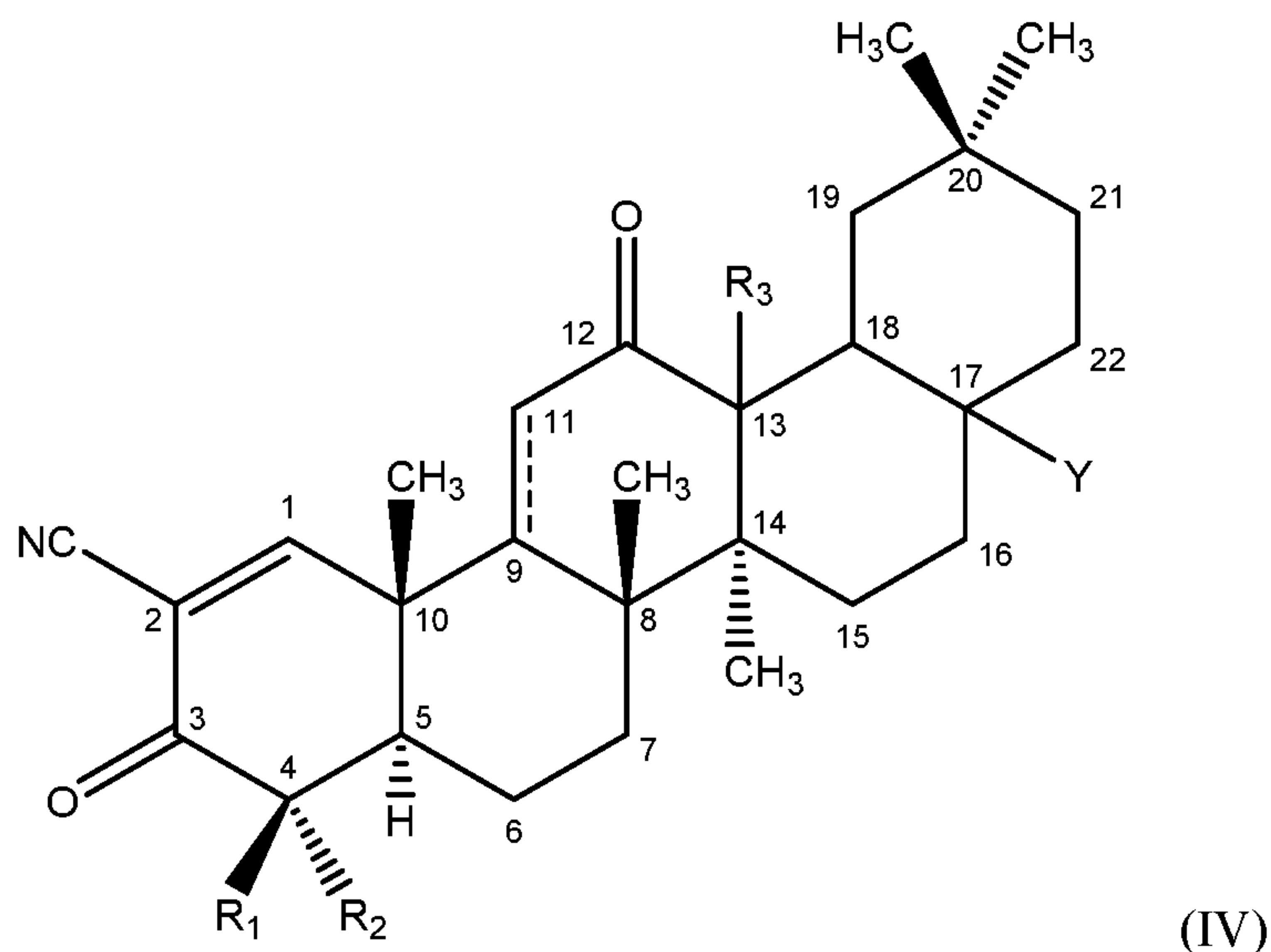
p is 0–6; and

R_f is –O– or –NR₇–; wherein:

R_7 is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted acyl_(C≤8);

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



wherein:

the bond between atoms 9 and 11 is a single bond or a double bond;

R_1 is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R_2 is amino,

heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8);

$-OR_a$, wherein:

R_a is hydrogen or alkyl_(C≤8), acyl_(C≤8), or a substituted version of either of these groups;

$-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R_5' is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), $-C(O)-$ alkoxy_(C≤8), substituted $-C(O)-$ alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R_6 is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

$-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or
a substituted version of any of these groups; and

5 q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either
of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), heteroaryl_(C≤8),

10 heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12),

acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8),

arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8),

alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

$-alkanediy l_{(C≤8)}-R_b$, $-alkenediy l_{(C≤8)}-R_b$, or a substituted version of any of

15 these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

aryl_(C≤8), heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8),

aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8),

alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8),

20 arylamino_(C≤8), aralkylamino_(C≤8), heteroarylamino_(C≤8),

alkylsulfonylamino_(C≤8), amido_(C≤8), $-OC(O)NH-alkyl_{(C≤8)}$,

$-OC(O)CH_2NHC(O)O-t-butyl$, $-OCH_2-alkylthio_{(C≤8)}$, or a

substituted version of any of these groups;

$-(CH_2)_pC(O)R_c$, wherein p is 0–6 and R_c is:

25 hydrogen, halo, hydroxy, amino, $-NHOH$, or mercapto; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),

aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8),

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8),

aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8),

30 acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),

alkoxy amino_(C≤8), heterocycloalkylamino_(C≤8),

–NHC(NO_H)–alkyl_(C≤8), –NH–amido_(C≤8), or a substituted version of any of these groups;

–NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),

aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8),

cycloalkoxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8),

acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8),

or a substituted version of any of these groups; or

Y is taken together with R₃ and is –(CH₂)_pC(O)R_f–, wherein

p is 0–6; and

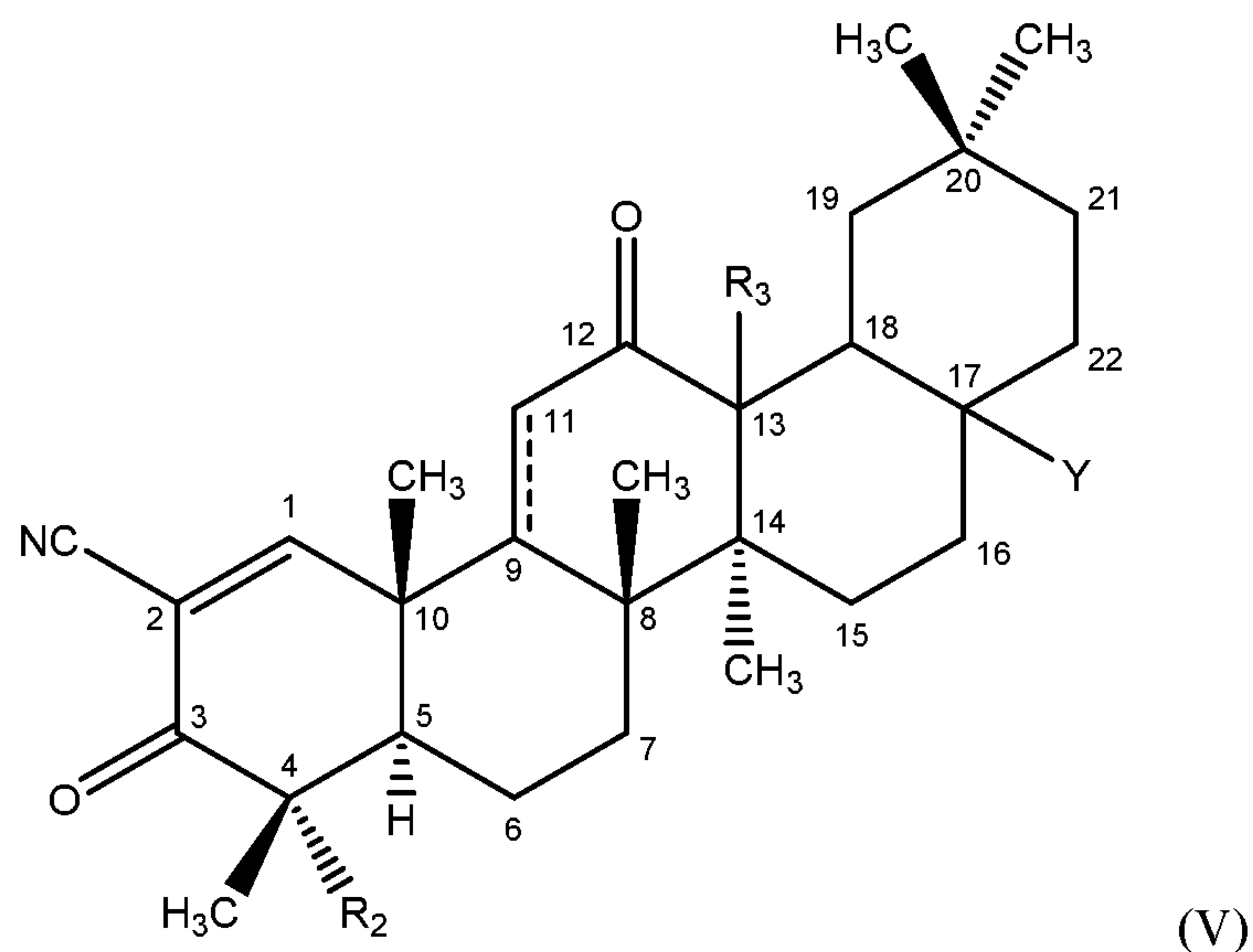
R_f is –O– or –NR₇–; wherein:

R₇ is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted

acyl_(C≤8);

or a pharmaceutically acceptable salt thereof.

In some embodiments, the compounds are further defined as:



wherein:

the bond between atoms 9 and 11 is a single bond or a double bond;

R₂ is amino,

heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8);

—OR_a, wherein:

5 R_a is hydrogen or alkyl_(C≤8), acyl_(C≤8), or a substituted version of either of these groups;

—(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

10 R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), —C(O)—alkoxy_(C≤8), substituted —C(O)—alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

—(CH₂)_q—C(O)—R_{5''}, wherein:

15 R_{5''} is amino, hydroxy, or mercapto; or alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

20 R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

25 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

—alkanediyl_(C≤8)—R_b, —alkenediyl_(C≤8)—R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

30 aryl_(C≤8), heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), heteroarylamino_(C≤8),

alkylsulfonylamino_(C≤8), amido_(C≤8), $-\text{OC}(\text{O})\text{NH}-\text{alkyl}_{(\text{C}\leq 8)}$,
 $-\text{OC}(\text{O})\text{CH}_2\text{NHC}(\text{O})\text{O}-t\text{-butyl}$, $-\text{OCH}_2-\text{alkylthio}_{(\text{C}\leq 8)}$, or a
substituted version of any of these groups;

$-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_c$, wherein p is 0–6 and R_c is:

5 hydrogen, halo, hydroxy, amino, $-\text{NHOH}$, or mercapto; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),
aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8),
alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8),
aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8),
10 acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),
alkoxyamino_(C≤8), heterocycloalkylamino_(C≤8),
 $-\text{NHC}(\text{NOH})-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{NH}-\text{amido}_{(\text{C}\leq 8)}$, or a
substituted version of any of these groups;

15 $-\text{NR}_d\text{C}(\text{O})\text{R}_e$, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),
aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8),
20 cycloalkoxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8),
acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8),
or a substituted version of any of these groups; or

Y is taken together with R_3 and is $-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_f-$, wherein

p is 0–6; and

25 R_f is $-\text{O}-$ or $-\text{NR}_7-$; wherein:

R_7 is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
acyl_(C≤8);

or a pharmaceutically acceptable salt thereof.

Chemical structure (VI) is a complex polycyclic molecule. It features a central ring system with several fused and fused rings. The carbons are numbered 1 through 22. Substituents include X, Y, R₁, R₂, R₃, H, CH₃, and H₃C. A carbonyl group (C=O) is present at position 12. The structure is labeled (VI) in the bottom right corner.

$$-(\text{CH}_2)_s\text{NR}_{5'}(\text{R}_6), \text{ wherein:}$$

s is 0, 1, 2, 3, or 4;

R₅' is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), $-C(O)-$ alkoxy_(C≤8), substituted $-C(O)-$ alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

$-(CH_2)_q-C(O)-R_5''$, wherein:

R₅'' is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or

a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

$-alkanediy l_{(C≤8)}-R_b$, $-alkenediy l_{(C≤8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),

aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),

dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),

heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),

$-OC(O)NH-alkyl_{(C≤8)}$, $-OC(O)CH_2NHC(O)O-t-butyl$,

$-OCH_2-alkylthio_{(C≤8)}$, or a substituted version of any of these groups;

$-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, $-NHOH$, or mercapto; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8), heterocycloalkylamino_(C≤8), $\text{—NHC(NO—H)—alkyl}_{(C\leq 8)}$, $\text{—NH—amido}_{(C\leq 8)}$, or a substituted version of any of these groups;

$\text{—NR}_d\text{C(O)R}_e$, wherein

5 R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),

aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-

10 amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of any of these groups; or

Y is taken together with R_3 and is $\text{—(CH}_2)_p\text{C(O)R}_f\text{—}$, wherein

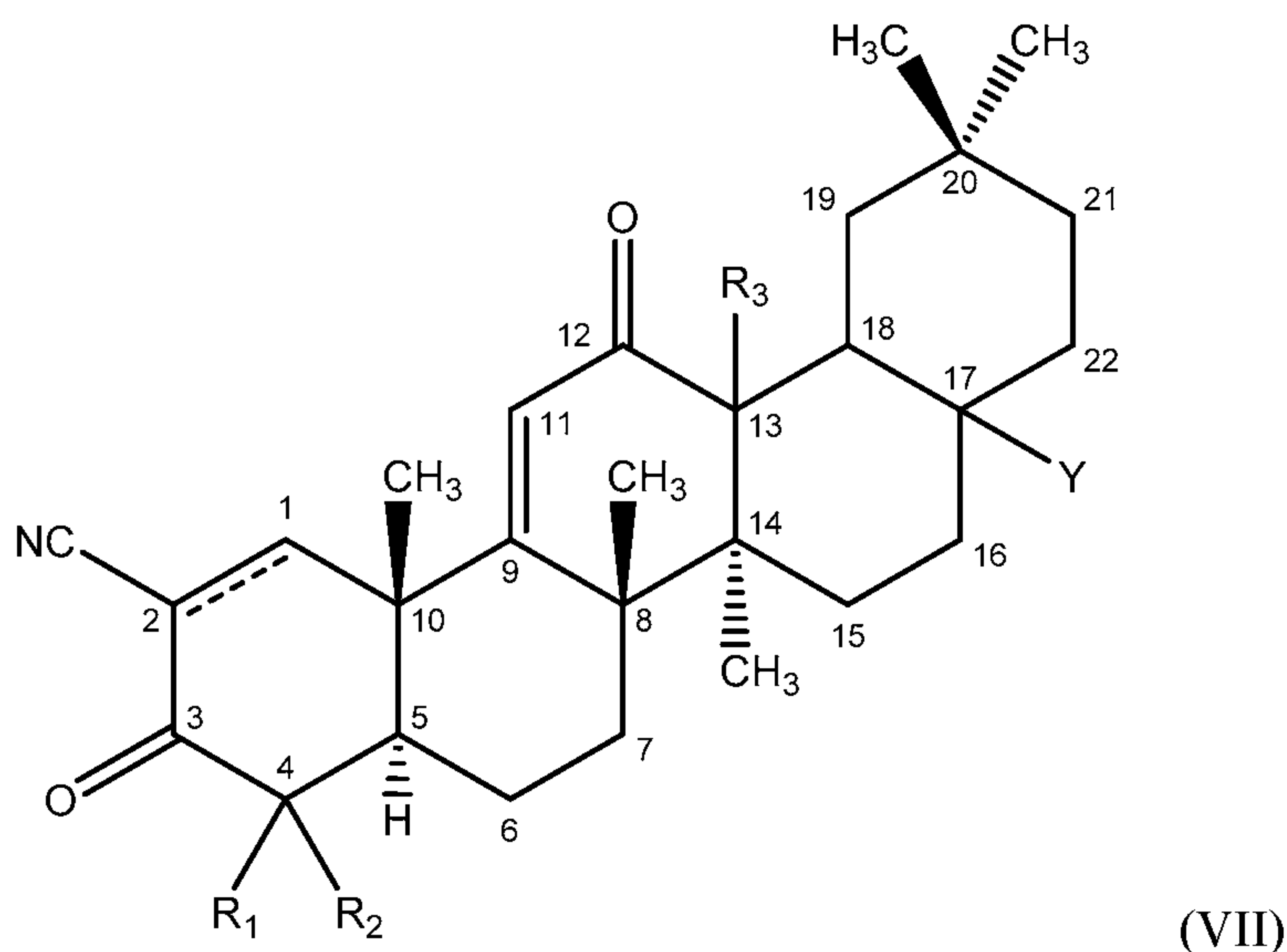
p is 0–6; and

R_f is —O— or $\text{—NR}_7\text{—}$; wherein:

15 R_7 is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



20 wherein:

the bond between atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is amino, cyano, halo, or hydroxy,

substituted alkyl_(C≤8), heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8),
 5 substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8),
 substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8); or

—OR_a, wherein:

R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12),
 aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or
 10 a substituted version of any of these groups;

—(CH₂)_m—(OCH₂)_n—R₅, wherein:

R₅ is hydroxy or acyl_(C≤8), alkoxy_(C≤8), acyloxy_(C≤8), alkylsilyloxy_(C≤8),
 or a substituted version of any of these groups;

m is 0, 1, 2, 3, or 4; and

15 n is 0, 1, 2, or 3;

—(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8),
 substituted acyl_(C≤8), —C(O)—alkoxy_(C≤8), substituted
 20 —C(O)—alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8),
 alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

—(CH₂)_q—C(O)—R_{5''}, wherein:

R_{5''} is amino, hydroxy, or mercapto; or

25 alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or
 a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either
 of these groups; or R₃ is taken together with Y as described below; and

30 Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12),
 heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8),
 aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

5 $-\text{alkanediy}l_{(C\leq 8)}-\text{R}_b$, $-\text{alkenediy}l_{(C\leq 8)}-\text{R}_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),

aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),

dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),

10 heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),

$-\text{OC}(\text{O})\text{NH}-\text{alkyl}_{(C\leq 8)}$, $-\text{OC}(\text{O})\text{CH}_2\text{NHC}(\text{O})\text{O}-t\text{-butyl}$,

$-\text{OCH}_2-\text{alkylthio}_{(C\leq 8)}$, or a substituted version of any of these groups;

$-(\text{CH}_2)_o\text{C}(\text{O})\text{R}_c$, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, $-\text{NHOH}$, or mercapto; or

15 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),

heterocycloalkylamino_(C≤8), $-\text{NHC}(\text{NOH})-\text{alkyl}_{(C\leq 8)}$, $-\text{NH}-\text{amido}_{(C\leq 8)}$,

or a substituted version of any of these groups;

20 $-\text{NR}_d\text{C}(\text{O})\text{R}_e$, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),

25 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-

amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of

any of these groups; or

Y is taken together with R_3 and is $-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_f-$, wherein

p is 0–6; and

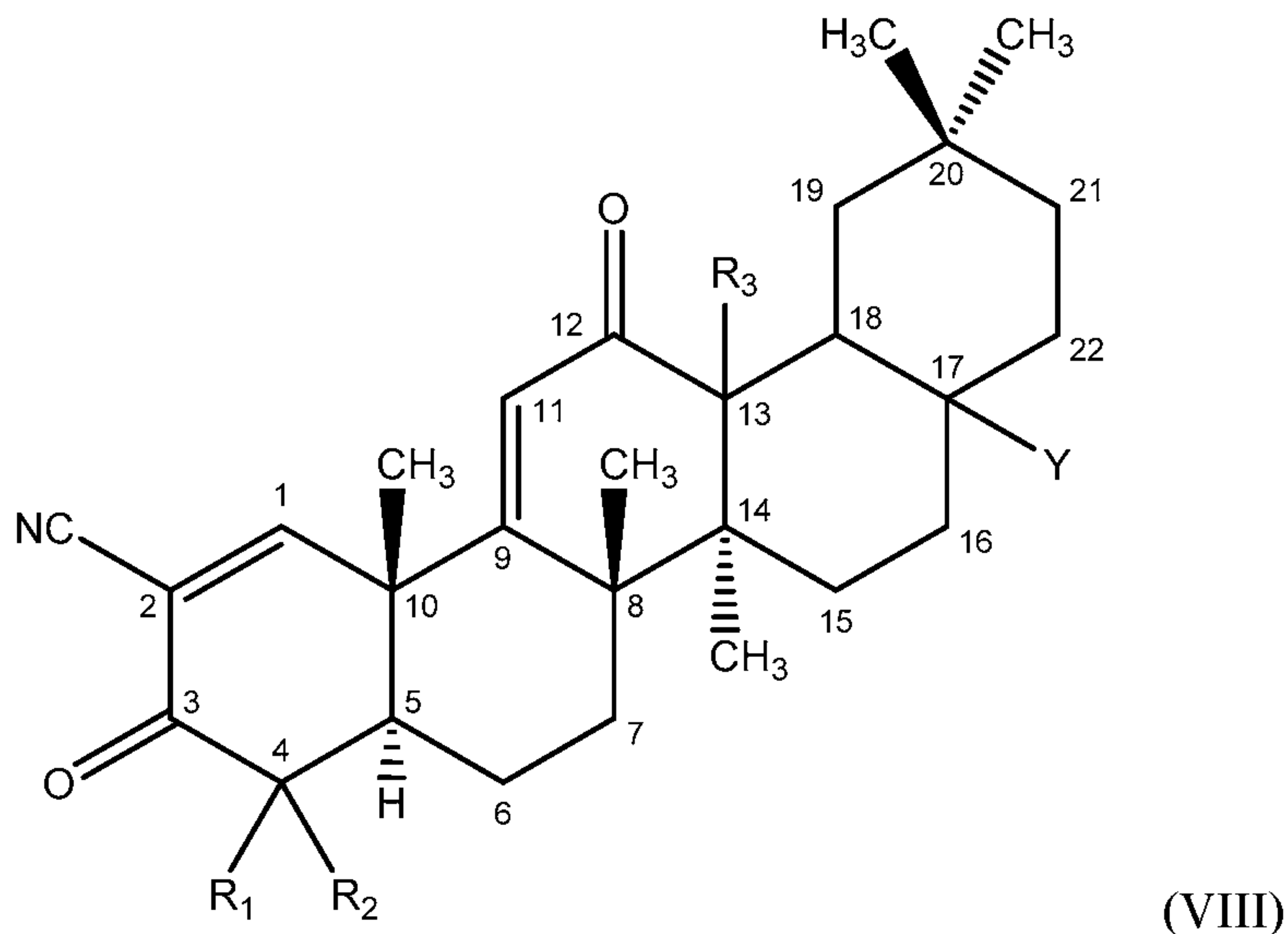
30 R_f is $-\text{O}-$ or $-\text{NR}_7-$; wherein:

R_7 is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted

acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

5 R_1 is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R_2 is amino, cyano, halo, or hydroxy,

substituted alkyl_(C≤8), heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8); or

–OR_a, wherein:

R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or a substituted version of any of these groups;

15 –(CH₂)_m–(OCH₂)_n–R₅, wherein:

R_5 is hydroxy or acyl_(C≤8), alkoxy_(C≤8), acyloxy_(C≤8), alkylsilyloxy_(C≤8), or a substituted version of any of these groups;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

20 –(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

$R_{5'}$ is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), –C(O)–alkoxy_(C≤8), substituted

$-\text{C}(\text{O})-\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{acyloxy}_{(\text{C}\leq 8)}$, substituted $\text{acyloxy}_{(\text{C}\leq 8)}$,
 $\text{alkylsilyloxy}_{(\text{C}\leq 8)}$, or substituted $\text{alkylsilyloxy}_{(\text{C}\leq 8)}$; and

R_6 is hydrogen, $\text{alkyl}_{(\text{C}\leq 8)}$, or substituted $\text{alkyl}_{(\text{C}\leq 8)}$; or

$-(\text{CH}_2)_q-\text{C}(\text{O})-\text{R}_5''$, wherein:

5 R_5'' is amino, hydroxy, or mercapto; or

$\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{alkylthio}_{(\text{C}\leq 8)}$, $\text{alkylamino}_{(\text{C}\leq 8)}$, $\text{dialkylamino}_{(\text{C}\leq 8)}$, or
a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or $\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{acyloxy}_{(\text{C}\leq 8)}$, or substituted version of either
10 of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

$\text{alkyl}_{(\text{C}\leq 8)}$, $\text{cycloalkyl}_{(\text{C}\leq 8)}$, $\text{alkenyl}_{(\text{C}\leq 8)}$, $\text{alkynyl}_{(\text{C}\leq 8)}$, $\text{aryl}_{(\text{C}\leq 12)}$, $\text{aralkyl}_{(\text{C}\leq 12)}$,
 $\text{heteroaryl}_{(\text{C}\leq 8)}$, $\text{heterocycloalkyl}_{(\text{C}\leq 12)}$, $\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{cycloalkoxy}_{(\text{C}\leq 8)}$,
 $\text{aryloxy}_{(\text{C}\leq 12)}$, $\text{acyloxy}_{(\text{C}\leq 8)}$, $\text{alkylamino}_{(\text{C}\leq 8)}$, $\text{dialkylamino}_{(\text{C}\leq 8)}$,
15 $\text{alkenylamino}_{(\text{C}\leq 8)}$, $\text{arylamino}_{(\text{C}\leq 8)}$, $\text{aralkylamino}_{(\text{C}\leq 8)}$, $\text{alkylthio}_{(\text{C}\leq 8)}$,
 $\text{acylthio}_{(\text{C}\leq 8)}$, $\text{alkylsulfonylamino}_{(\text{C}\leq 8)}$, or substituted versions of any of these
groups;

$-\text{alkanediyl}_{(\text{C}\leq 8)}-\text{R}_b$, $-\text{alkenediyl}_{(\text{C}\leq 8)}-\text{R}_b$, or a substituted version of any of these
groups, wherein R_b is:

20 hydrogen, hydroxy, halo, amino or mercapto; or

$\text{heteroaryl}_{(\text{C}\leq 8)}$, $\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{cycloalkoxy}_{(\text{C}\leq 8)}$, $\text{alkenyloxy}_{(\text{C}\leq 8)}$, $\text{aryloxy}_{(\text{C}\leq 8)}$,
 $\text{aralkoxy}_{(\text{C}\leq 8)}$, $\text{heteroaryloxy}_{(\text{C}\leq 8)}$, $\text{acyloxy}_{(\text{C}\leq 8)}$, $\text{alkylamino}_{(\text{C}\leq 8)}$,
 $\text{dialkylamino}_{(\text{C}\leq 8)}$, $\text{alkenylamino}_{(\text{C}\leq 8)}$, $\text{arylamino}_{(\text{C}\leq 8)}$, $\text{aralkylamino}_{(\text{C}\leq 8)}$,
 $\text{heteroarylamino}_{(\text{C}\leq 8)}$, $\text{alkylsulfonylamino}_{(\text{C}\leq 8)}$, $\text{amido}_{(\text{C}\leq 8)}$,
25 $-\text{OC}(\text{O})\text{NH}-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{OC}(\text{O})\text{CH}_2\text{NHC}(\text{O})\text{O}-t\text{-butyl}$,
 $-\text{OCH}_2-\text{alkylthio}_{(\text{C}\leq 8)}$, or a substituted version of any of these groups;

$-(\text{CH}_2)_o\text{C}(\text{O})\text{R}_c$, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, $-\text{NHOH}$, or mercapto; or

$\text{alkyl}_{(\text{C}\leq 8)}$, $\text{cycloalkyl}_{(\text{C}\leq 8)}$, $\text{alkenyl}_{(\text{C}\leq 8)}$, $\text{alkynyl}_{(\text{C}\leq 8)}$, $\text{aryl}_{(\text{C}\leq 8)}$, $\text{aralkyl}_{(\text{C}\leq 8)}$,
30 $\text{heteroaryl}_{(\text{C}\leq 8)}$, $\text{heterocycloalkyl}_{(\text{C}\leq 8)}$, $\text{alkylamino}_{(\text{C}\leq 8)}$, $\text{dialkylamino}_{(\text{C}\leq 8)}$,
 $\text{arylamino}_{(\text{C}\leq 8)}$, $\text{alkylsulfonylamino}_{(\text{C}\leq 8)}$, $\text{amido}_{(\text{C}\leq 8)}$, $\text{alkoxyamino}_{(\text{C}\leq 8)}$,
 $\text{heterocycloalkylamino}_{(\text{C}\leq 8)}$, $-\text{NHC}(\text{NOH})-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{NH}-\text{amido}_{(\text{C}\leq 8)}$,
or a substituted version of any of these groups;

–NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

5 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),
aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-
amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of
any of these groups; or

Y is taken together with R₃ and is –(CH₂)_pC(O)R_f–, wherein

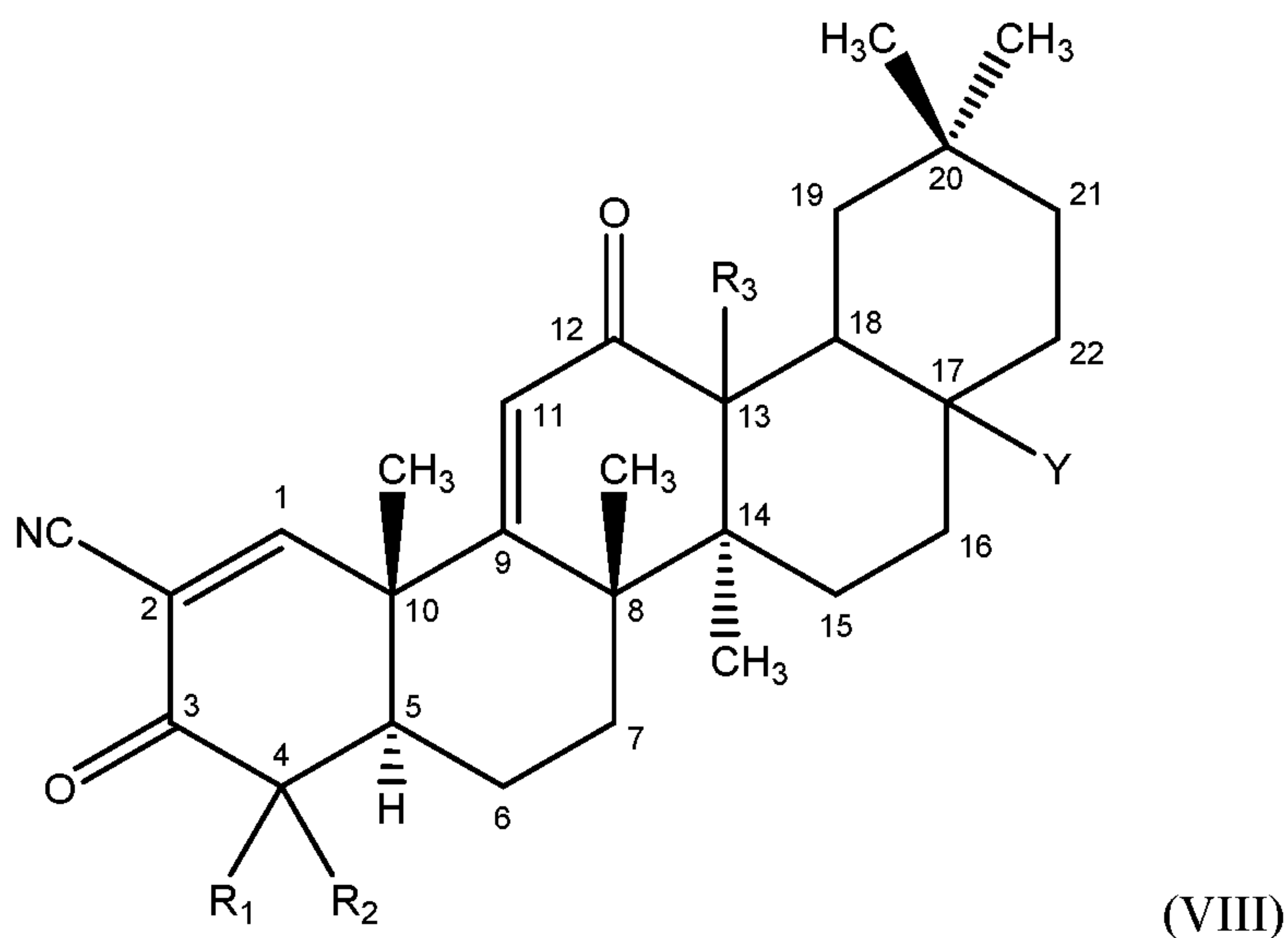
10 p is 0–6; and

R_f is –O– or –NR₇–; wherein:

R₇ is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

15 In some embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted
cycloalkyl_(C≤8);

20 R₂ is amino, cyano, halo, hydroxy, substituted alkyl_(C≤8), heteroaryl_(C≤8), substituted
heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted
amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or
dialkylamino_(C≤8);

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12),

5 heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8),
aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8),
acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these
groups;

10 -alkanediyl_(C≤8)-R_b, -alkenediyl_(C≤8)-R_b, or a substituted version of any of these
groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),

15 aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),
dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),
heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),
-OC(O)NH-alkyl_(C≤8), -OC(O)CH₂NHC(O)O-*t*-butyl,
-OCH₂-alkylthio_(C≤8), or a substituted version of any of these groups;

-(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

20 hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),

heterocycloalkylamino_(C≤8), -NHC(NO₂)-alkyl_(C≤8), -NH-amido_(C≤8),

25 or a substituted version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

30 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),

aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-

amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of any of these groups; or

Y is taken together with R₃ and is $-(CH_2)_pC(O)R_f-$, wherein

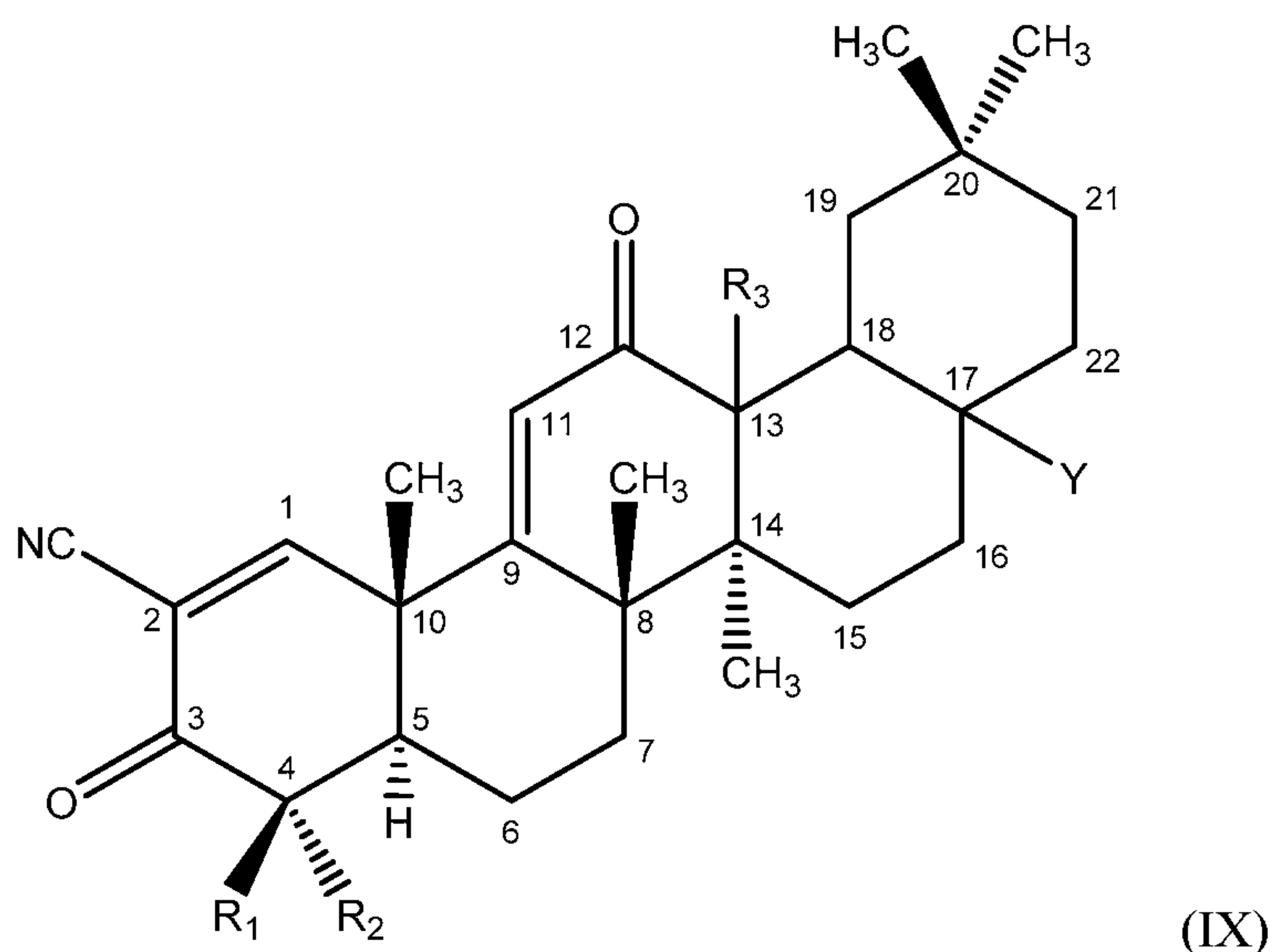
p is 0–6; and

5 R_f is $-O-$ or $-NR_7-$; wherein:

R₇ is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

15 R₂ is amino, cyano, halo, hydroxy, substituted alkyl_(C≤8), heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8);

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

20 Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

–alkanediyl_(C≤8)–R_b, –alkenediyl_(C≤8)–R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),

aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),

dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),

heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),

–OC(O)NH–alkyl_(C≤8), –OC(O)CH₂NHC(O)O–*t*-butyl,

–OCH₂–alkylthio_(C≤8), or a substituted version of any of these groups;

–(CH₂)_oC(O)R_c, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, –NHOH, or mercapto; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),

heterocycloalkylamino_(C≤8), –NHC(NOH)–alkyl_(C≤8), –NH–amido_(C≤8),

or a substituted version of any of these groups;

–NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),

aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-

amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of

any of these groups; or

Y is taken together with R₃ and is –(CH₂)_pC(O)R_f–, wherein

p is 0–6; and

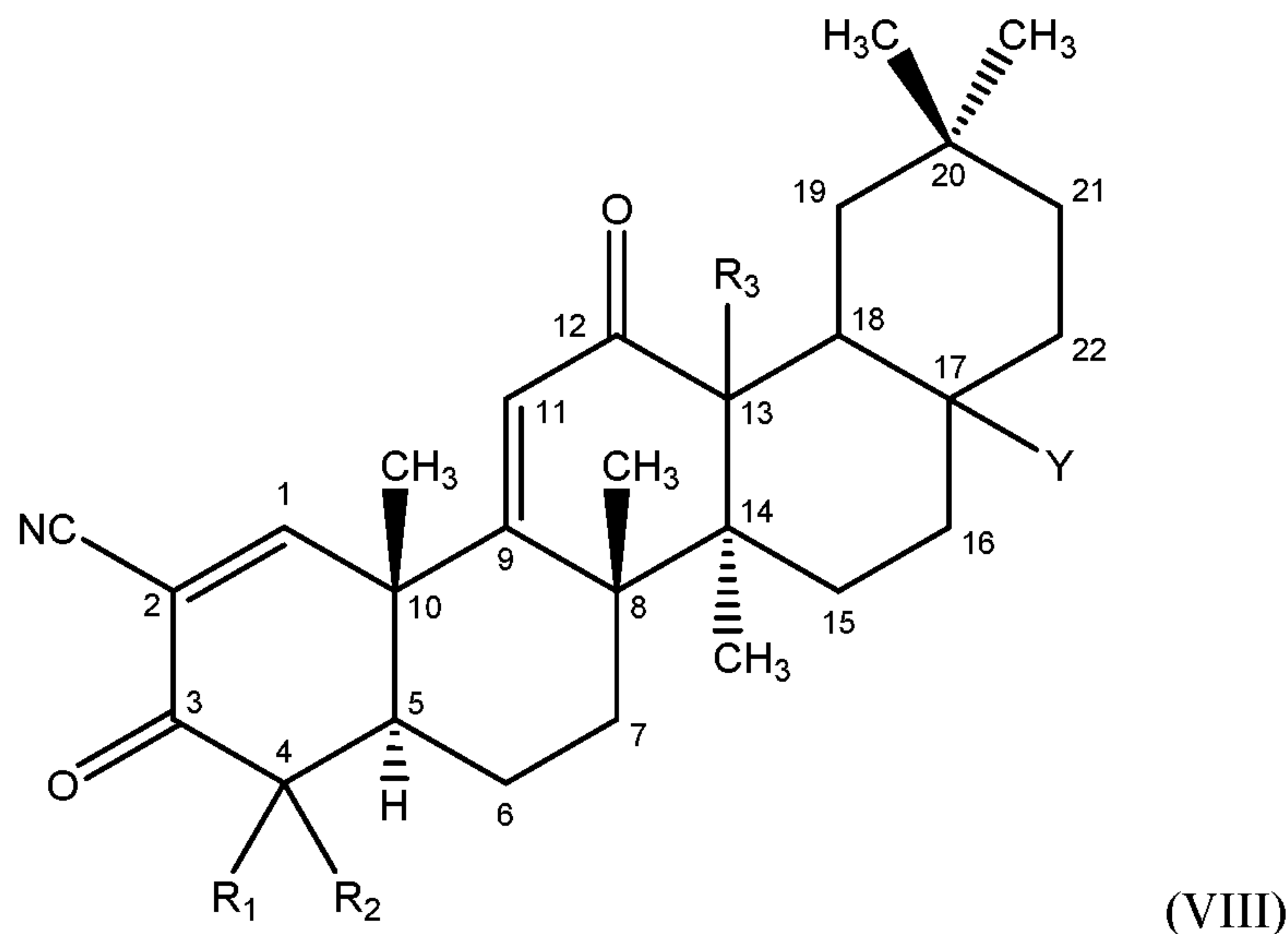
R_f is –O– or –NR₇–; wherein:

R₇ is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted

acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



wherein:

5 R_1 is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R_2 is $-OR_a$, wherein:

R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or a substituted version of any of these groups;

R_3 is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

15 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

20 $-alkanediyl_{(C≤8)}-R_b$, $-alkenediyl_{(C≤8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),
 aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),
 dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),
 heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),
 5 $-\text{OC}(\text{O})\text{NH}-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{OC}(\text{O})\text{CH}_2\text{NHC}(\text{O})\text{O}-t\text{-butyl}$,
 $-\text{OCH}_2-\text{alkylthio}_{(\text{C}\leq 8)}$, or a substituted version of any of these groups;

$-(\text{CH}_2)_o\text{C}(\text{O})\text{R}_c$, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, $-\text{NHOH}$, or mercapto; or
 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
 10 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
 arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),
 heterocycloalkylamino_(C≤8), $-\text{NHC}(\text{NOH})-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{NH}-\text{amido}_{(\text{C}\leq 8)}$,
 or a substituted version of any of these groups;

$-\text{NR}_d\text{C}(\text{O})\text{R}_e$, wherein

15 R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);
 R_e is hydrogen, hydroxy, amino; or
 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),
 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-
 20 amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of
 any of these groups; or

Y is taken together with R_3 and is $-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_f-$, wherein

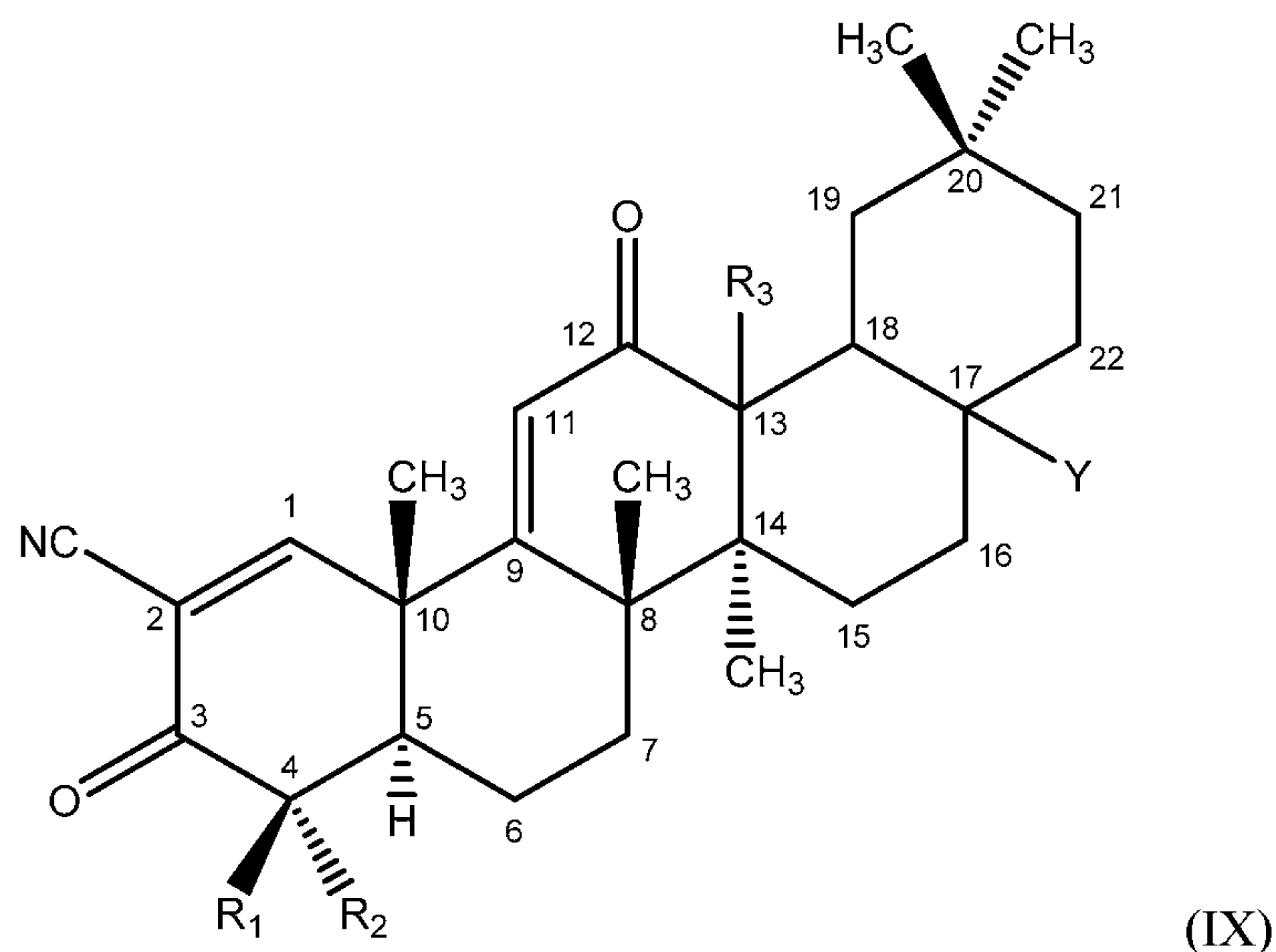
p is 0–6; and

R_f is $-\text{O}-$ or $-\text{NR}_7-$; wherein:

25 R_7 is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
 acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is -OR_a, wherein:

R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or a substituted version of any of these groups;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

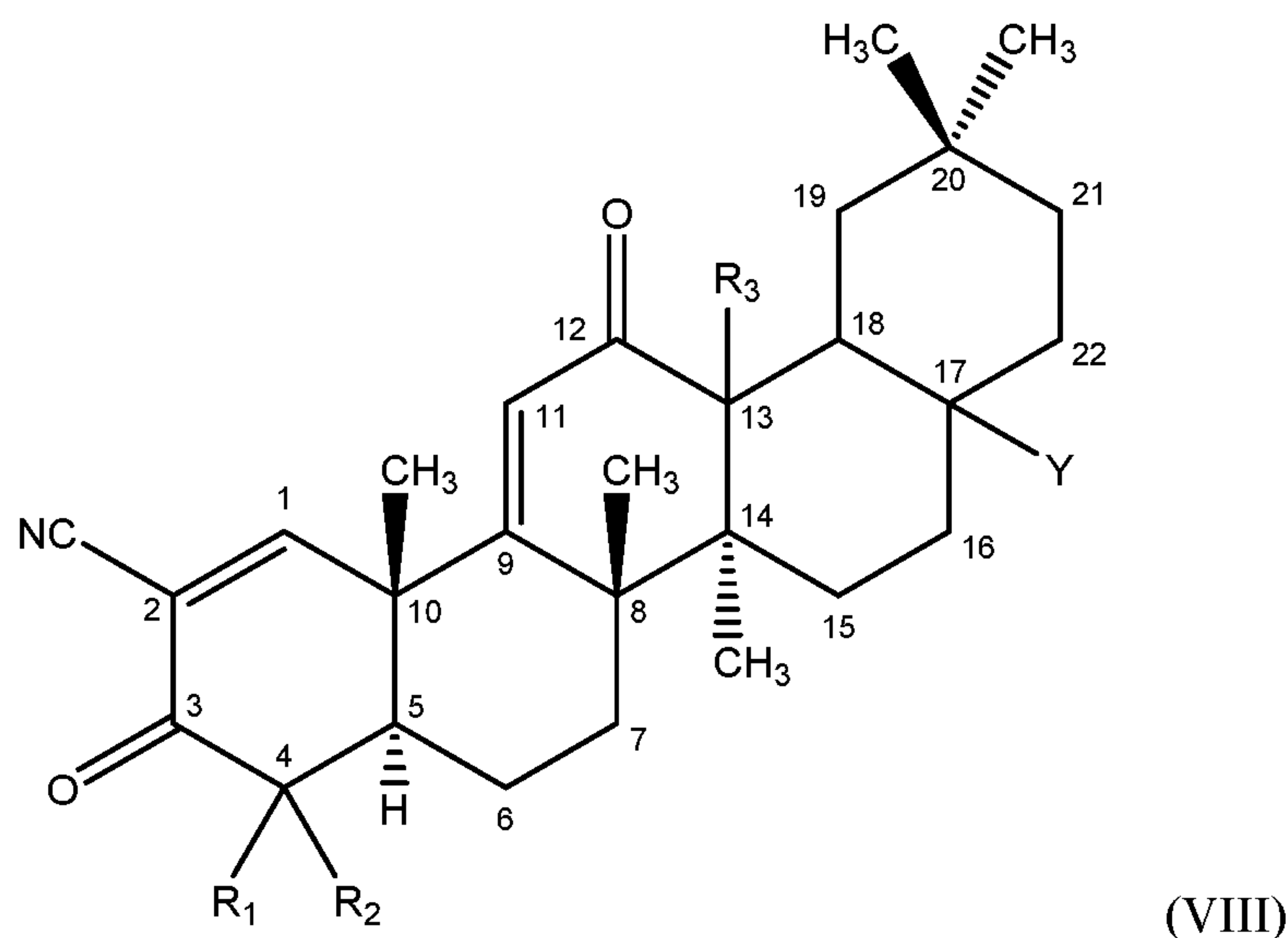
-alkanediyl_(C≤8)-R_b, -alkenediyl_(C≤8)-R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),

- dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),
heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),
–OC(O)NH–alkyl_(C≤8), –OC(O)CH₂NHC(O)O–*t*-butyl,
–OCH₂–alkylthio_(C≤8), or a substituted version of any of these groups;
- 5 –(CH₂)_oC(O)R_c, wherein o is 0–6 and R_c is:
hydrogen, halo, amino, –NHOH, or mercapto; or
alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),
10 heterocycloalkylamino_(C≤8), –NHC(NO₂)–alkyl_(C≤8), –NH–amido_(C≤8),
or a substituted version of any of these groups;
–NR_dC(O)R_e, wherein
R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);
R_e is hydrogen, hydroxy, amino; or
15 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),
aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-
amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of
any of these groups; or
20 Y is taken together with R₃ and is –(CH₂)_pC(O)R_f–, wherein
p is 0–6; and
R_f is –O– or –NR₇–; wherein:
R₇ is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
acyl_(C≤8);
25 or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is $-(CH_2)_m-(OCH_2)_n-R_5$, wherein:

R₅ is hydroxy or acyl_(C≤8), alkoxy_(C≤8), acyloxy_(C≤8), alkylsilyloxy_(C≤8), or a substituted version of any of these groups;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12),

heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8),

aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8),

acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

$-alkanediyl_{(C≤8)}-R_b$, $-alkenediyl_{(C≤8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),
 aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),
 dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),
 heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),
 5 $-\text{OC}(\text{O})\text{NH}-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{OC}(\text{O})\text{CH}_2\text{NHC}(\text{O})\text{O}-t\text{-butyl}$,
 $-\text{OCH}_2-\text{alkylthio}_{(\text{C}\leq 8)}$, or a substituted version of any of these groups;

$-(\text{CH}_2)_o\text{C}(\text{O})\text{R}_c$, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, $-\text{NHOH}$, or mercapto; or
 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
 10 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
 arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),
 heterocycloalkylamino_(C≤8), $-\text{NHC}(\text{NOH})-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{NH}-\text{amido}_{(\text{C}\leq 8)}$,
 or a substituted version of any of these groups;

$-\text{NR}_d\text{C}(\text{O})\text{R}_e$, wherein

15 R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);
 R_e is hydrogen, hydroxy, amino; or
 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),
 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-
 20 amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of
 any of these groups; or

Y is taken together with R_3 and is $-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_f-$, wherein

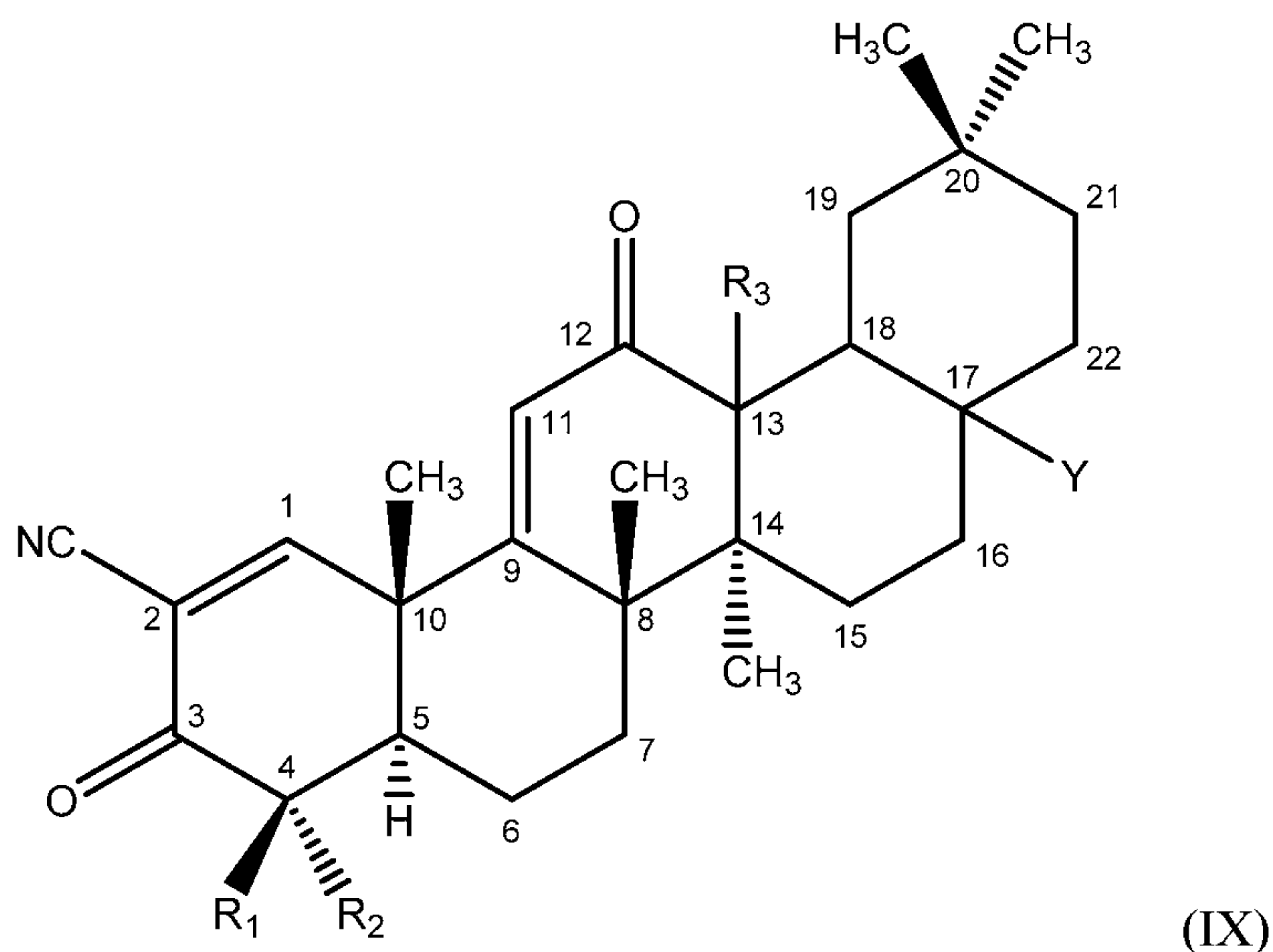
p is 0–6; and

R_f is $-\text{O}-$ or $-\text{NR}_7-$; wherein:

25 R_7 is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
 acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is $-(CH_2)_m-(OCH_2)_n-R_5$, wherein:

R₅ is hydroxy or acyl_(C≤8), alkoxy_(C≤8), acyloxy_(C≤8), alkylsilyloxy_(C≤8), or a substituted version of any of these groups;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12),

heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8),

aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8),

acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

$-alkanediyl_{(C≤8)}-R_b$, $-alkenediyl_{(C≤8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),
 aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),
 dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),
 heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),
 5 $-\text{OC}(\text{O})\text{NH}-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{OC}(\text{O})\text{CH}_2\text{NHC}(\text{O})\text{O}-t\text{-butyl}$,
 $-\text{OCH}_2-\text{alkylthio}_{(\text{C}\leq 8)}$, or a substituted version of any of these groups;

$-(\text{CH}_2)_o\text{C}(\text{O})\text{R}_c$, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, $-\text{NHOH}$, or mercapto; or

10 $\text{alkyl}_{(\text{C}\leq 8)}$, $\text{cycloalkyl}_{(\text{C}\leq 8)}$, $\text{alkenyl}_{(\text{C}\leq 8)}$, $\text{alkynyl}_{(\text{C}\leq 8)}$, $\text{aryl}_{(\text{C}\leq 8)}$, $\text{aralkyl}_{(\text{C}\leq 8)}$,
 $\text{heteroaryl}_{(\text{C}\leq 8)}$, $\text{heterocycloalkyl}_{(\text{C}\leq 8)}$, $\text{alkylamino}_{(\text{C}\leq 8)}$, $\text{dialkylamino}_{(\text{C}\leq 8)}$,
 $\text{arylamino}_{(\text{C}\leq 8)}$, $\text{alkylsulfonylamino}_{(\text{C}\leq 8)}$, $\text{amido}_{(\text{C}\leq 8)}$, $\text{alkoxyamino}_{(\text{C}\leq 8)}$,
 $\text{heterocycloalkylamino}_{(\text{C}\leq 8)}$, $-\text{NHC}(\text{NOH})-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{NH}-\text{amido}_{(\text{C}\leq 8)}$,
 or a substituted version of any of these groups;

$-\text{NR}_d\text{C}(\text{O})\text{R}_e$, wherein

15 R_d is hydrogen, $\text{alkyl}_{(\text{C}\leq 8)}$, or substituted $\text{alkyl}_{(\text{C}\leq 8)}$;

R_e is hydrogen, hydroxy, amino; or

$\text{alkyl}_{(\text{C}\leq 8)}$, $\text{cycloalkyl}_{(\text{C}\leq 8)}$, $\text{alkenyl}_{(\text{C}\leq 8)}$, $\text{alkynyl}_{(\text{C}\leq 8)}$, $\text{aryl}_{(\text{C}\leq 8)}$, $\text{aralkyl}_{(\text{C}\leq 8)}$,
 $\text{heteroaryl}_{(\text{C}\leq 8)}$, $\text{heterocycloalkyl}_{(\text{C}\leq 8)}$, $\text{alkoxy}_{(\text{C}\leq 8)}$, $\text{cycloalkoxy}_{(\text{C}\leq 8)}$,
 $\text{aryloxy}_{(\text{C}\leq 8)}$, $\text{aralkoxy}_{(\text{C}\leq 8)}$, $\text{heteroaryloxy}_{(\text{C}\leq 8)}$, $\text{acyloxy}_{(\text{C}\leq 8)}$, alkyl-
 20 $\text{amino}_{(\text{C}\leq 8)}$, $\text{dialkylamino}_{(\text{C}\leq 8)}$, $\text{arylamino}_{(\text{C}\leq 8)}$, or a substituted version of
 any of these groups; or

Y is taken together with R_3 and is $-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_f-$, wherein

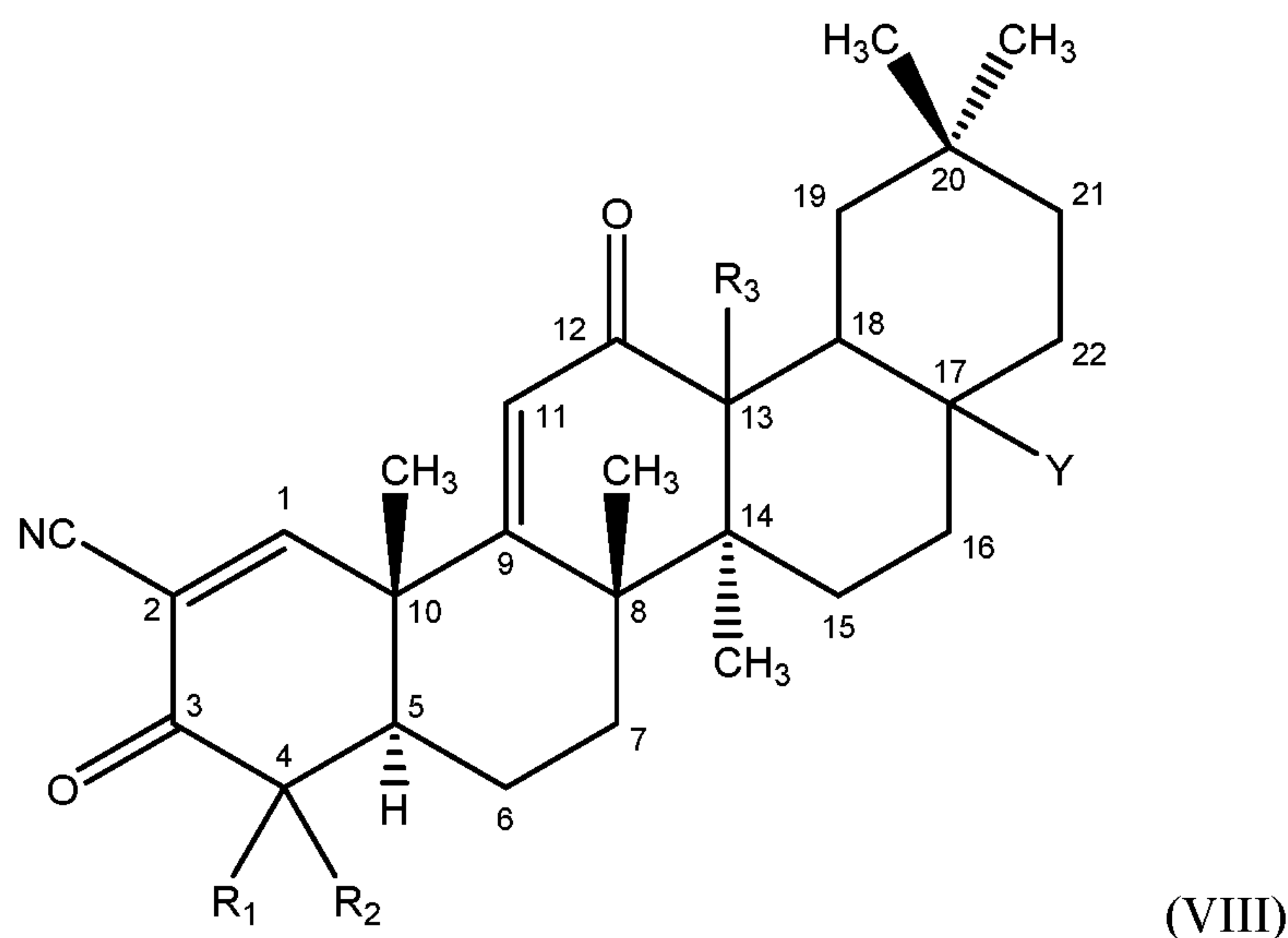
p is 0–6; and

R_f is $-\text{O}-$ or $-\text{NR}_7-$; wherein:

25 R_7 is hydrogen, $\text{alkyl}_{(\text{C}\leq 8)}$, substituted $\text{alkyl}_{(\text{C}\leq 8)}$, $\text{acyl}_{(\text{C}\leq 8)}$, or substituted
 $\text{acyl}_{(\text{C}\leq 8)}$;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is $-(CH_2)_sNR_{5'}(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), $-C(O)-$ alkoxy_(C≤8), substituted $-C(O)-$ alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

$-alkanediy1_{(C≤8)}-R_b$, $-alkenediy1_{(C≤8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),

aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),

dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),

5 heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),

–OC(O)NH–alkyl_(C≤8), –OC(O)CH₂NHC(O)O–*t*-butyl,

–OCH₂–alkylthio_(C≤8), or a substituted version of any of these groups;

–(CH₂)_oC(O)R_c, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, –NHOH, or mercapto; or

10 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),

heterocycloalkylamino_(C≤8), –NHC(NO₂)–alkyl_(C≤8), –NH–amido_(C≤8),

or a substituted version of any of these groups;

15 –NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),

heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),

20 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-

amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of

any of these groups; or

Y is taken together with R₃ and is –(CH₂)_pC(O)R_f–, wherein

p is 0–6; and

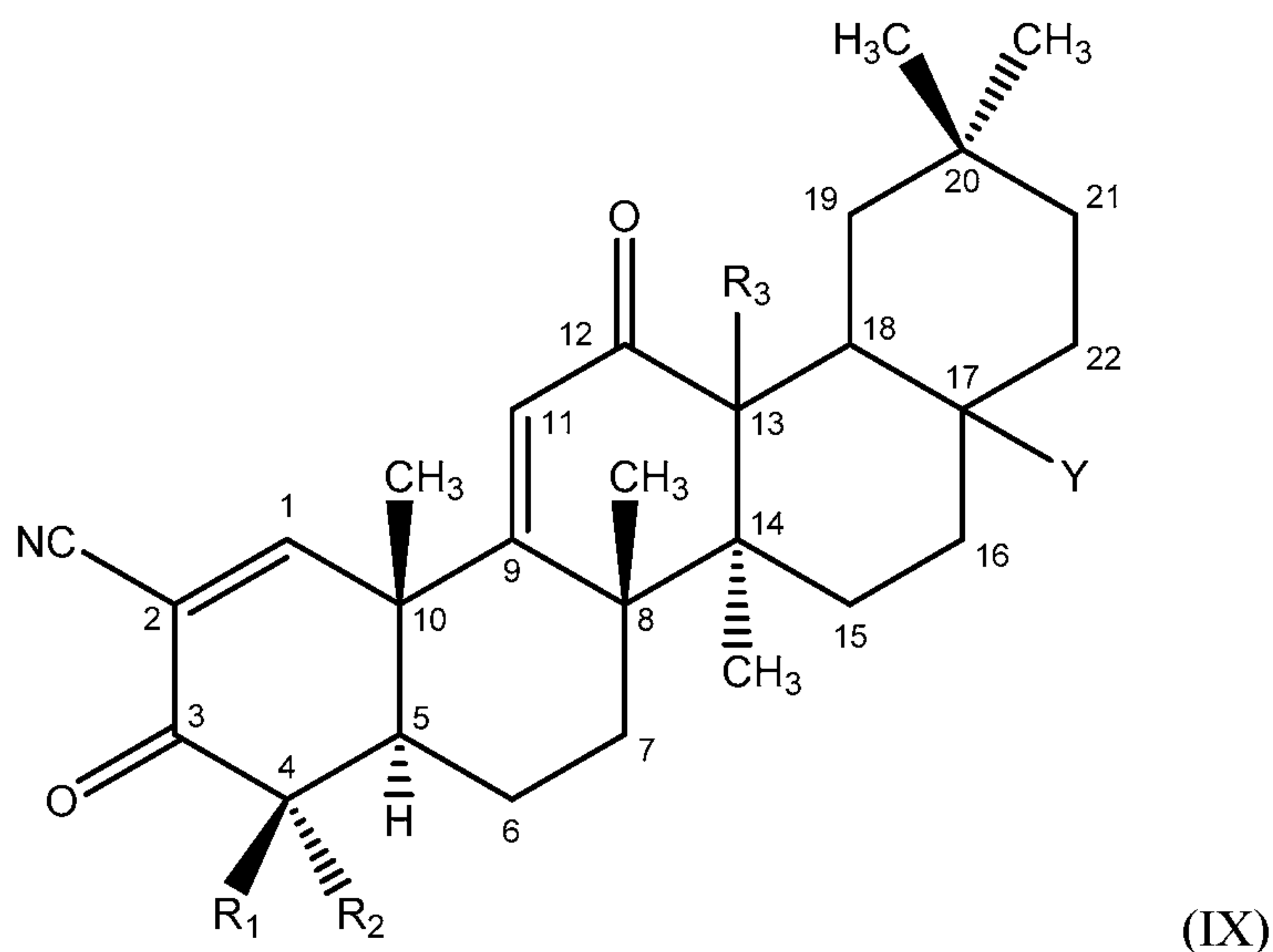
25 R_f is –O– or –NR₇–; wherein:

R₇ is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted

acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is $-(\text{CH}_2)_s\text{NR}_{5'}(\text{R}_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R₅' is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), -C(O)-alkoxy_(C≤8), substituted -C(O)-alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R₃ is hydrogen, hydroxy, or alkoxy(C_{≤8}), acyloxy(C_{≤8}), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

–alkanediyl_(C≤8)–R_b, –alkenediyl_(C≤8)–R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),
 aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),
 dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),
 5 heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),
 -OC(O)NH-alkyl_(C≤8), -OC(O)CH₂NHC(O)O-*t*-butyl,
 -OCH₂-alkylthio_(C≤8), or a substituted version of any of these groups;

-(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydrogen, halo, amino, -NHOH, or mercapto; or

10 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
 arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),
 heterocycloalkylamino_(C≤8), -NHC(NO₂)-alkyl_(C≤8), -NH-amido_(C≤8),
 or a substituted version of any of these groups;

15 -NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

20 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),
 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-
 amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of
 any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f-, wherein

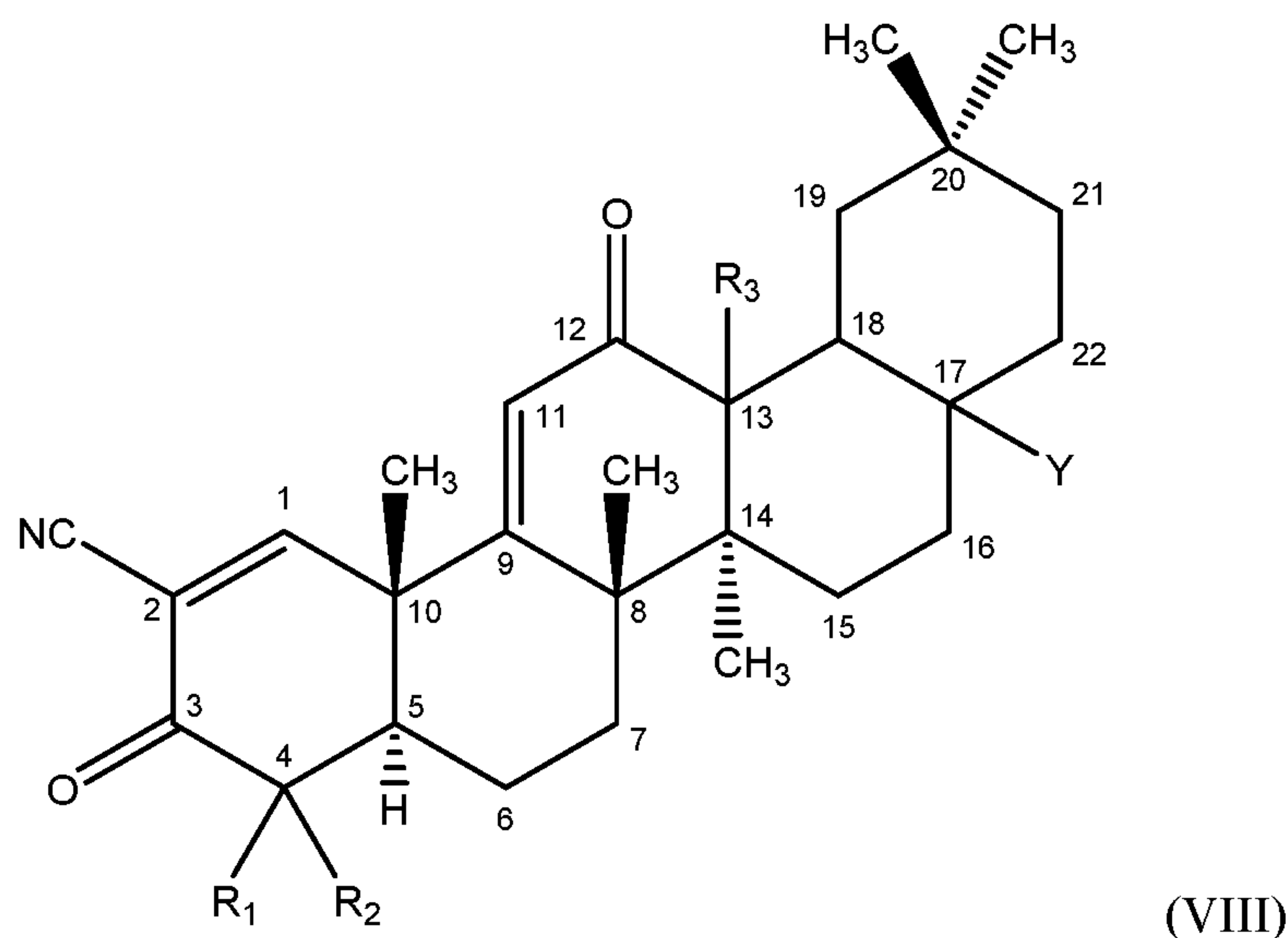
p is 0-6; and

25 R_f is -O- or -NR₇-; wherein:

R₇ is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
 acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is $-(CH_2)_q-C(O)-R_5''$, wherein:

R₅'' is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12),

heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8),

aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8),

acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

$-alkanediyl_{(C≤8)}-R_b$, $-alkenediyl_{(C≤8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),
 aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),
 dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),
 heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),
 5 $-\text{OC}(\text{O})\text{NH}-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{OC}(\text{O})\text{CH}_2\text{NHC}(\text{O})\text{O}-t\text{-butyl}$,
 $-\text{OCH}_2-\text{alkylthio}_{(\text{C}\leq 8)}$, or a substituted version of any of these groups;

$-(\text{CH}_2)_o\text{C}(\text{O})\text{R}_c$, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, $-\text{NHOH}$, or mercapto; or
 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
 10 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
 arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),
 heterocycloalkylamino_(C≤8), $-\text{NHC}(\text{NOH})-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{NH}-\text{amido}_{(\text{C}\leq 8)}$,
 or a substituted version of any of these groups;

$-\text{NR}_d\text{C}(\text{O})\text{R}_e$, wherein

15 R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);
 R_e is hydrogen, hydroxy, amino; or
 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),
 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-
 20 amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of
 any of these groups; or

Y is taken together with R_3 and is $-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_f-$, wherein

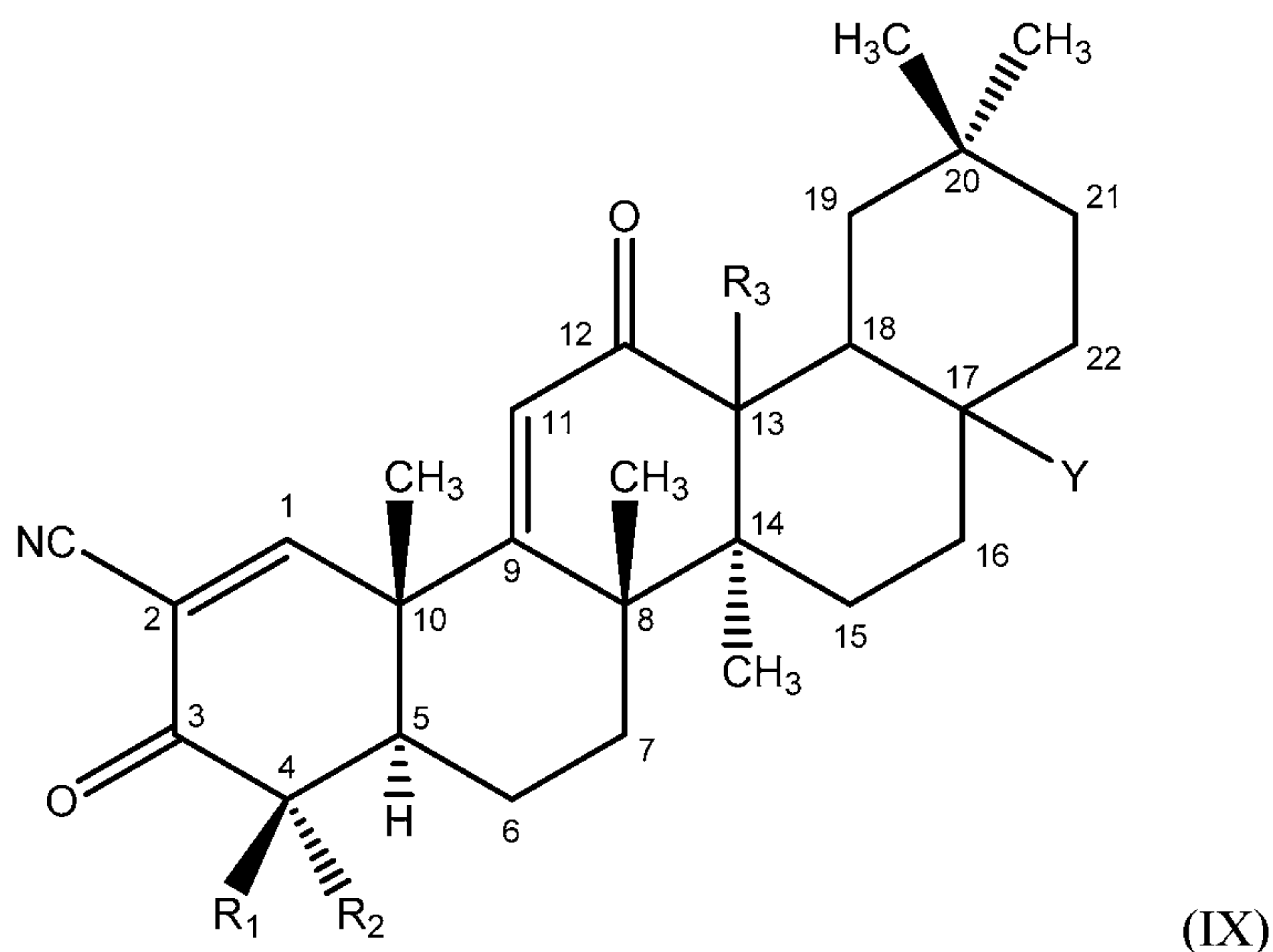
p is 0–6; and

R_f is $-\text{O}-$ or $-\text{NR}_7-$; wherein:

25 R_7 is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
 acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is $-(CH_2)_q-C(O)-R_5''$, wherein:

R₅'' is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12),

heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8),

aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),

alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8),

acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

$-alkanediyl_{(C≤8)}-R_b$, $-alkenediyl_{(C≤8)}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8),
 aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),
 dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8),
 heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8),
 5 $-\text{OC}(\text{O})\text{NH}-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{OC}(\text{O})\text{CH}_2\text{NHC}(\text{O})\text{O}-t\text{-butyl}$,
 $-\text{OCH}_2-\text{alkylthio}_{(\text{C}\leq 8)}$, or a substituted version of any of these groups;

$-(\text{CH}_2)_o\text{C}(\text{O})\text{R}_c$, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, $-\text{NHOH}$, or mercapto; or
 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
 10 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
 arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8),
 heterocycloalkylamino_(C≤8), $-\text{NHC}(\text{NOH})-\text{alkyl}_{(\text{C}\leq 8)}$, $-\text{NH}-\text{amido}_{(\text{C}\leq 8)}$,
 or a substituted version of any of these groups;

$-\text{NR}_d\text{C}(\text{O})\text{R}_e$, wherein

15 R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);
 R_e is hydrogen, hydroxy, amino; or
 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8), aralkyl_(C≤8),
 heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8),
 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkyl-
 20 amino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), or a substituted version of
 any of these groups; or

Y is taken together with R_3 and is $-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_f-$, wherein

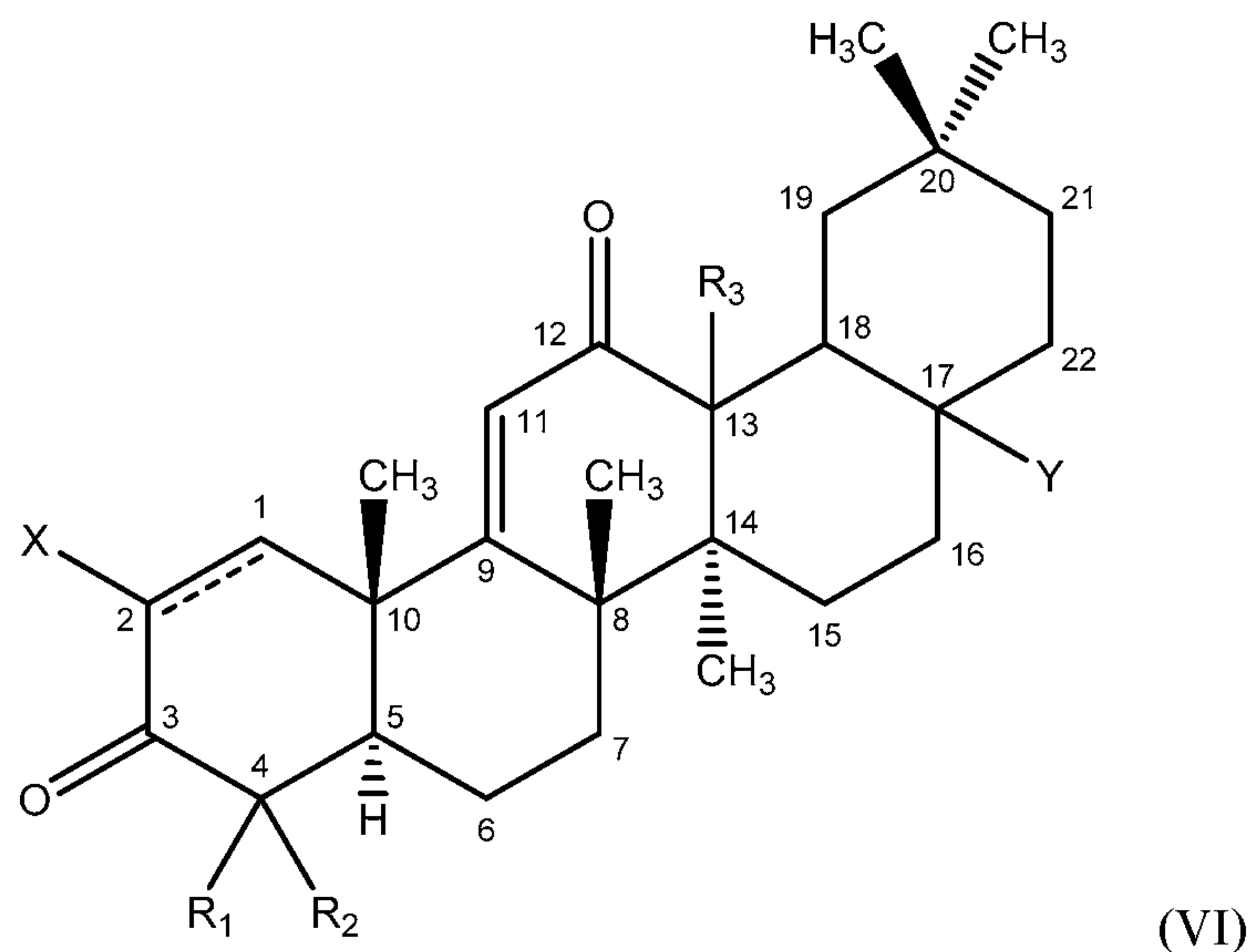
p is 0–6; and

R_f is $-\text{O}-$ or $-\text{NR}_7-$; wherein:

25 R_7 is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
 acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



wherein:

the bond between atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

X is cyano, heteroaryl_(C≤8), substituted heteroaryl_(C≤8), -CF₃, or -C(O)-R₄; wherein

R₄ is hydroxy, amino, or alkoxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkylsulfonylamino_(C≤8), or a substituted version of any of these groups;

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is amino, cyano, halo, or hydroxy,

haloalkyl_(C≤8), substituted cycloalkyl_(C≤8), heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8); or

-OR_a, wherein:

R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or a substituted version of any of these groups;

-(CH₂)_m-R_{5'''}, wherein:

R_{5'''} is alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

m is 0, 1, 2, 3, or 4;

-(CH₂)_{m2}-R_{5'''}, wherein:

R_5''' is hydroxy; and

m_2 is 2, 3, or 4;

$-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

5 R_5' is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), $-C(O)-$ alkoxy_(C≤8), substituted $-C(O)-$ alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R_6 is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

10 $-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

15 R_3 is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

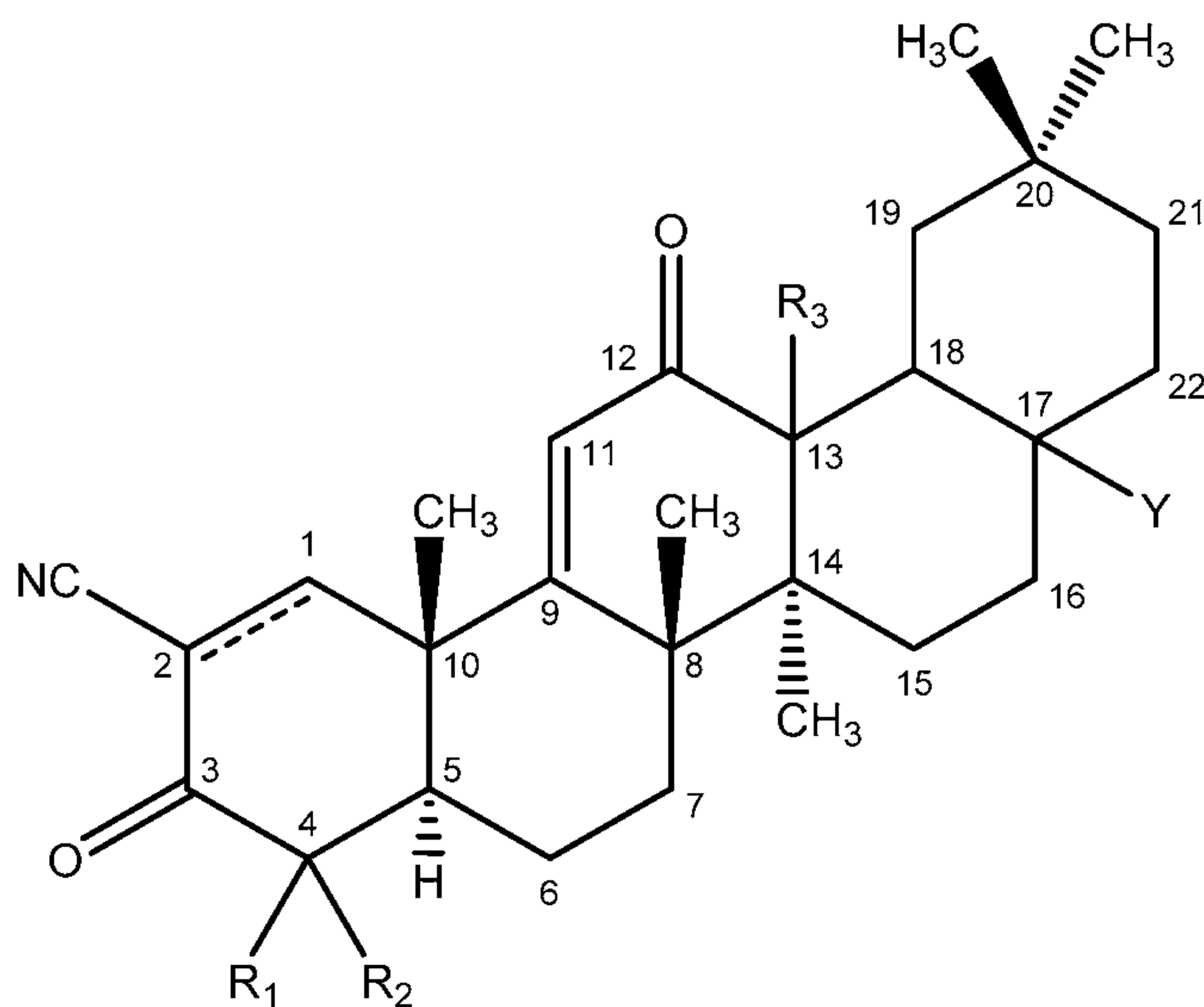
hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8),

20 heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



(VII)

wherein:

the bond between atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is amino, cyano, halo, or hydroxy,

haloalkyl_(C≤8), substituted cycloalkyl_(C≤8), heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8); or

—OR_a, wherein:

R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or a substituted version of any of these groups;

—(CH₂)_m—R_{5'''}, wherein:

R_{5'''} is alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

m is 0, 1, 2, 3, or 4; or

—(CH₂)_{m2}—R_{5'''}, wherein:

R_{5'''} is hydroxy; and

m₂ is 2, 3, or 4;

—(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), —C(O)—alkoxy_(C≤8), substituted —C(O)—alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

—(CH₂)_q—C(O)—R_{5''}, wherein:

R_{5''} is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy($C_{\leq 8}$), acyloxy($C_{\leq 8}$), or substituted version of either of these groups; and

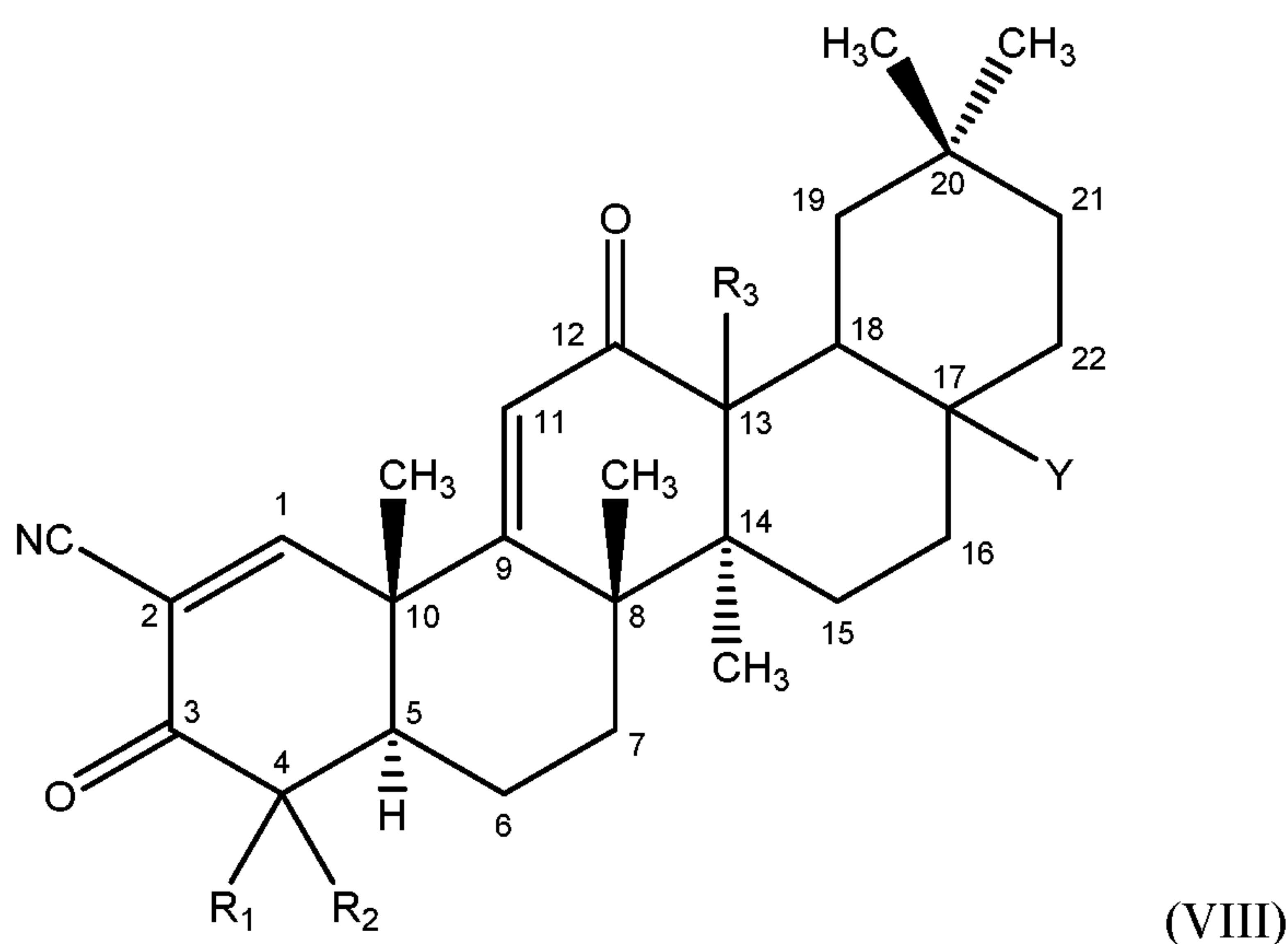
Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

hydroxy; or

5 alkoxy($C_{\leq 8}$), cycloalkoxy($C_{\leq 8}$), alkenyloxy($C_{\leq 8}$), aryloxy($C_{\leq 8}$), aralkoxy($C_{\leq 8}$), heteroaryloxy($C_{\leq 8}$), acyloxy($C_{\leq 8}$), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R_1 is hydrogen, alkyl($C_{\leq 8}$), cycloalkyl($C_{\leq 8}$), substituted alkyl($C_{\leq 8}$), or substituted cycloalkyl($C_{\leq 8}$);

R_2 is amino, cyano, halo, or hydroxy,

15 haloalkyl($C_{\leq 8}$), substituted cycloalkyl($C_{\leq 8}$), heteroaryl($C_{\leq 8}$), substituted heteroaryl($C_{\leq 8}$), acyl($C_{\leq 8}$), substituted acyl($C_{\leq 8}$), amido($C_{\leq 8}$), substituted amido($C_{\leq 8}$), alkylamino($C_{\leq 8}$), substituted alkylamino($C_{\leq 8}$), dialkylamino($C_{\leq 8}$), or dialkylamino($C_{\leq 8}$); or

$-OR_a$, wherein:

20 R_a is hydrogen or alkyl($C_{\leq 8}$), alkenyl($C_{\leq 8}$), alkynyl($C_{\leq 8}$), aryl($C_{\leq 12}$), aralkyl($C_{\leq 12}$), heteroaryl($C_{\leq 12}$), heterocycloalkyl($C_{\leq 8}$), acyl($C_{\leq 8}$), or a substituted version of any of these groups;

$-(CH_2)_m-R_5'''$, wherein:

R_5''' is alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

m is 0, 1, 2, 3, or 4; or

$-(CH_2)_{m_2}-R_5'''$, wherein:

5 R_5''' is hydroxy; and

m_2 is 2, 3, or 4;

$-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

10 R_5' is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), $-C(O)-$ alkoxy_(C≤8), substituted $-C(O)-$ alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R_6 is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

$-(CH_2)_q-C(O)-R_5''$, wherein:

15 R_5'' is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

20 R_3 is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

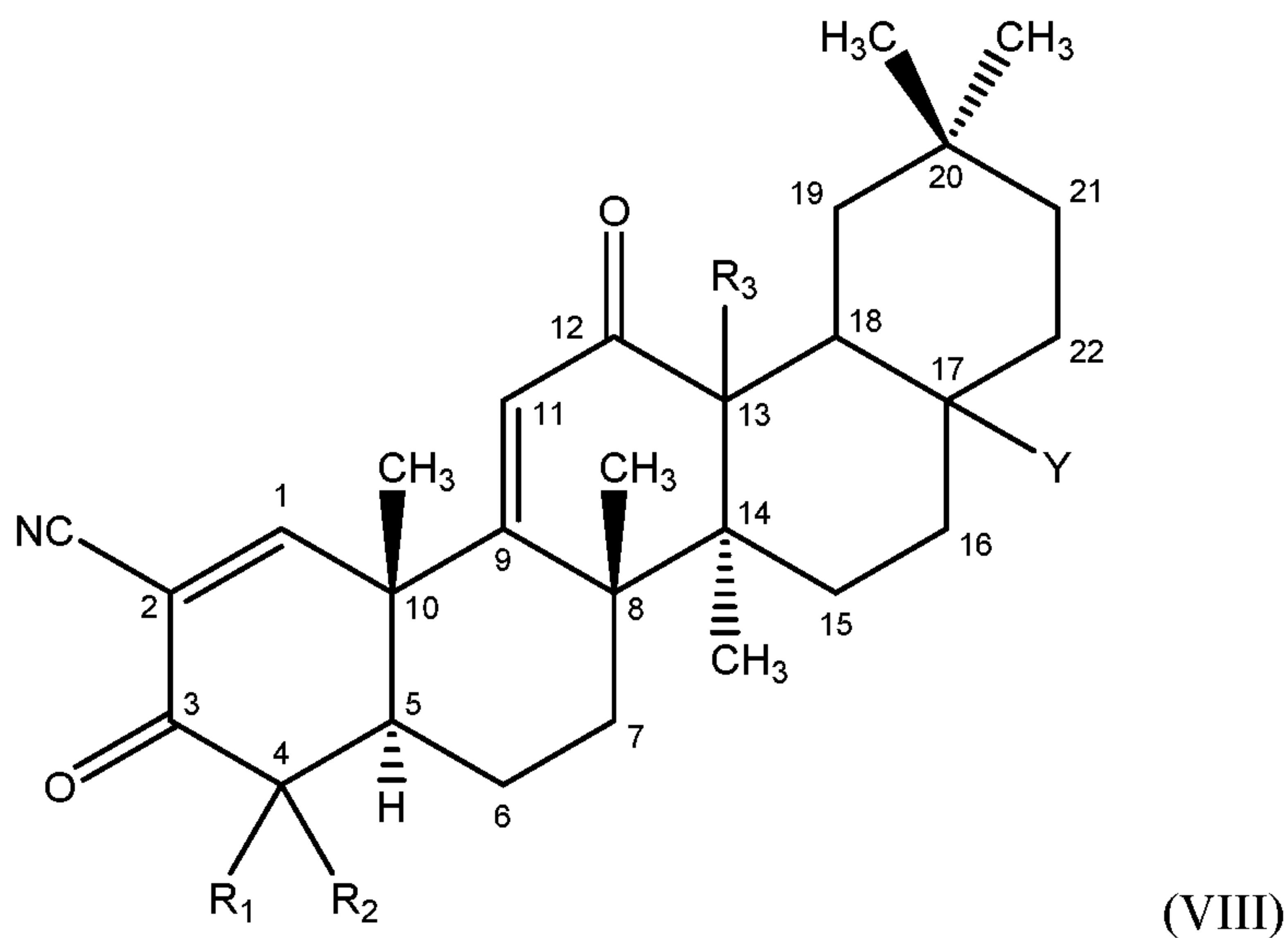
Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

hydroxy; or

25 alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is amino, cyano, halo, or hydroxy, haloalkyl_(C≤8), heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8);

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

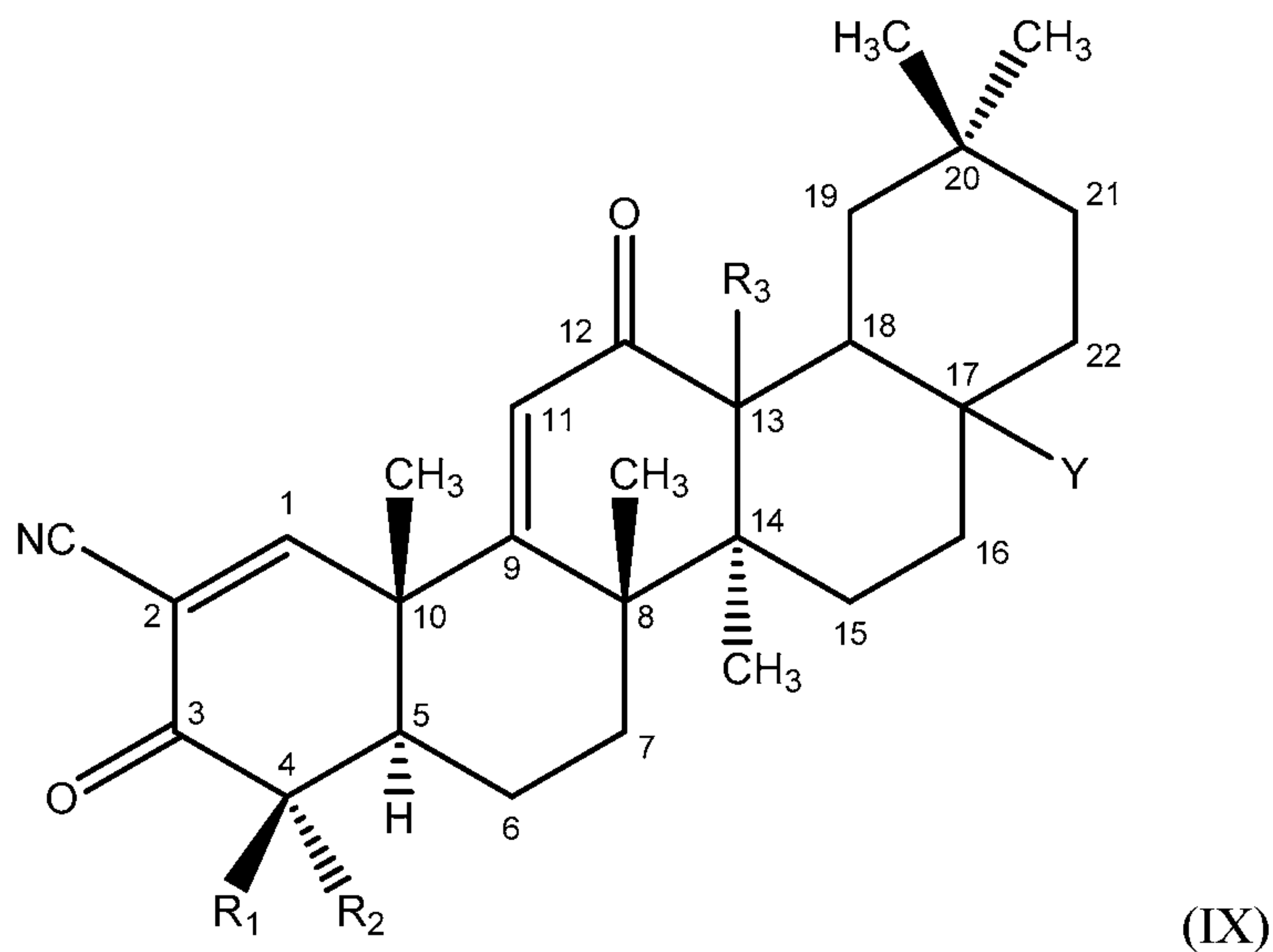
hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8),

heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is amino, cyano, halo, or hydroxy, haloalkyl_(C≤8), heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8);

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

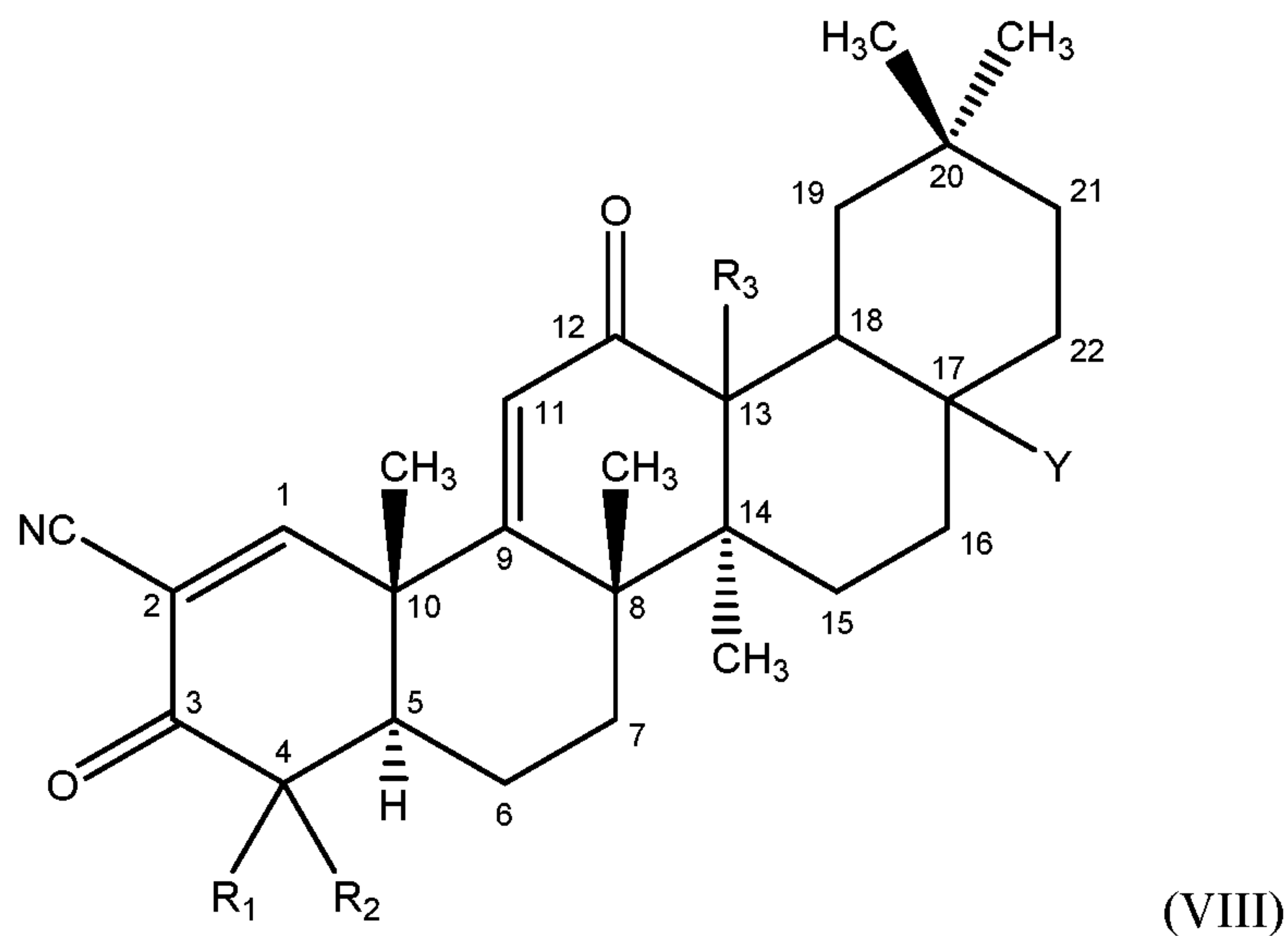
hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8),

heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is $-(CH_2)_m-R_5'''$, wherein:

R_{5'''} is alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

m is 0, 1, 2, 3, or 4; or

R₂ is $-(CH_2)_{m2}-R_5'''$, wherein:

R_{5'''} is hydroxy; and

m₂ is 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

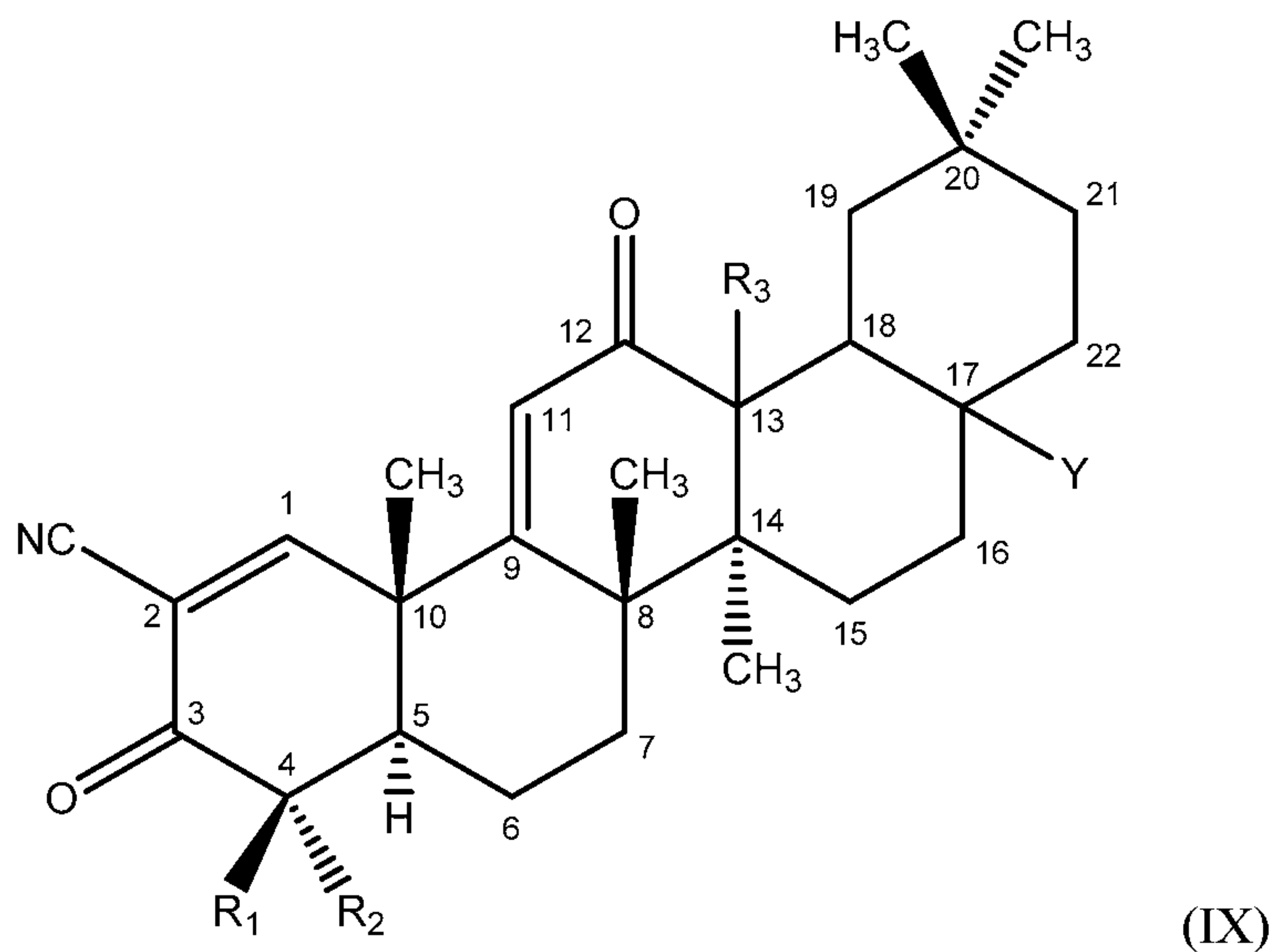
Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is $-(CH_2)_m-R_5'''$, wherein:

R_{5'''} is alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

m is 0, 1, 2, 3, or 4; or

R₂ is $-(CH_2)_{m2}-R_5'''$, wherein:

R_{5'''} is hydroxy; and

m₂ is 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

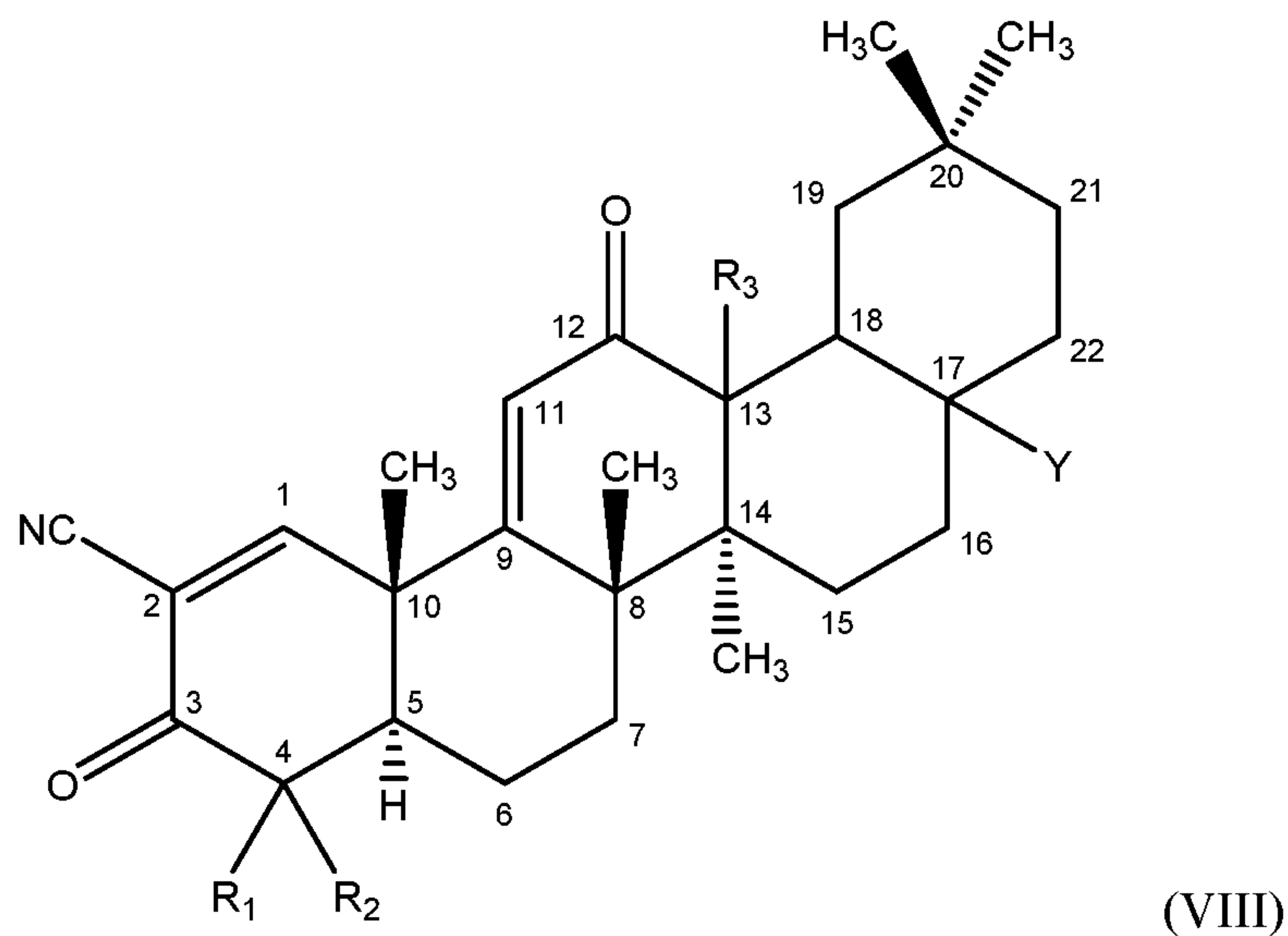
Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is -OR_a, wherein:

R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or a substituted version of any of these groups;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

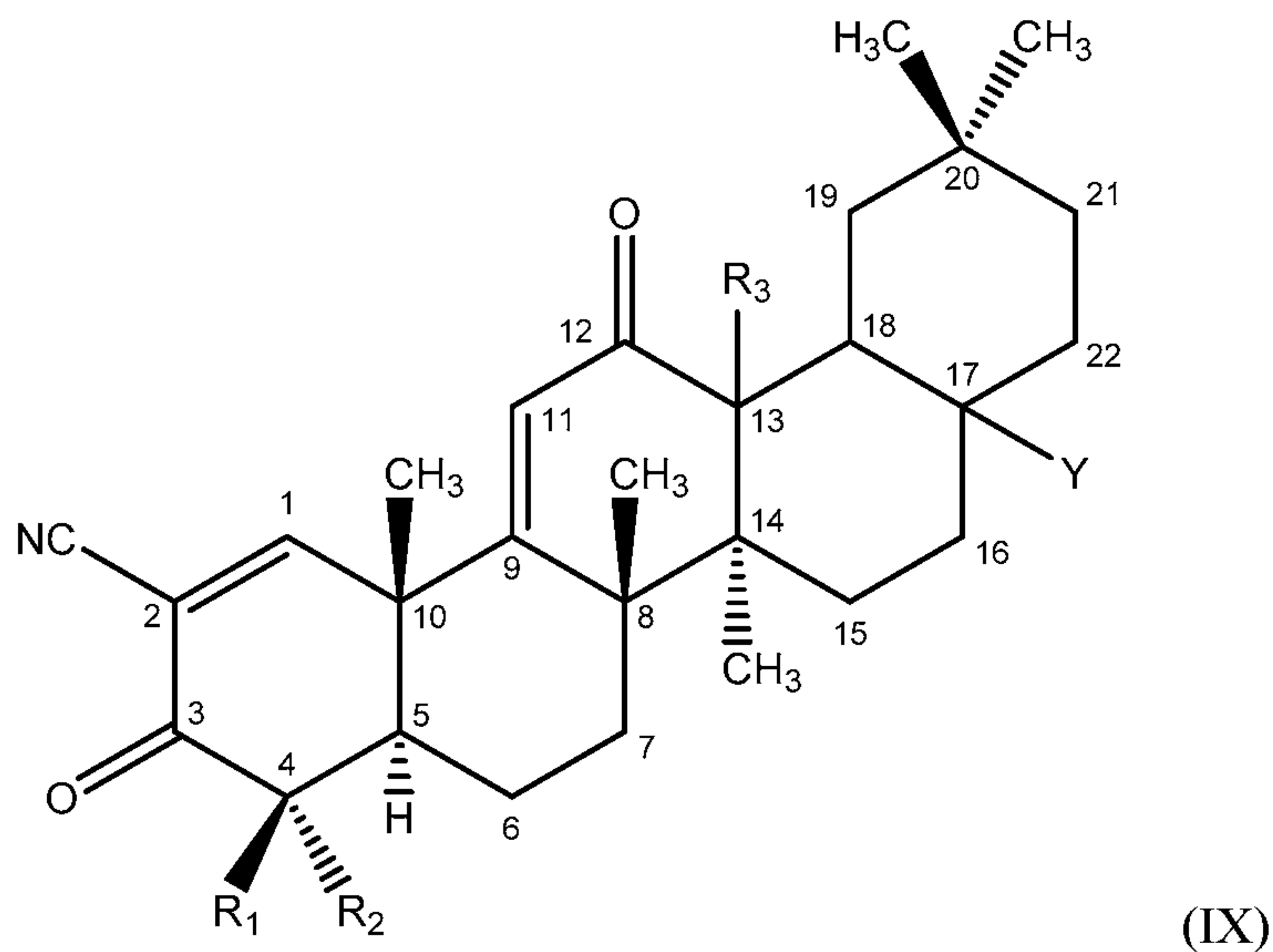
Y is -(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted
5 cycloalkyl_(C≤8);

R₂ is -OR_a, wherein:

R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12),
heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or a substituted version
of any of these groups;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either
10 of these groups; and

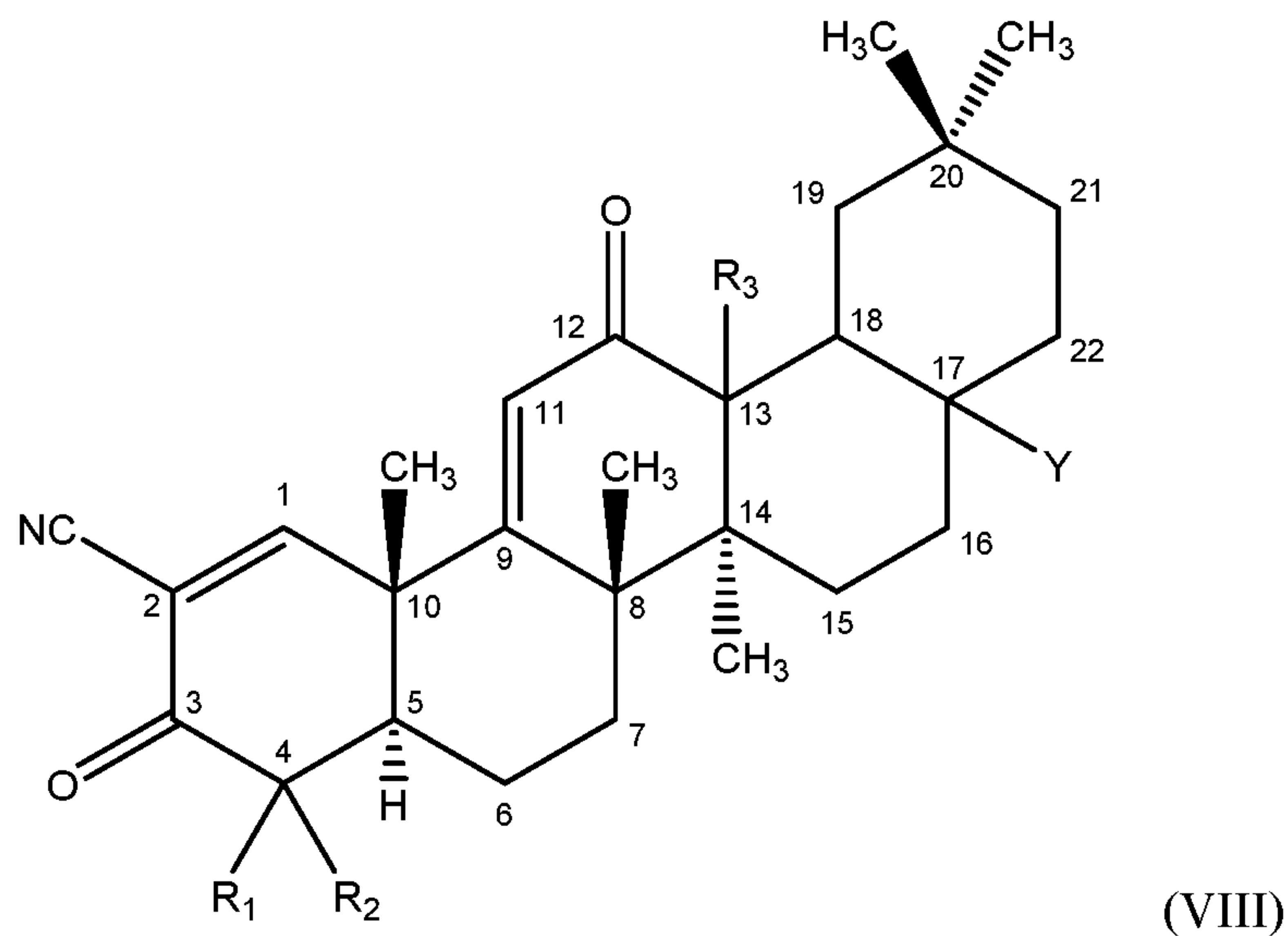
Y is -(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8),
15 heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these
groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R_1 is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R_2 is $-(CH_2)_sNR_{5'}(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

$R_{5'}$ is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), $-C(O)-$ alkoxy_(C≤8), substituted $-C(O)-$ alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R_6 is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_3 is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

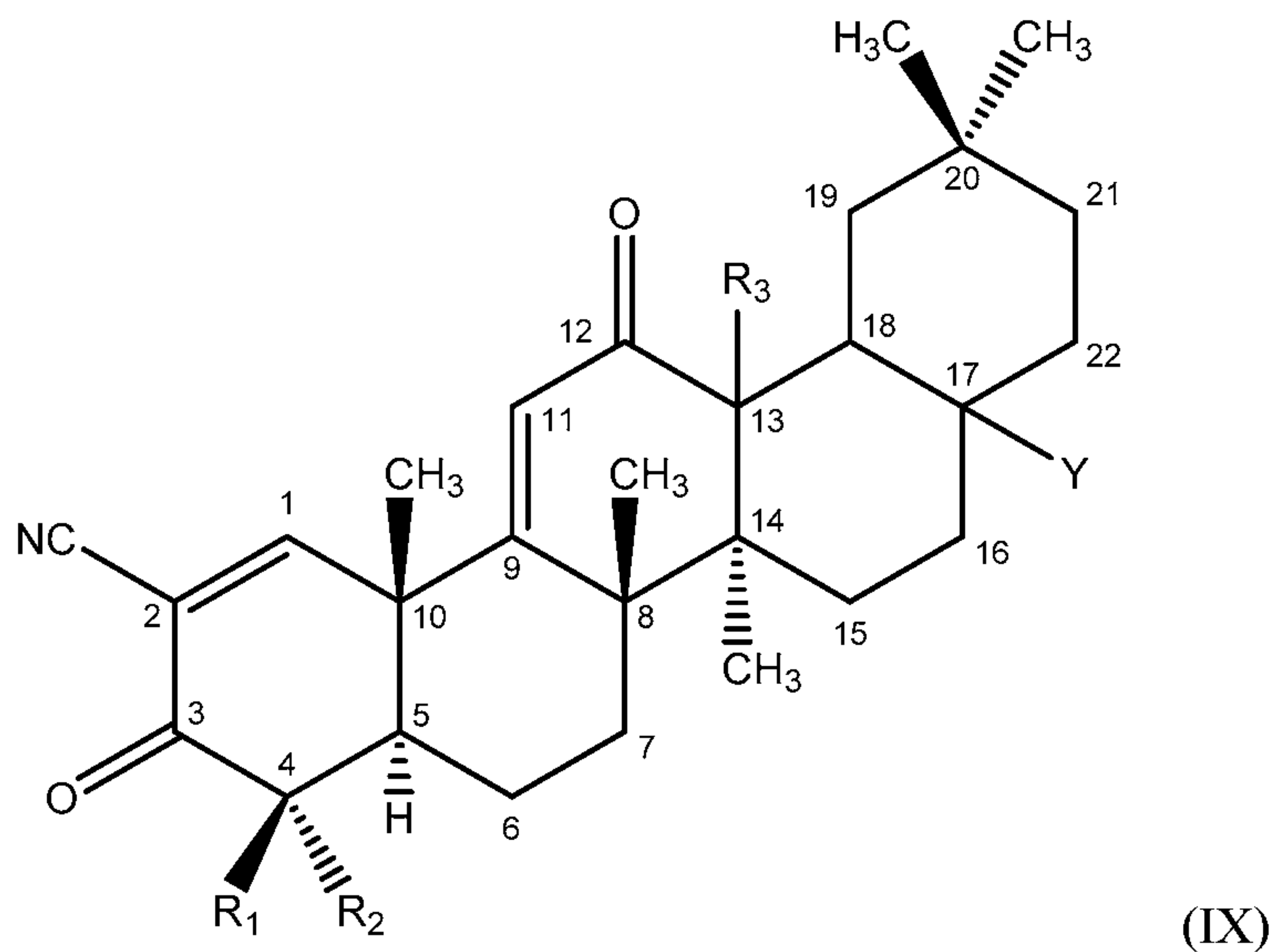
Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R_1 is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R_2 is $-(CH_2)_sNR_{5'}(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

$R_{5'}$ is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), $-C(O)-$ alkoxy_(C≤8), substituted $-C(O)-$ alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and

R_6 is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_3 is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

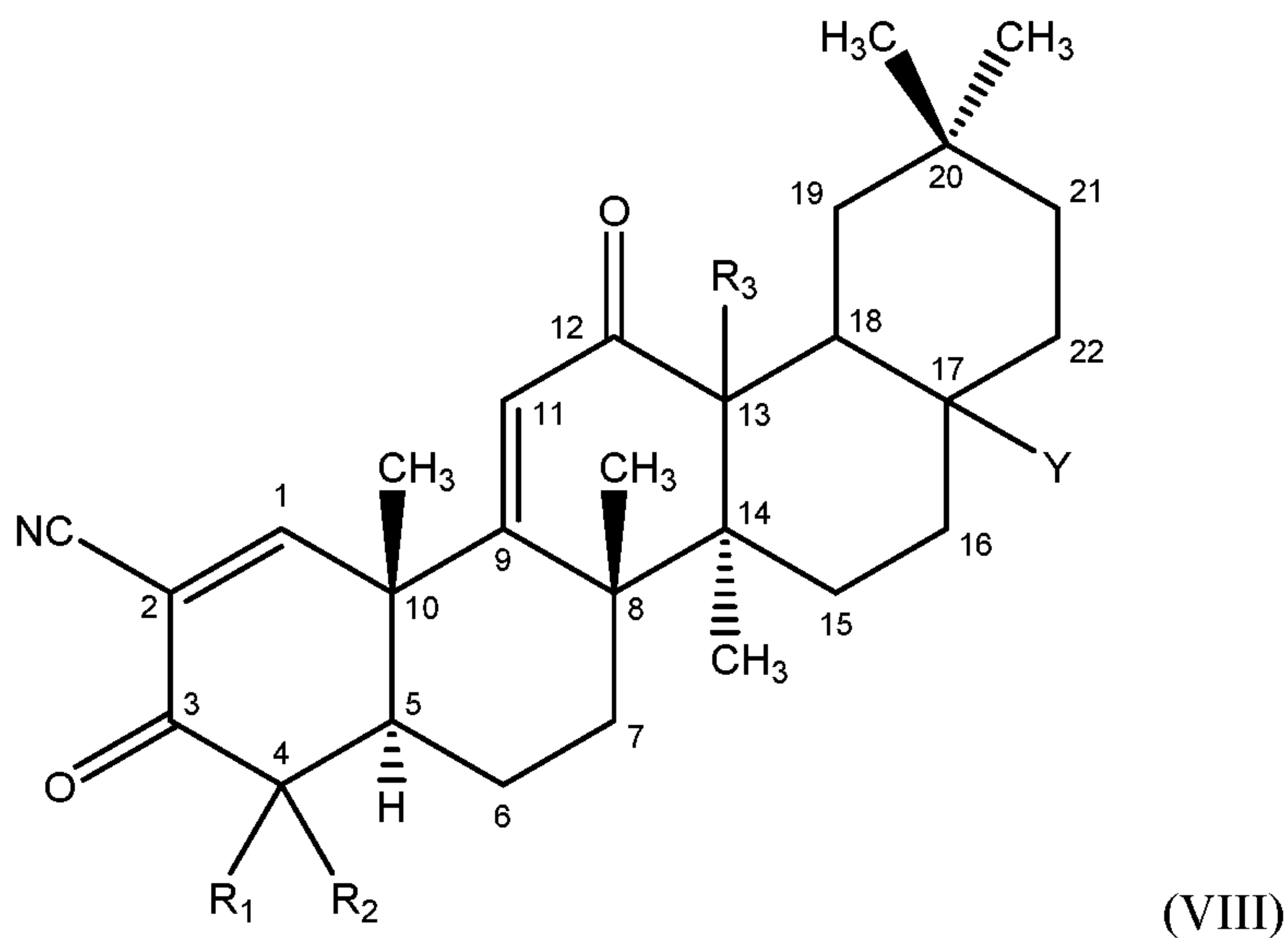
Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



wherein:

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₂ is $-(CH_2)_q-C(O)-R_{5''}$, wherein:

R_{5''} is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

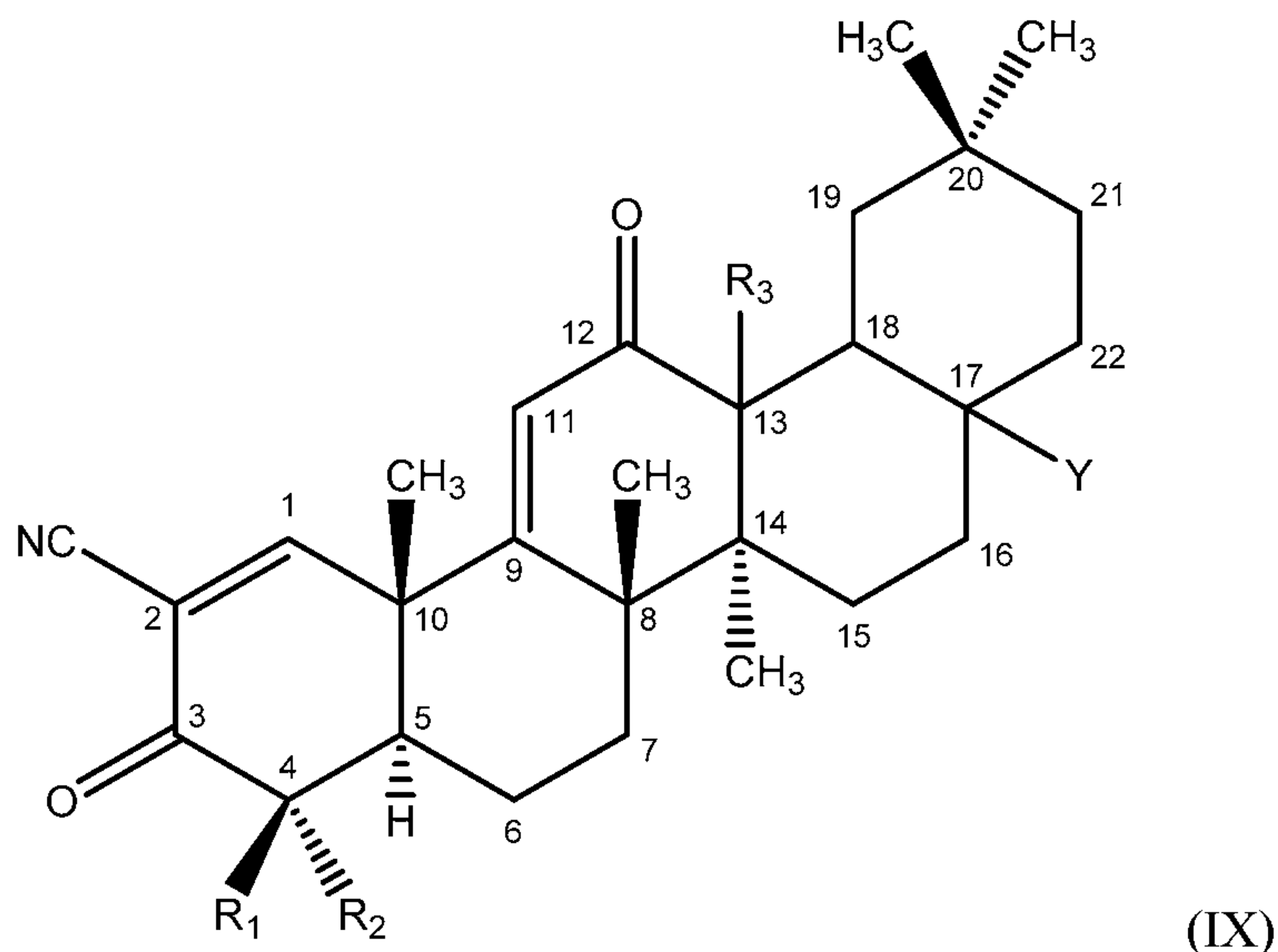
Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, the compounds are further defined as:



wherein:

R_1 is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R_2 is $-(CH_2)_q-C(O)-R_{5''}$, wherein:

$R_{5''}$ is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is:

hydroxy; or

alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In some embodiments, X is cyano. In some embodiments, the bond between atoms 1 and 2 are an epoxidized double bond. In other embodiments, the bond between atoms 1 and 2 are a double bond. In some embodiments, R_1 is hydrogen. In other embodiments, R_1 is alkyl_(C≤8) or substituted alkyl_(C≤8). In some embodiments, R_1 is alkyl_(C≤8), for example, R_1 is methyl.

In some embodiments, R_2 is amino. In other embodiments, R_2 is substituted alkyl_(C≤8), for example, R_2 is hydroxymethyl, difluoromethyl, acetoxymethyl, methoxyethyl, methoxymethyl, methyl carboxymethyl, 2-hydroxyethyl, or 1-hydroxyethyl. In some
 5 R_2 is haloalkyl_(C≤8), for example, R_2 is difluoromethyl. In other embodiments, R_2 is heteroaryl_(C≤8) or substituted heteroaryl_(C≤8), for example, R_2 is 2-methyloxadiazole. In other embodiments, R_2 is amido_(C≤8) or substituted amido_(C≤8), for example, R_2 is *N*-acetamide.

In other embodiments, R_2 is $-(CH_2)_m-(OCH_2)_n-R_5$, wherein: R_5 is hydroxy or acyl_(C≤8), alkoxy_(C≤8), acyloxy_(C≤8), alkylsilyloxy_(C≤8), or a substituted version of any of these
 10 groups; m is 0, 1, 2, 3, or 4; and n is 0, 1, 2, or 3. In some embodiments, R_5 is alkoxy_(C≤8) or substituted alkoxy_(C≤8), for example, R_5 is methoxy. In other embodiments, R_5 is acyloxy_(C≤8) or substituted acyloxy_(C≤8), for example, R_5 is $-OC(O)C_6H_5$. In other embodiments, R_5 is alkylsilyloxy_(C≤8) or substituted alkylsilyloxy_(C≤8), for example, R_5 is *t*-butyldimethylsiloxy. In some
 15 embodiments, m is 1 or 2. In some embodiments, m is 1. In other embodiments, m is 2. In some embodiments, n is 0 or 1. In some embodiments, n is 0. In other embodiments, n is 1.

In other embodiments, R_2 is $-(CH_2)_m-R_5'''$, wherein: R_5''' is alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and m is 0, 1, 2, 3, or 4. In other embodiments, R_2 is $-(CH_2)_{m_2}-R_5'''$, wherein: R_5''' is hydroxy; and m_2 is 2, 3, or 4. In some embodiments, R_5''' is alkoxy_(C≤8) or substituted alkoxy_(C≤8), for example, R_5''' is
 20 methoxy. In other embodiments, R_5''' is acyloxy_(C≤8) or substituted acyloxy_(C≤8), for example, R_5''' is $-OC(O)C_6H_5$. In other embodiments, R_5''' is alkylsilyloxy_(C≤8) or substituted alkylsilyloxy_(C≤8), for example, R_5''' is *t*-butyldimethylsiloxy. In some embodiments, m is 1 or 2. In some embodiments, m is 1. In other embodiments, m is 2. In some embodiments, m_2 is 2 or 3.

In other embodiments, R_2 is $-(CH_2)_sNR_5'(R_6)$, wherein: s is 0, 1, 2, 3, or 4; R_5' is
 25 hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), $-C(O)-$ alkoxy_(C≤8), substituted $-C(O)-$ alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8); and R_6 is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8). In some embodiments, s is 0 or 1. In some embodiments, s is 0. In other embodiments, s is 1. In some embodiments, R_5' is hydrogen. In other embodiments,
 30 R_5' is acyl_(C≤8), for example, R_5' is acetyl. In other embodiments, R_5' is $-C(O)-$ alkoxy_(C≤8), for example, R_5' is *tert*-butyloxycarbonyl. In some embodiments, R_6 is hydrogen.

In other embodiments, R_2 is $-(CH_2)_q-C(O)-R_5''$, wherein: R_5'' is amino, hydroxy, or mercapto; or alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups; and q is 0, 1, 2, 3, or 4. In some embodiments, R_5'' is amino.

In other embodiments, R_5'' is alkylamino $_{(C\leq 8)}$, for example, R_5'' is methylamino. In other embodiments, R_5'' is dialkylamino $_{(C\leq 8)}$, for example, R_5'' is dimethylamino. In other embodiments, R_5'' is hydroxy. In other embodiments, R_5'' is alkoxy $_{(C\leq 8)}$, for example, R_5'' is methoxy. In some embodiments, q is 0.

5 In other embodiments, R_2 is $-OR_a$, wherein: R_a is hydrogen or alkyl $_{(C\leq 8)}$, acyl $_{(C\leq 8)}$, or a substituted version of either of these groups. In some embodiments, R_a is hydrogen. In other embodiments, R_a is alkyl $_{(C\leq 8)}$ or substituted alkyl $_{(C\leq 8)}$. In other embodiments, R_a is acyl $_{(C\leq 8)}$ or substituted acyl $_{(C\leq 8)}$.

10 In some embodiments, Y is heteroaryl $_{(C\leq 8)}$ or substituted heteroaryl $_{(C\leq 8)}$, for example, Y is 3-methyl-1,2,4-oxadiazole or 2-methyl-1,3,4-oxadiazole. In other embodiments, Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is: hydrogen, halo, amino, $-NHOH$, or mercapto; or alkyl $_{(C\leq 8)}$, alkenyl $_{(C\leq 8)}$, alkynyl $_{(C\leq 8)}$, aryl $_{(C\leq 8)}$, aralkyl $_{(C\leq 8)}$, heteroaryl $_{(C\leq 8)}$, heterocycloalkyl $_{(C\leq 8)}$, alkylamino $_{(C\leq 8)}$, dialkylamino $_{(C\leq 8)}$, arylamino $_{(C\leq 8)}$, alkylsulfonylamino $_{(C\leq 8)}$, amido $_{(C\leq 8)}$, alkoxyamino $_{(C\leq 8)}$, heterocycloalkylamino $_{(C\leq 8)}$, $-NHC(NOH)-alkyl_{(C\leq 8)}$, $-NH-amido_{(C\leq 8)}$, or a substituted version of any of these groups. In some embodiments, o is 0, 1, or 2. In some
15 embodiments, o is 0. In some embodiments, R_c is alkylamino $_{(C\leq 8)}$ or substituted alkylamino $_{(C\leq 8)}$. In some embodiments, R_c is alkylamino $_{(C\leq 8)}$, for example, R_c is ethylamino. In other embodiments, R_c is substituted alkylamino $_{(C\leq 8)}$, for example, R_c is 2,2,2-trifluoroethylamino. In some embodiments, R_c is dialkylamino $_{(C\leq 8)}$ or substituted
20 dialkylamino $_{(C\leq 8)}$. In some embodiments, R_c is dialkylamino $_{(C\leq 8)}$, for example, R_c is dimethylamino.

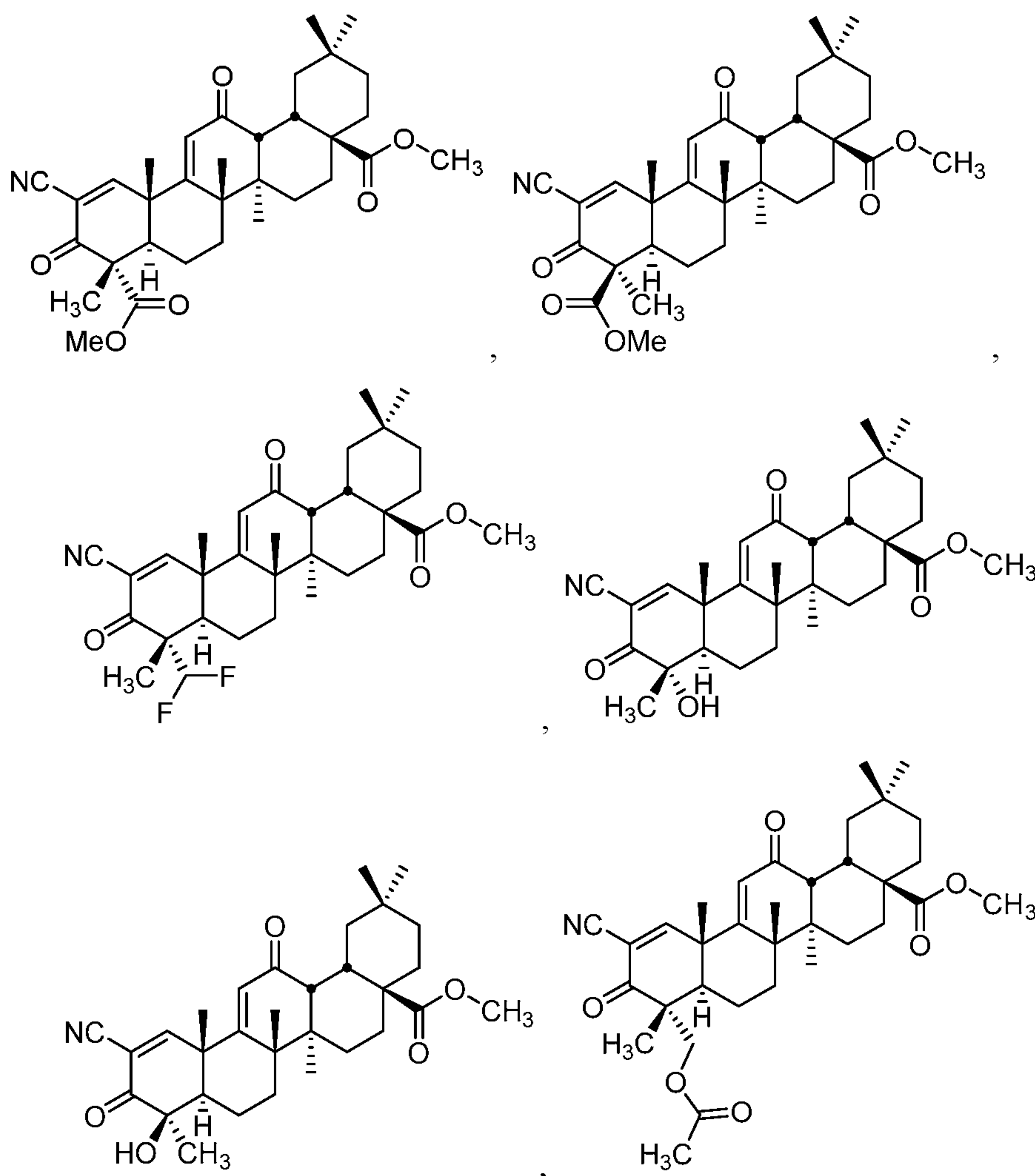
In other embodiments, Y is $-(CH_2)_oC(O)R_c$, wherein o is 0–6 and R_c is: hydroxy; or alkoxy $_{(C\leq 8)}$, alkenyloxy $_{(C\leq 8)}$, aryloxy $_{(C\leq 8)}$, aralkoxy $_{(C\leq 8)}$, heteroaryloxy $_{(C\leq 8)}$, acyloxy $_{(C\leq 8)}$, or a substituted version of any of these groups. In some embodiments, o is 0, 1, or 2. In some
25 embodiments, o is 0. In some embodiments, R_c is alkoxy $_{(C\leq 8)}$ or substituted alkoxy $_{(C\leq 8)}$. In some embodiments, R_c is alkoxy $_{(C\leq 8)}$, for example, R_c is methoxy.

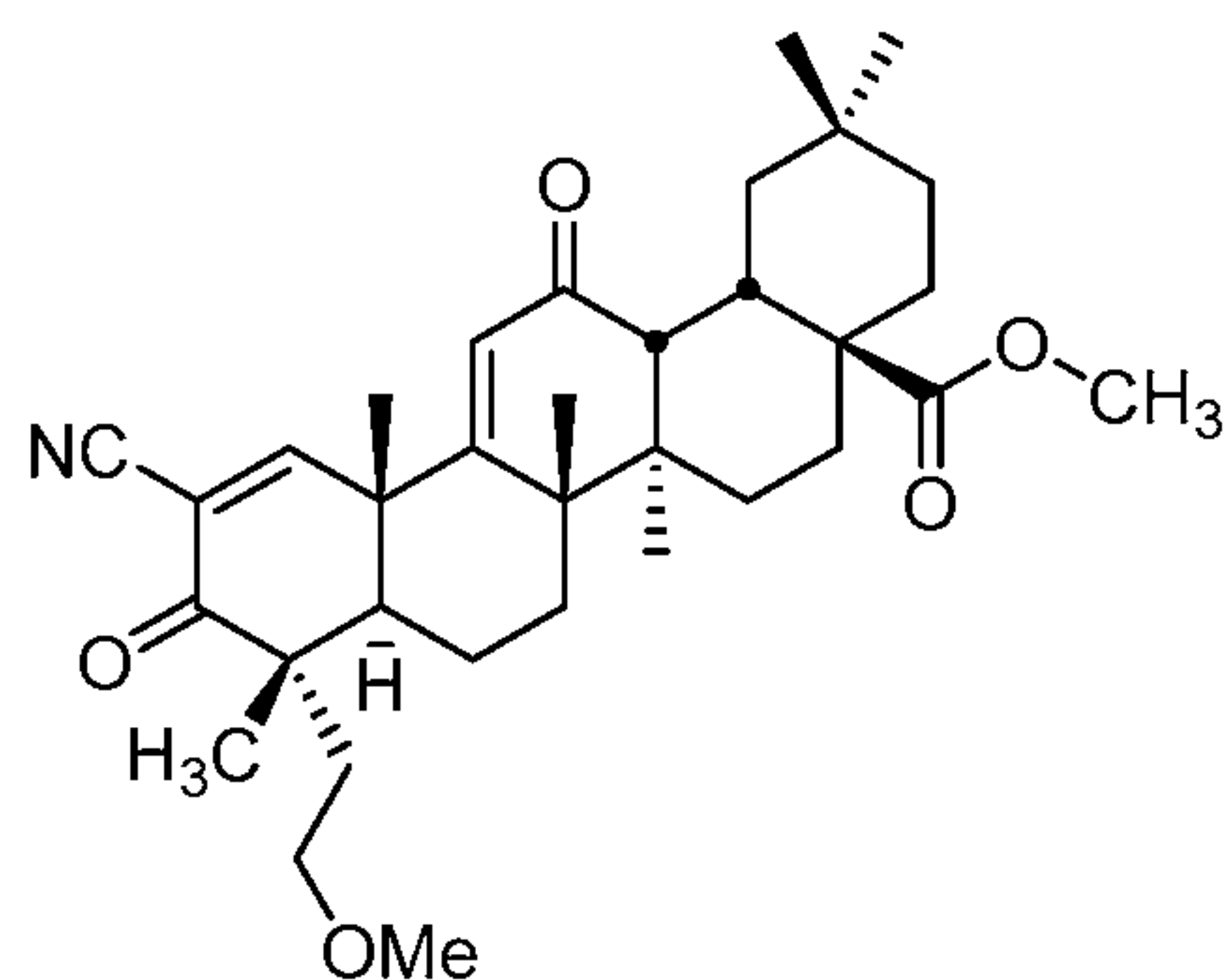
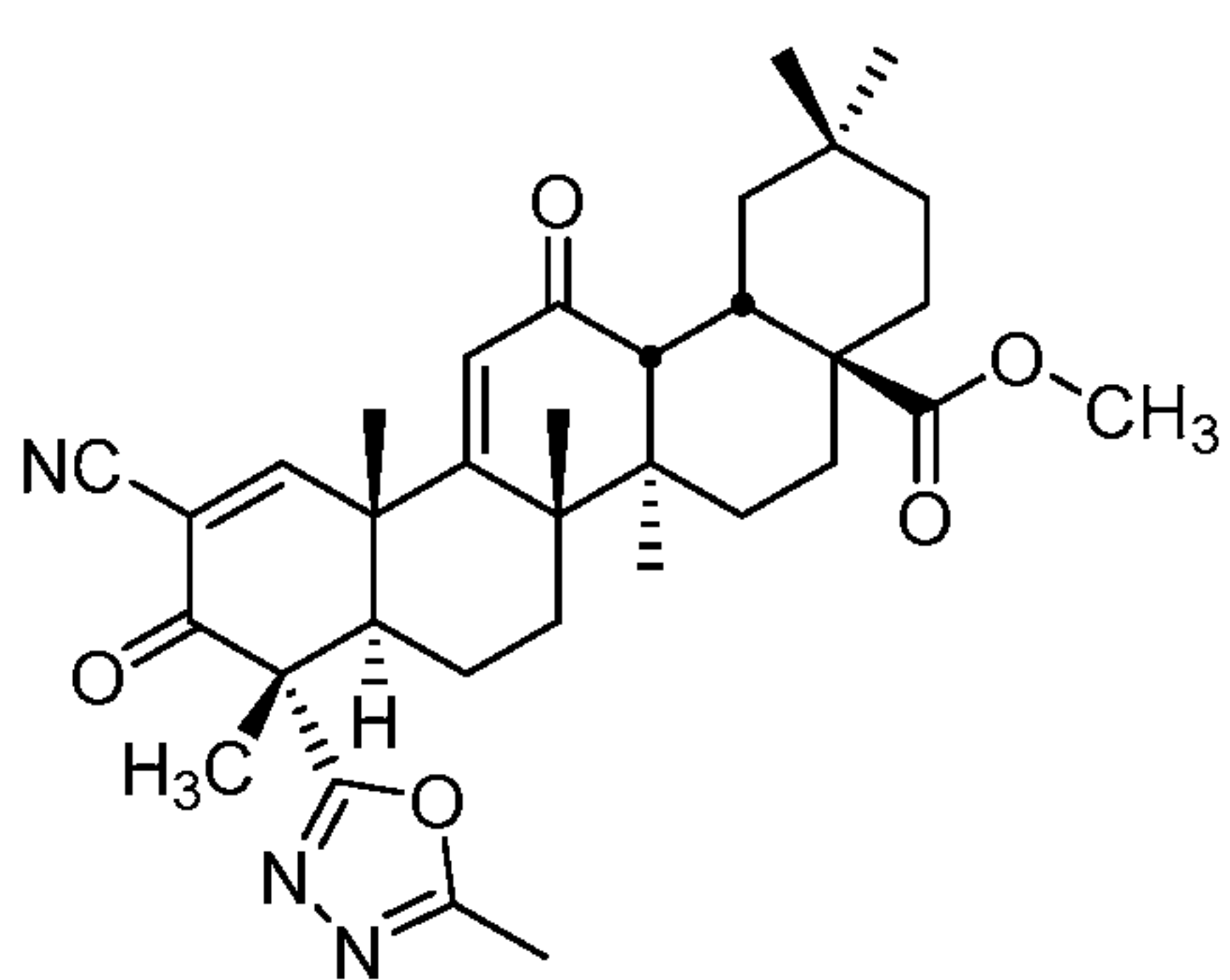
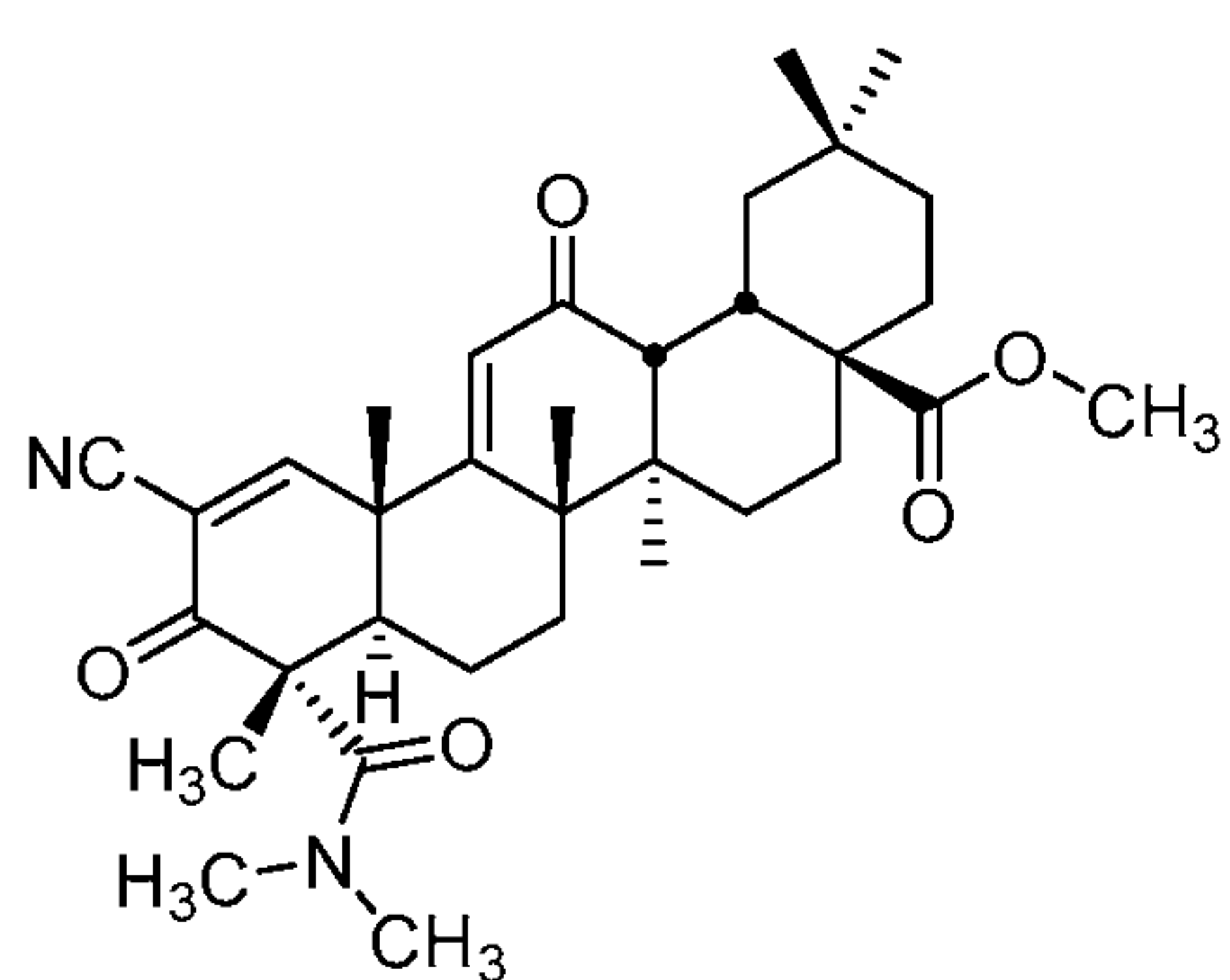
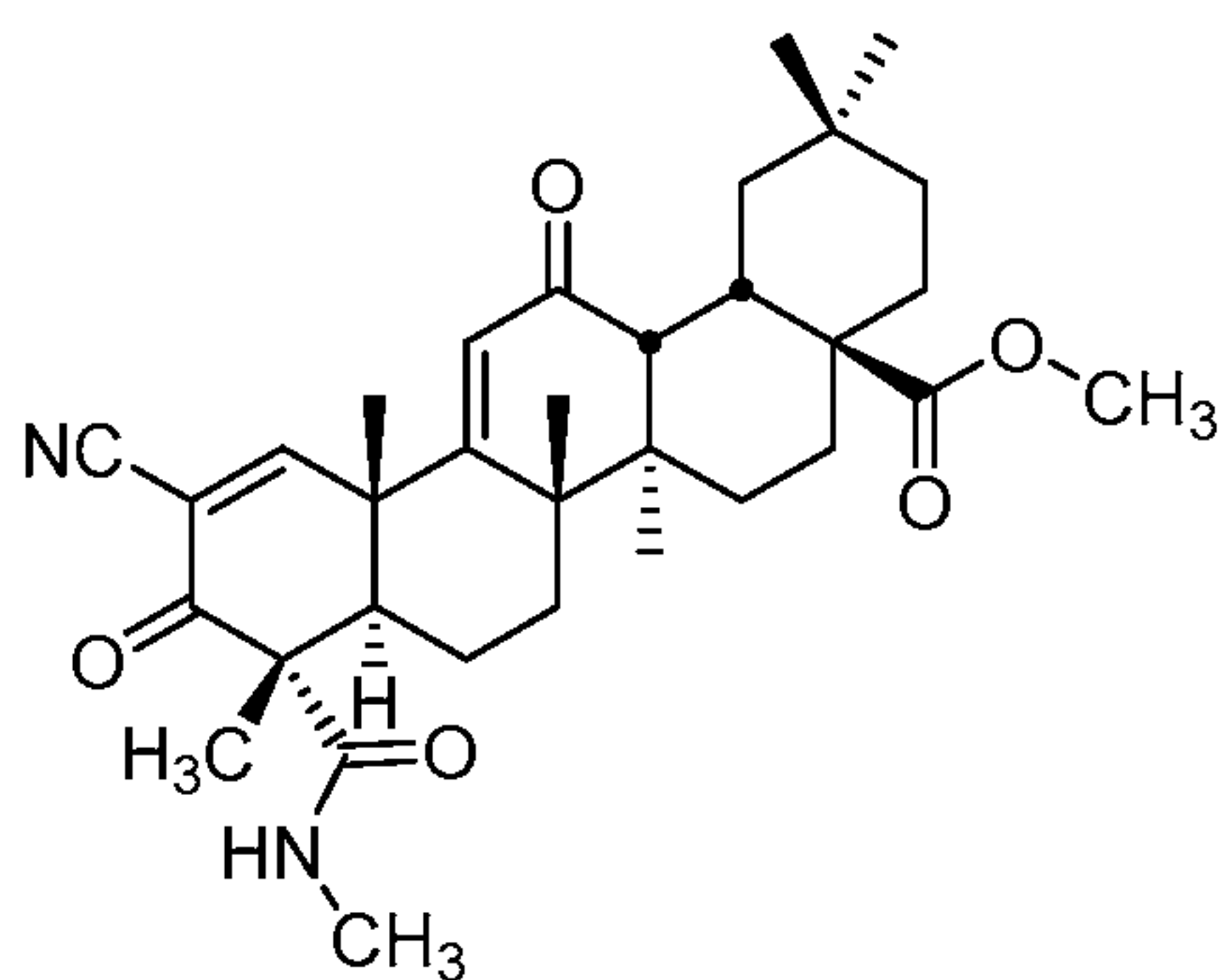
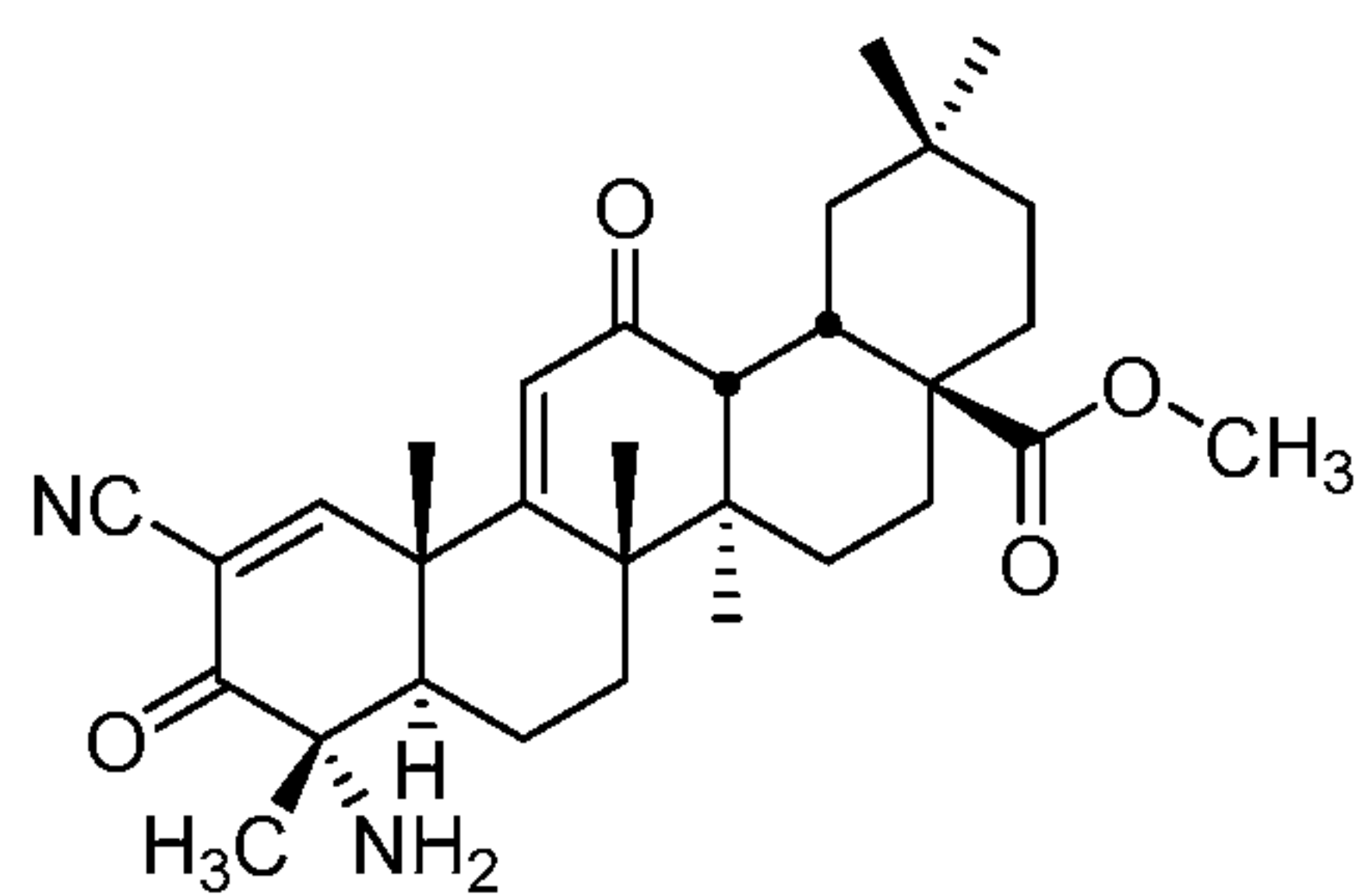
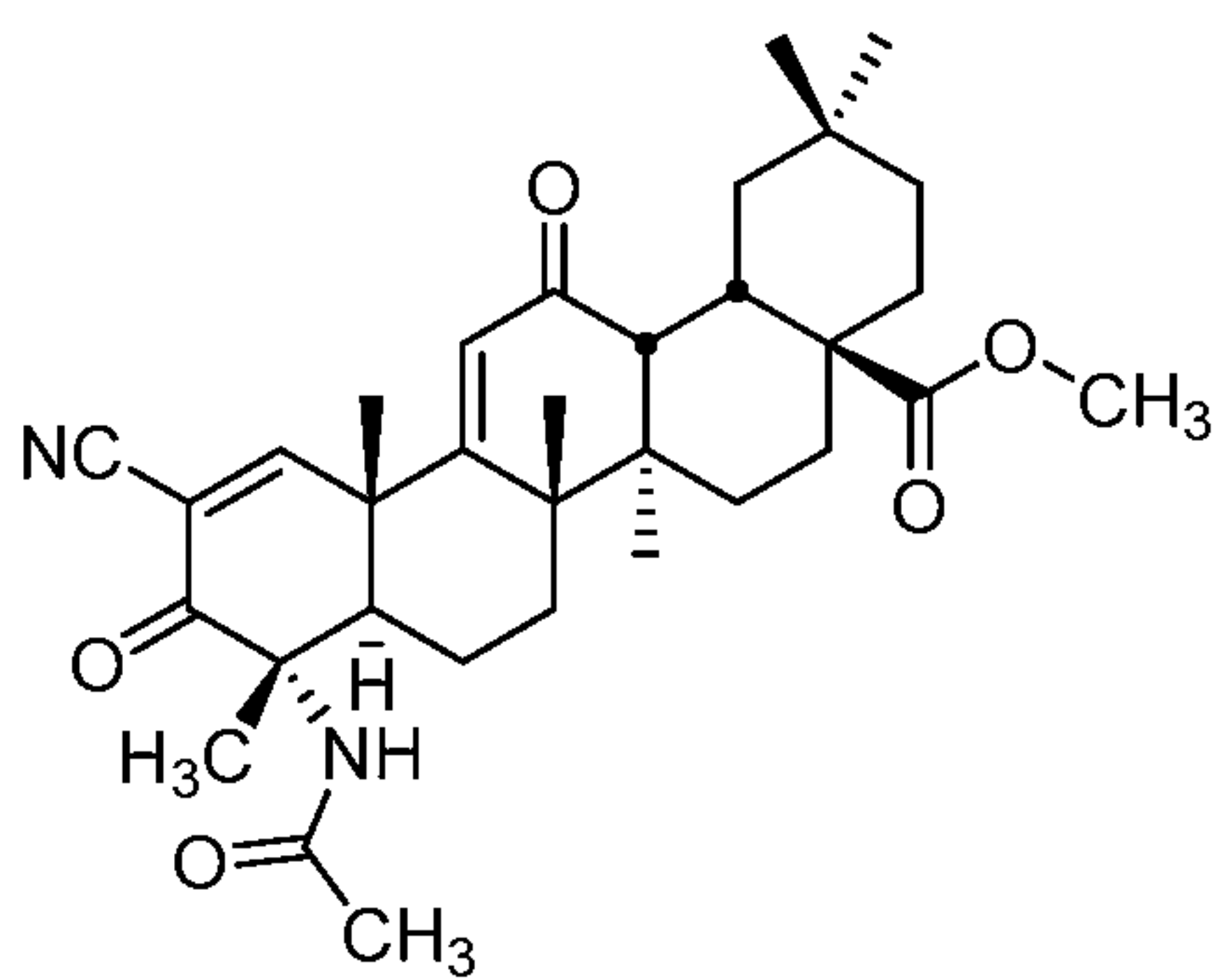
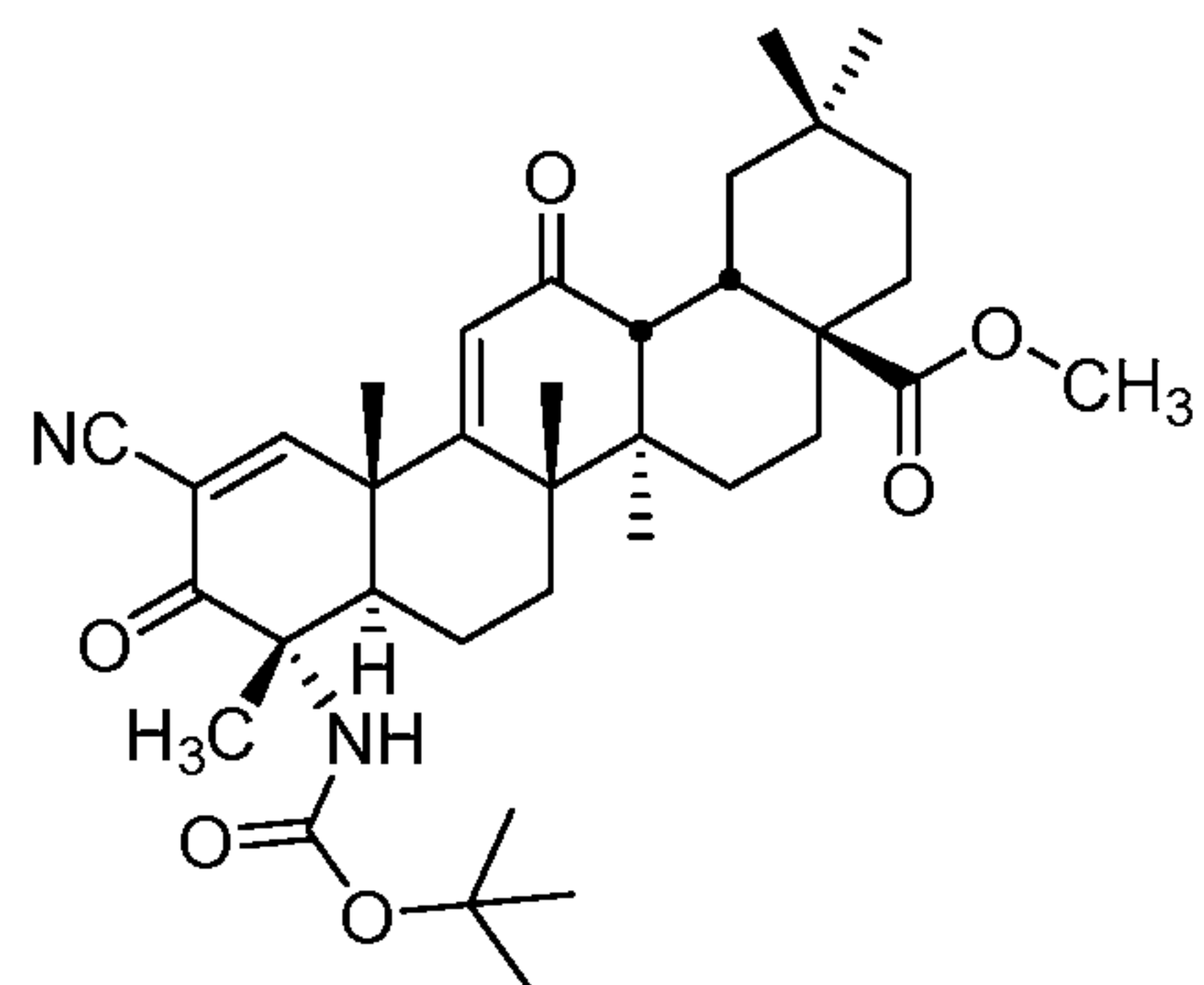
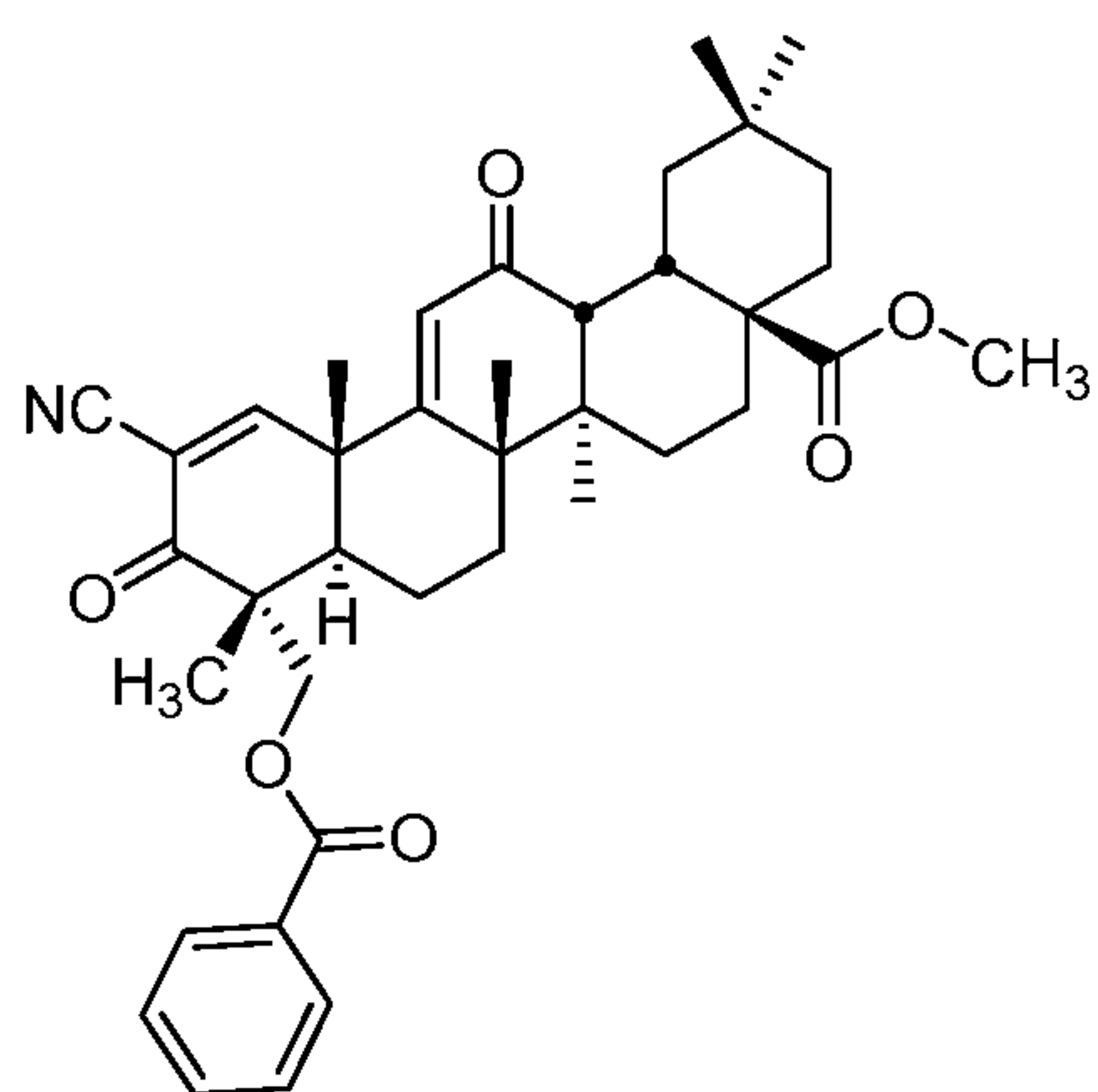
In other embodiments, Y is $-NR_dC(O)R_e$, wherein R_d is hydrogen, alkyl $_{(C\leq 8)}$, or substituted alkyl $_{(C\leq 8)}$; R_e is hydrogen, hydroxy, amino; or alkyl $_{(C\leq 8)}$, alkenyl $_{(C\leq 8)}$, alkynyl $_{(C\leq 8)}$, aryl $_{(C\leq 8)}$, aralkyl $_{(C\leq 8)}$, heteroaryl $_{(C\leq 8)}$, heterocycloalkyl $_{(C\leq 8)}$, alkoxy $_{(C\leq 8)}$, aryloxy $_{(C\leq 8)}$,
30 aralkoxy $_{(C\leq 8)}$, heteroaryloxy $_{(C\leq 8)}$, acyloxy $_{(C\leq 8)}$, alkylamino $_{(C\leq 8)}$, dialkylamino $_{(C\leq 8)}$, arylamino $_{(C\leq 8)}$, or a substituted version of any of these groups. In some embodiments, R_d is hydrogen. In some embodiments, R_e is alkyl $_{(C\leq 8)}$ or substituted alkyl $_{(C\leq 8)}$. In some embodiments, R_e is substituted alkyl $_{(C\leq 8)}$, for example, R_e is 1,1-difluoroethyl. In some

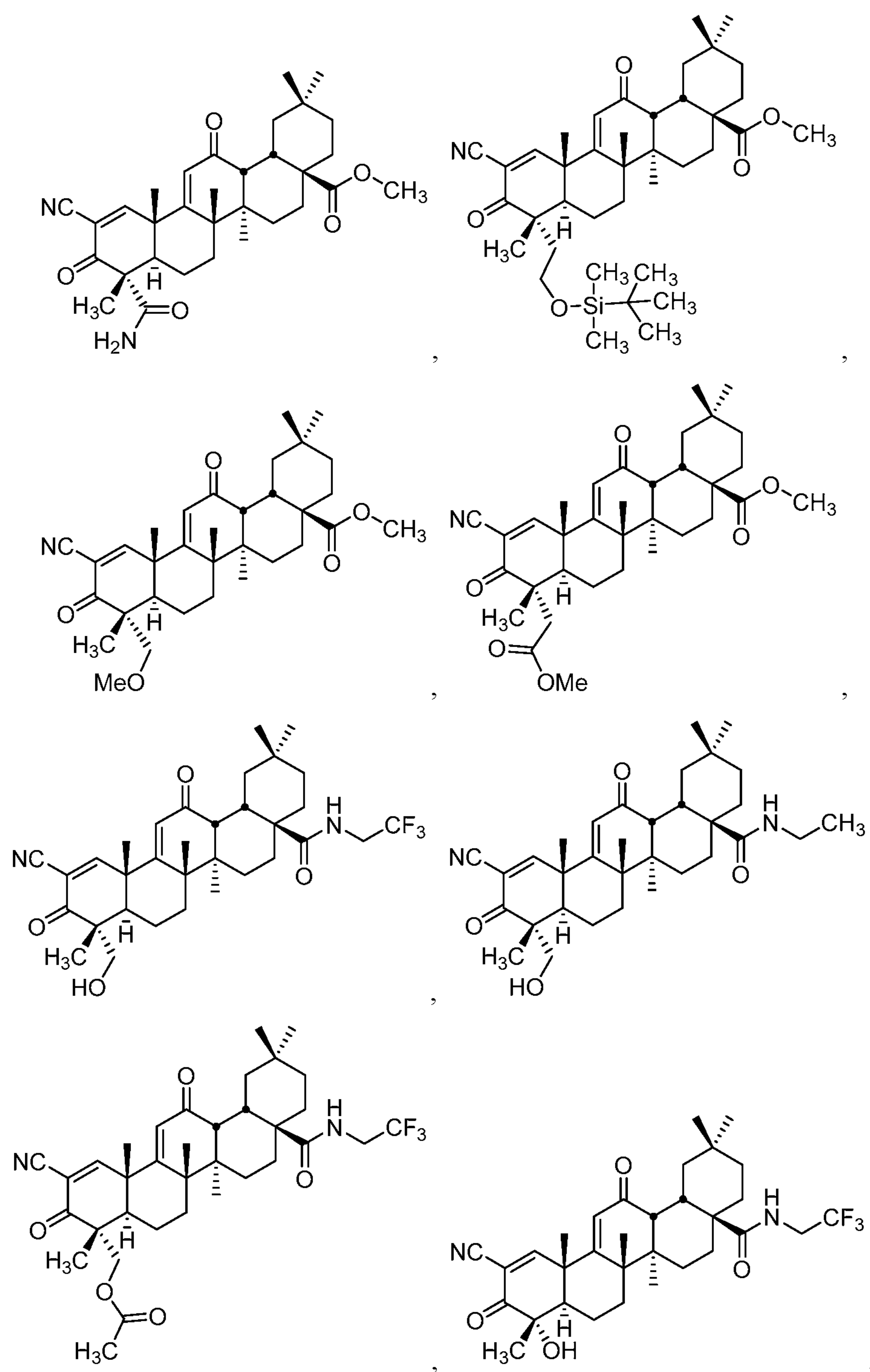
embodiments, R_e is alkoxy($C_{\leq 8}$) or substituted alkoxy($C_{\leq 8}$). In some embodiments, R_e is alkoxy($C_{\leq 8}$), for example, R_e is methoxy.

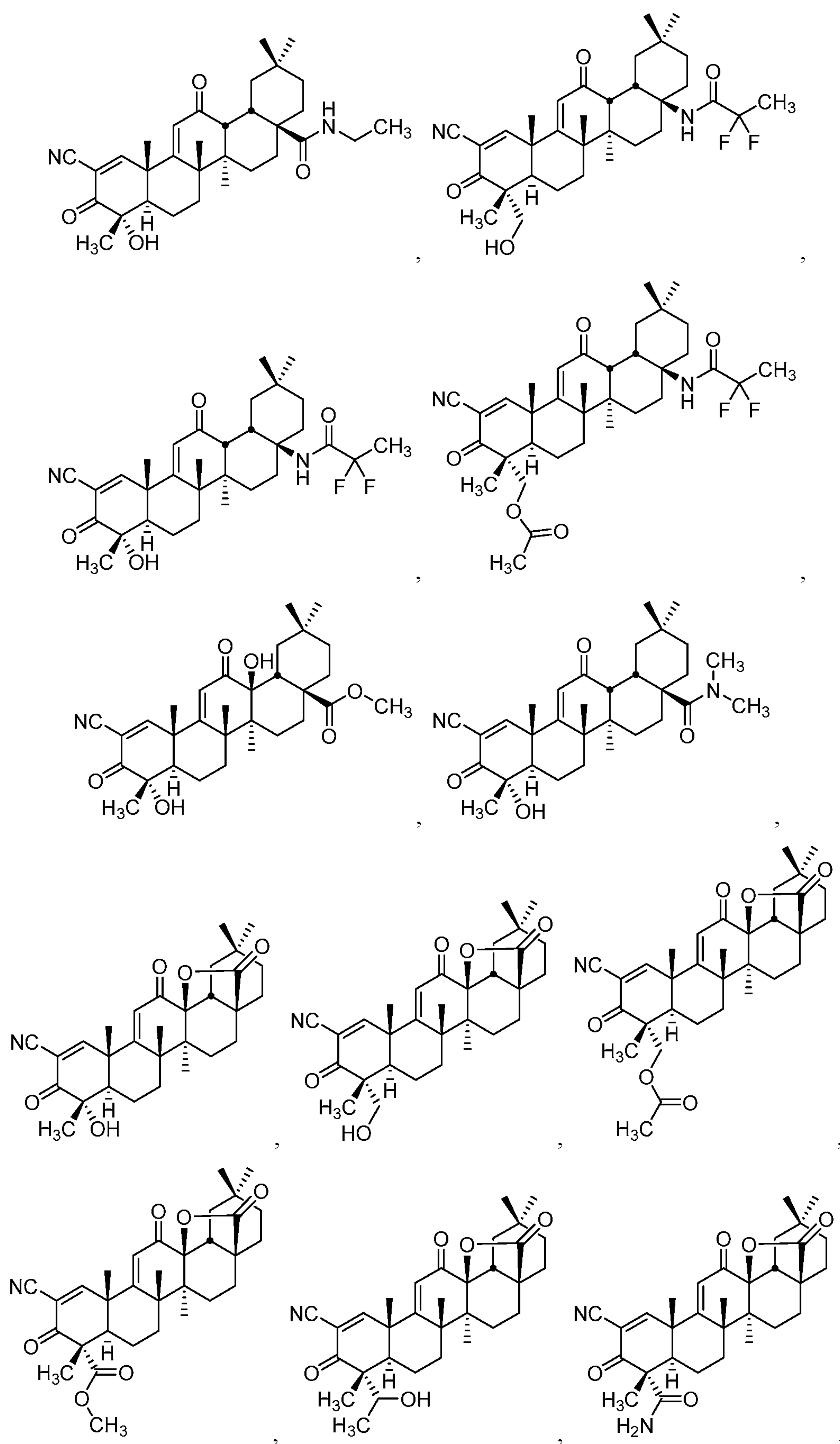
In other embodiments, Y is taken together with R_3 and is $-(CH_2)_pC(O)R_f-$, wherein p is 0–6; and R_f is $-O-$ or $-NR_7-$; wherein: R_7 is hydrogen, alkyl($C_{\leq 8}$), substituted alkyl($C_{\leq 8}$), acyl($C_{\leq 8}$), or substituted acyl($C_{\leq 8}$). In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, R_f is $-O-$. In some embodiments, R_3 is hydrogen. In other embodiments, R_3 is hydroxy.

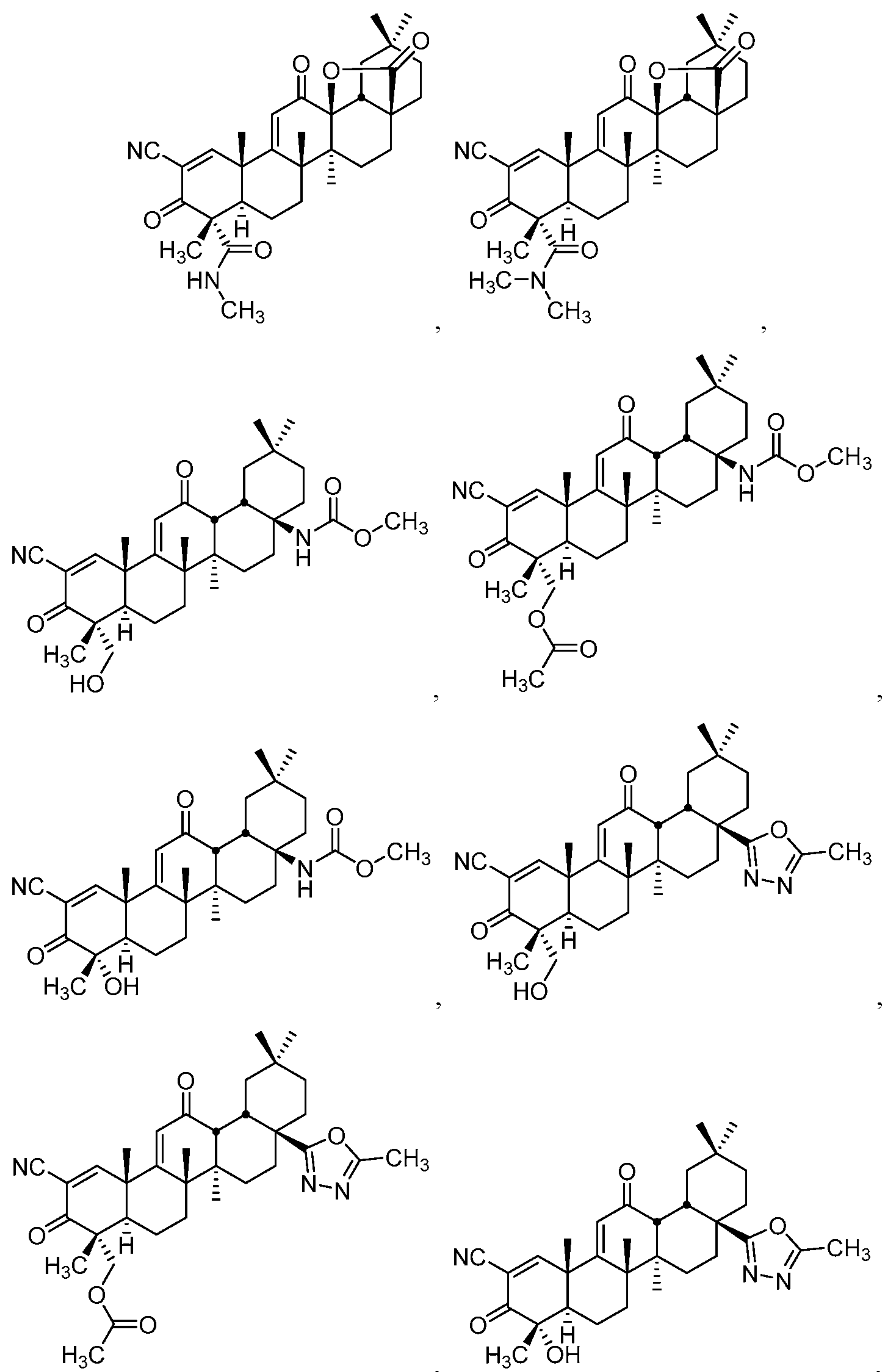
In some embodiments, the carbon atom 4 is in the α orientation. In other embodiments, the carbon atom 4 is in the β orientation. In some embodiments, the carbon atom 4 is in the S configuration. In other embodiments, the carbon atom 4 is in the R configuration. In some embodiments, the compounds are further defined as:



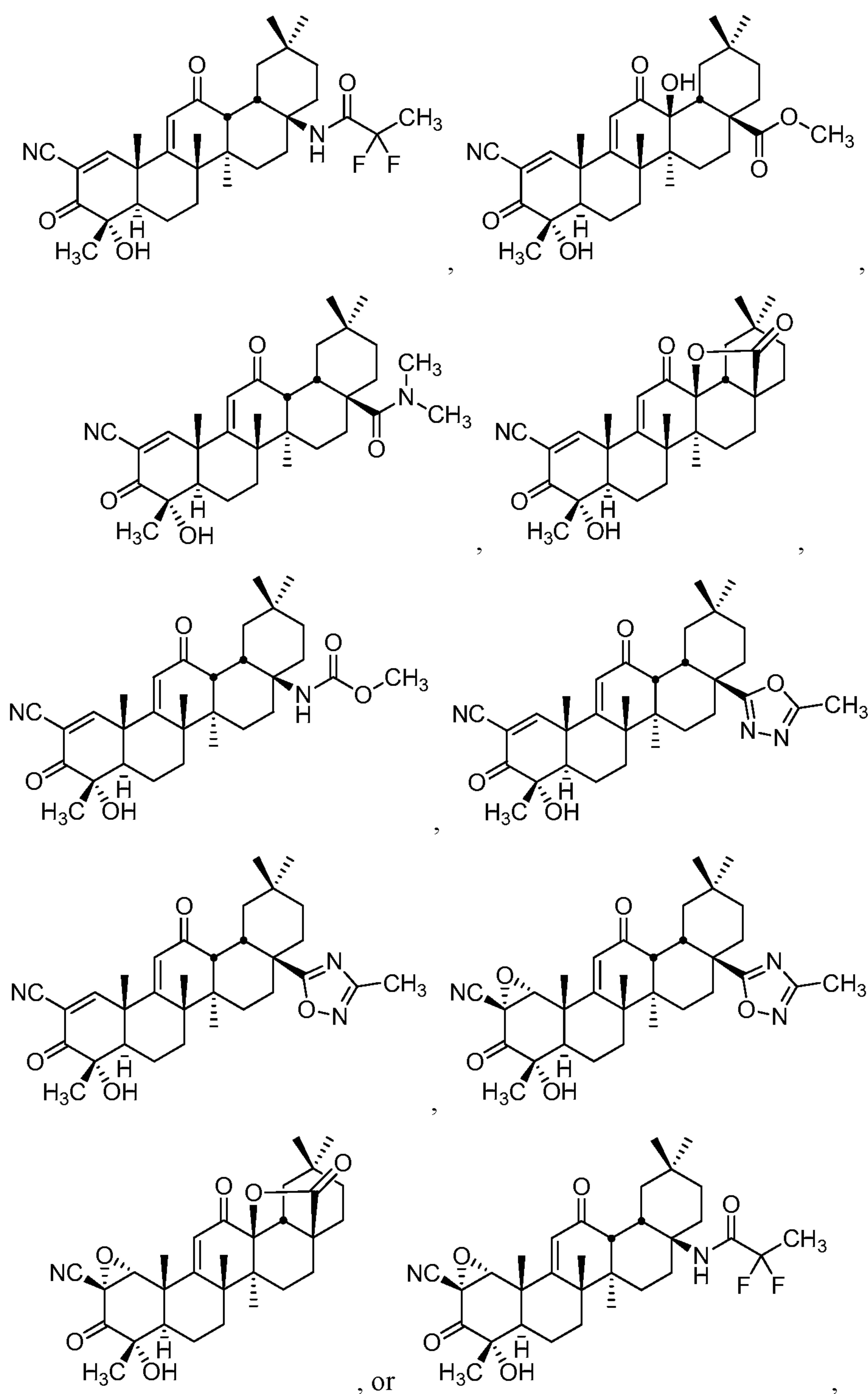






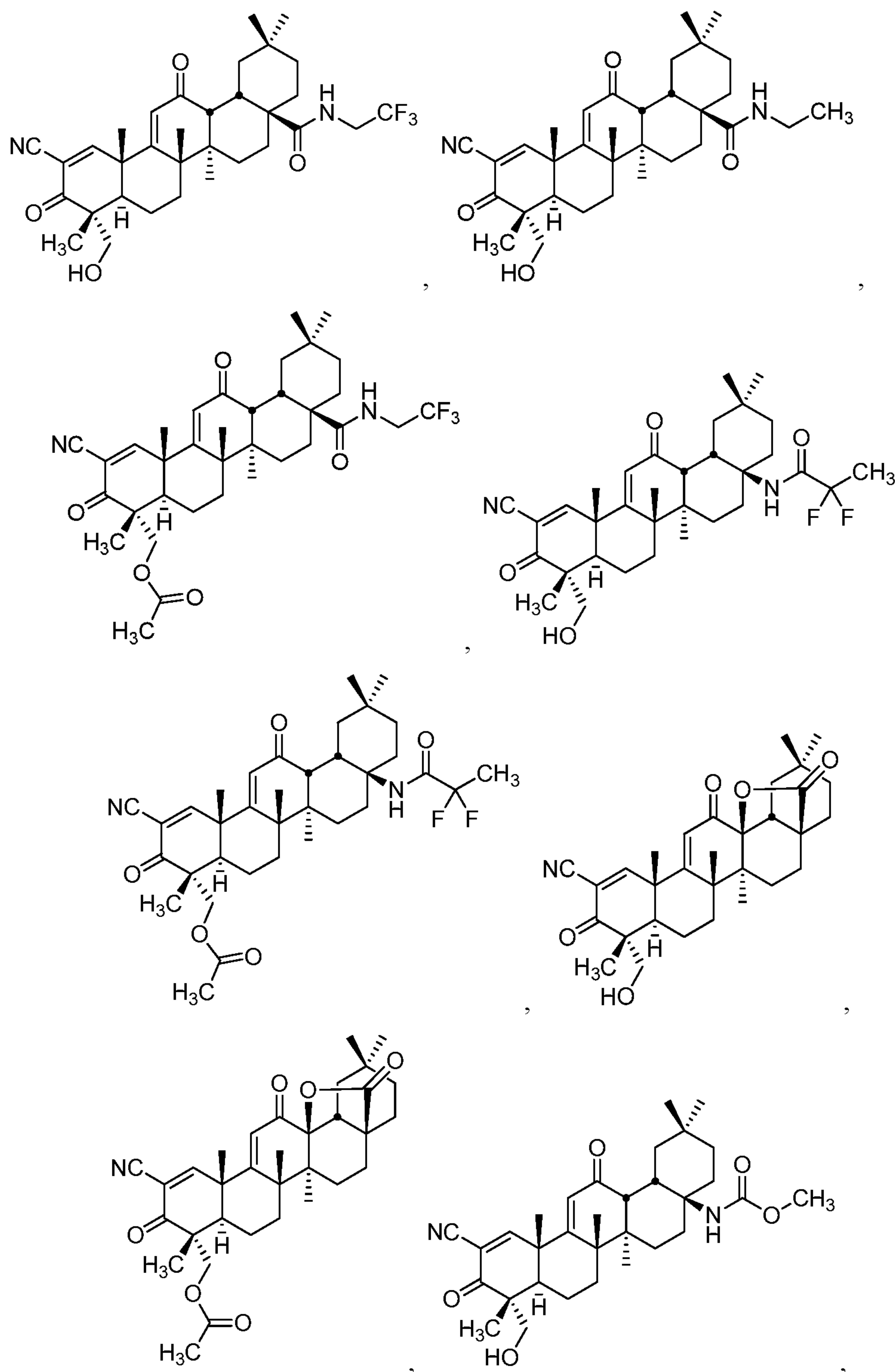


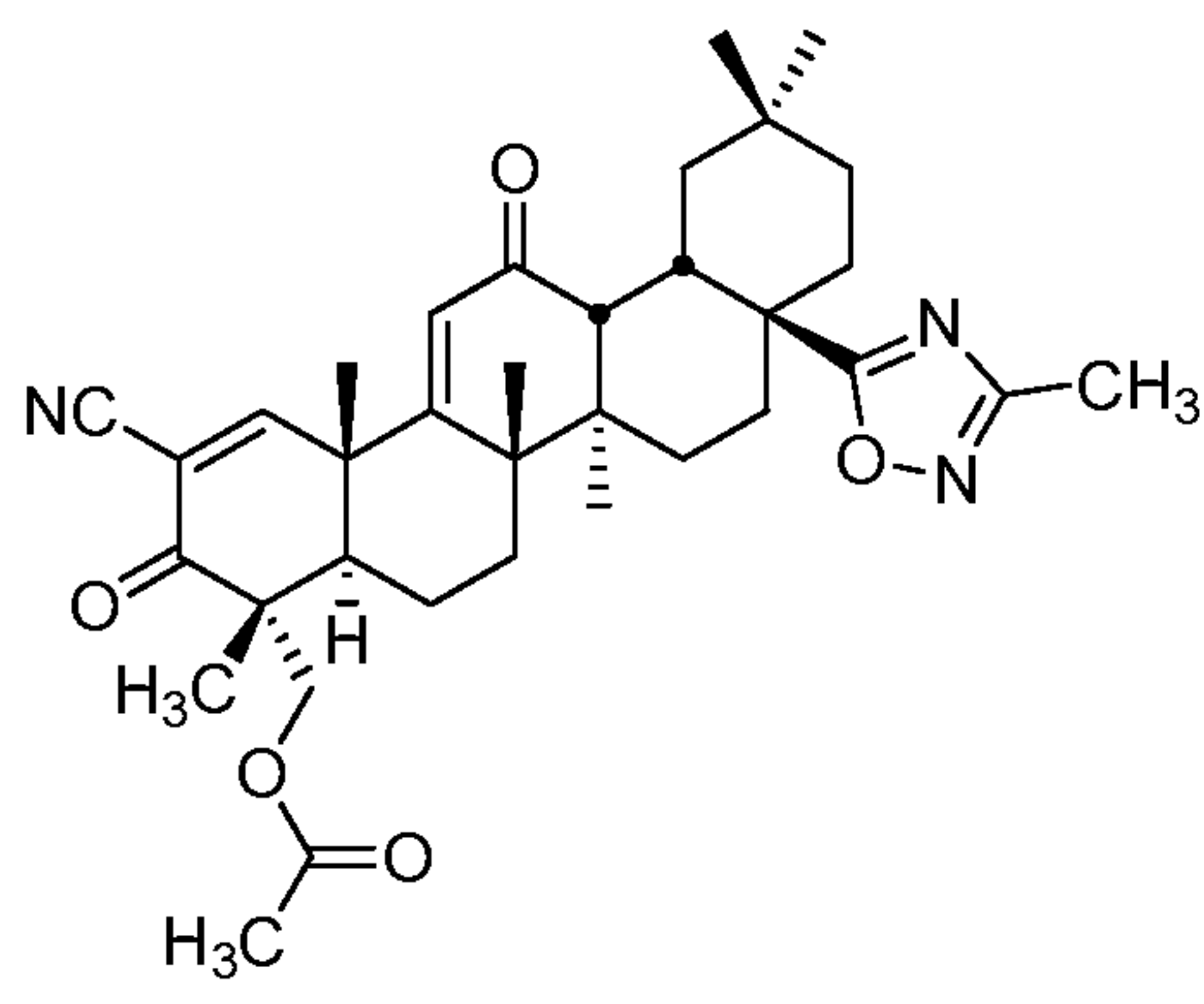
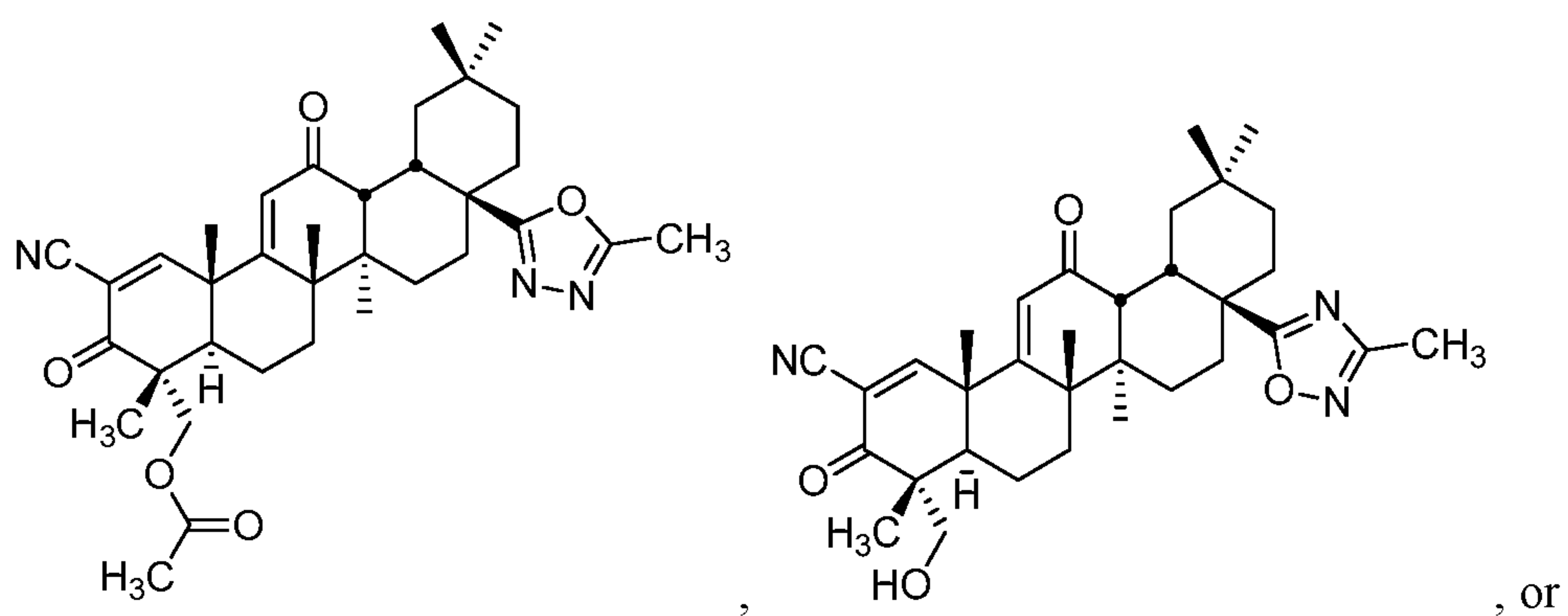
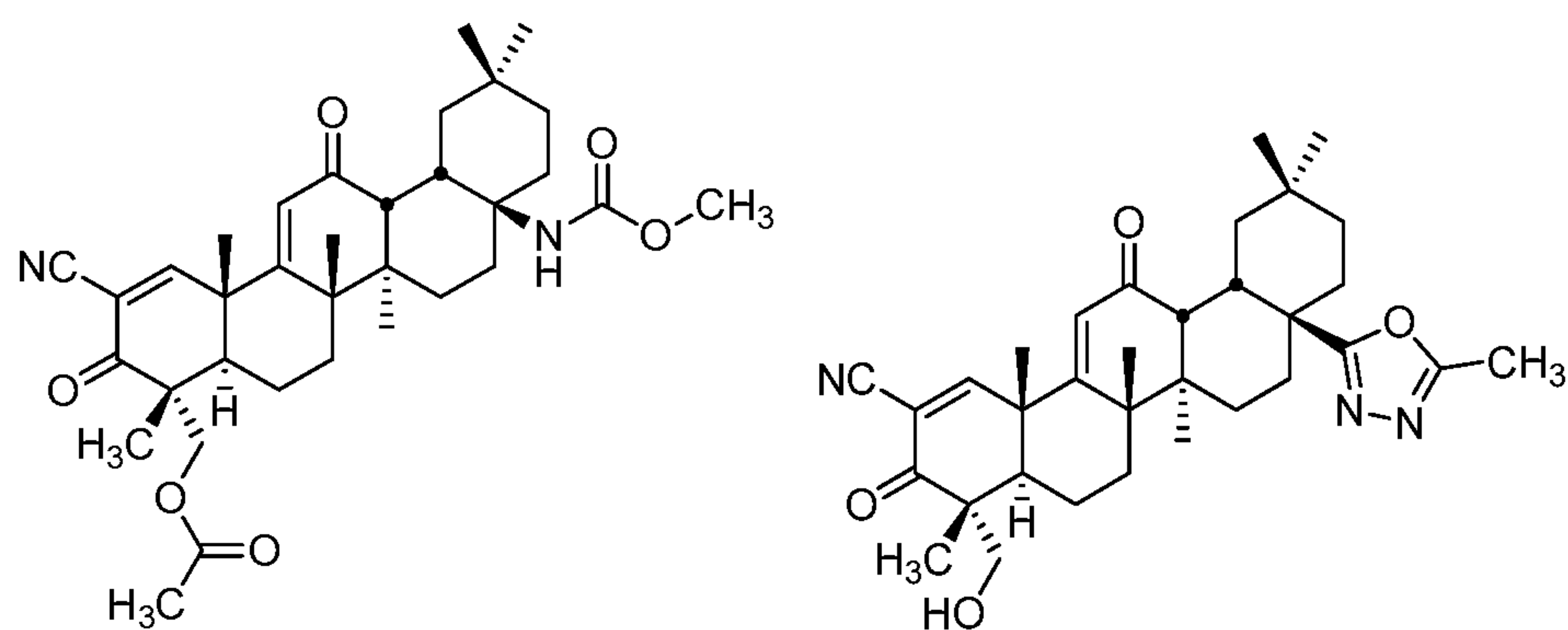




or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

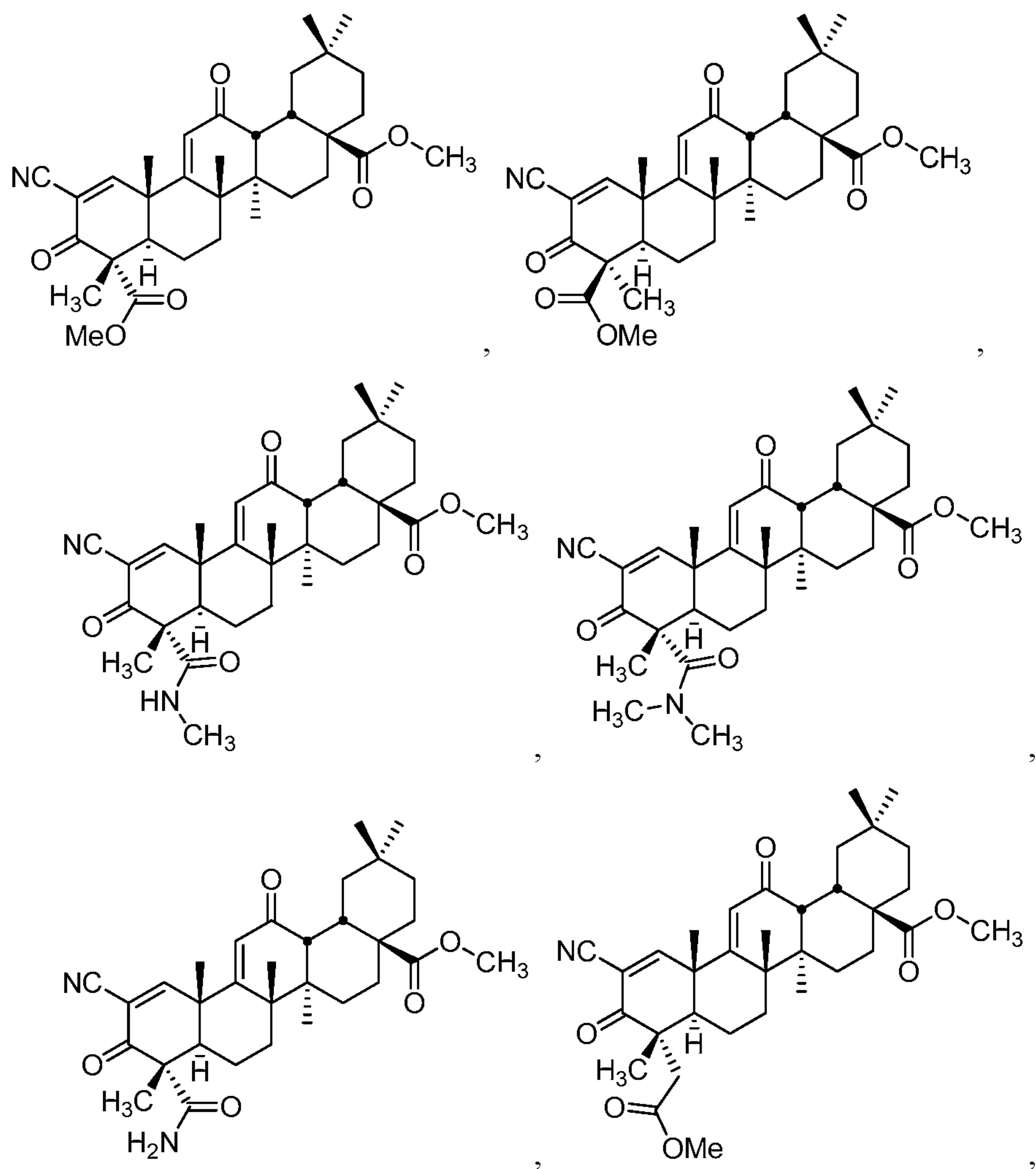
In other embodiments, the compounds are further defined as:

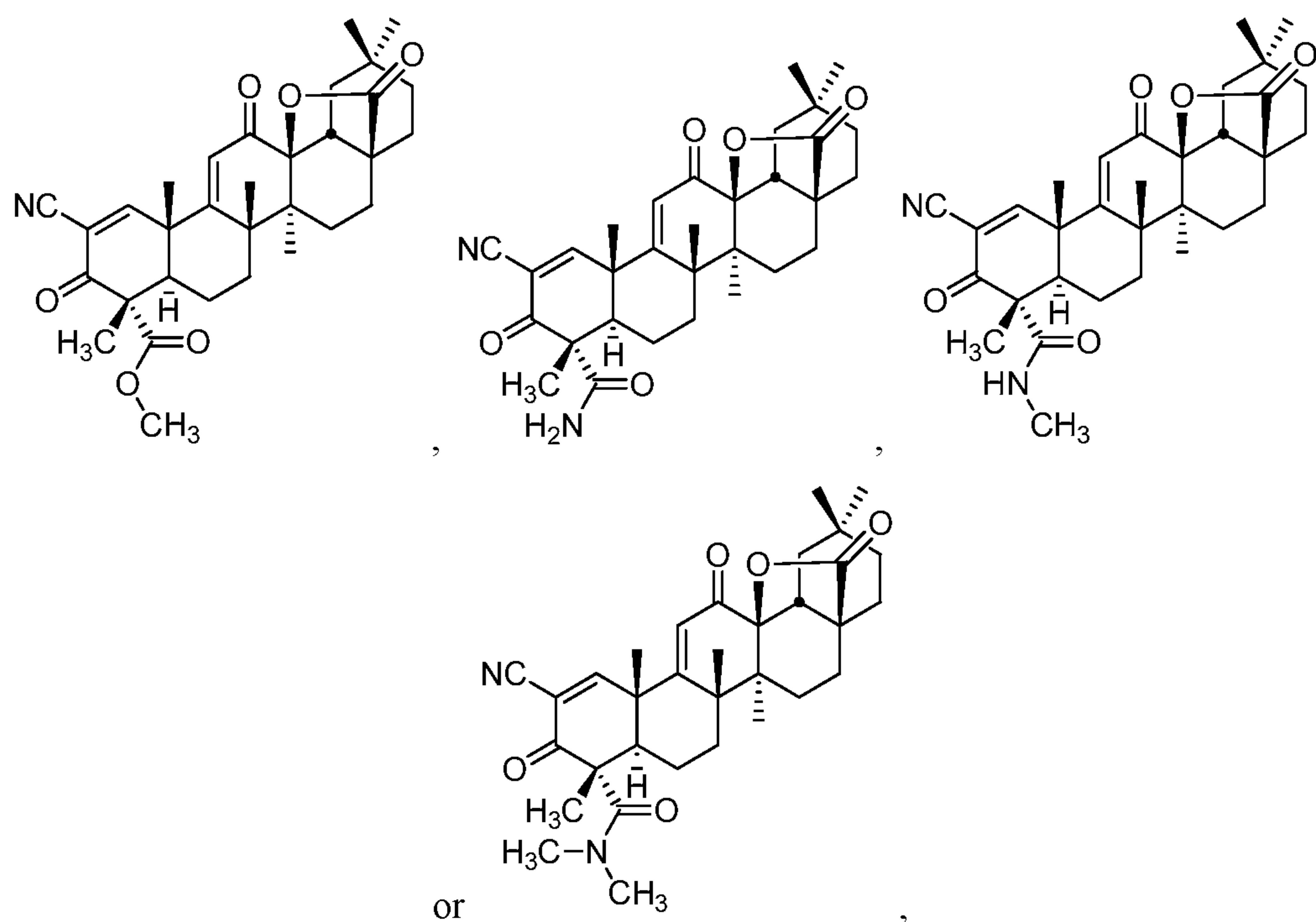




or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

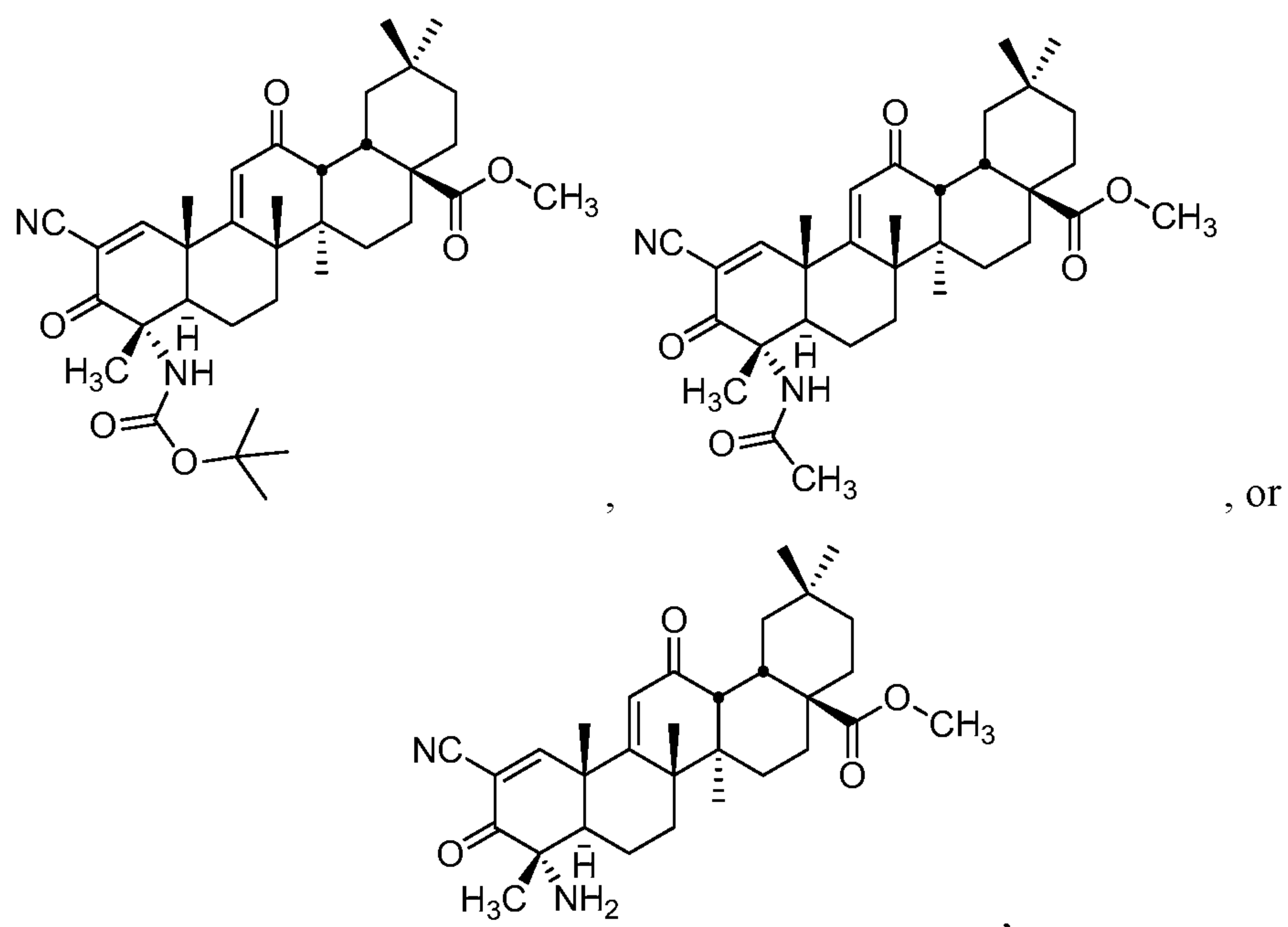
In other embodiments, the compounds are further defined as:





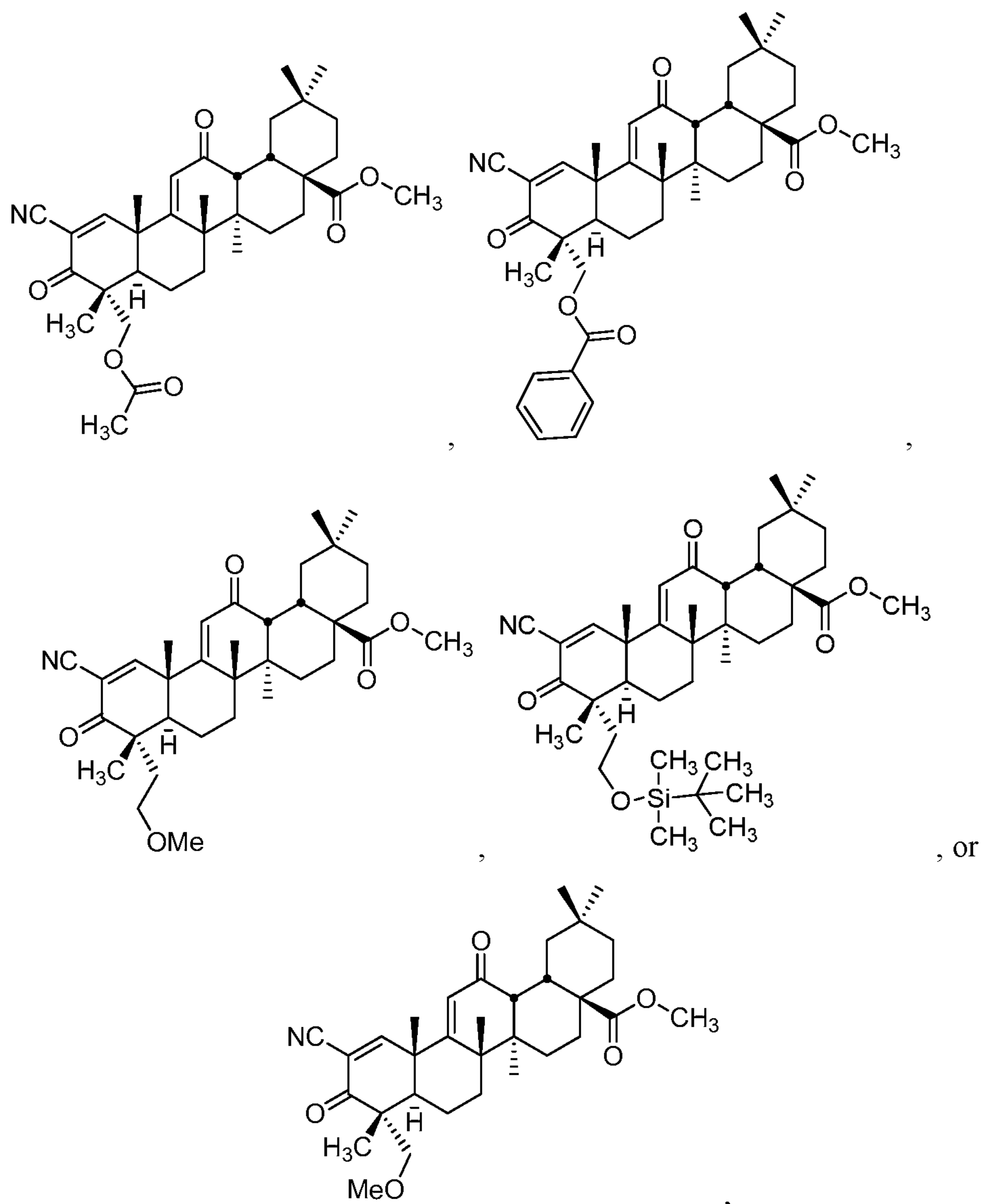
or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



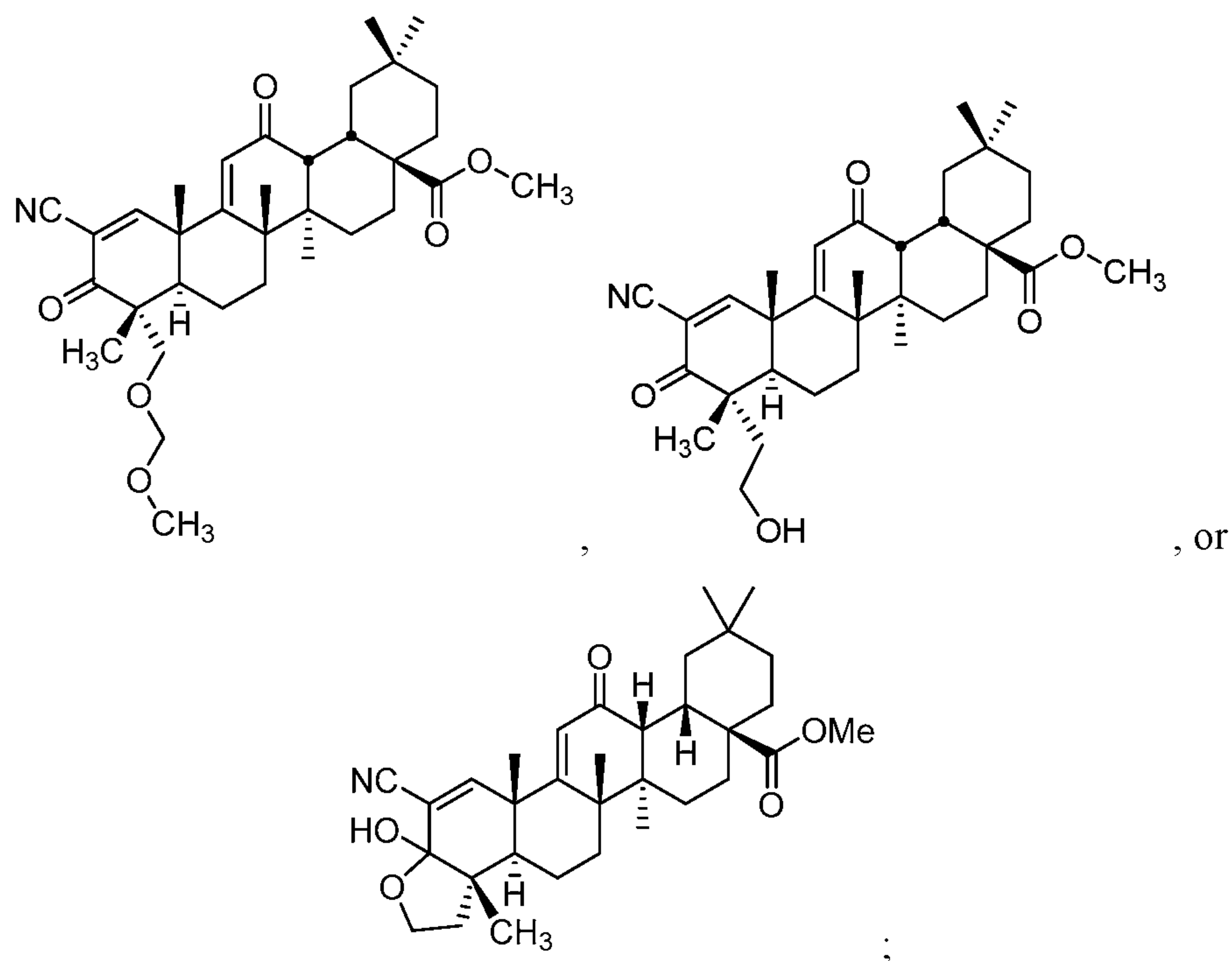
or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In other embodiments, the compounds are further defined as:



5 or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

In another aspect, the present disclosure provides compounds of the formula:



or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

5 In still yet another aspect, the present disclosure provides compounds further defined as:

dimethyl (4S,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-4,4a,5,6,6a,6b,7,8,9,10,11,12,12a,12b,13,14b-hexadecahydricene-4,8a(3H)-dicarboxylate;

10 dimethyl (4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-4,4a,5,6,6a,6b,7,8,9,10,11,12,12a,12b,13,14b-hexadecahydricene-4,8a(3H)-dicarboxylate;

15 methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-(difluoromethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-hydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-hydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

5 methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-9-(acetoxymethyl)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

10 methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-9-((benzoyloxy)methyl)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

15 methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-9-((tert-butoxycarbonyl)amino)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-9-acetamido-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

20 methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-9-amino-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

25 methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-9-(methylcarbamoyl)-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

30 methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-(dimethylcarbamoyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-9-(5-methyl-1,3,4-oxadiazol-2-yl)-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

5 methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-(2-methoxyethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

10 methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-9-carbamoyl-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

15 methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-9-(2-((tert-butyl)dimethylsilyl)oxy)ethyl)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

20 methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-(methoxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-(2-methoxy-2-oxoethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

25 (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-N-(2,2,2-trifluoroethyl)-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxamide;

30 (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-N-ethyl-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxamide;

((4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-8a-((2,2,2-trifluoroethyl)carbamoyl)-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicen-4-yl)methyl acetate;

5 (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-hydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-N-(2,2,2-trifluoroethyl)-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxamide;

10 (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-N-ethyl-9-hydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxamide;

15 N-((4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicen-4a(2H)-yl)-2,2-difluoropropanamide;

N-((4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-hydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicen-4a(2H)-yl)-2,2-difluoropropanamide;

20 ((4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-8a-(2,2-difluoropropanamido)-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicen-4-yl)methyl acetate;

25 methyl (4aS,6aS,6bR,8aR,9S,12aS,14aS,14bR)-11-cyano-9,14a-dihydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

30 (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-hydroxy-N,N,2,2,6a,6b,9,12a-octamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxamide;

(4S,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-4-hydroxy-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-2-carbonitrile;

5 (4R,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-4-(hydroxymethyl)-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-2-carbonitrile;

((4R,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picen-4-yl)methyl acetate;

10 methyl (4S,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-4-carboxylate;

15 (4R,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-4-((S)-1-hydroxyethyl)-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-2-carbonitrile;

(4S,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-4-carboxamide;

20 (4S,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-2-cyano-N,4,6a,6b,11,11,14b-heptamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-4-carboxamide;

(4S,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-2-cyano-N,N,4,6a,6b,11,11,14b-octamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-4-carboxamide;

25 methyl ((4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicen-4a(2H)-yl)carbamate;

30 ((4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-8a-((methoxycarbonyl)amino)-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicen-4-yl)methyl acetate;

methyl ((4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-hydroxy-

2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-

5 1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicen-4a(2H)-yl)carbamate;

(4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-4-(hydroxymethyl)-4,6a,6b,11,11,14b-

hexamethyl-8a-(5-methyl-1,3,4-oxadiazol-2-yl)-3,13-dioxo-

10 3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

((4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-8a-

(5-methyl-1,3,4-oxadiazol-2-yl)-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicen-4-yl)methyl acetate;

15 (4S,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-4-hydroxy-4,6a,6b,11,11,14b-hexamethyl-8a-

(5-methyl-1,3,4-oxadiazol-2-yl)-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

(4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-4-(hydroxymethyl)-4,6a,6b,11,11,14b-

20 hexamethyl-8a-(3-methyl-1,2,4-oxadiazol-5-yl)-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

((4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-8a-

(3-methyl-1,2,4-oxadiazol-5-yl)-3,13-dioxo-

25 3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicen-4-yl)methyl acetate;

(4S,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-4-hydroxy-4,6a,6b,11,11,14b-hexamethyl-8a-

(3-methyl-1,2,4-oxadiazol-5-yl)-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-carbonitrile;

30

(1aR,3S,3aR,5aS,5bR,7aS,11aS,11bR,13bS,13cR)-3-hydroxy-3,5a,5b,10,10,13b-hexamethyl-7a-(3-methyl-1,2,4-oxadiazol-5-yl)-2,12-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13b,13c-octadecahydropiceno[1,2-b]oxirene-1a(2H)-carbonitrile;

5 (1aR,3S,3aR,5aR,5bS,7aS,11aR,11bS,13bS,13cR)-3-hydroxy-3,5a,5b,10,10,13b-hexamethyl-2,12,15-trioxo-3,3a,4,5,5a,6,7,9,10,11,11a,12,13b,13c-tetradecahydro-2H,8H-11b,7a-(epoxymethano)piceno[1,2-b]oxirene-1a(5bH)-carbonitrile; and

10 *N*-((1aR,3S,3aR,5aS,5bR,7aS,11aS,11bR,13bS,13cR)-1a-cyano-3-hydroxy-3,5a,5b,10,10,13b-hexamethyl-2,12-dioxo-1a,3,3a,4,5,5a,5b,6,7,8,9,10,11,11a,11b,12,13b,13c-octadecahydropiceno[1,2-b]oxiren-7a(2H)-yl)-2,2-difluoropropanamide.

In yet another aspect, the present disclosure provides compounds further defined as:

15 methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-((methoxymethoxy)methyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

20 methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-(2-hydroxyethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate; and

25 methyl (3aS,3bR,5aS,5bR,7aS,11aS,11bR,13bS)-15-cyano-15a-hydroxy-3a,5a,5b,10,10,13b-hexamethyl-12-oxo-2,3,3a,4,5,5a,5b,6,7,8,9,10,11,11a,11b,12,13b,15a-octadecahydropiceno[3,4-b]furan-7a(3bH)-carboxylate.

In another aspect, the present disclosure provides pharmaceutical compositions comprising:

- (A) a compound described herein; and
- (B) an excipient or a pharmaceutically acceptable carrier.

30 In some embodiments, the compositions are formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially, intradermally, intralesionally,

intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, 5 topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion.

In still yet another aspect, the present disclosure provides methods of treating or preventing a disease or disorder in a patient in need thereof comprising administering to the 10 patient a therapeutically effective amount of a compound or composition described herein. In some embodiments, the patient is a mammal, for example, the patient is a human. In some embodiments, the disease or disorder is associated with increased production of cytokine IL-17. In some embodiments, the disease or disorder is associated with dysregulated angiogenesis.

15 In some embodiments, the disease or disorder is an autoimmune disease, organ rejection, asthma, cancer, a neurological disorder, a psychiatric disorder, a neuropsychiatric disorder, chronic pain syndrome, an inflammatory condition, or a cardiovascular disease. In some embodiments, the autoimmune disease is psoriasis, multiple sclerosis, scleroderma, rheumatoid arthritis, lupus, psoriatic arthritis, ankylosing spondylitis, Sjögren syndrome, 20 vitiligo, uveitis, systemic sclerosis, type 1 diabetes, myasthenia gravis, and inflammatory bowel disease. In some embodiments, the cardiovascular disease is vasculitis, atherosclerosis, myocardial infarction, myocarditis, heart failure, pulmonary hypertension, or stroke. In some embodiments, the neurological disorder is epilepsy, multiple sclerosis, spinal cord injury, Guillain-Barre syndrome, or a neurological disorder. In some embodiments, the 25 neurodegenerative disorder is Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or Huntington's disease. In some embodiments, the inflammatory condition is pancreatitis, hepatitis, pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, asthma, dermatitis, gastritis, esophagitis, irritable bowel syndrome, inflammatory bowel disease, nephritis, muscle wasting, or osteoarthritis. In some embodiments, the 30 chronic pain syndrome is fibromyalgia or neuropathic pain. In other embodiments, the disease or disorder is a severe inflammatory response to a pathogen. In some embodiments, the severe inflammatory response to a pathogen is from encephalitis, meningitis, *H. pylori*, *Toxoplasma gondii*, or *Leishmania spp.* In other embodiments, the disease or disorder is

obesity or a condition associated with obesity. In some embodiments, the condition associated with obesity are insulin resistance or fatty liver disease.

In some embodiments, the method comprises administering the compound once. In other embodiments, the method comprises administering the compound two or more times.

5 In still yet another aspect, the present disclosure provides methods of inhibiting the activity of an interleukin 17 comprising contacting the interleukin 17 with an effective amount of a compound or composition described herein. In some embodiments, the methods comprise inhibiting the activity of interleukin 17 *in vivo*. In some embodiments, the methods comprise contacting the interleukin comprises administering the compound to a patient in
10 need thereof. In some embodiments, the compounds also inhibit the production of nitric oxide *in vivo*. In some embodiments, the inhibition of interleukin 17 activity is sufficient to treat a disease or disorder. In some embodiments, the disease or disorder is associated with the misregulation of interleukin 17. In other embodiments, the disease or disorder is associated with inflammation. In other embodiments, the disease or disorder is associated
15 with the misregulation of nitric oxide production.

Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications
20 within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description. Note that simply because a particular compound is ascribed to one particular generic formula doesn't mean that it cannot also belong to another generic formula.

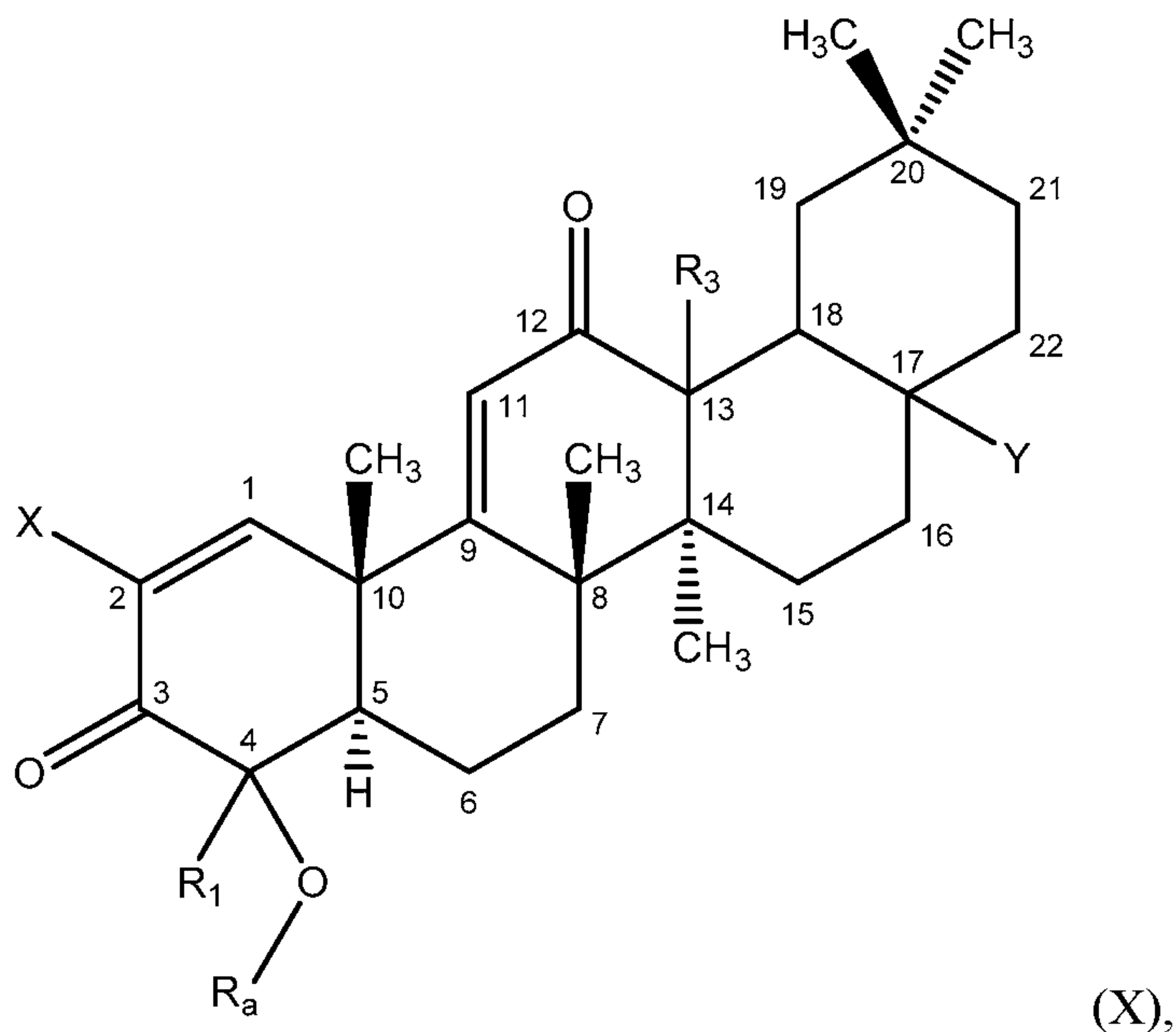
DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

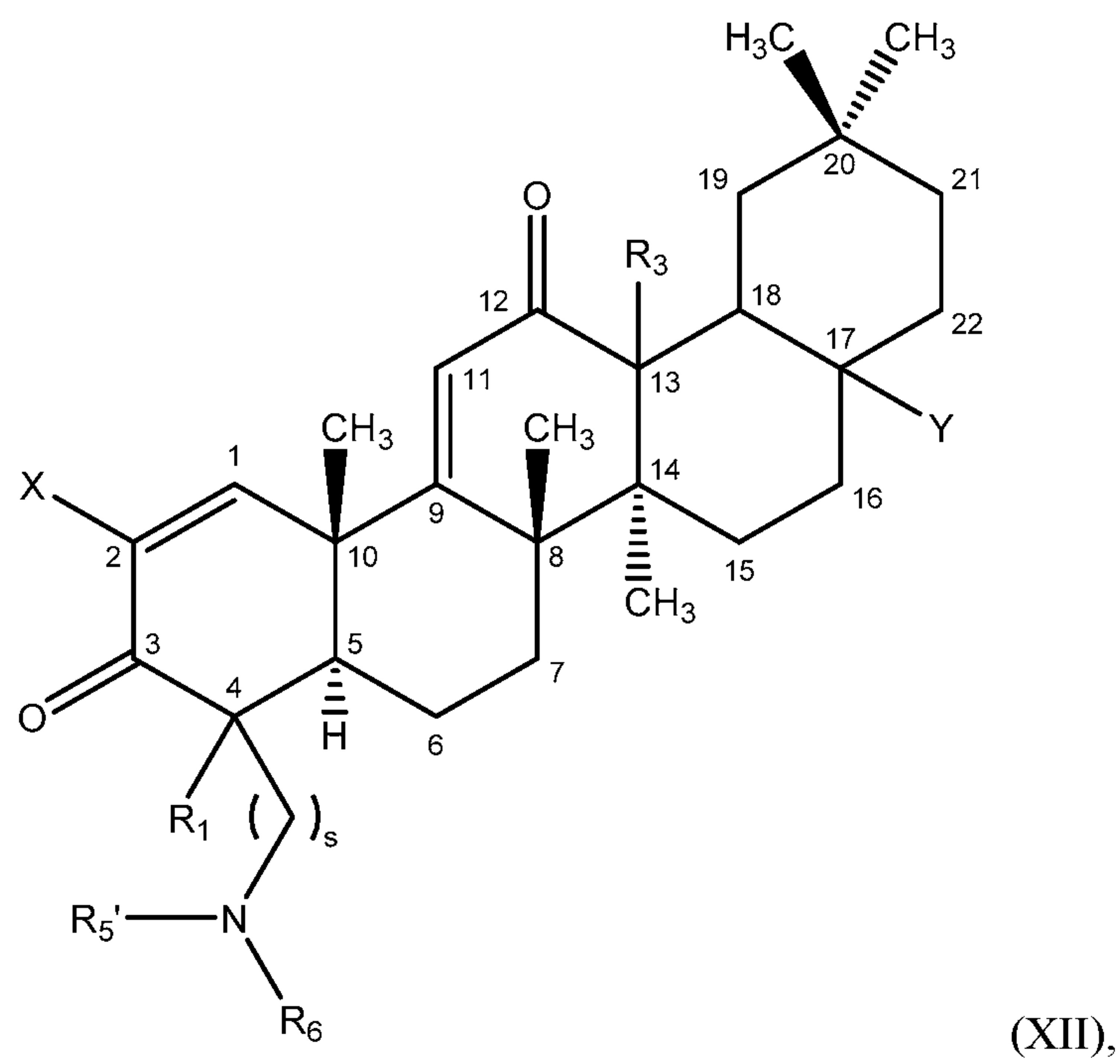
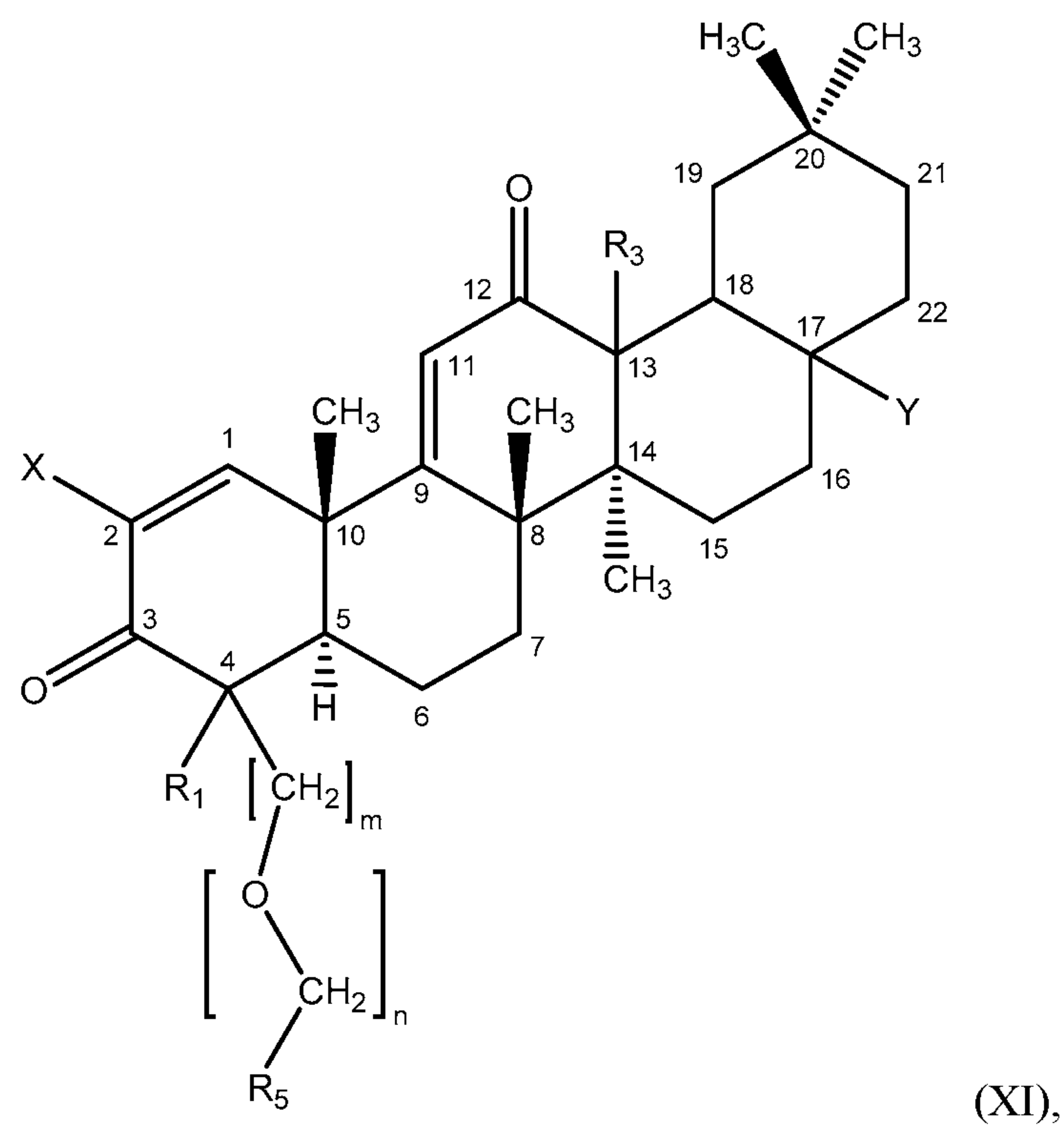
Disclosed herein are new compounds and compositions that may be used to prevent or inhibit excessive production of IL-17, reduce circulating levels of IL-17, and/or prevent or treat wide range of diseases or disorders, including those with inflammatory and autoimmune-related components.

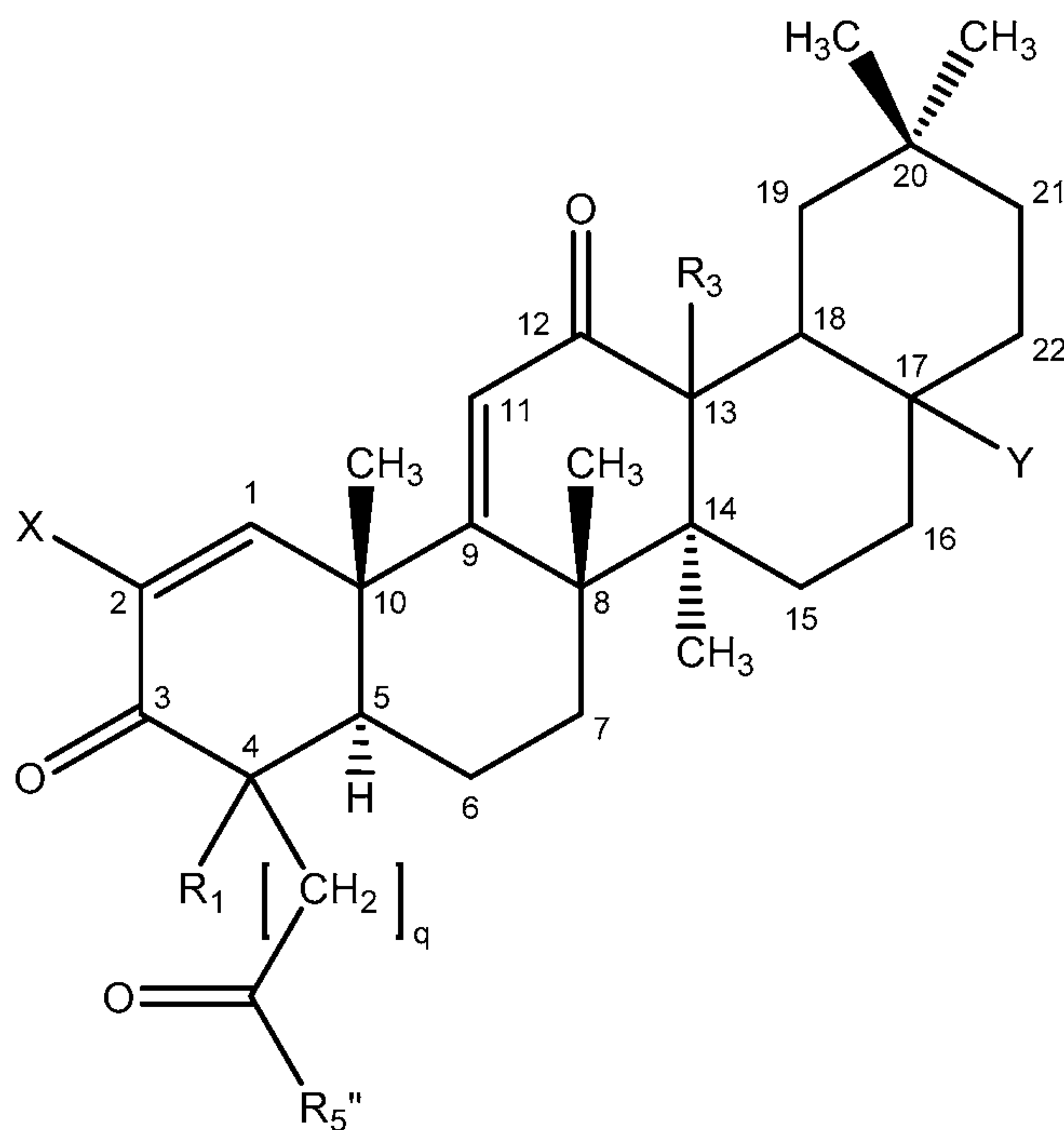
I. Compounds and Synthetic Methods

The compounds provided by the present disclosure are shown, for example, above in the summary of the invention section and in the claims below. They may be made using the methods outlined in the Examples section. These methods can be further modified and optimized using the principles and techniques of organic chemistry as applied by a person skilled in the art. Such principles and techniques are taught, for example, in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (2007), which is incorporated by reference herein.

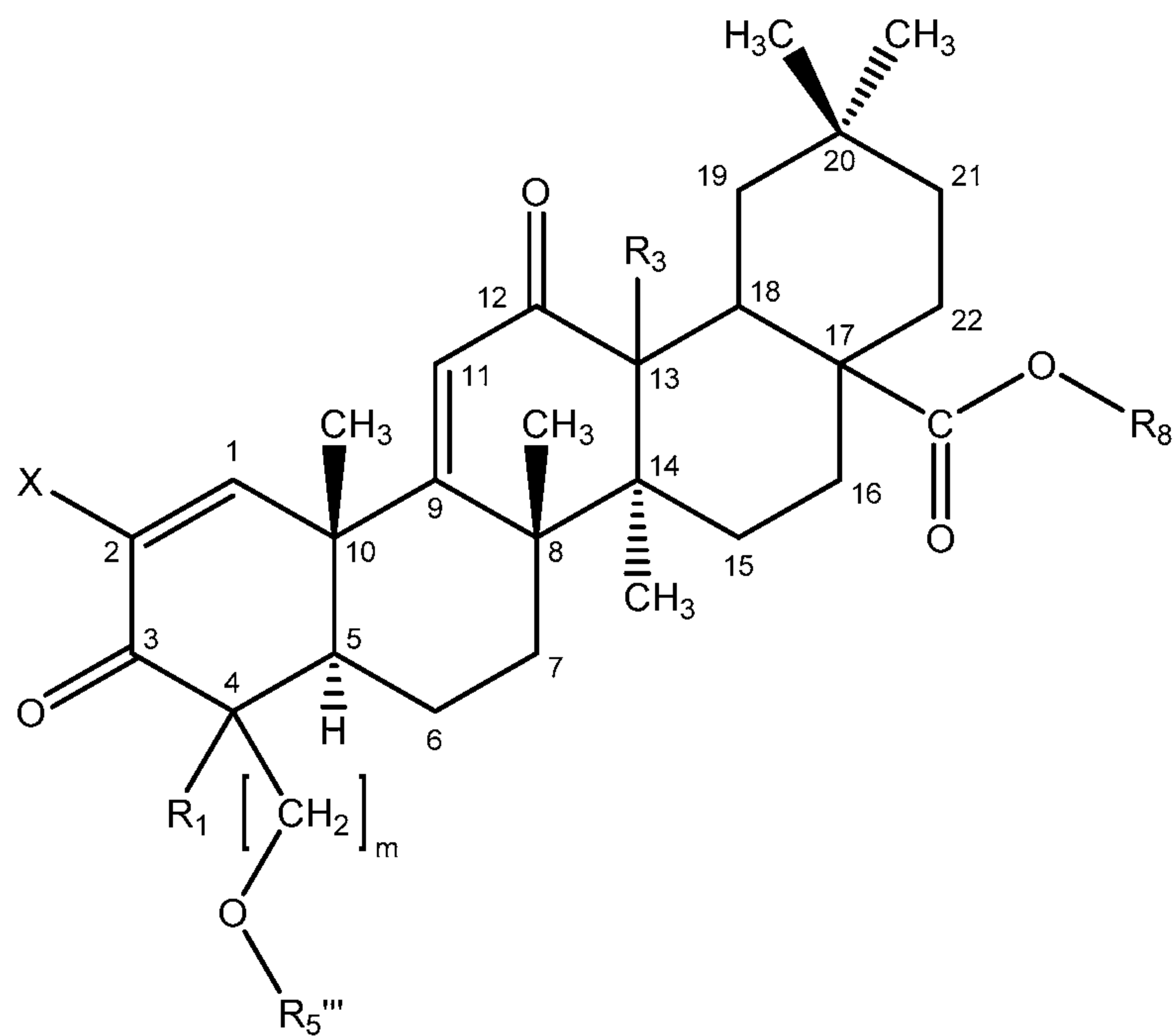
In some embodiments, the present disclosure provides compounds of the formula:







(XIII), or



(XIV)

wherein:

X is cyano, heteroaryl_(C≤8), substituted heteroaryl_(C≤8), -CF₃, or -C(O)-R₄; wherein

5 R₄ is hydroxy, amino, or alkoxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkylsulfonylamino_(C≤8), or a substituted version of any of these groups;
 R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted cycloalkyl_(C≤8);

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of either of these groups; or R₃ is taken together with Y as described below;

R_a is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8), acyl_(C≤8), or a substituted version of any of these groups;

R₅ is hydroxy or acyl_(C≤8), alkoxy_(C≤8), acyloxy_(C≤8), alkylsilyloxy_(C≤8), or a substituted version of any of these groups;

R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), -C(O)-alkoxy_(C≤8), substituted -C(O)-alkoxy_(C≤8), acyloxy_(C≤8), substituted acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted alkylsilyloxy_(C≤8);

R_{5''} is hydrogen, amino, hydroxy, or mercapto; or
alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), or a substituted version of any of these groups;

R_{5'''} is alkyl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8), alkylsilyl_(C≤8), or substituted alkylsilyl_(C≤8);

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R₈ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), or a substituted version of any of these groups;

m is 1, 2, 3, or 4;

n is 0, 1, 2, or 3;

q is 0, 1, 2, 3, or 4;

s is 0, 1, 2, 3, or 4; and

provided that if the compound is further defined by formulas I, III, and IV then Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of these groups;

–alkanediyl_(C≤8)–R_b, –alkenediyl_(C≤8)–R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8),

5 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8),

alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8),

arylamino_(C≤8), aralkylamino_(C≤8), heteroarylamino_(C≤8),

alkylsulfonylamino_(C≤8), amido_(C≤8), –OC(O)NH–alkyl_(C≤8),

–OC(O)CH₂NHC(O)O–*t*-butyl, –OCH₂–alkylthio_(C≤8), or a

10 substituted version of any of these groups;

–(CH₂)_oC(O)R_c, wherein o is 0–6 and R_c is:

hydrogen, halo, hydroxy, amino, –NHOH, or mercapto; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),

aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8),

15 cycloalkoxy_(C≤8), alkenyloxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8),

heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8),

dialkylamino_(C≤8), arylamino_(C≤8), alkylsulfonylamino_(C≤8),

amido_(C≤8), alkoxyamino_(C≤8), heterocycloalkylamino_(C≤8),

–NHC(NO₂)–alkyl_(C≤8), –NH–amido_(C≤8), or a substituted

20 version of any of these groups;

–NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),

25 aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8),

cycloalkoxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8),

acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8),

or a substituted version of any of these groups; or

Y is taken together with R₃ and is –(CH₂)_pC(O)R_f–, wherein

30 p is 0–6; and

R_f is –O– or –NR₇–; wherein:

R₇ is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted acyl_(C≤8); or

if the compound is further defined by formulas II, then Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

5 alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12), aralkyl_(C≤12), heteroaryl_(C≤8), heterocycloalkyl_(C≤12), alkoxy_(C≤8), cycloalkoxy_(C≤8), aryloxy_(C≤12), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), alkylthio_(C≤8), acylthio_(C≤8), alkylsulfonylamino_(C≤8), or substituted versions of any of
10 these groups;

–alkanediyl_(C≤8)–R_b, –alkenediyl_(C≤8)–R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C≤8), alkoxy_(C≤8), cycloalkoxy_(C≤8), alkenyloxy_(C≤8),
15 aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8), acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), alkenylamino_(C≤8), arylamino_(C≤8), aralkylamino_(C≤8), heteroarylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), –OC(O)NH–alkyl_(C≤8), –OC(O)CH₂NHC(O)O–*t*-butyl, –OCH₂–alkylthio_(C≤8), or a
20 substituted version of any of these groups;

–(CH₂)_oC(O)R_c, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, –NHOH, or mercapto; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),
aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8),
25 alkylamino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8), alkylsulfonylamino_(C≤8), amido_(C≤8), alkoxyamino_(C≤8), heterocycloalkylamino_(C≤8), –NHC(NO₂)–alkyl_(C≤8), –NH–amido_(C≤8), or a substituted version of any of these groups;

–NR_dC(O)R_e, wherein

30 R_d is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C≤8), cycloalkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤8),
 aralkyl_(C≤8), heteroaryl_(C≤8), heterocycloalkyl_(C≤8), alkoxy_(C≤8),
 cycloalkoxy_(C≤8), aryloxy_(C≤8), aralkoxy_(C≤8), heteroaryloxy_(C≤8),
 acyloxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8), arylamino_(C≤8),
 or a substituted version of any of these groups; or

Y is taken together with R₃ and is $-(CH_2)_pC(O)R_f-$, wherein

p is 0–6; and

R_f is $-O-$ or $-NR_7-$; wherein:

R₇ is hydrogen, alkyl_(C≤8), substituted alkyl_(C≤8), acyl_(C≤8), or substituted
 acyl_(C≤8);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

Compounds of the invention may contain one or more asymmetrically-substituted carbon or nitrogen atoms, and may be isolated in optically active or racemic form. Thus, all chiral, diastereomeric, racemic form, epimeric form, and all geometric isomeric forms of a chemical formula are intended, unless the specific stereochemistry or isomeric form is specifically indicated. Compounds may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. In some embodiments, a single diastereomer is obtained. The chiral centers of the compounds of the present invention can have the *S* or the *R* configuration. In some embodiments of the present disclosure, the heteroatom containing group on carbon atom 4 of the formulas I and X-XIV is oriented away from the viewer such that the group appears on the opposite face of the ring system from the viewer and on the same face of the ring system as the hydrogen atom at carbon atom 5. As would be obvious to a person of skill in the art, the specific stereochemical configuration of this carbon atom depends on the identity of the particular substituents at R₁ and R₂ and is either the *R* or the *S* configuration.

Without being bound by theory, in some embodiments, the compounds provided herein having an *S*-configuration at carbon atom 4 exhibit retained inhibition of hIL17 while exhibiting reduced NRF2 activation and/or reduced suppression of IFN γ -induced NO production compared with their respective diastereomers having an *R*-configuration at carbon atom 4. In some embodiments, the present disclosure provides compounds exhibiting an IC₅₀ < 100 nM for inhibition of hIL17 as measure by determining the concentration required to inhibit using fluorescently tagged anti-IL17 antibodies, for example, as described in Example 2. In some of these embodiments, the IC₅₀ is less than 90 nM, 80 nM, 70 nM, 60 nM, or 50

nM. In some embodiments, the present disclosure provides compounds exhibiting an $EC_{2\times} > 50$ nM for the activation of NRF2 as measured by determining the concentration requirement to increase GST ARE Luciferase reporter activity by 2-fold in AREc32 cells relative to DMSO treated cells, for example, as described in Example 2. In some of these embodiments, the $EC_{2\times}$ is greater than 60 nM, 70 nM, 80 nM, 90 nM, or 100 nM. In some embodiments, the present disclosure provides compounds exhibiting an $IC_{50} > 20$ nM for the suppression of IFN γ -induced NO production, as measured by the concentration required to suppress 50% of IFN γ -induced nitric oxide production normalized to cell viability measured using the WST-1 reagent, for example, as described in Example 2. In some of these embodiments, the IC_{50} is greater than 30 nM, 40 nM, 50 nM, 60 nM, or 70 nM.

Chemical formulas used to represent compounds of the invention will typically only show one of possibly several different tautomers. For example, many types of ketone groups are known to exist in equilibrium with corresponding enol groups. Similarly, many types of imine groups exist in equilibrium with enamine groups. Regardless of which tautomer is depicted for a given compound, and regardless of which one is most prevalent, all tautomers of a given chemical formula are intended.

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (*e.g.*, higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the indications stated herein or otherwise.

In addition, atoms making up the compounds of the present invention are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C .

Compounds of the present invention may also exist in prodrug form. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (*e.g.*, solubility, bioavailability, manufacturing, *etc.*), the compounds employed in some methods of the invention may, if desired, be delivered in prodrug form. Thus, the invention contemplates prodrugs of compounds of the present invention as well as methods of delivering prodrugs. Prodrugs of the compounds employed in the invention may be prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved,

either in routine manipulation or *in vivo*, to the parent compound. Accordingly, prodrugs include, for example, compounds described herein in which a hydroxy, amino, or carboxy group is bonded to any group that, when the prodrug is administered to a subject, cleaves to form a hydroxy, amino, or carboxylic acid, respectively.

5 It should be recognized that the particular anion or cation forming a part of any salt form of a compound provided herein is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (2002), which is incorporated herein by reference.

10 It will be appreciated that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as “solvates.” Where the solvent is water, the complex is known as a “hydrate.” It will also be appreciated that many organic compounds can exist in more than one solid form, including crystalline and amorphous forms. All solid forms of the
15 compounds provided herein, including any solvates thereof, are within the scope of the present invention.

II. Diseases Associated with Inflammatory Cytokine IL-17

Various reports have implicated the inflammatory cytokine IL-17 in the pathogenesis of many autoimmune diseases, including rheumatoid arthritis, psoriasis and psoriatic arthritis,
20 inflammatory bowel diseases (including but not limited to Crohn’s disease), multiple sclerosis, autoimmune nephritis, autoimmune uveitis, Type 1 diabetes, and ankylosing spondylitis. A type of T lymphocyte known as a Th17 cell is a primary source of IL-17. There are multiple members of the IL-17 family. The first identified member, IL-17A, is commonly referred to as IL-17. IL-17 is composed of two monomers linked by disulfide
25 bonds to form a homodimer (Miossec and Kolls, 2012). Aside from IL-17A, the other principal family member is IL-17F. Some evidence suggests that IL-17F and IL-17A, though they have many effects in common, may have different effects in certain settings such as lung inflammation. The IL-17 cytokines bind to IL-17 receptors (IL-17R) located in the membrane of select cell types. Although there are multiple subtypes of the IL-17 receptor, the
30 IL-17RA/IL-17RC complex is required for the activity of IL-17A and IL-17F. IL-17RA has the unusual property of signaling through a pathway that involves an adaptor protein (ACT1) rather than the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway employed by most interleukin receptors. Binding of IL-17A to IL-17RA activates

the pro-inflammatory nuclear factor-kappa B (NF- κ B) pathway and pro-inflammatory elements of the mitogen-activated protein kinase (MAPK) pathway such as JUN N-terminal kinase (JNK), p38 and extracellular signal-related kinase (ERK). IL-17 activity stimulates secretion of IL-6 and IL-8 from mesenchymal cells and leads to fever along with the
 5 accumulation of neutrophils in blood and tissue.

Aside from its contribution to acute inflammation, IL-17 also contributes to chronic inflammation (Miossec and Kolls, 2012). IL-17 stimulates the production of matrix metalloproteinases (MMPs), which among other effects can degrade cartilage in joints. IL-17 also increases the expression of receptor activator of NF- κ B ligand (RANKL) in osteoblasts,
 10 leading to differentiation and activation of osteoclasts and bone degradation. Depending on the target cell that is exposed to it, IL-17 may stimulate the production of IL-6, IL-8, IL-1, tumor necrosis factor (TNF), MMPs, nitric oxide, or several other proteins that are implicated in inflammatory conditions (*e.g.*, tissue factor, CCL20, G-CSF and GM-CSF).

Although IL-17 plays a role in the immune response to invading pathogens, excessive
 15 IL-17 activity has been implicated in pathologies associated with an excessive immune response to an infection. For example, IL-17 has been implicated in the severe neuroinflammation associated with *Toxoplasma gondii* infection and increased severity of lesions associated with *Leishmania* infection. In these and other cases, IL-17 appears to play a role in perpetuating the infection, promoting an excessive inflammatory response, and
 20 inhibiting clearance of the infectious agent (Waite and Skokos, 2012).

Drugs targeting IL-17 have entered clinical trials for a wide variety of inflammatory conditions, including psoriasis, rheumatoid arthritis, ankylosing spondylitis, uveitis, Behcet's disease, psoriatic arthritis, Crohn's disease, polymyalgia rheumatica, dry eye syndrome, multiple sclerosis, graft-versus-host disease, and asthma. Preclinical evidence also implicates
 25 IL-17 in the pathology of type 1 diabetes, and Th17 cells are elevated in patients with adult onset Still's disorder, another autoimmune disease. Activity of Th17 cells has been implicated in the development of graft-versus-host disease following allogeneic stem cell (*i.e.*, bone marrow) transplantation (Fujiwara, *et al.*, 2014). Given the large body of evidence to date, it is likely that therapies reducing the expression of IL-17 or otherwise reducing its
 30 levels in circulation or target tissues (*e.g.*, anti-IL17 monoclonal antibodies) could have broad applications in the treatment of autoimmune diseases and other inflammatory conditions.

Overproduction of IL-17 or elevated numbers of Th17 cells have been reported in patient studies or animal models of a large number of conditions, including autoimmune diseases, neurological disorders, cardiovascular diseases, cancer, psychiatric and

neuropsychiatric disorders, acute and chronic inflammatory conditions, chronic pain syndromes, organ rejection or graft-versus-host disease, or asthma and other allergic conditions.

Both the differentiation of Th17 cells and their production of IL-17 are regulated to a significant degree by the retinoid orphan receptor ROR γ t, a member of the nuclear hormone receptor family. Expression of ROR γ t is common to all types of Th17 cells, and plays a significant role in their differentiation as well as their activity. ROR γ also regulates the production of IL-17 in other cell types, including gamma delta T cells, innate lymphoid cells, and lymphoid tissue inducer cells (Bronner *et al.*, 2016). Inhibition of ROR γ t activity results in reduced expression of IL-17, and the identification of small molecule inhibitors of ROR γ t is currently an area of great interest in the pharmaceutical industry.

Compounds and compositions provided herein may be used to suppress IL-17 production in cultures of human T cells that are exposed to a mixture of cytokines known to induce differentiation into Th17 cells. In some embodiments, the ability to act as inverse agonists of ROR γ t is also demonstrated. Without wishing to be bound by any theory, it is believed that for examples ROR γ t-independent mechanisms appear to contribute to the suppression of IL-17 production. Thus, the compounds and compositions provided herein may be used for inhibiting differentiation of T cells into Th17 cells, as well as inhibiting production of IL-17 by mature Th17 cells. In both cases, the net result is a reduction in IL-17 levels. In some embodiments, the compounds provided herein may be used for the treatment or prevention of any of the disorders discussed in this section.

III. Pharmaceutical Formulations and Routes of Administration

For the purpose of administration to a patient in need of such treatment, pharmaceutical formulations (also referred to as pharmaceutical preparations, pharmaceutical compositions, pharmaceutical products, medicinal products, medicines, medications, or medicaments) comprise a therapeutically effective amount of a compound of the present invention formulated with one or more excipients and/or drug carriers appropriate to the indicated route of administration. In some embodiments, the compounds of the present invention are formulated in a manner amenable for the treatment of human and/or veterinary patients. In some embodiments, formulation comprises admixing or combining one or more of the compounds of the present invention with one or more of the following excipients: lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric

and sulfuric acids, gelatin, acacia, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol. In some embodiments, *e.g.*, for oral administration, the pharmaceutical formulation may be tableted or encapsulated. In some embodiments, the compounds may be dissolved or slurried in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, 5 peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Pharmaceutical formulations may be subjected to conventional pharmaceutical operations, such as sterilization and/or may contain drug carriers and/or excipients such as preservatives, stabilizers, wetting agents, emulsifiers, encapsulating agents such as lipids, dendrimers, polymers, proteins such as albumin, or nucleic acids, and buffers, *etc.*

10 Pharmaceutical formulations may be administered by a variety of methods, *e.g.*, orally or by injection (*e.g.* subcutaneous, intravenous, intraperitoneal, *etc.*). Depending on the route of administration, the compounds of the present invention may be coated in a material to protect the compound from the action of acids and other natural conditions which may inactivate the compound. To administer the active compound by other than parenteral 15 administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation. For example, the active compound may be administered to a patient in an appropriate carrier, for example, liposomes, or a diluent. Pharmaceutically acceptable diluents include saline and aqueous buffer solutions. Liposomes include water-in-oil-in-water CGF emulsions as well as conventional liposomes.

20 The compounds of the present invention may also be administered parenterally, intraperitoneally, intraspinally, or intracerebrally. Dispersions can be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

25 Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (such as, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and 30 vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic

agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

5 The compounds of the present invention can be administered orally, for example, with an inert diluent or an assimilable edible carrier. The compounds and other ingredients may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the compounds of the present invention may be incorporated with excipients and used in the form
10 of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. The percentage of the therapeutic compound in the compositions and preparations may, of course, be varied. The amount of the therapeutic compound in such pharmaceutical formulations is such that a suitable dosage will be obtained.

 In some embodiments, the therapeutic compound may also be administered topically
15 to the skin, eye, or mucosa. Alternatively, if local delivery to the lungs is desired the therapeutic compound may be administered by inhalation in a dry-powder or aerosol formulation.

 In some embodiments, it may be advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as
20 used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit containing a predetermined quantity of therapeutic compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. In some embodiments, the specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the therapeutic
25 compound and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such a therapeutic compound for the treatment of a selected condition in a patient. In some embodiments, active compounds are administered at a therapeutically effective dosage sufficient to treat a condition associated with a condition in a patient. For example, the efficacy of a compound can be evaluated in an animal model
30 system that may be predictive of efficacy in treating the disease in a human or another animal.

 In some embodiments, the effective dose range for the therapeutic compound can be extrapolated from effective doses determined in animal studies for a variety of different animals. In general a human equivalent dose (HED) in mg/kg can be calculated in accordance

with the following formula (see, *e.g.*, Reagan-Shaw *et al.*, *FASEB J.*, 22(3):659-661, 2008, which is incorporated herein by reference):

$$(a) \quad \text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times (\text{Animal } K_m / \text{Human } K_m)$$

5 Use of the K_m factors in conversion results in more accurate HED values, which are based on body surface area (BSA) rather than only on body mass. K_m values for humans and various animals are well known. For example, the K_m for an average 60 kg human (with a BSA of 1.6 m²) is 37, whereas a 20 kg child (BSA 0.8 m²) would have a K_m of 25. K_m for some relevant animal models are also well known, including: mice K_m of 3 (given a weight of
10 0.02 kg and BSA of 0.007); hamster K_m of 5 (given a weight of 0.08 kg and BSA of 0.02); rat K_m of 6 (given a weight of 0.15 kg and BSA of 0.025) and monkey K_m of 12 (given a weight of 3 kg and BSA of 0.24).

 Precise amounts of the therapeutic composition depend on the judgment of the practitioner and are peculiar to each individual. Nonetheless, a calculated HED dose provides
15 a general guide. Other factors affecting the dose include the physical and clinical state of the patient, the route of administration, the intended goal of treatment and the potency, stability and toxicity of the particular therapeutic formulation.

 The actual dosage amount of a compound of the present disclosure or composition comprising a compound of the present disclosure administered to a subject may be
20 determined by physical and physiological factors such as type of animal treated, age, sex, body weight, severity of condition, the type of disease being treated, previous or concurrent therapeutic interventions, idiopathy of the subject and on the route of administration. These factors may be determined by a skilled artisan. The practitioner responsible for administration will typically determine the concentration of active ingredient(s) in a
25 composition and appropriate dose(s) for the individual subject. The dosage may be adjusted by the individual physician in the event of any complication.

 In some embodiments, the therapeutically effective amount typically will vary from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about 750 mg/kg, from about 100 mg/kg to about 500 mg/kg, from about 1 mg/kg to about 250 mg/kg, from about 10
30 mg/kg to about 150 mg/kg in one or more dose administrations daily, for one or several days (depending of course of the mode of administration and the factors discussed above). Other suitable dose ranges include 1 mg to 10,000 mg per day, 100 mg to 10,000 mg per day, 500 mg to 10,000 mg per day, and 500 mg to 1,000 mg per day. In some particular embodiments, the amount is less than 10,000 mg per day with a range of 750 mg to 9,000 mg per day.

In some embodiments, the amount of the active compound in the pharmaceutical formulation is from about 2 to about 75 weight percent. In some of these embodiments, the amount is from about 25 to about 60 weight percent.

Single or multiple doses of the agents are contemplated. Desired time intervals for delivery of multiple doses can be determined by one of ordinary skill in the art employing no more than routine experimentation. As an example, subjects may be administered two doses daily at approximately 12 hour intervals. In some embodiments, the agent is administered once a day.

The agent(s) may be administered on a routine schedule. As used herein a routine schedule refers to a predetermined designated period of time. The routine schedule may encompass periods of time which are identical or which differ in length, as long as the schedule is predetermined. For instance, the routine schedule may involve administration twice a day, every day, every two days, every three days, every four days, every five days, every six days, a weekly basis, a monthly basis or any set number of days or weeks therebetween. Alternatively, the predetermined routine schedule may involve administration on a twice daily basis for the first week, followed by a daily basis for several months, *etc.* In other embodiments, the invention provides that the agent(s) may be taken orally and that the timing of which is or is not dependent upon food intake. Thus, for example, the agent can be taken every morning and/or every evening, regardless of when the subject has eaten or will eat.

IV. Combination Therapy

In addition to being used as a monotherapy, the compounds of the present invention may also find use in combination therapies. Effective combination therapy may be achieved with a single composition or pharmacological formulation that includes both agents, or with two distinct compositions or formulations, administered at the same time, wherein one composition includes a compound of this invention, and the other includes the second agent(s). Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to months.

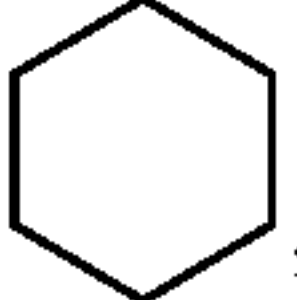
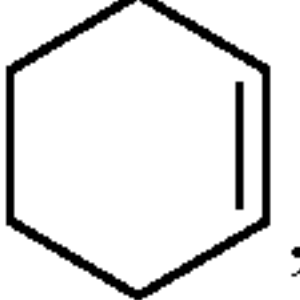
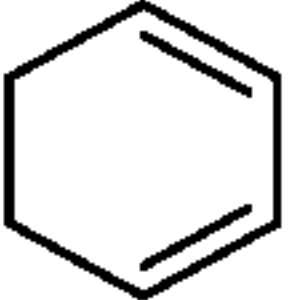
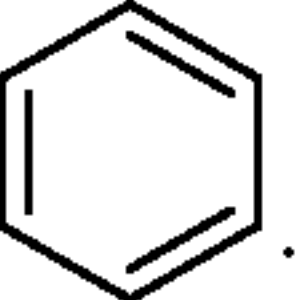
Non-limiting examples of such combination therapy include combination of one or more compounds of the invention with another anti-inflammatory agent, a chemotherapeutic agent, radiation therapy, an antidepressant, an antipsychotic agent, an anticonvulsant, a mood stabilizer, an anti-infective agent, an antihypertensive agent, a cholesterol-lowering agent or other modulator of blood lipids, an agent for promoting weight loss, an antithrombotic agent, an agent for treating or preventing cardiovascular events such as myocardial infarction or

stroke, an antidiabetic agent, an agent for reducing transplant rejection or graft-versus-host disease, an anti-arthritic agent, an analgesic agent, an anti-asthmatic agent or other treatment for respiratory diseases, or an agent for treatment or prevention of skin disorders. Compounds of the invention may be combined with agents designed to improve a patient's immune response to cancer, including (but not limited to) cancer vaccines. See Lu *et al.* (2011), which is incorporated herein by reference.

V. Definitions

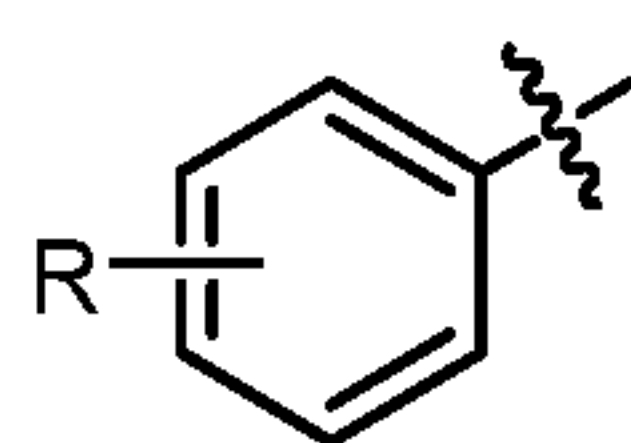
When used in the context of a chemical group: “hydrogen” means $-H$; “hydroxy” means $-OH$; “oxo” means $=O$; “carbonyl” means $-C(=O)-$; “carboxy” means $-C(=O)OH$ (also written as $-COOH$ or $-CO_2H$); “halo” means independently $-F$, $-Cl$, $-Br$ or $-I$; “amino” means $-NH_2$; “hydroxyamino” means $-NHOH$; “nitro” means $-NO_2$; imino means $=NH$; “cyano” means $-CN$; “isocyanate” means $-N=C=O$; “azido” means $-N_3$; in a monovalent context “phosphate” means $-OP(O)(OH)_2$ or a deprotonated form thereof; in a divalent context “phosphate” means $-OP(O)(OH)O-$ or a deprotonated form thereof; “mercapto” means $-SH$; and “thio” means $=S$; “sulfonyl” means $-S(O)_2-$; “hydroxysulfonyl” means $-S(O)_2OH$; “sulfonamide” means $-S(O)_2NH_2$; and “sulfinyl” means $-S(O)-$.

In the context of chemical formulas, the symbol “ $-$ ” means a single bond, “ $=$ ” means a double bond, and “ $\equiv$ ” means triple bond. An “epoxidized double bond” represents the group: . The symbol “ $----$ ” represents an optional bond, that is either no bond or a single bond. The symbol “ $====$ ” represents a single bond or a double bond. The symbol “ $=====$ ” may also be used to represent an epoxidized double bond. Thus, for example, the formula 

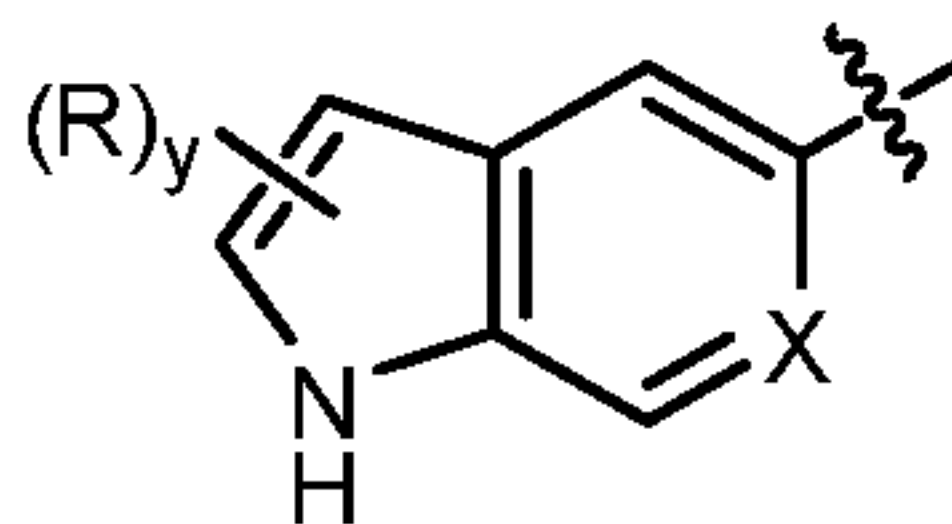
includes , , ,  and . And it is understood that no one such ring atom forms part of more than one double bond. Furthermore, it is noted that the covalent bond symbol “ $-$ ”, when connecting one or two stereogenic atoms, does not indicate any preferred stereochemistry. Instead, it covers all stereoisomers as well as mixtures thereof. The symbol “”, when drawn perpendicularly across a bond (*e.g.*, -CH₃ for methyl) indicates a point of attachment of the group. It is noted that the point of attachment is typically only identified in this manner for larger groups in order to assist the reader in unambiguously identifying a point of attachment. The symbol “” means a single bond where the group attached to the thick end of the wedge is “out of the page.” The symbol

“|||||” means a single bond where the group attached to the thick end of the wedge is “into the page”. The symbol “~~~~~” means a single bond where the geometry around a double bond (*e.g.*, either *E* or *Z*) is undefined. Both options, as well as combinations thereof are therefore intended. Any undefined valency on an atom of a structure shown in this application implicitly represents a hydrogen atom bonded to that atom. A bold dot on a carbon atom indicates that the hydrogen attached to that carbon is oriented out of the plane of the paper.

When a group “R” is depicted as a “floating group” on a ring system, for example, in the formula:



then R may replace any hydrogen atom attached to any of the ring atoms, including a depicted, implied, or expressly defined hydrogen, so long as a stable structure is formed. When a group “R” is depicted as a “floating group” on a fused ring system, as for example in the formula:



then R may replace any hydrogen attached to any of the ring atoms of either of the fused rings unless specified otherwise. Replaceable hydrogens include depicted hydrogens (*e.g.*, the hydrogen attached to the nitrogen in the formula above), implied hydrogens (*e.g.*, a hydrogen of the formula above that is not shown but understood to be present), expressly defined hydrogens, and optional hydrogens whose presence depends on the identity of a ring atom (*e.g.*, a hydrogen attached to group X, when X equals $-\text{CH}-$), so long as a stable structure is formed. In the example depicted, R may reside on either the 5-membered or the 6-membered ring of the fused ring system. In the formula above, the subscript letter “y” immediately following the group “R” enclosed in parentheses, represents a numeric variable. Unless specified otherwise, this variable can be 0, 1, 2, or any integer greater than 2, only limited by the maximum number of replaceable hydrogen atoms of the ring or ring system.

For the chemical groups and compound classes, the number of carbon atoms in the group or class is as indicated as follows: “C_n” defines the exact number (n) of carbon atoms in the group/class. “C_{≤n}” defines the maximum number (n) of carbon atoms that can be in

the group/class, with the minimum number as small as possible for the group/class in question, *e.g.*, it is understood that the minimum number of carbon atoms in the group “alkenyl_(C_{≤8})” or the class “alkene_(C_{≤8})” is two. Compare with “alkoxy_(C_{≤10})”, which designates alkoxy groups having from 1 to 10 carbon atoms. “C_n-n'” defines both the
 5 minimum (n) and maximum number (n') of carbon atoms in the group. Thus, “alkyl_(C₂₋₁₀)” designates those alkyl groups having from 2 to 10 carbon atoms. These carbon number indicators may precede or follow the chemical groups or class it modifies and it may or may not be enclosed in parenthesis, without signifying any change in meaning. Thus, the terms “C5 olefin”, “C5-olefin”, “olefin_(C5)”, and “olefin_{C5}” are all synonymous.

10 The term “saturated” when used to modify a compound or chemical group means the compound or chemical group has no carbon-carbon double and no carbon-carbon triple bonds, except as noted below. When the term is used to modify an atom, it means that the atom is not part of any double or triple bond. In the case of substituted versions of saturated groups, one or more carbon oxygen double bond or a carbon nitrogen double bond may be
 15 present. And when such a bond is present, then carbon-carbon double bonds that may occur as part of keto-enol tautomerism or imine/enamine tautomerism are not precluded. When the term “saturated” is used to modify a solution of a substance, it means that no more of that substance can dissolve in that solution.

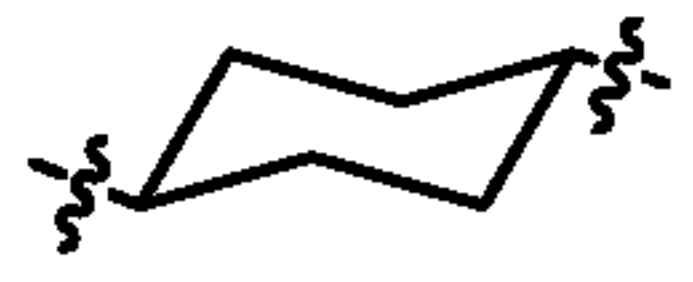
The term “aliphatic” when used without the “substituted” modifier signifies that the
 20 compound or chemical group so modified is an acyclic or cyclic, but non-aromatic hydrocarbon compound or group. In aliphatic compounds/groups, the carbon atoms can be joined together in straight chains, branched chains, or non-aromatic rings (alicyclic). Aliphatic compounds/groups can be saturated, that is joined by single carbon-carbon bonds (alkanes/alkyl), or unsaturated, with one or more carbon-carbon double bonds
 25 (alkenes/alkenyl) or with one or more carbon-carbon triple bonds (alkynes/alkynyl).

The term “aromatic” when used to modify a compound or a chemical group refers to a planar unsaturated ring of atoms with $4n + 2$ electrons in a fully conjugated cyclic π system.

The term “alkyl” when used without the “substituted” modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, a linear or branched
 30 acyclic structure, and no atoms other than carbon and hydrogen. The groups $-\text{CH}_3$ (Me), $-\text{CH}_2\text{CH}_3$ (Et), $-\text{CH}_2\text{CH}_2\text{CH}_3$ (*n*-Pr or propyl), $-\text{CH}(\text{CH}_3)_2$ (*i*-Pr, *i*Pr or isopropyl), $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ (*n*-Bu), $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ (*sec*-butyl), $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ (isobutyl), $-\text{C}(\text{CH}_3)_3$ (*tert*-butyl, *t*-butyl, *t*-Bu or *t*Bu), and $-\text{CH}_2\text{C}(\text{CH}_3)_3$ (*neo*-pentyl) are non-limiting

examples of alkyl groups. The term “alkanediyl” when used without the “substituted” modifier refers to a divalent saturated aliphatic group, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups $-\text{CH}_2-$ (methylene), $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, and $-\text{CH}_2\text{CH}_2\text{CH}_2-$ are non-limiting examples of alkanediyl groups. The term “alkylidene” when used without the “substituted” modifier refers to the divalent group $=\text{CRR}'$ in which R and R' are independently hydrogen or alkyl. Non-limiting examples of alkylidene groups include: $=\text{CH}_2$, $=\text{CH}(\text{CH}_2\text{CH}_3)$, and $=\text{C}(\text{CH}_3)_2$. An “alkane” refers to the class of compounds having the formula $\text{H}-\text{R}$, wherein R is alkyl as this term is defined above. When any of these terms is used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$. The following groups are non-limiting examples of substituted alkyl groups: $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{Cl}$, $-\text{CF}_3$, $-\text{CH}_2\text{CN}$, $-\text{CH}_2\text{C}(\text{O})\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{OCH}_3$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{C}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{NH}_2$, $-\text{CH}_2\text{N}(\text{CH}_3)_2$, and $-\text{CH}_2\text{CH}_2\text{Cl}$. The term “haloalkyl” is a subset of substituted alkyl, in which the hydrogen atom replacement is limited to halo (*i.e.* $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$) such that no other atoms aside from carbon, hydrogen and halogen are present. The group, $-\text{CH}_2\text{Cl}$ is a non-limiting example of a haloalkyl. The term “fluoroalkyl” is a subset of substituted alkyl, in which the hydrogen atom replacement is limited to fluoro such that no other atoms aside from carbon, hydrogen and fluorine are present. The groups $-\text{CH}_2\text{F}$, $-\text{CF}_3$, and $-\text{CH}_2\text{CF}_3$ are non-limiting examples of fluoroalkyl groups.

The term “cycloalkyl” when used without the “substituted” modifier refers to a monovalent saturated aliphatic group with a carbon atom as the point of attachment, said carbon atom forming part of one or more non-aromatic ring structures, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples include: $-\text{CH}(\text{CH}_2)_2$ (cyclopropyl), cyclobutyl, cyclopentyl, or cyclohexyl (Cy). The term “cycloalkanediyl” when used without the “substituted” modifier refers to a divalent saturated aliphatic group with two carbon atoms as points of attachment, no carbon-carbon double or

triple bonds, and no atoms other than carbon and hydrogen. The group  is a non-limiting example of cycloalkanediyl group. A “cycloalkane” refers to the class of compounds having the formula $\text{H}-\text{R}$, wherein R is cycloalkyl as this term is defined above.

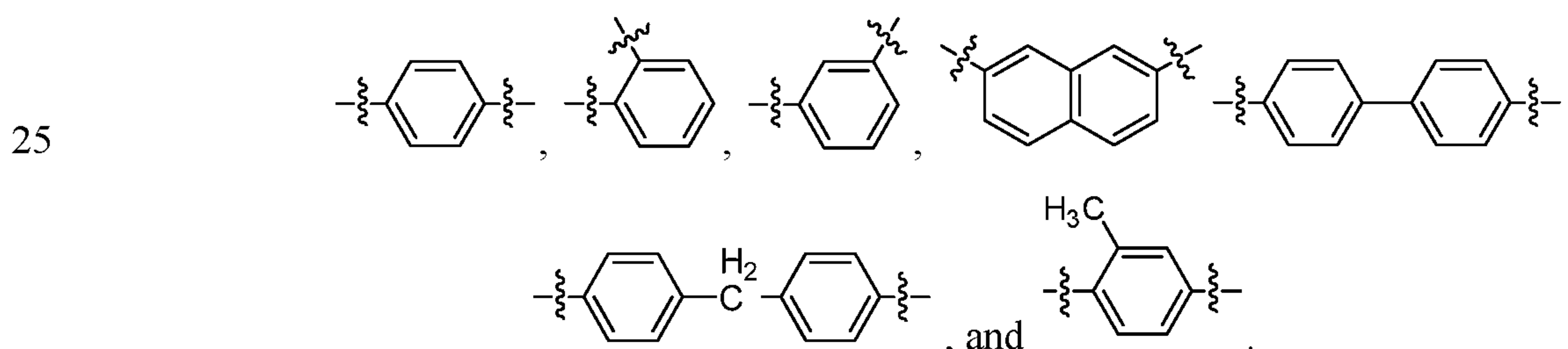
When any of these terms is used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or
 5 $-\text{S}(\text{O})_2\text{NH}_2$.

The term “alkenyl” when used without the “substituted” modifier refers to an monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched, acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting
 10 examples include: $-\text{CH}=\text{CH}_2$ (vinyl), $-\text{CH}=\text{CHCH}_3$, $-\text{CH}=\text{CHCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}=\text{CH}_2$ (allyl), $-\text{CH}_2\text{CH}=\text{CHCH}_3$, and $-\text{CH}=\text{CHCH}=\text{CH}_2$. The term “alkenediyl” when used without the “substituted” modifier refers to a divalent unsaturated aliphatic group, with two carbon atoms as points of attachment, a linear or branched, a linear or branched acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no
 15 atoms other than carbon and hydrogen. The groups $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{C}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}=\text{CHCH}_2-$, and $-\text{CH}_2\text{CH}=\text{CHCH}_2-$ are non-limiting examples of alkenediyl groups. It is noted that while the alkenediyl group is aliphatic, once connected at both ends, this group is not precluded from forming part of an aromatic structure. The terms “alkene” and “olefin” are synonymous and refer to the class of compounds having the formula $\text{H}-\text{R}$, wherein R is
 20 alkenyl as this term is defined above. Similarly the terms “terminal alkene” and “ α -olefin” are synonymous and refer to an alkene having just one carbon-carbon double bond, wherein that bond is part of a vinyl group at an end of the molecule. When any of these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$,
 25 $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$. The groups $-\text{CH}=\text{CHF}$, $-\text{CH}=\text{CHCl}$ and $-\text{CH}=\text{CHBr}$ are non-limiting examples of substituted alkenyl groups.

The term “alkynyl” when used without the “substituted” modifier refers to a
 30 monovalent unsaturated aliphatic group with a carbon atom as the point of attachment, a linear or branched acyclic structure, at least one carbon-carbon triple bond, and no atoms other than carbon and hydrogen. As used herein, the term alkynyl does not preclude the presence of one or more non-aromatic carbon-carbon double bonds. The groups $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{CCH}_3$, and $-\text{CH}_2\text{C}\equiv\text{CCH}_3$ are non-limiting examples of alkynyl groups. An “alkyne”

refers to the class of compounds having the formula H-R, wherein R is alkynyl. When any of these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃, -CN, -SH, -OCH₃, -OCH₂CH₃, -C(O)CH₃, -NHCH₃, -NHCH₂CH₃, -N(CH₃)₂, -C(O)NH₂,
 5 -C(O)NHCH₃, -C(O)N(CH₃)₂, -OC(O)CH₃, -NHC(O)CH₃, -S(O)₂OH, or -S(O)₂NH₂.

The term “aryl” when used without the “substituted” modifier refers to a monovalent unsaturated aromatic group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of a one or more six-membered aromatic ring structure, wherein the ring atoms are all carbon, and wherein the group consists of no atoms other than carbon
 10 and hydrogen. If more than one ring is present, the rings may be fused or unfused. As used herein, the term does not preclude the presence of one or more alkyl or aralkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, -C₆H₄CH₂CH₃ (ethylphenyl), naphthyl, and a monovalent
 15 group derived from biphenyl. The term “arenediyl” when used without the “substituted” modifier refers to a divalent aromatic group with two aromatic carbon atoms as points of attachment, said carbon atoms forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. As used herein, the term does not preclude the
 20 presence of one or more alkyl, aryl or aralkyl groups (carbon number limitation permitting) attached to the first aromatic ring or any additional aromatic ring present. If more than one ring is present, the rings may be fused or unfused. Unfused rings may be connected via one or more of the following: a covalent bond, alkanediyl, or alkenediyl groups (carbon number limitation permitting). Non-limiting examples of arenediyl groups include:



An “arene” refers to the class of compounds having the formula H-R, wherein R is aryl as that term is defined above. Benzene and toluene are non-limiting examples of arenes. When any of these terms are used with the “substituted” modifier one or more hydrogen atom has
 30 been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂, -CO₂H, -CO₂CH₃,

–CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –NHCH₃, –NHCH₂CH₃, –N(CH₃)₂,
 –C(O)NH₂, –C(O)NHCH₃, –C(O)N(CH₃)₂, –OC(O)CH₃, –NHC(O)CH₃, –S(O)₂OH, or
 –S(O)₂NH₂.

The term “aralkyl” when used without the “substituted” modifier refers to the
 5 monovalent group –alkanediyl–aryl, in which the terms alkanediyl and aryl are each used in a
 manner consistent with the definitions provided above. Non-limiting examples are:
 phenylmethyl (benzyl, Bn) and 2-phenyl-ethyl. When the term aralkyl is used with the
 “substituted” modifier one or more hydrogen atom from the alkanediyl and/or the aryl group
 has been independently replaced by –OH, –F, –Cl, –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃,
 10 –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –NHCH₃, –NHCH₂CH₃, –N(CH₃)₂,
 –C(O)NH₂, –C(O)NHCH₃, –C(O)N(CH₃)₂, –OC(O)CH₃, –NHC(O)CH₃, –S(O)₂OH, or
 –S(O)₂NH₂. Non-limiting examples of substituted aralkyls are: (3-chlorophenyl)-methyl, and
 2-chloro-2-phenyl-eth-1-yl.

The term “heteroaryl” when used without the “substituted” modifier refers to a
 15 monovalent aromatic group with an aromatic carbon atom or nitrogen atom as the point of
 attachment, said carbon atom or nitrogen atom forming part of one or more aromatic ring
 structures wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein
 the heteroaryl group consists of no atoms other than carbon, hydrogen, aromatic nitrogen,
 aromatic oxygen and aromatic sulfur. If more than one ring is present, the rings may be fused
 20 or unfused. As used herein, the term does not preclude the presence of one or more alkyl,
 aryl, and/or aralkyl groups (carbon number limitation permitting) attached to the aromatic
 ring or aromatic ring system. Non-limiting examples of heteroaryl groups include furanyl,
 imidazolyl, indolyl, indazolyl (Im), isoxazolyl, methylpyridinyl, oxazolyl, phenylpyridinyl,
 pyridinyl (pyridyl), pyrrolyl, pyrimidinyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl,
 25 triazinyl, tetrazolyl, thiazolyl, thienyl, and triazolyl. The term “N-heteroaryl” refers to a
 heteroaryl group with a nitrogen atom as the point of attachment. A “heteroarene” refers to
 the class of compounds having the formula H–R, wherein R is heteroaryl. Pyridine and
 quinoline are non-limiting examples of heteroarenes. When these terms are used with the
 “substituted” modifier one or more hydrogen atom has been independently replaced by –OH,
 30 –F, –Cl, –Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃,
 –C(O)CH₃, –NHCH₃, –NHCH₂CH₃, –N(CH₃)₂, –C(O)NH₂, –C(O)NHCH₃, –C(O)N(CH₃)₂,
 –OC(O)CH₃, –NHC(O)CH₃, –S(O)₂OH, or –S(O)₂NH₂.

The term “heterocycloalkyl” when used without the “substituted” modifier refers to a
 monovalent non-aromatic group with a carbon atom or nitrogen atom as the point of

attachment, said carbon atom or nitrogen atom forming part of one or more non-aromatic ring structures wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the heterocycloalkyl group consists of no atoms other than carbon, hydrogen, nitrogen, oxygen and sulfur. If more than one ring is present, the rings may be fused or unfused. As
 5 used herein, the term does not preclude the presence of one or more alkyl groups (carbon number limitation permitting) attached to the ring or ring system. Also, the term does not preclude the presence of one or more double bonds in the ring or ring system, provided that the resulting group remains non-aromatic. Non-limiting examples of heterocycloalkyl groups include aziridinyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl,
 10 thiomorpholinyl, tetrahydrofuranyl, tetrahydrothiofuranyl, tetrahydropyranyl, pyranly, oxiranyl, and oxetanyl. The term “*N*-heterocycloalkyl” refers to a heterocycloalkyl group with a nitrogen atom as the point of attachment. *N*-pyrrolidinyl is an example of such a group. When these terms are used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$,
 15 $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$, $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$.

The term “acyl” when used without the “substituted” modifier refers to the group $-\text{C}(\text{O})\text{R}$, in which R is a hydrogen, alkyl, cycloalkyl, alkenyl, aryl, aralkyl or heteroaryl, as
 20 those terms are defined above. The groups $-\text{CHO}$, $-\text{C}(\text{O})\text{CH}_3$ (acetyl, Ac), $-\text{C}(\text{O})\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{CH}(\text{CH}_2)_2$, $-\text{C}(\text{O})\text{C}_6\text{H}_5$, $-\text{C}(\text{O})\text{C}_6\text{H}_4\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_2\text{C}_6\text{H}_5$, $-\text{C}(\text{O})$ (imidazolyl) are non-limiting examples of acyl groups. A “thioacyl” is defined in an analogous manner, except that the oxygen atom of the group $-\text{C}(\text{O})\text{R}$ has been replaced with a sulfur atom, $-\text{C}(\text{S})\text{R}$. The term “aldehyde” corresponds to an alkane, as
 25 defined above, wherein at least one of the hydrogen atoms has been replaced with a $-\text{CHO}$ group. When any of these terms are used with the “substituted” modifier one or more hydrogen atom (including a hydrogen atom directly attached to the carbon atom of the carbonyl or thiocarbonyl group, if any) has been independently replaced by $-\text{OH}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{I}$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{CH}_3$, $-\text{CN}$, $-\text{SH}$, $-\text{OCH}_3$, $-\text{OCH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{CH}_3$,
 30 $-\text{NHCH}_3$, $-\text{NHCH}_2\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NHCH}_3$, $-\text{C}(\text{O})\text{N}(\text{CH}_3)_2$, $-\text{OC}(\text{O})\text{CH}_3$, $-\text{NHC}(\text{O})\text{CH}_3$, $-\text{S}(\text{O})_2\text{OH}$, or $-\text{S}(\text{O})_2\text{NH}_2$. The groups, $-\text{C}(\text{O})\text{CH}_2\text{CF}_3$, $-\text{CO}_2\text{H}$ (carboxyl), $-\text{CO}_2\text{CH}_3$ (methylcarboxyl), $-\text{CO}_2\text{CH}_2\text{CH}_3$, $-\text{C}(\text{O})\text{NH}_2$ (carbamoyl), and $-\text{CON}(\text{CH}_3)_2$, are non-limiting examples of substituted acyl groups.

The term “alkoxy” when used without the “substituted” modifier refers to the group $-OR$, in which R is an alkyl, as that term is defined above. Non-limiting examples include: $-OCH_3$ (methoxy), $-OCH_2CH_3$ (ethoxy), $-OCH_2CH_2CH_3$, $-OCH(CH_3)_2$ (isopropoxy), $-OC(CH_3)_3$ (*tert*-butoxy), $-OCH(CH_2)_2$, $-O$ -cyclopentyl, and $-O$ -cyclohexyl. The terms “cycloalkoxy”, “alkenyloxy”, “alkynyloxy”, “aryloxy”, “aralkoxy”, “heteroaryloxy”, “heterocycloalkoxy”, and “acyloxy”, when used without the “substituted” modifier, refers to groups, defined as $-OR$, in which R is cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, and acyl, respectively. The term “alkylthio” and “acylthio” when used without the “substituted” modifier refers to the group $-SR$, in which R is an alkyl and acyl, respectively. The term “alcohol” corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with a hydroxy group. The term “ether” corresponds to an alkane, as defined above, wherein at least one of the hydrogen atoms has been replaced with an alkoxy group. When any of these terms is used with the “substituted” modifier one or more hydrogen atom has been independently replaced by $-OH$, $-F$, $-Cl$, $-Br$, $-I$, $-NH_2$, $-NO_2$, $-CO_2H$, $-CO_2CH_3$, $-CN$, $-SH$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-NHCH_3$, $-NHCH_2CH_3$, $-N(CH_3)_2$, $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-OC(O)CH_3$, $-NHC(O)CH_3$, $-S(O)_2OH$, or $-S(O)_2NH_2$.

The term “alkylamino” when used without the “substituted” modifier refers to the group $-NHR$, in which R is an alkyl, as that term is defined above. Non-limiting examples include: $-NHCH_3$ and $-NHCH_2CH_3$. The term “dialkylamino” when used without the “substituted” modifier refers to the group $-NRR'$, in which R and R' can be the same or different alkyl groups, or R and R' can be taken together to represent an alkanediyl. Non-limiting examples of dialkylamino groups include: $-N(CH_3)_2$ and $-N(CH_3)(CH_2CH_3)$. The terms “cycloalkylamino”, “alkenylamino”, “alkynylamino”, “arylamino”, “aralkylamino”, “heteroarylamino”, “heterocycloalkylamino”, “alkoxyamino”, and “alkylsulfonylamino” when used without the “substituted” modifier, refers to groups, defined as $-NHR$, in which R is cycloalkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heterocycloalkyl, alkoxy, and alkylsulfonyl, respectively. A non-limiting example of an arylamino group is $-NHC_6H_5$. The term “amido” (acylamino), when used without the “substituted” modifier, refers to the group $-NHR$, in which R is acyl, as that term is defined above. A non-limiting example of an amido group is $-NHC(O)CH_3$. The term “alkylimino” when used without the “substituted” modifier refers to the divalent group $=NR$, in which R is an alkyl, as that term is defined above. When any of these terms is used with the “substituted” modifier one or more hydrogen atom attached to a carbon atom has been independently replaced by $-OH$, $-F$, $-Cl$,

–Br, –I, –NH₂, –NO₂, –CO₂H, –CO₂CH₃, –CN, –SH, –OCH₃, –OCH₂CH₃, –C(O)CH₃, –NHCH₃, –NHCH₂CH₃, –N(CH₃)₂, –C(O)NH₂, –C(O)NHCH₃, –C(O)N(CH₃)₂, –OC(O)CH₃, –NHC(O)CH₃, –S(O)₂OH, or –S(O)₂NH₂. The groups –NHC(O)OCH₃ and –NHC(O)NHCH₃ are non-limiting examples of substituted amido groups.

5 The use of the word “a” or “an,” when used in conjunction with the term “comprising” in the claims and/or the specification may mean “one,” but it is also consistent with the meaning of “one or more,” “at least one,” and “one or more than one.”

 Throughout this application, the term “about” is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the
10 value, or the variation that exists among the study subjects.

 The term “acetal” is used to describe a carbonyl group which have reacted with two hydroxy or a dihydroxy containing compounds to form a diether of a geminal diol of the structure R₂C(OR')₂ arising from the carbonyl group of the structure: R₂C(O), wherein neither R' is not hydrogen and each R' may be the same, different, or may be taken together
15 to form a ring. A “mixed acetal” is an acetal wherein R' are both different. “Acetal” may be used to describe the carbonyl group, which is an aldehyde, wherein one or both R groups are hydrogen atoms, or a ketone, wherein neither R group is a hydrogen atom. “Ketal” is a subgroup of “acetal” wherein the carbonyl group is a ketone. The term “hemiacetal” is used to describe a carbonyl group which has been reacted with one hydroxy containing compound
20 to form a monoether of a geminal diol forming a group of the structure: R₂C(OH)OR', wherein R' is not hydrogen. “Hemiacetal” may be used to describe the carbonyl group that is an aldehyde, wherein one or both R groups are hydrogen atoms, or a ketone, wherein neither R group is a hydrogen atom. Analogous to “ketal”, a “hemiketal” is a subgroup of “hemiacetal” wherein the carbonyl group is a ketone.

25 The terms “comprise,” “have” and “include” are open-ended linking verbs. Any forms or tenses of one or more of these verbs, such as “comprises,” “comprising,” “has,” “having,” “includes” and “including,” are also open-ended. For example, any method that “comprises,” “has” or “includes” one or more steps is not limited to possessing only those one or more steps and also covers other unlisted steps.

30 The term “effective,” as that term is used in the specification and/or claims, means adequate to accomplish a desired, expected, or intended result. “Effective amount,” “Therapeutically effective amount” or “pharmaceutically effective amount” when used in the context of treating a patient or subject with a compound means that amount of the compound

which, when administered to a subject or patient for treating a disease, is sufficient to effect such treatment for the disease.

As used herein, the term “IC₅₀” refers to an inhibitory dose which is 50% of the maximum response obtained. This quantitative measure indicates how much of a particular drug or other substance (inhibitor) is needed to inhibit a given biological, biochemical or chemical process (or component of a process, i.e. an enzyme, cell, cell receptor or microorganism) by half.

An “isomer” of a first compound is a separate compound in which each molecule contains the same constituent atoms as the first compound, but where the configuration of those atoms in three dimensions differs.

As used herein, the term “normal” or “normality” refers to the concentration of a solution wherein the molar concentration is divided by the equivalence factor. The equivalence factor is the number of ions which are obtained from a compound when it has dissociated in a solution. For a solution such as HCl, the solution is 1 N in both protons and 1 N concentration of chloride ions, whereas a solution of CaCl₂ is 1 N in calcium ions and 2 N in chloride ions.

As used herein, the term “patient” or “subject” refers to a living mammalian organism, such as a human, monkey, cow, sheep, goat, dog, cat, mouse, rat, guinea pig, or transgenic species thereof. In certain embodiments, the patient or subject is a primate. Non-limiting examples of human subjects are adults, juveniles, infants and fetuses.

As generally used herein “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues, organs, and/or bodily fluids of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications commensurate with a reasonable benefit/risk ratio.

“Pharmaceutically acceptable salts” means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, 2-naphthalenesulfonic acid, 3-phenylpropionic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, acetic acid, aliphatic mono- and dicarboxylic acids, aliphatic sulfuric acids, aromatic sulfuric acids, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, carbonic

acid, cinnamic acid, citric acid, cyclopentanepropionic acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, glycolic acid, heptanoic acid, hexanoic acid, hydroxynaphthoic acid, lactic acid, laurylsulfuric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, muconic acid, *o*-(4-hydroxybenzoyl)benzoic acid, oxalic acid, *p*-chlorobenzenesulfonic acid, phenyl-substituted alkanoic acids, propionic acid, *p*-toluenesulfonic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, tartaric acid, tertiarybutylacetic acid, trimethylacetic acid, and the like. Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like. It should be recognized that the particular anion or cation forming a part of any salt of this invention is not critical, so long as the salt, as a whole, is pharmacologically acceptable. Additional examples of pharmaceutically acceptable salts and their methods of preparation and use are presented in *Handbook of Pharmaceutical Salts: Properties, and Use* (P. H. Stahl & C. G. Wermuth eds., Verlag Helvetica Chimica Acta, 2002).

The term “pharmaceutically acceptable carrier,” as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical agent.

“Prevention” or “preventing” includes: (1) inhibiting the onset of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease, and/or (2) slowing the onset of the pathology or symptomatology of a disease in a subject or patient which may be at risk and/or predisposed to the disease but does not yet experience or display any or all of the pathology or symptomatology of the disease.

A “stereoisomer” or “optical isomer” is an isomer of a given compound in which the same atoms are bonded to the same other atoms, but where the configuration of those atoms in three dimensions differs. “Enantiomers” are stereoisomers of a given compound that are mirror images of each other, like left and right hands. “Diastereomers” are stereoisomers of a given compound that are not enantiomers. Chiral molecules contain a chiral center, also referred to as a stereocenter or stereogenic center, which is any point, though not necessarily an atom, in a molecule bearing groups such that an interchanging of any two groups leads to a

stereoisomer. In organic compounds, the chiral center is typically a carbon, phosphorus or sulfur atom, though it is also possible for other atoms to be stereocenters in organic and inorganic compounds. A molecule can have multiple stereocenters, giving it many stereoisomers. In compounds whose stereoisomerism is due to tetrahedral stereogenic centers (e.g., tetrahedral carbon), the total number of hypothetically possible stereoisomers will not exceed 2^n , where n is the number of tetrahedral stereocenters. Molecules with symmetry frequently have fewer than the maximum possible number of stereoisomers. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Alternatively, a mixture of enantiomers can be enantiomerically enriched so that one enantiomer is present in an amount greater than 50%. Typically, enantiomers and/or diastereomers can be resolved or separated using techniques known in the art. It is contemplated that for any stereocenter or axis of chirality for which stereochemistry has not been defined, that stereocenter or axis of chirality can be present in its *R* form, *S* form, or as a mixture of the *R* and *S* forms, including racemic and non-racemic mixtures. As used herein, the phrase “substantially free from other stereoisomers” means that the composition contains $\leq 15\%$, more preferably $\leq 10\%$, even more preferably $\leq 5\%$, or most preferably $\leq 1\%$ of another stereoisomer(s).

“Treatment” or “treating” includes (1) inhibiting a disease in a subject or patient experiencing or displaying the pathology or symptomatology of the disease (e.g., arresting further development of the pathology and/or symptomatology), (2) ameliorating a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease (e.g., reversing the pathology and/or symptomatology), and/or (3) effecting any measurable decrease in a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

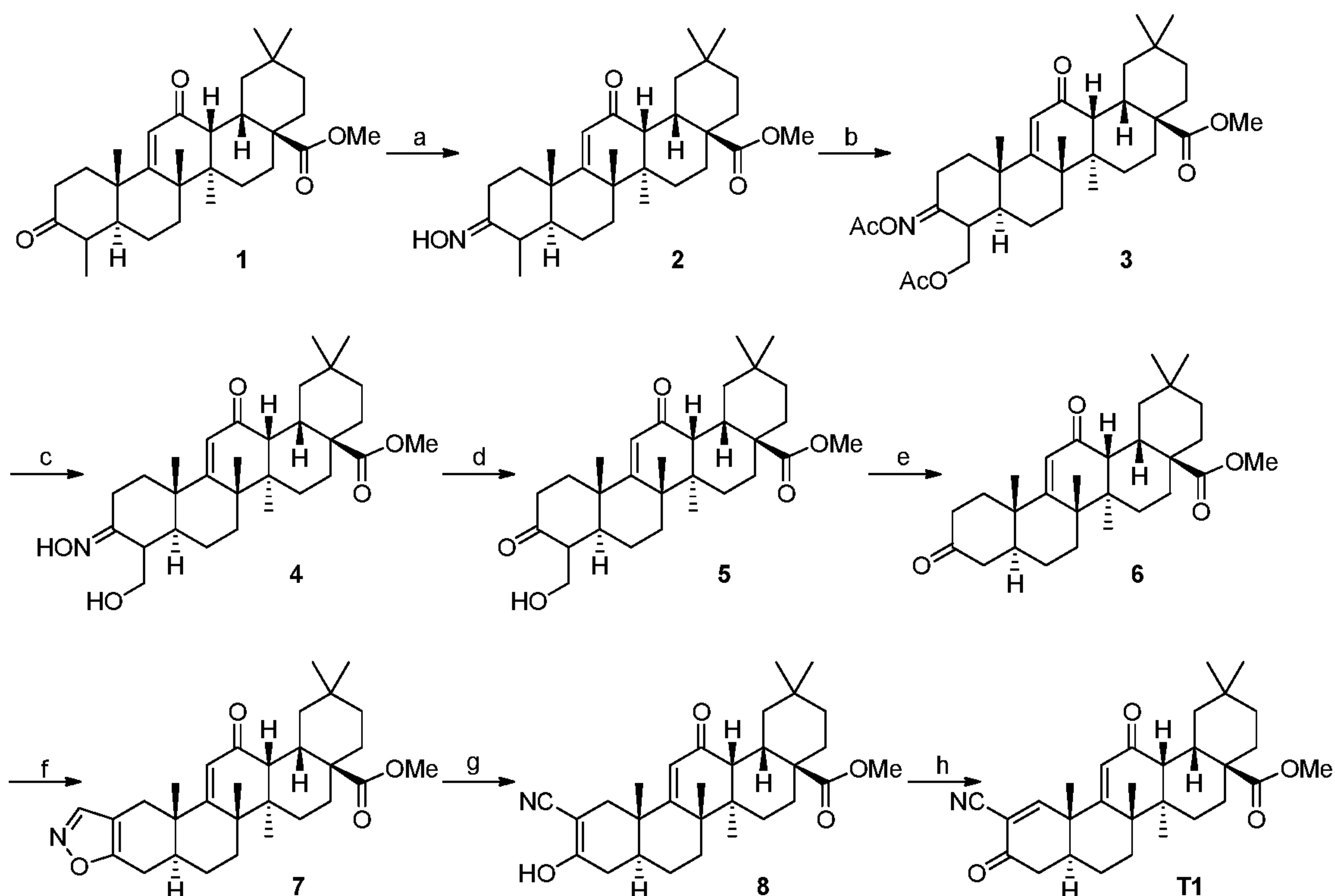
Other abbreviations used herein are as follows: NO, nitric oxide; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; FBS, fetal bovine serum; IFN γ or IFN- γ , interferon- γ ; TNF α or TNF- α , tumor necrosis factor- α ; IL-1 β , interleukin-1 β ; IL17 or IL-17, interleukin 17; HO-1, inducible heme oxygenase; Me, methyl; Bn, benzyl; Et, ethyl; Ph, phenyl; Ac, acetyl; Bz, benzoyl; Ts, tosyl; Boc, *t*-butyloxycarbonyl; quant., quantitative; aq., aqueous; w/w, weight per weight; $^{\circ}\text{C}$, degrees Celsius, N, normal or normality; h or hr, hours; rt, room temperature; TLC, thin layer chromatography; DMSO, dimethyl sulfoxide; EtOAc, ethyl acetate; DMF, *N,N*-dimethylformamide; DMA, dimethylacetamide; MeCN, acetonitrile; MTBE, methyl *t*-butylether; Et₂O, diethyl ether; THF, tetrahydrofuran; MeOH, methanol, EtOH, ethanol; *i*PrOH, isopropanol; Pd/C, palladium on carbon; Py, pyridine; DIPEA,

diisopropylethylamine; DMAP, dimethylaminopyridine; mCPBA, *m*-chloroperoxybenzoic acid; MOMCl, methoxymethyl chloride; TBSCl, *t*-butyldimethylsilyl chloride; SEMCl, 2-(trimethylsilyl)ethoxymethyl chloride; DMP, Dess Martin periodinane; T₃P®, propylphosphonic anhydride; DPPA, diphenylphosphoryl azide; PPTS, pyridinium *p*-toluenesulfonate; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DAST, diethylaminosulfur trifluoride; TMSCHN₂, trimethylsilyldiazomethane; DBDMH, 1,3-dibromo-5,5-dimethylhydantoin.

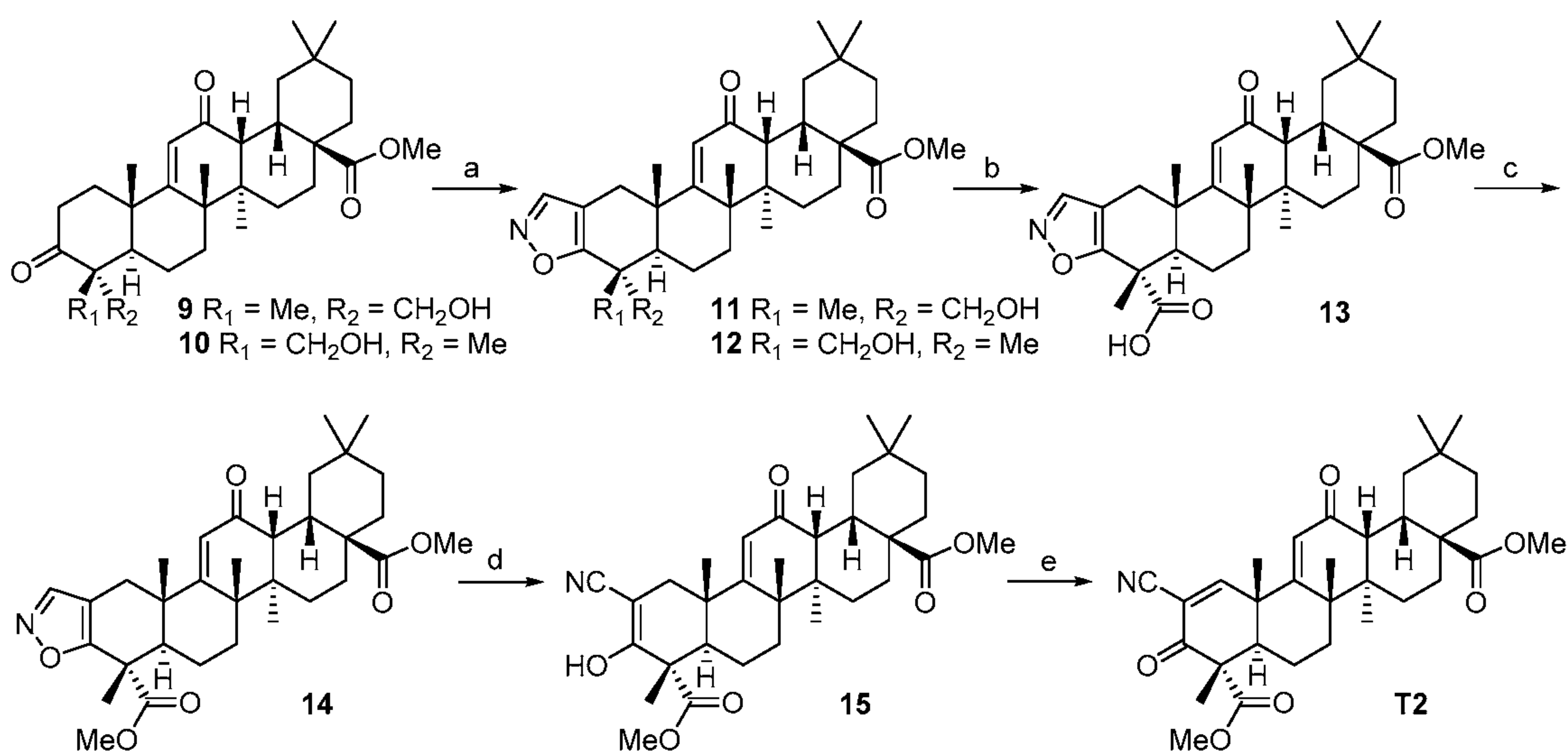
The above definitions supersede any conflicting definition in any reference that is incorporated by reference herein. The fact that certain terms are defined, however, should not be considered as indicative that any term that is undefined is indefinite. Rather, all terms used are believed to describe the invention in terms such that one of ordinary skill can appreciate the scope and practice the present invention.

VI. Examples

The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1: Synthesis and Characterization**Scheme 1**

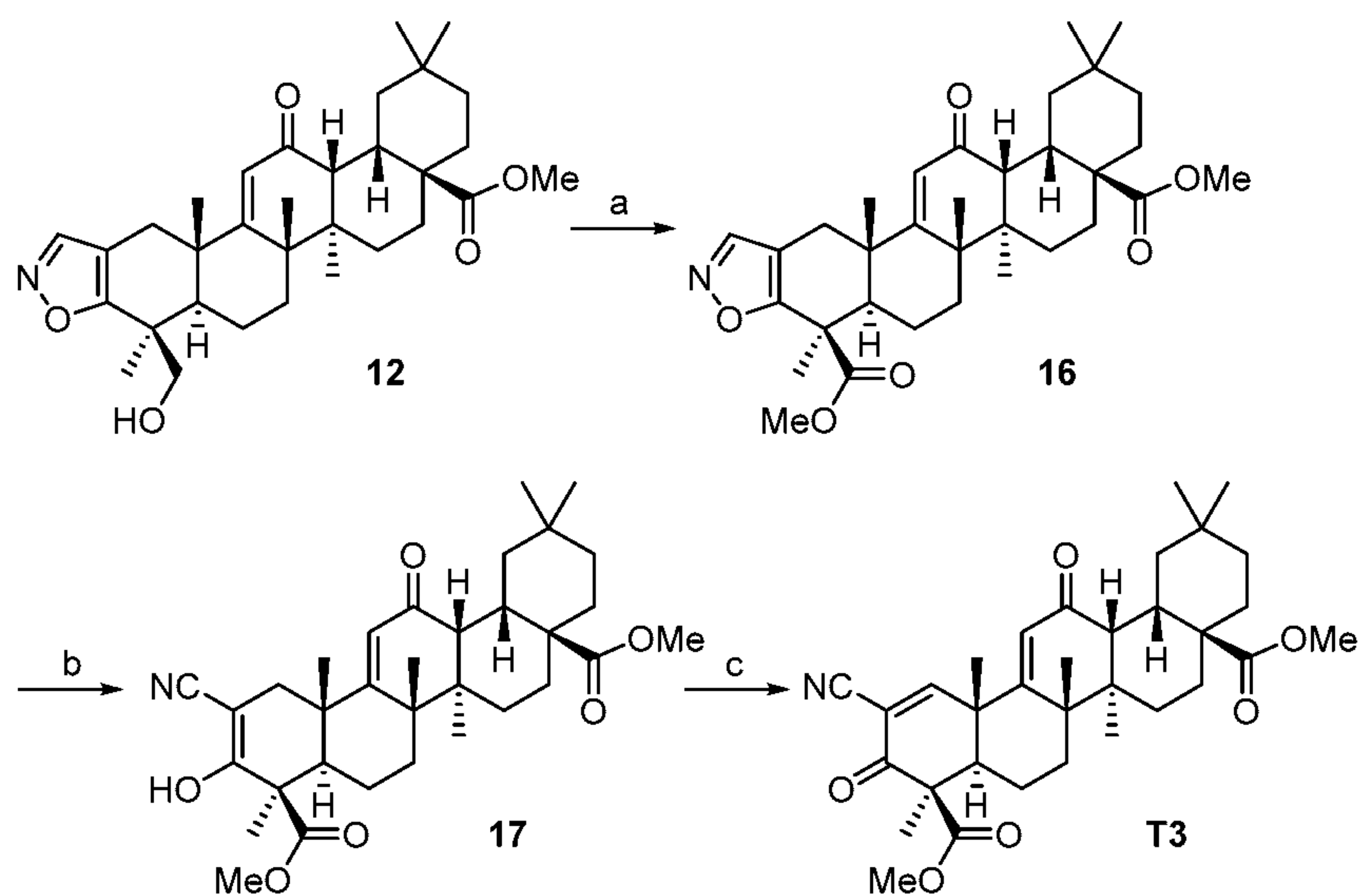
Reagents and conditions: a) $\text{NH}_2\text{OH}\cdot\text{HCl}$, NaOAc , CH_2Cl_2 , MeOH , 60°C ; b) AcOH , Ac_2O ; $\text{PhI}(\text{OAc})_2$, $\text{Pd}(\text{OAc})_2$, $\text{ClCH}_2\text{CH}_2\text{Cl}$, $60\text{--}80^\circ\text{C}$, 43% from **1**; c) K_2CO_3 , MeOH , rt; d) sodium bisulfite, aq. EtOH , 80°C , 73% from **3**; e) Jones reagent, acetone, 0°C ; $80\text{--}120^\circ\text{C}$, vacuum, 81%; f) HCO_2Et , NaOMe , MeOH , THF , 0°C –rt; $\text{NH}_2\text{OH}\cdot\text{HCl}$, aq. EtOH , 55°C , 44%; g) NaOMe , MeOH , THF , 55°C , 51%; h) DBDMH , DMF , 0°C ; Py , 55°C , 80%.

Scheme 2

10

Reagents and conditions: a) HCO_2Et , NaOMe , MeOH , $0\text{ }^\circ\text{C}$; $\text{NH}_2\text{OH}\cdot\text{HCl}$, aq. EtOH , $55\text{ }^\circ\text{C}$, 57%; b) Jones reagent, acetone, $0\text{ }^\circ\text{C}$ -rt, 88%; c) TMSCHN_2 , Et_2O , toluene, MeOH , $0\text{ }^\circ\text{C}$, 84%; d) NaOMe , MeOH , $55\text{ }^\circ\text{C}$, quantitative yield; e) DBDMH , DMF , $0\text{ }^\circ\text{C}$; Py , $55\text{ }^\circ\text{C}$, 77%.

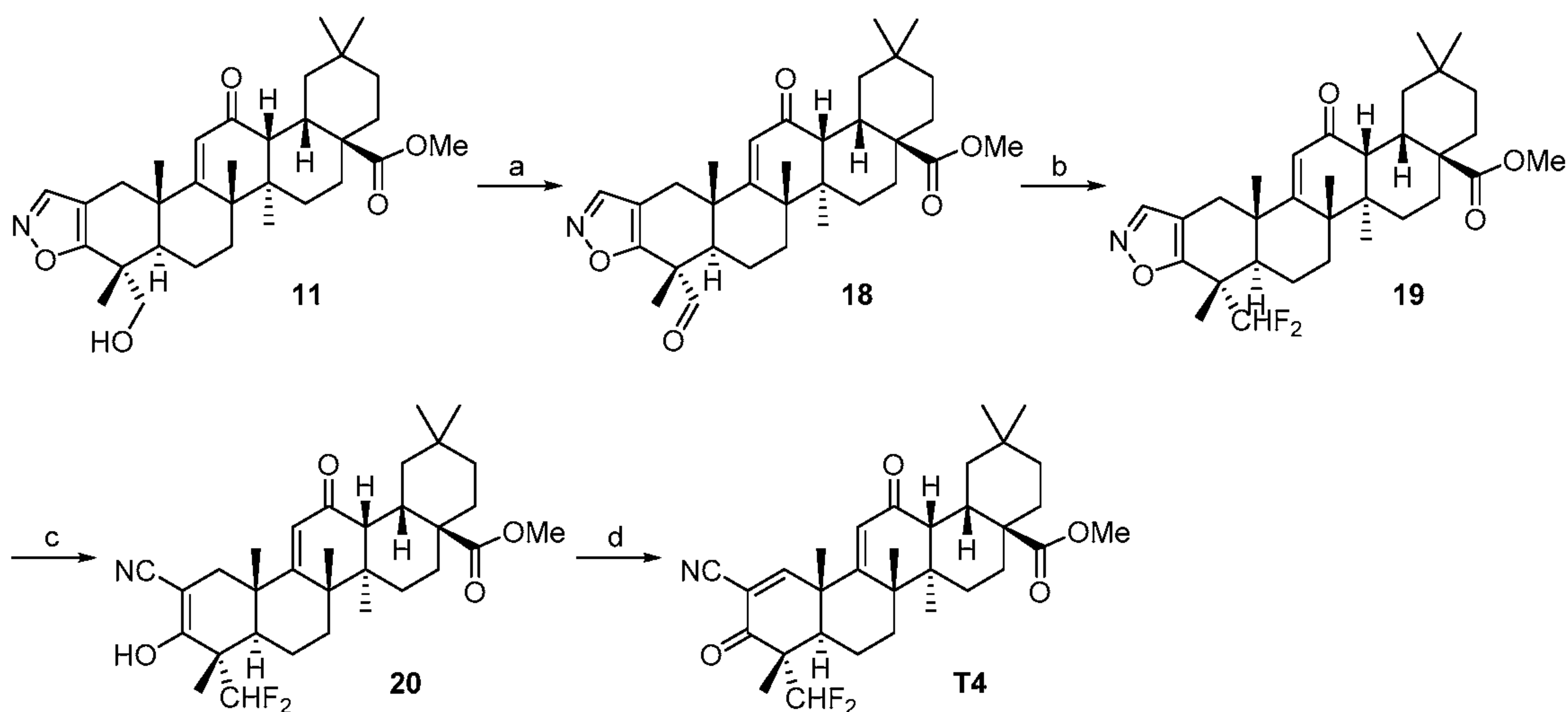
Scheme 3



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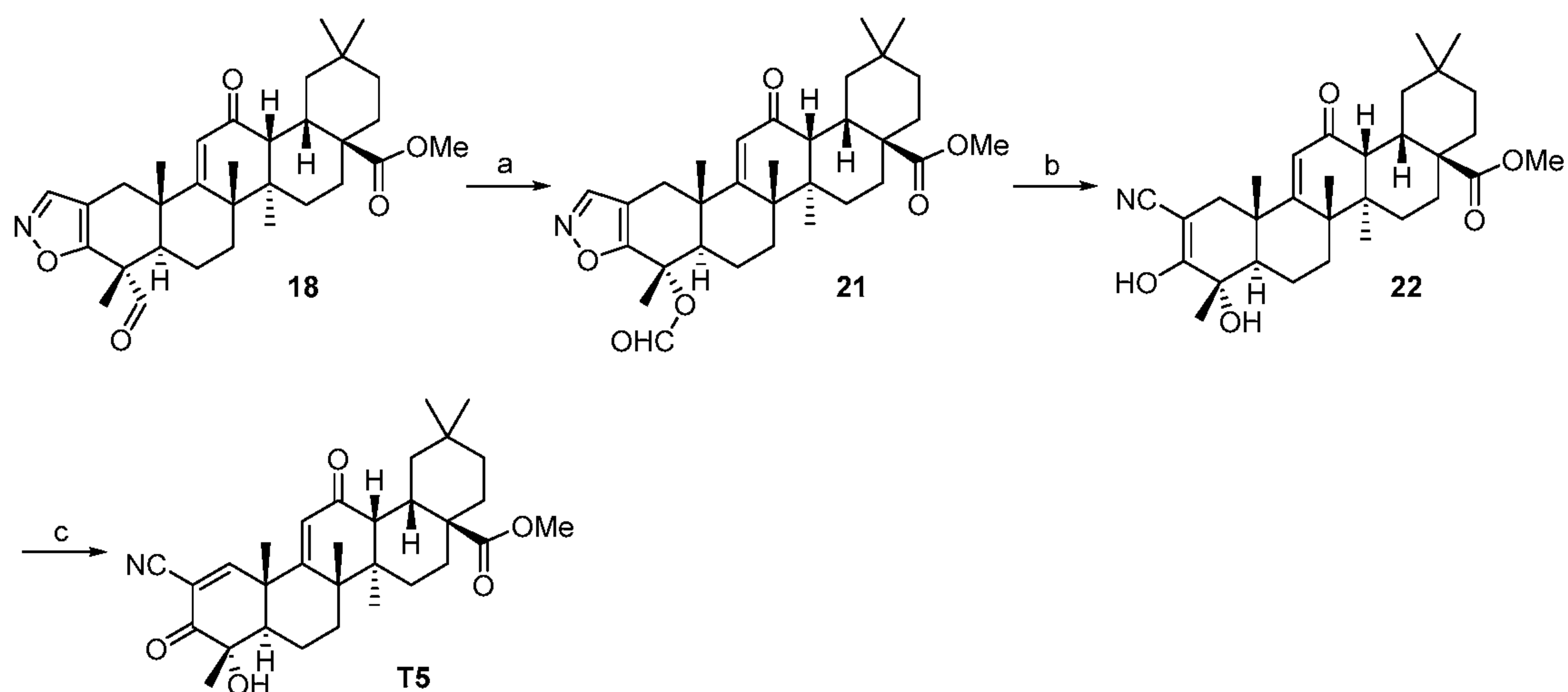
Reagents and conditions: a) i) Jones reagent, acetone, $0\text{ }^\circ\text{C}$ -rt; ii) TMSCHN_2 , Et_2O , toluene, MeOH , $0\text{ }^\circ\text{C}$, 49% from 12; b) NaOMe , MeOH , $55\text{ }^\circ\text{C}$, 75%; c) DBDMH , DMF , $0\text{ }^\circ\text{C}$; Py , $55\text{ }^\circ\text{C}$, 74%.

Scheme 4

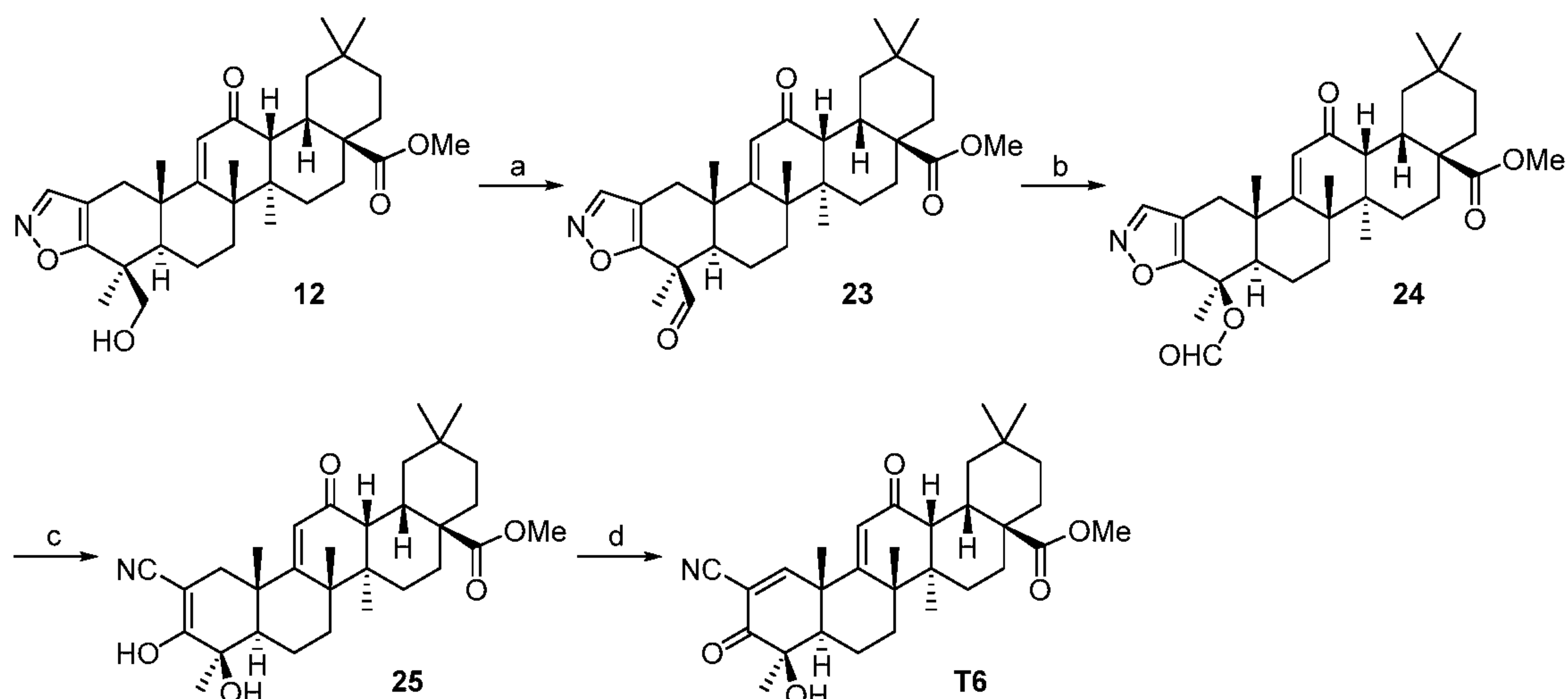


10

Reagents and conditions: a) $(\text{COCl})_2$, DMSO , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$; Et_3N , $-78\text{ }^\circ\text{C}$ -rt, 86%; b) i) DAST , CH_2Cl_2 , rt; ii) NaBH_4 , MeOH , $0\text{ }^\circ\text{C}$, 32%; c) NaOMe , MeOH , $55\text{ }^\circ\text{C}$, 82%; d) DBDMH , DMF , $0\text{ }^\circ\text{C}$; Py , $55\text{ }^\circ\text{C}$, 86%.

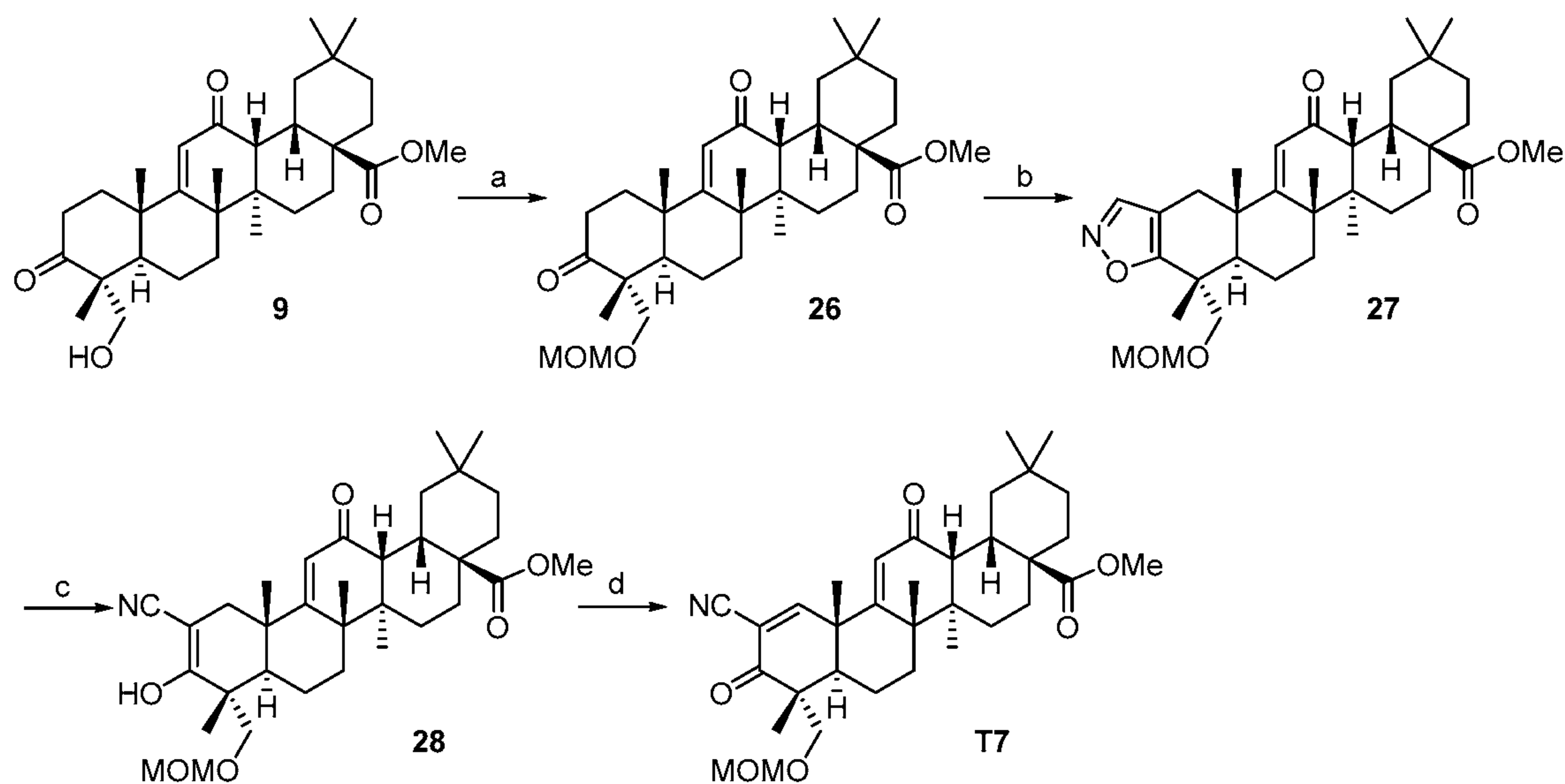
Scheme 5

Reagents and conditions: a) Na_2HPO_4 , *m*-CPBA, CH_2Cl_2 , rt, 86%; b) NaOMe, MeOH, 55 °C, 98%; c) DBDMH, DMF, 0 °C; Py, 55 °C, 80%.

5 Scheme 6

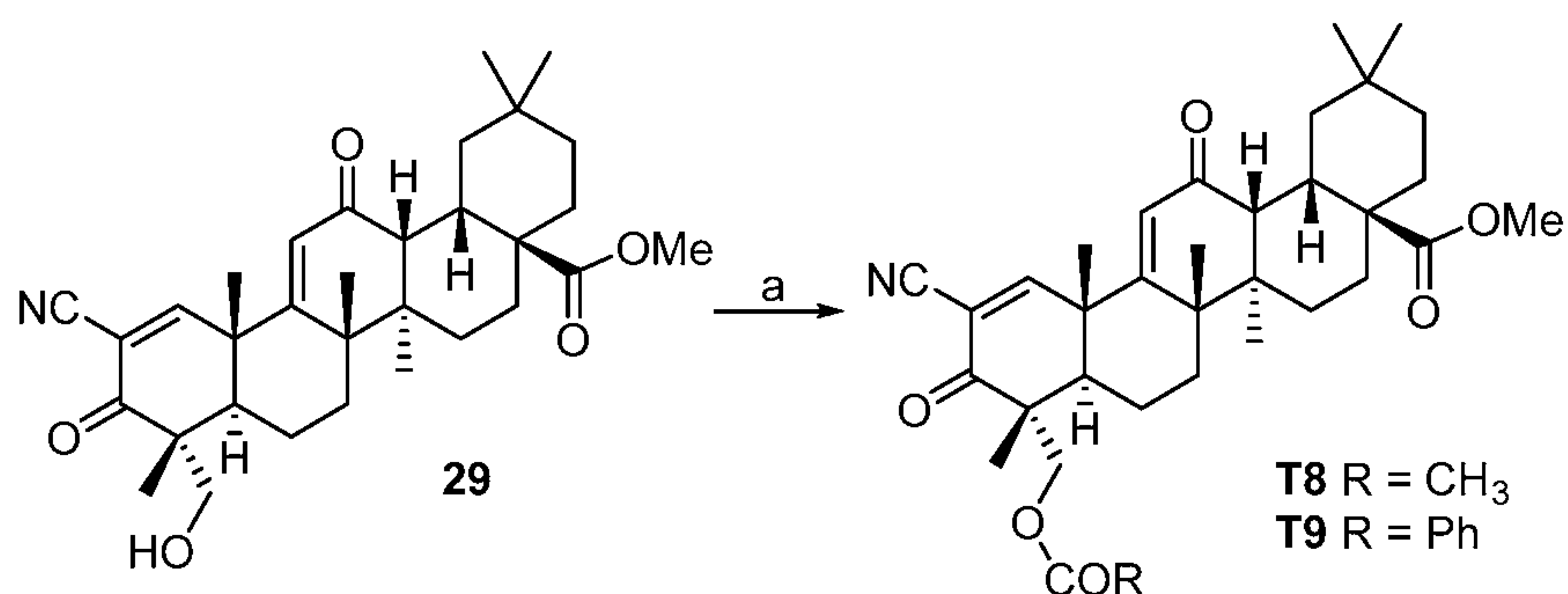
Reagents and conditions: a) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78 °C; Et_3N , -78 °C-rt, 72%; b) Na_2HPO_4 , *m*-CPBA, CH_2Cl_2 , rt, 63%; c) NaOMe, MeOH, 55 °C, 68%; d) DBDMH, DMF, 0 °C; Py, 55 °C, 63%.

Scheme 7



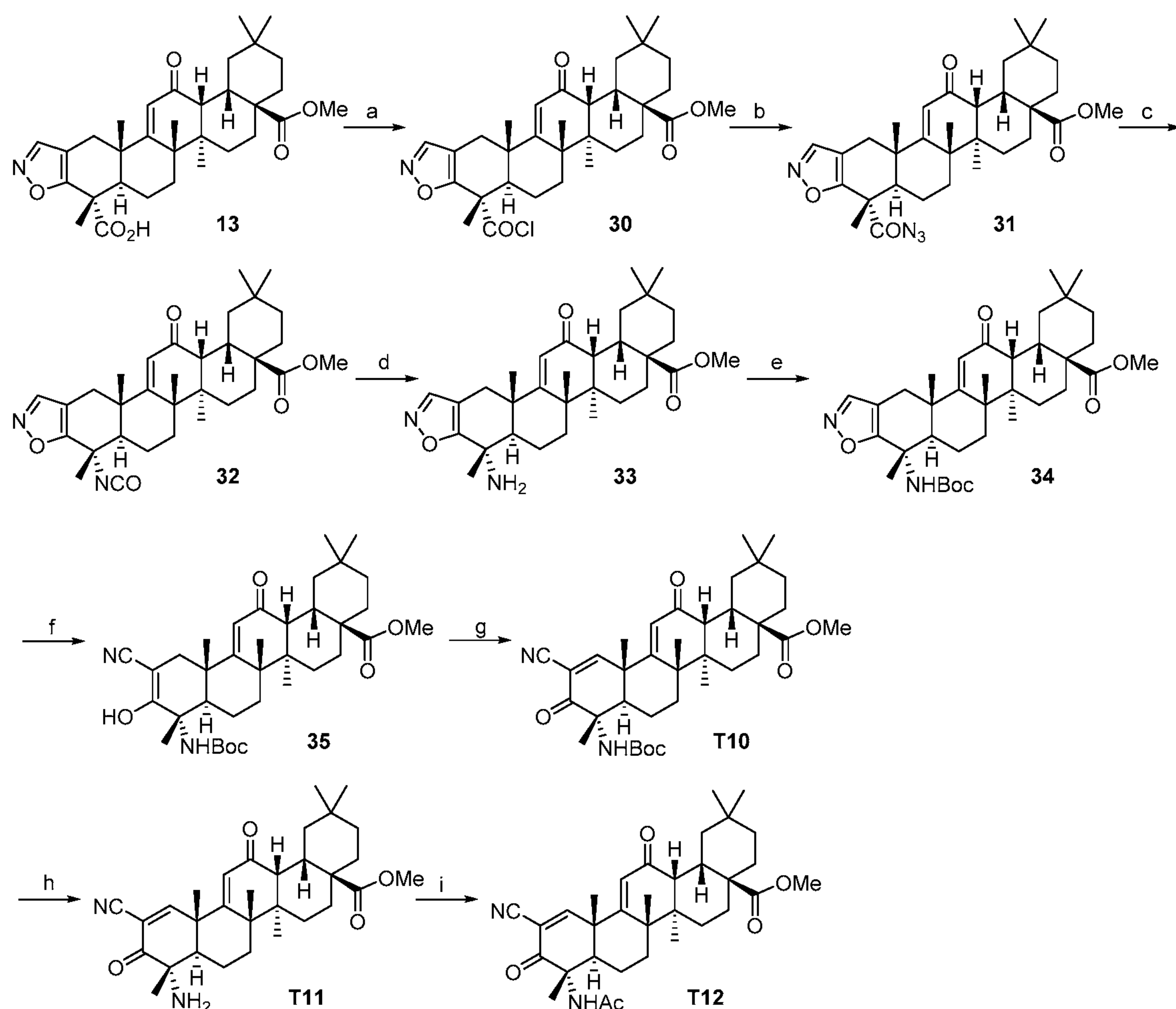
Reagents and conditions: a) MOMCl, DIPEA, 0 °C-rt, 90%; b) i) HCO₂Et, NaOMe, MeOH, 0 °C-rt; ii) NH₂OH·HCl, aq. EtOH, 55 °C, 61%; c) NaOMe, MeOH, THF, 55 °C, quant.; d) DBDMH, DMF, 0 °C; Py, 55 °C, 85%.

Scheme 8



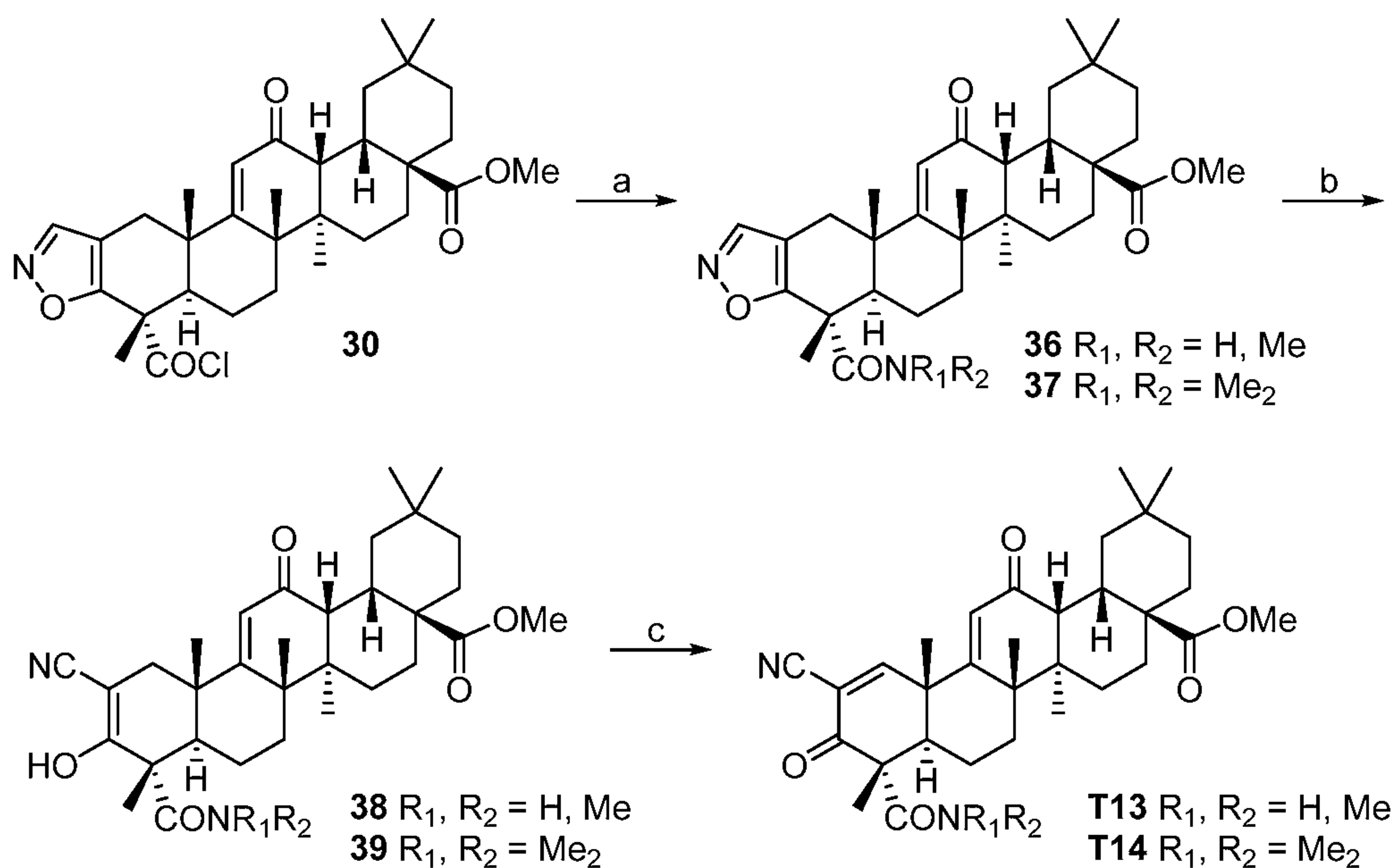
Reagents and conditions: a) Ac₂O, DMAP, Py, rt, 32% for **T8**; a) BzCl, DMAP, Py, CH₂Cl₂, rt, 70% for **T9**.

Scheme 9



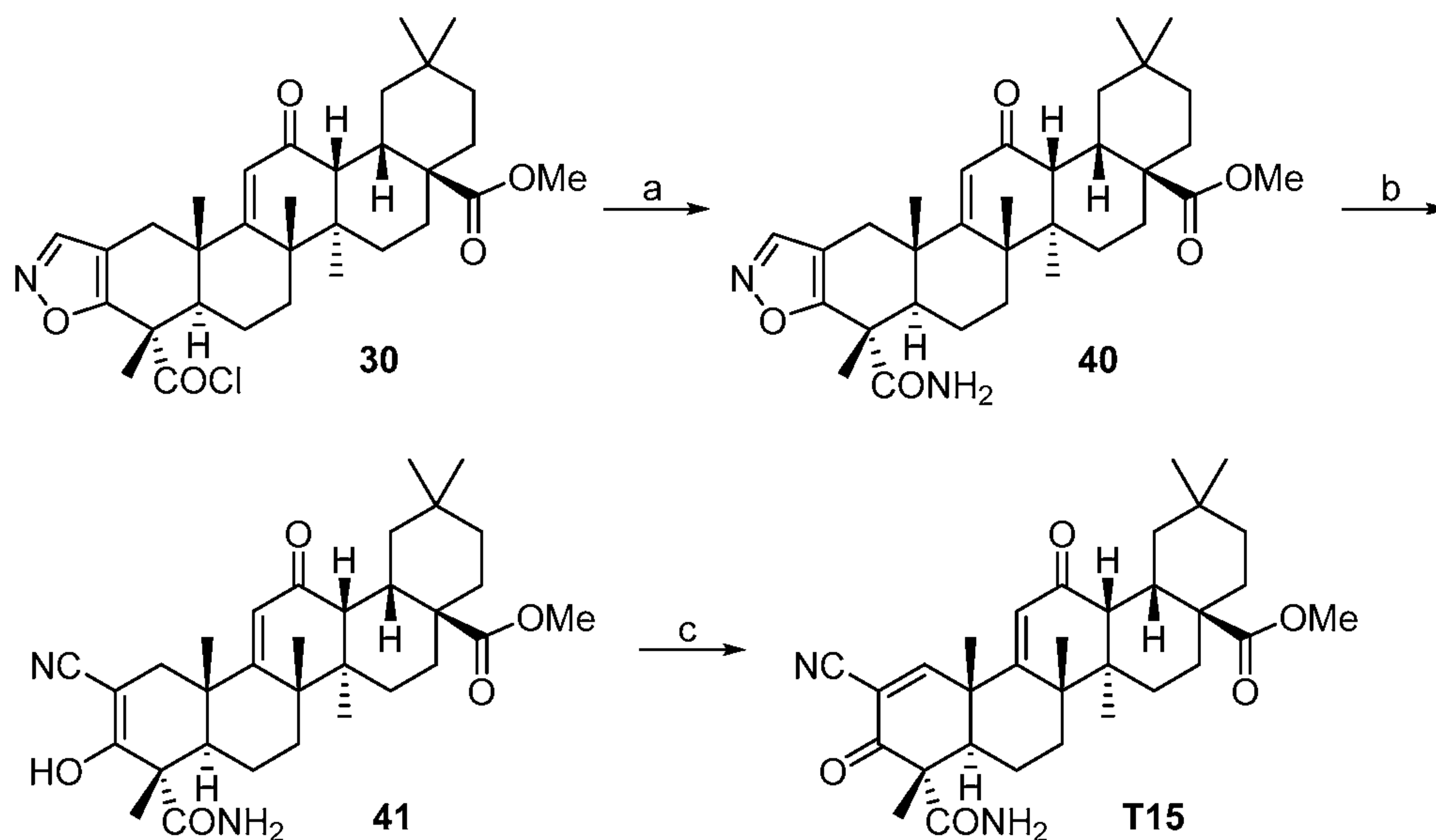
Reagents and conditions: a) $(\text{COCl})_2$, DMF, CH_2Cl_2 , rt; b) NaN_3 , toluene, acetone, water, rt; c) toluene, 85 °C, 83% from **13**; d) aq. HCl, MeCN, rt, quant.; e) $(\text{Boc})_2\text{O}$, THF, 55 °C, 69%; f) K_2CO_3 , MeOH, rt, 89%; g) DDQ, toluene 85 °C, 61%; h) $\text{CF}_3\text{CO}_2\text{H}$, CH_2Cl_2 , rt, 33%; i) AcCl , Et_3N , CH_2Cl_2 , rt, 40%.

Scheme 10



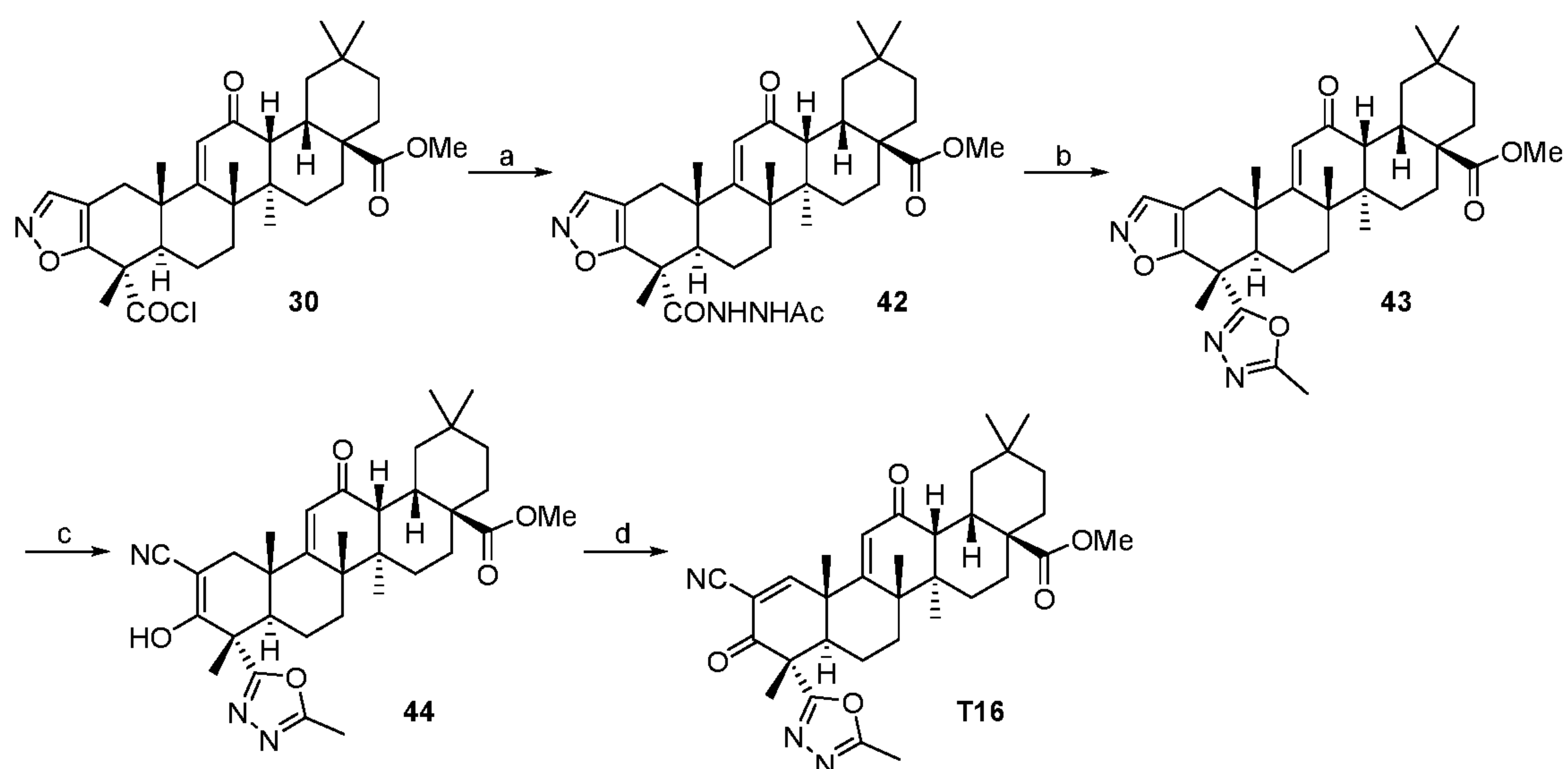
Reagents and conditions: a) $R_1R_2NH \cdot HCl$, Et_3N , CH_2Cl_2 , $0^\circ C$, 84% for **36**; 88% for **37**; b) K_2CO_3 , $MeOH$, rt; c) DDQ , benzene, reflux, **T13**: 51% from **36**; **T14**: 20% from **37**.

5 Scheme 11



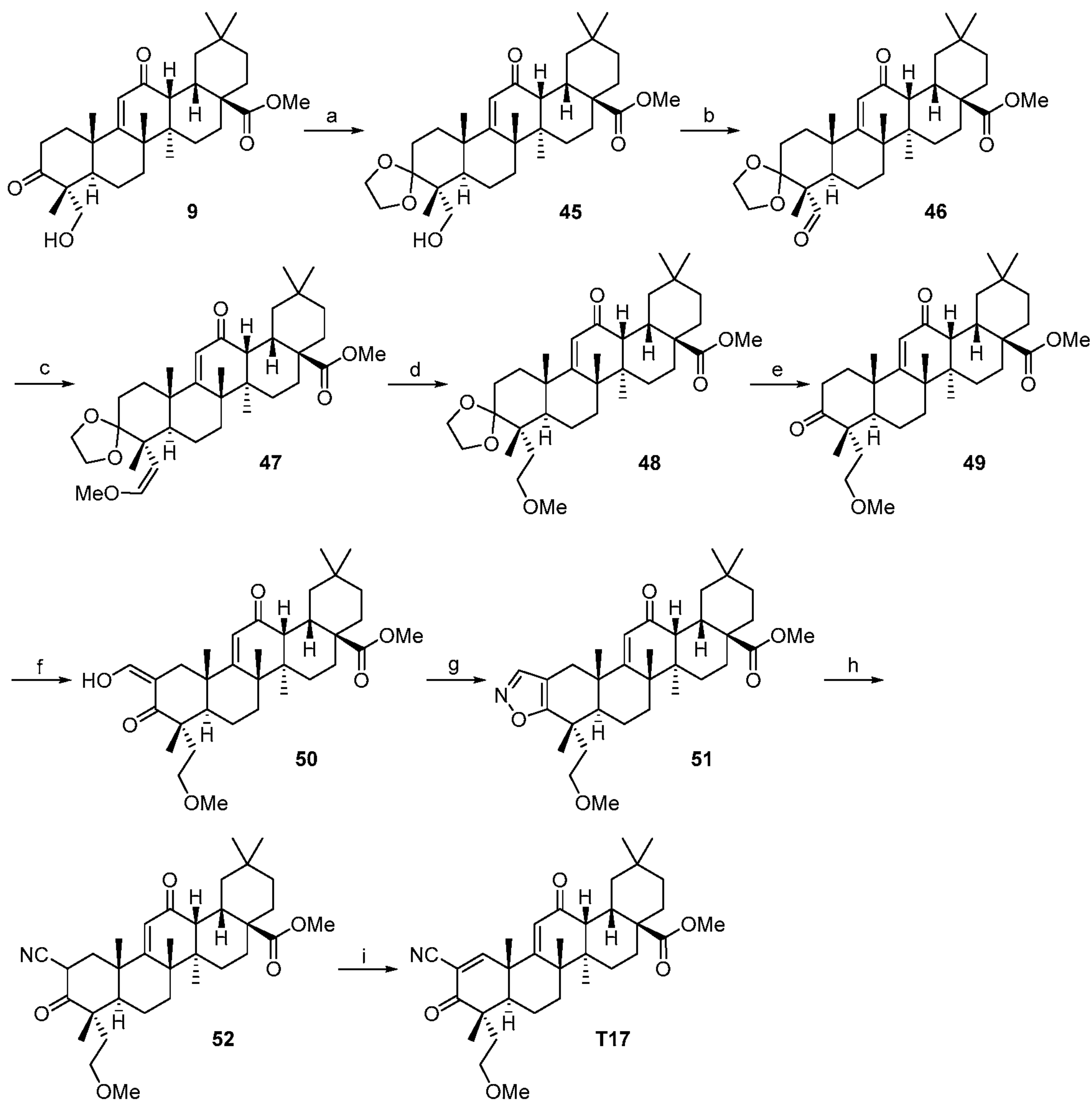
Reagents and conditions: a) NH_3 , $MeOH$, CH_2Cl_2 , rt, 52%; b) K_2CO_3 , $MeOH$, rt, 66%; c) $DBDMH$, DMF , $0^\circ C$; Py , $55^\circ C$, 65%.

Scheme 12



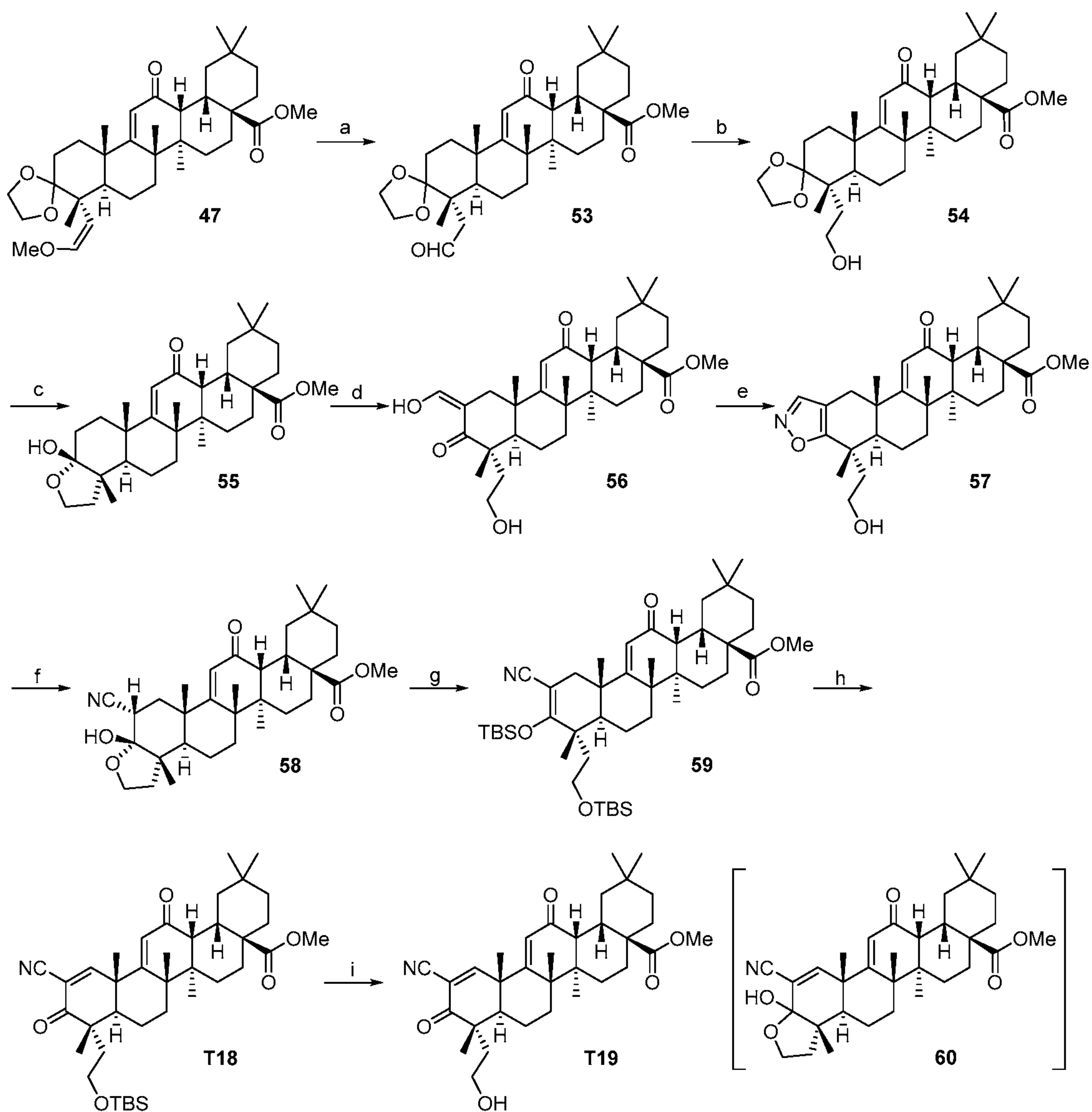
Reagents and conditions: a) AcNHNH_2 , Et_3N , Et_2O , CH_2Cl_2 , rt, 78%; b) $\text{TsOH} \cdot \text{H}_2\text{O}$, toluene, reflux, 86%; c) K_2CO_3 , MeOH , rt, quant.; d) DDQ , benzene, reflux, 60%.

Scheme 13



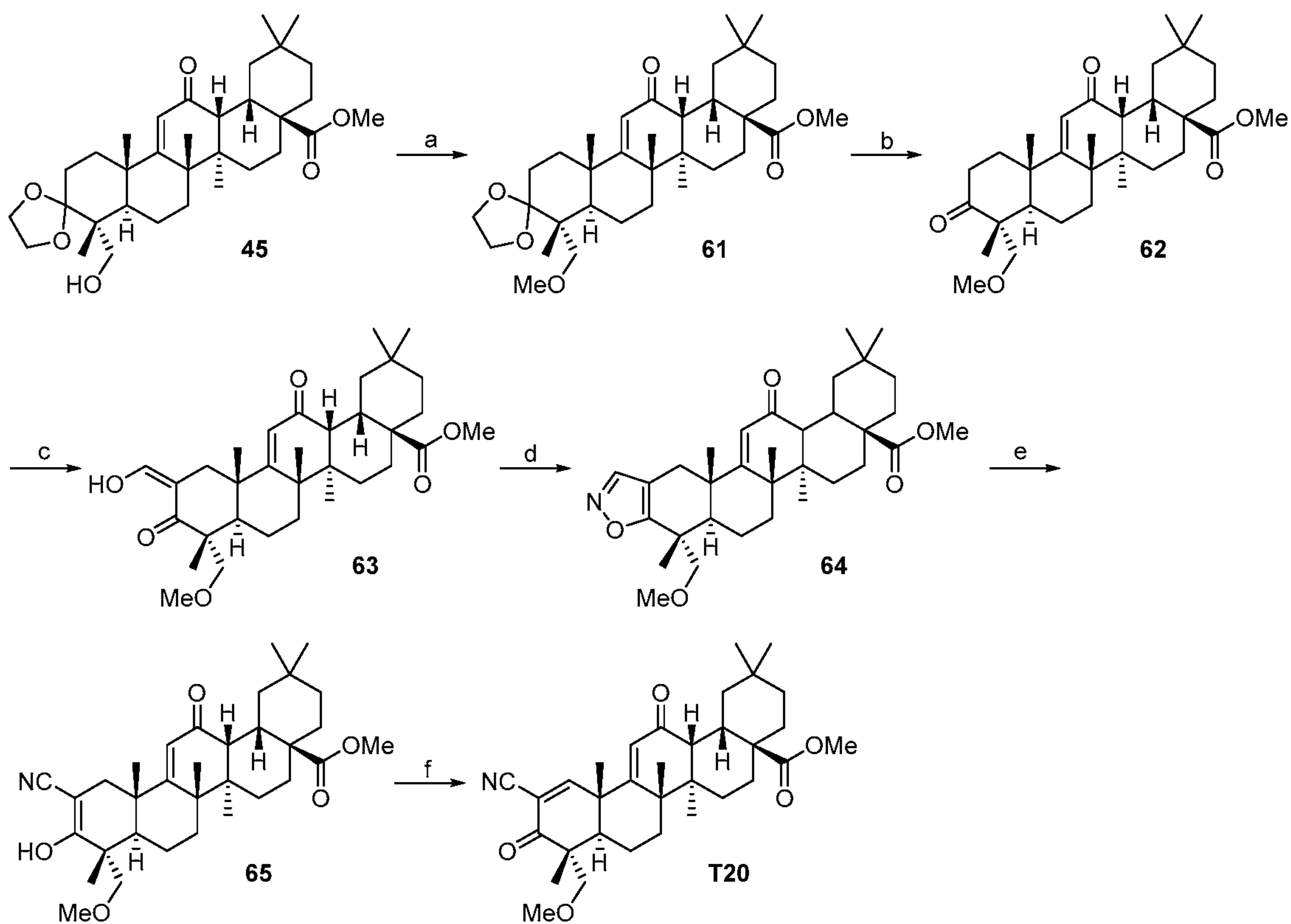
Reagents and conditions: a) $(\text{CH}_2\text{OH})_2$, PPTS, benzene, reflux, 73%; b) Dess-Martin periodinane, CH_2Cl_2 , rt, 95%; c) (methoxymethyl)triphenylphosphonium chloride, *n*-BuLi, THF, hexane, 0 °C-rt, 78%; d) H_2 , 10% Pd/C, EtOAc, rt, quant.; e) aq. HCl, MeOH, rt, 95%; f) HCO_2Et , NaOMe, MeOH, rt, 81%; g) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, 50 °C-rt, 96%; h) NaOMe, MeOH, THF, rt, 96%; i) DDQ, benzene, rt, 15%.

Scheme 14



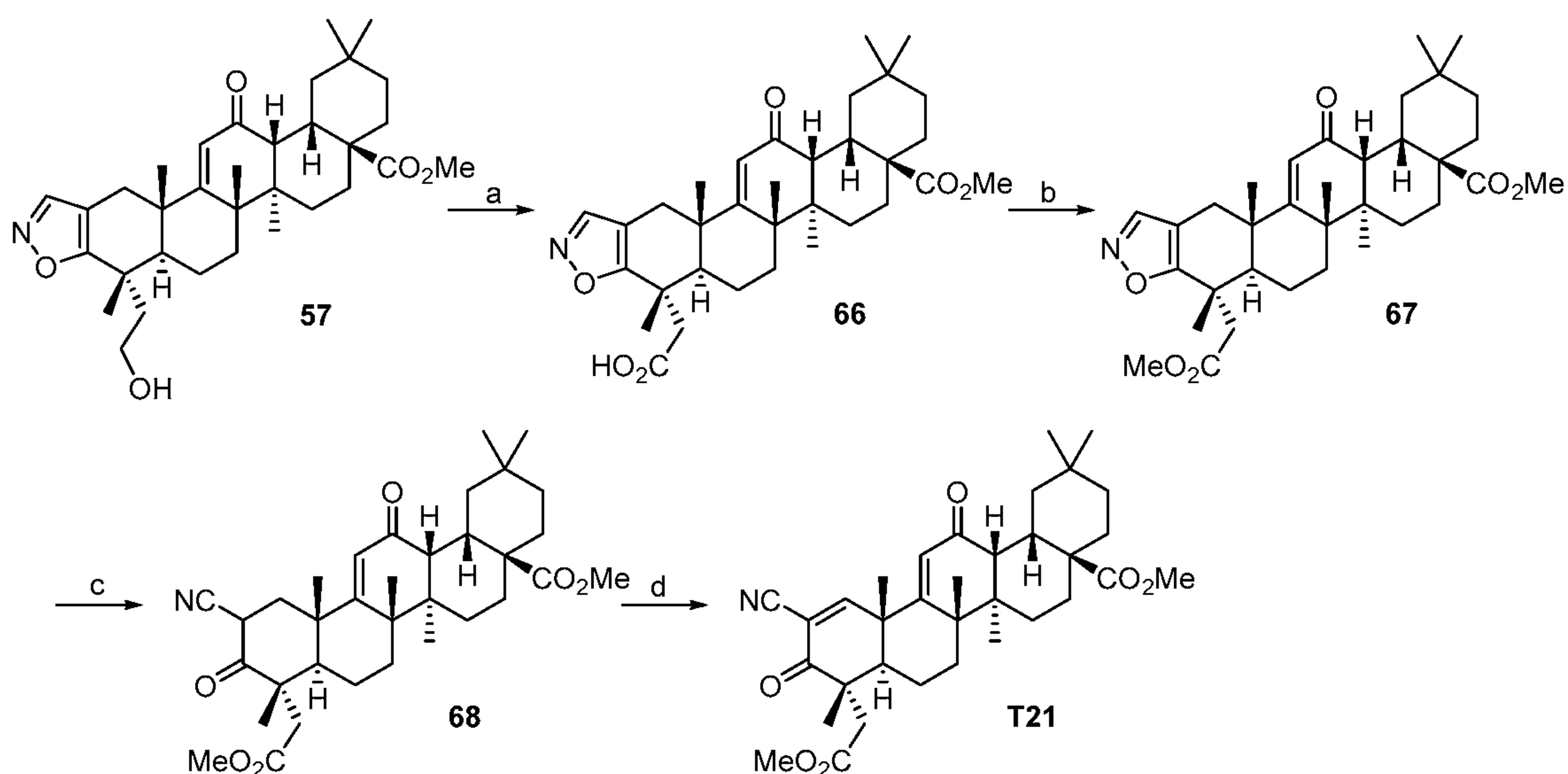
Reagents and conditions: a) aq. HCl, THF, rt, 92%; b) NaBH₄, THF, EtOH, 0 °C, quant.; c) aq. HCl, THF, rt, quant.; d) HCO₂Et, NaOMe, MeOH, 0 °C-rt, quant.; e) NH₂OH·HCl, aq. EtOH, 50 °C, quant.; f) K₂CO₃, MeOH, rt, 65%; g) TBSCl, Et₃N, DMAP, CH₂Cl₂, rt, 98%; h) DBDMH, DMF, 0 °C-rt; Py, 60 °C, 47%; i) HF·Py, MeCN, water, rt, 57%.

Scheme 15



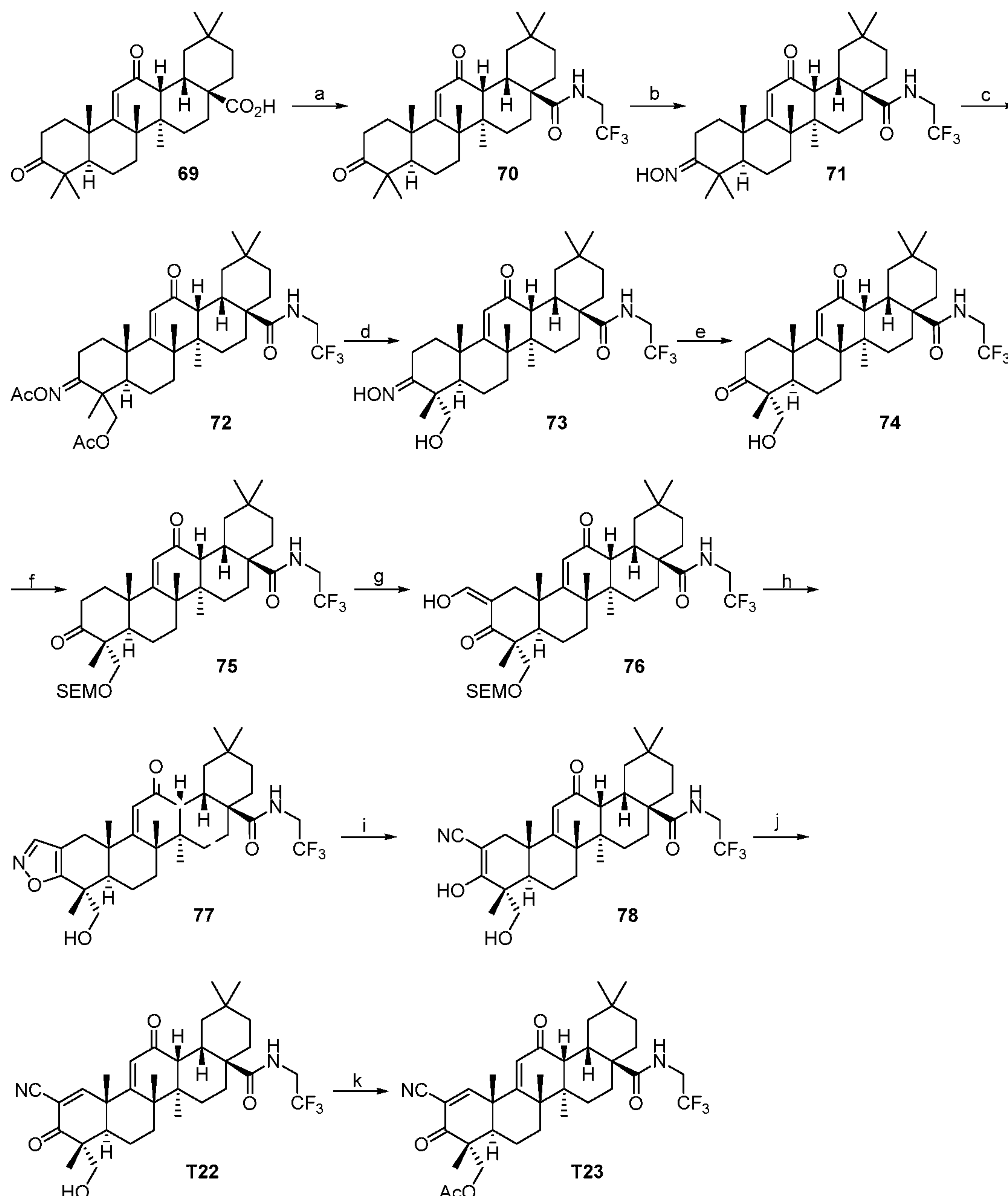
Reagents and conditions: a) NaH, THF, 0 °C; MeI, rt-45 °C, 28%; b) aq. HCl, THF, rt, 99%;
 c) HCO₂Et, NaOMe, MeOH, 0 °C-rt, 98%; d) NH₂OH·HCl, aq. EtOH, 50 °C, quant.; e)
 5 K₂CO₃, MeOH, rt, 62%; f) DBDMH, DMF, 0 °C; Py, 55 °C, 61%.

Scheme 16



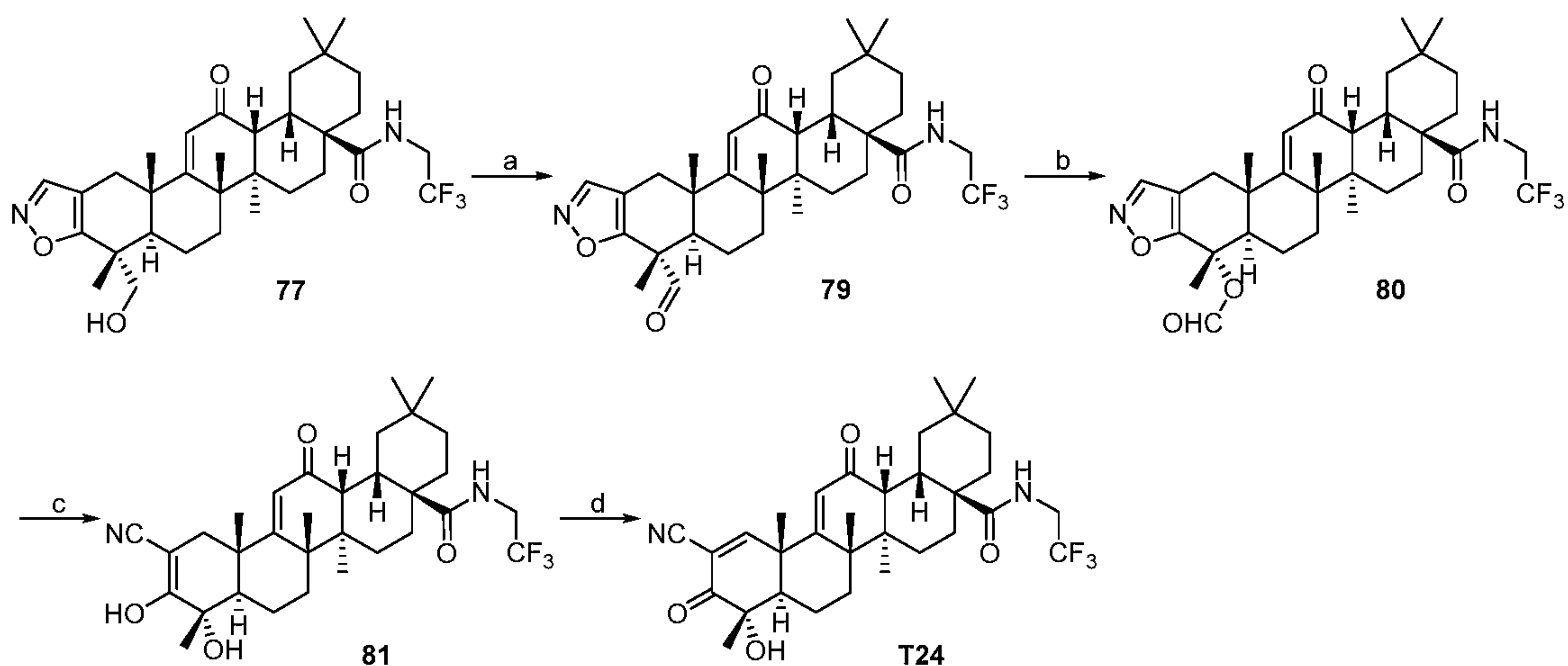
Reagents and conditions: a) Jones reagent, acetone, 0 °C-rt, 92%; b) TMSCHN₂, hexane,
 THF, MeOH, 0 °C-rt, 62%; c) Et₃N, MeCN, 70 °C, quant.; d) DBDMH, DMF, 0 °C; Py, 60
 10 °C, 63%.

Scheme 17



Reagents and conditions: a) i) $(\text{COCl})_2$, DMF, CH_2Cl_2 , rt; ii) $\text{CF}_3\text{CH}_2\text{NH}_2 \cdot \text{HCl}$, Et_3N , CH_2Cl_2 , rt, 81%; b) $\text{NH}_2\text{OH} \cdot \text{HCl}$, NaOAc , CH_2Cl_2 , EtOH , 60°C , quant.; c) AcOH , Ac_2O ; 5 $\text{PhI}(\text{OAc})_2$, $\text{Pd}(\text{OAc})_2$, $\text{ClCH}_2\text{CH}_2\text{Cl}$, 70°C , 38%; d) K_2CO_3 , MeOH , rt, 67%; e) sodium bisulfite, aq. EtOH , 80°C , 85%; f) SEMCl , DIPEA , CH_2Cl_2 , 0°C -rt, 51%; g) HCO_2Et , NaOMe , MeOH , rt, 97%; h) $\text{NH}_2\text{OH} \cdot \text{HCl}$, EtOH , 50°C , 92%; i) K_2CO_3 , MeOH , rt, 92%; j) DDQ , benzene, dioxane, 85°C , 32%; k) Ac_2O , NaOAc , rt, 52%.

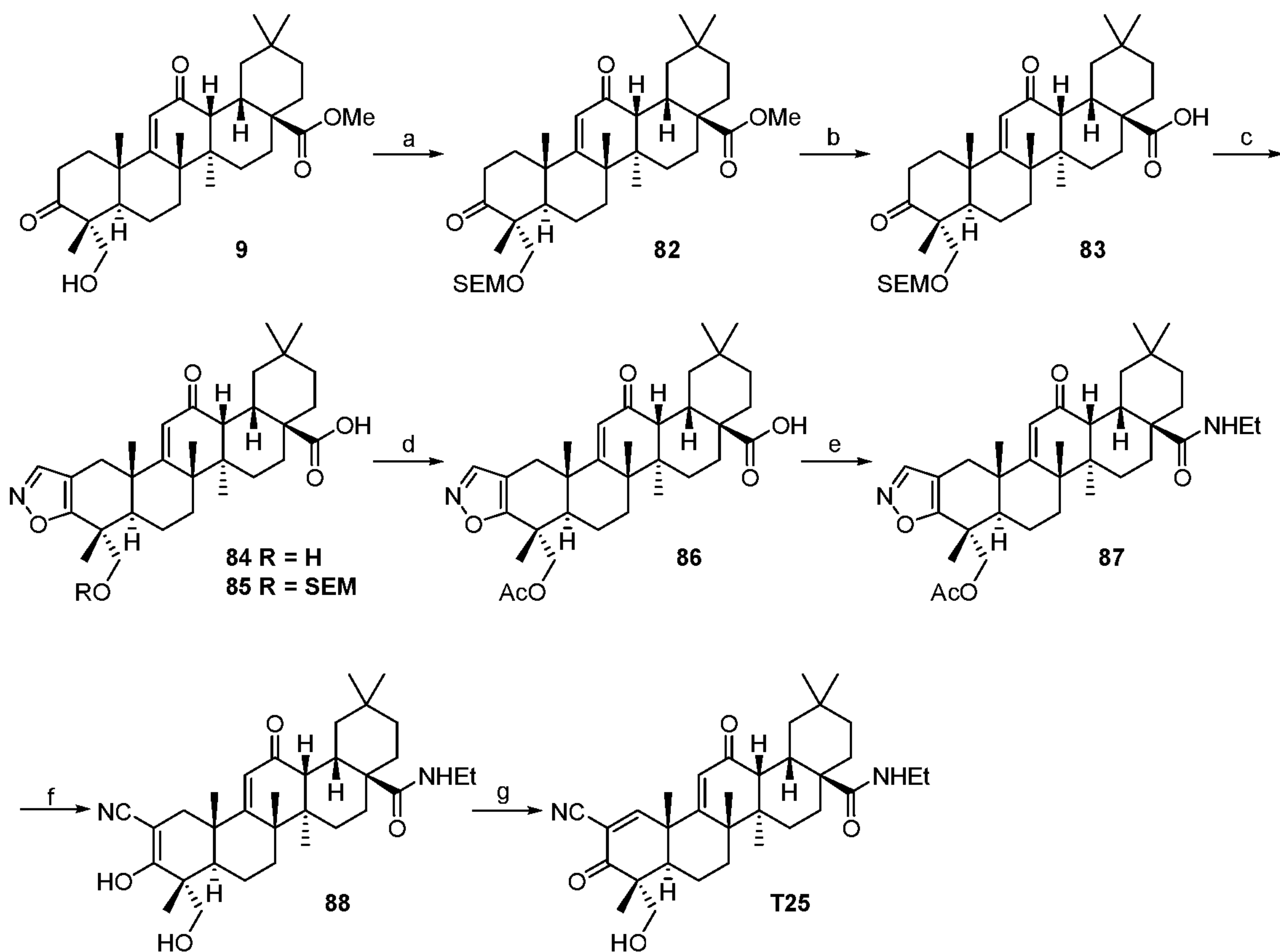
Scheme 18



Reagents and conditions: a) Dess-Martin periodinane, CH₂Cl₂, rt, quant.; b) *m*-CPBA, Na₂HPO₄, CH₂Cl₂, rt, 81%; c) NaOMe, MeOH, rt, 89%; d) DBDMH, DMF, 0 °C; Py, 60 °C, 59%.

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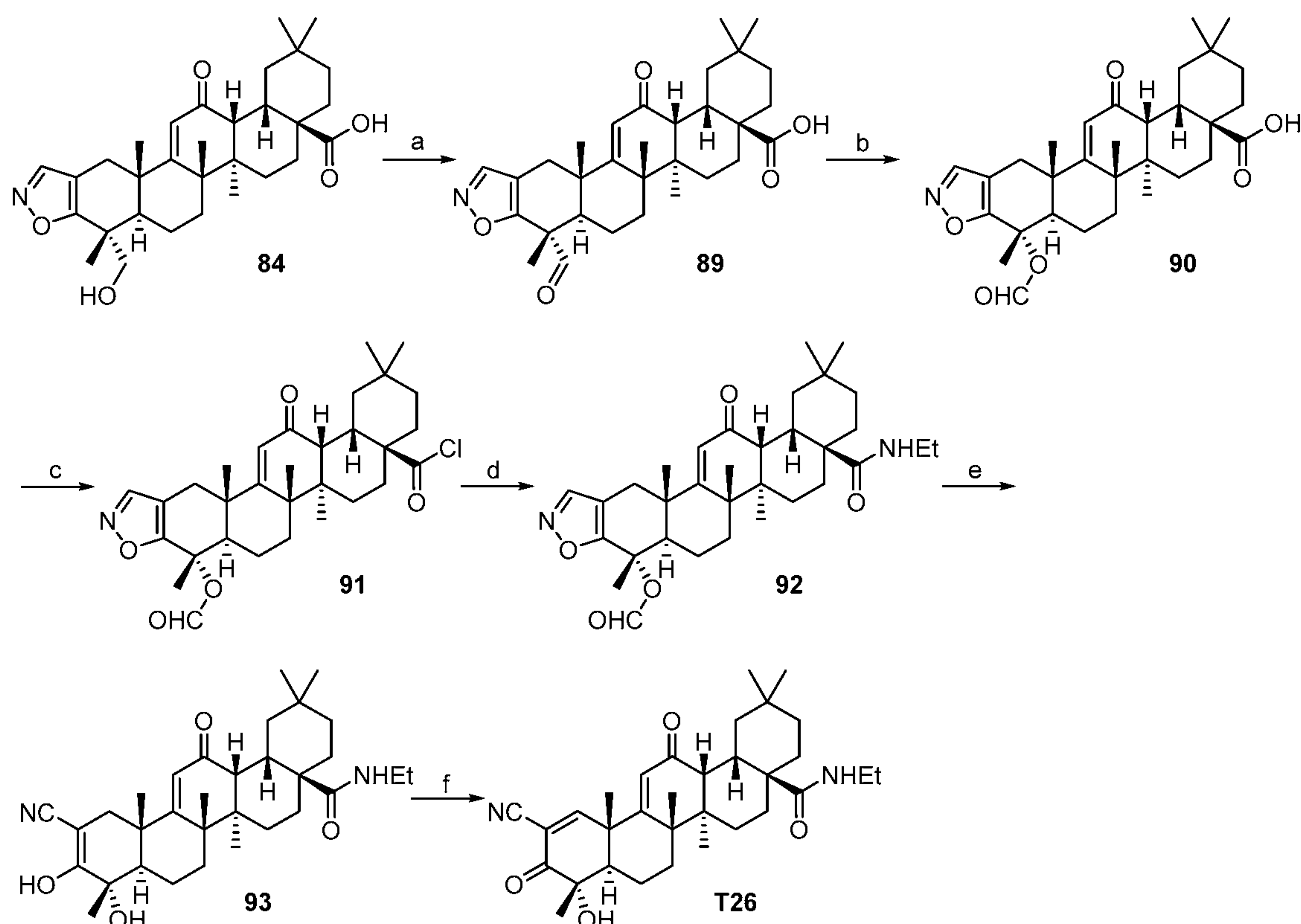
Scheme 19



Reagents and conditions: a) SEMCl, DIPEA, CH₂Cl₂, 0 °C-rt, 96%; b) LiBr, NaOAc, DMA, 150 °C, 53%; c) i) HCO₂Et, NaOMe, MeOH, 0 °C-rt ; ii) NH₂OH HCl, aq. EtOH, 55 °C, 26% for **84**; 30% for **85**; d) Py, Ac₂O, DMAP, rt, 97%; e) i) (COCl)₂, DMF, CH₂Cl₂, 0 °C-rt; ii) EtNH₂, Et₃N, Et₂O, rt, 56%; f) K₂CO₃, MeOH, rt, 54%; g) DDQ, benzene, reflux, 31%.

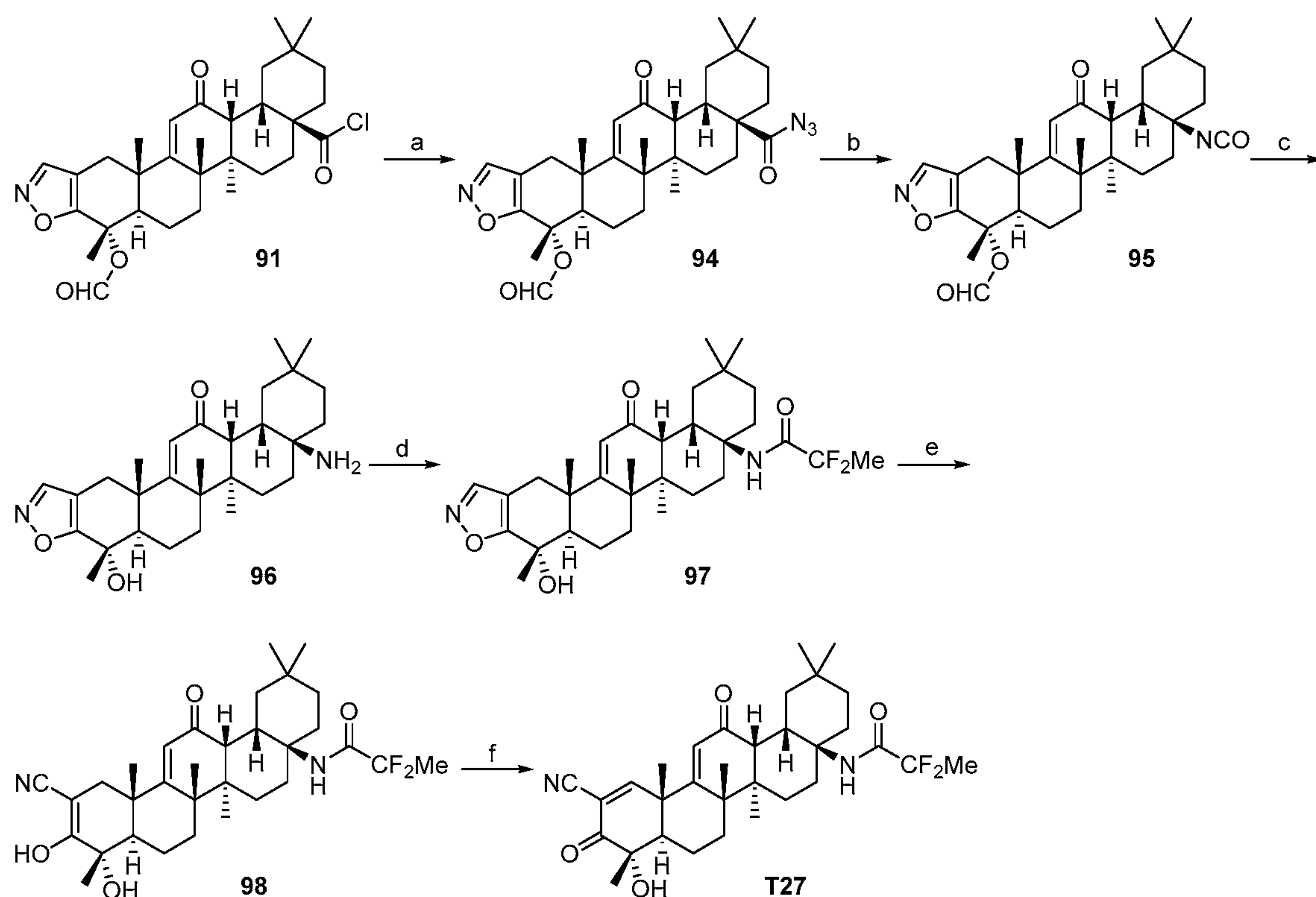
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Scheme 20



Reagents and conditions: a) Dess-Martin periodinane, Na_2HPO_4 , CH_2Cl_2 , rt; b) *m*-CPBA, Na_2HPO_4 , CH_2Cl_2 , rt, 50% from **84**; c) $(\text{COCl})_2$, DMF, CH_2Cl_2 , 0 °C-rt; d) EtNH_2 , THF, CH_2Cl_2 , rt, 60% from **90**; e) K_2CO_3 , MeOH, rt, 83%; f) DBDMH, DMF, 0 °C; Py, 55 °C, 77%.

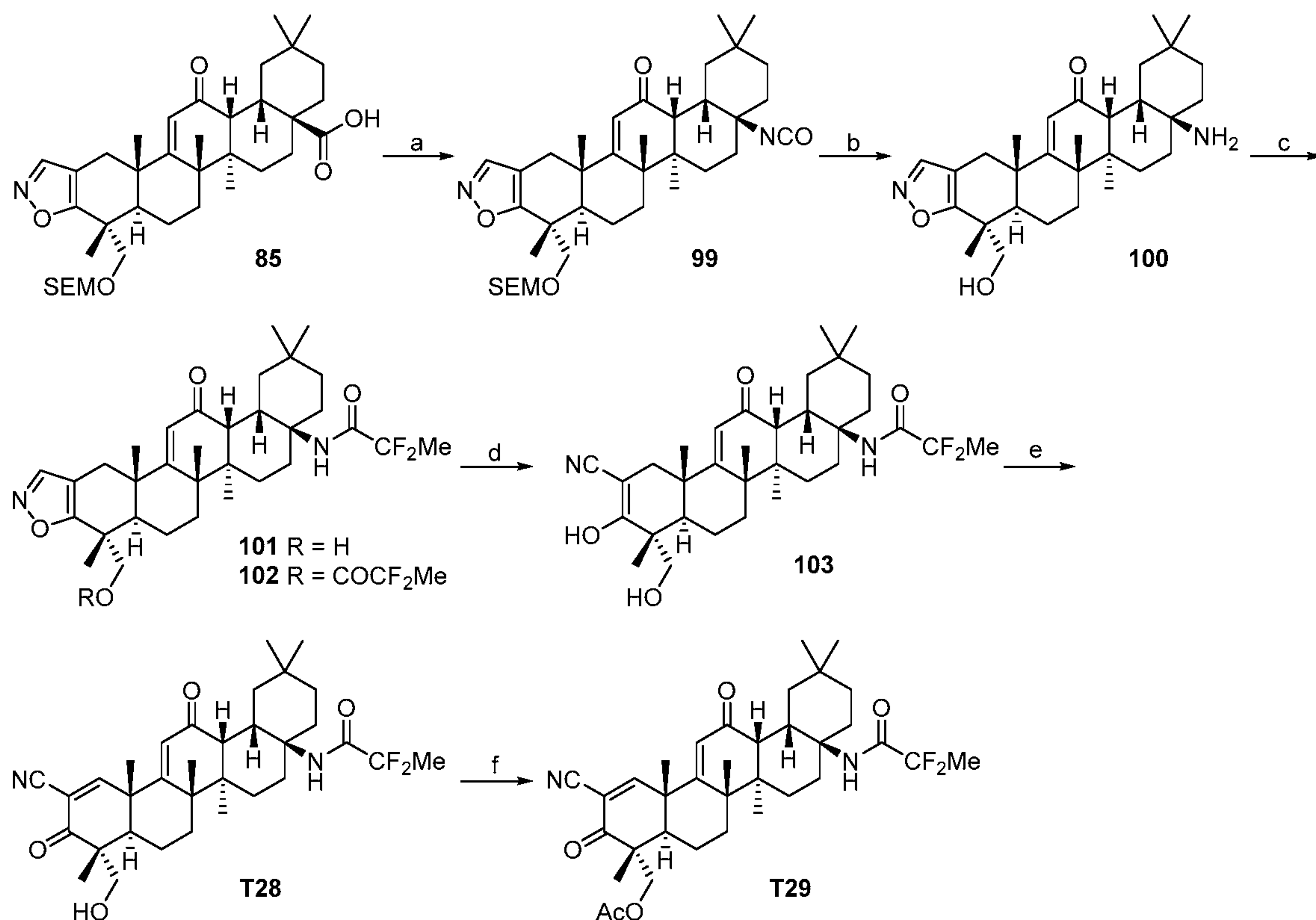
Scheme 21



Reagents and conditions: a) NaN₃, toluene, acetone, water, 0 °C-rt, 60%; b) toluene, 85 °C; c) conc. aq. HCl, MeCN, rt; d) MeCF₂CO₂H, T₃P®, Et₃N, EtOAc, CH₂Cl₂, rt, 20% from **94**; e) K₂CO₃, MeOH, rt, 95%; f) DBDMH, DMF, 0 °C; Py, 55 °C, 68%.

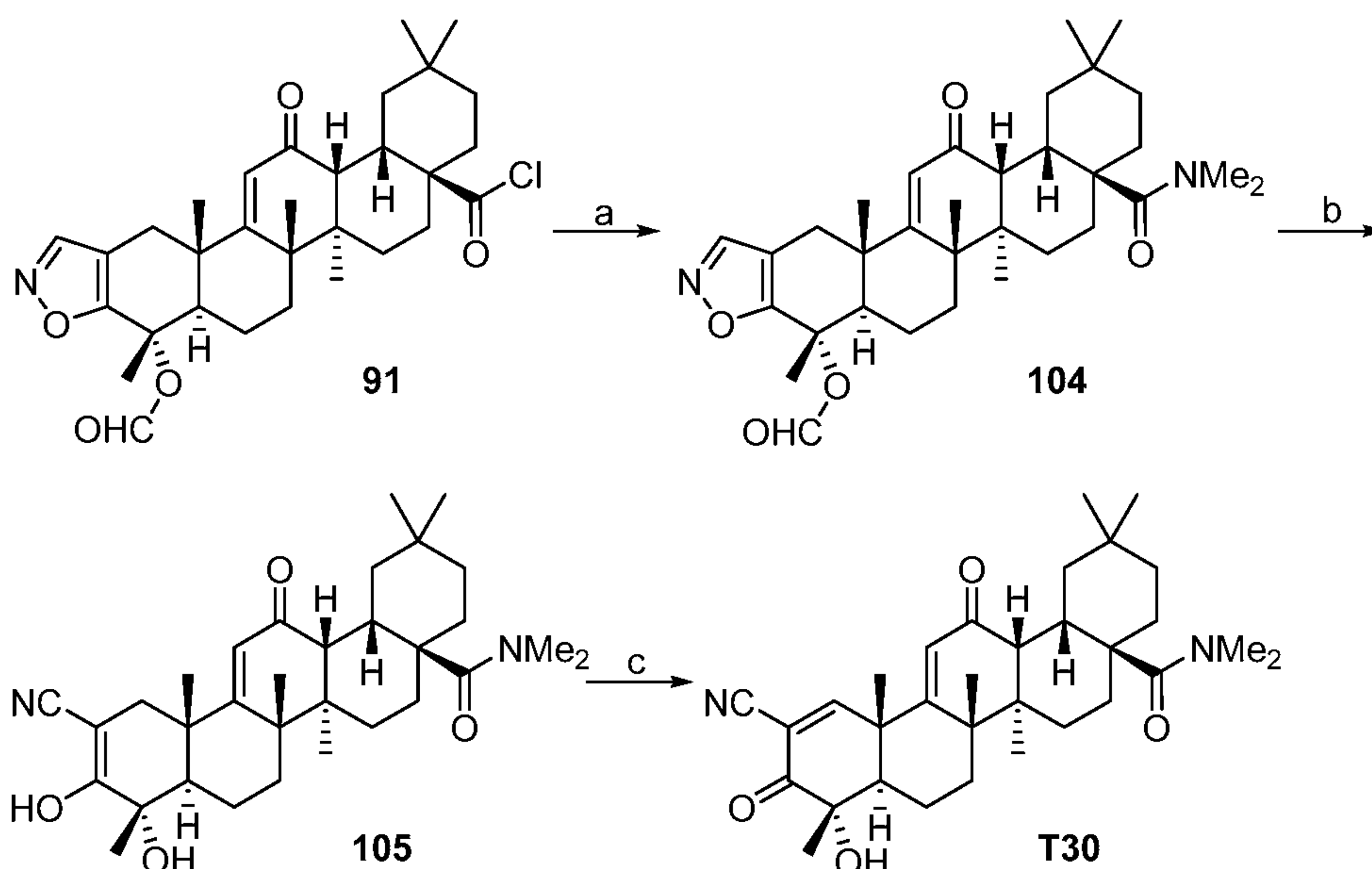
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Scheme 22



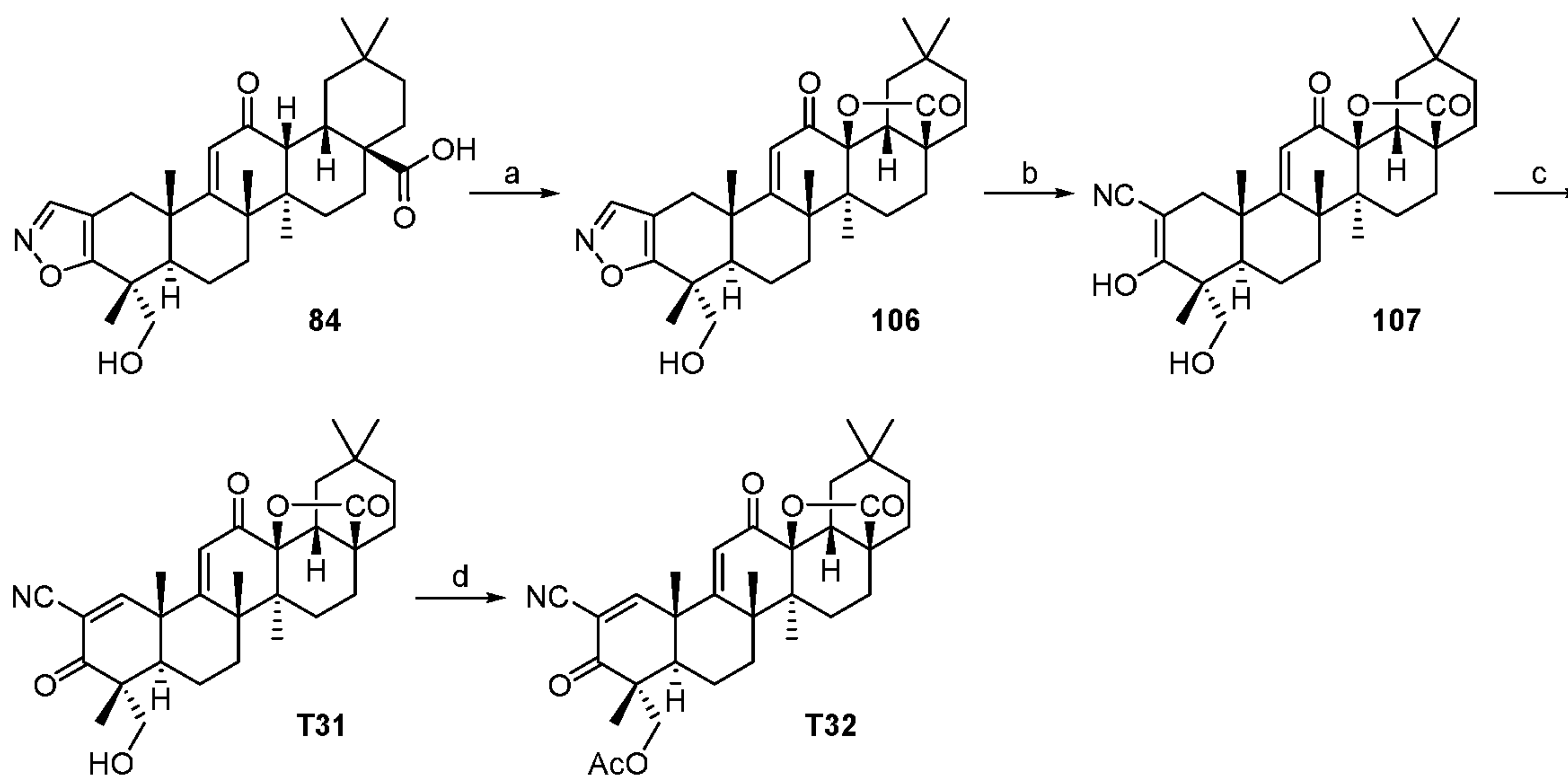
Reagents and conditions: a) i) DPPA, Et₃N, benzene, 0 °C-rt; ii) benzene, reflux, quant.; b) conc. aq. HCl, MeCN, rt, quant.; c) MeCF₂CO₂H, T₃P®, Et₃N, EtOAc, CH₂Cl₂, rt; d) K₂CO₃, MeOH, rt, 31% yield from 100; e) DBDMH, DMF, 0 °C; Py, 60 °C, 43%; f) Ac₂O, NaOAc, rt, 58%.

Scheme 23

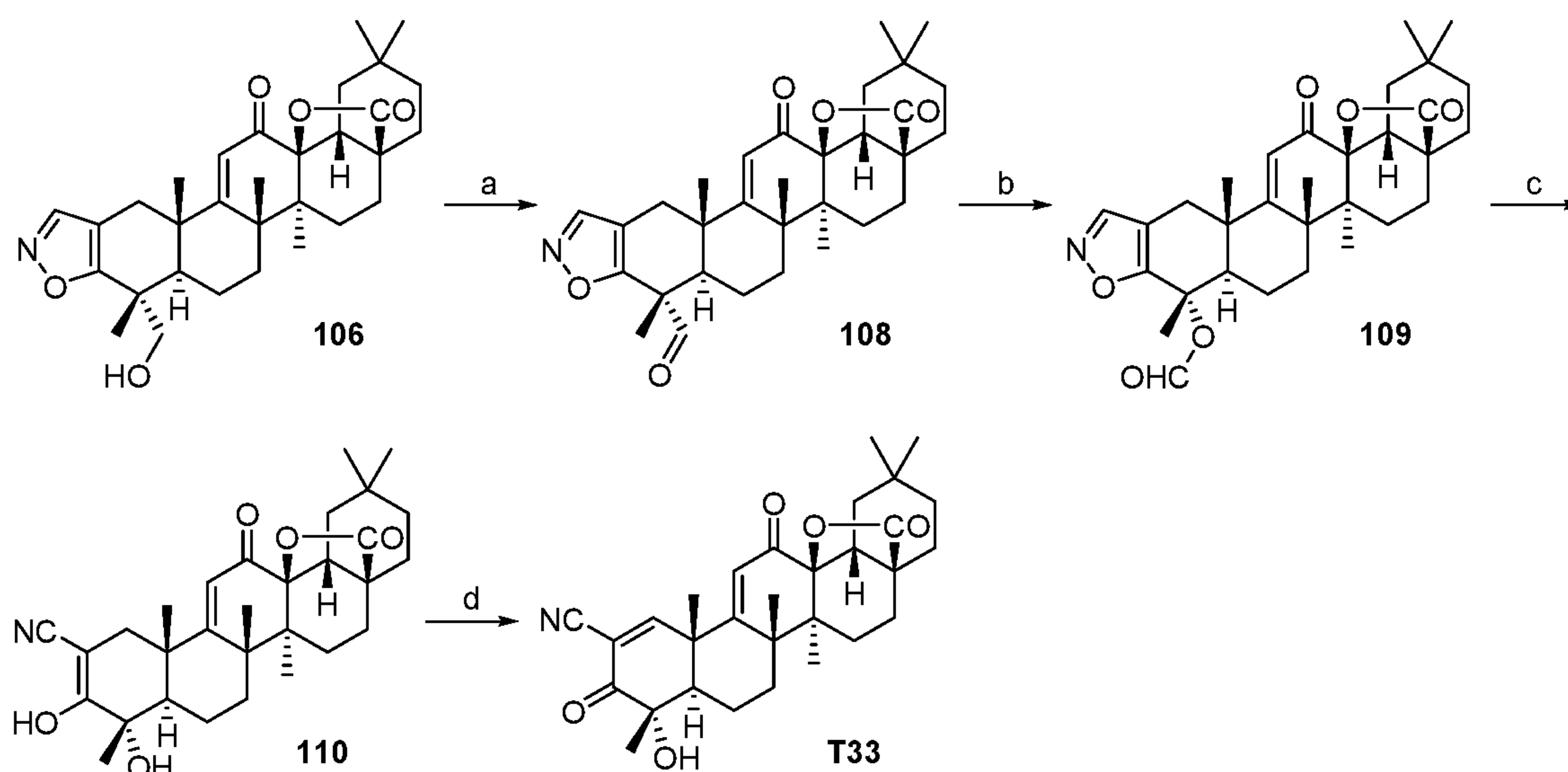


Reagents and conditions: a) Me₂NH·HCl, Et₃N, rt, 86%; b) K₂CO₃, MeOH, rt, quant.; c) DDQ, benzene, reflux, 31%.

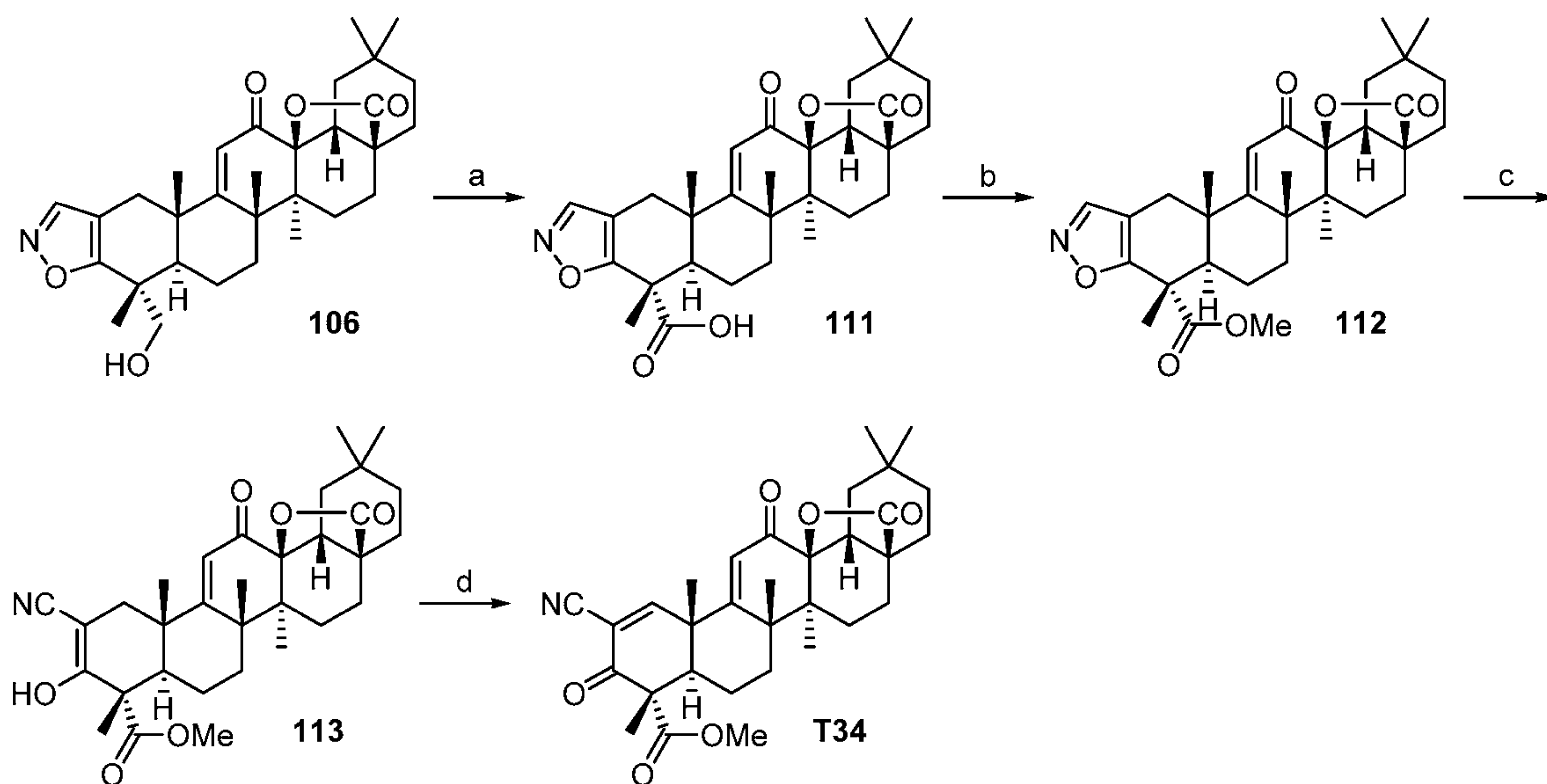
Scheme 24



5 Scheme 25

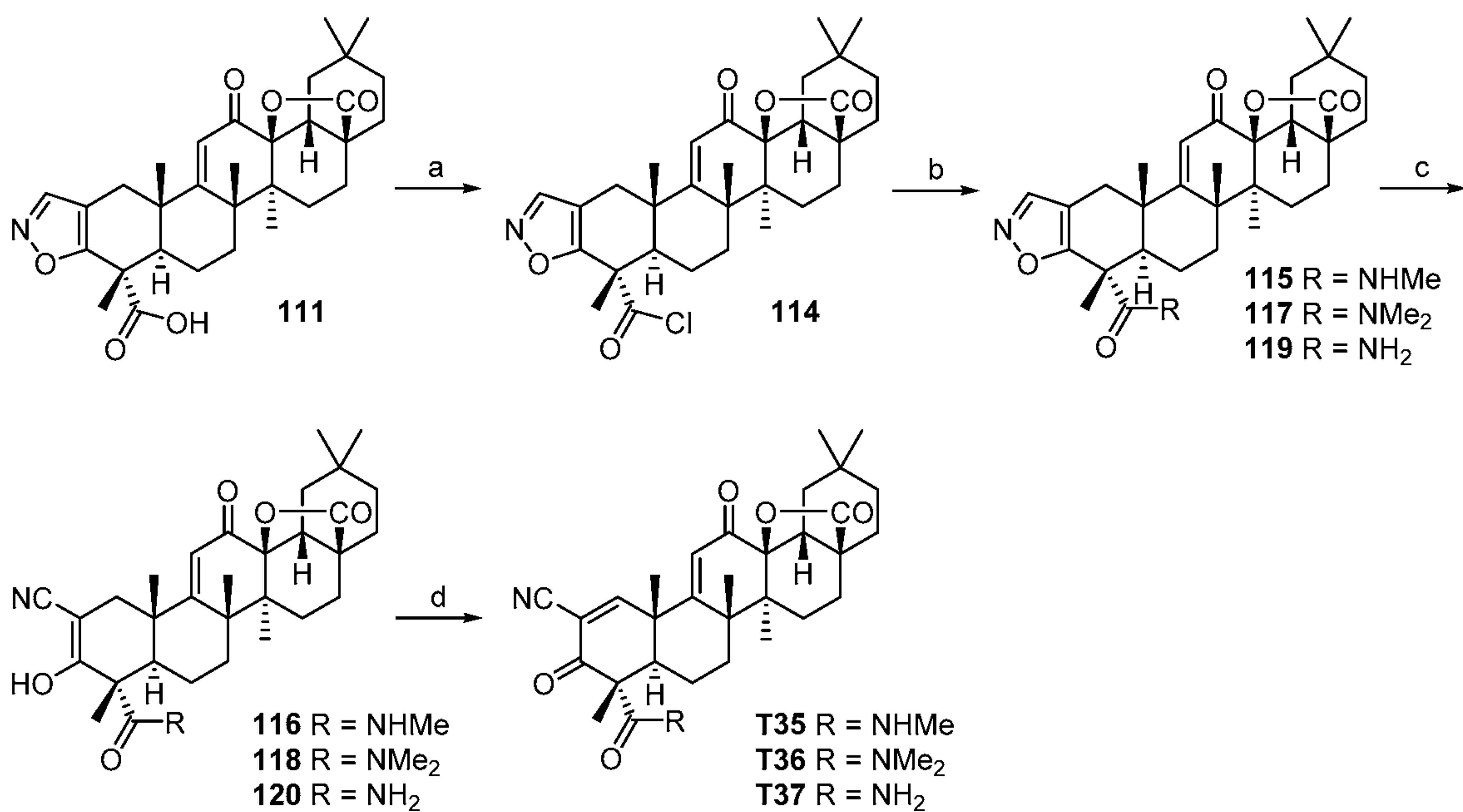


Scheme 26



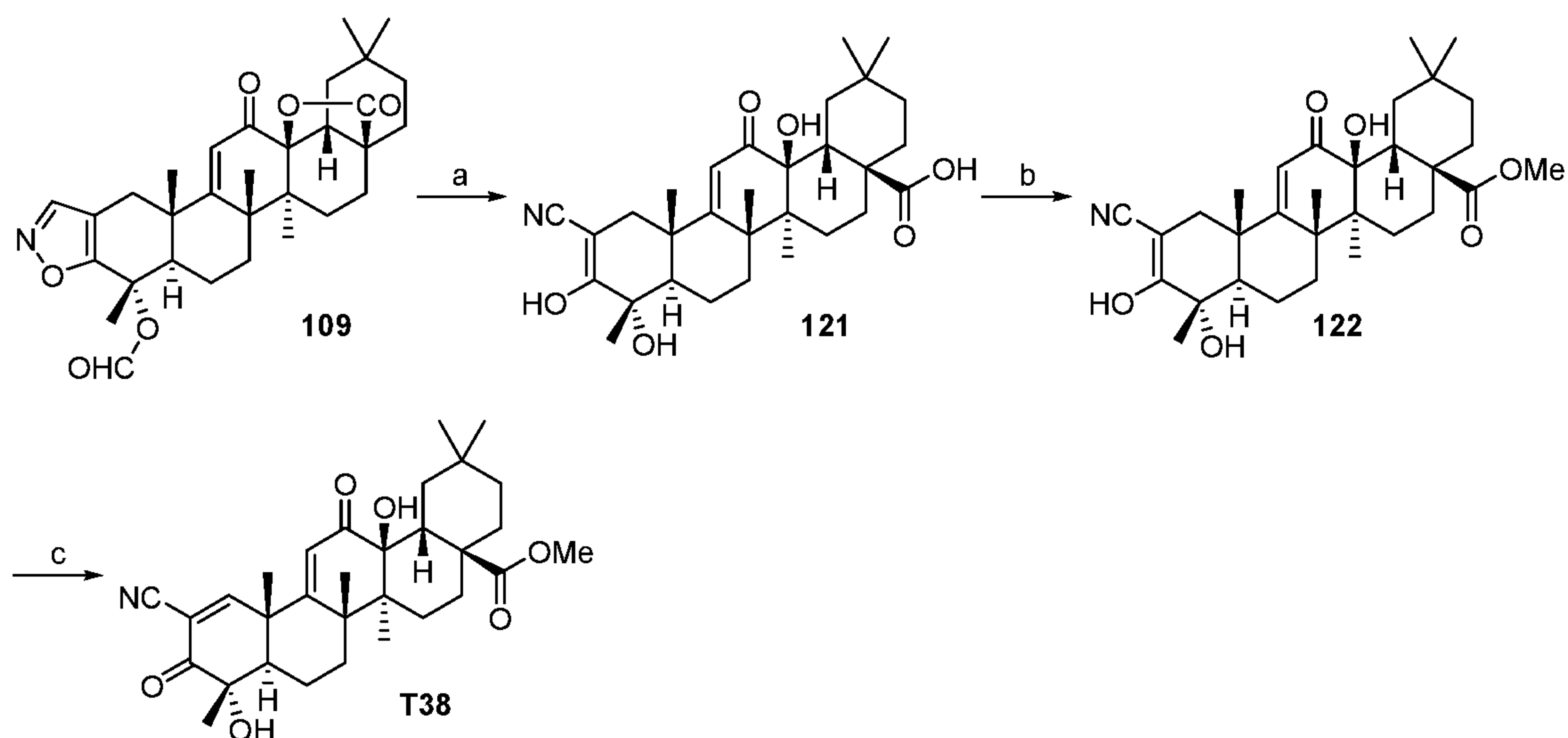
Reagents and conditions: a) Jones reagent, acetone, 0 °C-rt, 61%; b) TMSCHN₂, Et₂O, toluene, MeOH, 0 °C, 77%; c) K₂CO₃, MeOH, rt, quantitative yield; d) DBDMH, DMF, 0 °C; Py, 55 °C, 83%.

Scheme 27



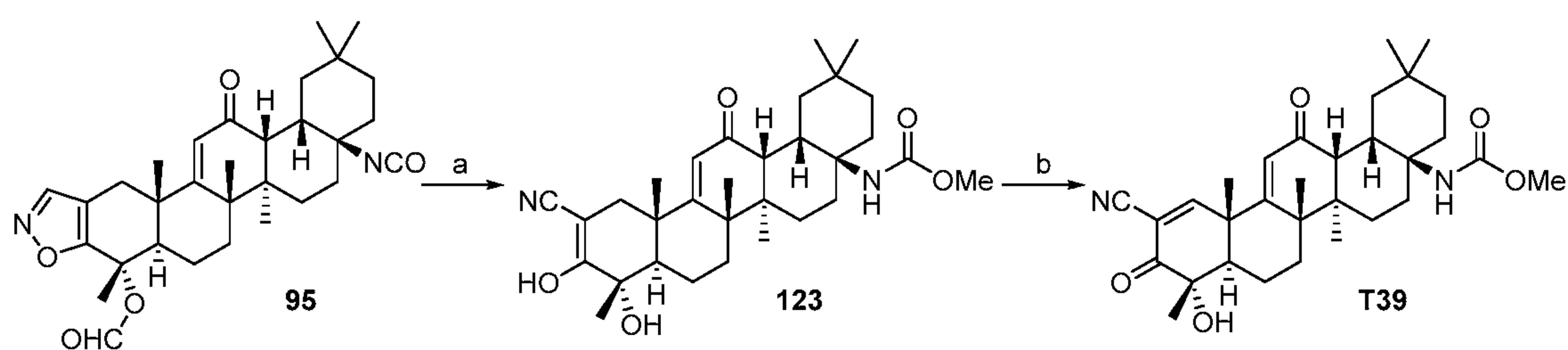
Reagents and conditions: a) (COCl)₂, DMF, CH₂Cl₂, 0 °C-rt, quant.; b) **115** and **117**: RH·HCl, Et₃N, CH₂Cl₂, rt, 75% for **115**; 73% for **117**; **119**: NH₃, MeOH, CH₂Cl₂, 0 °C, 74%; c) K₂CO₃, MeOH, rt, 97% for **116**; quant. for **118**; quant. for **120**; d) DBDMH, DMF; Py, 55 °C, 70% for **T35**; 65% for **T36**; 66% for **T37**.

Scheme 28



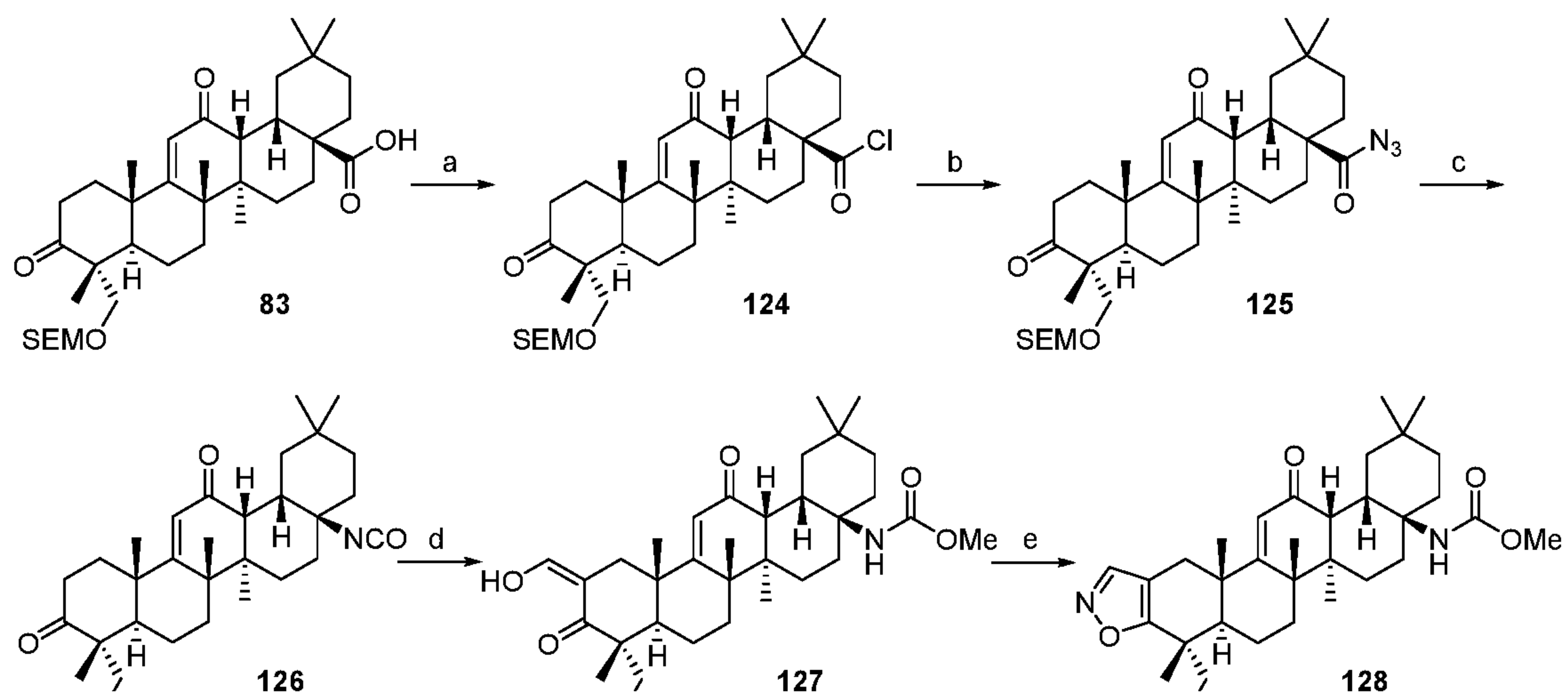
Reagents and conditions: a) aq. NaOH, THF, EtOH, 0 °C; b) TMSCHN₂, Et₂O, toluene, MeOH, 0 °C, 67% from **109**; c) DBDMH, DMF, 0 °C; Py, 55 °C, 74%.

5 Scheme 29



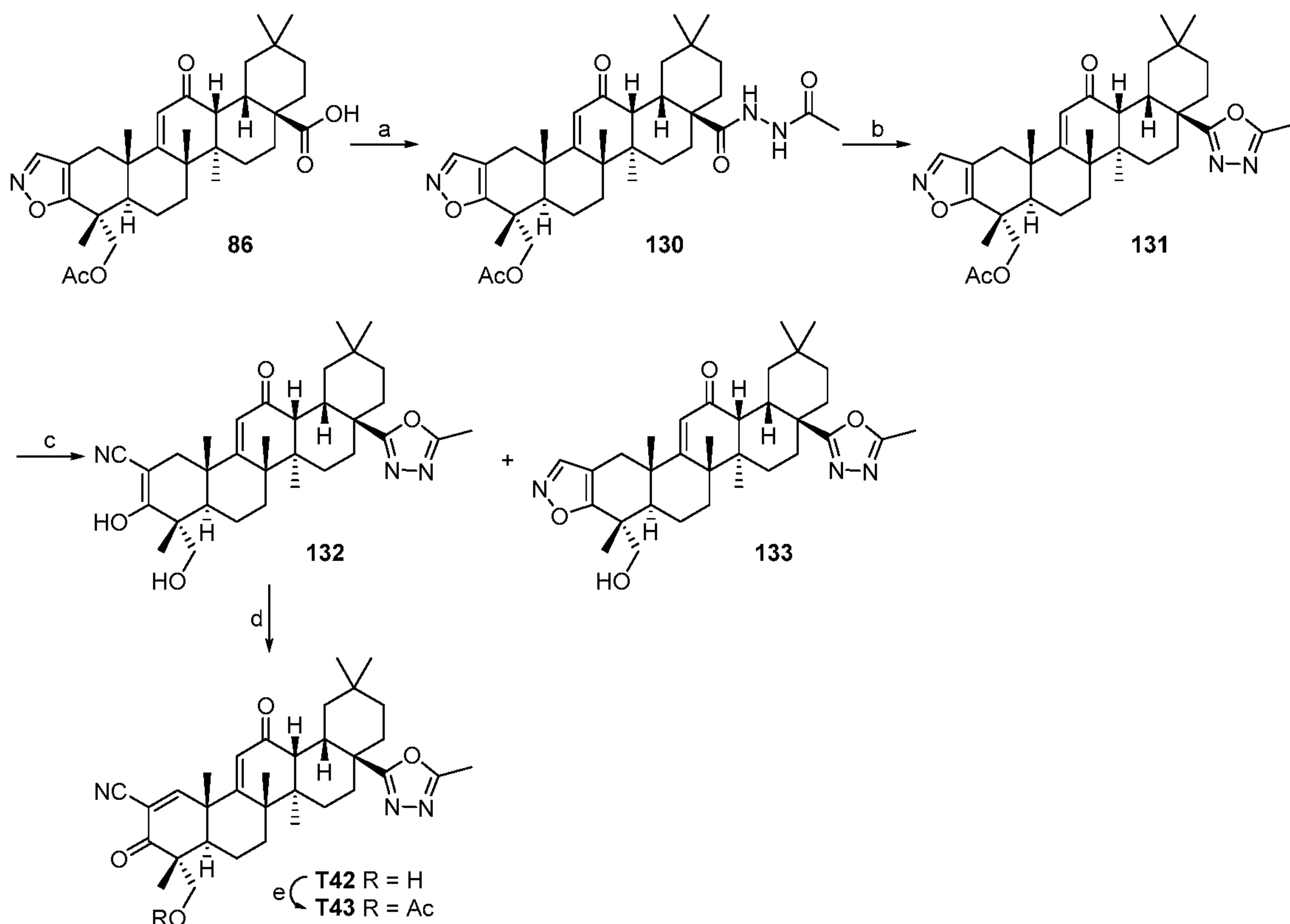
Reagents and conditions: a) NaOMe, MeOH, rt-55 °C, 66%; b) DBDMH, DMF, 0 °C; Py, 55 °C, 88%.

Scheme 30



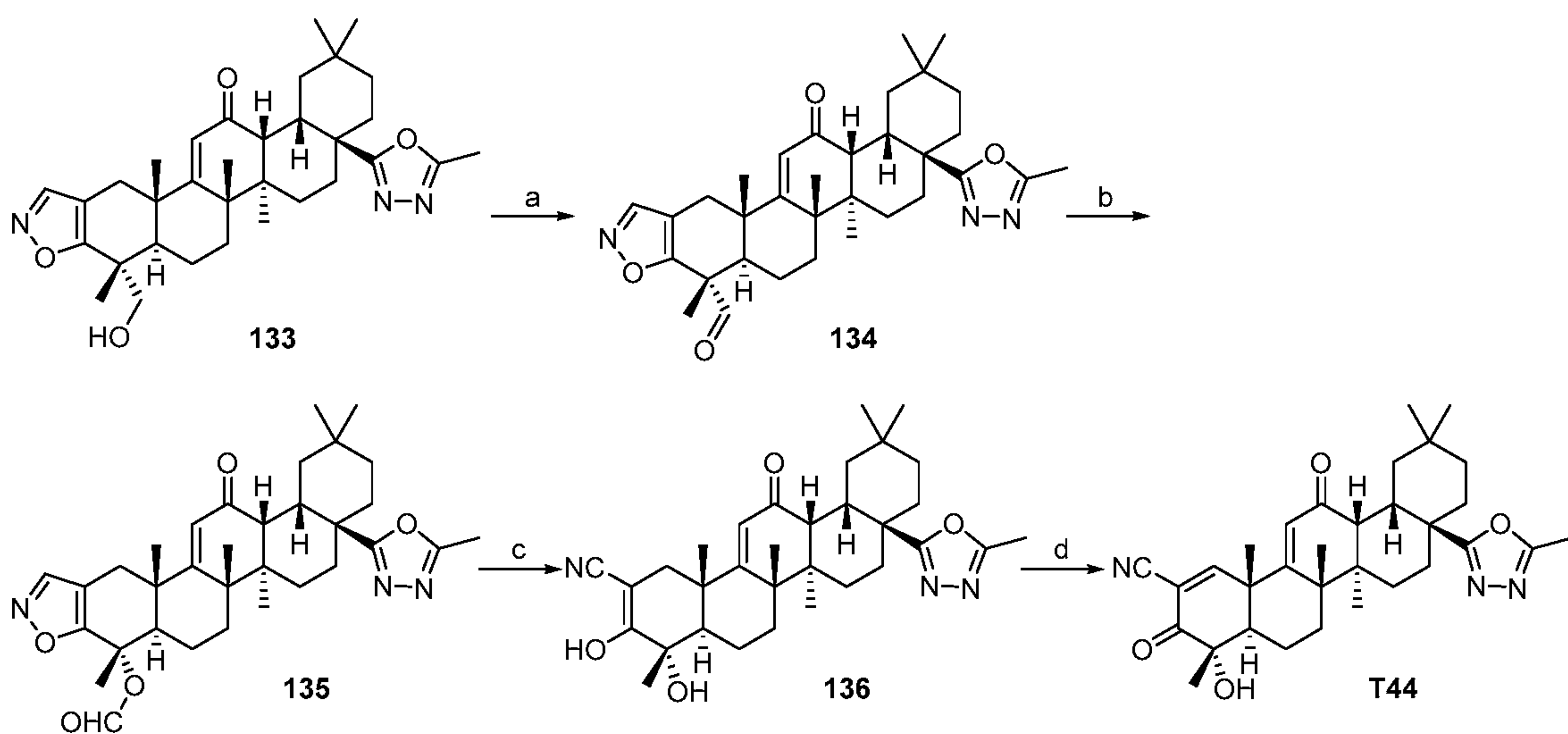
Reagents and conditions: a) $(\text{COCl})_2$, Py, CH_2Cl_2 , 0 °C-rt; b) NaN_3 , toluene, acetone, water, rt, 96% from **83**; c) toluene, 80 °C, 93%; d) i) NaOMe, MeOH, 0 °C; ii) HCO_2Et , NaOMe, MeOH, rt, quant.; e) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, 50 °C, quant.; f) K_2CO_3 , MeOH, rt, 62%; g) DDQ, dioxane, 80 °C, 15%; h) Ac_2O , NaOAc, rt, 80%.

Scheme 31



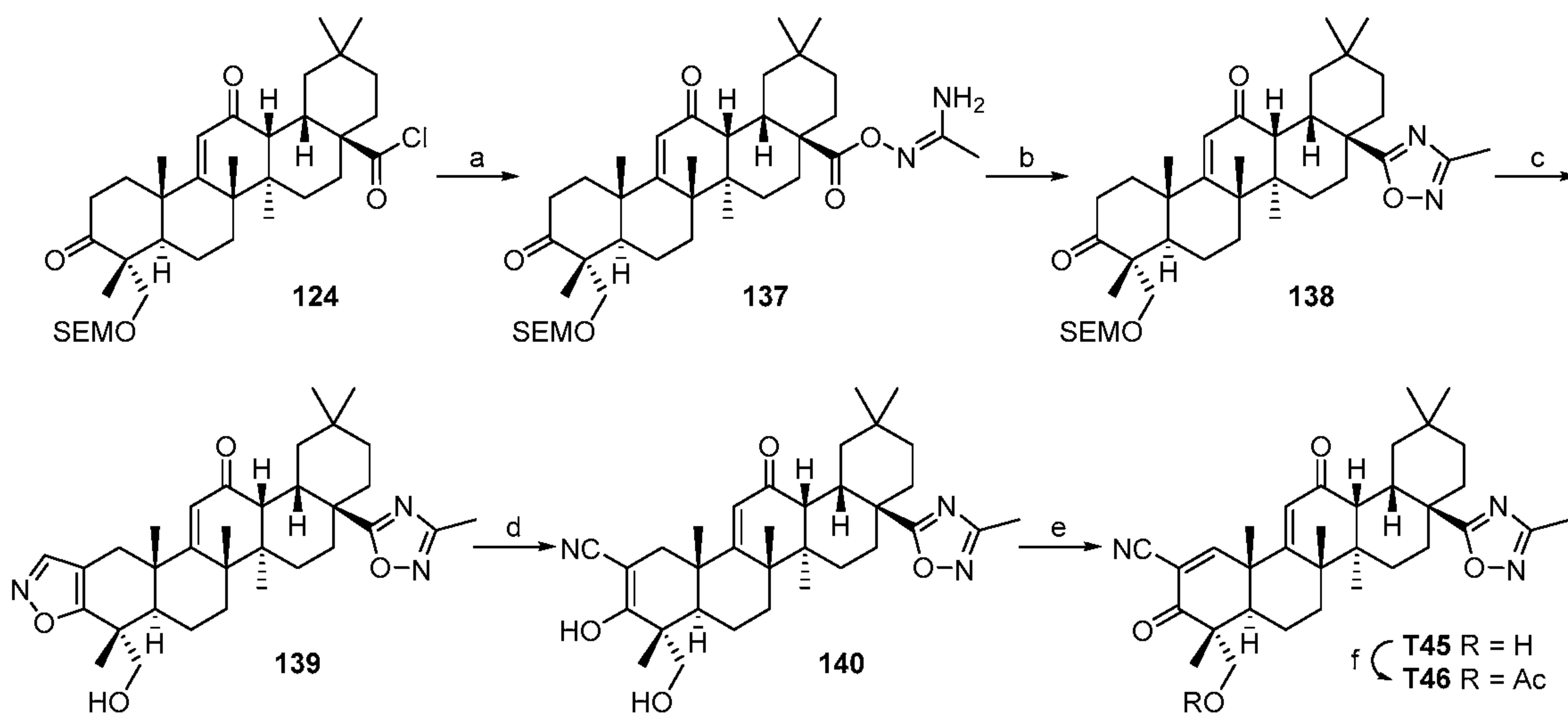
Reagents and conditions: a) i) $(\text{COCl})_2$, DMF, CH_2Cl_2 , rt; ii) AcNHNH_2 , Et_3N , Et_2O , CH_2Cl_2 , rt, quant.; b) $\text{TsOH} \cdot \text{H}_2\text{O}$, toluene, reflux, 81%; c) K_2CO_3 , MeOH, rt, 44% for **132**; 31% for **133**; d) DDQ, benzene, reflux, 47%; e) Ac_2O , DMAP, Py, rt, 34%.

Scheme 32



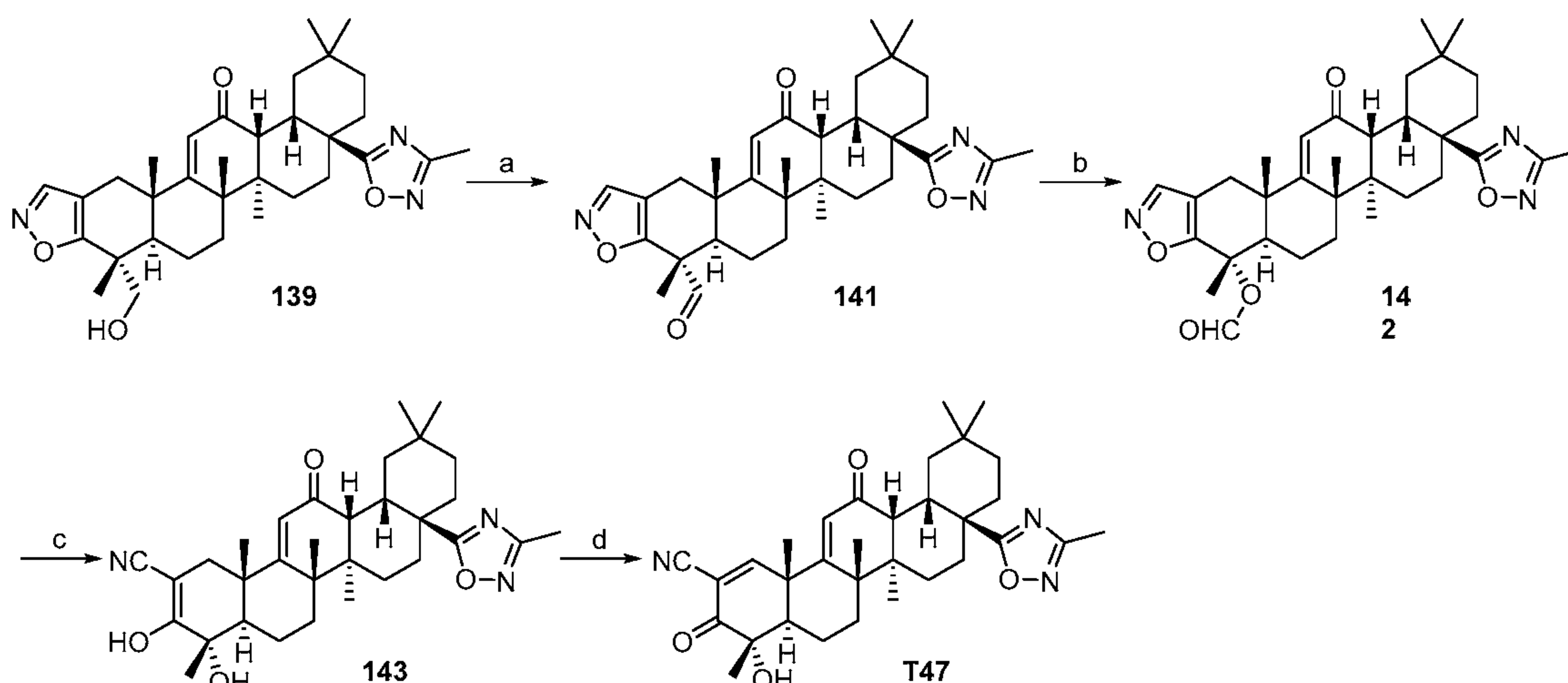
Reagents and conditions: a) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C ; Et_3N , -78°C -rt, 80%; b) $m\text{-CPBA}$, Na_2HPO_4 , CH_2Cl_2 , rt; c) K_2CO_3 , MeOH, rt, 66% from **134**; d) DDQ, benzene, reflux, 77%.

Scheme 33

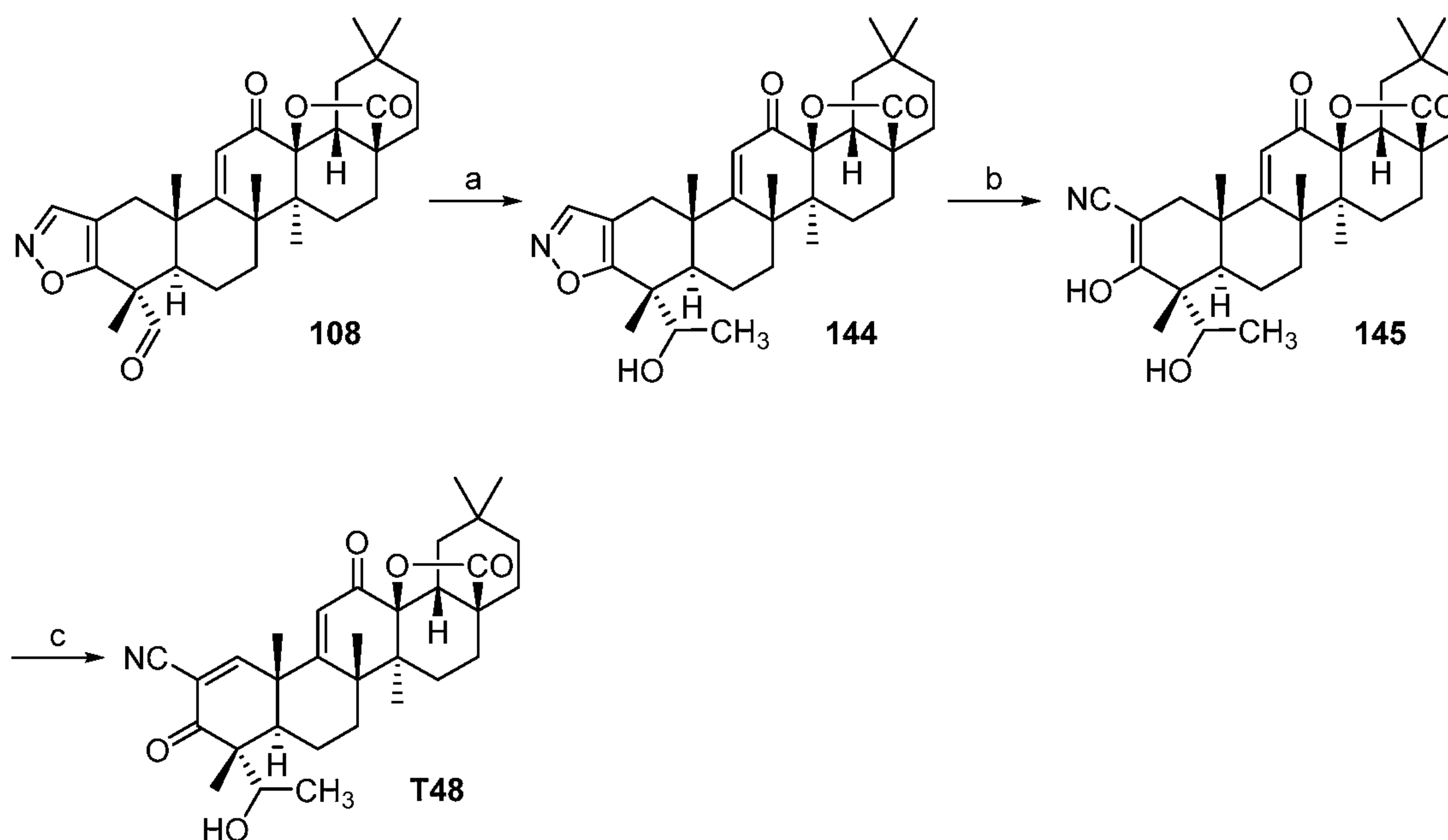


Reagents and conditions: a) acetamide oxime, Et_3N , CH_2Cl_2 , 0 °C, 83%; b) Bu_4NOH , THF, rt, 71%; c) i) HCO_2Et , NaOMe , MeOH , 0 °C-rt; ii) $\text{NH}_2\text{OH}\cdot\text{HCl}$, aq. EtOH , 55 °C, 76%; d) K_2CO_3 , MeOH , rt, quant.; e) DBDMH , DMF , 0 °C; Py , 55 °C, 64%; f) AcCl , Et_3N , CH_2Cl_2 , 82%.

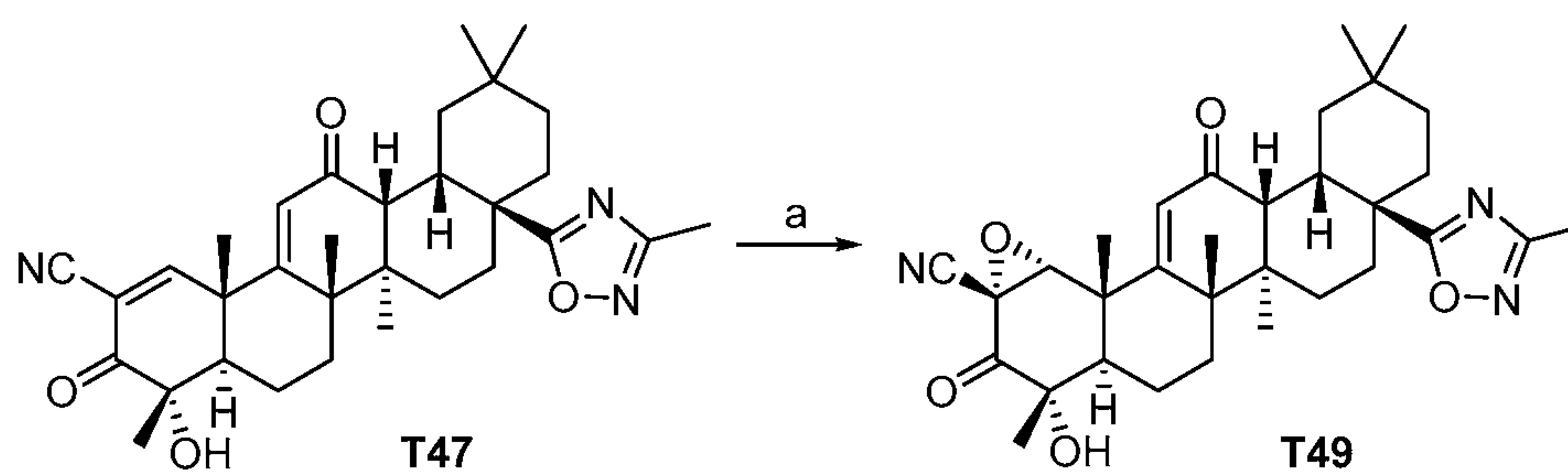
Scheme 34



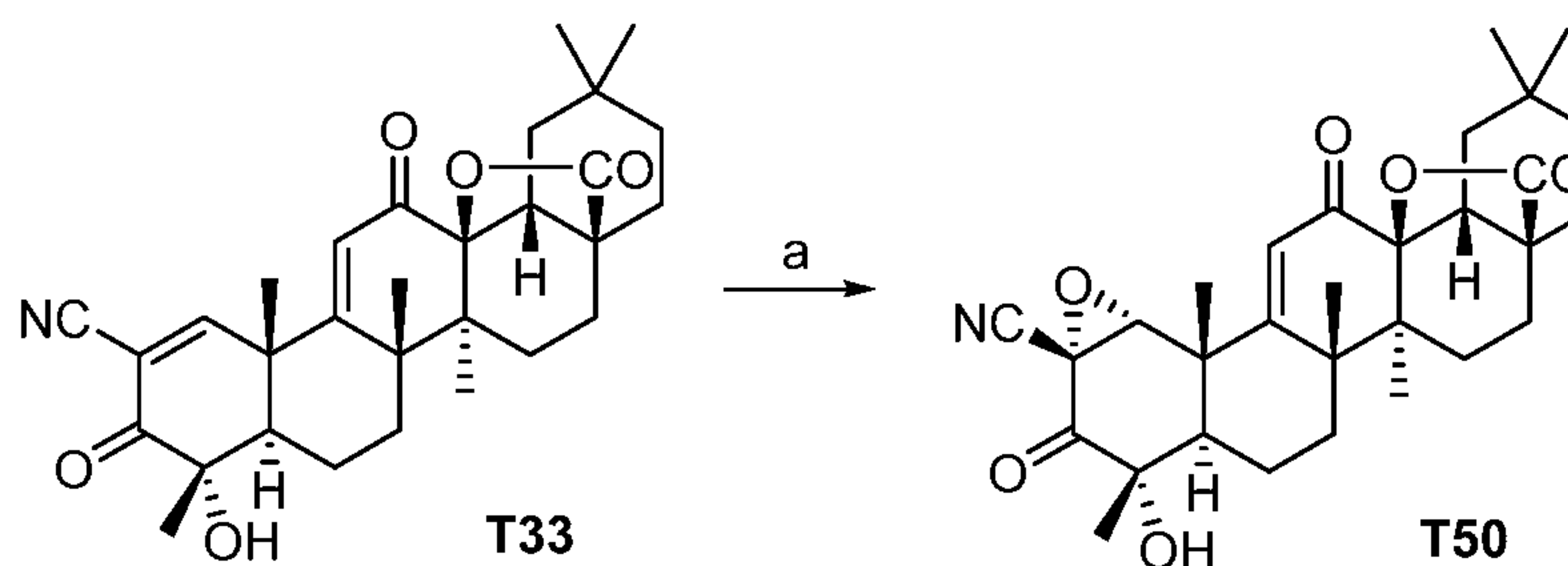
Reagents and conditions: a) Dess-Martin periodinane, CH_2Cl_2 , rt; b) $m\text{-CPBA}$, Na_2HPO_4 , CH_2Cl_2 , rt, 51% from 139; c) K_2CO_3 , MeOH , rt, 99%; d) DBDMH , DMF , 0 °C; Py , 55 °C, 65%.

Scheme 35

Reagents and conditions: a) MeMgCl, THF, -78 °C, 60%; b) K₂CO₃, MeOH, rt, 40%; c) DBDMH, DMF, 0 °C; Py, 55 °C, 28%.

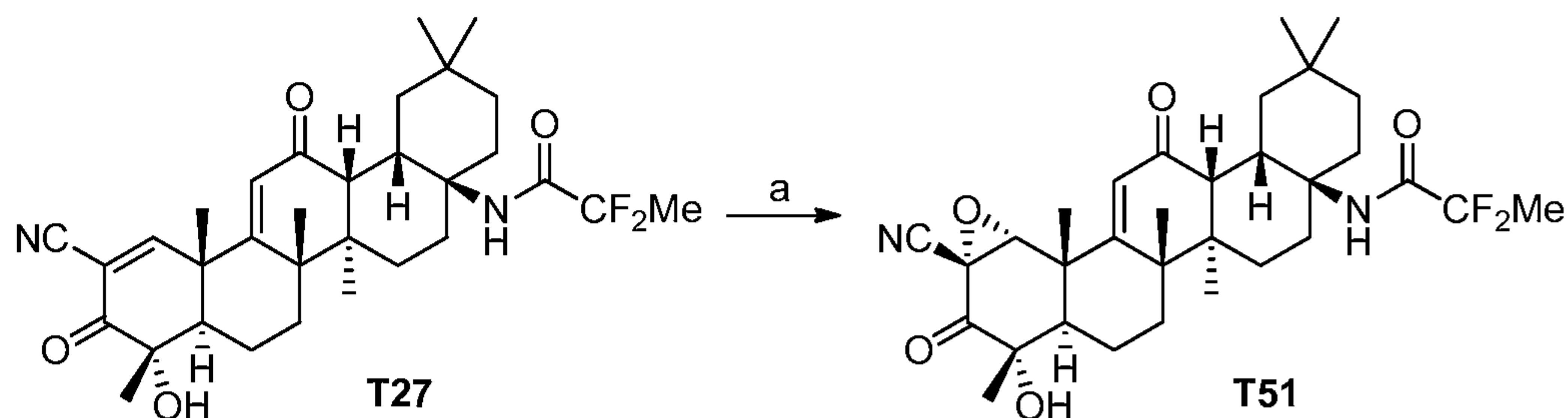
5 Scheme 36

Reagents and conditions: a) aq. H₂O₂, MeCN, rt, 85%.

Scheme 37

10 Reagents and conditions: a) aq. H₂O₂, MeCN, rt, 26%.

Scheme 38



Reagents and conditions: a) aq. H₂O₂, MeCN, rt, 49%.

Experimental Procedure

5 **Compound 2:** A mixture of compound **1** (1.16 g, 2.48 mmol), NaOAc (466 mg, 5.68 mmol) and NH₂OH·HCl (398 mg, 5.73 mmol) in CH₂Cl₂ (12 mL) and MeOH (12 mL) were heated at 60 °C for 1.5 h. EtOAc was added. The mixture was washed with water. The organic extract was dried over Na₂SO₄, filtered and concentrated to give oxime **2** as a white foam. *m/z* = 484.3 (M+1).

10 **Compound 3:** Compound **2** (all obtained from the last step) was dissolved in AcOH (2.9 mL). Ac₂O (0.35 mL, 3.71 mmol) was added. After the reaction was stirred at room temperature for 1 h, ClCH₂CH₂Cl (5.8 mL), PhI(OAc)₂ (1.195 g, 3.71 mmol) and Pd(OAc)₂ (28 mg, 0.13 mmol) were added. The mixture was stirred at 60 °C for 15 h, and at 80 °C for 3 h. Additional amount of Pd(OAc)₂ (28 mg, 0.13 mmol) was added. The mixture was at
15 stirred 80 °C for another 3 h, and was cooled to room temperature. The solvent was removed. Aq. NaHCO₃ was added. The product was extracted with EtOAc. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% EtOAc in hexanes) to give compound **3** (629 mg, 43% yield from **1**) as a light orange foam. *m/z* = 584.3 (M+1).

20 **Compound 4:** To a mixture of compound **3** (627 mg, 1.07 mmol) in MeOH (22 mL) was added K₂CO₃ (742 mg, 5.37 mmol) at 0 °C. The reaction was stirred at room temperature for 1.5 h. CH₂Cl₂ and 12 N aq. HCl (0.90 mL, 1.08 mmol) were added. The mixture was washed with water, and the aq. wash was extracted with CH₂Cl₂. The combined organic extract was dried over Na₂SO₄, filtered and concentrated to give compound **4** as a
25 light yellow foam. *m/z* = 500.2 (M+1).

Compound 5: To a mixture of compound **4** (all obtained from the last step) in EtOH (7.5 mL) and water (2.5 mL) was added sodium bisulfite (mixture of NaHSO₃ and Na₂S₂O₅, ≥ 58.5% SO₂, 410 mg, 3.75 mmol). The reaction was heated at 80 °C for 1 h. Additional

amount of sodium bisulfite (mixture of NaHSO_3 and $\text{Na}_2\text{S}_2\text{O}_5$, $\geq 58.5\%$ SO_2 , 100 mg, 0.91 mmol) was added. The mixture was heated at 80 °C for another 3 h, and cooled to room temperature. EtOAc was added. The mixture was washed with water. The organic extract was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **5** (380 mg, 73% yield from **3**) as a white solid. $m/z = 485.2$ (M+1).

Compound 6: Compound **5** (51.6 mg, 0.11 mmol) was dissolved in acetone (1 mL), and cooled to 0 °C. Jones reagent (2.5 M) was added until the orange color persisted. The mixture was stirred until compound **5** was completely consumed. During the reaction, if the mixture turned green, additional amount of Jones reagent (2.5 M) was added until the orange color persisted. *i*-PrOH was added to quench the reaction. EtOAc was added. The mixture was washed with water. The organic extract was dried over Na_2SO_4 , filtered and concentrated to give a mixture of compound **6** ($m/z = 455.2$ (m+1)) and the C4-acid ($m/z = 499.2$ (m+1)) as a white solid. The mixture was heated under vacuum at 80 °C for 2 h, and 120 °C for 3 h. The residue was purified by column chromatography (Silica gel, 0-40% EtOAc in hexanes and then, 15% EtOAc in CH_2Cl_2) to give compound **6** (39 mg, 81% yield) as a white solid. $m/z = 455.2$ (M+1).

Compound 7: To a mixture of compound **6** (39 mg, 0.086 mmol) in HCO_2Et (196 μL , 2.44 mmol) was added NaOMe (25% w/w in MeOH, 279 μL , 1.21 mmol) at 0 °C. The mixture was stirred at room temperature for 10 min. THF (0.3 mL) was added. The reaction was stirred at room temperature for another 5 h. MTBE was added, followed by 6 N aq. HCl (0.22 mL, 1.32 mmol). EtOAc was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4 , filtered and concentrated. The residue was dissolved in EtOH (4 mL) and water (0.2 mL). $\text{NH}_2\text{OH}\cdot\text{HCl}$ (9 mg, 0.13 mmol) was added. The mixture was heated at 55 °C for 18 h, and cooled to room temperature. EtOAc was added. The mixture was washed with water. The organic extract was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-10% EtOAc in CH_2Cl_2) to give compound **7** (18 mg, 44% yield) as a white solid. $m/z = 480.2$ (M+1).

Compound 8: To a mixture of compound **7** (17 mg, 0.035 mmol) in MeOH (0.70 mL) was added NaOMe (25% w/w in MeOH, 12 μL , 0.052 mmol) at room temperature. The mixture was heated at 55 °C for 30 min. THF (0.35 mL) was added. The mixture was heated at 55 °C for another 2 h. Additional amount of MeOH (0.70 mL) and NaOMe (25% w/w in MeOH, 12 μL , 0.052 mmol) were added. The reaction was heated at 55 °C for an additional

1 h, and cooled to room temperature. MTBE and CH₂Cl₂ were added. The mixture was washed with water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-70% EtOAc in hexanes) to give compound **8** (8.7 mg, 51% yield) as a white foam. $m/z = 480.2$ (M+1).

5 **Compound T1:** To a solution of compound **8** (8.7 mg, 0.018 mmol) in DMF (0.1 mL) was added a solution of 1,3-dibromo-5,5-dimethylhydantoin (2.6 mg, 0.009 mmol) in DMF (21 μ L) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (5 μ L, 0.062 mmol) was added. The reaction was heated at 55 °C for 3 h, and cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic
10 extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% EtOAc in hexanes) to give compound **T1** (7 mg, 80% yield) as a white solid. $m/z = 478.2$ (M+1); ¹H NMR (500 MHz, CDCl₃) δ 8.06 (s, 1H), 6.03 (s, 1H), 3.70 (s, 3H), 3.05 (m, 1H), 2.96 (d, 1H, 4.7 Hz), 2.50-2.55 (m, 2H), 2.12 (m, 1H), 1.42 (s, 3H), 1.33 (s, 3H), 1.16-1.95 (m, 14H), 1.03 (s, 3H), 1.01(s, 3H), 0.90 (s, 3H).

15 **Compound 11 and 12:** To a mixture of compound **9** and **10** (2.9/1, 500 mg, 1.00 mmol) in HCO₂Et (2.42 mL, 30.18 mmol) was added NaOMe (25% w/w in MeOH, 3.43 mL, 14.85 mmol) at 0 °C. The reaction was stirred at 0 °C for 30 min. MTBE was added, followed by 6 N aq. HCl (2.70 mL, 16.20 mmol). EtOAc was added. The mixture was washed with water. The organic extract was dried with MgSO₄, filtered and concentrated.
20 The residue was dissolved in EtOH (10 mL) and water (1 mL). NH₂OH·HCl (105 mg, 1.51 mmol) was added. The mixture was heated at 55 °C for 2 h, and cooled to room temperature. EtOH was removed by evaporation. EtOAc was added. The mixture was washed with water and brine. The organic extract was dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give
25 compound **11** (280 mg, 53% yield) as a white foam. $m/z = 524.2$ (M+1). From the column, also get compound **12** (35 mg, 6.7% yield) as a white solid. $m/z = 524.2$ (M+1).

30 **Compound 13:** Compound **11** (80 mg, 0.15 mmol) was dissolved in acetone (1.5 mL), and cooled to 0 °C. Jones reagent (2.5 M) was added until the orange color persisted. The mixture was stirred at 0 °C for 2 h, and at room temperature for 1 h. During the reaction, additional small amount of Jones reagent was added to maintain the orange color of the mixture. *i*-PrOH was added to quench the reaction. EtOAc was added. The mixture was washed with water. The organic extract was dried over Na₂SO₄, filtered and concentrated to

give compound **13** (72 mg, 88% yield) as an off-white solid. $m/z = 538.2$ (M+1). Compound **13** was used in the next step without further purification.

Compound 14: Compound **13** (72 mg, 0.13 mmol) was dissolved in toluene (1.2 mL) and MeOH (0.4 mL), and was cooled to 0 °C. Trimethylsilyldiazomethane (2 M in Et₂O, 0.15 mL, 0.30 mmol) was added at 0 °C, and stirred for 10 min. AcOH was added to quench the reaction. EtOAc was added. The mixture was washed with aq. NaHCO₃, and water. The organic extract was dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-25% EtOAc in hexanes) to give compound **14** (62 mg, 84% yield) as a white foam. $m/z = 552.2$ (M+1).

Compound 15: To a mixture of compound **14** (60 mg, 0.11 mmol) in MeOH (1.1 mL) was added NaOMe (25% w/w in MeOH, 37 µL, 0.16 mmol) at room temperature. The mixture was heated at 55 °C for 1 h, and was cooled to room temperature. MTBE was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated to give compound **15** (60 mg, quantitative yield) as a white foam. $m/z = 552.2$ (M+1). Compound **15** was used in the next step without further purification.

Compound T2: To a solution of compound **15** (60 mg, 0.11 mmol) in DMF (0.54 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (16 mg, 0.056 mmol) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (26 µL, 0.32 mmol) was added. The reaction was heated at 55 °C for 2 h, and was cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-30% EtOAc in hexanes) to give compound **T2** (46 mg, 77% yield) as a white solid. $m/z = 550.2$ (M+1); ¹H NMR (500 MHz, CDCl₃) δ 8.07 (s, 1H), 5.97 (s, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.03 (m, 1H), 2.94 (d, 1H, $J = 4.6$ Hz), 2.55 (dd, 1H, $J = 2.0, 12.4$ Hz), 1.52 (s, 3H), 1.44 (s, 3H), 1.31 (s, 3H), 1.15-1.95 (m, 14H), 1.03 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H).

Compound 16: Compound **12** (35 mg, 0.067 mmol) was dissolved in acetone (0.7 mL), and cooled to 0 °C. Jones reagent (2.5 M) was added until the orange color persisted. The mixture was stirred at 0 °C for 1 h, and at room temperature for 2 h. During the reaction, additional small amount of Jones reagent was added to maintain the orange color of the mixture. *i*-PrOH was added to quench the reaction. EtOAc was added. The mixture was washed with water. The organic extract was dried over Na₂SO₄, filtered and concentrated to

give the crude acid, which was dissolved in toluene (0.6 mL) and MeOH (0.2 mL), and was cooled to 0 °C. Trimethylsilyldiazomethane (2 M in Et₂O, 70 µL, 0.14 mmol) was added at 0 °C, and stirred for 10 min. AcOH was added to quench the reaction. EtOAc was added. The mixture was washed with aq. NaHCO₃, and water. The organic extract was dried over
5 MgSO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **16** (18 mg, 49% yield from **12**) as a white foam. $m/z = 552.2$ (M+1).

Compound 17: To a mixture of compound **16** (18 mg, 0.033 mmol) in MeOH (0.33 mL) was added NaOMe (25% w/w in MeOH, 11 µL, 0.048 mmol) at room temperature. The
10 mixture was heated at 55 °C for 40 min, and was cooled to room temperature. MTBE was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes). The product was purified again by column chromatography (Silica gel, 0-5% MeOH in CH₂Cl₂) to give compound **17** (13.5 mg, 75%
15 yield) as a white foam. $m/z = 552.2$ (M+1).

Compound T3: To a solution of compound **17** (13.5 mg, 0.024 mmol) in DMF (0.12 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (3.5 mg, 0.012 mmol) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (6 µL, 0.074 mmol) was added. The reaction was heated at 55 °C for 3.5 h, and was cooled to room temperature. EtOAc was
20 added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-30% EtOAc in hexanes) to give compound **T3** (10 mg, 74% yield) as a white solid. $m/z = 550.2$ (M+1); ¹H NMR (500 MHz, CDCl₃) δ 7.91 (s, 1H), 5.94 (s, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.02 (m, 1H), 2.94 (m, 1H), 1.56 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.12-
25 2.13 (m, 15 H), 0.99 (s, 3H), 0.98 (s, 3H), 0.89 (s, 3H).

Compound 18: To a solution of (COCl)₂ (0.121 mL, 1.43 mmol) in CH₂Cl₂ (1.5 mL) was added DMSO (0.203 mL, 2.86 mmol) dropwise at -78 °C, and stirred for 30 min. Compound **11** (312 mg, 0.60 mmol) in CH₂Cl₂ (3 mL) was added at -78 °C, and stirred for another 1 h. Et₃N (0.60 mL, 4.31 mmol) was added. The cold bath was removed, and the
30 reaction was stirred at ambient temperature for 30 min. Water was added. The product was extracted with CH₂Cl₂. The combined organic extract was washed with aq. NaHCO₃ and water, dried with MgSO₄, and concentrated. The residue was purified by column

chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **18** (268 mg, 86% yield) as a white foam. $m/z = 522.3$ (M+1).

Compound 19: To a solution of compound **18** (60 mg, 0.11 mmol) in CH₂Cl₂ (2.3 mL) was added DAST (0.40 mL, 3.03 mmol) at room temperature. The reaction was stirred for 60 h at room temperature. EtOAc was added. The mixture was washed with aq. CaCl₂. The organic extract was dried with MgSO₄, and concentrated. The residue was purified by column chromatography (Silica gel, 0-35% EtOAc in hexanes) to give a mixture of compound **18** and **19** (51 mg, **18/19** = 1.5/1). The mixture of compound **18** and **19** was dissolved in MeOH (3.5 mL), and was cooled to 0 °C. NaBH₄ (20 mg, 0.53 mmol) was added. The reaction was stirred at 0 °C for 10 min. EtOAc was added. The mixture was washed with aq. 1N HCl, and water. The organic extract was dried with MgSO₄, and concentrated. The residue was purified by column chromatography (Silica gel, 0-90% EtOAc in hexanes) to give compound **19** (20 mg, 32% yield) as a white foam. $m/z = 544.3$ (M+1).

Compound 20: To a mixture of compound **19** (22 mg, 0.040 mmol) in MeOH (0.40 mL) was added NaOMe (25% w/w in MeOH, 14 µL, 0.061 mmol) at room temperature. The mixture was heated at 55 °C for 40 min, and was cooled to room temperature. MTBE was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **20** (18 mg, 82% yield) as a white foam. $m/z = 544.2$ (M+1).

Compound T4: To a solution of compound **20** (17 mg, 0.031 mmol) in DMF (0.16 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (4.5 mg, 0.016 mmol) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (8 µL, 0.099 mmol) was added. The reaction was heated at 55 °C for 4.5 h, and was cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-35% EtOAc in hexanes) to give compound **T4** (14.5 mg, 86% yield) as a white foam. $m/z = 542.3$ (M+1); ¹H NMR (500 MHz, CDCl₃) δ 8.14 (s, 1H), 5.99 (s, 1H), 5.93 (t, 1H, $J = 55.8$ Hz), 3.70 (s, 3H), 3.05 (m, 1H), 2.96 (d, 1H, $J = 4.7$ Hz), 2.46 (d, 1H, $J = 10.4$ Hz), 1.50 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.17-2.11 (m, 14H), 1.05 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H).

Compound 21: Na₂HPO₄ (49 mg, 0.35 mmol) and *m*-CPBA (≤ 77%, 65 mg, 0.29 mmol) were added to a solution of compound **18** (100 mg, 0.19 mmol) in CH₂Cl₂ (3.8 mL).

After stirring at room temperature for 6 h, aq. Na₂SO₃ was added. The mixture was extracted with CH₂Cl₂. The organic extract was washed with aq. NaHCO₃, dried with MgSO₄, and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% EtOAc in hexanes) to give compound **21** (89 mg, 86% yield) as a white solid. $m/z = 538.3$ (M+1).

5 **Compound 22:** To a solution of compound **21** (89 mg, 0.17 mmol) in MeOH (1.8 mL) was added NaOMe (25% w/w in MeOH, 60 μ L, 0.26 mmol). The reaction was heated at 55 °C for 1 h, and was cooled to room temperature. MTBE was added. The mixture was washed with 1N aq. HCl, and water. The organic extract was dried with MgSO₄, and concentrated to give compound **22** (83 mg, 98% yield) as a white foam. $m/z = 510.3$ (M+1).

10 Compound **22** was used in the next step without further purification.

Compound T5: To a solution of compound **22** (83 mg, 0.16 mmol) in DMF (0.8 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (23 mg, 0.080 mmol) at 0 °C. After stirring at 0 °C for 1 h, pyridine (40 μ L, 0.50 mmol) was added. The reaction was heated at 55 °C for 2.5 h. EtOAc was added. The mixture was washed with 1 N aq. HCl and water.

15 Organic extract was dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-60% EtOAc in hexanes) to give **T5** (66 mg, 80% yield) as a white foam. $m/z = 508.3$ (M+1); ¹H NMR (500 MHz, CDCl₃) δ 8.01 (s, 1H), 5.90 (s, 1H), 3.70 (s, 3H), 3.24 (s, 1H), 3.03 (m, 1H), 2.94 (d, 1H, $J = 4.7$ Hz), 2.13 (m, 1H), 2.02 (d, 1H, $J = 10.5$ Hz), 1.54 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.16-1.95 (m, 13 H), 1.01 (s, 20 3H), 1.00 (s, 3H), 0.90 (s, 3H).

Compound 23: To a solution of (COCl)₂ (24 μ L, 0.28 mmol) in CH₂Cl₂ (1 mL) was added DMSO (41 μ L, 0.57 mmol) dropwise at -78 °C. The reaction was stirred for 30 min. Compound **12** (60 mg, 0.11 mmol) in CH₂Cl₂ (2 mL) was added at -78 °C, and stirred for another 1 h. Et₃N (0.239 mL, 1.72 mmol) was added. The cold bath was removed, and the 25 reaction was stirred at ambient temperature for 30 min. Water was added. The product was extracted with CH₂Cl₂. The combined organic extract was washed with aq. NaHCO₃ and water, dried with MgSO₄, and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% EtOAc in hexanes) to give compound **23** (43 mg, 72% yield) as a white foam. $m/z = 522.3$ (M+1).

30 **Compound 24:** Na₂HPO₄ (21 mg, 0.15 mmol) and *m*-CPBA ($\leq 77\%$, 28 mg, 0.12 mmol) were added to a solution of compound **23** (43 mg, 0.082 mmol) in CH₂Cl₂ (1.6 mL). After the reaction was stirred at room temperature for 5 h, additional amount of Na₂HPO₄ (10 mg, 0.070 mmol) and *m*-CPBA ($\leq 77\%$, 14 mg, 0.062 mmol) were added. The reaction was

stirred at room temperature overnight. Aq. Na₂SO₃ was added. The mixture was extracted with EtOAc. The organic extract was washed with aq. NaHCO₃, dried with MgSO₄, and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% EtOAc in hexanes) to give compound **24** (28 mg, 63% yield) as a white solid. $m/z = 538.3$ (M+1).

5 **Compound 25:** To a solution of compound **24** (28 mg, 0.052 mmol) in MeOH (0.52 mL) was added NaOMe (25% w/w in MeOH, 24 μ L, 0.10 mmol). The reaction was heated at 55 °C for 1.5 h, and was cooled to room temperature. MTBE was added. The mixture was washed with 1N aq. HCl, and water. The organic extract was dried with MgSO₄, and concentrated. The residue was purified by column chromatography (Silica gel, 0-100%
10 EtOAc in hexanes) to give compound **25** (18 mg, 68% yield) as a white foam. $m/z = 510.3$ (M+1).

Compound T6: To a solution of compound **25** (17.5 mg, 0.034 mmol) in DMF (0.17 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (4.9 mg, 0.017 mmol) at 0 °C. After stirring at 0 °C for 1 h, pyridine (9 μ L, 0.11 mmol) was added. The reaction was heated
15 at 55 °C for 11 h. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. Organic extract was dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% EtOAc in hexanes) to give **T6** (11 mg, 63% yield) as a white foam. $m/z = 508.3$ (M+1); ¹H NMR (500 MHz, CDCl₃) δ 8.17 (s, 1H), 5.98 (s, 1H), 3.70 (s, 3H), 3.05 (m, 1H), 2.96 (d, 1H, $J = 4.6$ Hz), 2.20 (s, 1H), 1.52 (s, 3H), 1.45
20 (s, 3H), 1.34 (s, 3H), 1.00 (s, 6H), 1.17-2.02 (m, 15H), 0.90 (s, 3H).

Compound 26: To a solution of compound **9** (1.00 g, 2.00 mmol) in CH₂Cl₂ (8 mL) was added chloromethyl methyl ether (0.46 mL, 6.05 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h, and then concentrated. The residue was purified by column chromatography (Silica gel, 0-30% EtOAc in hexanes) to give compound **26** (0.98 g, 90%
25 yield) as a white foam. $m/z = 543.4$ (M+1).

Compound 27: To a mixture of compound **26** (955 mg, 1.76 mmol) in HCO₂Et (4.3 mL, 53.5 mmol) was added NaOMe (25% w/w in MeOH, 6.1 mL, 26.4 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. MTBE was added, followed by 3 N aq. HCl. The mixture was extracted with EtOAc. The organic extract was washed with water, dried
30 with Na₂SO₄, filtered and concentrated. The residue was dissolved in EtOH (18 mL) and water (2 mL). NH₂OH·HCl (185 mg, 2.66 mmol) was added. The mixture was heated at 55 °C for 6 h, then cooled to room temperature and concentrated. EtOAc was added. The mixture was washed with water. The organic extract was dried over Na₂SO₄, filtered and

concentrated. The residue was purified by column chromatography (Silica gel, 0-70% EtOAc in hexanes) to give compound **27** (615 mg, 61% yield) as a white foam. $m/z = 568.4$ (M+1).

Compound 28: To a mixture of compound **27** (200 mg, 0.35 mmol) in MeOH (3.5 mL) and THF (1 mL) was added NaOMe (25% w/w in MeOH, 0.16 mL, 0.69 mmol) at room temperature. The mixture was heated at 55 °C for 2 h. MTBE was added. The mixture was washed with aq. NaH₂PO₄. The aqueous wash was back extracted with MTBE. The organic extract was dried over Na₂SO₄, filtered and concentrated to give compound **28** (210 mg, quantitative yield) as a light yellow foam. $m/z = 568.4$ (M+1).

Compound T7: To a solution of compound **28** (all obtained from the last step) in DMF (1 mL) was added a solution of 1,3-dibromo-5,5-dimethylhydantoin (53 mg, 0.19 mmol) in DMF (0.8 mL) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (90 µL, 1.12 mmol) was added. The reaction was heated at 55 °C for 20 h, and cooled to room temperature. EtOAc was added. The mixture was washed with aq. Na₂SO₃, 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-45% EtOAc in hexanes) to give compound **T7** (170 mg, 85% yield) as a white foam. $m/z = 566.2$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 5.98 (s, 1H), 4.49 (AB, 2H), 3.72 (d, 1H, $J = 9.2$ Hz), 3.68 (s, 3H), 3.43 (d, 1H, $J = 9.2$ Hz), 3.26 (s, 3H), 3.03 (m, 1H), 2.92 (d, 1H, $J = 4.4$ Hz), 2.45 (dd, 1H, $J = 1.2, 10.8$ Hz), 1.47 (s, 3H), 1.31 (s, 3H), 1.14-1.94 (m, 14H), 1.05 (s, 3H), 1.02 (s, 3H), 0.99 (s, 3H), 0.88 (s, 3H).

Compound T8: To a solution of compound **29** (32 mg, 0.061 mmol) in pyridine (0.3 mL) was added Ac₂O (30 µL, 0.32 mmol) and catalytic amount of DMAP at room temperature. The reaction was stirred for 30 min. Aq. NaHCO₃ was added, and the mixture was stirred for 5 min. The product was extracted with EtOAc. The organic extract was washed with aq. NaHCO₃, aq. 1 N HCl and water, dried with Na₂SO₄, and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% EtOAc in hexanes) to give compound **T8** (11 mg, 32% yield) as a white foam. $m/z = 564.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 5.98 (s, 1H), 4.30 (d, 1H, $J = 10.8$ Hz), 4.14 (d, 1H, $J = 11.6$ Hz), 3.70 (s, 3H), 3.05 (m, 1H), 2.94 (d, 1H, $J = 4.4$ Hz), 2.07 (dd, 1H, $J = 2.0, 11.6$ Hz), 1.99 (s, 3H), 1.51 (s, 3H), 1.32 (s, 3H), 1.18-1.95 (m, 14H), 1.12 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.89 (s, 3H).

Compound T9: To a solution of compound **29** (37 mg, 0.071 mmol) and pyridine (57 µL, 0.71 mmol) in CH₂Cl₂ (0.35 mL) was added BzCl (13 µL, 0.11 mmol) and catalytic

amount of DMAP at room temperature. The reaction was stirred for 1 h. EtOAc was added. The mixture was washed with aq. 1 N HCl and water, dried with Na₂SO₄, and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% EtOAc in hexanes) to give compound **T9** (31 mg, 70% yield) as a white foam. $m/z = 626.3$ (M+1); ¹H NMR (400
5 MHz, CDCl₃) δ 8.08 (s, 1H), 7.88 (m, 2H), 7.57 (m, 1H), 7.43 (m, 2H), 5.97 (s, 1H), 4.58 (d, 1H, $J = 11.2$ Hz), 4.39 (d, 1H, $J = 11.2$ Hz), 3.69 (s, 3H), 3.01 (m, 1H), 2.92 (d, 1H, $J = 4.4$ Hz), 2.20 (m, 1H), 1.54 (s, 3H), 1.31 (s, 3H), 1.21 (s, 3H), 1.10-1.87 (m, 14H), 0.98 (s, 3H), 0.87 (s, 3H), 0.85 (s, 3H).

Compound 30: To a solution of compound **13** (112 mg, 0.21 mmol) in CH₂Cl₂ (2
10 mL) was added (COCl)₂ (53 μ L, 0.62 mmol) and catalytic amount of DMF at 0 °C. The reaction was stirred at room temperature for 2 h, and concentrated. The residue was dissolved in toluene, and concentrated again to give compound **30** as a yellow solid. Compound **30** was used in the next step without further purification.

Compound 31: Compound **30** (all obtained in the last step) was dissolved in toluene
15 (1 mL). NaN₃ (17 mg, 0.26 mmol), acetone (2 mL) and water (0.5 mL) were added at room temperature. The reaction was stirred at room temperature for 1 h. Toluene was added. The mixture was washed with water. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **31** as a white foam. $m/z = 563.3$ (M+1).

Compound 32: Compound **31** (all obtained in the last step) was dissolved in toluene
20 (2 mL), and heated at 85 °C for 2 h. The solution was cooled, and concentrated to give compound **32** (92 mg, 83% yield from **13**) as a yellow foam. $m/z = 535.3$ (M+1).

Compound 33: Compound **32** (92 mg, 0.17 mmol) was dissolved in MeCN (1.7 mL) at room temperature. 12 N aq. HCl (0.34 mL, 4.08 mmol) was added. The reaction was stirred at room temperature for 2 h, and was cooled to 0 °C. 3 N aq. NaOH (1.36 mL, 4.08
25 mmol), EtOAc, and aq. NaHCO₃ were added. The mixture was stirred until a clear two phase solution was obtained. The organic extract was separated, dried with Na₂SO₄, and concentrated to give compound **33** (90 mg, quantitative yield) as a white foam.

Compound 34: Compound **33** (90 mg, 0.18 mmol) and (Boc)₂O (82 mg, 0.38 mmol) were dissolved in THF (2 mL), and heated at 55 °C for 16 h. After concentration, the residue
30 was purified by column chromatography (Silica gel, 0-40% EtOAc in hexanes) to give compound **34** (74 mg, 69% yield) as a white foam. $m/z = 609.4$ (M+1).

Compound 35: Compound **34** (74 mg, 0.12 mmol) and K₂CO₃ (50 mg, 0.36 mmol) in MeOH (1.2 mL) were stirred at room temperature for 5 h. EtOAc was added. The mixture

was washed with 1N aq. HCl and water. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **35** (66 mg, 89% yield) as a white foam. $m/z = 609.3$ (M+1). Compound **35** was used in the next step without further purification.

Compound T10: DDQ (30 mg, 0.13 mmol) was added to a solution of compound **35** (66 mg, 0.11 mmol) in toluene (1.1 mL). The reaction was heated at 85 °C for 2.5 h, and was cooled to room temperature. CH₂Cl₂ was added. The mixture was washed with aq. NaHCO₃. The aq. washes were extracted again with CH₂Cl₂. The combined organic extract was dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-10% EtOAc in CH₂Cl₂) to give compound **T10** (40 mg, 61% yield) as a white foam. $m/z = 551.3$ (M-C₄H₈); ¹H NMR (400 MHz, CDCl₃) δ 7.97 (s, 1H), 5.96 (s, 1H), 4.76 (b, 1H), 3.69 (s, 3H), 3.02 (m, 1H), 2.91 (d, 1H, $J = 4.4$ Hz), 2.90 (m, 1H), 1.50 (s, 3H), 1.38 (s, 9H), 1.31 (s, 3H), 1.25 (s, 3H), 1.16-1.94 (m, 14H), 1.01 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H).

Compound T11: Compound **T10** (40 mg, 0.066 mmol) was dissolved in CH₂Cl₂ (1 mL). CF₃CO₂H (0.1 mL) was added. The reaction was stirred at room temperature for 2 h. EtOAc was added. The mixture was washed with aq. NaHCO₃. The organic extract was dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-10% MeOH in CH₂Cl₂) to give compound **T11** (11 mg, 33% yield) as a white foam. $m/z = 507.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 1H), 5.93 (s, 1H), 3.69 (s, 3H), 3.03 (m, 1H), 2.93 (d, 1H, $J = 4.4$ Hz), 2.18 (m, 1H), 1.33 (s, 3H), 1.21 (s, 3H), 1.18-1.85 (m, 16H), 1.00 (s, 6H), 1.00 (s, 3H), 0.90 (s, 3H).

Compound T12: To a solution of compound **T11** (16 mg, 0.031 mmol) in CH₂Cl₂ (0.6 mL) were added Et₃N (13 μL, 0.093 mmol) and AcCl (4 μL, 0.056 mmol) at room temperature. The reaction was stirred for 30 min. EtOAc was added. The mixture was washed with 1N aq. HCl and aq. NaHCO₃. The organic extract was dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% acetone in hexanes) to give compound **T12** (7 mg, 40% yield) as a white foam. $m/z = 549.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 7.95 (s, 1H), 5.98 (s, 1H), 5.76 (s, 1H), 3.69 (s, 3H), 3.03 (m, 1H), 2.90 (d, 1H, $J = 4.4$ Hz), 2.86 (dd, 1H, $J = 4.0, 10.3$ Hz), 1.97 (s, 3H), 1.49 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.12-1.95 (m, 14H), 0.99 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H).

Compound 36: To the suspension of MeNH₂·HCl (25 mg, 0.37 mmol) in CH₂Cl₂ (0.8 mL) was added Et₃N (100 μL, 0.72 mmol) at 0 °C. After the reaction was stirred for 10 min, compound **30** (100 mg, 0.18 mmol) in CH₂Cl₂ (1 mL) was added. The reaction was

stirred at 0 °C for 30 min. The solvent was removed. The residue was purified by column chromatography (Silica gel, 0-70% EtOAc in hexanes) to give compound **36** (83 mg, 84% yield) as a white solid. $m/z = 551.3$ (M+1).

Compound 37: To the suspension of Me₂NH·HCl (30 mg, 0.37 mmol) in CH₂Cl₂ (0.8 mL) was added Et₃N (100 µL, 0.72 mmol) at 0 °C. After the reaction was stirred for 10 min, compound **30** (100 mg, 0.18 mmol) in CH₂Cl₂ (1 mL) was added. The reaction was stirred at 0 °C for 30 min. The solvent was removed. The residue was purified by column chromatography (Silica gel, 0-50% EtOAc in hexanes) to give compound **37** (89 mg, 88% yield). $m/z = 565.3$ (M+1).

Compound 38: Compound **36** (83 mg, 0.15 mmol) and K₂CO₃ (63 mg, 0.46 mmol) in MeOH (1.5 mL) were stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1N aq. HCl. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **38** as a white foam. $m/z = 551.3$ (M+1). Compound **38** was used in the next step without further purification.

Compound T13: DDQ (38 mg, 0.17 mmol) was added to a solution of compound **38** (all obtained from the last step) in benzene (1.5 mL). The reaction was heated at reflux for 2.5 h and was cooled to room temperature. CH₂Cl₂ was added. The mixture was washed with aq. NaHCO₃. The organic extract was dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% acetone in hexanes) to give compound **T13** (42 mg, 51% yield from **36**) as a white foam. $m/z = 549.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1H), 6.35 (q, 1H, $J = 4.4$ Hz), 5.99 (s, 1H), 3.69 (s, 3H), 3.04 (m, 1H), 2.95 (d, 1H, $J = 4.8$ Hz), 2.92 (dd, 1H, $J = 3.2, 10.4$ Hz), 2.81 (d, 3H, $J = 4.8$ Hz), 1.54 (s, 3H), 1.47 (s, 3H), 1.31 (s, 3H), 1.16-1.96 (m, 14H), 1.05 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H).

Compound 39: Compound **37** (86 mg, 0.15 mmol) and K₂CO₃ (63 mg, 0.46 mmol) in MeOH (1.5 mL) were stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1N aq. HCl. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **39** as a white foam. $m/z = 565.3$ (M+1). Compound **39** was used in the next step without further purification.

Compound T14: DDQ (38 mg, 0.17 mmol) was added to a solution of compound **39** (all obtained from the last step) in benzene (1.5 mL). The reaction was heated at reflux for 2.5 h, and was cooled to room temperature. CH₂Cl₂ was added. The mixture was washed with aq. NaHCO₃. The organic extract was dried with Na₂SO₄, filtered and concentrated.

The residue was purified by column chromatography (Silica gel, 0-40% acetone in hexanes) to give partially purified compound **T14**, which was purified again by column chromatography (Silica gel, 0-60% EtOAc in hexanes) to give compound **T14** (17 mg, 20% yield from **37**) as a white foam. $m/z = 563.3$ (M+1); ^1H NMR (400 MHz, CDCl_3) δ 8.06 (s, 1H), 5.95 (s, 1H), 3.69 (s, 3H), 3.03 (m, 1H), 2.94 (d, 1H, $J = 4.8$ Hz), 2.84 (bs, 6H), 2.19 (d, 1H, $J = 12.2$ Hz), 1.56 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.14-1.94 (m, 14H), 1.01 (s, 3H), 1.00 (s, 3H), 0.89 (s, 3H).

Compound 40: Compound **30** (70 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (1.3 mL). NH_3 (2 M in MeOH, 0.13 mL, 0.26 mmol) was added at room temperature. After stirring for 1 h, additional amount of NH_3 (2 M in MeOH, 0.13 mL, 0.26 mmol) was added, and the reaction was stirred for another 2 h. EtOAc was added. The mixture was washed with 1 N aq. HCl. The organic extract was dried with Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-80% EtOAc in hexanes) to give compound **40** (35 mg, 52% yield) as a white foam. $m/z = 537.2$ (M+1).

Compound 41: Compound **40** (35 mg, 0.10 mmol) and K_2CO_3 (35 mg, 0.25 mmol) in MeOH (1.3 mL) were stirred at room temperature overnight. EtOAc was added. The mixture was washed with 1N aq. HCl and water. The organic extract was dried with Na_2SO_4 , filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% acetone in hexanes) to give compound **41** (23 mg, 66% yield) as a white solid. $m/z = 537.3$ (M+1).

Compound T15: To a solution of compound **41** (23 mg, 0.043 mmol) in DMF (0.4 mL) was added a solution of 1,3-dibromo-5,5-dimethylhydantoin (6 mg, 0.021 mmol) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (10 μL , 0.12 mmol) was added. The reaction was heated at 55 °C for 5 h, and cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% acetone in hexanes) to give compound **T15** (15 mg, 65% yield) as a white foam. $m/z = 535.3$ (M+1); ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 6.29 (b, 1H), 6.00 (s, 1H), 5.43 (b, 1H), 3.69 (s, 3H), 3.03 (m, 1H), 2.96 (d, 1H, $J = 4.6$ Hz), 2.85 (dd, 1H, $J = 3.6, 10.3$ Hz), 1.58 (s, 3H), 1.48 (s, 3H), 1.31 (s, 3H), 1.16-1.96 (m, 14H), 1.05 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H).

Compound 42: To a suspension of compound **30** (30 mg, 0.054 mmol) in Et_2O (0.5 mL) was added a solution of acethydrazide (12 mg, 0.16 mmol) and Et_3N (15 μL , 0.11 mmol)

in CH₂Cl₂ (0.5 mL) at room temperature. The reaction was stirred at room temperature for 30 min. Aq. NaHCO₃ was added. The product was extracted with EtOAc. The organic extract was washed with water, dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **42** (26 mg, 78% yield) as a white foam. $m/z = 594.2$ (M+1).

Compound 43: Compound **42** (24 mg, 0.040 mmol) and TsOH·H₂O (5 mg, 0.026 mmol) in toluene (3 mL) were heated at reflux with a Dean-Stark apparatus for 1 h. After cooled to room temperature, the reaction mixture was purified by column chromatography (Silica gel, 0-60% EtOAc in hexanes) to give compound **43** (20 mg, 86% yield) as a white foam. $m/z = 576.2$ (M+1).

Compound 44: Compound **43** (20 mg, 0.035 mmol) and K₂CO₃ (17 mg, 0.12 mmol) in MeOH (0.8 mL) were stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1N aq. HCl. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **44** (21 mg, quantitative yield) as a white foam. $m/z = 576.3$ (M+1). Compound **44** was used in the next step without further purification.

Compound T16: A mixture of DDQ (9.1 mg, 0.040 mmol) and compound **44** (21 mg, 0.036 mmol) in benzene (1.6 mL) was heated at reflux for 1 h, and was cooled to room temperature. CH₂Cl₂ and aq. NaHCO₃ were added. The product was extracted with CH₂Cl₂. The organic extract was washed with aq. NaHCO₃, dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-35% acetone in hexanes) to give compound **T16** (12.6 mg, 60% yield) as a yellow foam. $m/z = 574.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1H), 5.99 (s, 1H), 3.69 (s, 3H), 3.03 (m, 1H), 2.95 (d, 1H, $J = 4.8$ Hz), 2.55 (s, 3H), 2.72 (dd, 1H, $J = 1.9, 12.2$ Hz), 1.80-1.98 (m, 3H), 1.72 (s, 3H), 1.62 (s, 3H), 1.33 (s, 3H), 1.04 (s, 3H), 1.13-1.77 (m, 11H), 1.00 (s, 3H), 0.91 (s, 3H).

Compound 45: A mixture of compound **9** (0.30 g, 0.60 mmol), ethylene glycol (0.3 mL, 5.39 mmol), and PPTS (25 mg, 0.10 mmol) in benzene (70 mL) was heated to reflux employing a Dean-Stark trap for 6 h. The mixture was cooled, and diluted with EtOAc. The mixture was washed with sat. NaHCO₃ solution (30 mL), brine (30 mL), dried over MgSO₄, filtered, concentrated, and dried under vacuum to give compound **45** (239 mg, 73% yield) as a white solid. $m/z = 543.5$ (M + 1).

Compound 46: A mixture of compound **45** (0.77 g, 1.42 mmol) and Dess-Martin periodinane (0.78 g, 1.84 mmol) in CH₂Cl₂ (100 mL) was stirred overnight. The reaction

mixture was poured into a flask containing a solution of Na₂S₂O₃ (2.2 g) in water (25 mL) and sat. aq. NaHCO₃ (50 mL). The mixture was stirred until the phases cleared. The organic layer was collected, and the aqueous layer was extracted with additional CH₂Cl₂ (100 mL). The combined organic extracts were dried over MgSO₄, filtered, concentrated, and dried under vacuum to give compound **46** (0.73 g, 95% yield) as a white solid. $m/z = 541.3$ ($M + 1$).

Compound 47: (Methoxymethyl)triphenylphosphonium chloride (3.72 g, 10.86 mmol) was suspended in THF (30 mL) and cooled in an ice bath. *n*-BuLi (1.6 M solution in hexane, 5.66 mL, 9.05 mmol) was added dropwise. The orange-red mixture was stirred for 20 min. A solution of compound **46** (0.98 g, 1.81 mmol) in THF (10 mL) was added dropwise over 5 min. The flask was rinsed with THF (3 mL) and the solution was added to the reaction mixture. The mixture was allowed to slowly warm to room temperature and stirred for 3 h. The mixture was cooled again in an ice bath and quenched by the rapid addition of sat. aq. KH₂PO₄ (50 mL). The mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (25 mL), dried over MgSO₄, and concentrated to give a light yellow-brown oil. Flash chromatography (Silica gel, 25% EtOAc in hexanes) gave compound **47** (0.80 g, 78% yield) as a white solid. $m/z = 569.4$ ($M + 1$). ¹H NMR spectrum confirms *cis*-olefin stereochemistry.

Compound 48: 10% Pd/C (17 mg) was added to a solution of compound **47** (114 mg, 0.20 mmol) in EtOAc (5 mL). The flask was evacuated and purged three times with H₂. The mixture was stirred overnight under a H₂ balloon. Additional 10% Pd/C (28 mg) was added and the flask was evacuated and purged three times with H₂. The flask was stirred under H₂ for 3 d. The mixture was filtered, and the filtrate was concentrated to give compound **48** (127 mg, quantitative yield) as an oil. $m/z = 571.5$ ($M + 1$).

Compound 49: A mixture of compound **48** (127 mg, 0.20 mmol) in MeOH (15 mL) and 1N aq. HCl (3 mL) was stirred overnight. Additional 1N aq. HCl (1 mL) was added and the mixture was slowly concentrated via rotary evaporation ($T < 35$ °C). The mixture was diluted with brine. The product was extracted with EtOAc. The organic extract was dried over MgSO₄, filtered, and concentrated to give compound **49** (100 mg, 95% yield) as a glass. $m/z = 527.5$ ($M + 1$).

Compound 50: Compound **49** (100 mg, 0.19 mmol) was taken up in HCO₂Et (10 mL), and NaOMe (5.4 M solution in MeOH, 0.2, 1.08 mmol) was added. The mixture was stirred overnight, and then quenched with sat. aq. KH₂PO₄ solution (20 mL). The product

was extracted with EtOAc (100 mL). The organic extract was dried over MgSO₄, filtered, and concentrated to give compound **50** (85 mg, 81% yield) as a glass. $m/z = 555.5$ ($M + 1$).

Compound 51: Compound **50** (85 mg, 0.15 mmol) was mixed with NH₂OH·HCl (25 mg, 0.36 mmol) in EtOH (10 mL). The mixture was briefly heated at 50 °C, then stirred at
5 room temperature, monitoring by TLC. The EtOH was repeatedly removed via rotary evaporation at 50 °C and added back to the reaction mixture until the reaction appeared to be complete by TLC. The mixture was stirred overnight, concentrated, and diluted with sat. aq. NaHCO₃ (20 mL). The product was extracted with EtOAc (100 mL). The organic extract was dried over MgSO₄, filtered, and concentrated to give compound **51** (81 mg, 96% yield)
10 as a glass. $m/z = 552.5$ ($M + 1$).

Compound 52: Compound **51** (81 mg, 0.15 mmol) was taken up in THF (10 mL). MeOH (1 mL) and NaOMe (5.4 M solution in MeOH, 0.2 mL, 1.08 mmol) were added. After stirring for 4.5 h, the mixture was quenched with sat. aq. KH₂PO₄ (20 mL). The product was extracted with EtOAc (100 mL). The organic extract was dried over MgSO₄,
15 filtered, and concentrated to compound **52** (78 mg, 96% yield) as a glass. $m/z = 552.5$ ($M + 1$).

Compound T17: A mixture of compound **52** (78 mg, 0.14 mmol) and DDQ (42 mg, 0.18 mmol) in benzene (20 mL) was stirred at room temperature for 3 d. The mixture was diluted with EtOAc (100 mL), and washed with sat. aq. NaHCO₃ (2 × 20 mL). The organic
20 extract was dried over MgSO₄, filtered, and concentrated to a glass. Flash chromatography (Silica gel, 25% EtOAc in hexanes) gave compound **T17** (11.6 mg, 15% yield) as a glass/foam. $m/z = 550.5$ ($M + 1$); ¹H NMR (400 MHz, CDCl₃) δ 7.95 (s, 1H), 5.98 (s, 1H), 3.70 (s, 3H), 3.34 (m, 1H), 3.24 (m, 1H), 3.18 (s, 3H), 3.05 (m, 1H), 2.93 (d, 1H, $J = 4.0$ Hz), 1.47 (s, 3H), 1.32 (s, 3H), 1.15 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.97-2.35 (m, 17H), 0.90 (s,
25 3H).

Compound 53: Compound **47** (234 mg, 0.41 mmol) was taken up in THF (6 mL) and water (1 mL). 1N aq. HCl (0.6 mL) was added and the solution was stirred for 2 d. The solution was diluted with sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, and
30 concentrated to give a white foam. Flash chromatography (Silica gel, 33% EtOAc in hexanes) gave compound **53** (210 mg, 92% yield) as a white solid. $m/z = 555.5$ ($M + 1$).

Compound 54: Compound **53** (205 mg, 0.37 mmol) was taken up in THF (4 mL) and EtOH (1 mL), and cooled in an ice bath. NaBH₄ (4 mg, 0.11 mmol) was added and the

mixture was stirred for 20 min. Additional NaBH₄ (14 mg, 0.37 mmol) was added in portions over 90 min. After stirring for an additional 30 min, the mixture was carefully quenched with sat. aq. KH₂PO₄ (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give compound **54** (208 mg, quantitative yield) as a white solid. $m/z = 557.5$ (M + 1).

Compound 55: Compound **54** (207 mg, 0.37 mmol) was taken up in THF (7 mL) and 3 N aq. HCl (1.5 mL) was added. The solution was stirred for 3 h, then carefully neutralized with sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give compound **55** (208 mg, quantitative yield) as a white solid. $m/z = 513.5$ (M + 1).

Compound 56: Compound **55** (150 mg, 0.29 mmol) was taken up in HCO₂Et (5 mL) and cooled in an ice bath. NaOMe (30 wt.% solution in MeOH, 0.53 g, 2.95 mmol) was added. The mixture was allowed to warm to room temperature and stirred overnight, and cooled again in an ice bath. Sat. aq. KH₂PO₄ (20 mL) was added. The mixture was extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give compound **56** (170 mg, quantitative yield) as a light yellow foam. $m/z = 541.4$ (M + 1).

Compound 57: Compound **56** (0.29 mmol) was taken up in EtOH (5 mL) and water (0.5 mL). NH₂OH·HCl (60 mg, 0.87 mmol) was added and the mixture was heated at 50 °C overnight. The solution was cooled and concentrated, then diluted with sat. aq. NaHCO₃ (20 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give compound **57** (160 mg, quantitative yield) as a light yellow foamy solid. $m/z = 538.5$ (M + 1).

Compound 58: Compound **57** (0.29 mmol) was taken up in MeOH (8 mL) and K₂CO₃ (160 mg, 1.16 mmol) was added. The mixture was stirred overnight, and then concentrated. The residue was diluted with sat. aq. KH₂PO₄ (20 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give a light yellow glass. Flash chromatography (Silica gel, 33% EtOAc in hexanes) gave compound **58** (102 mg, 65% yield) as a white solid. $m/z = 538.5$ (M + 1). ¹H NMR (500 MHz, CDCl₃) δ 5.74 (s, 1H), 4.06 (dt,

1H, $J = 3.2, 9.2$ Hz), 3.89 (q, 1H, $J = 8.8$ Hz), 3.69 (s, 3H), 3.12 (dd, 1H, $J = 3.6, 13.2$ Hz), 3.02 (m, 1H), 2.84 (d, 1H, $J = 4.4$ Hz), 2.54 (s, 1H), 2.18 (dd, 1H, $J = 3.9, 13.0$ Hz), 1.26 (s, 3H), 1.23 (s, 3H), 1.10-2.08 (m, 18H), 1.09 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H), 0.90 (s, 3H).

Compound 59: Compound **58** (43 mg, 0.080 mmol) was taken up in CH₂Cl₂ (2 mL).

5 Et₃N (0.056 mL, 0.40 mmol) was added, followed by TBSCl (24 mg, 0.16 mmol) and DMAP (1 mg). The solution was stirred for 4 h, then diluted with sat. aq. NaHCO₃ (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give compound **59** (60 mg, 98% yield) as a white foam. $m/z = 766.5$ ($M + 1$).

10 **Compound T18:** Compound **59** (60 mg, 0.078 mmol) was taken up in DMF (2 mL) and cooled in an ice bath. 1,3-dibromo-5,5-dimethylhydantoin (11 mg, 0.039 mmol) was added and the solution was allowed to warm to room temperature and stirred for 1 h. Pyridine (0.2 mL) was added and the solution was heated at 60 °C for 3 h. The solution was cooled, diluted with sat. aq. NaHCO₃ (20 mL), and extracted with EtOAc (2 × 50 mL). The
15 combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give a yellow oil. Flash chromatography (Silica gel, 5% EtOAc in CH₂Cl₂) gave compound **T18** (24 mg, 47% yield) as a white solid. $m/z = 650.5$ ($M + 1$); ¹H NMR (400 MHz, CDCl₃) δ 7.95 (s, 1H), 5.98 (s, 1H), 3.69 (s, 3H), 3.59 (m, 2H), 3.04 (m, 1H), 2.94 (d, 1H, $J = 4.4$ Hz), 2.41 (m, 1H), 2.34 (d, 1H, $J = 10.6$ Hz), 1.49 (s, 3H), 1.32 (s,
20 3H), 1.12 (s, 3H), 1.10-1.95 (m, 15H), 1.01 (s, 6H), 0.91 (s, 3H), 0.82 (s, 9H), 0.01 (s, 3H), 0.01 (s, 3H).

Compound T19: Compound **T18** (17 mg, 0.026 mmol) was taken up in MeCN (2 mL). Water (3 drops) and HF-pyridine (70% solution, 3 drops) were added. The solution was stirred overnight, then diluted with sat. aq. NaHCO₃ (20 mL), and extracted with EtOAc
25 (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give a white foam. Flash chromatography (Silica gel, 10% EtOAc in CH₂Cl₂) gave compound **T19** (8 mg, 57% yield) as a white foam; $m/z = 536.4$ ($M + 1$). In CDCl₃, compound **T19** exist as a mixture with compound **60**. ¹H NMR (400 MHz, CDCl₃) δ 7.99 (s, 0.5H), 7.00 (s, 0.5H), 5.97 (s, 0.5 H), 5.84 (s, 0.5H), 3.70
30 (s, 1.5H), 3.69 (s, 1.5H), 1.49 (s, 1.5H), 1.39 (s, 1.5H), 1.32 (s, 1.5H), 1.29 (s, 1.5H), 1.25 (s, 1.5H), 1.16 (s, 1.5H), 1.14 (s, 1.5H), 1.00 (s, 1.5H), 0.99 (s, 1.5H), 0.97 (s, 1.5H), 0.90 (s, 1.5H), 0.89 (s, 1.5H).

Compound 61: To a stirring solution of NaH (0.049 g, 1.22 mmol) in THF (3.0 mL) at 0 °C was added dropwise a solution of compound **45** (0.49 g, 0.902 mmol) in THF (4.0 mL). The mixture was stirred at 0 °C for 30 min. MeI (0.124 mL, 1.99 mmol) was added. The mixture was warmed to room temperature, stirred for 4 h, and then warmed to 45 °C, stirred for 18 h. The reaction was cooled to 0 °C, quenched with sat. aq. NH₄Cl, and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with water, dried over MgSO₄ and concentrated. Flash chromatography (Silica gel, 50% EtOAc in hexanes) gave compound **61** (0.143 g, 28% yield) as a white solid. $m/z = 557.5$ (M + 1).

Compound 62: A mixture of compound **61** (0.143 g, 0.257 mmol), 3 N aq. HCl (1.2 mL, 3.6 mmol) and THF (5.0 mL) was stirred at room temperature for 20 h. The mixture was neutralized with sat. aq. NaHCO₃, and extracted with EtOAc (3 × 20 mL). The organic extracts were washed with brine, dried over MgSO₄ and concentrated. The residue was dried under high vacuum to afford compound **62** (0.130 g, 99% yield) as a colorless, sticky solid. $m/z = 513.5$ (M + 1).

Compound 63: Compound **62** (0.130 g, 0.254 mmol) was taken up in HCO₂Et (6.0 mL) and cooled to 0 °C. NaOMe (30 wt.% solution in MeOH, 0.46 g, 2.55 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 18 h. The mixture was diluted with sat. aq. KH₂PO₄, and extracted with EtOAc (3 × 20 mL). The organic extracts were washed with brine, dried over MgSO₄ and concentrated. The residue was dried under high vacuum to afford compound **63** (0.135 g, 98%) as a light orange foam. $m/z = 541.5$ (M + 1).

Compound 64: Compound **63** (0.135 g, 0.249 mmol) was taken up in EtOH (5 mL) and H₂O (0.5 mL). NH₂OH·HCl (0.052 g, 0.748 mmol) was added and the mixture stirred at 50 °C for 18 h. The mixture was cooled, concentrated, diluted with sat. aq. NaHCO₃, and extracted with EtOAc (3 × 15 mL). The organic extracts were washed with brine, dried over MgSO₄ and concentrated. The residue was dried under high vacuum to afford compound **64** (0.134 g, quantitative yield) as a light yellow foam. $m/z = 538.4$ (M + 1).

Compound 65: A mixture of compound **64** (0.134 g, 0.249 mmol) and K₂CO₃ (0.139 g, 1.00 mmol) in MeOH (6 mL) was stirred at room temperature for 20 h. The mixture was concentrated, diluted with sat. aq. KH₂PO₄, and extracted with EtOAc (3 × 15 mL). The organic extracts were washed with brine, dried over MgSO₄ and concentrated. Flash chromatography (Silica gel, 25% EtOAc in hexanes) gave compound **65** (0.082 g, 62% yield) as a light yellow foam. $m/z = 538.4$ (M + 1).

Compound T20: To a stirring solution of compound **65** (0.080 g, 0.148 mmol) in DMF (1.5 mL) at 0 °C was added 1,3-dibromo-5,5-dimethylhydantoin (0.022 g, 0.073 mmol). The mixture stirred at 0 °C for 1 h. Pyridine (0.08 mL, 0.993 mmol) was added. The reaction was heated to 55 °C, stirred for 3 h, and cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The aq. wash was back-extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with water, dried over Na₂SO₄, and concentrated. Flash chromatography (Silica gel, 25% EtOAc in hexanes) gave compound **T20** (0.048 g, 61%) as white solid. $m/z = 536.4$ ($M + 1$); ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 5.97 (s, 1H), 3.68 (s, 3H), 3.53 (d, 1H, $J = 9.0$ Hz), 3.32 (d, 1H, $J = 9.0$ Hz), 3.22 (s, 3H), 3.04 (m, 1H), 2.92 (d, 1H, $J = 4.7$ Hz), 2.42 (d, 1H, $J = 9.5$ Hz), 1.46 (s, 3H), 1.30 (s, 3H), 1.15-1.95 (m, 14H), 1.02 (s, 6H), 0.99 (s, 3H), 0.89 (s, 3H).

Compound 66: A solution of compound **57** (109 mg, 0.20 mmol) in acetone (2 mL) was cooled in an ice bath. Jones reagent (2.5 M) was added dropwise until the orange color persisted. The mixture was allowed to warm to room temperature and stirred 15 min. Additional small amounts of Jones reagent were added over 30 minutes to maintain the orange color of the reaction mixture. After stirring another 20 min., the mixture was cooled again in an ice bath and *i*-PrOH was added to quench the reaction. Most of the solvent was removed via concentration. The mixture was diluted with water (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give compound **66** (103 mg, 92% yield) as a white foam. $m/z = 552.4$ ($M + 1$).

Compound 67: Crude compound **66** (100 mg, 0.20 mmol) was taken up in THF (3 mL) and MeOH (1 mL) and cooled in an ice bath. Trimethylsilyldiazomethane (2M solution in hexane, 0.5 mL, 1.0 mmol) was added dropwise and the solution was stirred for 30 min. The solution was allowed to warm to room temperature and stirred 2 h. The solution was concentrated to give a light yellow solid. Flash chromatography (Silica gel, 33% EtOAc in hexane) gave compound **67** (64 mg, 62% yield) as a white solid. $m/z = 566.4$ ($M + 1$).

Compound 68: Compound **67** (61 mg, 0.11 mmol) was suspended in MeCN (2 mL) and Et₃N (1 mL) was added. The mixture was heated at 70 °C overnight and then concentrated. The mixture was diluted with sat. aq. KH₂PO₄ (20 mL), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (20 mL), dried over MgSO₄, concentrated, and dried under vacuum to give compound **68** (65 mg, quantitative yield) as an off-white solid. $m/z = 566.4$ ($M + 1$).

Compound T21: To a stirring solution of compound **68** (0.058 g, 0.102 mmol) in DMF (2 mL) was added dropwise a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.015 g, 0.052 mmol) in DMF (1 mL) at 0 °C under N₂. After 30 min, pyridine (0.1 mL, 1.2 mmol) was added. The reaction was heated to 60 °C, and stirred under N₂ for 4 h. The sample was cooled, concentrated, and then partitioned between sat. aq. KH₂PO₄ (20 mL) and EtOAc (20 mL). The organic extract was washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 50% EtOAc in hexanes) to give compound **T21** (0.036 g, 63% yield) as an off-white foamy solid. *m/z* = 564.4 (*M* + 1); ¹H NMR (400 MHz, CDCl₃) δ 7.99 (s, 1H), 5.97 (s, 1H), 3.69 (s, 3H), 3.60 (s, 3H), 3.07 (d, 1H, *J* = 6.5 Hz), 3.04 (m, 1H), 2.91 (d, 1H, *J* = 4.7 Hz), 2.62 (d, 1H, *J* = 6.5 Hz), 2.21 (dd, 1H, *J* = 1.8, 11.9 Hz), 1.50 (s, 3H), 1.31 (s, 3H), 1.17 (s, 3H), 1.15-1.94 (m, 14H), 1.00 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H).

Compound 70: To a stirring solution of compound **69** (2.00 g, 4.27 mmol) and DMF (5 drops) in CH₂Cl₂ (43 mL) was added (COCl)₂ (1.1 mL, 12.8 mmol) dropwise at room temperature under N₂. The mixture was stirred for 3 h, concentrated, and then vacuum dried for 30 min. The resultant yellow solid was dissolved in CH₂Cl₂ (40 mL), and was added dropwise to a stirring suspension of trifluoroethylamine hydrochloride (1.16 g, 8.56 mmol) and Et₃N (3.0 mL, 21.5 mmol) in CH₂Cl₂ (40 mL) at room temperature under N₂. After addition, the solution was stirred for 1 h, concentrated, and then partitioned between sat. aq. KH₂PO₄ (100 mL) and EtOAc (100 mL). The organic extract was washed with brine (100 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 50% EtOAc in hexanes) to give compound **70** (1.90 g, 81% yield) as a light yellow foamy solid. *m/z* = 550 (*M*+1).

Compound 71: A mixture of compound **70** (1.90 g, 3.46 mmol), NH₂OH·HCl (0.48 g, 6.91 mmol) and NaOAc (0.57 g, 6.94 mmol) in CH₂Cl₂ (8.5 mL) and EtOH (8.5 mL) was heated at 60 °C under N₂ for 2 h, and then filtered hot. The filtrate was concentrated, and partitioned between sat. aq. NaHCO₃ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over MgSO₄, filtered and concentrated to give compound **71** (2.52 g, quantitative yield) as an off-white solid. *m/z* = 565 (*M*+1).

Compound 72: To a stirring suspension of compound **71** (all obtained from the last step) in AcOH (10 mL) was added Ac₂O (0.50 mL, 5.30 mmol) dropwise at room temperature under N₂. After stirring at room temperature overnight, the solution was treated with 1,2-dichloroethane (25 mL), iodosobenzene diacetate (1.67 g, 5.18 mmol) and Pd(OAc)₂

(0.039 g, 0.17 mmol). The sample was degassed, and then heated at 70 °C under N₂ overnight. The sample was cooled, concentrated, and then partitioned between brine (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 50% EtOAc in hexanes) to give compound **72** (0.89 g, 38% yield) as a light yellow foamy solid. $m/z = 665$ (M+1). ¹H NMR indicates compound **72** is a mixture of C4 diastereomers (C4 α -CH₂OAc/C4 β -CH₂OAc = 4/1).

Compound 73: To a stirring solution compound **72** (0.89 g, 1.33 mmol) in MeOH (20 mL) was added K₂CO₃ (0.92 g, 6.66 mmol) in one portion at 0 °C under N₂. After stirring at 0 °C for 1.5 h, the mixture was filtered. The filtrate was concentrated, and then partitioned between sat. aq. KH₂PO₄ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 50% EtOAc in CH₂Cl₂) to give compound **73** (0.52 g, 67% yield) as a yellow foamy solid. $m/z = 581$ (M+1).

Compound 74: To a stirring solution of compound **73** (0.49 g, 0.85 mmol) in EtOH (20 mL) and water (5 mL) was added sodium bisulfite (0.31 g, 2.98 mmol) in one portion at room temperature under N₂. The mixture was heated at 80 °C for 2.5 h, cooled, concentrated, and partitioned between brine (50 mL) and CHCl₃ (50 mL). The organic extract was dried over MgSO₄, filtered and concentrated to give compound **74** (0.41 g, 85% yield) as an off-white solid. $m/z = 536$ (M-CH₂O+1).

Compound 75: To a stirring solution of compound **74** (0.41 g, 0.72 mmol) and N,N-diisopropylethylamine (0.44 mL, 2.53 mmol) in CH₂Cl₂ (10 mL) was added 2-(trimethylsilyl)ethoxymethyl chloride (0.26 mL, 1.47 mmol) dropwise at 0 °C under N₂. After slowly warming to room temperature overnight, the sample was concentrated, and then partitioned between sat. aq. KH₂PO₄ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 50% EtOAc in hexanes) to give compound **75** (0.25 g, 51% yield) as a white solid. $m/z = 696$ (M+1).

Compound 76: To a stirring solution of compound **75** (0.25 g, 0.36 mmol) in HCO₂Et (5 mL) was added NaOMe (30 wt.% solution in methanol, 0.34 mL, 1.81 mmol) at room temperature under N₂. The mixture was stirred for 2 h, and then partitioned between sat. aq. KH₂PO₄ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine

(50 mL), dried over MgSO_4 , filtered and concentrated to give compound **76** (0.26 g, 97% yield) as a tan foamy solid. $m/z = 724$ ($M+1$).

Compound 77: A mixture of compound **76** (0.26 g, 0.36 mmol) and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (0.061 g, 0.88 mmol) in ethanol (20 mL) was heated at 50 °C under N_2 overnight. The sample was cooled, concentrated, and partitioned between sat. aq. NaHCO_3 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (50 mL), dried over MgSO_4 , filtered and concentrated to give compound **77** (0.19 g, 92% yield) as a light yellow foamy solid. $m/z = 591$ ($M+1$). Compound **77** is contaminated with 2-(trimethylsilyl)ethanol, and was used in the next step without further purification.

Compound 78: A solution of compound **77** (0.19 g, 0.33 mmol) in methanol (20 mL) was treated with K_2CO_3 (0.23 g, 1.66 mmol) at room temperature. After stirring for 6.5 h, the reaction mixture was filtered through a pad of Celite®. The filtrate was concentrated and partitioned between sat. aq. KH_2PO_4 (15 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over MgSO_4 , filtered and concentrated to give compound **78** (0.18 g, 92% yield) as a light yellow foamy solid. $m/z = 591$ ($M+1$). Compound **78** is contaminated with 2-(trimethylsilyl)ethanol, and was used in the next step without further purification.

Compound T22: A suspension of compound **78** (0.16 g, 0.26 mmol) and DDQ (0.073 g, 0.32 mmol) in benzene (20 mL) and dioxane (10 mL) was heated at 85 °C under N_2 for 1 h. The reaction mixture was cooled, concentrated and partitioned between sat. aq. NaHCO_3 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over MgSO_4 , filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 50% EtOAc in hexanes) to give compound **T22** (0.050 g, 32% yield) as a tan foamy solid. $m/z = 589$ ($M+1$); ^1H NMR (400 MHz, CDCl_3) δ 8.09 (s, 1H), 6.10 (b, 1H), 6.00 (s, 1H), 3.95 (m, 2H), 3.93 (d, 1H, $J = 11.5$ Hz), 3.51 (d, 1H, $J = 10.9$ Hz), 3.05 (d, 1H, $J = 4.6$ Hz), 2.93 (m, 1H), 2.37 (d, 1H, $J = 9.6$ Hz), 1.52 (s, 3H), 1.31 (s, 3H), 1.15-2.09 (m, 15H), 1.06 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H).

Compound T23: A mixture of compound **T22** (0.028 g, 0.049 mmol) and NaOAc (0.020 g, 0.24 mmol) in Ac_2O (1.0 mL, 10.6 mmol) was stirred at room temperature under N_2 overnight. The reaction mixture was concentrated, suspended into CH_2Cl_2 (1 mL) and purified by column chromatography (Silica gel, 50% EtOAc in hexanes) to give compound **T23** (0.016 g, 52% yield) as an off-white foamy solid. $m/z = 631$ ($M+1$); ^1H NMR (400 MHz, CDCl_3) δ 8.06 (s, 1H), 6.02 (t, 1H, $J = 6.5$ Hz), 5.99 (s, 1H), 4.31 (d, 1H, $J = 11.0$ Hz),

4.15 (d, 1H, $J = 11.0$ Hz), 3.96 (m, 2H), 3.05 (d, 1H, $J = 4.5$ Hz), 2.94 (m, 1H), 2.06 (m, 2H), 1.99 (s, 3H), 1.51 (s, 3H), 1.31 (s, 3H), 1.17-1.86 (m, 13H), 1.12 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H).

Compound 79: To a stirring solution of compound **77** (0.31 g, 0.52 mmol) in CH_2Cl_2 (25 mL) was added Dess-Martin periodinane (0.28 g, 0.66 mmol) at room temperature under N_2 . The mixture was stirred at room temperature overnight. 5% aq. $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) and sat. aq. NaHCO_3 (25 mL) were added, and the mixture was stirred for 1 h. The organic extract was separated, washed with brine (25 mL), dried over MgSO_4 , filtered and concentrated to give compound **79** (0.31 g, quantitative yield) an off-white foamy solid. $m/z = 589$ (M+1).

Compound 80: To a stirring solution of compound **79** (0.31 g, 0.52 mmol) in CH_2Cl_2 (10 mL) was added Na_2HPO_4 (0.15 g, 1.06 mmol) and *m*-CPBA ($\leq 77\%$, 0.18 g, 0.80 mmol) at room temperature under N_2 . After stirring for 1 h, the mixture was treated with an aqueous solution of Na_2SO_3 (0.66 g in water (10 mL)), and stirred for 30 min. The organic extract was washed with sat. aq. NaHCO_3 (25 mL) and brine (25 mL), dried over MgSO_4 , filtered and concentrated to give compound **80** (0.26 g, 81% yield) as an off-white foamy solid. $m/z = 605$ (M+1).

Compound 81: To a solution of compound **80** (0.26 g, 0.43 mmol) in methanol (10 mL) was added NaOMe (30 wt% solution in methanol, 0.24 mL, 1.30 mmol) at room temperature under N_2 . The mixture was stirred for 1 h, concentrated, and then partitioned between sat. aq. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over MgSO_4 , filtered and concentrated to give compound **81** (0.22 g, 89% yield) as a tan foamy solid. $m/z = 577$ (M+1).

Compound T24: To a stirring solution of compound **81** (0.22 g, 0.38 mmol) in DMF (8 mL) was added a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.054 g, 0.19 mmol) in DMF (2 mL) dropwise at 0 °C under N_2 . After 30 min, pyridine (0.31 mL, 3.83 mmol) was added. The reaction was heated to 60 °C and stirred for 4 h under N_2 . The mixture was cooled, concentrated, and then partitioned between sat. aq. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over MgSO_4 , filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 50% EtOAc in hexanes) to give compound **T24** (0.129 g, 59% yield) as light yellow solid. $m/z = 575$ (M+1); ^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 1H), 6.04 (t, 1H, $J = 6.5$ Hz), 5.92 (s, 1H),

4.02 (m, 1H), 3.90 (m, 1H), 3.24 (s, 1H), 3.04 (d, 1H, $J = 4.6$ Hz), 2.93 (m, 1H), 1.54 (s, 3H), 1.32 (s, 3H), 1.32 (s, 3H), 1.17-2.15 (m, 15H), 1.02 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H).

Compound 82: To a stirring solution of compound **9** (5.3 g, 10.64 mmol) and *N,N*-diisopropylethylamine (6.49 mL, 37.24 mmol) in CH_2Cl_2 (80 mL) was added 2-(trimethylsilyl)ethoxymethyl chloride (3.77 mL, 21.28 mmol) dropwise at 0 °C. The reaction was stirred at room temperature overnight. Aq. NaHCO_3 was added. The mixture was stirred for 5 min, and extracted with CH_2Cl_2 . The organic extract was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-30% EtOAc in hexanes) to give compound **82** (6.4 g, 96% yield) as a white foam. $m/z = 629.4$ (M+1).

Compound 83: A mixture of compound **82** (7.43 g, 11.81 mmol), LiBr (10.27 g, 118.2 mmol) and NaOAc (2.42 g, 29.6 mmol) in *N,N*-dimethylacetamide (120 mL) was heated at 150 °C with N_2 bubbled through the reaction mixture for 6 h, and then cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% acetone in hexanes) to give compound **83** (3.85 g, 53% yield) as a white foam. $m/z = 615.4$ (M+1).

Compound 84 and 85: To a mixture of compound **83** (5.5 g, 8.94 mmol) in HCO_2Et (37 mL, 447 mmol) was added NaOMe (25% w/w in MeOH, 20.5 mL, 89.4 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h, and was cooled to 0 °C. MTBE was added, followed by 1 N aq. HCl (89 mL, 89 mmol). EtOAc was added. The mixture was washed with water. The organic extract was dried with Na_2SO_4 , filtered and concentrated. The residue was dissolved in EtOH (90 mL) and water (9 mL). $\text{NH}_2\text{OH}\cdot\text{HCl}$ (804 mg, 11.6 mmol) was added. The mixture was heated at 55 °C for 3 h, cooled to room temperature, and concentrated. EtOAc was added. The mixture was washed with water. The organic extract was dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% acetone in hexanes) to give compound **84** (1.22 g, 26 % yield) and **85** (1.77 g, 30 % yield). Compound **84**: white solid, $m/z = 510.3$ (M+1); Compound **85**: white solid, $m/z = 640.4$ (M+1).

Compound 86: A mixture of compound **84** (105 mg, 0.206 mmol), pyridine (0.5 mL, 6.18 mmol), acetic anhydride (0.250 mL, 2.68 mmol) and DMAP (2.5 mg, 0.02 mmol) was stirred at room temperature for 30 minutes. Aq. NaHCO_3 and EtOAc were added. The mixture was stirred for 60 min, and extracted with EtOAc. The organic extract was washed

with 1N aq. HCl solution and water. The organic extract was dried over Na₂SO₄, filtered and concentrated to give compound **86** (110 mg, 97% yield) as a white foam. $m/z = 552.3$ (M+1).

Compound 87: To a stirring solution of compound **86** (110 mg, 0.199 mmol) in CH₂Cl₂ (2 mL) was added (COCl)₂ (51 μ L, 0.60 mmol) at room temperature followed by one drop of DMF. The reaction was stirred at room temperature for 2 h, and concentrated. The residue was dissolved in toluene, and concentrated again to give the acid chloride as a yellow foam. The acid chloride was suspended in Et₂O (2 mL). EtNH₂ (2M in THF, 0.3 mL, 0.6 mmol) and Et₃N (55 μ L, 0.40 mmol) in CH₂Cl₂ (2 mL) were added. The reaction was stirred at room temperature for 30 min. Aq. NaHCO₃ and EtOAc were added. The mixture was extracted with EtOAc. The organic extracts were washed with water, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-60% EtOAc in hexanes) to give compound **87** (65 mg, 56% yield) as a white foam. $m/z = 579.4$ (M+1).

Compound 88: To a solution of compound **87** (64 mg, 0.110 mmol) in MeOH (2 mL), was added K₂CO₃ (61 mg, 0.44 mmol). The mixture was stirred for 14 h, and concentrated. The residue was diluted with water, and extracted with EtOAc. The organic extract was dried over Na₂SO₄, filtered and concentrated to give compound **88** (32 mg, 54% yield) as a white foam. $m/z = 537.3$ (M+1).

Compound T25: To a solution of compound **88** (32 mg, 0.06 mmol) in benzene (2 mL), was added DDQ (16.2 mg, 0.07 mmol). The mixture was stirred for 30 min at reflux, and cooled to room temperature. CH₂Cl₂ was added. The mixture was washed with water, dried over Na₂SO₄, filtered and concentrated to give **T25** (10 mg, 31% yield) as a white foam. $m/z = 535.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 5.98 (s, 1H), 5.79 (t, 1H, $J = 5.9$ Hz), 3.92 (d, 1H, $J = 10.9$ Hz), 3.51 (d, 1H, $J = 10.9$ Hz), 3.32 (m, 2H), 3.06 (d, 1H, $J = 4.6$ Hz), 2.85 (m, 1H), 2.37 (m, 1H), 1.52 (s, 3H), 1.34 (s, 3H), 1.15-2.01 (m, 15H), 1.13 (t, 3H, $J = 7.2$ Hz), 1.06 (s, 3H), 1.03 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H).

Compound 89: A mixture of compound **84** (445 mg, 0.87 mmol), Na₂HPO₄ (495 mg, 3.49 mmol) and Dess-Martin periodinane (740 mg, 1.75 mmol) in CH₂Cl₂ (10 mL) was stirred at room temperature overnight. 10% aq. Na₂S₂O₃ (50 mL) was added. The mixture was stirred for 10 min, and was extracted with CH₂Cl₂ (4 $\times$ 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered, concentrated to give compound **89** (500 mg) as an off-white foam. $m/z = 508.3$ (M + 1). Compound **89** was used in the next step without further purification.

Compound 90: Na₂HPO₄ (495 mg, 3.49 mmol) and *m*-CPBA ($\leq 77\%$, 292 mg, 1.31 mmol) were added to a solution of compound **89** (all obtained from the last step) in CH₂Cl₂ (10 mL). After stirring at room temperature for 1 h, aq. Na₂SO₃ was added. The mixture was stirred for 5 min, and was extracted with CH₂Cl₂. The organic extract was dried
5 with Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (C18, 10-100% MeCN in water) to give compound **90** (227 mg, 50% yield from **84**) as a white solid. $m/z = 524.3$ (M+1).

Compound 91: To a solution of compound **90** (70 mg, 0.13 mmol) in CH₂Cl₂ (2.6 mL) was added (COCl)₂ (34 μ L, 0.40 mmol) and catalytic amount of DMF at 0 °C. The
10 reaction was stirred at room temperature for 2 h, and concentrated. The residue was dissolved in toluene, and concentrated again to give compound **91** (70 mg) as a yellow foam.

Compound 92: Compound **91** (60 mg, 0.11 mmol) was dissolved in CH₂Cl₂ (1.1 mL). EtNH₂ (2 M in THF, 0.12 mL, 0.24 mmol) was added at room temperature. After stirring for 30 min, the mixture was concentrated. The residue was purified by column
15 chromatography (Silica gel, 0-50% EtOAc in hexanes) to give compound **92** (38 mg, 60% yield from **90**) as a light yellow foam. $m/z = 551.3$ (M+1).

Compound 93: A mixture of compound **92** (36 mg, 0.065 mmol) and K₂CO₃ (36 mg, 0.26 mmol) in MeOH (1.3 mL) was stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried with
20 Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% acetone in hexanes) to give compound **93** (30 mg, 83% yield) as a white solid. $m/z = 523.3$ (M+1).

Compound T26: To a solution of compound **93** (30 mg, 0.057 mmol) in DMF (0.4 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (8.2 mg, 0.029 mmol) at 0 °C. After the
25 reaction was stirred at 0 °C for 1h, pyridine (14 μ L, 0.17 mmol) was added. The reaction was heated at 55 °C for 2 h, and cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% acetone in hexanes) to give compound **T26** (23 mg, 77% yield) as a white
30 foam. $m/z = 521.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 1H), 5.91 (s, 1H), 5.77 (t, 1H, $J = 5.7$ Hz), 3.31 (m, 2H), 3.26 (s, 1H), 3.06 (d, 1H, $J = 4.6$ Hz), 2.86 (m, 1H), 1.92-2.14 (m, 3H), 1.72-1.85 (m, 4H), 1.60 (s, 3H), 1.35 (s, 3H), 1.31 (s, 3H), 1.13 (t, 3H, $J = 7.2$ Hz), 1.10-1.60 (m, 8H), 1.01 (s, 3H), 0.99 (s, 3H), 0.89 (s, 3H).

Compound 94: Compound **91** (123 mg, 0.23 mmol) was dissolved in toluene (1.2 mL) and acetone (2.4 mL), and cooled to 0 °C. The solution of NaN₃ (19 mg, 0.29 mmol) in water (0.6 mL) was added. The reaction was stirred at room temperature for 3 h. EtOAc was added. The mixture was washed with sat. aq. NaHCO₃ and water. The organic extract was dried with Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 0-35% EtOAc in hexanes) to give compound **94** (72 mg, 60% yield) as a white foam. $m/z = 549.3$ (M+1).

Compound 95: A solution of compound **94** (100 mg, 0.18 mmol) in toluene (2 mL) was heated at 85 °C for 2 h. The solution was concentrated to give compound **95**, which was used in the next step without further purification. $m/z = 521.3$ (M+1).

Compound 96: To a solution of compound **95** (all obtained from the last step) in CH₂Cl₂ (1.7 mL) was added 12 N aq. HCl (0.34 mL, 4.08 mmol) at 0 °C. After stirring at room temperature for 2 h, the mixture was treated with sat. aq. NaHCO₃ to adjust pH > 7, and was extracted with EtOAc. The organic extract was dried with Na₂SO₄, and concentrated to give the crude compound **96** (85 mg) as a yellow foam. $m/z = 467.3$. The crude product was contaminated with a major impurity, and was carried on to the next step without further purification.

Compound 97: To a solution of compound **96** (all obtained from the last step) and 2,2-difluoropropionic acid (25 mg, 0.23 mmol) in CH₂Cl₂ (2 mL) was added propylphosphonic anhydride (≥50 wt.% in EtOAc, 224 μL, 0.38 mmol) and Et₃N (79 μL, 0.56 mmol) at room temperature. The mixture was stirred at room temperature for 2 h. Sat. aq. NaHCO₃ was added. The mixture was stirred for 30 min, and then extracted with EtOAc. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% EtOAc in hexanes) to give compound **97** (20 mg, 20% yield from **94**) as a white foam. $m/z = 559.3$ (M+1).

Compound 98: A mixture of compound **97** (20 mg, 0.036 mmol) and K₂CO₃ (30 mg, 0.22 mmol) in MeOH (1.4 mL) was stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **98** (19 mg, 95% yield) as a white foam. $m/z = 559.4$ (M+1).

Compound T27: To a solution of compound **98** (19 mg, 0.034 mmol) in DMF (0.4 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (5 mg, 0.017 mmol) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (8 μL, 0.099 mmol) was added. The reaction

was heated at 55 °C for 2 h, and cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% EtOAc in hexanes) to give compound **T27** (13 mg, 68% yield) as a white solid. $m/z = 557.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 1H), 5.93 (s, 1H), 5.91 (bs, 1H), 3.24 (s, 1H), 2.98 (d, 1H, $J = 4.6$ Hz), 2.81 (m, 1H), 1.78 (t, 3H, $J = 19.3$ Hz), 1.55 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 1.16-2.18 (m, 15H), 1.05 (s, 3H), 1.03 (s, 3H), 0.90 (s, 3H).

Compound 99: To a stirring solution of compound **85** (0.65 g, 1.02 mmol) and Et₃N (0.42 mL, 3.01 mmol) in benzene (25 mL) was added dropwise diphenylphosphorylazide (0.33 mL, 1.53 mmol) at 0 °C. After slowly warming to room temperature overnight, the mixture was concentrated, and then partitioned between sat. aq. KH₂PO₄ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over MgSO₄, filtered and concentrated. The resultant light yellow oil (0.92 g) was dissolved into benzene (50 mL), and heated at reflux for 2 h. The sample was cooled, and concentrated. The residue was purified by column chromatography (Silica gel, 25% EtOAc in hexanes) to give compound **99** (0.72 g, quantitative yield). $m/z = 637$ (M+1). Compound **99** was contaminated with diphenylphosphorylazide, and was used in the next step without further purification.

Compound 100: A solution of compound **99** (all obtained from the last step) in CH₃CN (20 mL) was treated with 12 N aq. HCl (2.1 mL, 25.2 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h, concentrated, and then vacuum dried overnight. The resultant gummy oil was carefully partitioned between sat. aq. NaHCO₃ (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over MgSO₄, filtered and concentrated to give compound **100** (0.52 g, quantitative yield) as a tan foamy solid. $m/z = 481$ (M+1). Compound **100** was contaminated with diphenylphosphorylazide, and was used in the next step without further purification.

Compound 101 and 102: To a stirring solution of compound **100** (0.27 g, 0.56 mmol), 2,2-difluoropropionic acid (0.094 g, 0.85 mmol) and Et₃N (0.24 mL, 1.72 mmol) in CH₂Cl₂ (50 mL) was added propylphosphonic anhydride (50 wt.% solution in EtOAc, 0.34 mL, 0.57 mmol) dropwise at room temperature. After stirring overnight, the mixture was concentrated, and then partitioned between sat. aq. KH₂PO₄ (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over MgSO₄, filtered and concentrated to give a mixture of compound **101** and compound **102** (0.12 g) as an off-white

foamy solid. **101**: $m/z = 573$ (M+1); **102**: $m/z = 665$ (M+1). The mixture was carried on to the next step without separation.

Compound 103: To a solution of compound **101** and **102** (0.12 g, all obtained from the last step) in methanol (20 mL) was added K_2CO_3 (0.13 g, 0.94 mmol). The mixture was stirred at room temperature for 4 h, and then filtered through a pad of Celite®. The filtrate was concentrated, and partitioned between sat. aq. KH_2PO_4 (50 mL) and EtOAc (50 mL). The organic extract was washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated to give compound **103** (100 mg, 31% yield from **100**) as a light yellow foamy solid. $m/z = 573$ (M+1).

Compound T28: To a stirring solution of compound **103** (0.100 g, 0.174 mmol) in DMF (5 mL) was added a solution of 1,3-dibromo-5,5-dimethylhydantoin (0.025 g, 0.087 mmol) in DMF (1 mL) dropwise at 0 °C. After 30 min, pyridine (0.14 mL, 1.73 mmol) was added. The mixture was heated to 60 °C, stirred for 4 h, cooled, and concentrated. The residue was partitioned between sat. aq. KH_2PO_4 (25 mL) and EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 20% EtOAc in CH_2Cl_2) to give compound **T28** (0.043 g, 43% yield) as an off-white foamy solid. $m/z = 571.3$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 6.01 (s, 1H), 5.93 (bs, 1H), 3.93 (dd, 1H, $J = 5.5, 10.6$ Hz), 3.51 (dd, 1H, $J = 5.4, 11.0$ Hz), 3.02 (d, 1H, $J = 4.0$ Hz), 2.79 (m, 1H), 2.39 (d, 1H, $J = 7.9$ Hz), 1.78 (t, 3H, $J = 19.5$ Hz), 1.53 (s, 3H), 1.43 (s, 3H), 1.15-2.15 (m, 15H), 1.07 (s, 3H), 1.06 (s, 6H), 0.91 (s, 3H).

Compound T29: A mixture of compound **T28** (0.038 g, 0.066 mmol) and NaOAc (0.027 g, 0.33 mmol) in Ac_2O (1.0 mL, 10.6 mmol) was stirred at room temperature overnight. The sample was filtered and the solid was washed with CH_2Cl_2 . The filtrate was concentrated and purified by column chromatography (Silica gel, 10% EtOAc in CH_2Cl_2) to give compound **T29** (0.024 g, 58% yield) as an off-white solid. $m/z = 613$ (M+1, 30%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 6.01 (s, 1H), 5.91 (bs, 1H), 4.31 (d, 1H, $J = 11.1$ Hz), 4.16 (d, 1H, $J = 11.0$ Hz), 3.01 (d, 1H, $J = 4.8$ Hz), 2.81 (m, 1H), 1.99 (s, 3H), 1.78 (t, 3H, $J = 19.5$ Hz), 1.53 (s, 3H), 1.42 (s, 3H), 1.17-2.13 (m, 15H), 1.13 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H), 0.90 (s, 3H).

Compound 104: Compound **91** (33 mg, 0.061 mmol) was dissolved in CH_2Cl_2 (1 mL). Et_3N (27 μ L, 0.19 mmol) and $Me_2NH \cdot HCl$ (10 mg, 0.122 mmol) were added at room temperature. After stirring for 30 min, the mixture was concentrated. The residue was

purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **104** (29 mg, 86% yield) as a white foam. $m/z = 551.3$ (M+1).

Compound 105: A mixture of compound **104** (29 mg, 0.053 mmol) and K_2CO_3 (29 mg, 0.21 mmol) in MeOH (1 mL) was stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried with Na_2SO_4 , filtered, and concentrated to give compound **105** (30 mg, quantitative yield). $m/z = 523.3$ (M+1). Compound **105** was used in the next step without further purification.

Compound T30: DDQ (14 mg, 0.062 mmol) was added to a solution of compound **105** (all obtained from the last step) in benzene (1.1 mL). The reaction was heated at reflux for 1 h, and cooled to room temperature. CH_2Cl_2 was added. The mixture was washed with aq. $NaHCO_3$. Organic extract was dried with Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography to give compound **T30** (9 mg, 31% yield) as a white solid. $m/z = 521.2$ (M+1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 5.86 (s, 1H), 3.27 (d, 1H, $J = 4.7$ Hz), 3.25 (s, 1H), 3.18 (m, 1H), 3.08 (s, 6H), 1.95-2.04 (m, 3H), 1.53 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.16-1.90 (m, 12H), 1.01 (s, 3H), 1.01 (s, 3H), 0.90 (s, 3H).

Compound 106: Compound **84** (125 mg, 0.25 mmol) and [hydroxy(tosyloxy)iodo]benzene (125 mg, 0.32 mmol) and CH_2Cl_2 (4 mL) in a sealed vial was heated at 55 °C for 2 h, and then cooled to room temperature. The mixture was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes). The mixed fractions were concentrated, and purified again by column chromatography (Silica gel, 0-40% acetone in hexanes). The purified fractions were combined and concentrated to give compound **106** (43 mg, 35% yield) as a white solid. $m/z = 508.3$ (M+1).

Compound 107: To a solution of compound **106** (38 mg, 0.075 mmol) in MeOH (1.5 mL) was added K_2CO_3 (31 mg, 0.22 mmol) at room temperature. After stirring for 16 h, the mixture was diluted with EtOAc, washed with 1 N aq. HCl and water. The organic extract was dried with Na_2SO_4 , filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% acetone in hexanes) to give compound **107** (33 mg, 87% yield) as a white solid. $m/z = 508.3$ (M+1).

Compound T31: DDQ (18 mg, 0.079 mmol) was added to a solution of compound **107** (33 mg, 0.065 mmol) in benzene (1.3 mL). The reaction was heated at reflux for 1 h, and at room temperature for 1 h. Sat. aq. $NaHCO_3$ was added. The mixture was extracted with CH_2Cl_2 . The organic extract was dried with Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% acetone in hexanes) to give

compound **T31** (17 mg, 52% yield) as a white foam. $m/z = 506.2$ (M+1); ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 6.22 (s, 1H), 3.94 (dd, 1H, $J = 5.9, 10.9$ Hz), 3.52 (dd, 1H, $J = 5.6, 10.8$ Hz), 2.97 (dd, 1H, $J = 3.4, 13.7$ Hz), 2.45 (dd, 1H, $J = 2.1, 11.8$ Hz), 2.10 (dt, 1H, $J = 6.0, 13.4$ Hz), 1.60 (s, 3H), 1.54 (s, 3H), 1.22-1.93 (m, 14H), 1.08 (s, 3H), 1.05 (s, 3H),
5 0.97 (s, 6H).

Compound T32: To the solution of compound **T31** (11 mg, 0.022 mmol) in CH_2Cl_2 (0.4 mL) was added Et_3N (9 μL , 0.065 mmol) and AcCl (10 vol.% solution in CH_2Cl_2 , 23 μL , 0.033 mmol) sequentially at room temperature. After stirring for 30 min, the mixture was diluted with EtOAc and sat. aq. NaHCO_3 , and then stirred for another 5 min. The organic
10 extract was washed with 1 N aq. HCl and water, dried with Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% EtOAc in hexanes) to give compound **T32** (12 mg, 99% yield) as a white foam. $m/z = 548.2$ (M+1); ^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 1H), 6.23 (s, 1H), 4.33 (d, 1H, $J = 11.0$ Hz), 4.13 (d, 1H, $J = 11.0$ Hz), 2.97 (dd, 1H, $J = 3.4, 13.7$ Hz), 1.99 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H),
15 1.24-2.16 (m, 15H), 1.16 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H).

Compound 108: To a solution of $(\text{COCl})_2$ (18 μL , 0.22 mmol) in CH_2Cl_2 (0.6 mL) was added DMSO (28 μL , 0.39 mmol) dropwise at -78°C , and stirred for 30 min. Compound **106** (42 mg, 0.082 mmol) in CH_2Cl_2 (1 mL) was added at -78°C , and stirred for another 1 h. Et_3N (81 μL , 0.58 mmol) was added. The cold bath was removed, and the
20 reaction was stirred at ambient temperature for 30 min. EtOAc was added, and the mixture was washed with sat. aq. NaHCO_3 and water. The organic extract was dried with Na_2SO_4 , and concentrated to give compound **108** as an off-white solid. $m/z = 506.3$ (M+1). Compound **108** was used in the next step without further purification.

Compound 109: Na_2HPO_4 (22 mg, 0.15 mmol) and m -CPBA ($\leq 77\%$, 28 mg, 0.12 mmol) were added to a solution of compound **108** (all obtained from the last step) in CH_2Cl_2 (1.7 mL). After stirring at room temperature for 16 h, aq. Na_2SO_3 was added. The mixture was stirred for 5 min, and was extracted with CH_2Cl_2 . The organic extract was dried with Na_2SO_4 , filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 0-35% EtOAc in hexanes) to give compound **109** (28 mg, 65%
30 yield from **106**) as a white solid. $m/z = 522.3$ (M+1).

Compound 110: A mixture of compound **109** (28 mg, 0.053 mmol) and K_2CO_3 (30 mg, 0.22 mmol) in MeOH (1 mL) was stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried

with Na₂SO₄, filtered, and concentrated to give compound **110** (29 mg, quantitative yield) as a white foam. $m/z = 494.2$ (M+1).

Compound T33: To a solution of compound **110** (29 mg, 0.059 mmol) in DMF (0.2 mL) was added the solution of 1,3-dibromo-5,5-dimethylhydantoin (8.4 mg, 0.029 mmol) in DMF (0.2 mL) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (14 μL, 0.17 mmol) was added. The reaction was heated at 55 °C for 2 h, and cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% acetone in hexanes) to give compound **T33** (19 mg, 66% yield) as a white solid. $m/z = 492.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 6.16 (s, 1H), 3.23 (s, 1H), 2.96 (dd, 1H, $J = 3.4, 13.8$ Hz), 1.62 (s, 3H), 1.56 (s, 3H), 1.35 (s, 3H), 1.23-2.17 (m, 15H), 1.02(s, 3H), 0.97 (s, 6H).

Compound 111: Compound **106** (226 mg, 0.52 mmol) was dissolved in acetone (5 mL), and cooled to 0 °C. Jones reagent (2.5 M) was added until the orange color persisted. The mixture was stirred at 0 °C for 2 h, and at room temperature for 1 h. During the reaction, additional small amount of Jones reagent was added to maintain the orange color of the mixture. *i*-PrOH was added to quench the reaction. The solvent was removed, and EtOAc was added. The mixture was washed with water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% acetone in hexanes) to give compound **111** (167 mg, 61% yield) as a white solid. $m/z = 522.3$ (M+1).

Compound 112: Compound **111** (38 mg, 0.073 mmol) was dissolved in toluene (1 mL) and MeOH (0.3 mL), and was cooled to 0 °C. Trimethylsilyldiazomethane (2 M in Et₂O, 73 μL, 0.14 mmol) was added at 0 °C, and stirred for 15 min. AcOH was added to quench the reaction. The mixture was concentrated. The residue was purified by column chromatography (Silica gel, 0-50% EtOAc in hexanes) to give compound **112** (30 mg, 77% yield) as a white solid. $m/z = 536.2$ (M+1).

Compound 113: A mixture of compound **112** (30 mg, 0.056 mmol) and K₂CO₃ (46 mg, 0.33 mmol) in MeOH (2 mL) was stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **113** (35 mg, quantitative yield) as a white foam. $m/z = 536.3$ (M+1).

Compound T34: To a solution of compound **113** (all obtained from the last step) in DMF (0.6 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (9 mg, 0.031 mmol) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (16 µL, 0.20 mmol) was added. The reaction was heated at 55 °C for 4 h, and was cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-35% acetone in hexanes) to give compound **T34** (25 mg, 83% yield) as a white foam. $m/z = 534.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.04 (s, 1H), 6.22 (s, 1H), 3.76 (s, 3H), 2.97 (dd, 1H, $J = 3.4, 13.1$ Hz), 2.61 (dd, 1H, $J = 1.9, 12.5$ Hz), 2.11 (dt, 1H, $J = 6.0, 13.2$ Hz), 1.60 (s, 3H), 1.55 (s, 3H), 1.47 (s, 3H), 1.25-2.01 (m, 13H), 1.05 (s, 3H), 0.97 (s, 6H).

Compound 114: To a solution of compound **111** (124 mg, 0.24 mmol) in CH₂Cl₂ (2.4 mL) was added (COCl)₂ (60 µL, 0.71 mmol) and catalytic amount of DMF at 0 °C. The reaction was stirred at room temperature for 2 h, and concentrated. The residue was dissolved in toluene, and concentrated again to give compound **114** (131 mg, quantitative yield) as a yellow solid. $m/z = 540.2, 542.2$ (M+1). Compound **114** was used in the next step without further purification.

Compound 115: To the suspension of MeNH₂·HCl (11 mg, 0.16 mmol) in CH₂Cl₂ (0.8 mL) was added Et₃N (44 µL, 0.32 mmol) at room temperature. After the reaction was stirred for 5 min, compound **114** (43 mg, 0.079 mmol) in CH₂Cl₂ (0.8 mL) was added. The reaction was stirred at room temperature for 1 h. The solvent was removed. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **115** (32 mg, 75% yield) as a white solid. $m/z = 535.3$ (M+1).

Compound 116: Compound **115** (31 mg, 0.058 mmol) and K₂CO₃ (48 mg, 0.35 mmol) in MeOH (1.2 mL) were stirred at room temperature for 18 h. EtOAc was added. The mixture was washed with 1N aq. HCl and water. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **116** (30 mg, 97% yield) as a white foam. $m/z = 535.4$ (M+1). Compound **116** was used in the next step without further purification.

Compound T35: To a solution of compound **116** (30 mg, 0.056 mmol) in DMF (0.5 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (8 mg, 0.028 mmol) at 0 °C. After the reaction was stirred at 0 °C for 30 min, and then, at room temperature for 30 min, pyridine (14 µL, 0.17 mmol) was added. The reaction was heated at 55 °C for 4 h, and was cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water.

The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-60% acetone in hexanes) to give compound **T35** (21 mg, 70% yield) as a white foam. $m/z = 533.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.12 (s, 1H), 6.39 (q, 1H, $J = 5.5$ Hz), 6.23 (s, 1H), 2.94-3.03 (m, 2H), 2.83 (d, 3H, $J = 4.7$ Hz), 2.11 (dt, 1H, $J = 6.0, 13.4$ Hz), 1.57 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H), 1.25-1.95 (m, 13H), 1.07 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Compound 117: To the suspension of Me₂NH·HCl (14 mg, 0.17 mmol) in CH₂Cl₂ (0.8 mL) was added Et₃N (44 μ L, 0.32 mmol) at room temperature. After the reaction was stirred for 5 min, compound **114** (43 mg, 0.079 mmol) in CH₂Cl₂ (0.8 mL) was added. The reaction was stirred at room temperature for 1 h. The solvent was removed. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **117** (32 mg, 73% yield) as a white foam. $m/z = 549.3$ (M+1).

Compound 118: Compound **117** (31 mg, 0.056 mmol) and K₂CO₃ (47 mg, 0.34 mmol) in MeOH (1.2 mL) were stirred at room temperature for 18 h. EtOAc was added. The mixture was washed with 1N aq. HCl and water. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **118** (31 mg, quantitative yield) as a white foam. $m/z = 549.3$ (M+1). Compound **118** was used in the next step without further purification.

Compound T36: To a solution of compound **118** (31 mg, 0.056 mmol) in DMF (0.5 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (8 mg, 0.028 mmol) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (14 μ L, 0.17 mmol) was added. The reaction was heated at 55 °C for 3 h, and was cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-80% EtOAc in hexanes) to give compound **T36** (20 mg, 65% yield) as a white foam. $m/z = 547.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 6.21 (s, 1H), 2.97 (dd, 1H, $J = 3.4, 13.7$ Hz), 2.85 (bs, 6H), 2.25 (dd, 1H, $J = 1.5, 11.8$ Hz), 2.09 (dt, 1H, $J = 5.6, 13.2$ Hz), 1.65 (s, 3H), 1.55 (s, 3H), 1.44 (s, 3H), 1.24-2.00 (m, 13H), 1.03 (s, 3H), 0.97 (s, 3H), 0.96 (s, 3H).

Compound 119: To the solution of compound **114** (45 mg, 0.083 mmol) in CH₂Cl₂ (0.9 mL) was added NH₃ (2 M solution in MeOH, 0.17 mL, 0.34 mmol) at 0 °C. After the reaction was stirred for 30 min, additional amount of NH₃ (2 M solution in MeOH, 0.04 mL, 0.08 mmol) was added. The reaction was stirred at 0 °C for another 20 min. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried

over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-60% acetones in hexanes) to give compound **119** (32 mg, 74% yield) as a white solid. $m/z = 521.3$ (M+1).

Compound 120: A mixture of compound **119** (32 mg, 0.061 mmol) and K₂CO₃ (48 mg, 0.35 mmol) in MeOH (2.4 mL) was stirred at room temperature for 16 h, and concentrated. EtOAc was added. The mixture was washed with 1N aq. HCl. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **120** (34 mg, quantitative yield) as a white foam. $m/z = 521.3$ (M+1). Compound **120** was used in the next step without further purification.

Compound T37: To a solution of compound **120** (all obtained from the last step) in DMF (0.5 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (9 mg, 0.031 mmol) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (16 µL, 0.20 mmol) was added. The reaction was heated at 55 °C for 3 h, and was cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-60% acetone in hexanes) to give compound **T37** (21 mg, 66% yield) as a white foam. $m/z = 519.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 6.34 (bs, 1H), 6.24 (s, 1H), 5.42 (bs, 1H), 2.91-2.98 (m, 2H), 2.13 (dt, 1H, $J = 5.9, 13.3$ Hz), 1.61 (s, 3H), 1.56 (s, 3H), 1.53 (s, 3H), 1.25-1.95 (m, 13H), 1.07 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H).

Compound 121: Compound **109** (122 mg, 0.23 mmol) was dissolved in EtOH (3 mL) and THF (1.5 mL), and was cooled to 0 °C. 10% aq. NaOH (0.69 mL, 1.73 mmol) was added. The mixture was stirred at room temperature for 5 h. MTBE and 1 N aq. HCl (4 mL) were added. The mixture was extracted with EtOAc. The organic extract was washed with water, dried with Na₂SO₄, and concentrated to give compound **121** as a white foam. $m/z = 494.3$ (M-17). Compound **121** was used in the next step without further purification.

Compound 122: Compound **121** (all obtained from the last step) was dissolved in toluene (6 mL) and MeOH (2 mL), and was cooled to 0 °C. Trimethylsilyldiazomethane (2 M in Et₂O, 0.13 mL, 0.26 mmol) was added dropwise at 0 °C. After stirring for 15 min, the reaction mixture was treated with additional amount of trimethylsilyldiazomethane (2 M in Et₂O, 0.20 mL, 0.40 mmol) dropwise at 0 °C. During the addition, the reaction was monitored by TLC. When compound **121** was completely consumed, the reaction was quenched with AcOH, and concentrated. The residue was purified by column

chromatography (Silica gel, 0-60% EtOAc in hexanes) to give compound **122** (82 mg, 67% yield from **109**) as a white foam. $m/z = 508.3$ (M-17).

Compound T38: To a solution of compound **122** (80 mg, 0.15 mmol) in DMF (0.8 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (22 mg, 0.077 mmol) at 0 °C. After the
5 reaction was stirred at 0 °C for 1 h, pyridine (37 μ L, 0.46 mmol) was added. The reaction was heated at 55 °C for 3 h, and was cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% EtOAc in hexanes) to give compound **T38** (59 mg, 74% yield) as a white
10 foam. $m/z = 506.3$ (M-17); ¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 1H), 5.90 (s, 1H), 3.69 (s, 3H), 3.28 (s, 1H), 2.86 (m, 1H), 2.25 (dt, 1H, $J = 4.1, 13.3$ Hz), 1.56 (s, 3H), 1.50 (s, 3H), 1.31 (s, 3H), 1.07-2.13 (m, 14H), 1.02 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H).

Compound 123: To a mixture of compound **95** (50 mg, 0.096 mmol) in MeOH (1 mL) was added NaOMe (25% w/w in MeOH, 90 μ L, 0.39 mmol) at room temperature. The
15 mixture was stirred at room temperature for 2 h, heated at 55 °C for 1 h, and then, cooled to room temperature. EtOAc and 1 N aq. HCl were added. The organic extract was washed with water, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% acetone in hexanes) to give compound **123** (33 mg, 66% yield) as a white foam. $m/z = 525.3$ (M+1).

Compound T39: To a solution of compound **123** (32 mg, 0.061 mmol) in DMF (0.4 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (9 mg, 0.031 mmol) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (15 μ L, 0.19 mmol) was added. The reaction was heated at 55 °C for 2 h, and cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over
25 Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-55% EtOAc in hexanes) to give compound **T39** (28 mg, 88% yield) as a white foam. $m/z = 523.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.01 (s, 1H), 5.91 (s, 1H), 4.38 (s, 1H), 3.62 (s, 3H), 3.24 (s, 1H), 3.08 (d, 1H, $J = 4.7$ Hz), 2.72 (m, 1H), 1.55 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H), 1.10-2.19 (m, 15H), 1.03 (s, 3H), 1.01 (s, 3H), 0.89 (s, 3H).

Compound 124: To a solution of compound **83** (100 mg, 0.16 mmol) and pyridine (26 μ L, 0.32 mmol) in CH₂Cl₂ (1.6 mL) was added (COCl)₂ (41 μ L, 0.49 mmol) at 0 °C. The reaction was stirred at 0 °C for 10 min, and then at room temperature for 2 h, and concentrated. The residue was mixed with toluene, and concentrated again to give compound

124 as a light yellow foam. $m/z = 633.4$ (M+1). Compound **124** was used in the next step without further purification.

Compound 125: To a solution of compound **124** (all obtained in the last step) in toluene (1 mL) was added NaN₃ (12.6 mg, 0.19 mmol), acetone (2 mL) and water (0.5 mL) at room temperature. The reaction was stirred at room temperature for 1 h. EtOAc was added. The mixture was washed with water and aq. NaHCO₃. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **125** (100 mg, 96% yield from **83**) as a light yellow foam. $m/z = 640.4$ (M+1). Compound **125** was used in the next step without further purification.

Compound 126: Compound **125** (100 mg, 0.16 mmol) was dissolved in toluene (2 mL), and heated at 80 °C for 2 h. The solution was cooled, and concentrated to give compound **126** (90 mg, 93% yield) as a light yellow foam. $m/z = 612.4$ (M+1). Compound **126** was used in the next step without further purification.

Compound 127: Compound **126** (330 mg, 0.54 mmol) was dissolved in MeOH (2 mL) at 0 °C, and NaOMe (30 wt.% in methanol, 150 mg, 0.83 mmol) was added. The reaction mixture was stirred for 1 h, and the solvent was removed under vacuum. The crude reaction mixture was dissolved in HCO₂Et (5 mL), and NaOMe (30 wt.% in methanol, 500 mg, 2.78 mmol) was added. After stirring at room temperature for 2 h, the reaction mixture was neutralized by the addition of sat. aq. KH₂PO₄, and was extracted with EtOAc. The organic extract was washed with brine, then dried with MgSO₄, and concentrated to give compound **127** (360 mg, quantitative yield). $m/z = 672$ (M+1).

Compound 128: Compound **127** (355 mg, 0.53 mmol) was dissolved in EtOH. NH₂OH·HCl (75 mg, 1.1 mmol) was added. The reaction mixture was stirred overnight at 50 °C. After cooling to room temperature, the reaction mixture was concentrated. The residue was diluted with EtOAc, and the mixture was washed with aq. NaHCO₃. The organic extract was dried with MgSO₄, and concentrated to give compound **128** (285 mg, quantitative yield). $m/z = 539$ (M+1).

Compound 129: Compound **128** (160 mg, 0.30 mmol) was dissolved in MeOH (5 mL), and K₂CO₃ (165 mg, 1.2 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. The reaction was neutralized by the addition of sat. aq. KH₂PO₄, and was extracted with EtOAc. The organic extract was washed with brine, dried with MgSO₄, and concentrated. The crude product was purified by column chromatography (Silica gel, 10-

50% EtOAc in hexanes) to give compound **129** (100 mg, 62% yield) as a foam. $m/z = 539$ (M+1).

Compound T40: To a solution of compound **129** (80 mg, 0.15 mmol) in dioxane (2 mL) was added DDQ (70 mg, 0.31 mmol), and the solution was heated at 80 °C for 1 h. After cooling, the mixture was diluted with EtOAc (25 mL), washed with sat. aq. NaHCO₃ and brine, dried over MgSO₄, and concentrated. The crude product was purified by column chromatography (Silica gel, 15-50% EtOAc in hexanes) to give compound **T40** (12 mg, 15% yield) as an off-white solid. $m/z = 537$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 5.99 (s, 1H), 4.39 (s, 1H), 3.92 (dd, 1H, $J = 4.7, 10.9$ Hz), 3.62 (s, 3H), 3.51 (dd, 1H, $J = 4.3, 10.9$ Hz), 3.11 (d, 1H, $J = 4.7$ Hz), 2.70 (m, 1H), 2.38 (dd, 1H, $J = 3.1, 10.2$ Hz), 1.53 (s, 3H), 1.45 (s, 3H), 1.10-2.08 (m, 15H), 1.08 (s, 3H), 1.04 (s, 6H), 0.89 (s, 3H).

Compound T41: A mixture of compound **T40** (37 mg, 0.069 mmol), Ac₂O (3 mL), and NaOAc (30 mg, 0.37 mmol) was stirred at room temperature for 16 h. The reaction was quenched with sat. aq. KH₂PO₄, and was extracted with EtOAc. The organic phase was dried over Mg₂SO₄ and concentrated to give compound **T41** (32 mg, 80% yield) as an off-white solid. $m/z = 579$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 5.99 (s, 1H), 4.38 (s, 1H), 4.31 (d, 1H, $J = 11.0$ Hz), 4.15 (d, 1H, $J = 11.0$ Hz), 3.62 (s, 3H), 3.11 (d, 1H, $J = 4.7$ Hz), 2.72 (m, 1H), 2.08 (dd, 1H, $J = 2.4, 11.5$ Hz), 1.99 (s, 3H), 1.53 (s, 3H), 1.45 (s, 3H), 1.13 (s, 3H), 1.10-2.05 (m, 14H), 1.04 (s, 3H), 1.02 (s, 3H), 0.89 (s, 3H).

Compound 130: To a solution of compound **86** (102 mg, 0.18 mmol) in CH₂Cl₂ (1.8 mL) was added (COCl)₂ (47 μL, 0.56 mmol) and catalytic amount of DMF at 0 °C. The reaction was stirred at room temperature for 2 h, and concentrated. The residue was dissolved in toluene, and concentrated again to give the acid chloride as a brown foam. The acid chloride was dissolved in CH₂Cl₂ (1 mL). Et₃N (52 μL, 0.37 mmol) and acethydrazide (41 mg, 0.56 mmol) in CH₂Cl₂ (1 mL) were added at room temperature. The reaction was stirred at room temperature for 30 min. Aq. NaHCO₃ was added. The product was extracted with EtOAc. The organic extract was washed with water, dried with Na₂SO₄, filtered and concentrated to give compound **130** (114 mg, quantitative yield) as an off-white foam. $m/z = 608.4$ (M+1).

Compound 131: Compound **130** (114 mg, 0.18 mmol) and TsOH·H₂O (23 mg, 0.12 mmol) in toluene (5 mL) were heated at reflux with a Dean-Stark apparatus for 1 h. After cooling to room temperature, the mixture was washed with sat. aq. NaHCO₃, dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography

(Silica gel, 0-30% acetone in hexanes) to give compound **131** (90 mg, 81% yield) as a white foam. $m/z = 590.3$ (M+1).

Compound 132 and 133: Compound **131** (88 mg, 0.15 mmol) and K_2CO_3 (63 mg, 0.46 mmol) in MeOH (1.5 mL) were stirred at room temperature for 1 h. EtOAc was added. The mixture was washed with 1N aq. HCl. The organic extract was dried with Na_2SO_4 , filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 0-35% acetone in hexanes) to give compound **132** (36 mg, 44% yield) and compound **133** (25 mg, 31% yield). Compound **132**: white foam, $m/z = 548.3$; Compound **133**: white foam, $m/z = 548.3$.

Compound T42: DDQ (18 mg, 0.079 mmol) was added to a solution of compound **132** (36 mg, 0.066 mmol) in benzene (0.6 mL) at room temperature. The mixture was refluxed for 1 h, and cooled to room temperature. The mixture was diluted with CH_2Cl_2 , and washed with sat. aq. $NaHCO_3$. The aqueous wash was back extracted with CH_2Cl_2 . The combined organic extract was washed with aq. $NaHCO_3$, dried with Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-40% acetone in hexanes) to give compound **T42** (20 mg, 47% yield) as a white foam. $m/z = 546.3$ (M+1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 5.96 (s, 1H), 3.92 (dd, 1H, $J = 6.1, 10.9$ Hz), 3.50 (dd, 1H, $J = 5.8, 10.9$ Hz), 3.12 (m, 1H), 2.94 (d, 1H, $J = 4.6$ Hz), 2.52 (s, 3H), 2.36 (m, 1H), 2.19 (dt, 1H, $J = 4.1, 13.3$ Hz), 1.49 (s, 3H), 1.20-2.03 (m, 14H), 1.19 (s, 3H), 1.06 (s, 3H), 1.05 (s, 6H), 0.94 (s, 3H).

Compound T43: To a solution of compound **T42** (15 mg, 0.027 mmol) in pyridine (0.1 mL) was added Ac_2O (50 μ L, 0.53 mmol) and catalytic amount of DMAP at room temperature. The reaction was stirred for 10 min, and was quenched with sat. aq. $NaHCO_3$. After stirring for 5 min, the mixture was extracted with EtOAc. The organic extract was washed with 1 N aq. HCl and water, dried with Na_2SO_4 , and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **T43** (5.5 mg, 34% yield) as a white foam. $m/z = 588.3$ (M+1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.97 (s, 1H), 4.30 (d, 1H, $J = 11.0$ Hz), 4.14 (d, 1H, $J = 11.0$ Hz), 3.12 (m, 1H), 2.97 (d, 1H, $J = 4.6$ Hz), 2.52 (s, 3H), 1.99 (s, 3H), 1.48 (s, 3H), 1.20-2.25 (m, 15H), 1.19 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H), 0.94 (s, 3H).

Compound 134: To a solution of $(COCl)_2$ (10 μ L, 0.12 mmol) in CH_2Cl_2 (0.5 mL) was added DMSO (16 μ L, 0.23 mmol) dropwise at $-78^\circ C$, and stirred for 30 min. Compound **133** (25 mg, 0.046 mmol) in CH_2Cl_2 (0.5 mL) was added at $-78^\circ C$, and stirred for

another 1 h. Et₃N (45 μ L, 0.32 mmol) was added. The cold bath was removed, and the reaction was stirred at ambient temperature for 30 min. EtOAc was added, and the mixture was washed with sat. aq. NaHCO₃ and water. The organic extract was dried with Na₂SO₄, and concentrated. The residue was purified by column chromatography (Silica gel, 0-25% acetone in hexanes) to give compound **134** (20 mg, 80% yield) as a white foam. $m/z = 546.3$ (M+1).

Compound 135: Na₂HPO₄ (10 mg, 0.070 mmol) and *m*-CPBA ($\leq 77\%$, 13 mg, 0.58 mmol) were added to a solution of compound **134** (20 mg, 0.037 mmol) in CH₂Cl₂ (0.8 mL). After stirring at room temperature for 3 h, aq. Na₂SO₃ was added. The mixture was stirred for 5 min, and was extracted with EtOAc. The organic extract was washed with sat. aq. NaHCO₃, dried with Na₂SO₄, filtered, and concentrated to give compound **135**. $m/z = 562.3$ (M+1). Compound **135** was used in the next step without further purification.

Compound 136: A mixture of compound **135** (all obtained from the last step) and K₂CO₃ (15 mg, 0.11 mmol) in MeOH (0.8 mL) was stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried with Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography to give compound **136** (13 mg, 66% yield from **134**) as a white foam. $m/z = 534.3$ (M+1).

Compound T44: DDQ (7 mg, 0.031 mmol) was added to a solution of compound **136** (13 mg, 0.024 mmol) in benzene (0.5 mL) at room temperature. The mixture was refluxed for 1.5 h, and cooled to room temperature. The mixture was diluted with CH₂Cl₂, and washed with sat. aq. NaHCO₃. The aqueous wash was back extracted with CH₂Cl₂. The combined organic extract was washed with aq. NaHCO₃, dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **T44** (10 mg, 77% yield) as a white foam. $m/z = 532.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 7.99 (s, 1H), 5.89 (s, 1H), 3.23 (s, 1H), 3.11 (m, 1H), 2.97 (d, 1H, $J = 4.6$ Hz), 2.52 (s, 3H), 1.50 (s, 3H), 1.31 (s, 3H), 1.21-2.22 (m, 15H), 1.20 (s, 3H), 1.04 (s, 3H), 1.04 (s, 3H), 0.94 (s, 3H).

Compound 137: To a solution of compound **124** (300 mg, 0.47 mmol) in CH₂Cl₂ (5 mL) was added Et₃N (0.27 mL, 1.94 mmol) and acetamide oxime (54 mg, 0.73 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. Water was added. The mixture was extracted with CH₂Cl₂. The combined organic extract was dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-100%

EtOAc in hexanes) to give compound **137** (263 mg, 83% yield) as a white foam. $m/z = 671.4$ (M+1).

Compound 138: To a solution of compound **137** (200 mg, 0.30 mmol) in THF (0.8 mL) was added tetrabutylammonium hydroxide (40% aq. solution, 0.2 mL) at room temperature. After stirring for 2 h, the reaction was diluted with EtOAc, and was washed with water. The aqueous wash was back extracted with EtOAc. The combined organic extract was dried with Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-20% acetone in hexanes) to give compound **138** (140 mg, 71% yield) as a white foam. $m/z = 653.4$ (M+1).

Compound 139: To a mixture of compound **138** (160 mg, 0.25 mmol) in HCO₂Et (0.59 mL, 7.34 mmol) was added NaOMe (25% w/w in MeOH, 0.84 mL, 3.63 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. MTBE was added, followed by 6 N aq. HCl (0.61 mL, 3.66 mmol). EtOAc was added. The mixture was washed with water. The organic extract was dried with Na₂SO₄, filtered and concentrated. The residue was dissolved in EtOH (2 mL) and water (0.2 mL). NH₂OH·HCl (26 mg, 0.38 mmol) was added. The mixture was heated at 55 °C for 18 h, and cooled to room temperature. EtOAc was added. The mixture was washed with water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-100% EtOAc in hexanes) to give compound **139** (102 mg, 76% yield) as a white foam. $m/z = 548.3$ (M+1).

Compound 140: Compound **139** (50 mg, 0.091 mmol) and K₂CO₃ (75 mg, 0.54 mmol) in MeOH (1 mL) were stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1N aq. HCl. The organic extract was dried with Na₂SO₄, filtered, and concentrated to give compound **140** (50 mg, quantitative yield) as a white foam, $m/z = 548.3$.

Compound T45: To a solution of compound **140** (50 mg, 0.091 mmol) in DMF (0.5 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (13 mg, 0.045 mmol) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (22 µL, 0.27 mmol) was added. The reaction was heated at 55 °C for 5 h, and cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-45% EtOAc in hexanes) to give compound **T45** (32 mg, 64% yield) as a yellow foam. $m/z = 546.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 5.97 (s, 1H), 3.92 (dd,

1H, $J = 6.1, 10.9$ Hz), 3.50 (dd, 1H, $J = 5.7, 10.9$ Hz), 3.24 (m, 1H), 3.03 (dd, 1H, $J = 4.6$ Hz), 2.37 (s, 3H), 2.19 (dt, 1H, $J = 4.1, 13.8$ Hz), 1.48 (s, 3H), 1.19-1.97 (m, 15H), 1.12 (s, 3H), 1.06 (s, 3H), 1.05 (s, 3H), 1.05 (s, 3H), 0.94 (s, 3H).

Compound T46: To the solution of compound **T45** (17 mg, 0.031 mmol) in CH_2Cl_2 (0.6 mL) was added Et_3N (13 μL , 0.093 mmol) and AcCl (3.5 μL , 0.049 mmol) sequentially at room temperature. After stirring for 30 min, the mixture was diluted with EtOAc and sat. aq. NaHCO_3 , and then stirred for another 5 min. The organic extract was washed with water, dried with Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-30% acetone in hexanes) to give compound **T46** (15 mg, 82% yield) as a white solid. $m/z = 588.4$ (M+1); ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 5.98 (s, 1H), 4.30 (d, 1H, $J = 11.0$ Hz), 4.14 (d, 1H, $J = 11.0$ Hz), 3.24 (m, 1H), 3.03 (d, 1H, $J = 4.6$ Hz), 2.37 (s, 3H), 2.19 (dt, 1H, $J = 4.1, 13.8$ Hz), 2.05 (dd, 1H, $J = 3.2, 10.8$ Hz), 1.99 (s, 3H), 1.48 (s, 3H), 1.20-1.98 (m, 13H), 1.12 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 1.04 (s, 3H), 0.93 (s, 3H).

Compound 141: To a solution of compound **139** (40 mg, 0.073 mmol) in CH_2Cl_2 (1.5 mL) was added Dess-Martin periodinane (64 mg, 0.15 mmol) at room temperature. After the reaction mixture was stirred for 2 h, aq. Na_2SO_3 was added. The mixture was stirred for 10 min, and was extracted with MTBE. The combined organic extracts were washed with sat. aq. NaHCO_3 , dried over Na_2SO_4 , filtered, and concentrated to give compound **141**. Compound **141** was used in the next step without further purification.

Compound 142: Na_2HPO_4 (22 mg, 0.15 mmol) and m -CPBA ($\leq 77\%$, 28 mg, 0.13 mmol) were added to a solution of compound **141** (all obtained from the last step) in CH_2Cl_2 (1.7 mL). After stirring at room temperature for 2 h, aq. Na_2SO_3 was added. The mixture was stirred for 10 min, and was extracted with EtOAc. The organic extract was washed with sat. aq. NaHCO_3 , dried with Na_2SO_4 , filtered, and concentrated to give compound **142** (21 mg, 51% yield from **139**) as a white foam. $m/z = 562.4$ (M+1).

Compound 143: A mixture of compound **142** (21 mg, 0.037 mmol) and K_2CO_3 (31 mg, 0.22 mmol) in MeOH (0.75 mL) was stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried with Na_2SO_4 , filtered, and concentrated to give compound **143** (20 mg, 99% yield) as a glass. $m/z = 534.3$ (M+1).

Compound T47: To a solution of compound **143** (20 mg, 0.037 mmol) in DMF (0.2 mL) was added the solution of 1,3-dibromo-5,5-dimethylhydantoin (5.4 mg, 0.019

mmol) in DMF (0.2 mL) at 0 °C. After the reaction was stirred at 0 °C for 1 h, pyridine (9 μ L, 0.11 mmol) was added. The reaction was heated at 55 °C for 4 h, and cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified
5 by column chromatography (Silica gel, 0-40% EtOAc in hexanes) to give compound **T47** (13 mg, 65% yield) as a white foam. m/z = 532.3 (M+1); ¹H NMR (400 MHz, CDCl₃) δ 7.99 (s, 1H), 5.89 (s, 1H), 3.23 (s, 1H), 3.22 (m, 1H), 3.02 (d, 1H, J = 4.7 Hz), 2.38 (s, 3H), 2.20 (dt, 1H, J = 4.1, 13.8 Hz), 1.50 (s, 3H), 1.30 (s, 3H), 1.19-2.13 (m, 14H), 1.13 (s, 3H), 1.04 (s, 3H), 1.04 (s, 3H), 0.94 (s, 3H).

10 **Compound 144:** Compound **108** (110 mg, 0.22 mmol) was dissolved in THF (2.2 mL), and was cooled to -78 °C. Methylmagnesium chloride (3 M in THF, 0.29 mL, 0.87 mmol) was added, and the mixture was stirred at -78 °C for 2 h. The reaction was quenched with aq. NH₄Cl. The mixture was extracted with EtOAc. The organic extract was washed with 1 N aq. HCl, and water, dried with Na₂SO₄, filtered and concentrated. The residue was
15 purified by column chromatography (Silica gel, 0-45% EtOAc in hexanes) to give compound **144** (68 mg, 60% yield) as a white foam. m/z = 522.3 (M+1).

Compound 145: A mixture of compound **144** (91 mg, 0.17 mmol) and K₂CO₃ (144 mg, 1.04 mmol) in MeOH (2 mL) was stirred at room temperature for 16 h. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried
20 with Na₂SO₄, filtered, and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% EtOAc in hexanes) to give compound **145** (36 mg, 40% yield) as a glass. m/z = 522.3 (M+1).

Compound T48: To a solution of compound **145** (36 mg, 0.069 mmol) in DMF (0.6 mL) was added 1,3-dibromo-5,5-dimethylhydantoin (10 mg, 0.035 mmol) at 0 °C. After the
25 reaction was stirred at 0 °C for 1 h, pyridine (66 μ L, 0.82 mmol) was added. The reaction was heated at 55 °C for 16 h, and cooled to room temperature. EtOAc was added. The mixture was washed with 1 N aq. HCl and water. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-60% EtOAc in hexanes) to give compound **T48** (10 mg, 28% yield) as a white
30 solid. **T48** is a 3:1 mixture of diastereomers. m/z = 520.3 (M+1); ¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 0.25H), 7.93 (s, 0.75H), 6.23 (s, 0.75H), 6.21 (s, 0.25H), 3.80-3.92 (m, 1H), 2.98 (m, 1H), 1.54 (s, 0.75H), 1.53 (s, 0.75H), 1.52 (s, 2.25H), 1.49 (s, 2.25H), 1.34 (s,

0.75H), 1.31 (d, 2.25H, $J = 6.2$ Hz), 1.22 (d, 0.75H, $J = 6.6$ Hz), 1.19 (s, 2.25H), 1.17-2.60 (m, 16H), 1.07 (s, 2.25H), 1.06 (s, 0.75H), 0.97 (s, 6H).

Compound T49: To a solution of compound **T47** (100 mg, 0.19 mmol) in MeCN (2 mL) was added 30% aq. H₂O₂ (28 μ L, 0.28 mmol) at room temperature. After stirring for 5 h, additional amount of 30% aq. H₂O₂ (300 μ L, 3 mmol) was added. The reaction was stirred at room temperature overnight. EtOAc was added. The mixture was washed with water and 10% aq. Na₂SO₃. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-50% EtOAc in hexanes) to give compound **T49** (88 mg, 85% yield) as a white foamy solid. $m/z = 548.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 6.05 (s, 1H), 4.26 (s, 1H), 3.24 (m, 1H), 3.04 (d, 1H, $J = 4.8$ Hz), 2.61 (s, 1H), 2.38 (s, 3H), 2.21 (ddd, 1H, $J = 4.0, 14.0, 14.0$ Hz), 1.41 (s, 3H), 1.30 (s, 3H), 1.21-2.02 (m, 14H), 1.10 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H).

Compound T50: To a solution of compound **T33** (100 mg, 0.19 mmol) in MeCN (2 mL) was added 30% aq. H₂O₂ ((300 μ L, 3 mmol) at room temperature. After stirring overnight, additional amount of MeCN (10 mL) and 30% aq. H₂O₂ ((300 μ L, 3 mmol) were added. The reaction was stirred at room temperature for another 6 h. EtOAc was added. The mixture was washed with water and 10% aq. Na₂SO₃. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (Silica gel, 0-60% EtOAc in hexanes) to give compound **T50** (27 mg, 26% yield) as a white solid. $m/z = 508.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 6.28 (s, 1H), 4.30 (s, 1H), 2.97 (dd, 1H, $J = 2.8, 13.6$ Hz), 2.61 (s, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.34 (s, 3H), 1.24-2.16 (m, 15H), 1.07 (s, 3H), 0.98 (s, 6H).

Compound T51: To a solution of compound **T27** (2 mg, 3.76 μ mol) in MeCN (0.3 mL) was added 30% aq. H₂O₂ (30 μ L, 0.3 mmol) at room temperature. After stirring for 3 h, CH₂Cl₂ and 10% aq. Na₂SO₃ were added. The mixture was extracted with CH₂Cl₂. The organic extract was dried over Na₂SO₄, filtered and concentrated. The residue was purified by preparative TLC (Silica gel, 50% EtOAc in hexanes) to give compound **T51** (1 mg, 49% yield) as a white solid. $m/z = 573.3$ (M+1); ¹H NMR (400 MHz, CDCl₃) δ 6.09 (s, 1H), 5.90 (b, 1H), 4.28 (s, 1H), 2.99 (d, 1H, $J = 5.2$ Hz), 2.80 (m, 1H), 2.60 (s, 1H), 1.78 (t, 3H, $J = 19.2$ Hz), 1.46 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.16-2.09 (m, 15H), 1.09 (s, 3H), 1.06 (s, 3H), 0.91 (s, 3H).

Example 2: Biological Activity Methods and Materials

A. Nitric Oxide Production Assay and Cell Viability

RAW 264.7 mouse macrophages were plated in 96-well plates at a density of 30,000 cells per well in triplicate in RPMI 1640 + 0.5% FBS and incubated at 37 °C with 5% CO₂ in a humidified atmosphere. The next day, cells were pre-treated with DMSO (vehicle) or test compound (concentration ranges of 0.4 - 200 nM or 2 - 1000 nM) for 2 hours and then treated with recombinant mouse IFN γ (R&D Systems) for 24 hours. Nitric oxide concentration in media was determined using the Griess reagent system (Promega). Cell viability was determined using WST-1 reagent (Roche). Values from test compound samples were normalized to those from DMSO/IFN γ -treated samples. IC₅₀ values were determined based on the suppression of IFN γ -induced Nitric Oxide production normalized to cell viability.

B. AREc32 Luciferase Reporter Assay

The AREc32 luciferase reporter assay allows for quantitative assessment of the endogenous activity of the Nrf2 transcription factor in cultured mammalian cells. AREc32 cells are derived from MCF-7 human breast carcinoma cells that were stably transfected with a reporter construct that contains the firefly luciferase gene located downstream of eight copies of the rat GSTA2 antioxidant response element (ARE) sequence (Wang *et al.*, 2006; CXR Biosciences). Active NRF2 binds to the ARE sequences and increases expression of the firefly luciferase gene. To assess the NRF2-activating potential of the test compounds, AREc32 cells were plated in black 96-well plates at a density of 20,000 cells per well in triplicate in DMEM + 10% FBS + 0.8 mg/mL Geneticin and incubated at 37 °C with 5% CO₂ in a humidified atmosphere. The next day, cells were treated with DMSO (vehicle) or test compound (concentration ranges of 0.4 – 200 nM or 2 – 1000 nM) for 19 hours. Luciferase activity was determined using the ONE-Glo Luciferase assay (Promega). The luminescence signal was measured on a BMG Pherastar microplate reader. The mean luminescence value from test compound-treated wells was normalized to that from DMSO-treated wells and was represented as fold-induction. Data were analyzed using GraphPad Prism version 6.00 for Windows, GraphPad Software, La Jolla California USA. A non-linear regression curve with log (agonist) vs. response using a variable slope was used to fit the data. Where applicable, a maximum threshold value of 50-fold over DMSO was set. EC_{2x} values were interpolated from the curve. EC_{2x} corresponds to the concentration of test compound required to increase GST ARE Luciferase reporter activity by 2-fold.

C. ROR γ Assay and Cell Viability

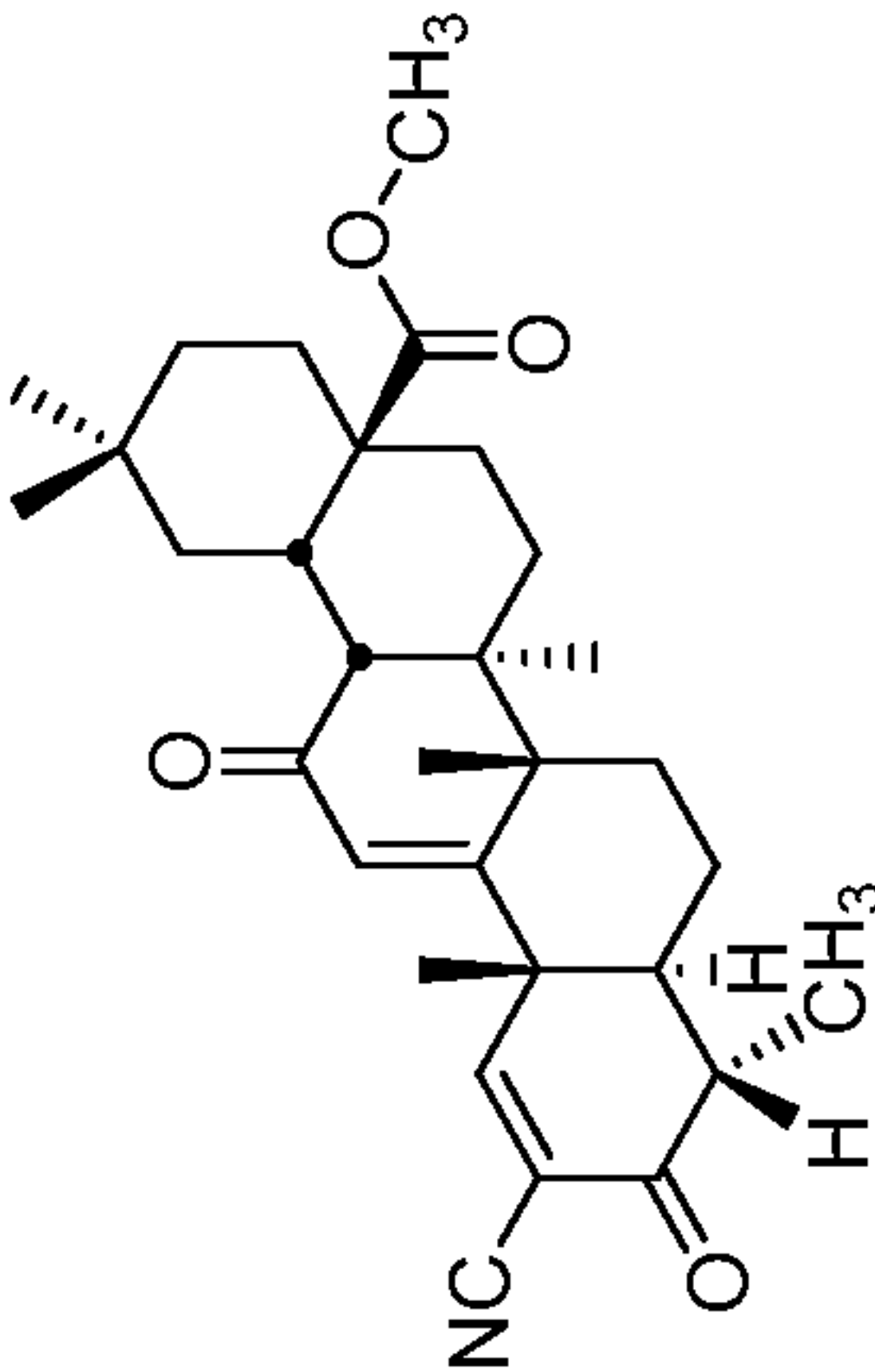
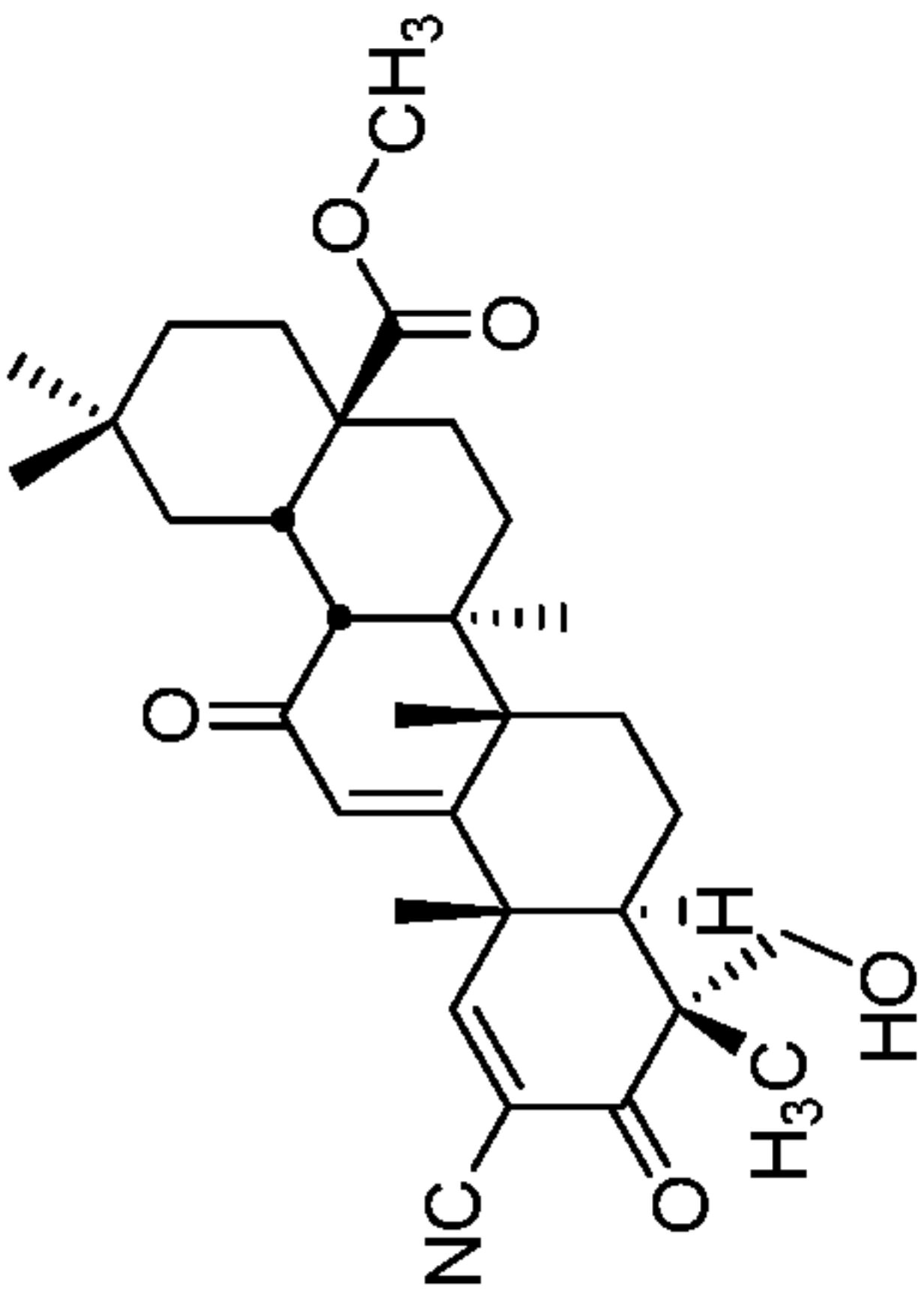
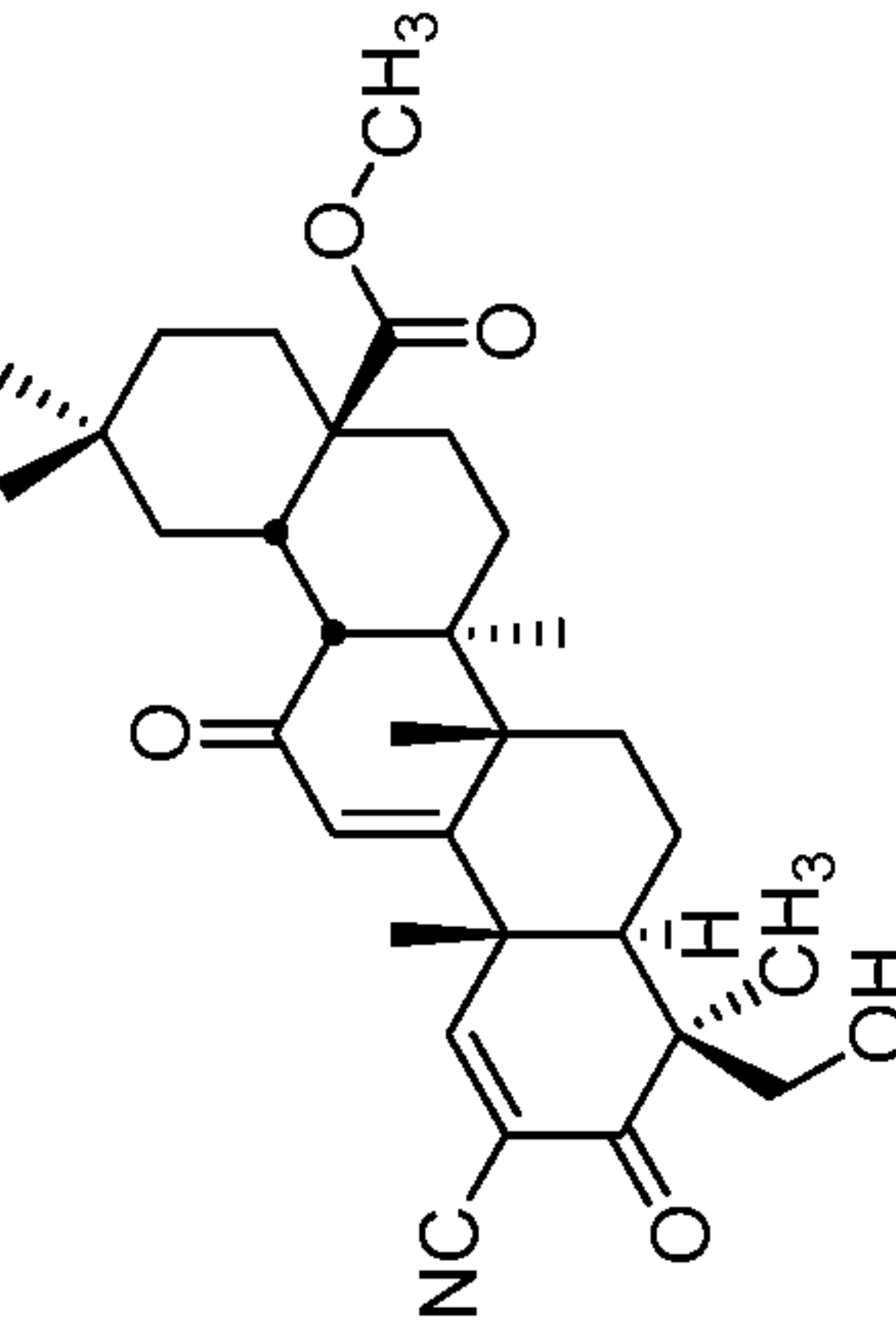
The ROR γ assay system was purchased from Indigo Biosciences. This nuclear receptor assay utilizes a human cell line that has been engineered to express a hybrid form of the Human RAR-related Orphan Receptor Gamma (ROR γ) at high levels. The N-terminal DNA binding domain (DBD) of the native ROR γ receptor was substituted with the yeast GAL4-DBD to generate the GAL4-ROR γ hybrid nuclear receptor. The reporter cell line is transfected with a plasmid that encodes the beetle luciferase gene under the control of the GAL4 upstream activating sequence (UAS). GAL4 binds to the UAS and increases transcription of downstream target genes. The GAL4-ROR γ hybrid is constitutively active; therefore, the principle application of this reporter assay system is to screen test compounds to quantify inverse-agonist activities against human ROR γ . To assess the ROR γ inverse-agonist activity of the test compounds, reporter cells were plated in white 96-well plates in triplicate and were treated with DMSO (vehicle) or test compound (concentration ranges of 0.4 – 200 nM or 2 – 1000 nM) at 37 °C with 5% CO₂ in a humidified atmosphere for 23 hours. After this incubation, luciferin was added to the wells and luciferase activity was determined by measuring the luminescence signal using a BMG Pherastar microplate reader. Viability was determined using the Live Cell Multiplex Assay (Indigo Biosciences). Values from test compound samples were normalized to those from DMSO-treated samples. Data were analyzed using GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla California USA). A non-linear regression analysis with log (inhibitor) vs. normalized response using a variable slope was applied to fit the data and determine the IC₅₀ values for inhibition of ROR γ and cell viability.

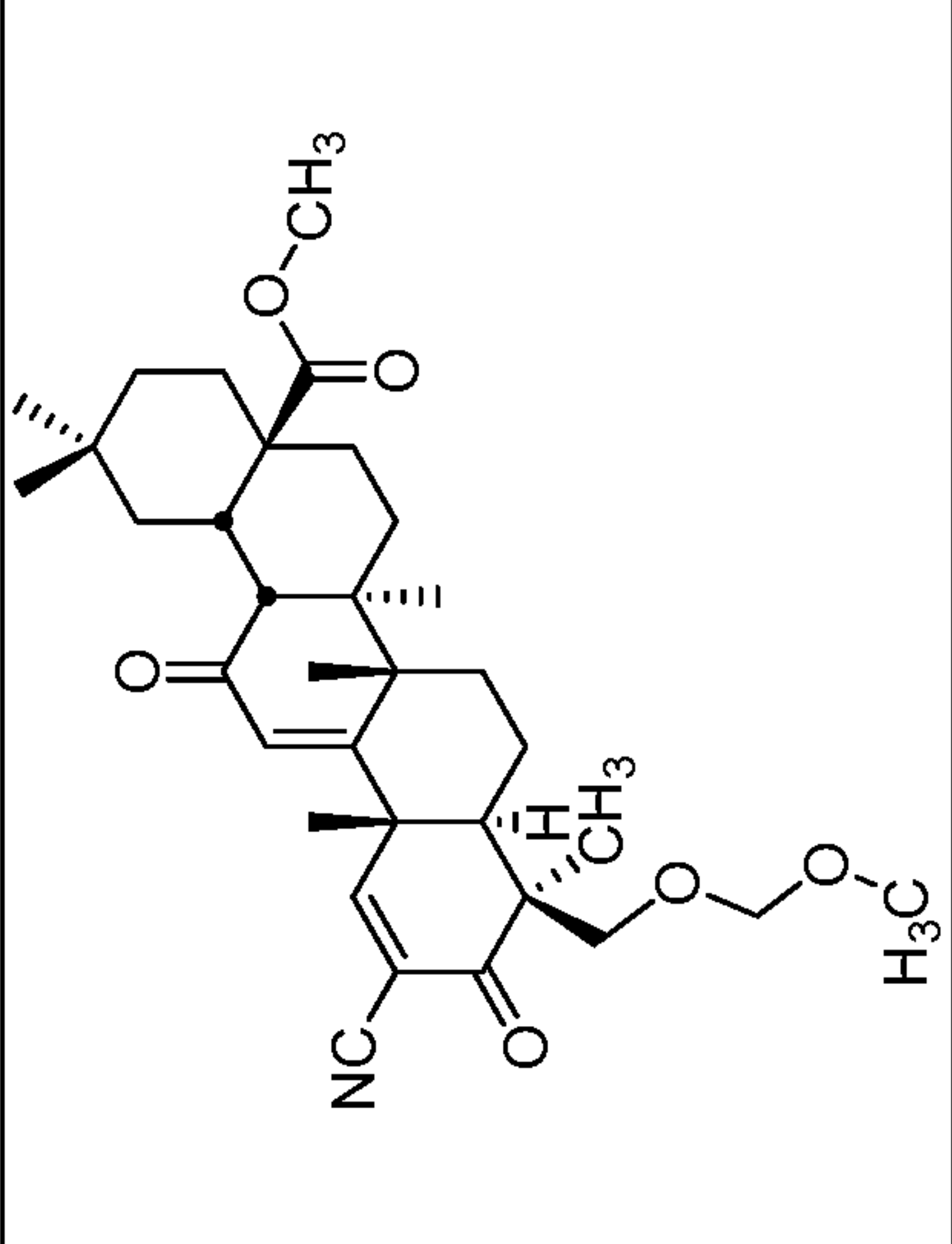
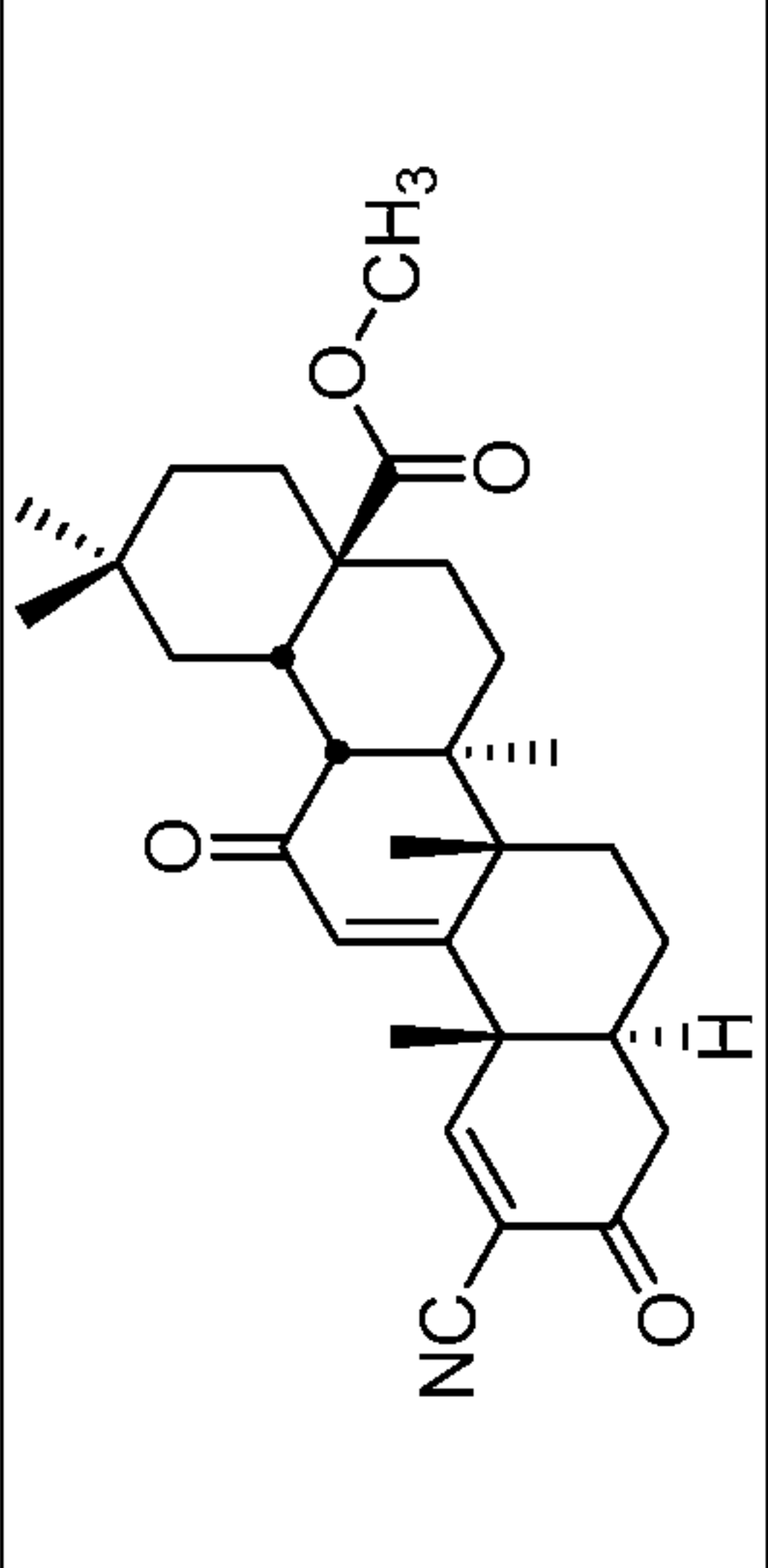
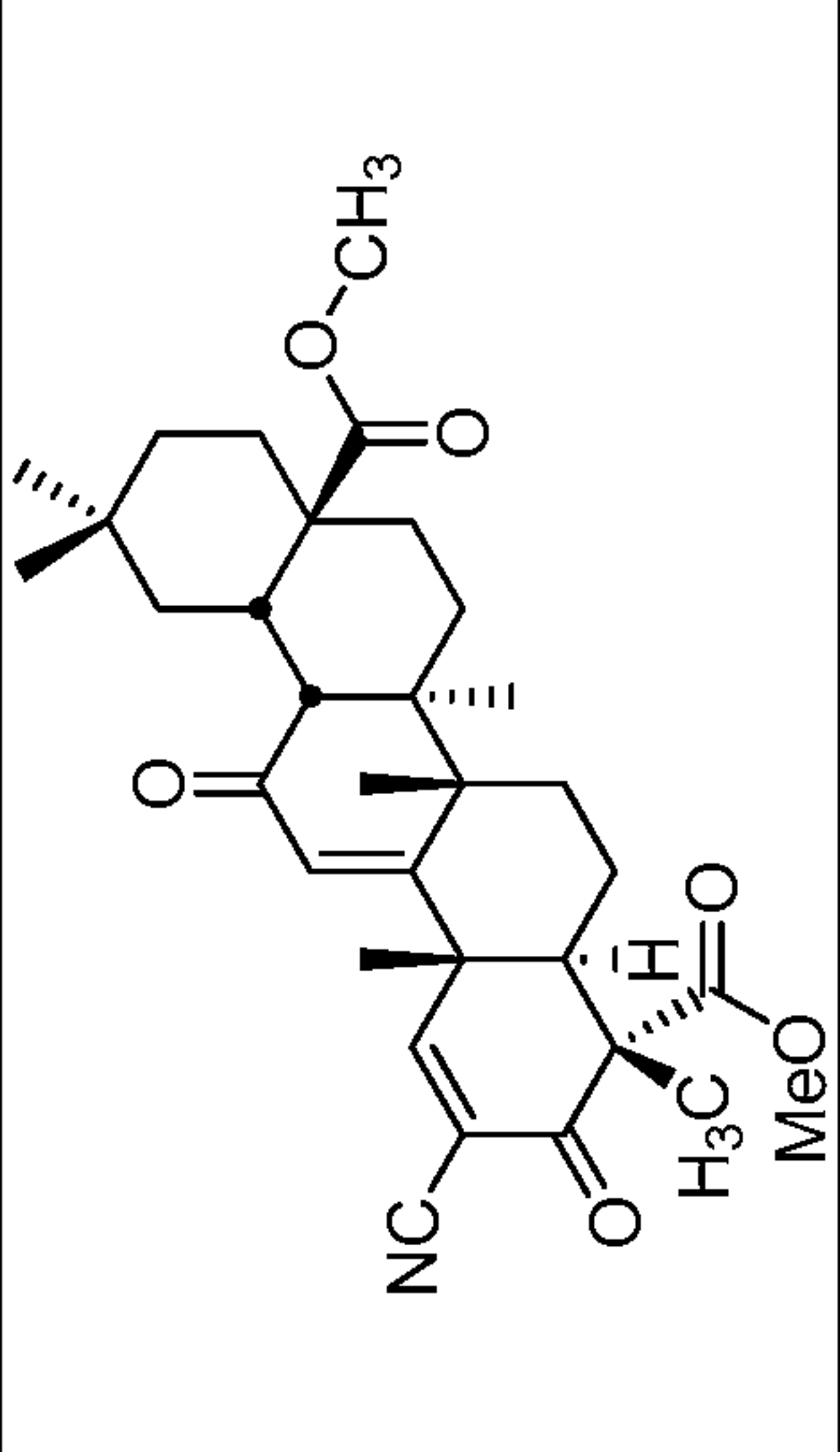
D. IL-17 Release from Differentiated Primary Human T-Cells and Cell Viability

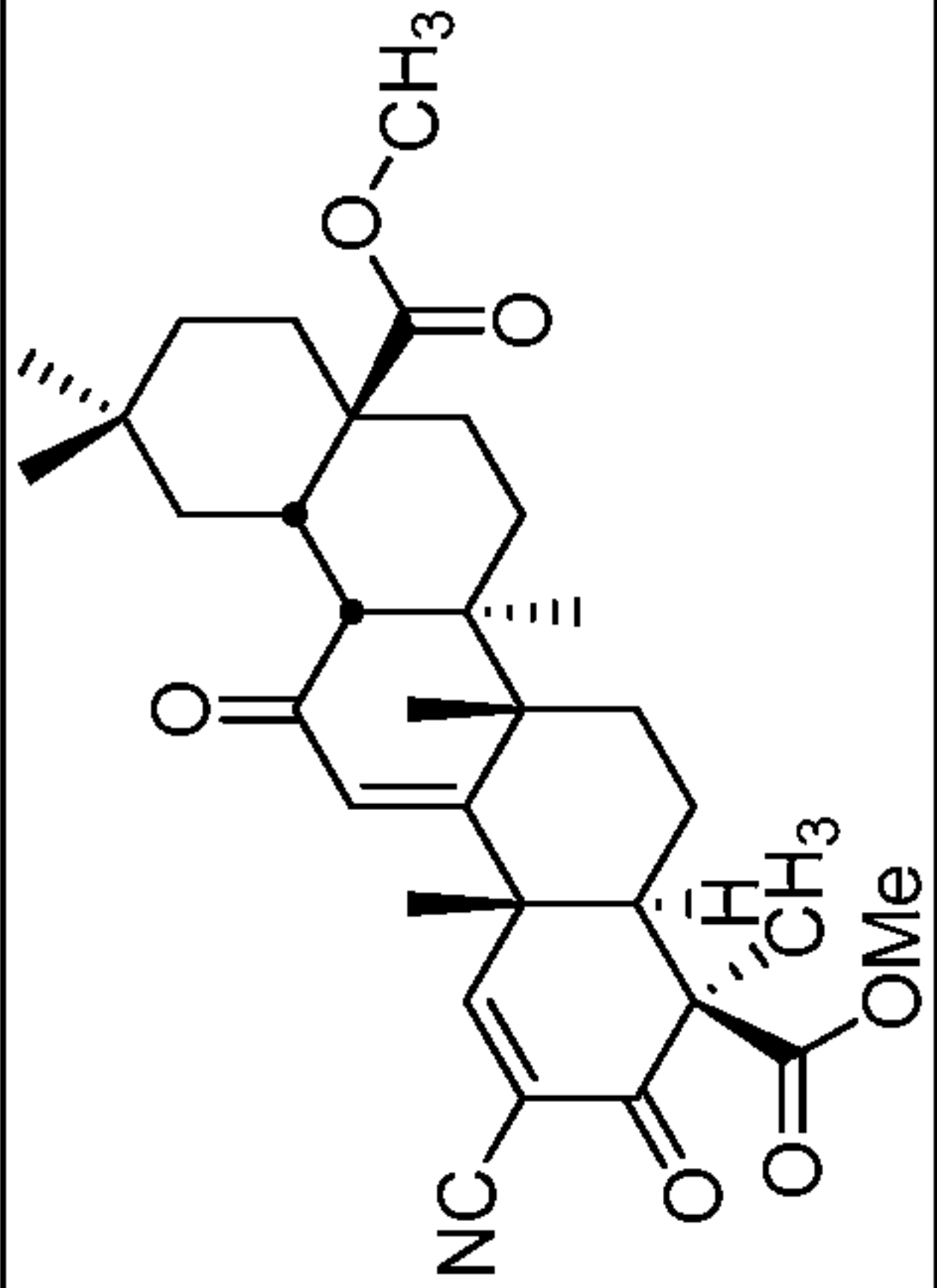
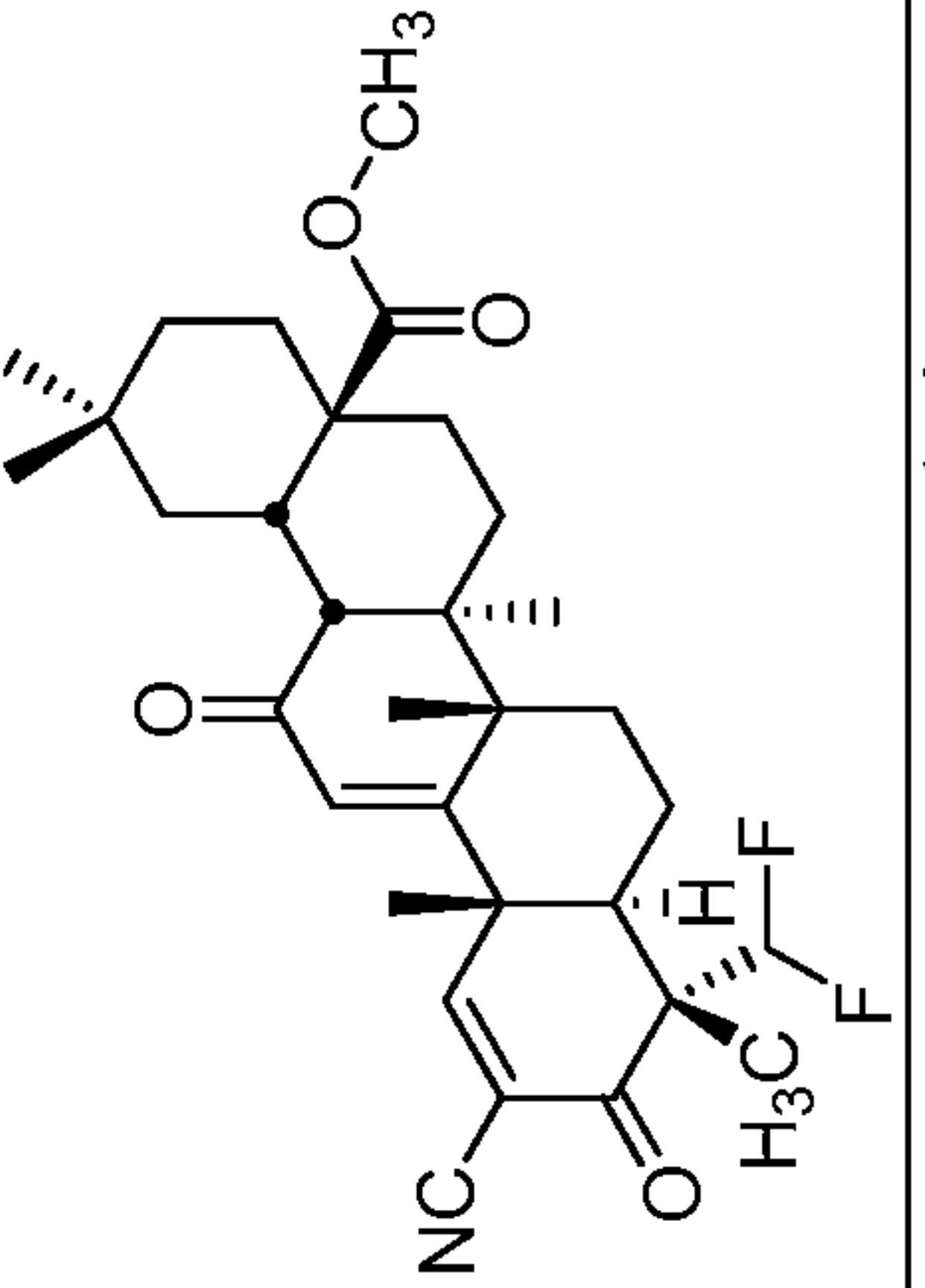
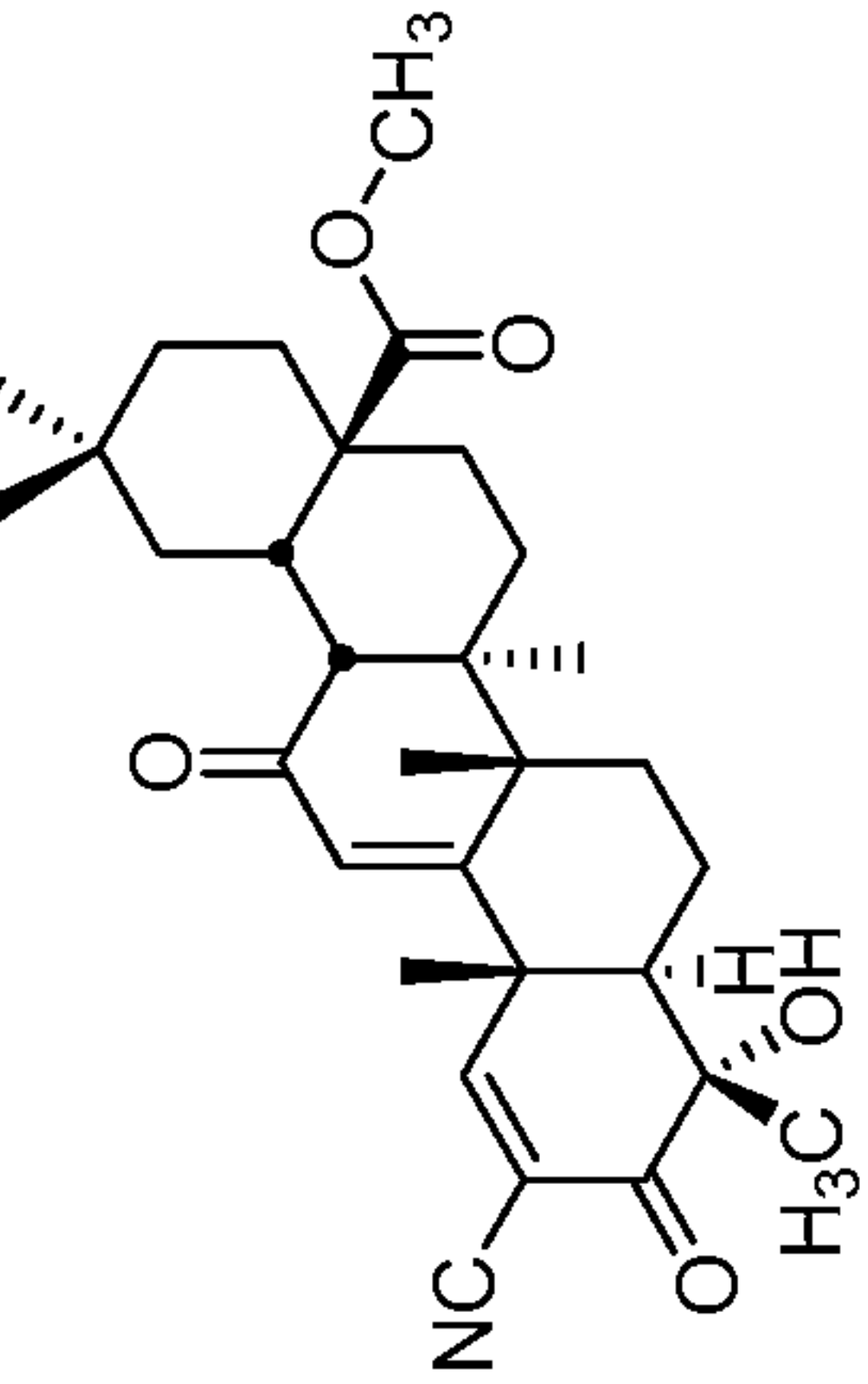
Primary human cryopreserved CD4⁺ T Cells (Lonza, donor #0000402103) were plated in Lymphocyte Growth Medium-3 (LGM-3, Lonza) according to the manufacturer's recommendations, and allowed to recover for approximately 3 hours at 37 °C with 5% CO₂ in a humidified atmosphere. After the recovery step, cells were collected by centrifugation and re-plated in 96-well plates at a density of ~140,000 cells per well in LGM-3 medium that contained DMSO (vehicle) or test compound (2 – 500 nM or 4-1000 nM concentration range). Triplicate wells were plated for each test condition. DMSO (final concentration ≤0.1%) was used as the vehicle. Immediately after plating, CD4⁺ T cells were activated by adding Dynabeads Human T-Activator CD3/CD28 (Life Technologies; bead-to-cell ratio of 1:2.5) and differentiated into Th17 cells by adding a mixture of the following cytokines:

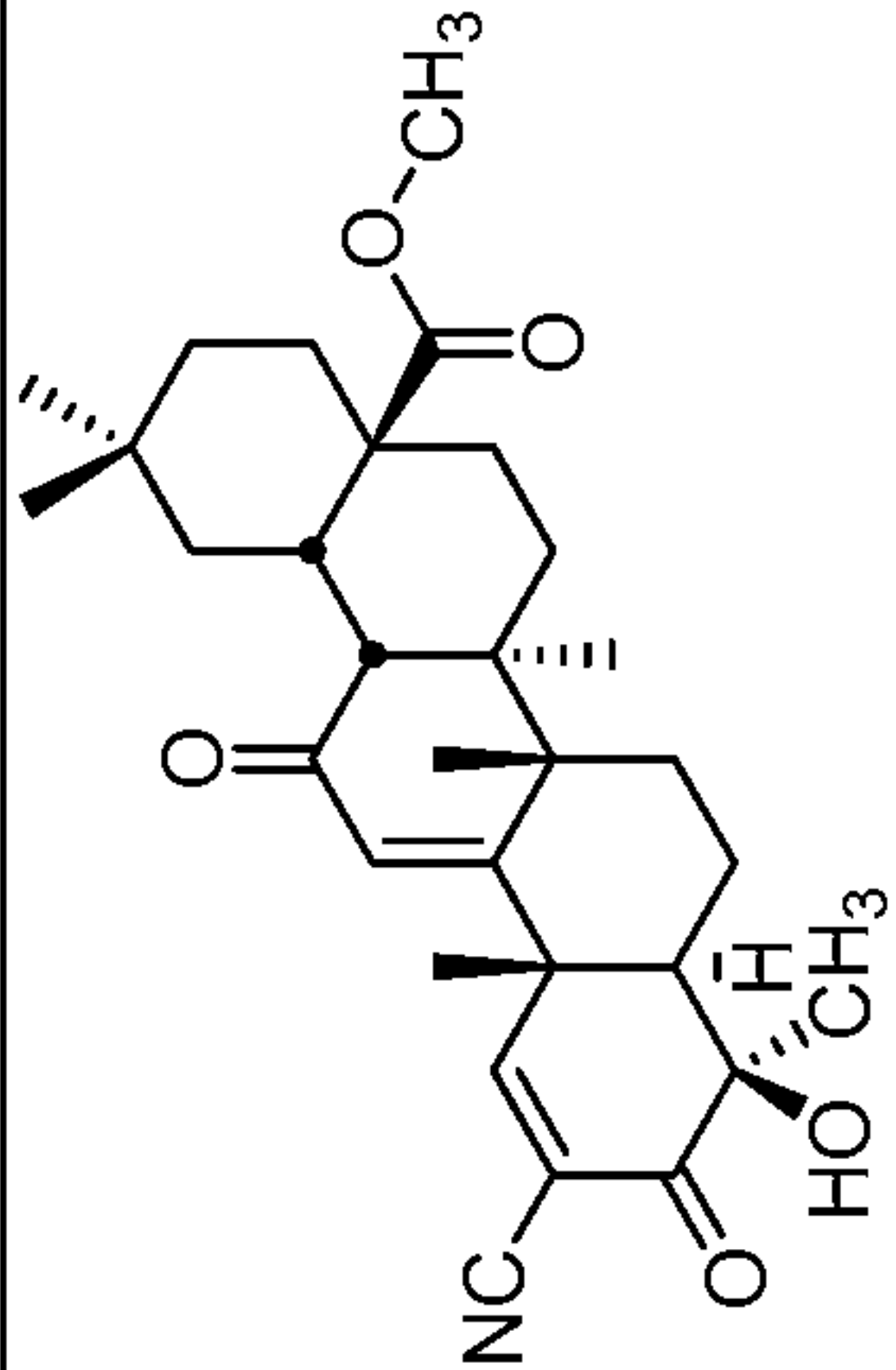
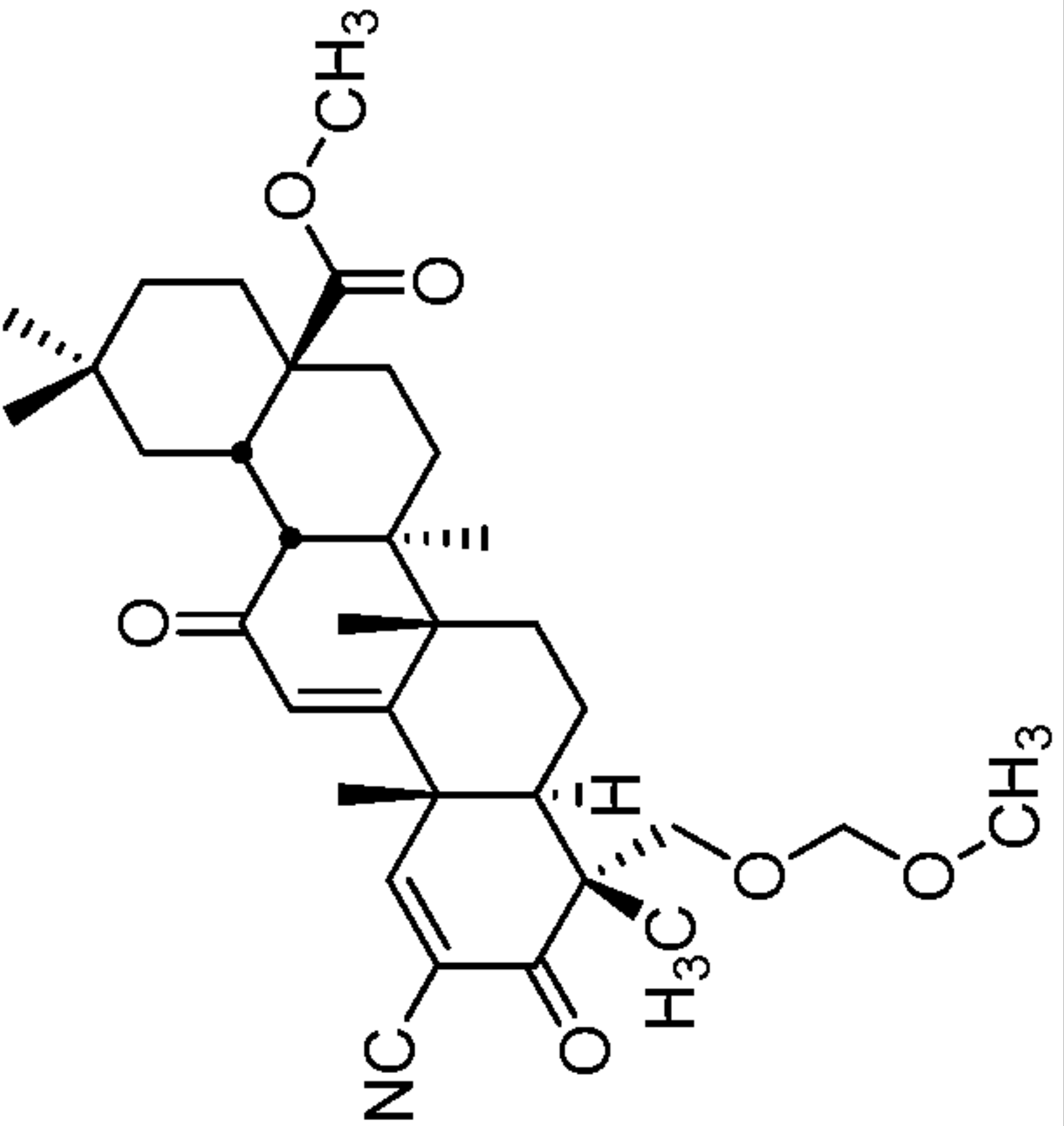
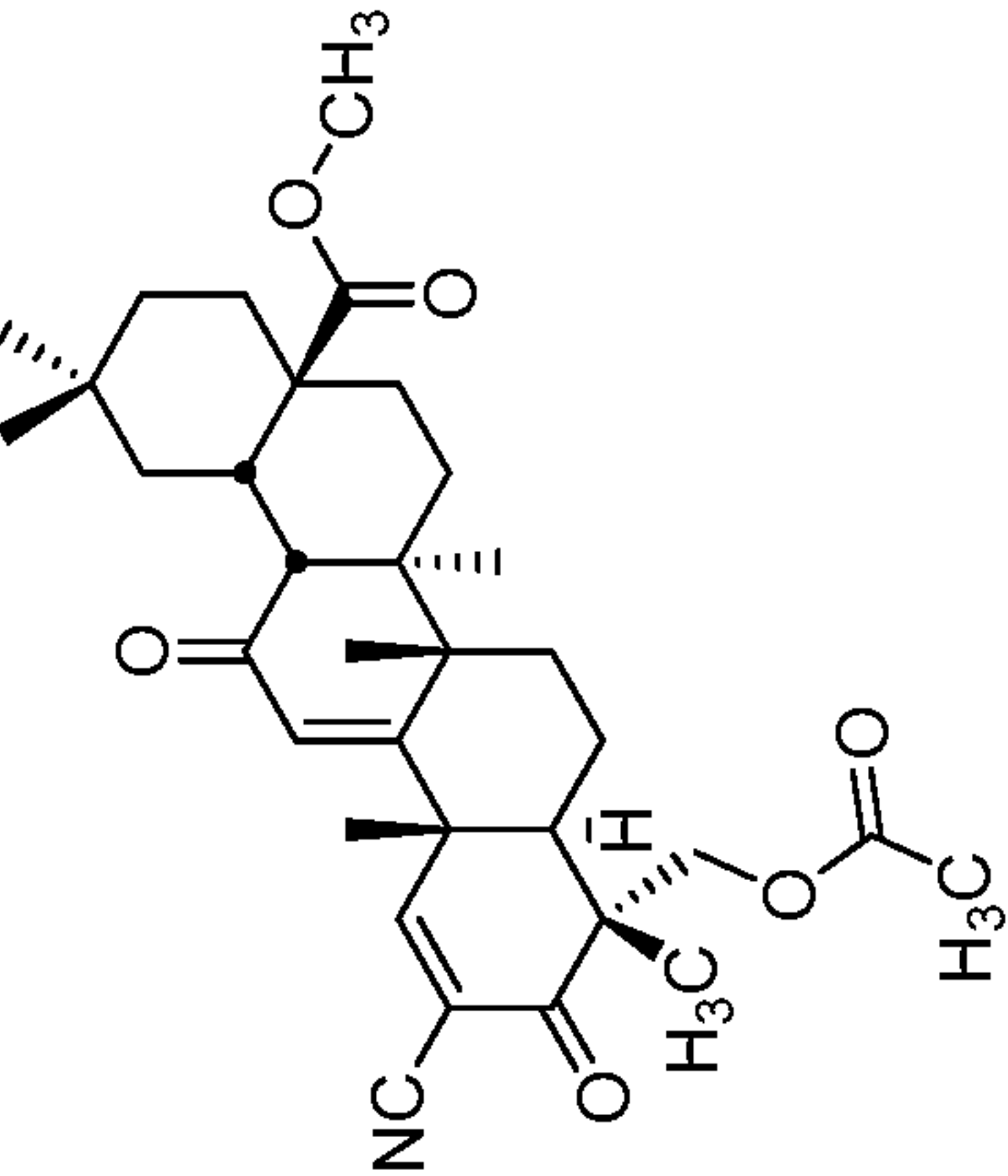
transforming growth factor- β (TGF- β , 5 ng/mL), IL-6 (20 ng/mL), IL-23 (20 ng/mL), and IL-1 β (10 ng/mL). Undifferentiated control cells received only cytokine IL-2 (50 ng/mL). All human recombinant cytokines were purchased from R&D Systems. Following a 46-hour incubation at 37 °C with 5% CO₂ in a humidified atmosphere, the plates were centrifuged for 3 minutes at 250 $\times$ g, and half of the supernatant was transferred to a new plate to be used in the IL-17A assay (see below). Cell viability was assessed in the original plate using the CyQuant Direct Assay (Life Technologies). CyQuant values from test compound samples were normalized to those from DMSO-treated samples. The concentration of IL-17A in the supernatant was measured using the Homogeneous Time-Resolved Fluorescence (HTRF) assay (Cisbio Bioassays) according to the manufacturer's protocol. The assay was performed at room temperature in low volume, solid white 384-well plates (Greiner Bio-One). Samples and standards (serially-diluted human recombinant IL-17A (0 to 5,000 pg/mL concentration range; Cisbio Bioassays) were incubated with the anti-human IL-17A antibody conjugate for 16 hours and fluorescence was measured using a Pherastar *FS* microplate reader (BMG Labtech) in the HTRF mode (excitation at 337 nm and emission at 665 nm and 620 nm). IL-17A concentrations were assessed in duplicate aliquots of supernatant from each well resulting in a total of six readings per test condition. The 665 nm/620 nm signal ratio was calculated and the concentration of IL-17A in each sample was determined by interpolation from the standard curve. IL-17A values from test compound samples were normalized to those from DMSO-treated samples. Data were analyzed using GraphPad Prism version 6.00 for Windows (GraphPad Software, La Jolla California USA). A non-linear regression analysis with log (inhibitor) vs. normalized response using a variable slope was applied to fit the data and determine the IC₅₀ values for inhibition of IL-17A levels and cell viability.

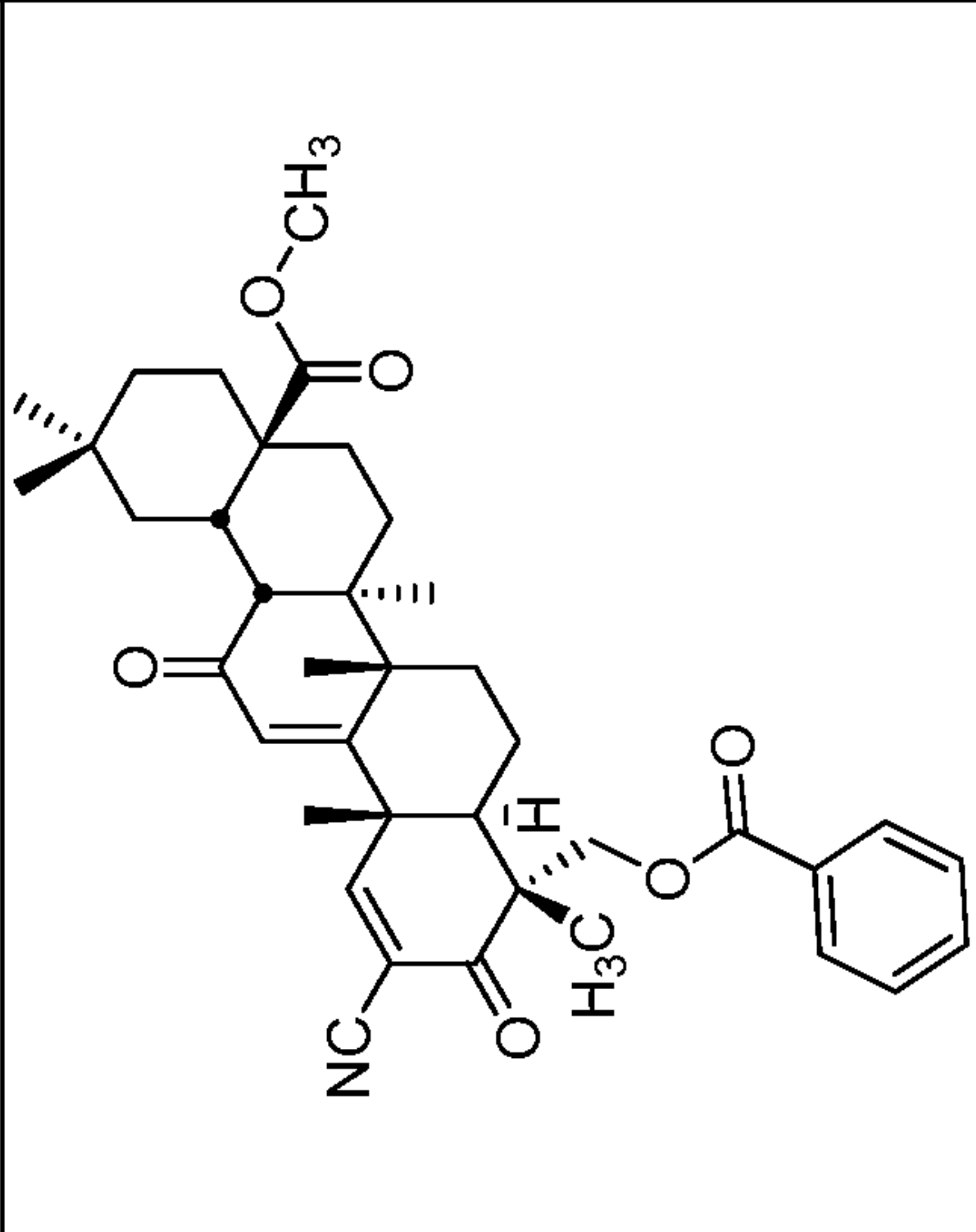
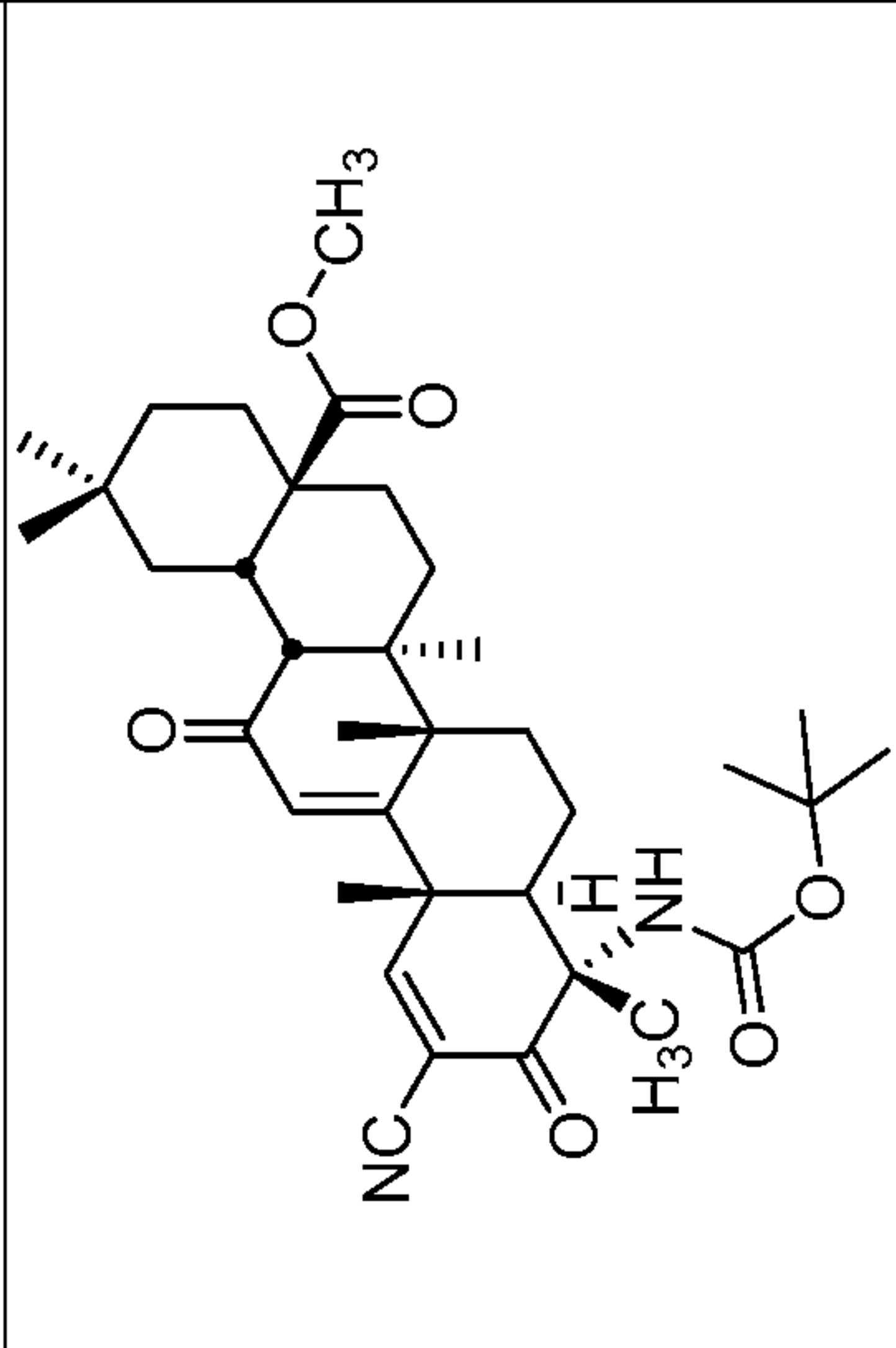
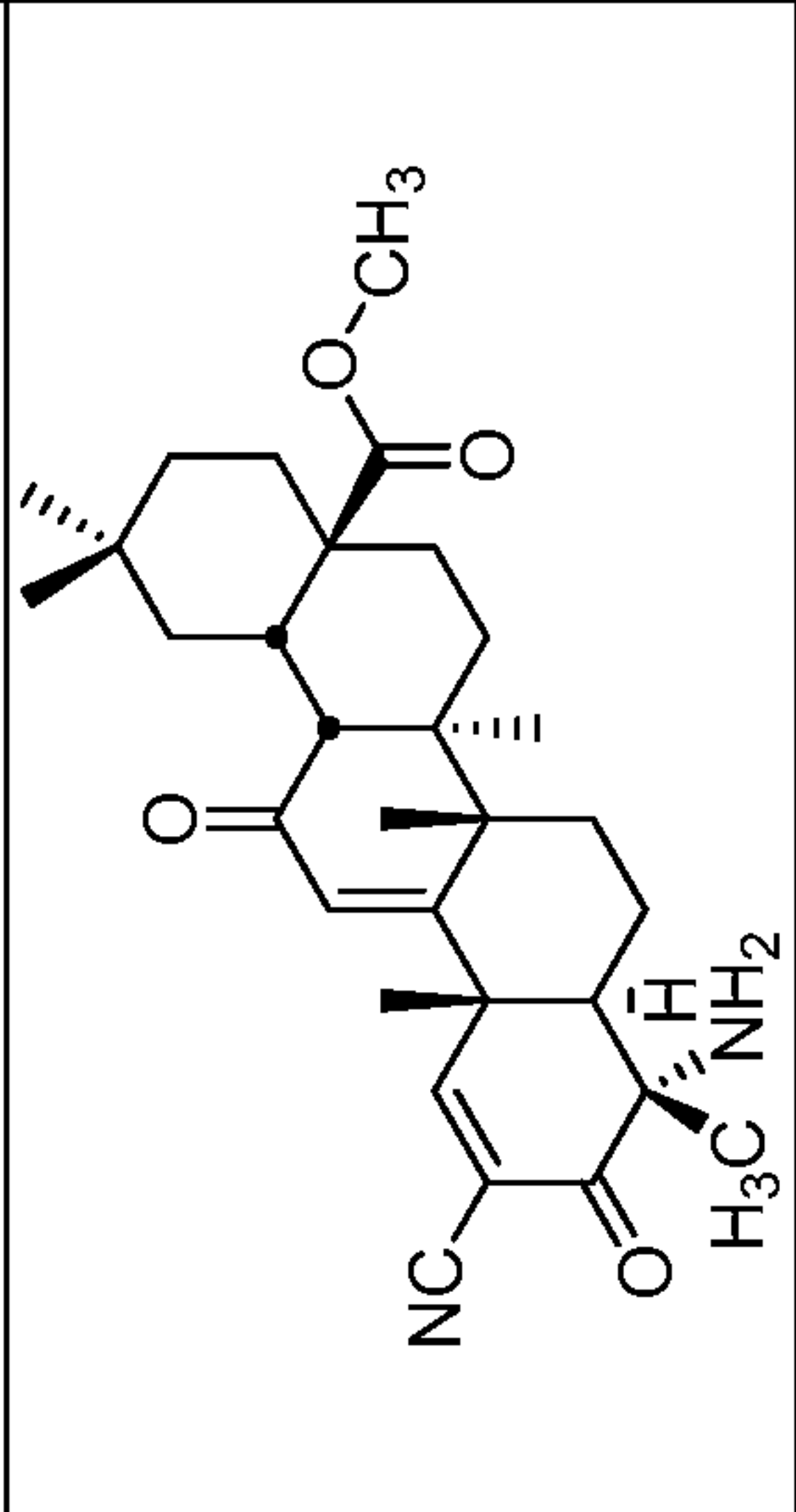
Table 1: Inhibition of hIL17, ROR γ , and NO production and NRF2 Activation of the Compounds

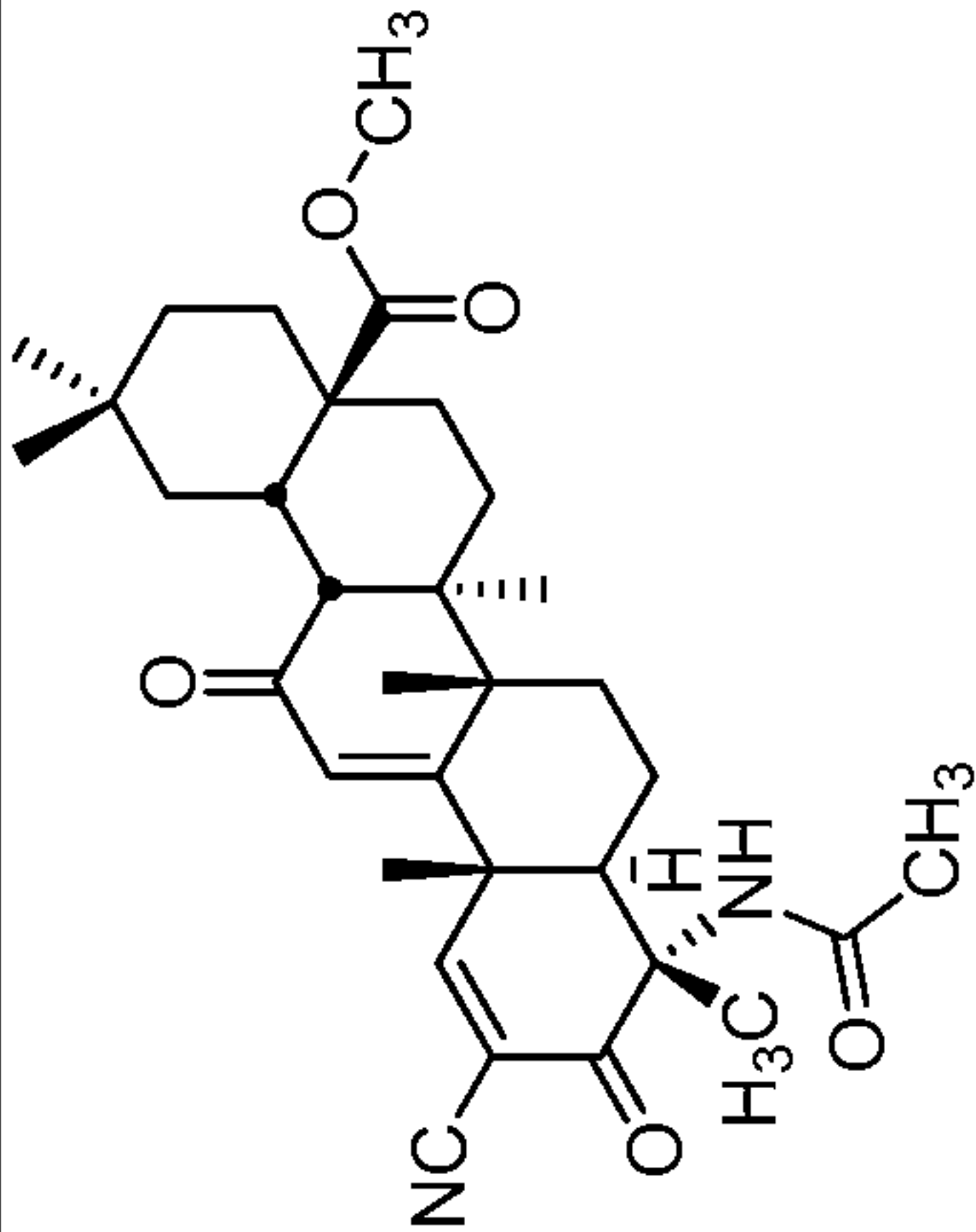
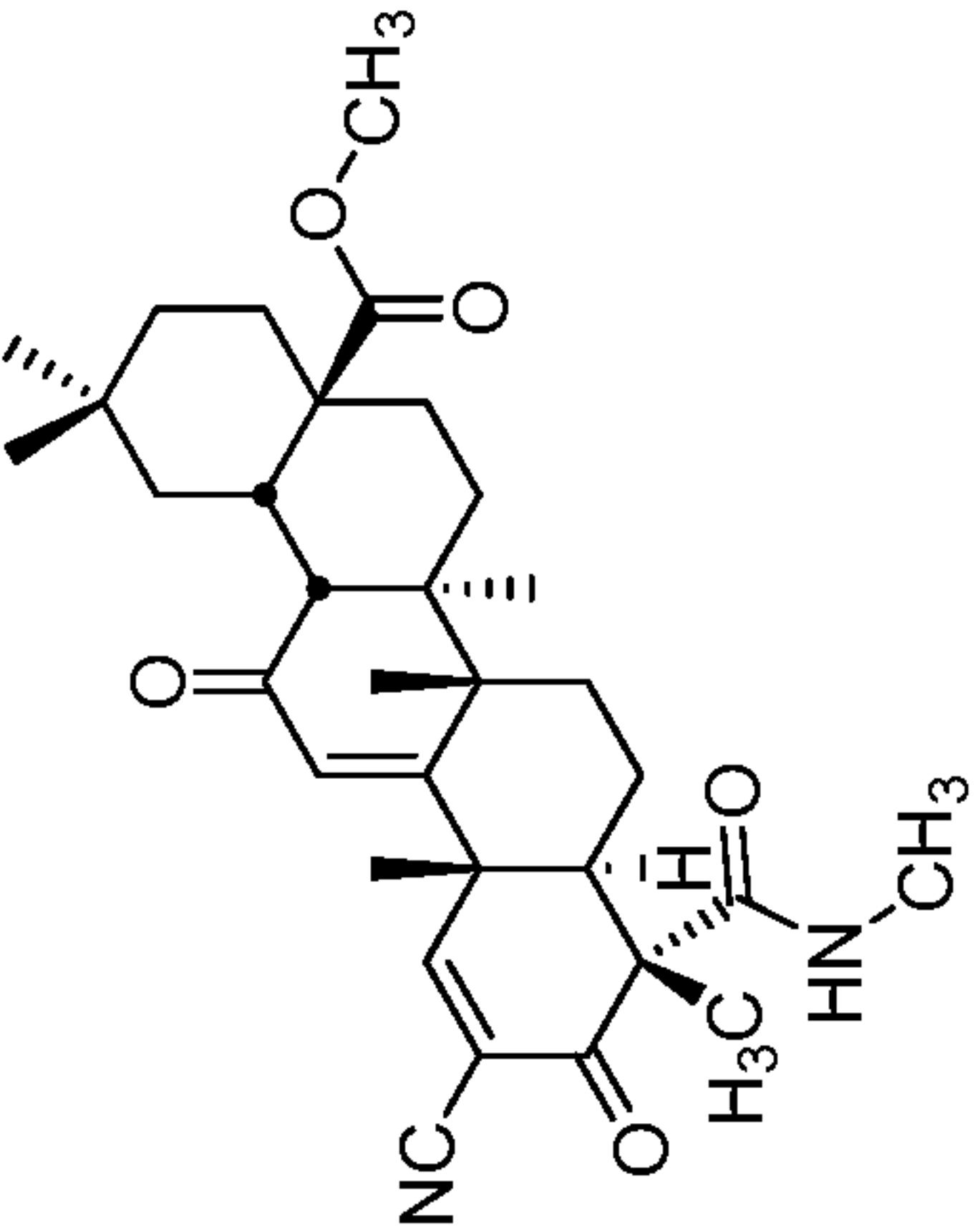
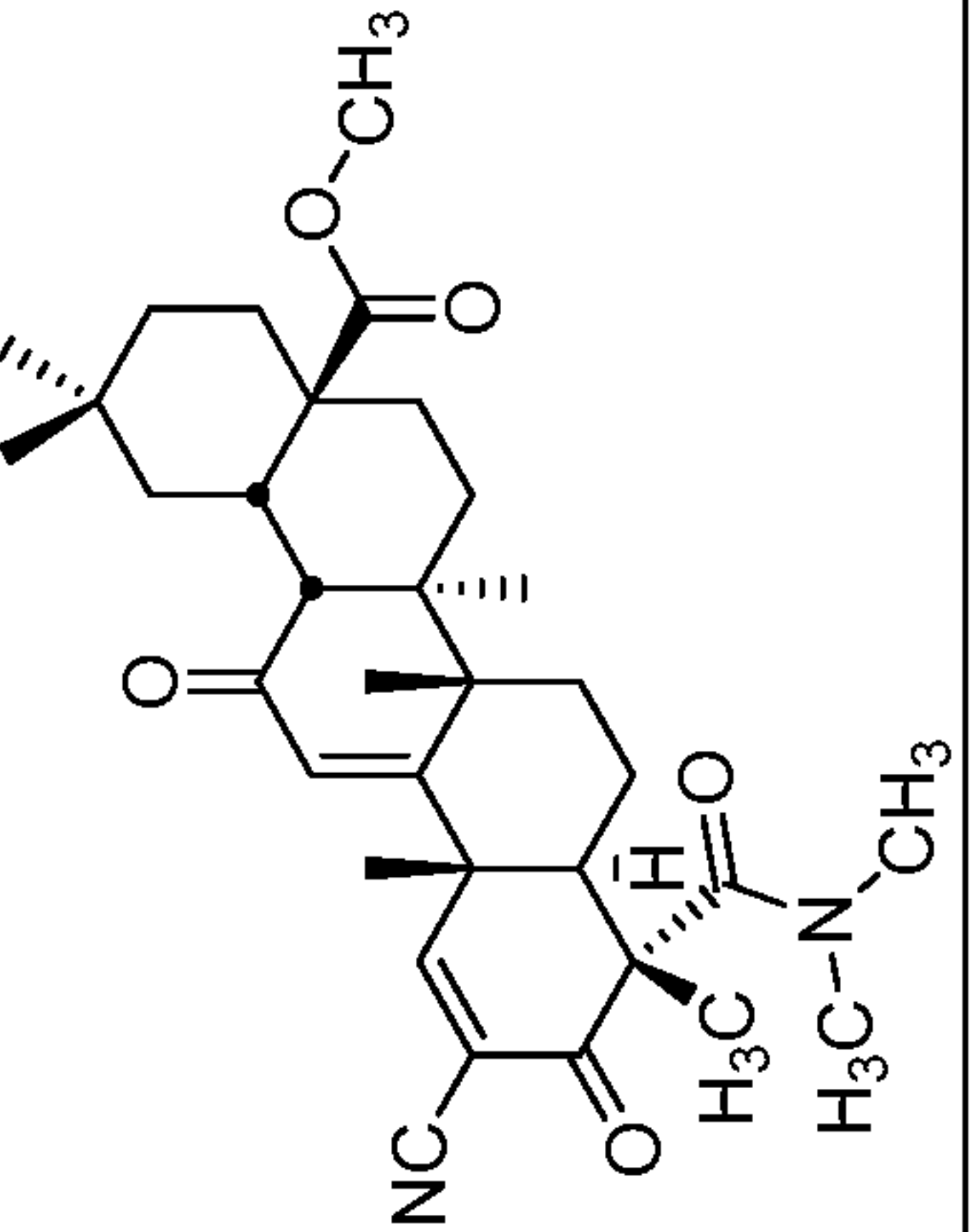
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
Comparison Compound #1		25	127	11	1.2
Comparison Compound #300		18	152	34	7.4
Comparison Compound #301		17	144	8	1.8

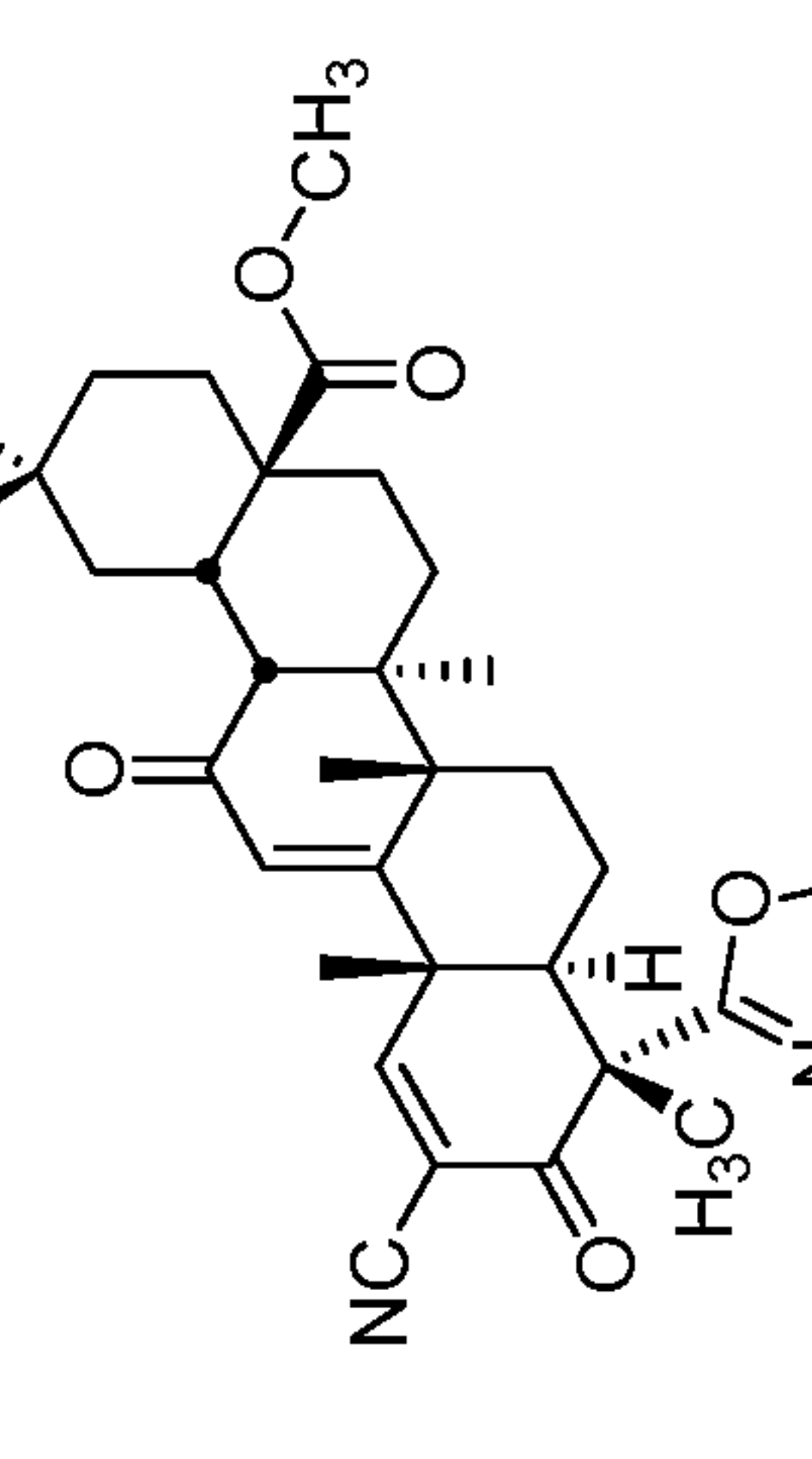
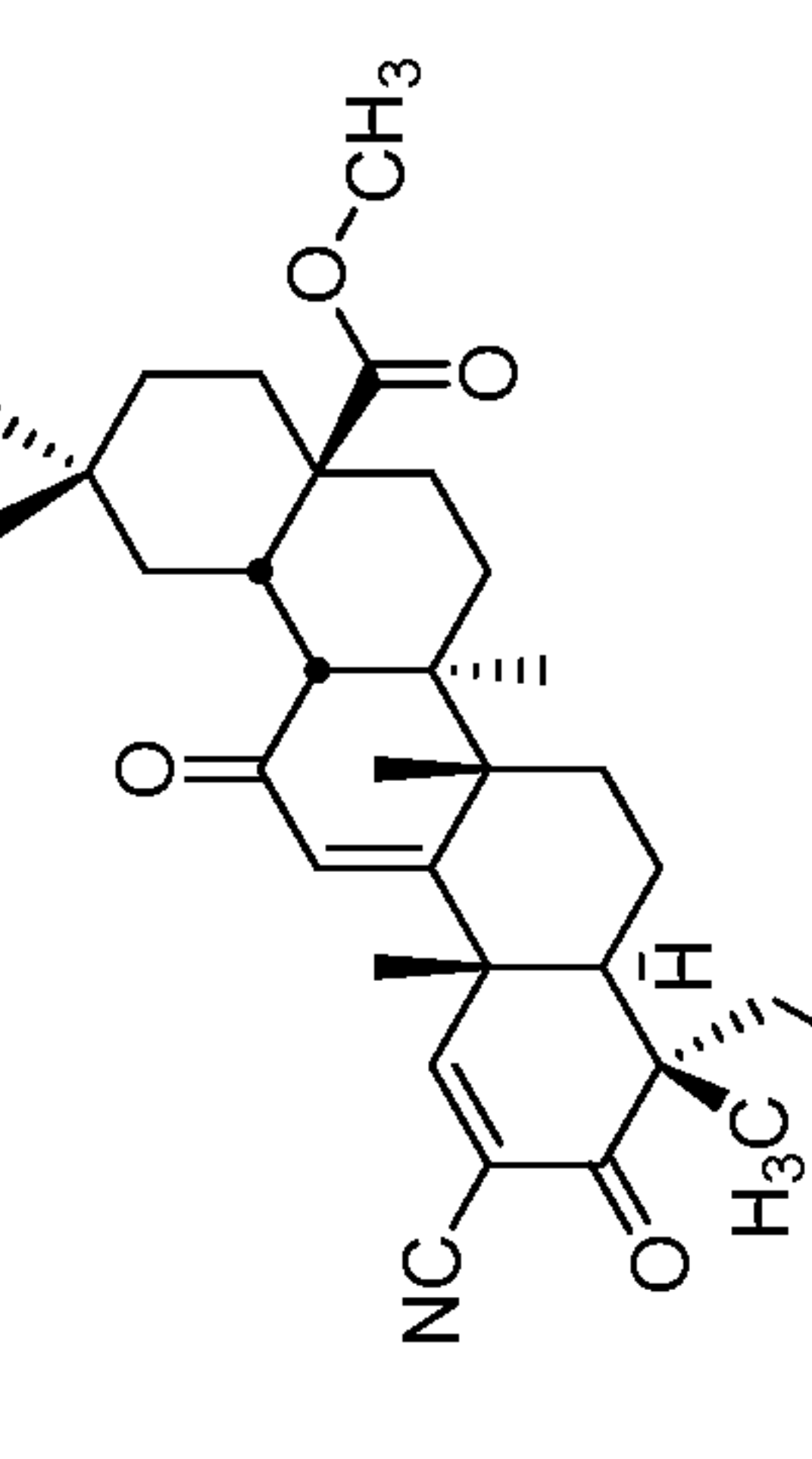
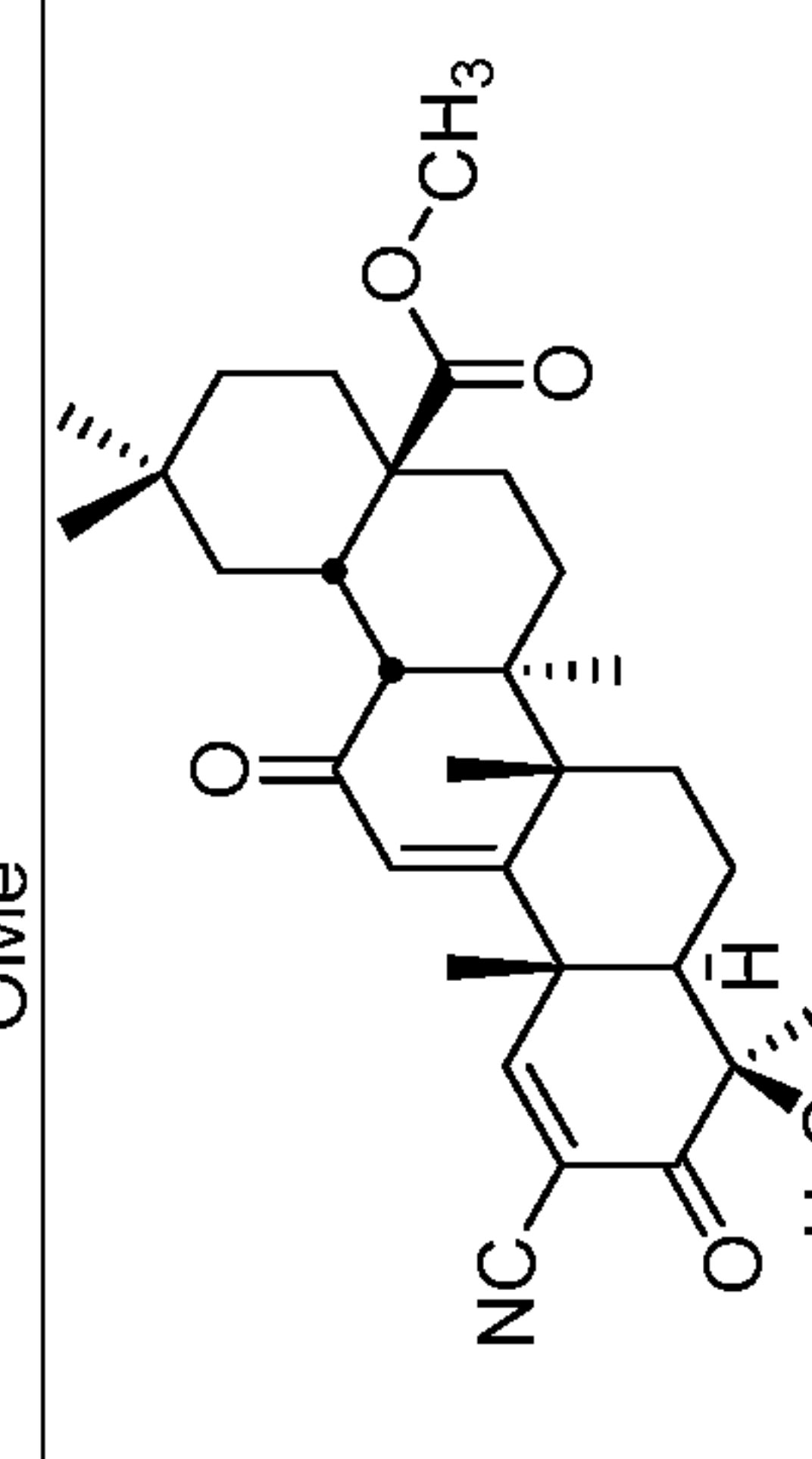
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Comparison Compound #302		24	91	78	13.1
T1		40	144	50	8.1
T2		19	216	204	92.0

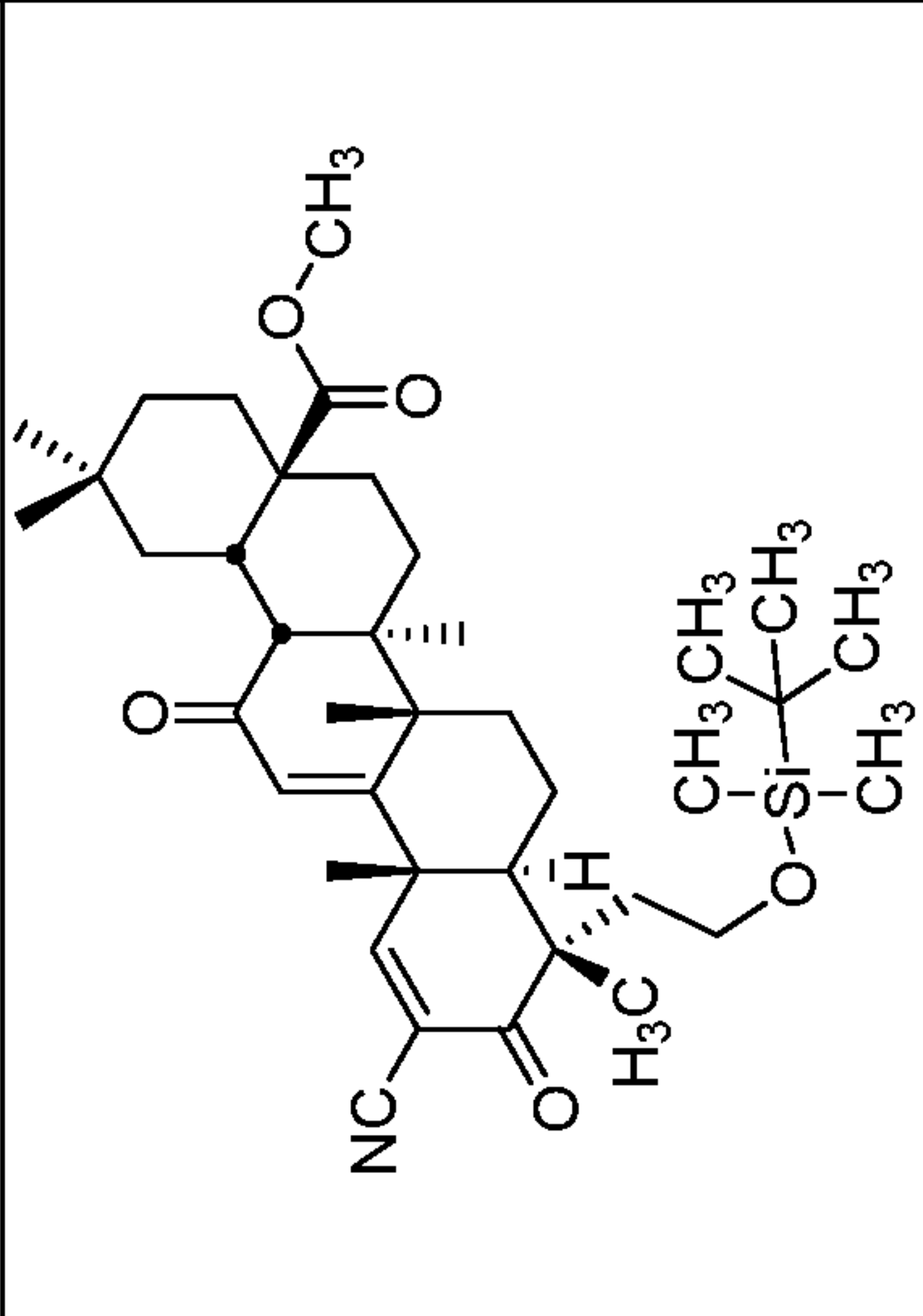
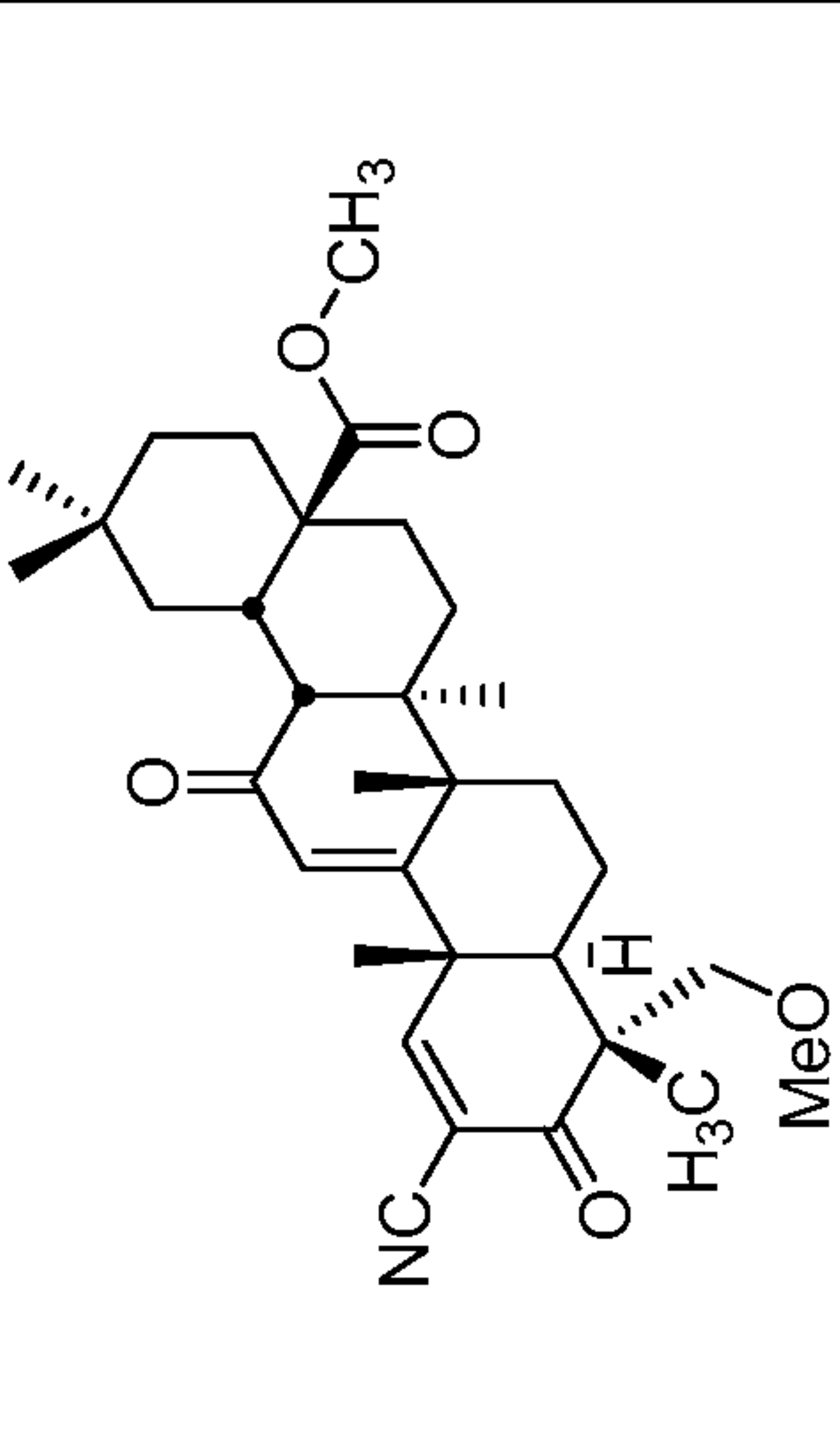
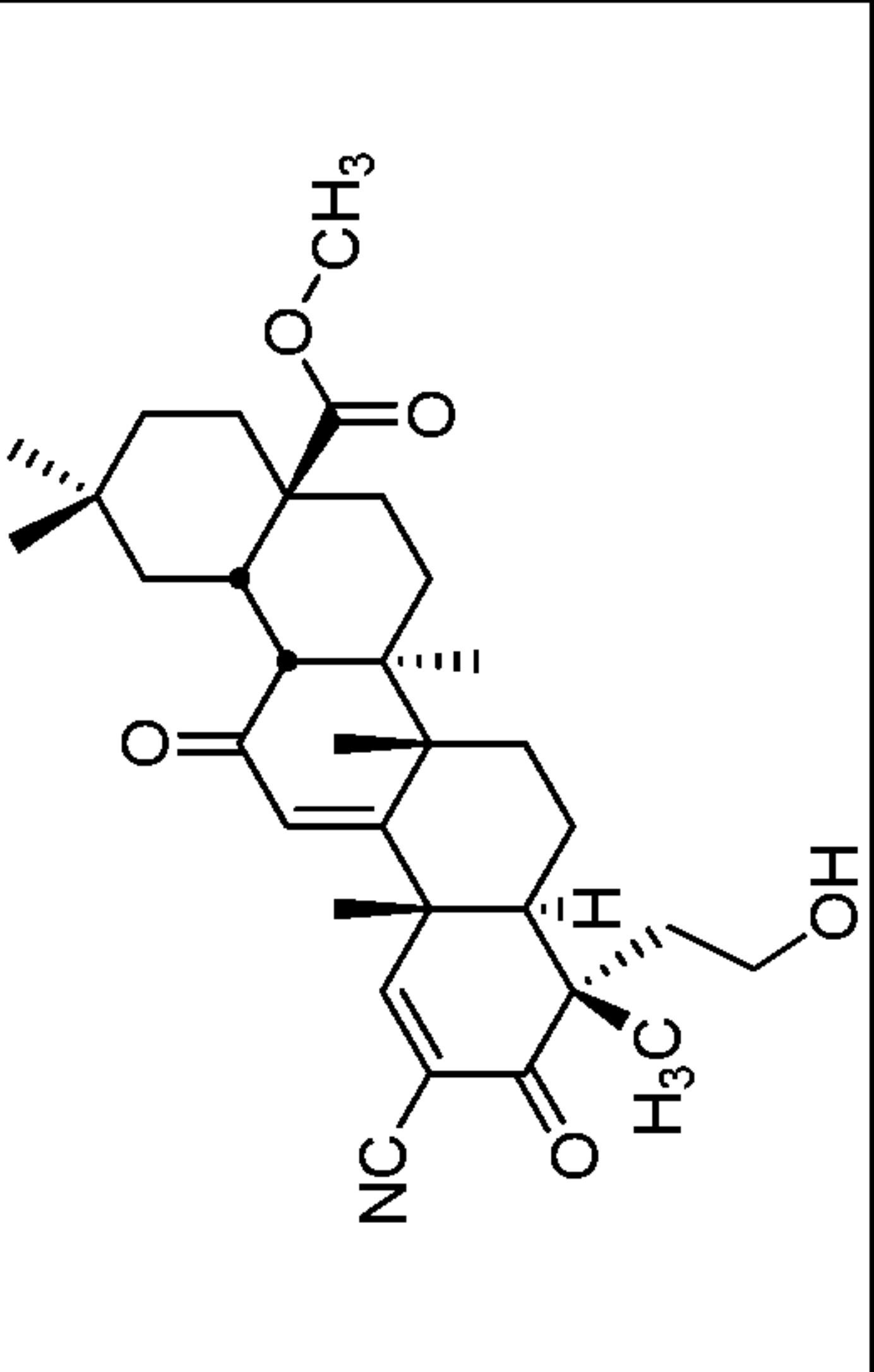
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T3		18	169	48	22.3
T4		29	234	36	19.6
T5		18	115	56	22.6

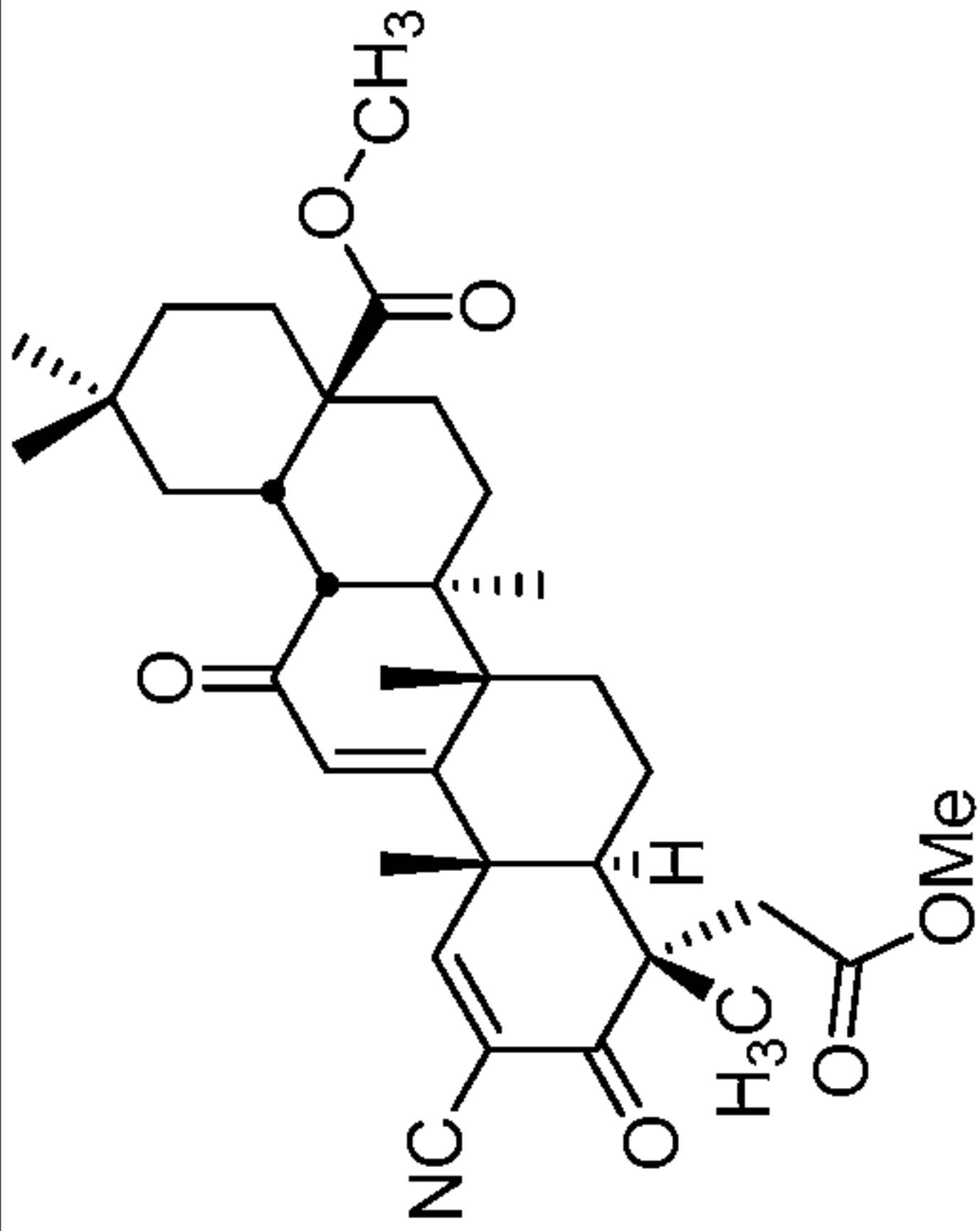
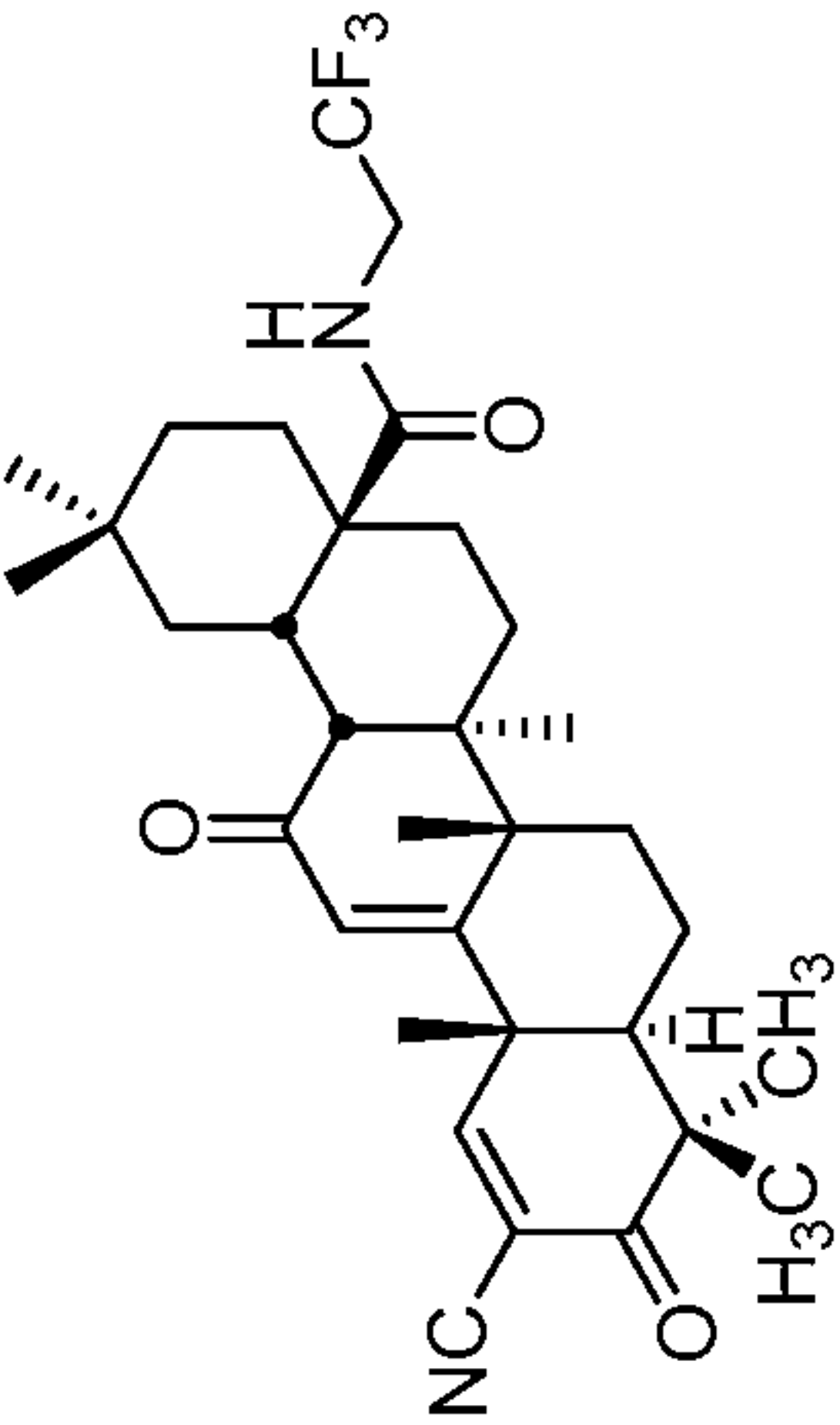
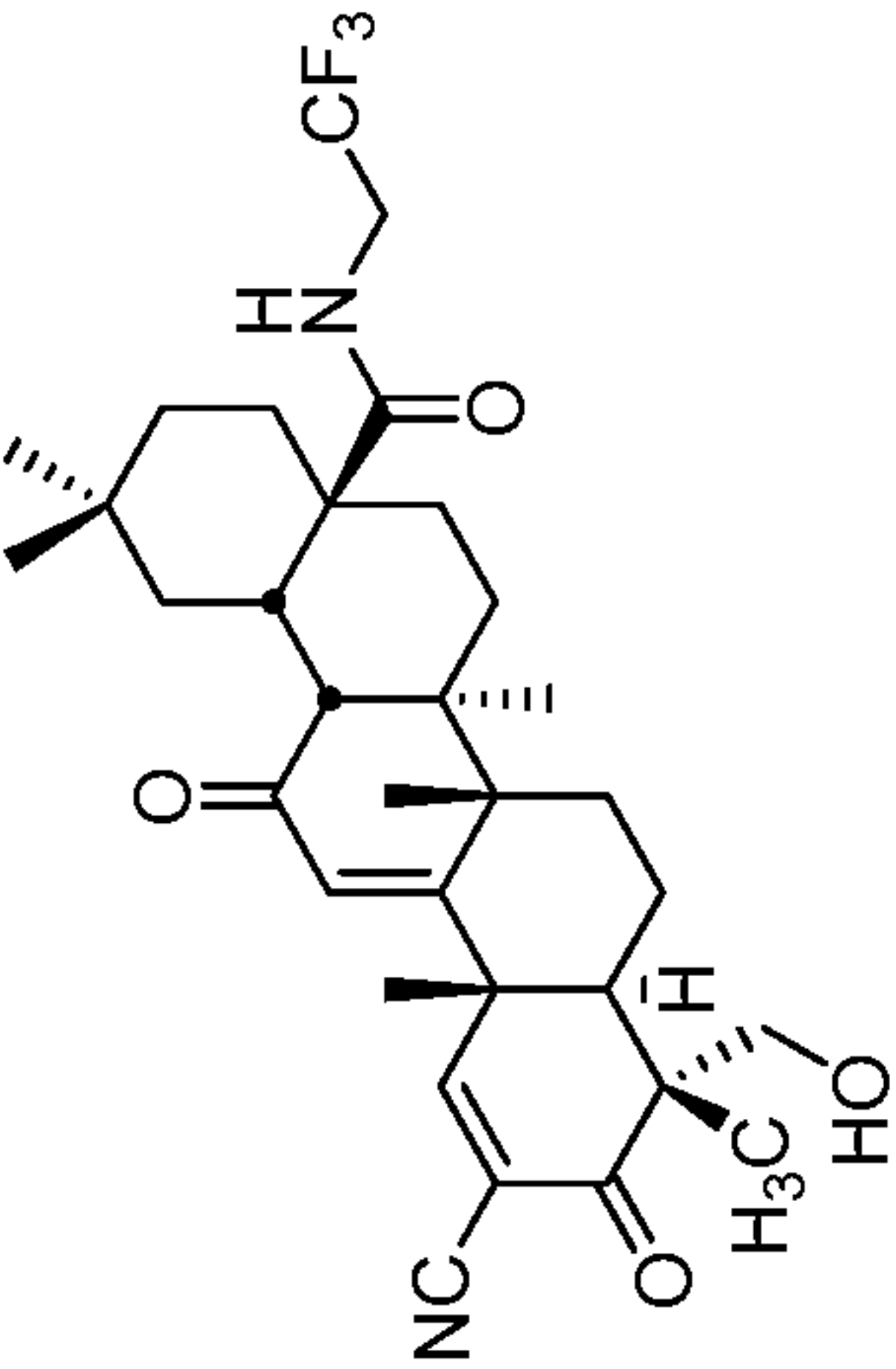
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T6		32	115	30	9.2
T7		27	251	270	95.1
T8		24	109	276	74.6

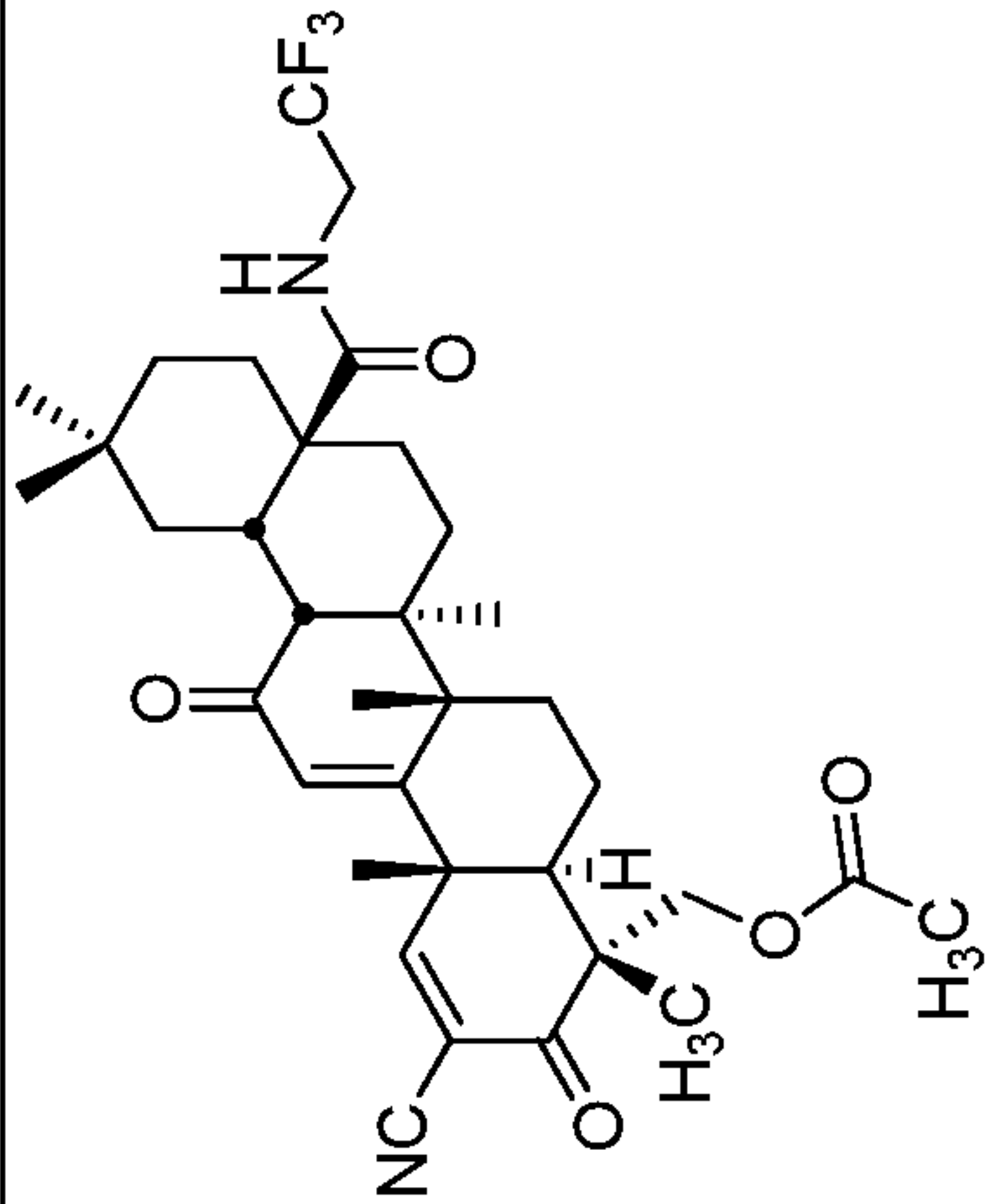
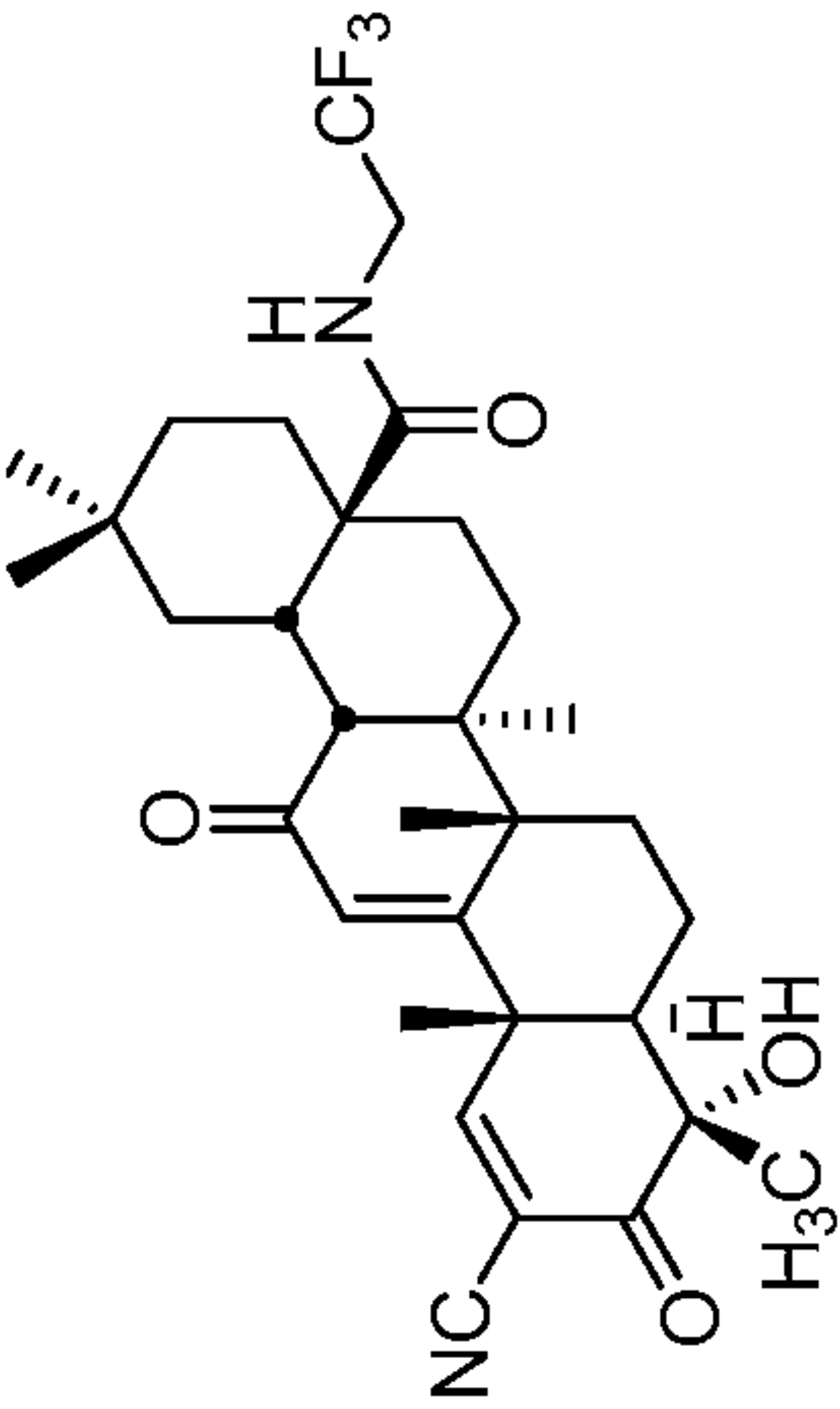
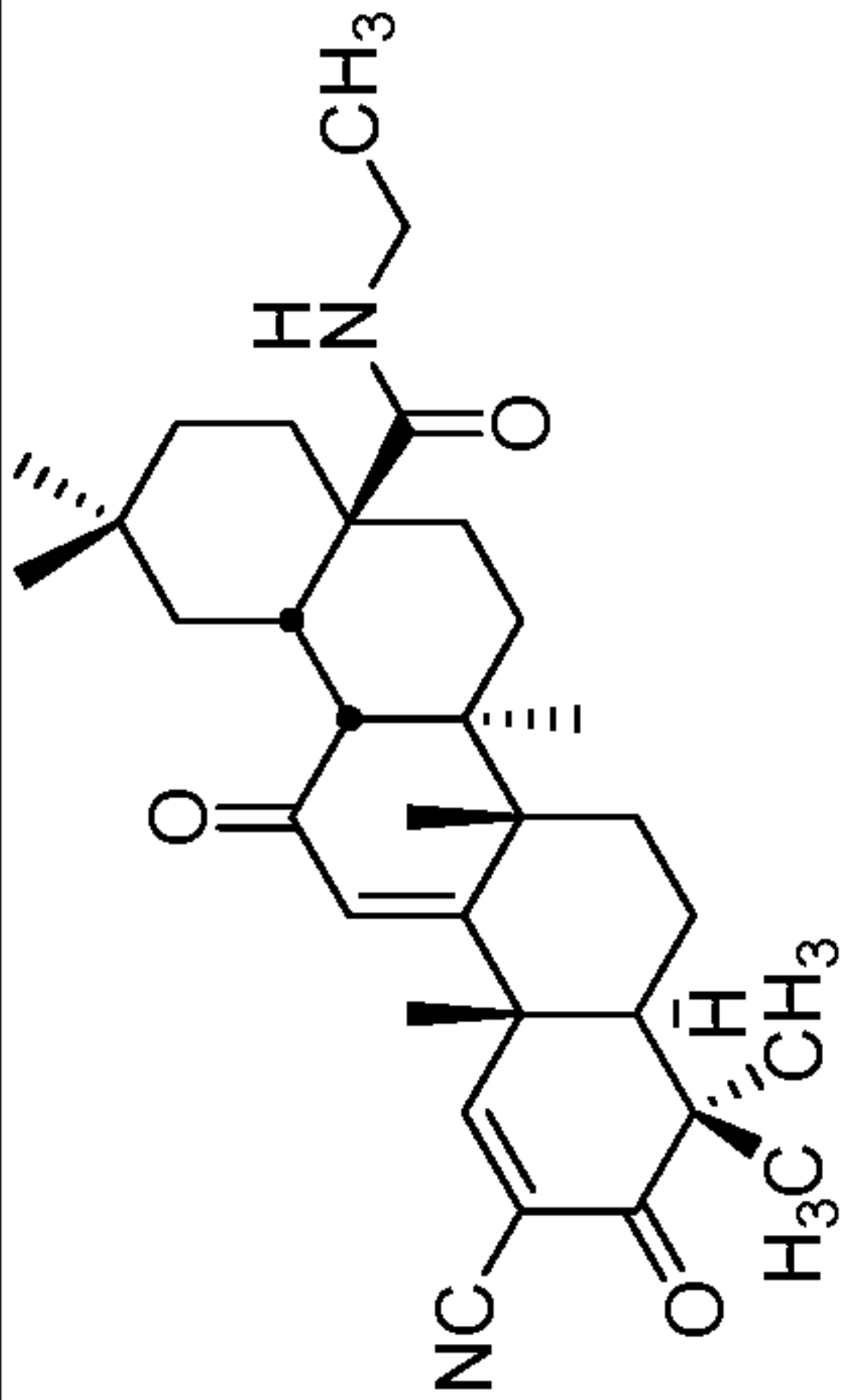
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T9		37	361	962	191.2
T10		204	1075	>1000	414.0
T11		75	146	477	601.0

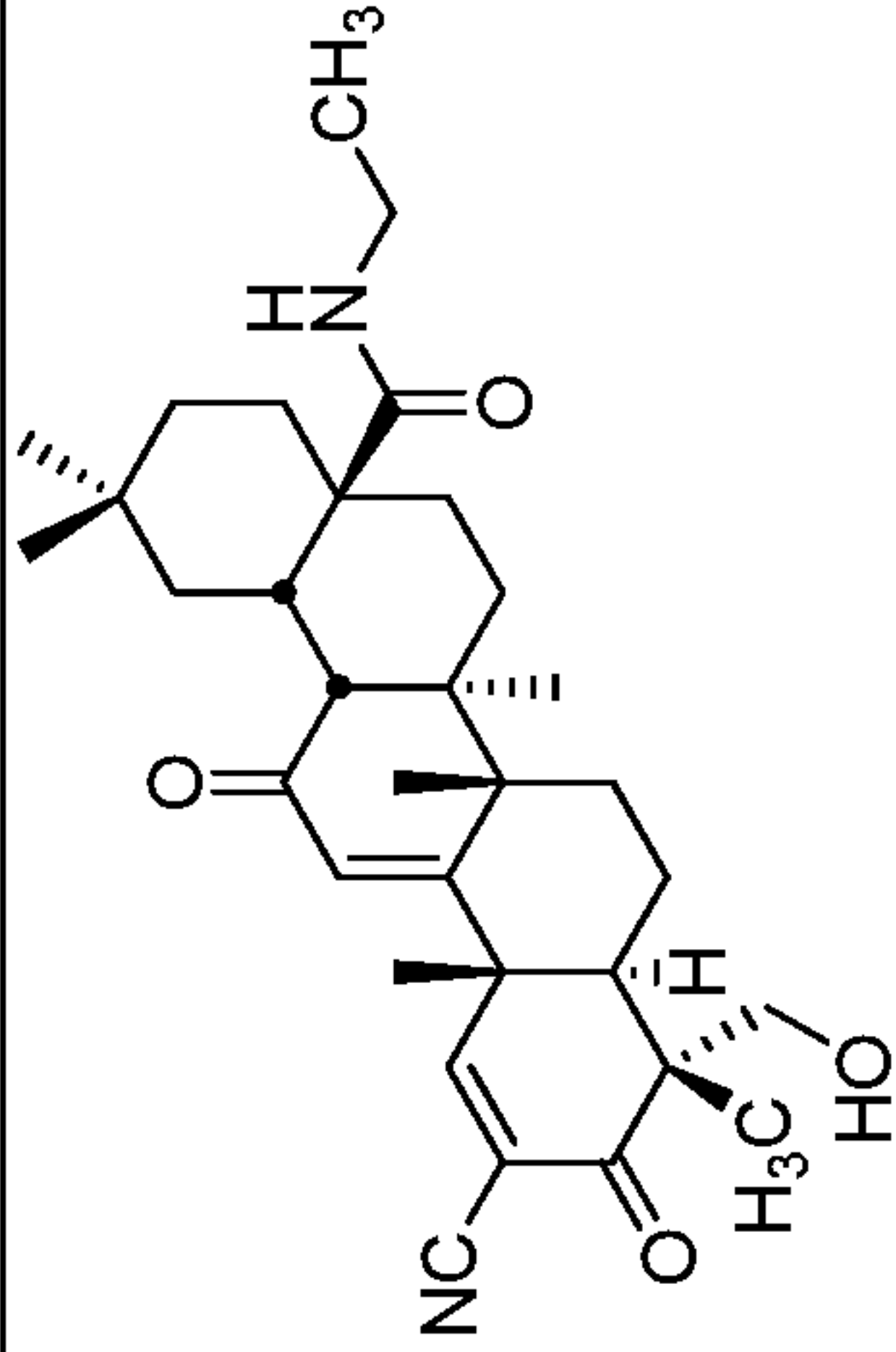
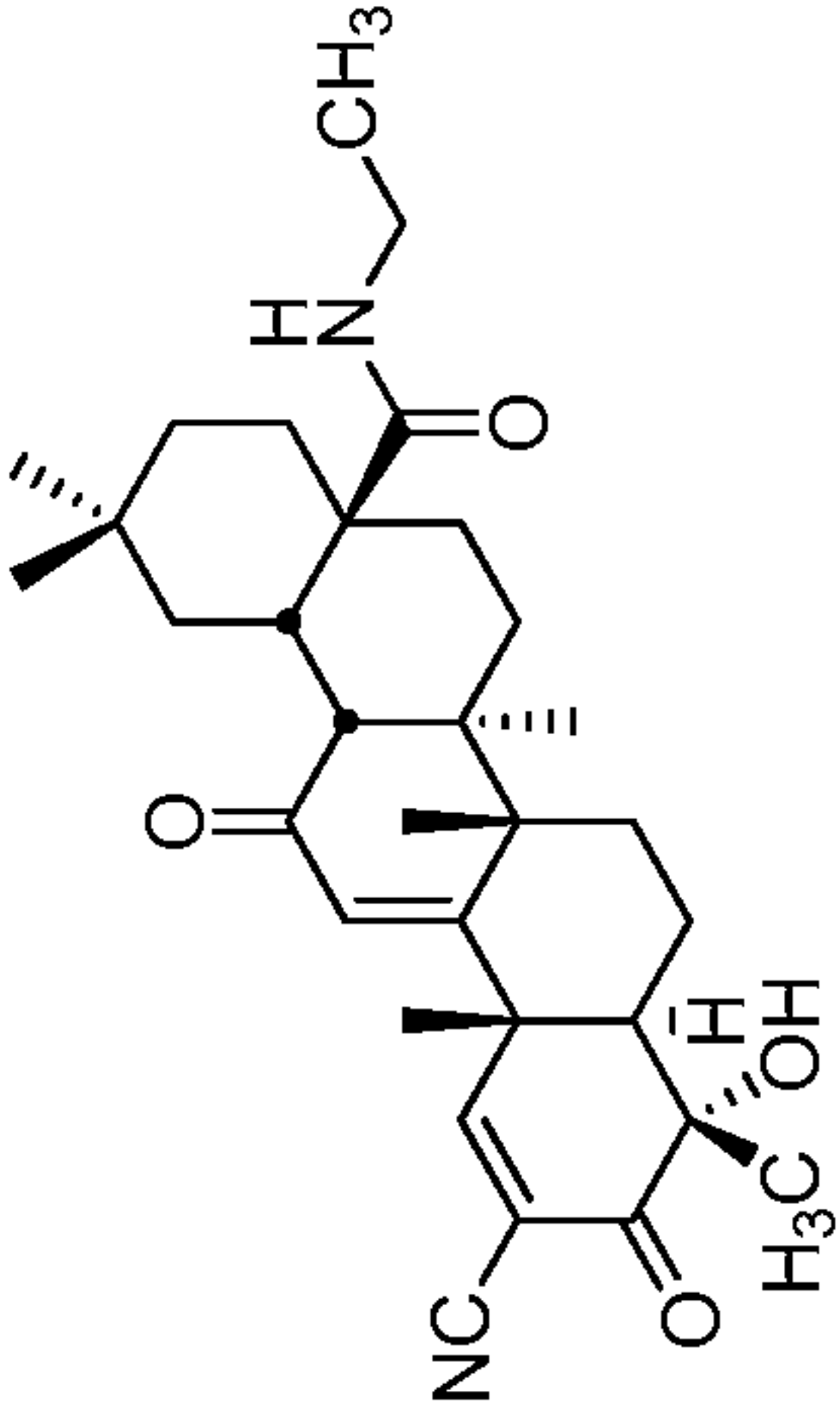
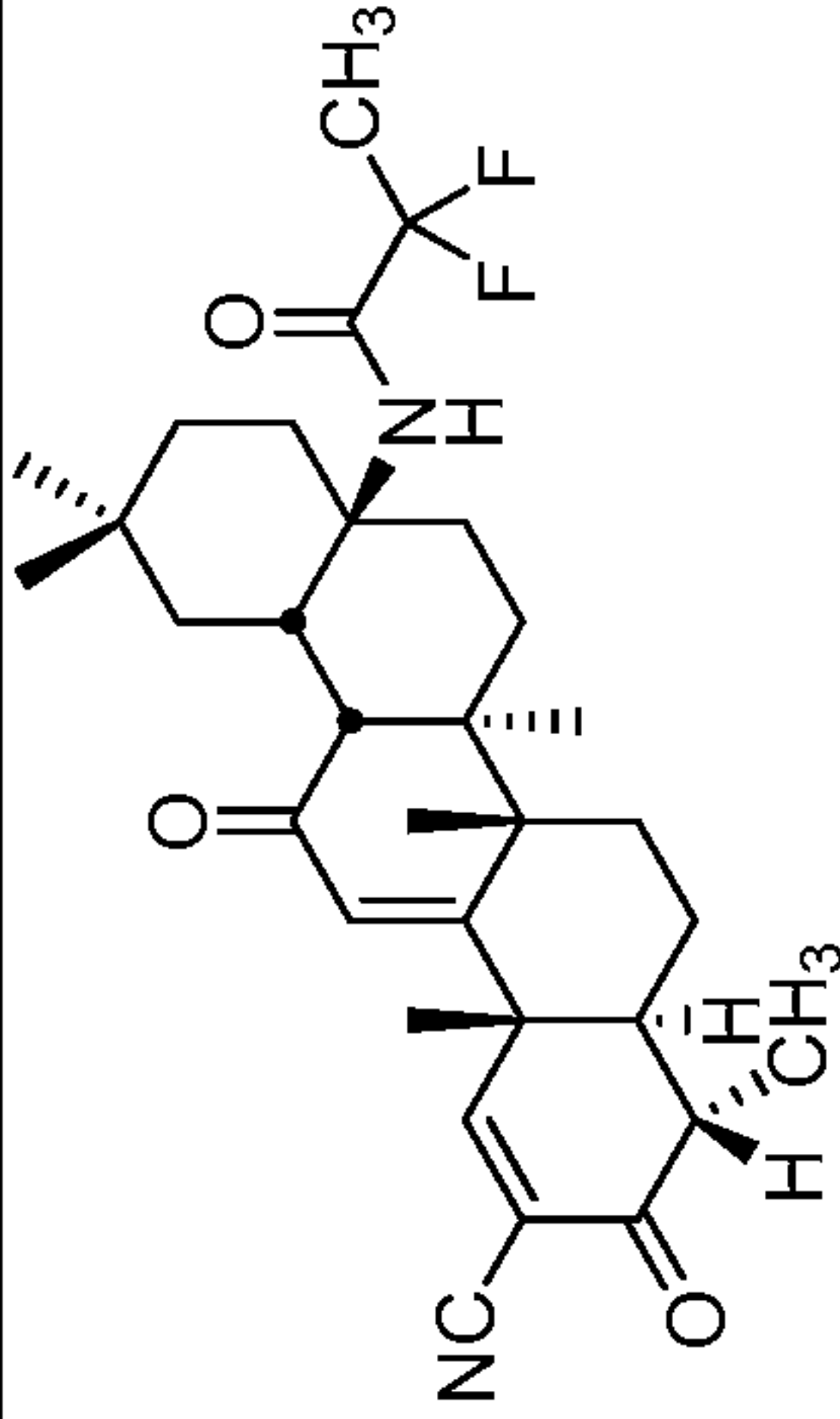
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T12		81	419	>1000	>1000
T13		49	161	567	295.2
T14		46	139	>1000	164.5

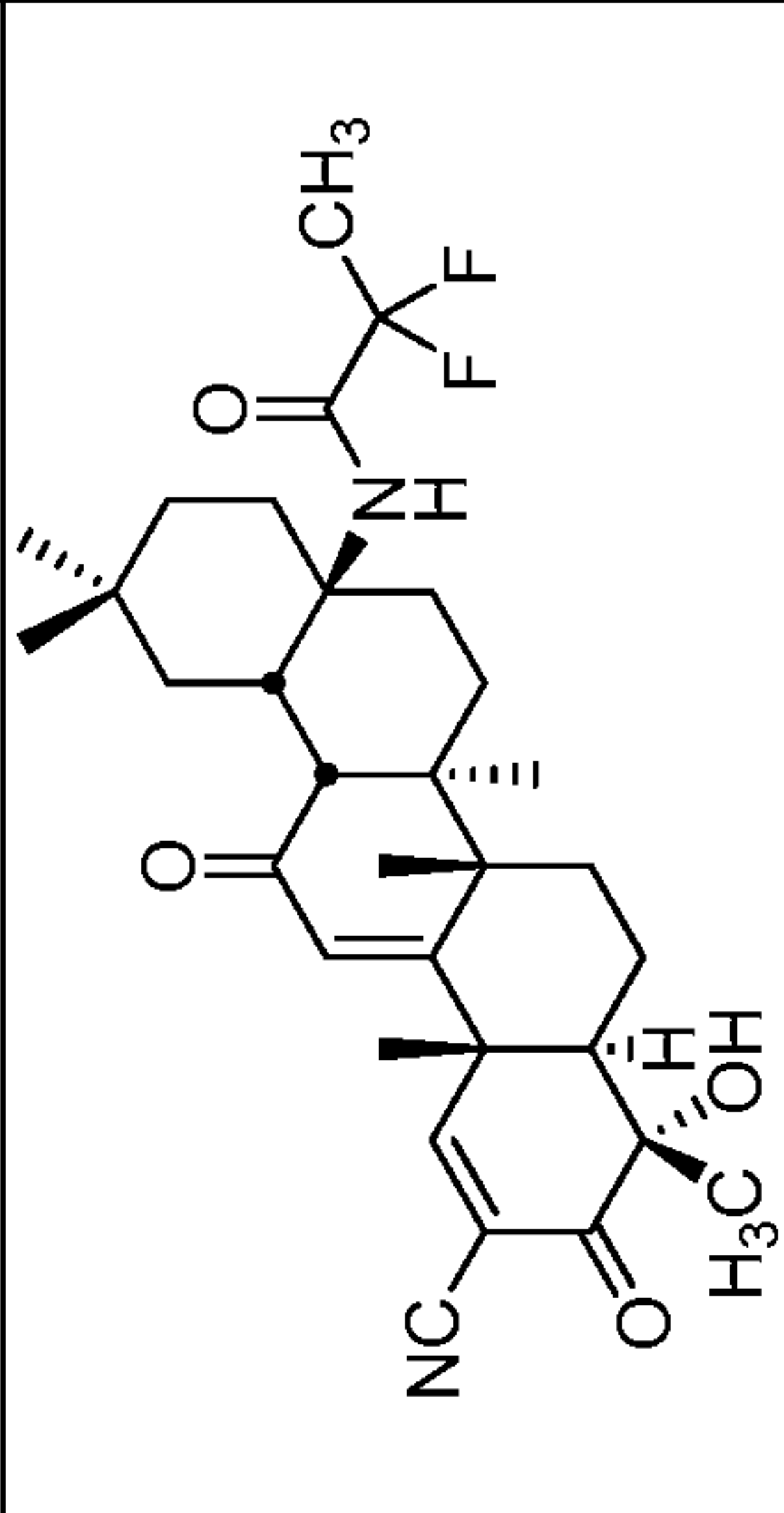
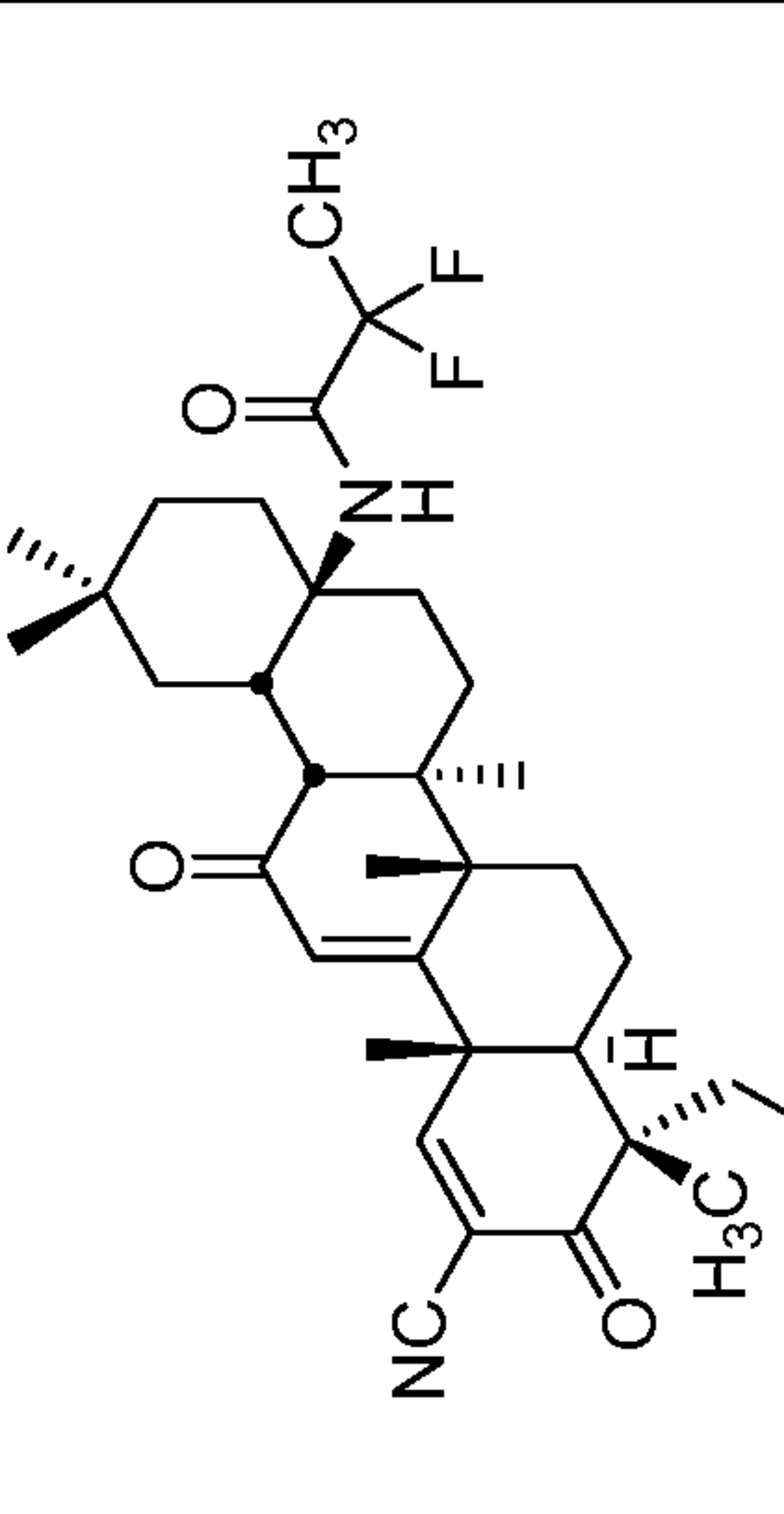
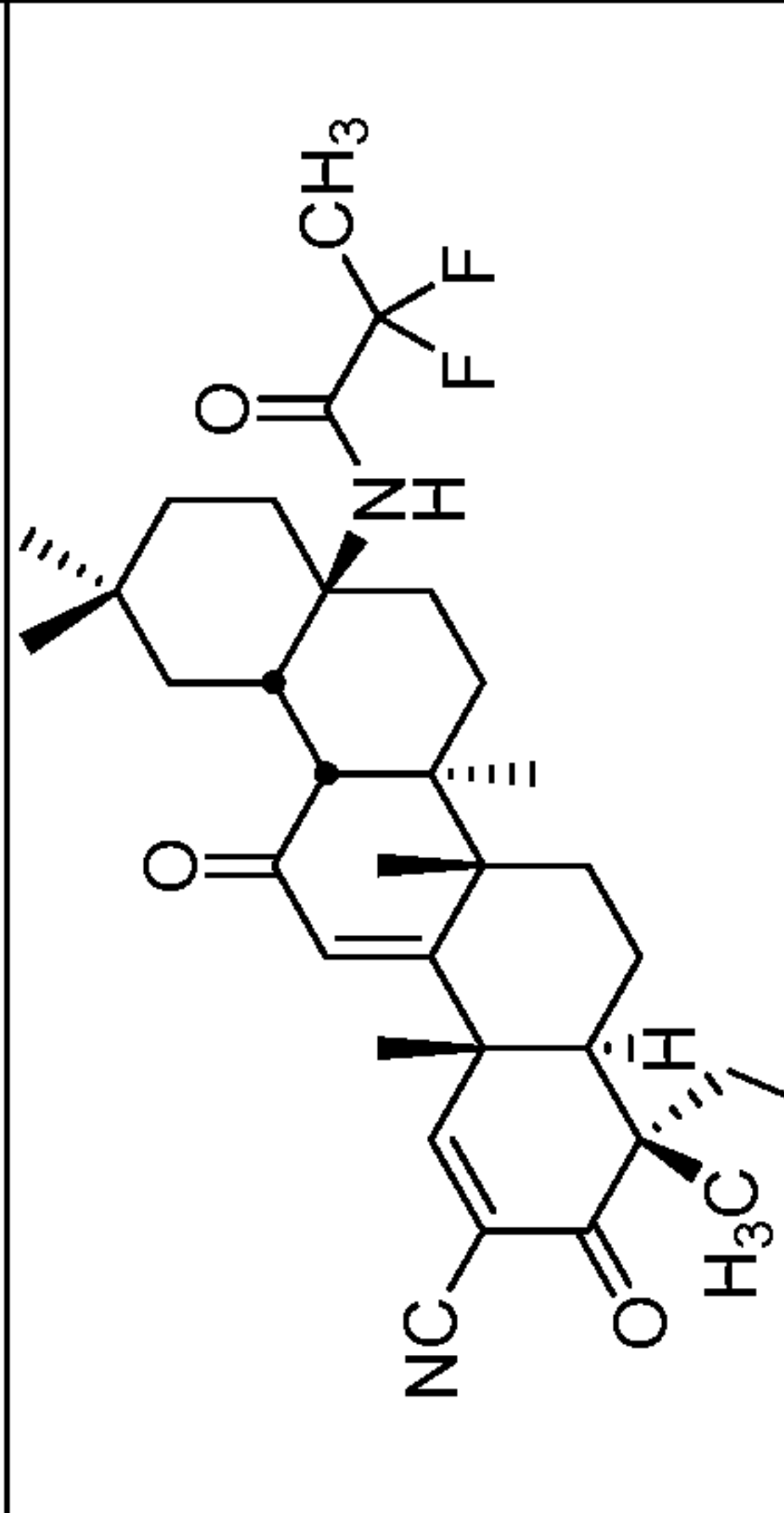
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T16		92	406	>1000	614.7
T17		30	250	64	19.5
T15		65	206	612	714.4

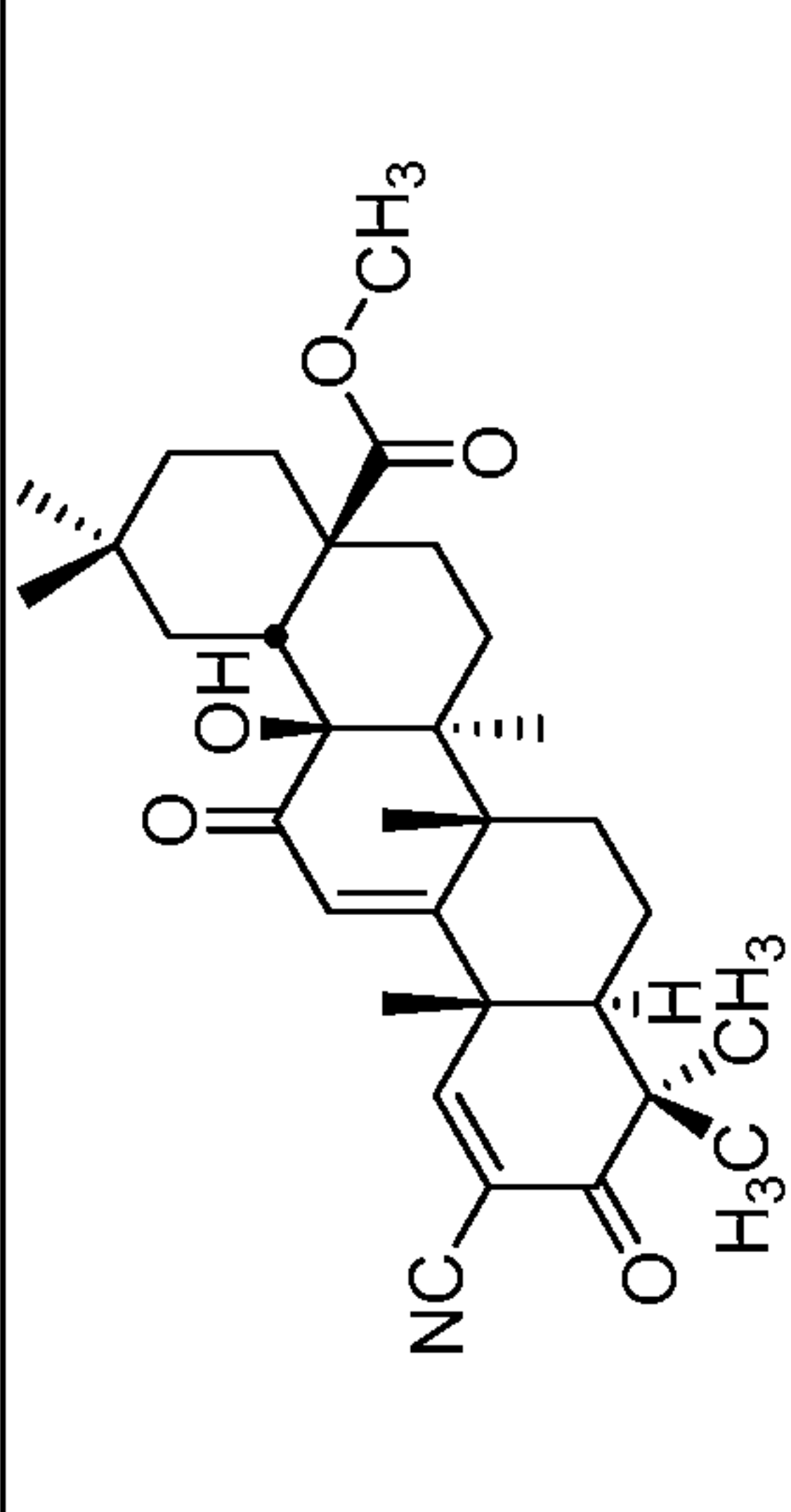
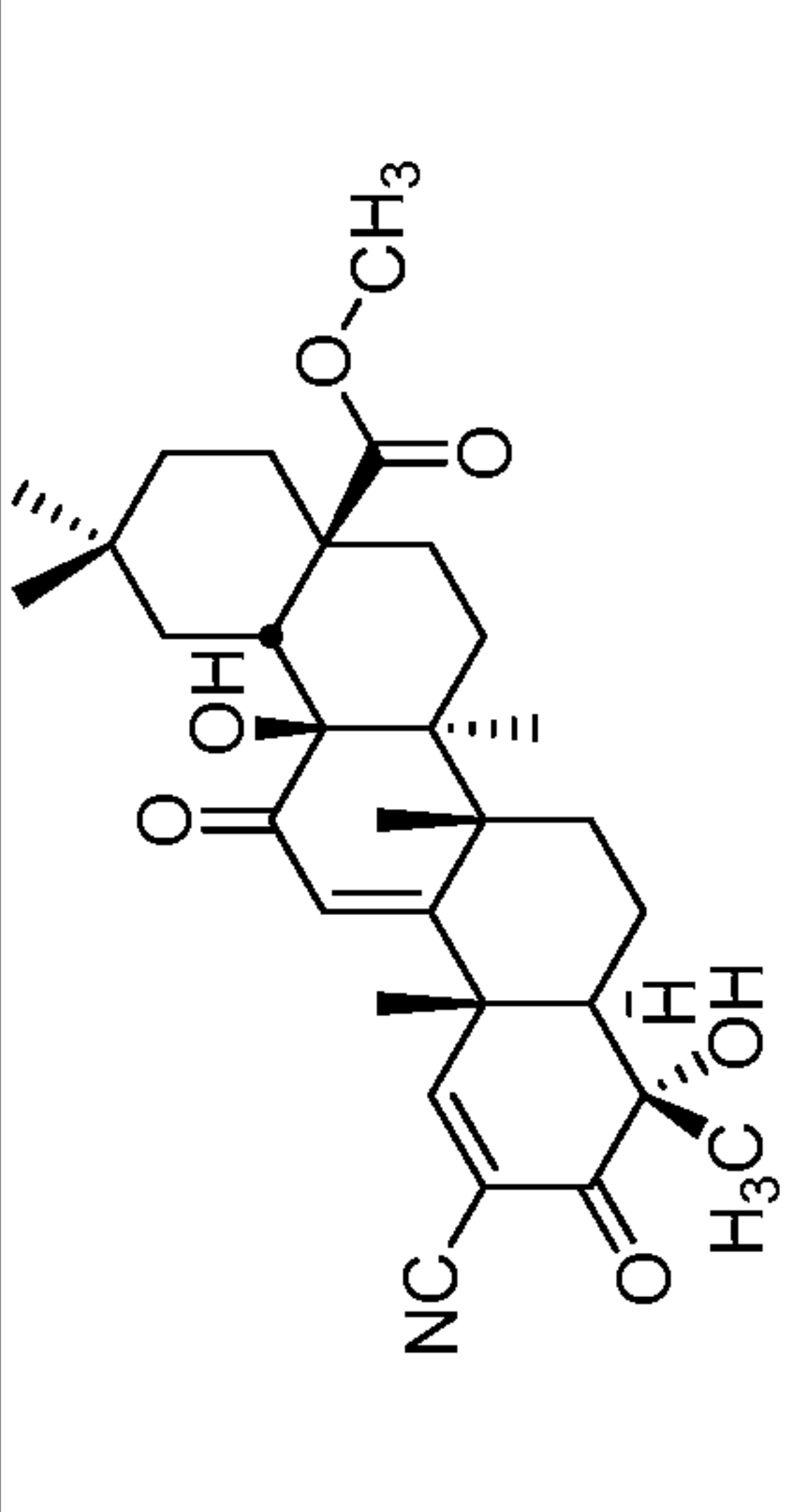
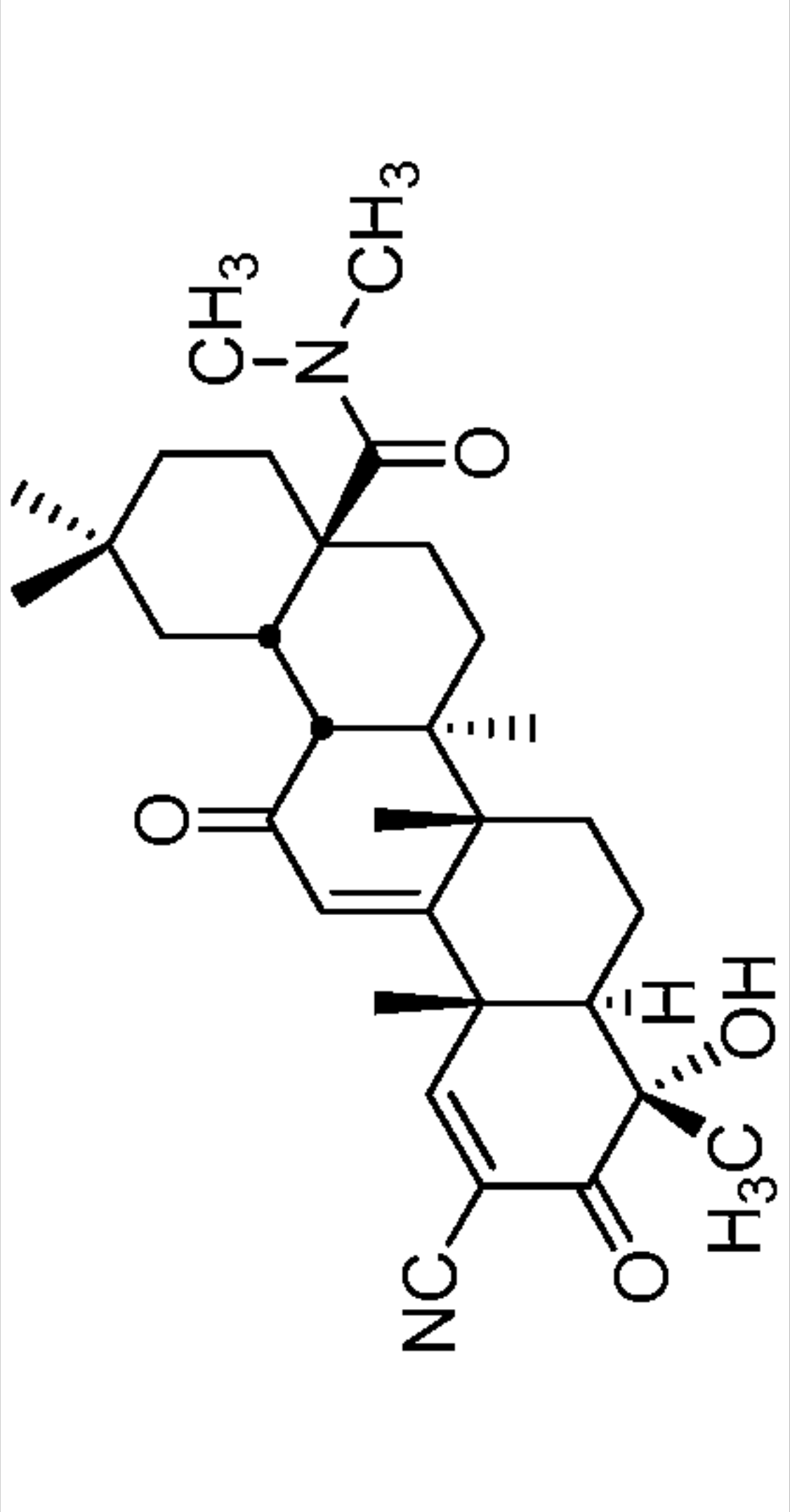
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T18		24	583	585	78.5
T20		21	223	175	15.6
T19		15	233	76	17.4

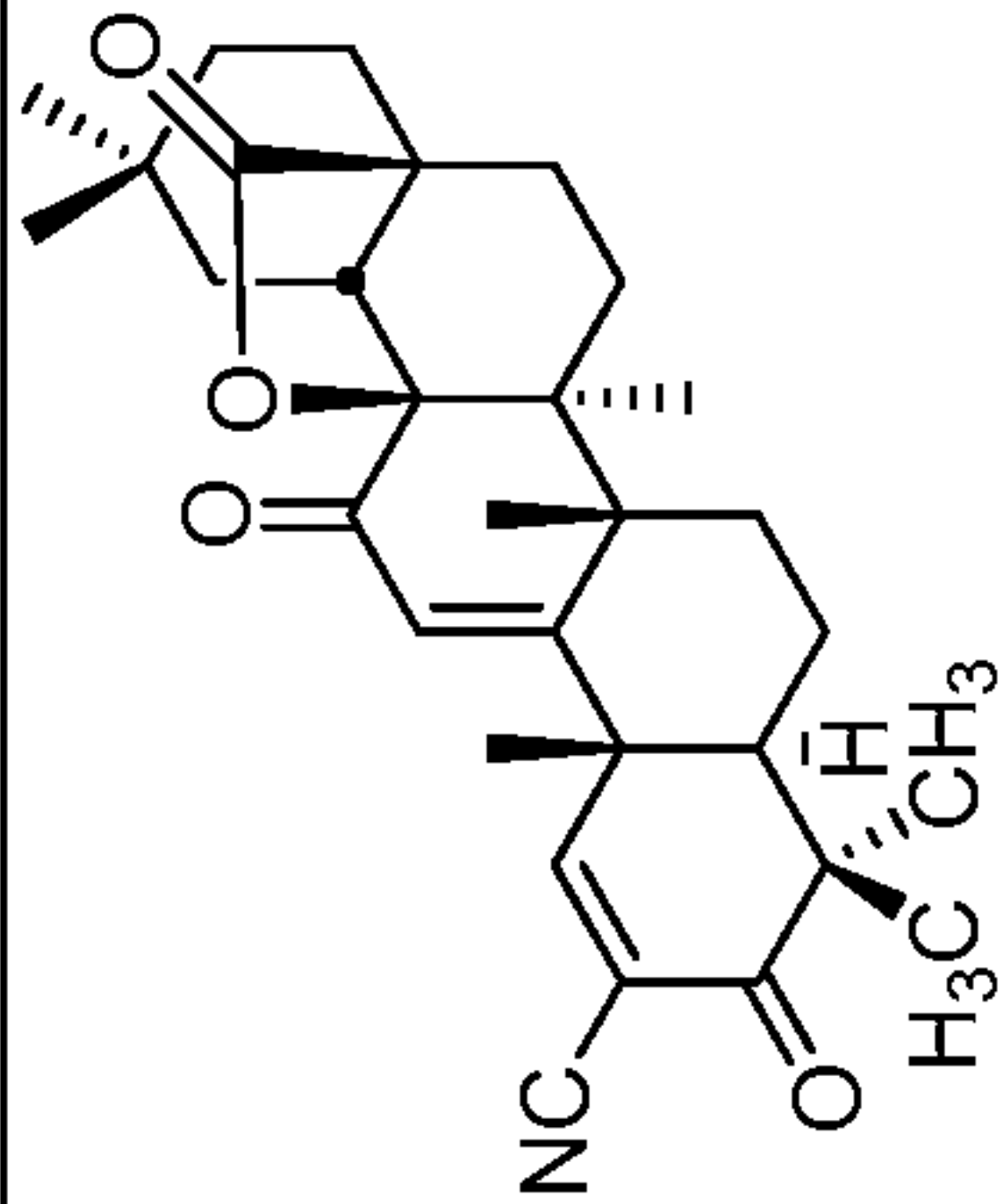
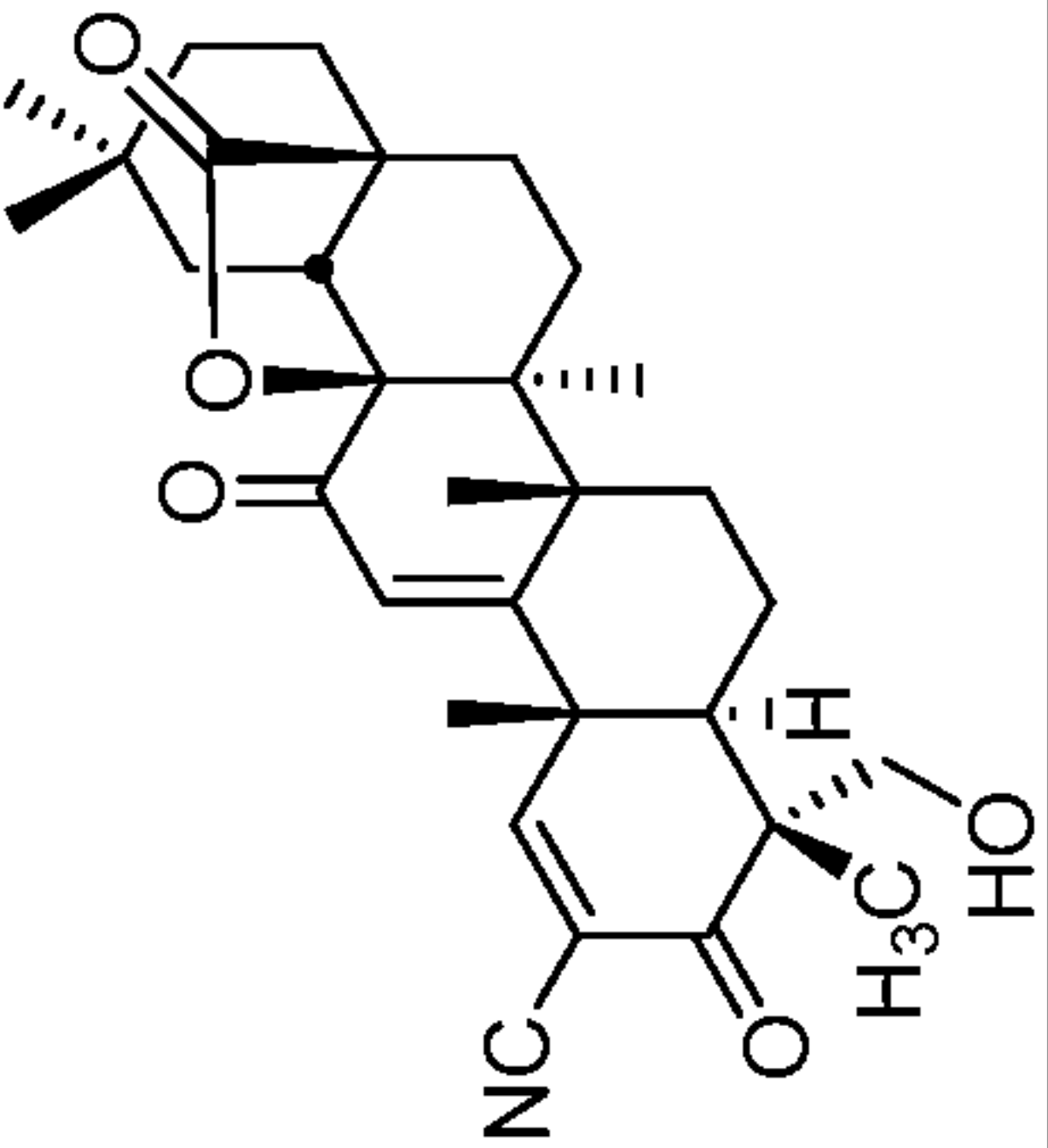
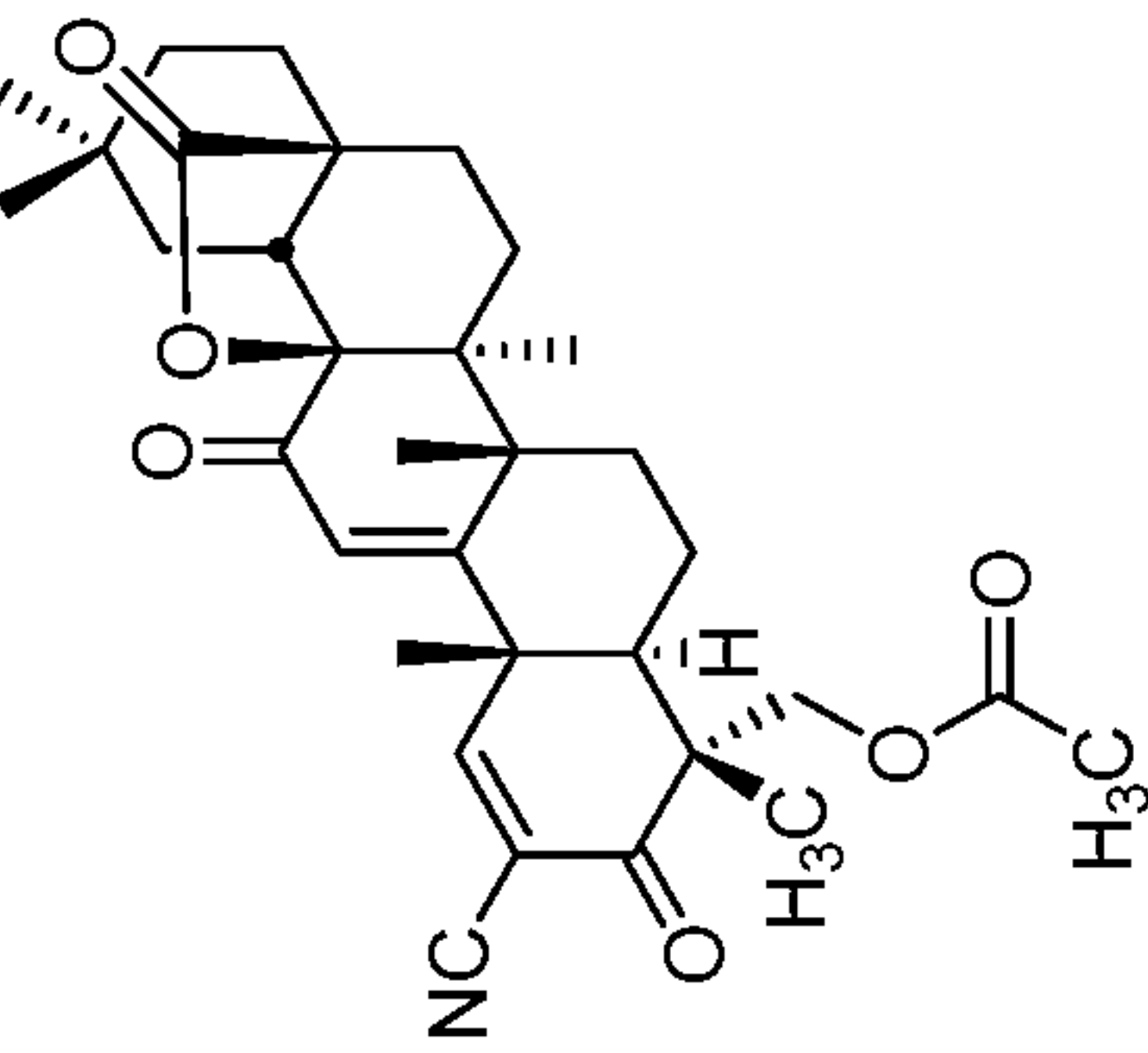
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T21		33	203	269	104.6
Comparison Compound #2		40	104	53	4.5
T22		50	256	103	13.5

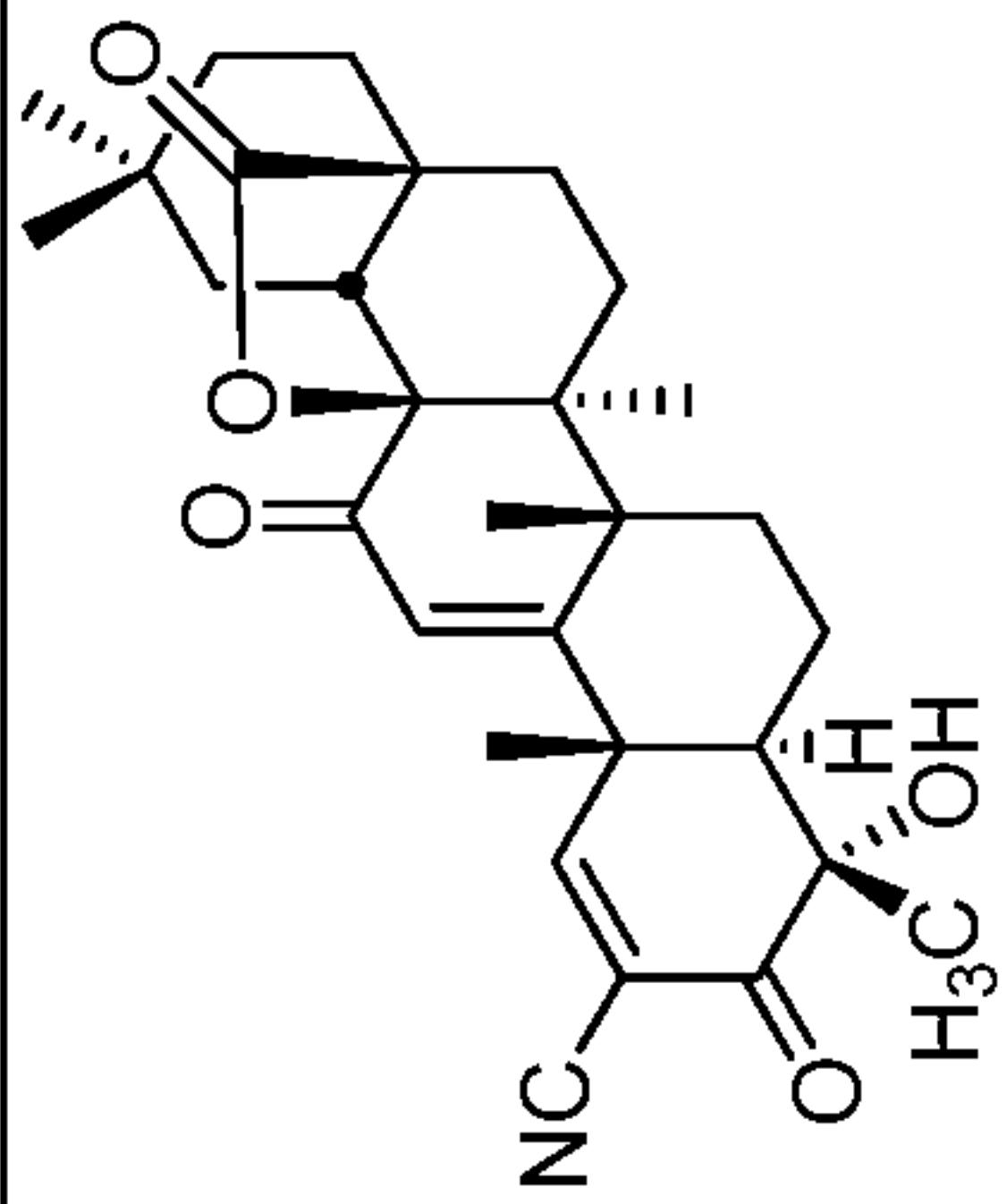
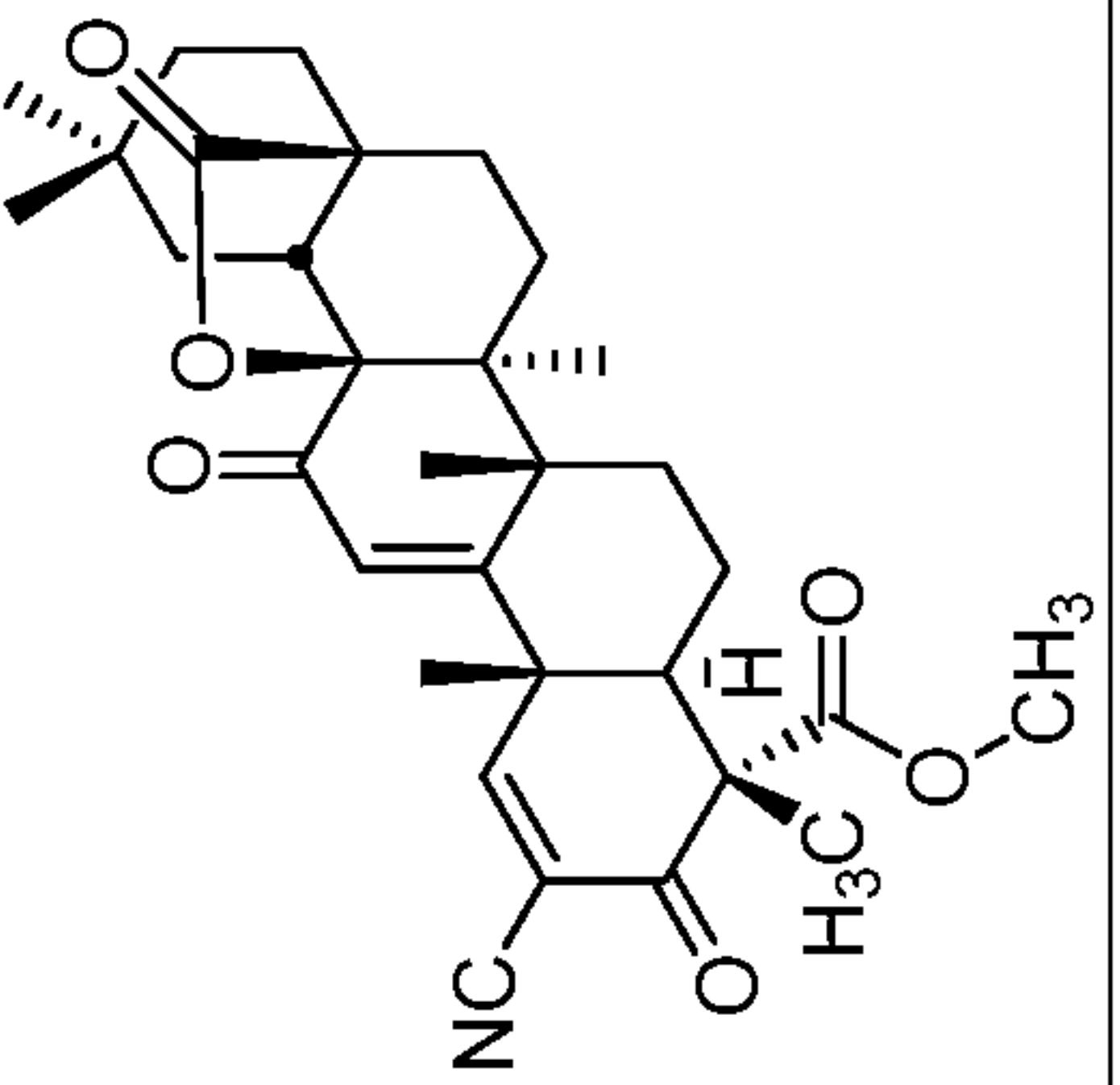
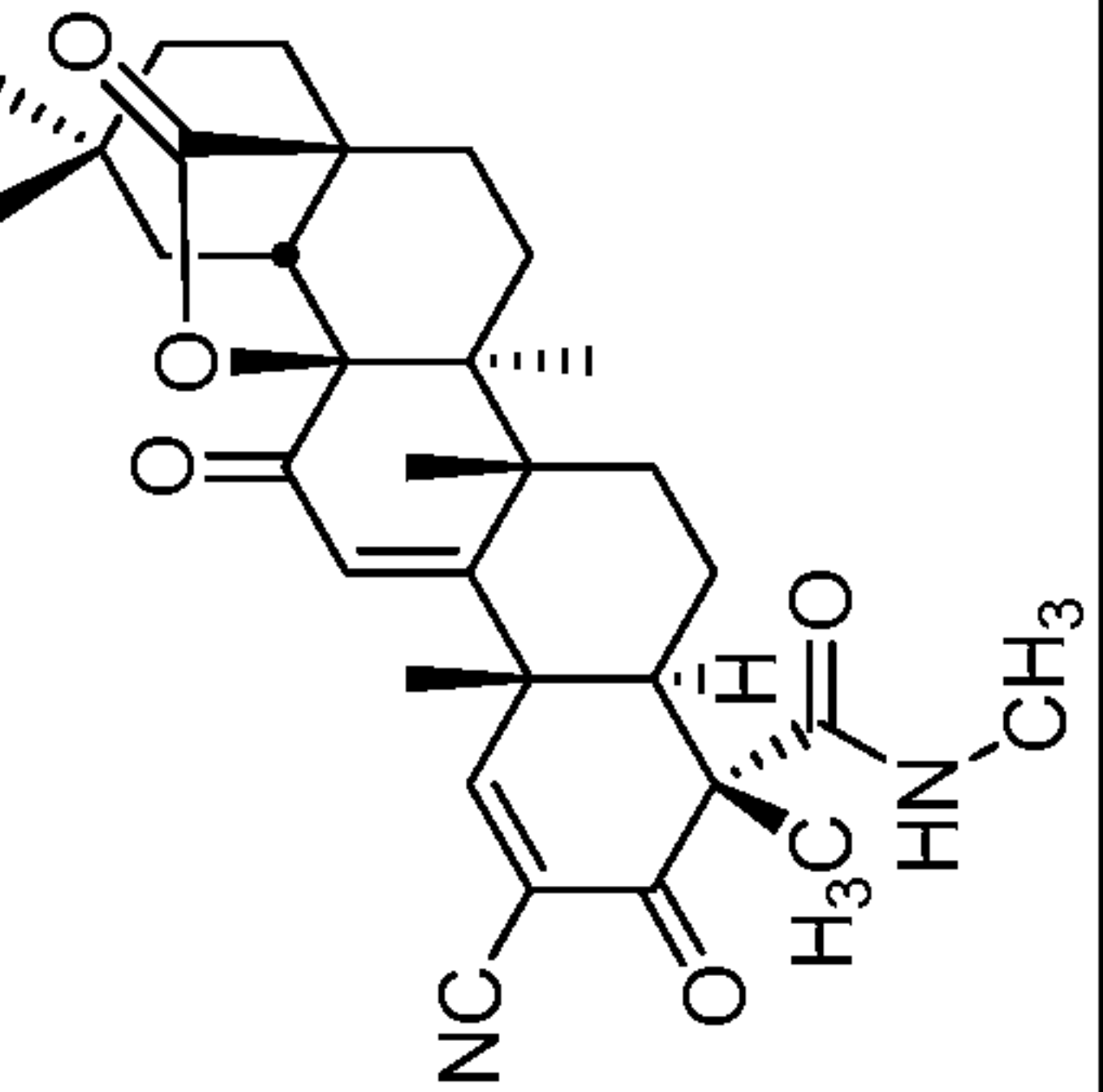
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T23		68	145	484	150.3
T24		37	197	406	184.4
Comparison Compound #3		81	204	32	3.4

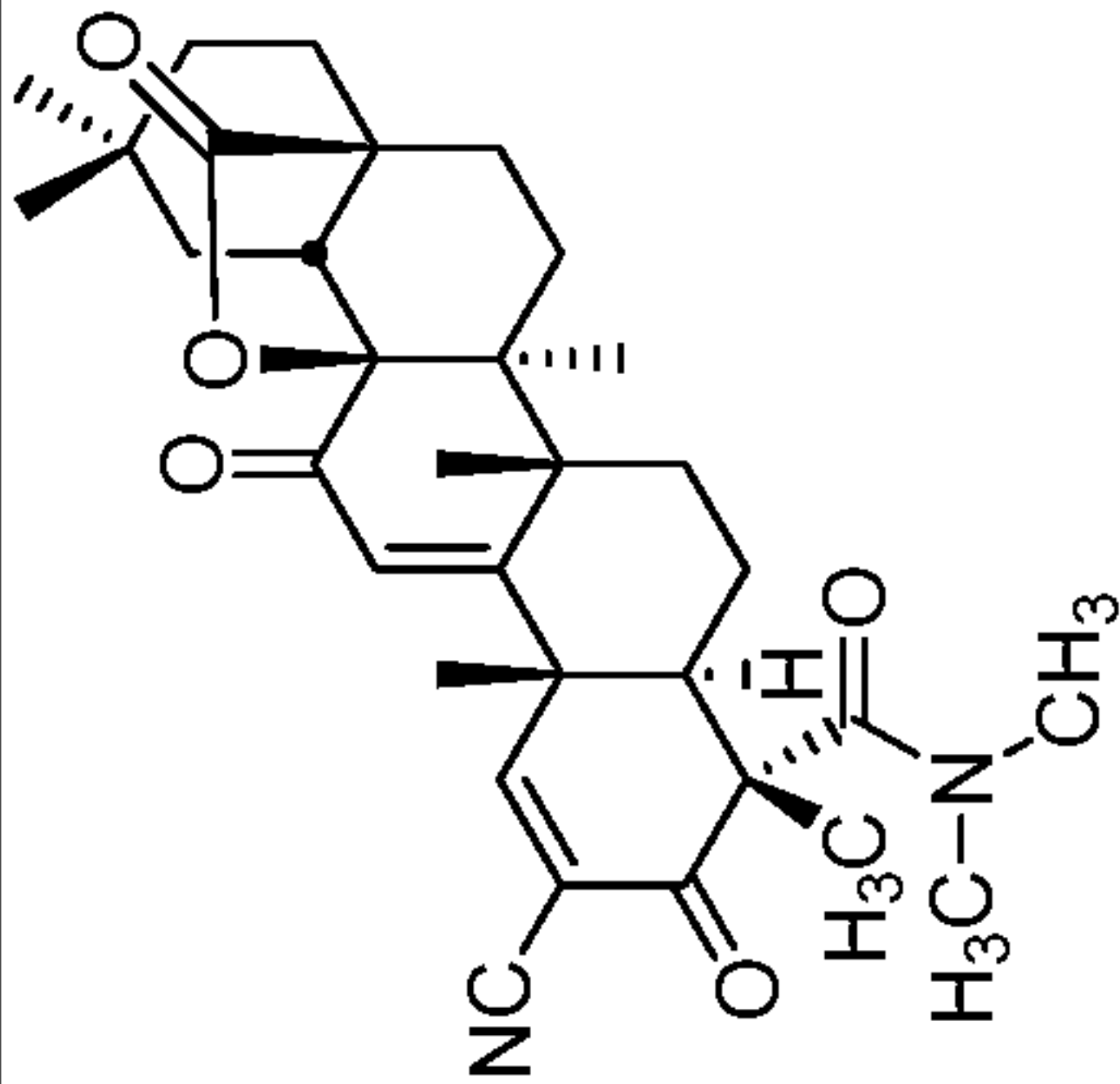
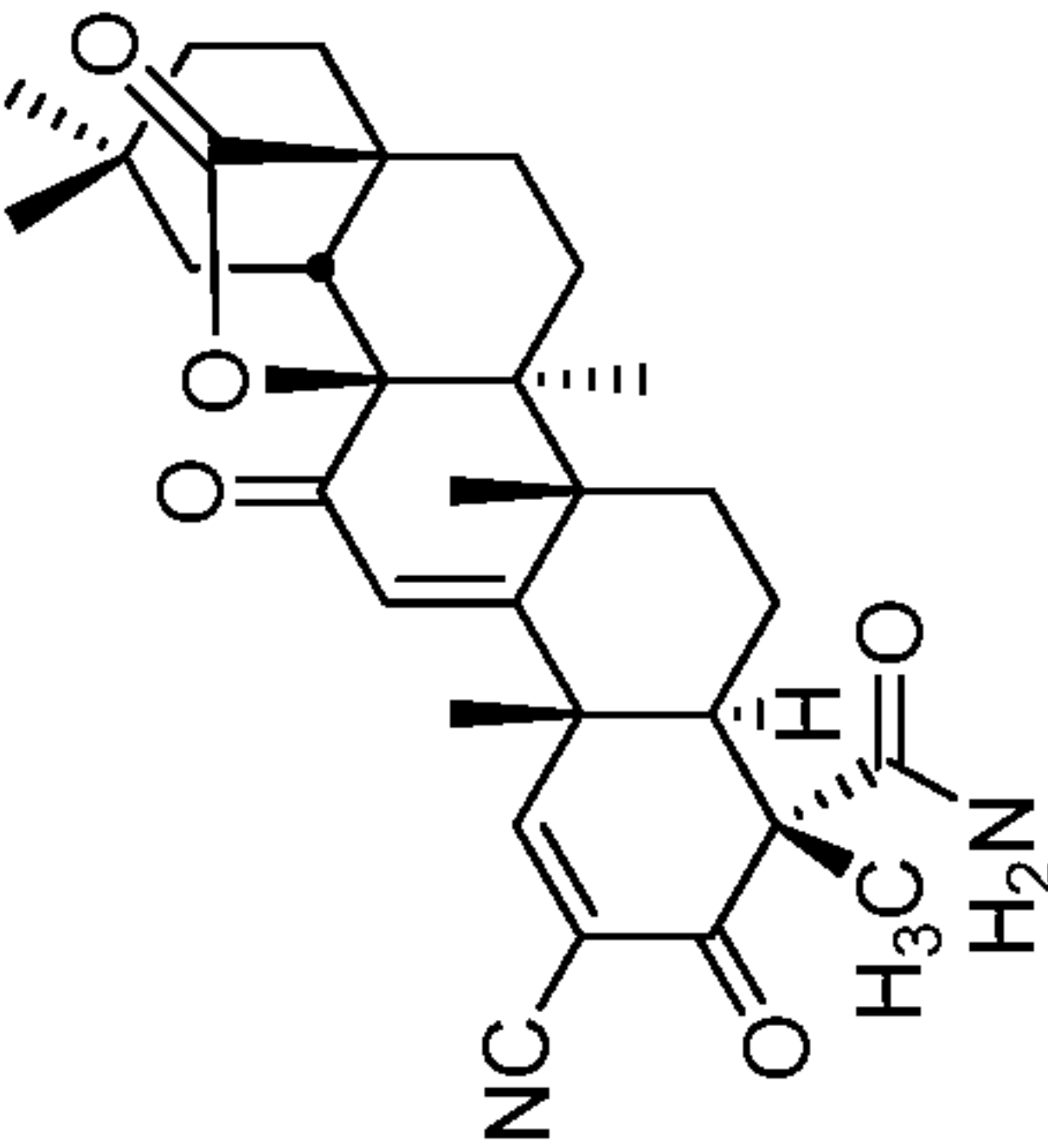
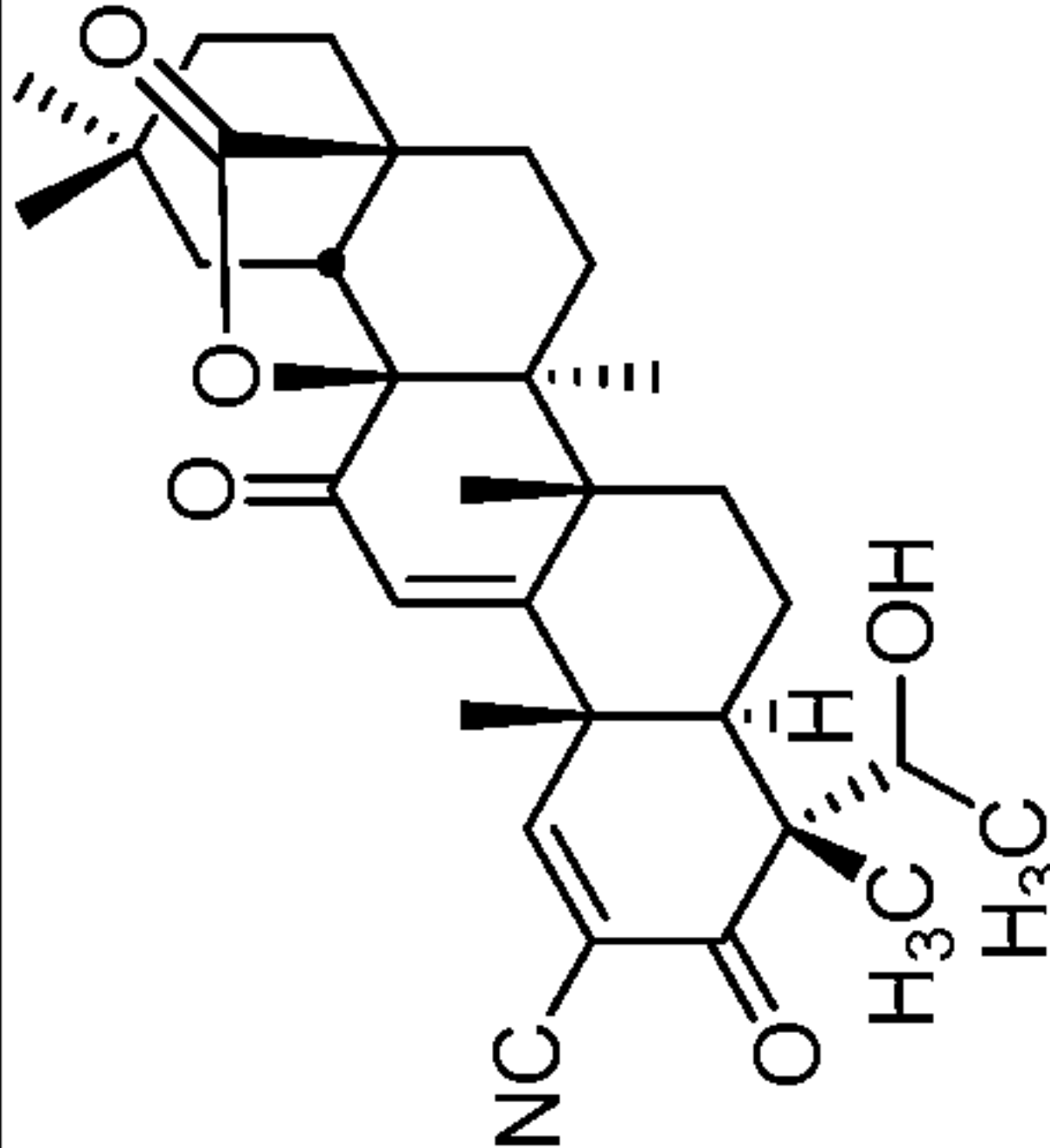
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T25		67	536	131	16.0
T26		132	292	463	370.0
Comparison Compound #4		38	177	11	0.6

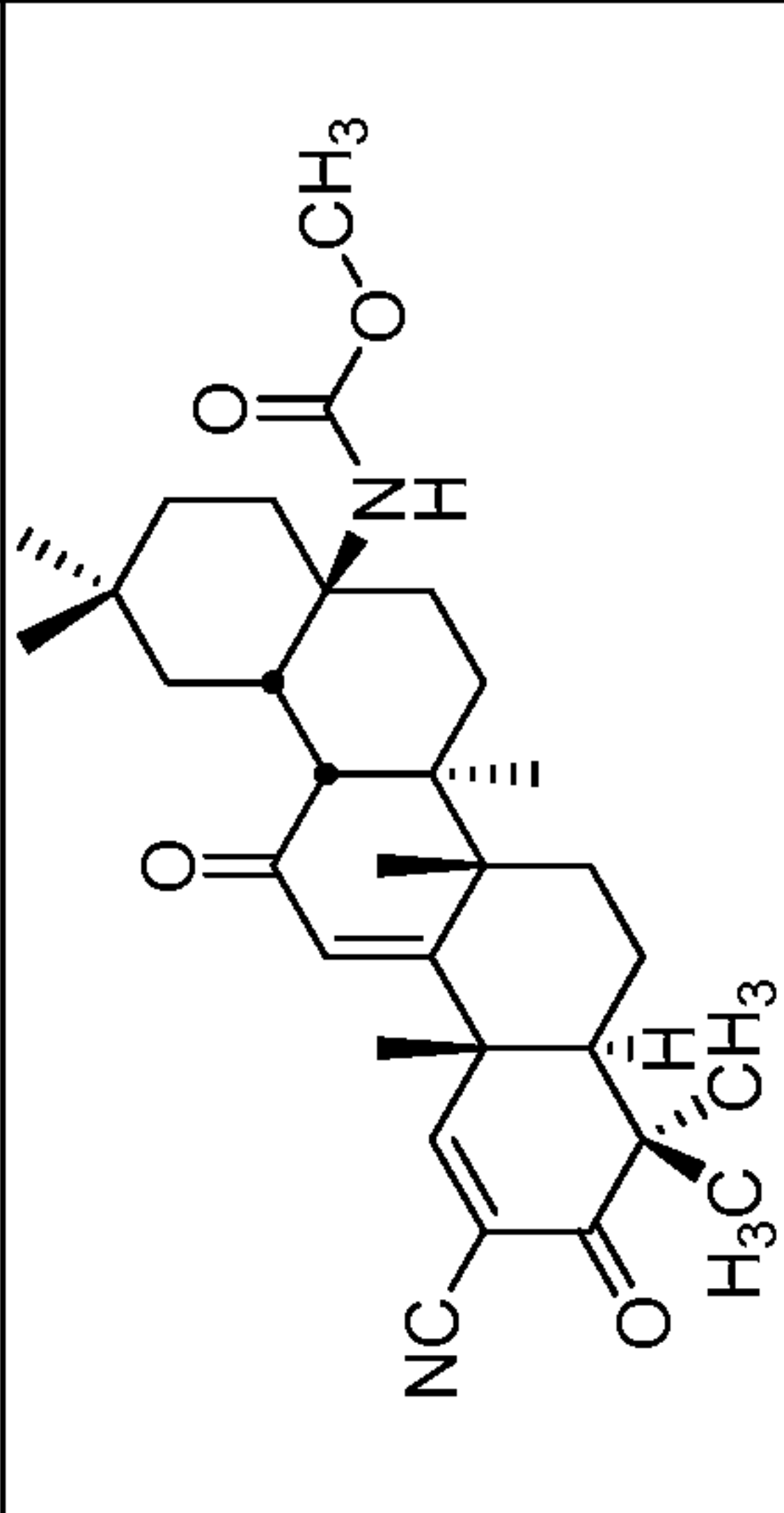
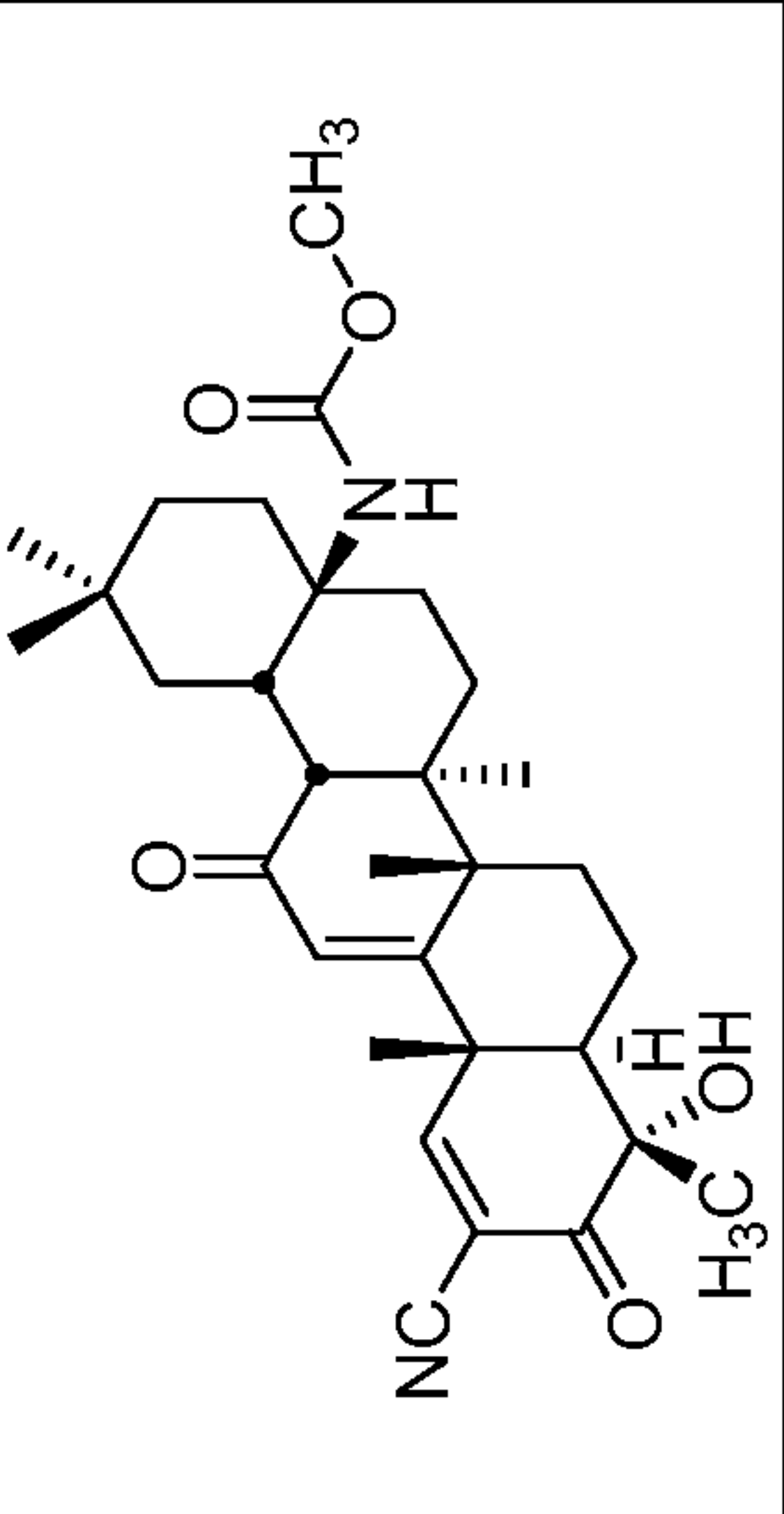
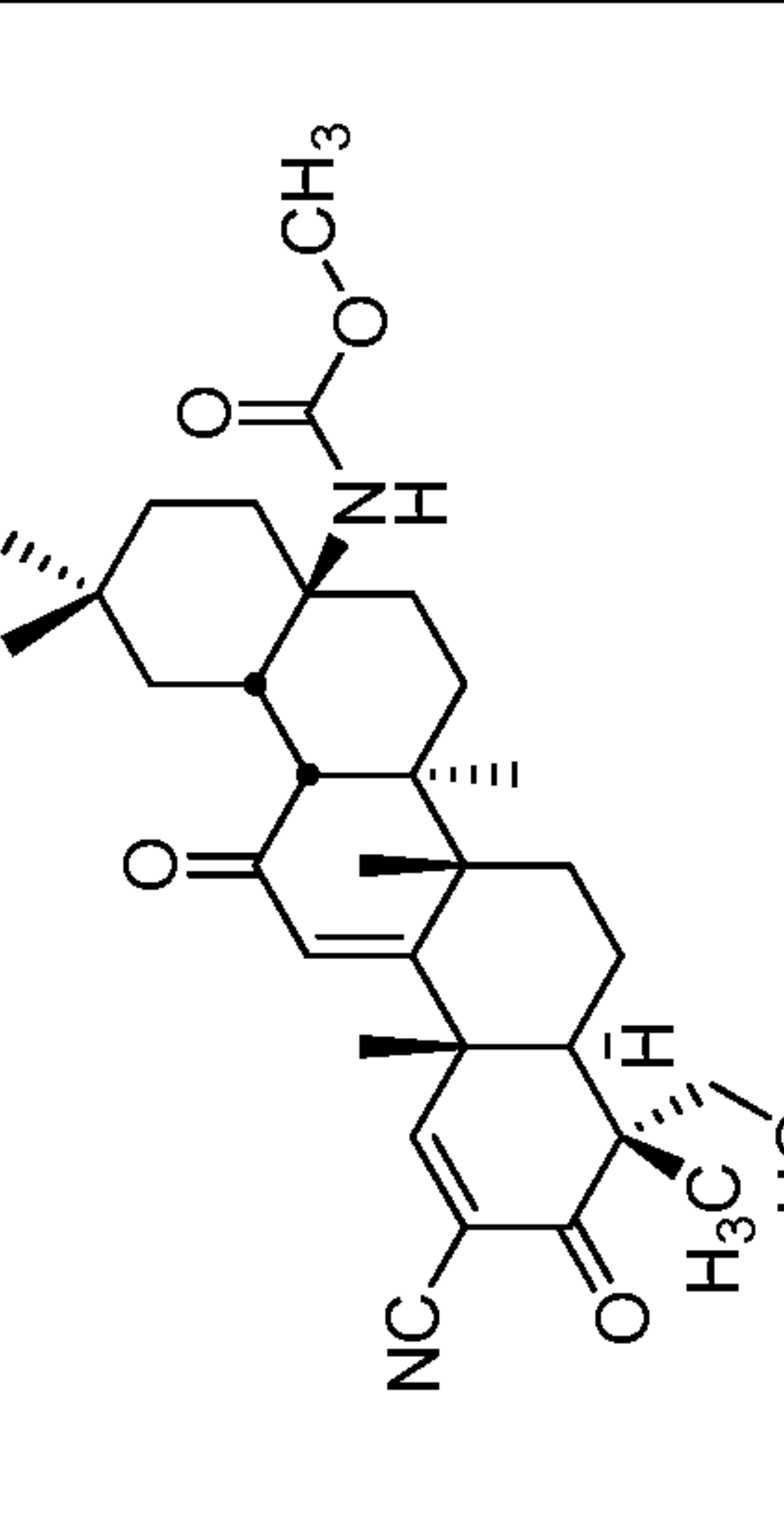
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T27		62	410	396	145.8
T28		67	463	117	21.1
T29		37	141	360	118.3

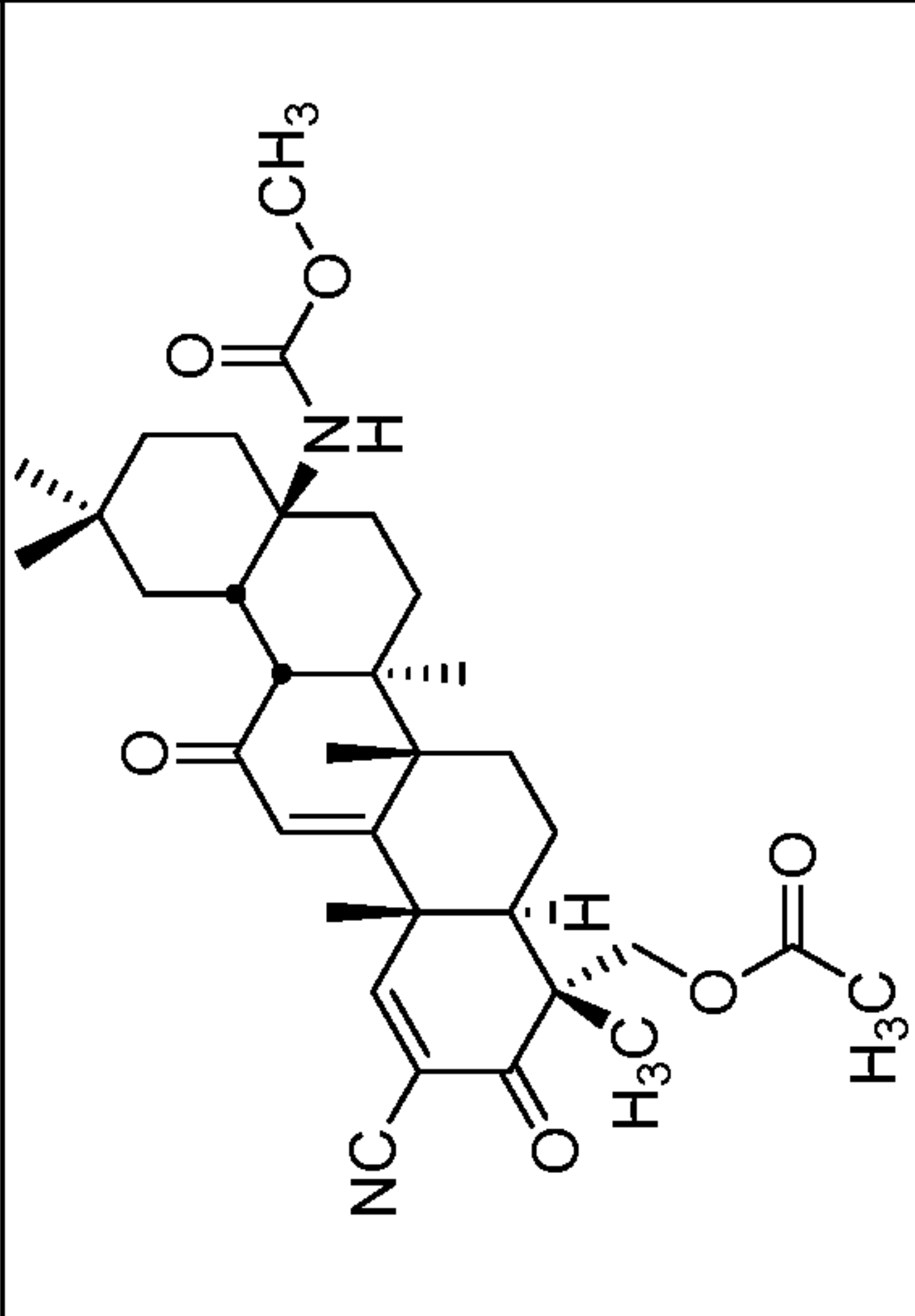
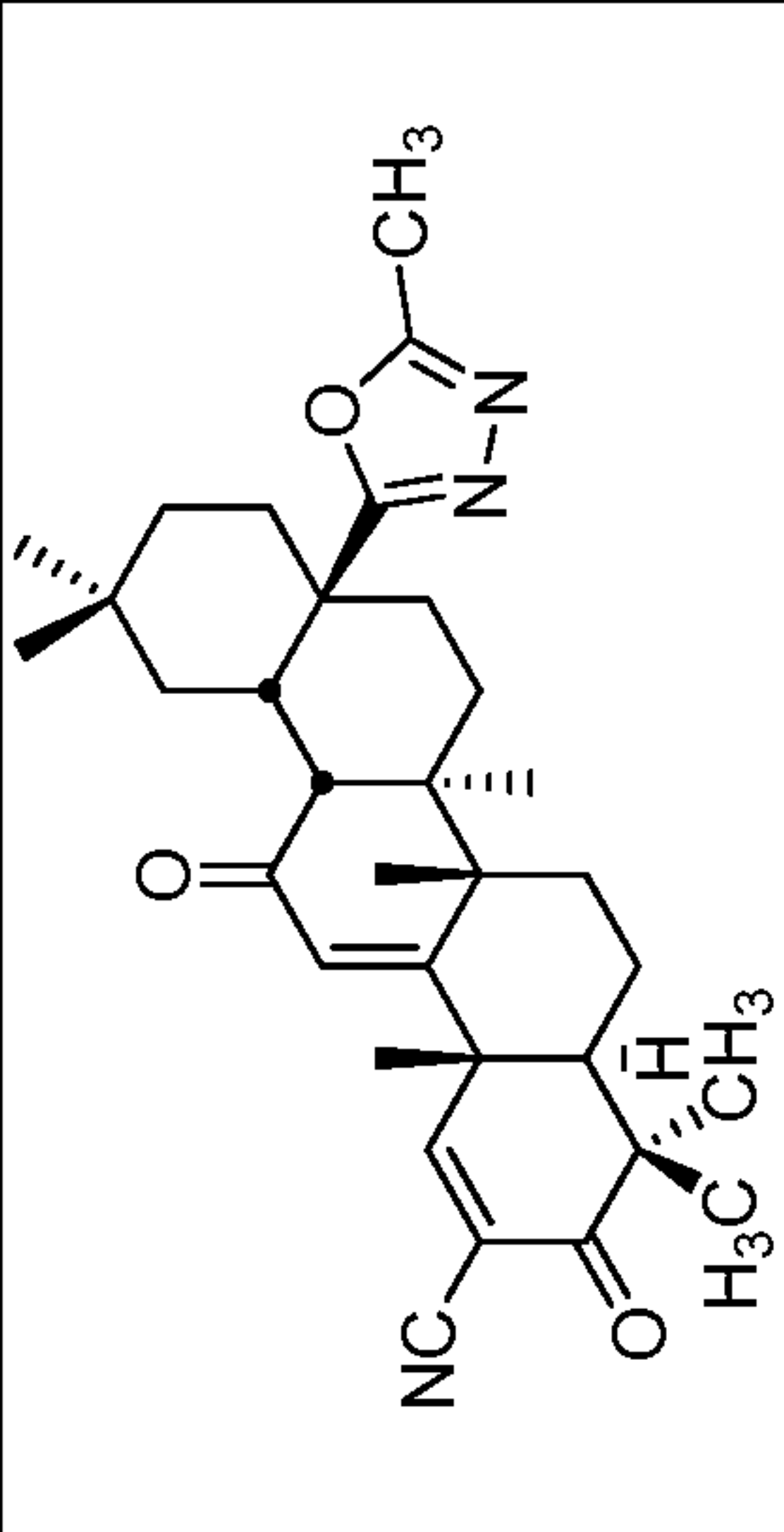
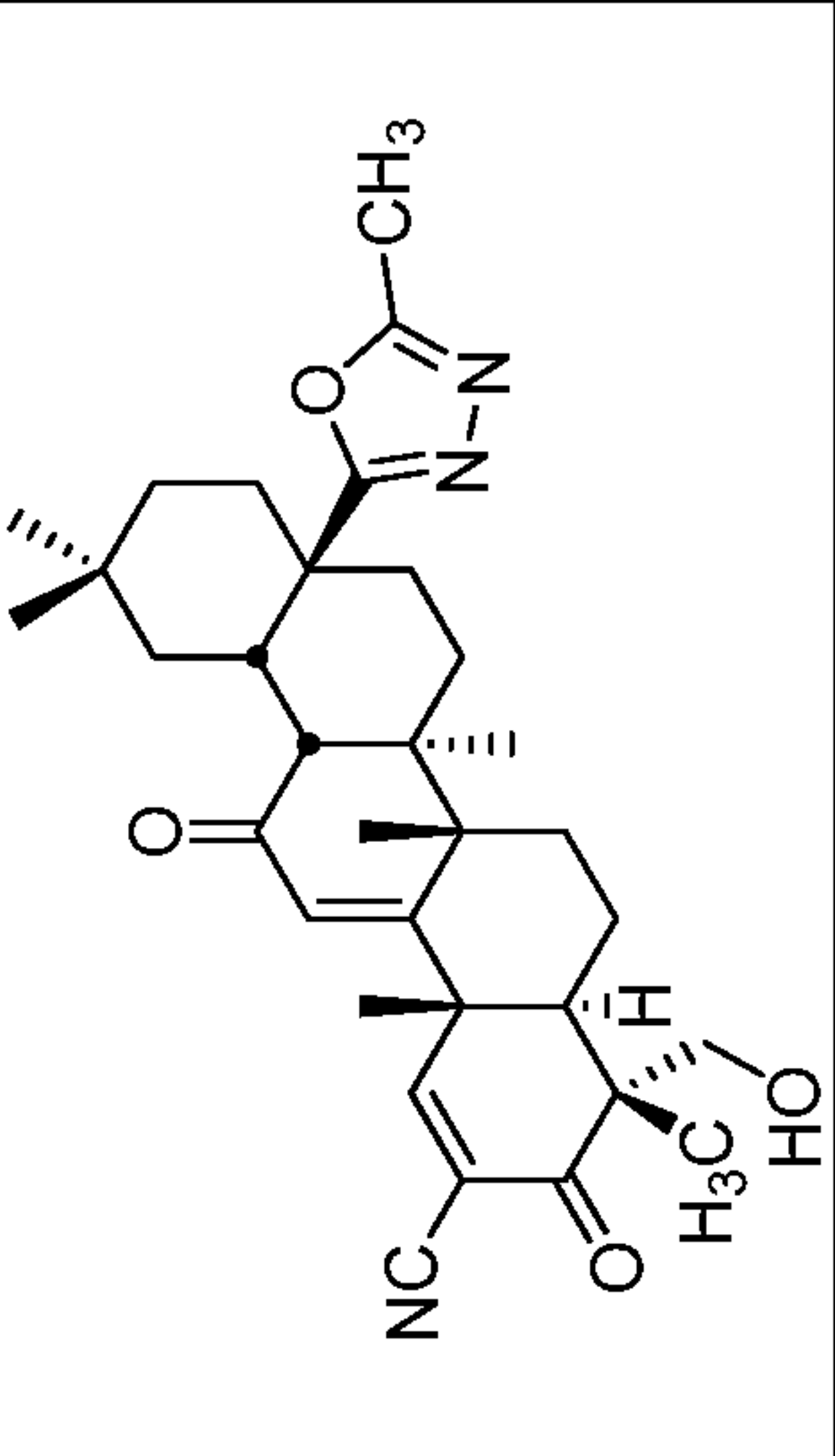
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Comparison Compound #5		15	135	2	1.6
T38		16	177	80	57.2
T30		59	164	448	173.0

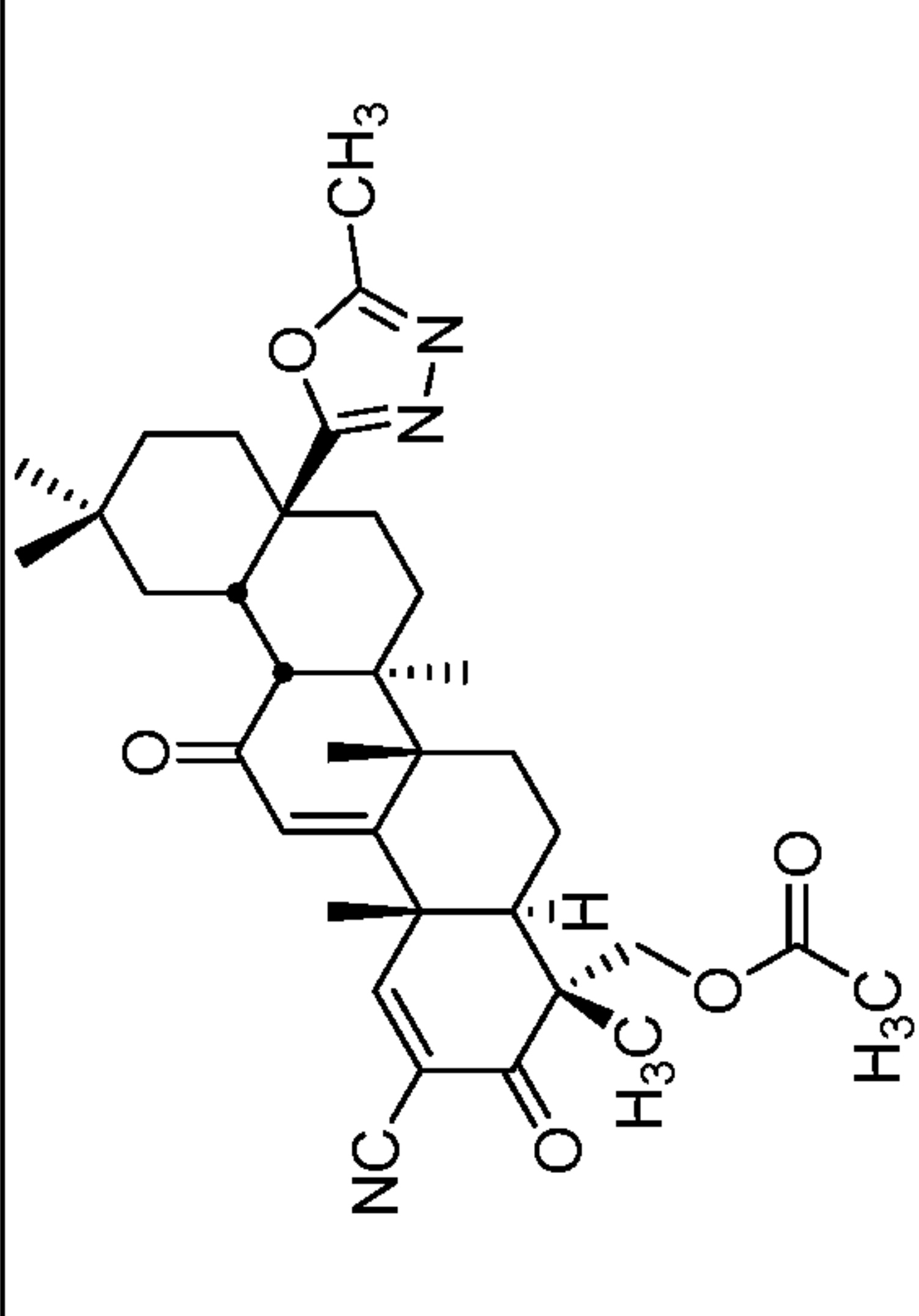
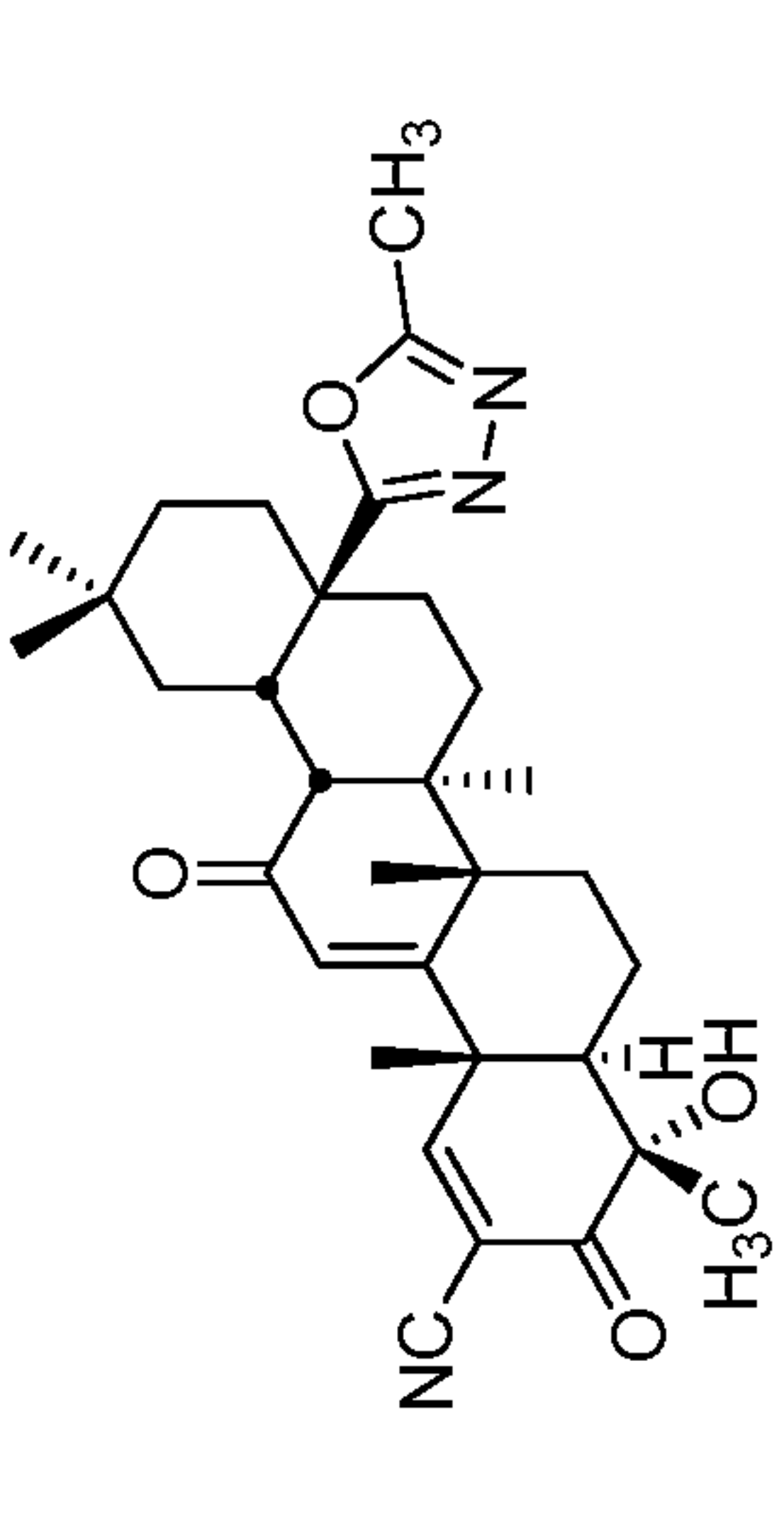
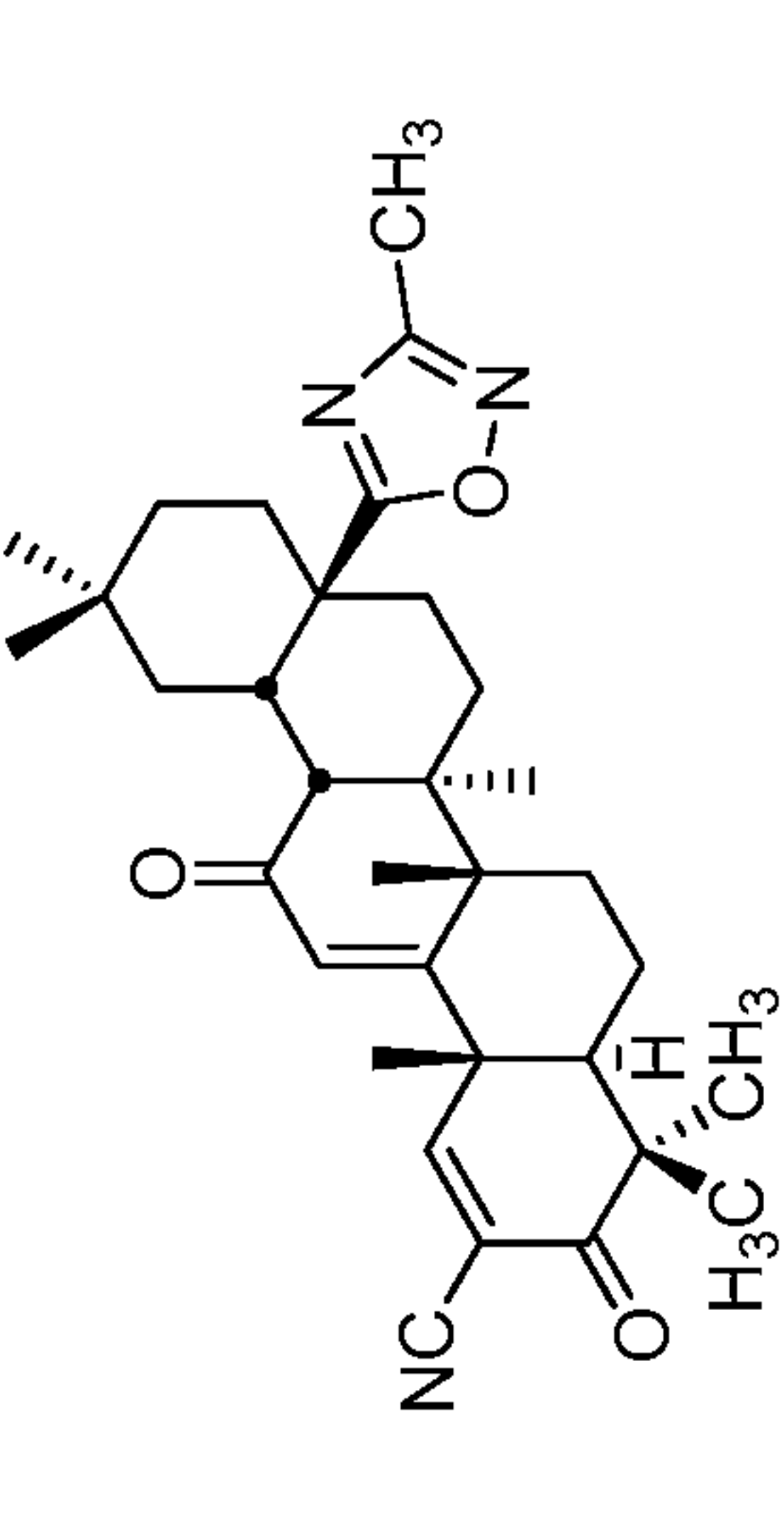
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
Comparison Compound #6		15	159	2	0.7
T31		20	177	21	10.5
T32		28	118	243	114.6

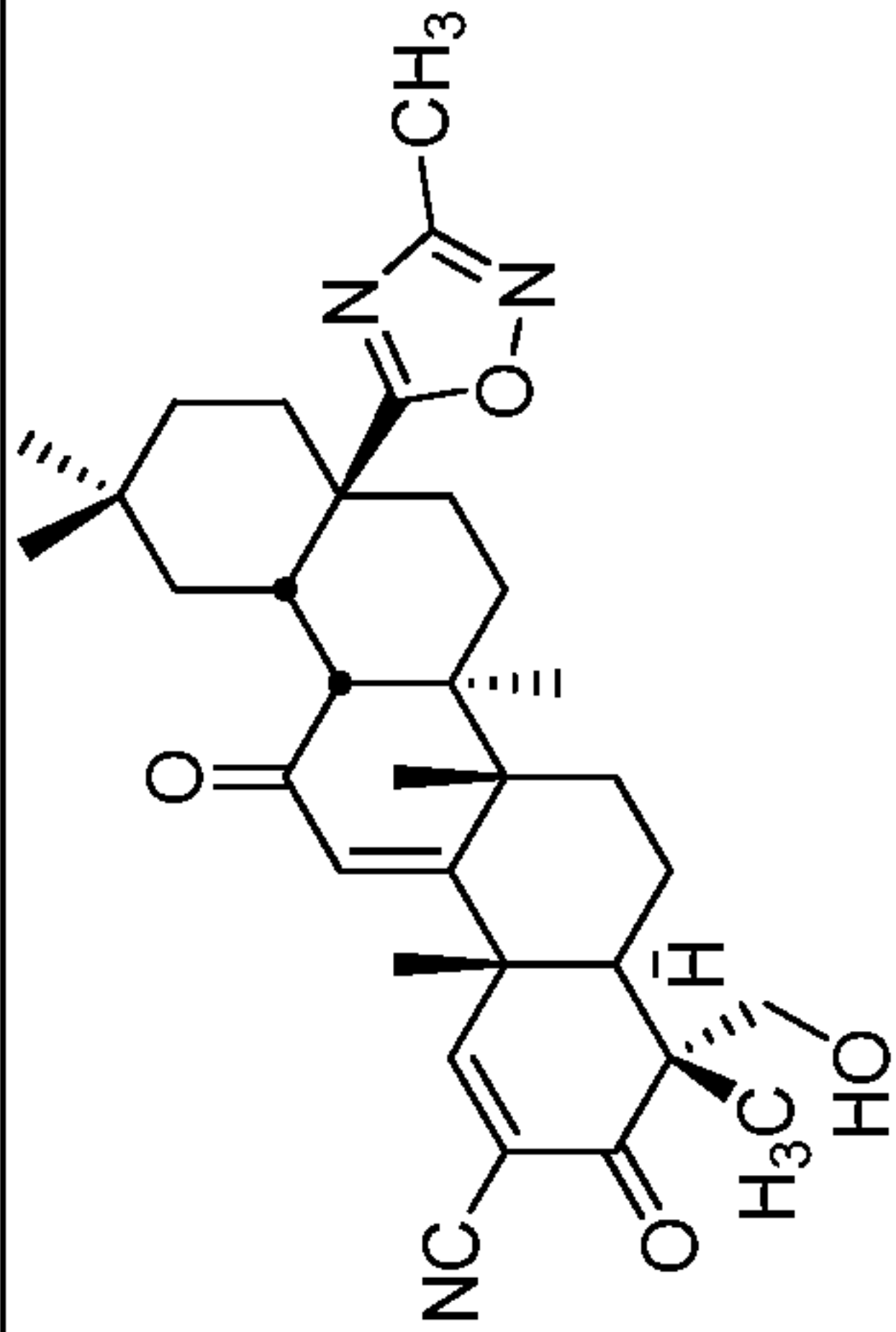
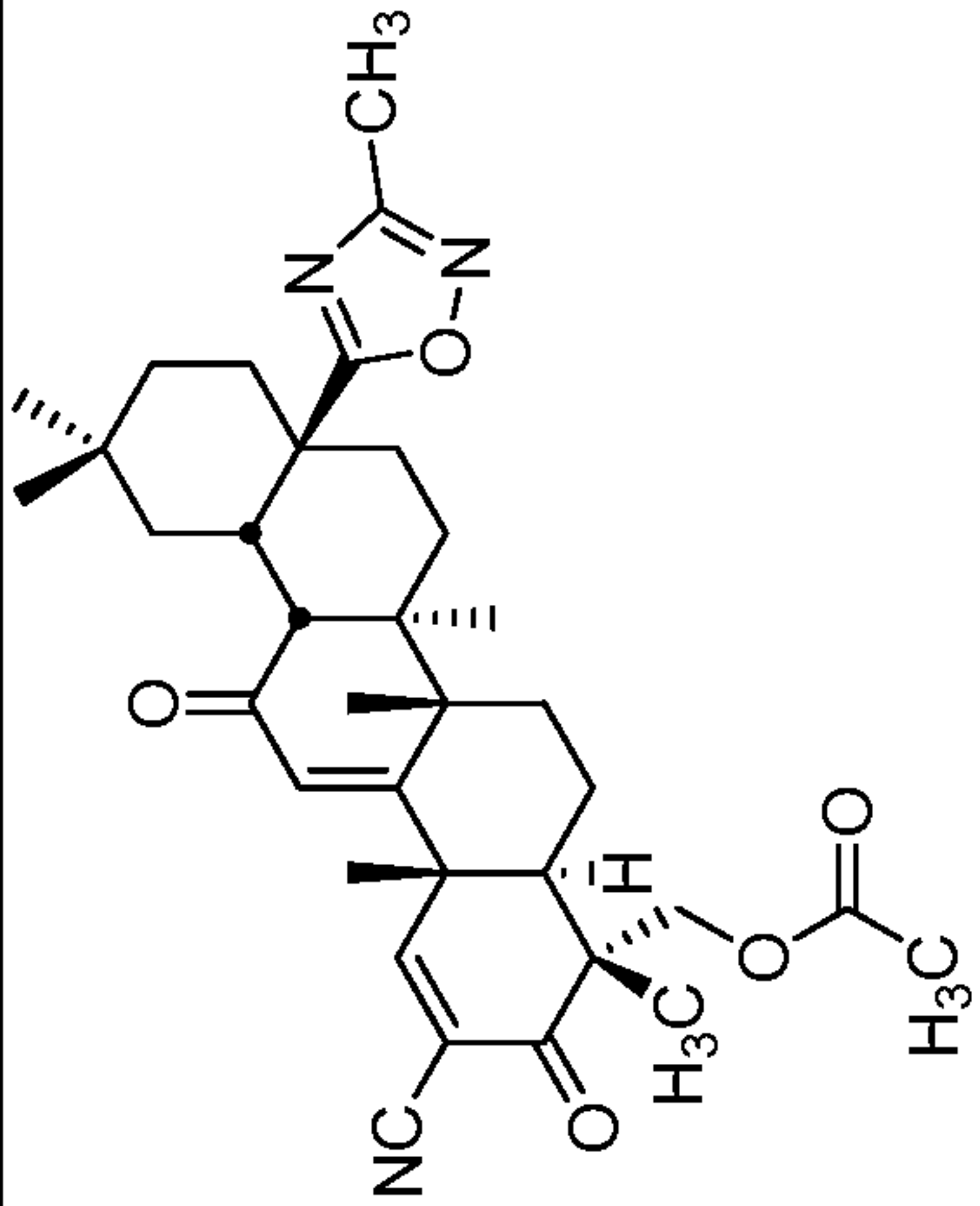
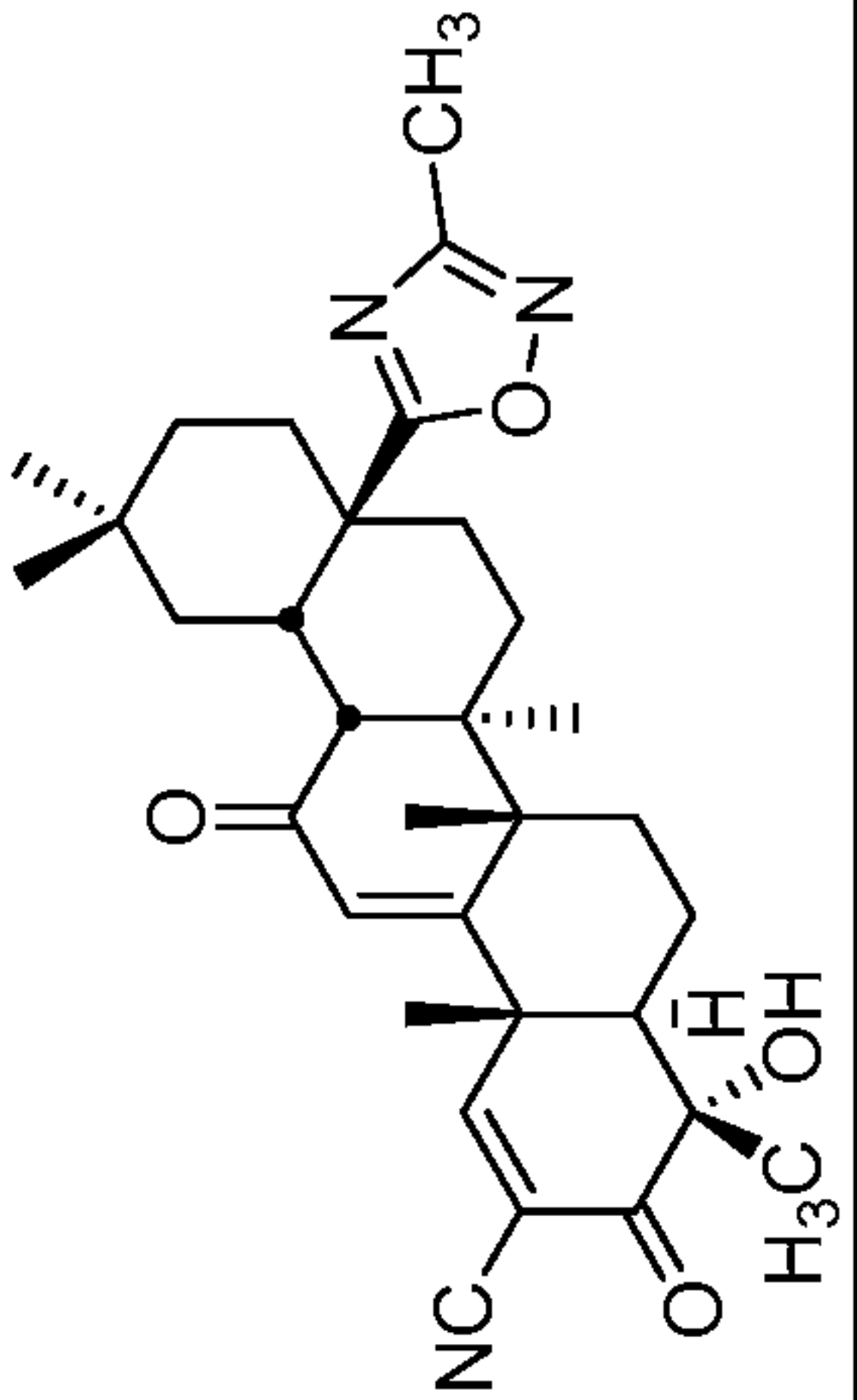
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T33		25	220	120	79.9
T34		46	268	377	382.9
T35		68	413	>1000	>1000

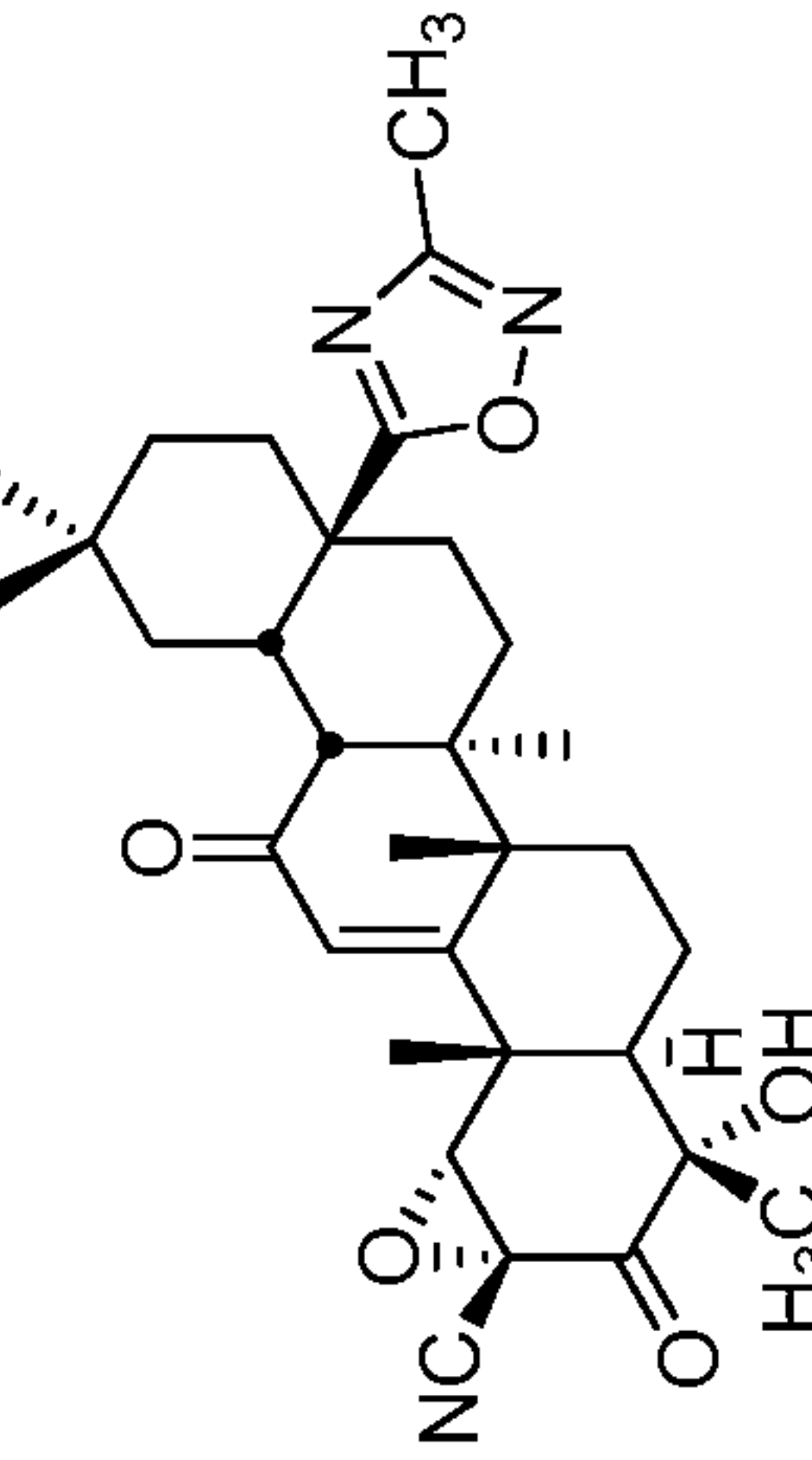
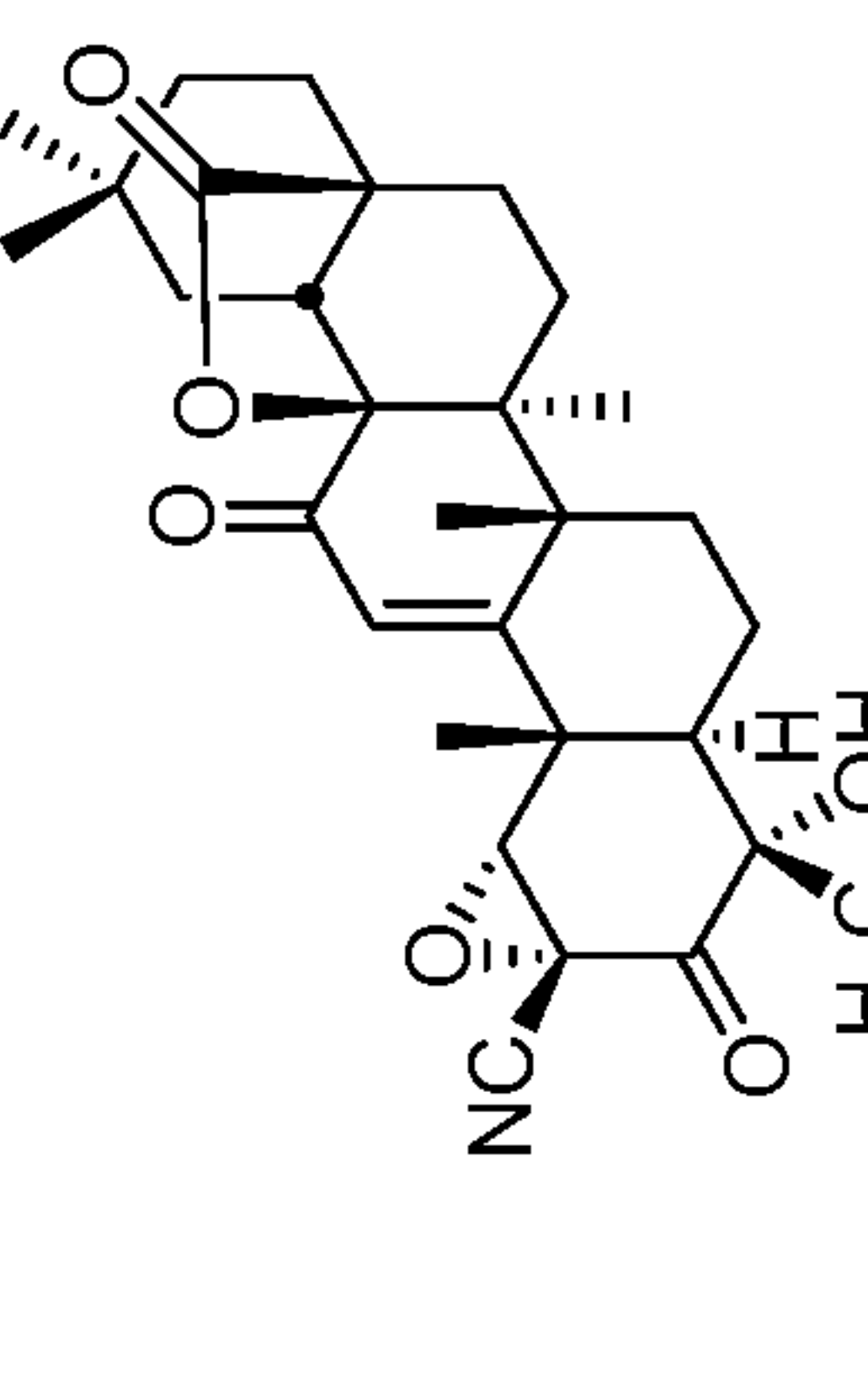
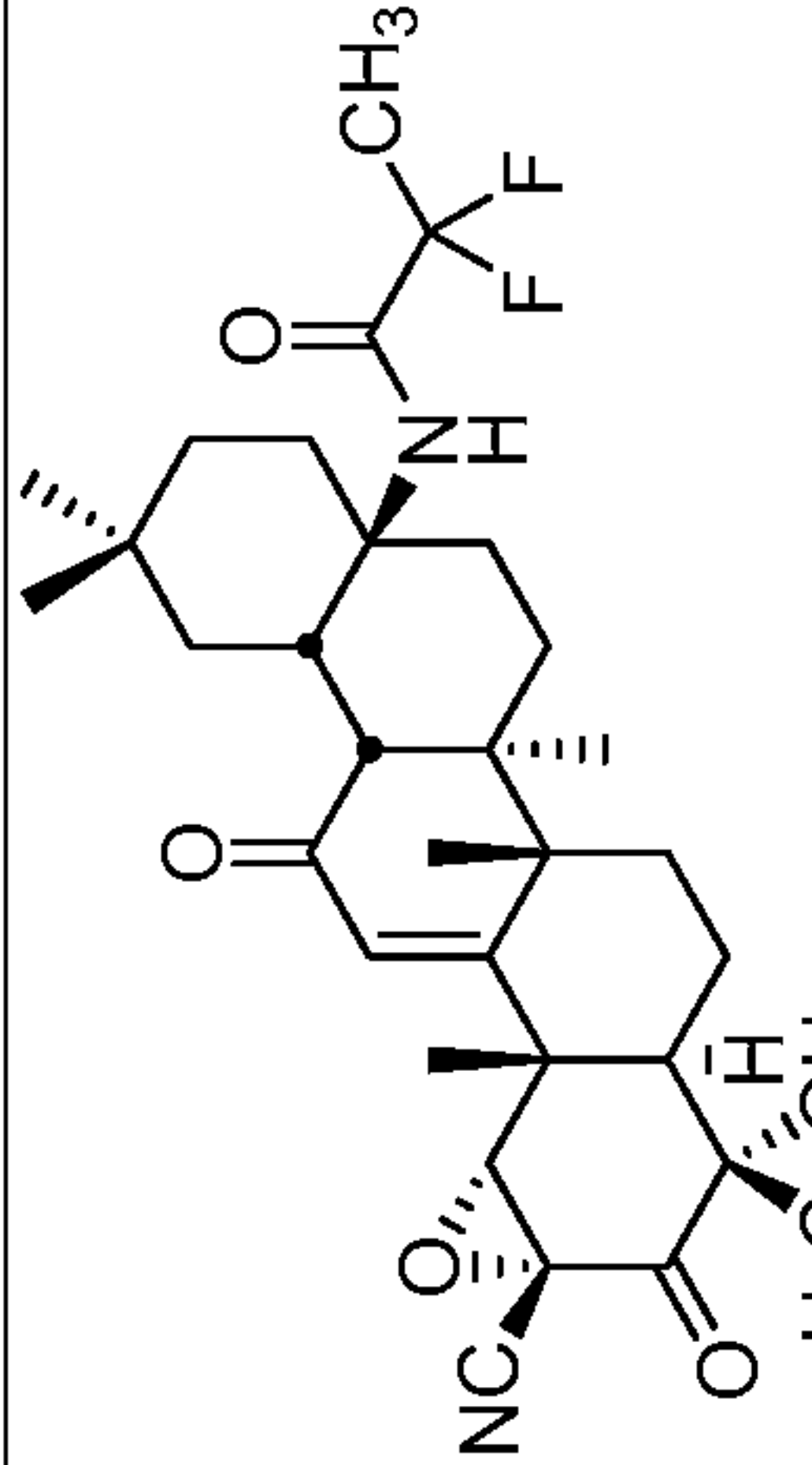
Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T36		126	533	>1000	>1000
T37		336	1354	>1000	>1000
T48		13	162	3	1.2

Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
Comparison Compound #7		27	371	20	2.4
T39		47	364	218	91.2
T40		37	698	130	24.6

Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T41		35	135	330	151.4
Comparison Compound #8		32	222	15	2.0
T42		101	389	97	10.4

Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T43		46	146	369	109.6
T44		50	236	156	72.8
Comparison Compound #9		18	176	12	1.2

Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T45		17	165	47	6.9
T46		13	115	366	100.7
T47		17	139	79	35.8

Compound ID	Structure	hIL17 IC ₅₀ (nM)	ROR γ IC ₅₀ (nM)	NRF2 ARE 2X (nM)	NO IC ₅₀ (nM)
T49		18	608	244	37.5
T50		11	1042	162	65.4
T51		139	1686	840	118.6

* * * * *

All of the compounds, compositions, and methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the disclosure may have focused on several embodiments or may have been described
5 in terms of preferred embodiments, it will be apparent to those of skill in the art that variations and modifications may be applied to the compounds, compositions, and methods without departing from the spirit, scope, and concept of the invention. All variations and modifications apparent to those skilled in the art are deemed to be within the spirit, scope, and concept of the invention as defined by the appended claims.

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The following references to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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U.S. Patent No. 7,943,778

U.S. Patent No. 8,124,799

U.S. Patent No. 8,129,429

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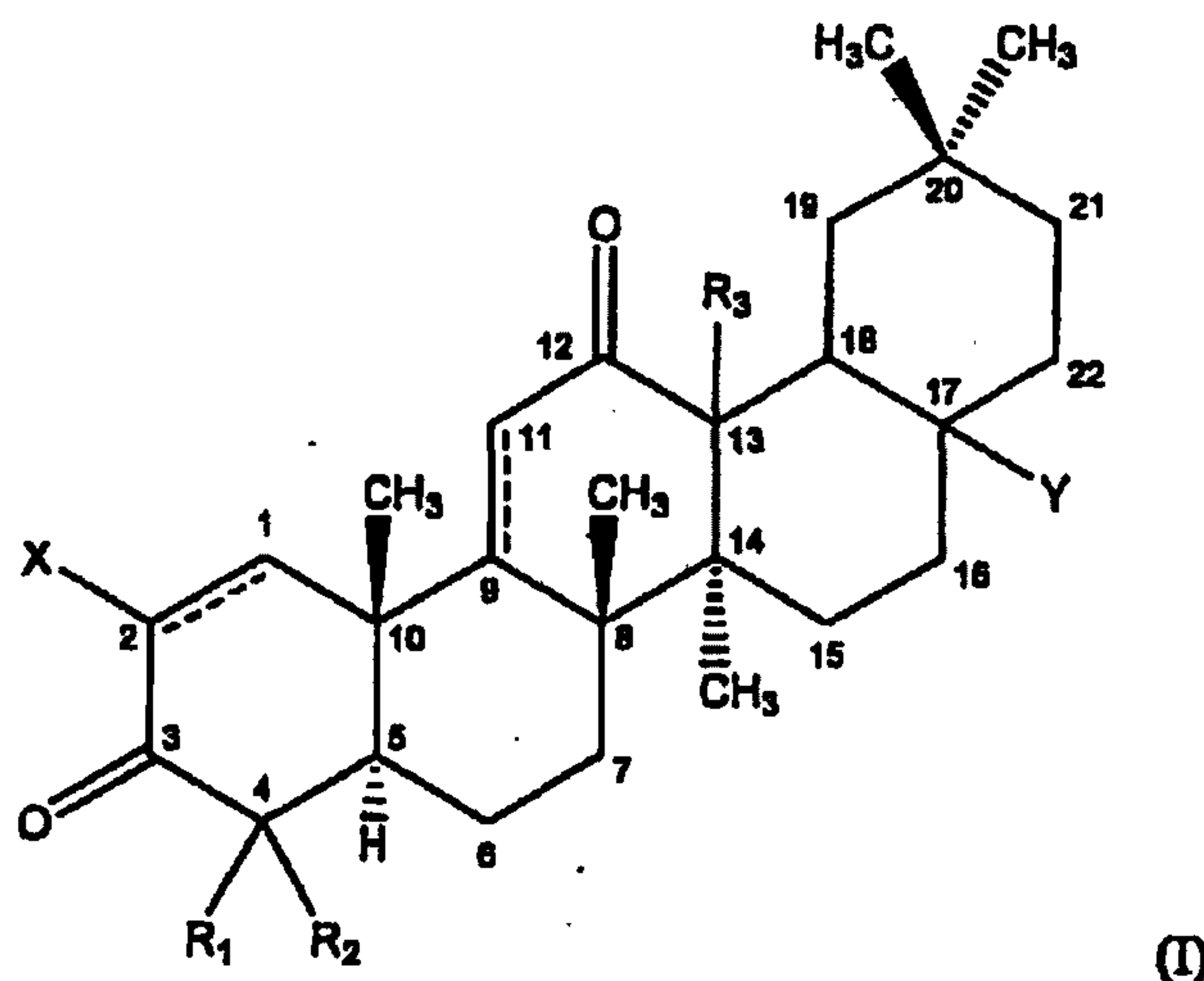
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ARTICLE 34 AMENDMENTS

1. A compound of the formula:



wherein:

the bond between atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

the bond between atoms 9 and 11 is a single bond or a double bond;

X is cyano, heteroaryl_(C₁₋₈), substituted heteroaryl_(C₁₋₈), -CF₃, or -C(O)-R₄; wherein

R₄ is hydroxy, amino, or alkoxy_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), alkylsulfonylamino_(C₁₋₈), or a substituted version of any of these groups;

R₁ is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R₃ is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

wherein variables R₂ and Y are defined according to either Group A or B, wherein for Group A:

R₂ is amino, cyano, halo, or hydroxy, substituted alkyl_(C₁₋₈), substituted cycloalkyl_(C₃₋₈), heteroaryl_(C₁₋₈), substituted heteroaryl_(C₁₋₈), acyl_(C₁₋₈), substituted acyl_(C₁₋₈),

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amido_(C₁₋₈), substituted amido_(C₁₋₈), alkylamino_(C₁₋₈), substituted alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), or dialkylamino_(C₁₋₈);

-OR₄, wherein:

R₄ is hydrogen or alkyl_(C₁₋₈), alkenyl_(C₁₋₈), alkynyl_(C₁₋₈), aryl_(C₁₋₁₂), aralkyl_(C₁₋₁₂), heteroaryl_(C₁₋₁₂), heterocycloalkyl_(C₁₋₈), acyl_(C₁₋₈), or a substituted version of any of these groups;

-(CH₂)_m-(OCH₂)_n-R₅, wherein:

R₅ is hydroxy or acyl_(C₁₋₈), alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or a substituted version of any of these groups;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

-(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

R_{5'} is hydrogen, alkyl_(C₁₋₈), alkoxy_(C₁₋₈), substituted alkoxy_(C₁₋₈), acyl_(C₁₋₈), substituted acyl_(C₁₋₈), -C(O)-alkoxy_(C₁₋₈), substituted -C(O)-alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), substituted acyloxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or substituted alkylsilyloxy_(C₁₋₈); and

R₆ is hydrogen, alkyl_(C₁₋₈), or substituted alkyl_(C₁₋₈); or

-(CH₂)_q-C(O)-R_{5''}, wherein:

R_{5''} is amino, hydroxy, or mercapto; or

alkoxy_(C₁₋₈), alkylthio_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C₁₋₈), cycloalkyl_(C₁₋₈), alkenyl_(C₁₋₈), alkynyl_(C₁₋₈), aryl_(C₁₋₁₂), heteroaryl_(C₁₋₈), heterocycloalkyl_(C₁₋₁₂), alkoxy_(C₁₋₈), cycloalkoxy_(C₁₋₈), aryloxy_(C₁₋₁₂), acyloxy_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), alkenylamino_(C₁₋₈), arylamino_(C₁₋₈), aralkylamino_(C₁₋₈), alkylthio_(C₁₋₈), acylthio_(C₁₋₈), alkylsulfonylamino_(C₁₋₈), or substituted versions of any of these groups;

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-alkanediyl_(CS)-R_b, -alkenediyl_(CS)-R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or
 aryl_(CS), heteroaryl_(CS), alkoxy_(CS), cycloalkoxy_(CS),
 alkenyloxy_(CS), aryloxy_(CS), aralkoxy_(CS), hetero-
 aryloxy_(CS), acyloxy_(CS), alkylamino_(CS), dialkyl-
 amino_(CS), alkenylamino_(CS), arylamino_(CS), aralkyl-
 amino_(CS), heteroarylamino_(CS), alkylsulfonyl-
 amino_(CS), amido_(CS), -OC(O)NH-alkyl_(CS),
 -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio_(CS),
 or a substituted version of any of these groups;

-(CH₂)_pC(O)R_c, wherein p is 0-6 and R_c is:

hydrogen, halo, amino, -NHOH, or mercapto; or
 alkyl_(CS), cycloalkyl_(CS), alkenyl_(CS), alkynyl_(CS),
 aryl_(CS), aralkyl_(CS), heteroaryl_(CS), hetero-
 cycloalkyl_(CS), alkylamino_(CS), dialkyl-
 amino_(CS), arylamino_(CS), alkylsulfonyl-
 amino_(CS), amido_(CS), alkoxyamino_(CS), hetero-
 cycloalkylamino_(CS), -NHC(NOH)-alkyl_(CS),
 -NH-amido_(CS), or a substituted version of any
 of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(CS), or substituted alkyl_(CS);

R_e is hydrogen, hydroxy, amino; or

alkyl_(CS), cycloalkyl_(CS), alkenyl_(CS), alkynyl_(CS), aryl_(CS),
 aralkyl_(CS), heteroaryl_(CS), heterocycloalkyl_(CS),
 alkoxy_(CS), cycloalkoxy_(CS), aryloxy_(CS), aralkoxy_(CS),
 heteroaryloxy_(CS), acyloxy_(CS), alkylamino_(CS),
 dialkylamino_(CS), arylamino_(CS), or a substituted version
 of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

p is 0-6; and

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R_1 is $-O-$ or $-NR_7-$; wherein:

R_7 is hydrogen, alkyl($C_{\leq 8}$), substituted alkyl($C_{\leq 8}$), acyl($C_{\leq 8}$), or substituted acyl($C_{\leq 8}$); or

for Group B:

R_2 is amino, cyano, halo, or hydroxy,

haloalkyl($C_{\leq 8}$), substituted cycloalkyl($C_{\leq 8}$), heteroaryl($C_{\leq 8}$), substituted heteroaryl($C_{\leq 8}$), acyl($C_{\leq 8}$), substituted acyl($C_{\leq 8}$), amido($C_{\leq 8}$), substituted amido($C_{\leq 8}$), alkylamino($C_{\leq 8}$), substituted alkylamino($C_{\leq 8}$), or dialkylamino($C_{\leq 8}$); or

$-OR_8$, wherein:

R_8 is hydrogen or alkyl($C_{\leq 8}$), alkenyl($C_{\leq 8}$), alkynyl($C_{\leq 8}$), aryl($C_{\leq 12}$), aralkyl($C_{\leq 12}$), heteroaryl($C_{\leq 12}$), heterocycloalkyl($C_{\leq 8}$), acyl($C_{\leq 8}$), or a substituted version of any of these groups;

$-(CH_2)_m-R_5'''$, wherein:

R_5''' is alkoxy($C_{\leq 8}$), acyloxy($C_{\leq 8}$), substituted alkoxy($C_{\leq 8}$), substituted acyloxy($C_{\leq 8}$), alkylsilyloxy($C_{\leq 8}$), or substituted alkylsilyloxy($C_{\leq 8}$); and

m is 0, 1, 2, 3, or 4;

$-(CH_2)_{m2}-R_5'''$, wherein:

R_5''' is hydroxy; and

m_2 is 2, 3, or 4;

$-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R_5' is hydrogen, alkyl($C_{\leq 8}$), alkoxy($C_{\leq 8}$), substituted alkoxy($C_{\leq 8}$), acyl($C_{\leq 8}$), substituted acyl($C_{\leq 8}$), $-C(O)-$ alkoxy($C_{\leq 8}$), substituted $-C(O)-$ alkoxy($C_{\leq 8}$), acyloxy($C_{\leq 8}$), substituted acyloxy($C_{\leq 8}$), alkylsilyloxy($C_{\leq 8}$), or substituted alkylsilyloxy($C_{\leq 8}$); and

R_6 is hydrogen, alkyl($C_{\leq 8}$), or substituted alkyl($C_{\leq 8}$); or

$-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy($C_{\leq 8}$), alkylthio($C_{\leq 8}$), alkylamino($C_{\leq 8}$), dialkylamino($C_{\leq 8}$), or a substituted version of any of these groups; and

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q is 0, 1, 2, 3, or 4; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

alkoxy_(C₁₋₈), cycloalkoxy_(C₃₋₈), alkenyloxy_(C₂₋₈), aryloxy_(C₁₋₈), aralkoxy_(C₁₋₈),

heteroaryloxy_(C₁₋₈), acyloxy_(C₁₋₈), or a substituted version of any

of these groups;

wherein when the terms alkyl, alkanediyl, alkylidene, cycloalkyl, cycloalkanediyl,

alkenyl, alkenediyl, alkynyl, aryl, arenediyl, aralkyl, heteroaryl,

heterocycloalkyl, acyl, thioacyl, alkoxy, cycloalkoxy, alkenyloxy, alkynyloxy,

aryloxy, aralkoxy, heteroaryloxy, heterocycloalkoxy, acyloxy, alkylthio,

acylthio, alkylamino, dialkylamino, cycloalkylamino, alkenylamino,

alkynylamino, arylamino, aralkylamino, heteroarylamino,

heterocycloalkylamino, alkoxyamino, alkylsulfonylamino, amido, and

alkylimino are used with the substituted modifier, one or more hydrogen atom

has been independently replaced by -OH, -F, -Cl, -Br, -I, -NH₂, -NO₂,

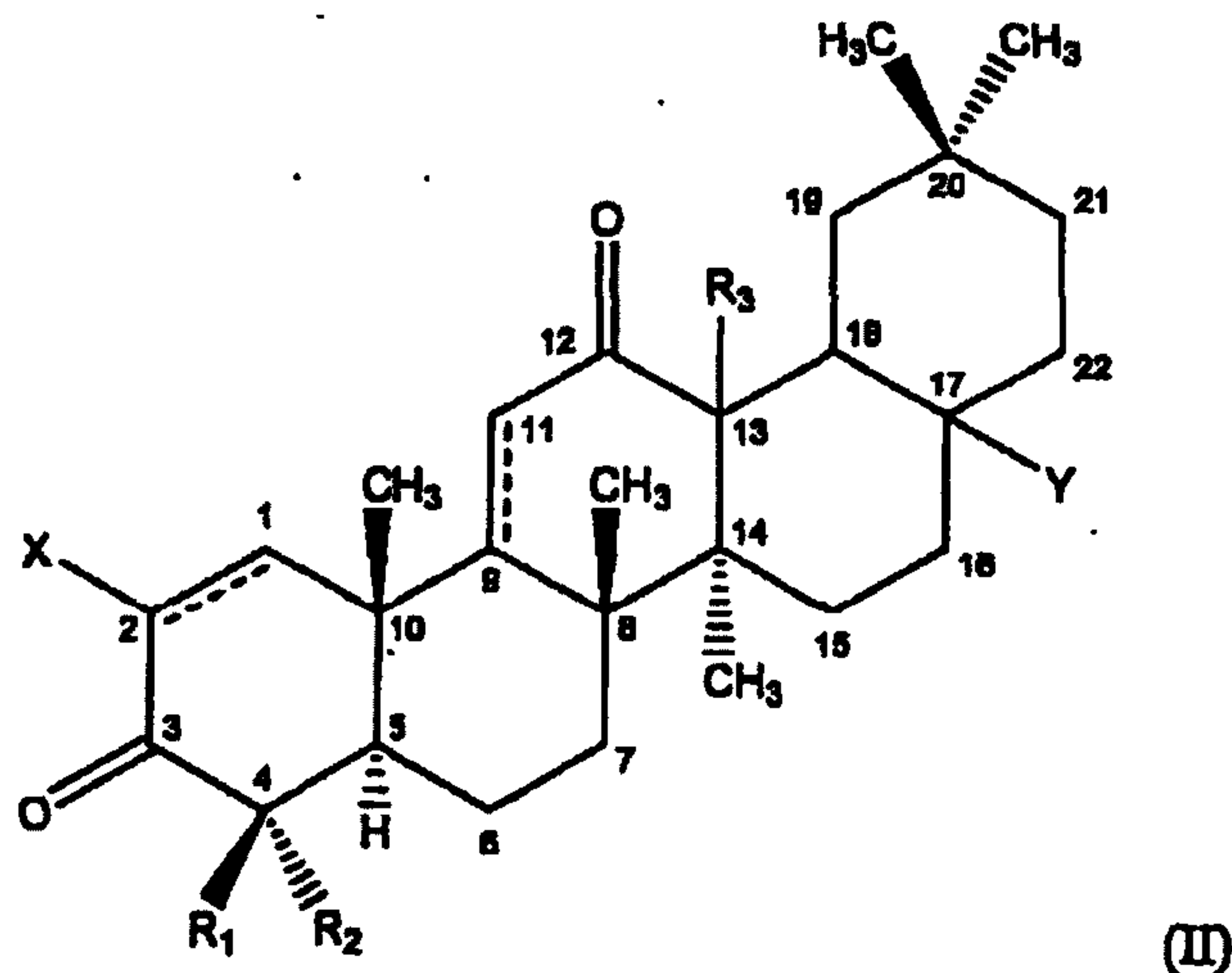
-CO₂H, -CO₂CH₃, -CN, -SH, -OCH₃, -OCH₂CH₃, -C(O)CH₃, -NHCH₃,

-NHCH₂CH₃, -N(CH₃)₂, -C(O)NH₂, -C(O)NHCH₃, -C(O)N(CH₃)₂,

-OC(O)CH₃, -NHC(O)CH₃, -S(O)₂OH or -S(O)₂NH₂;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

2. The compound of claim 1 further defined as:



wherein:

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the bond between atoms 1 and 2 is a single bond, an epoxidized double bond,
or a double bond;

the bond between atoms 9 and 11 is a single bond or a double bond;

X is cyano, heteroaryl_(C≤8), substituted heteroaryl_(C≤8), -CF₃, or -C(O)-R₄;

wherein

R₄ is hydroxy, amino, or alkoxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
alkylsulfonylamino_(C≤8), or a substituted version of any of these
groups;

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted
cycloalkyl_(C≤8);

R₂ is amino,

heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8), substituted acyl_(C≤8),
amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8), substituted
alkylamino_(C≤8), dialkylamine_(C≤8), or dialkylamino_(C≤8);

-OR_a, wherein:

R_a is hydrogen or alkyl_(C≤8), acyl_(C≤8), or a substituted version of
either of these groups;

-(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8),
acyl_(C≤8), substituted acyl_(C≤8), -C(O)-alkoxy_(C≤8),
substituted -C(O)-alkoxy_(C≤8), acyloxy_(C≤8), substituted
acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted
alkylsilyloxy_(C≤8); and

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

-(CH₂)_q-C(O)-R_{3''}, wherein:

R_{3''} is amino, hydroxy, or mercapto; or

alkoxy_(C≤8), alkylthio_(C≤8), alkylamino_(C≤8), dialkyl-
amino_(C≤8), or a substituted version of any of these
groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy_(C≤8), acyloxy_(C≤8), or substituted version of
either of these groups; or R₃ is taken together with Y as described below;
and

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Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₁₂), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₁₂), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), aryloxy(C₁₋₁₂), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), alkylthio(C₁₋₈), acylthio(C₁₋₈), alkylsulfonylamino(C₁₋₈), or substituted versions of any of these groups;

-alkanediyl(C₁₋₈)-R_b, -alkenediyl(C₁₋₈)-R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

aryl(C₁₋₈), heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), heteroarylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), -OC(O)NH-alkyl(C₁₋₈), -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(C₁₋₈), or a substituted version of any of these groups;

-(CH₂)_pC(O)R_c, wherein p is 0-6 and R_c is:

hydrogen, halo, hydroxy, amino, -NHOH, or mercapto; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), alkoxyamino(C₁₋₈), heterocycloalkylamino(C₁₋₈), -NHC(NO₂)-alkyl(C₁₋₈), -NH-amido(C₁₋₈), or a substituted version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(C₁₋₈), or substituted alkyl(C₁₋₈);

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R_e is hydrogen, hydroxy, amino; or

alkyl(csa), cycloalkyl(csa), alkenyl(csa), alkynyl(csa), aryl(csa),
aralkyl(csa), heteroaryl(csa), heterocycloalkyl(csa),
alkoxy(csa), cycloalkoxy(csa), aryloxy(csa), aralkoxy(csa),
heteroaryloxy(csa), acyloxy(csa), alkylamino(csa),
dialkylamino(csa), arylamino(csa), or a substituted version
of any of these groups; or

Y is taken together with R_3 and is $-(CH_2)_pC(O)R_f$, wherein

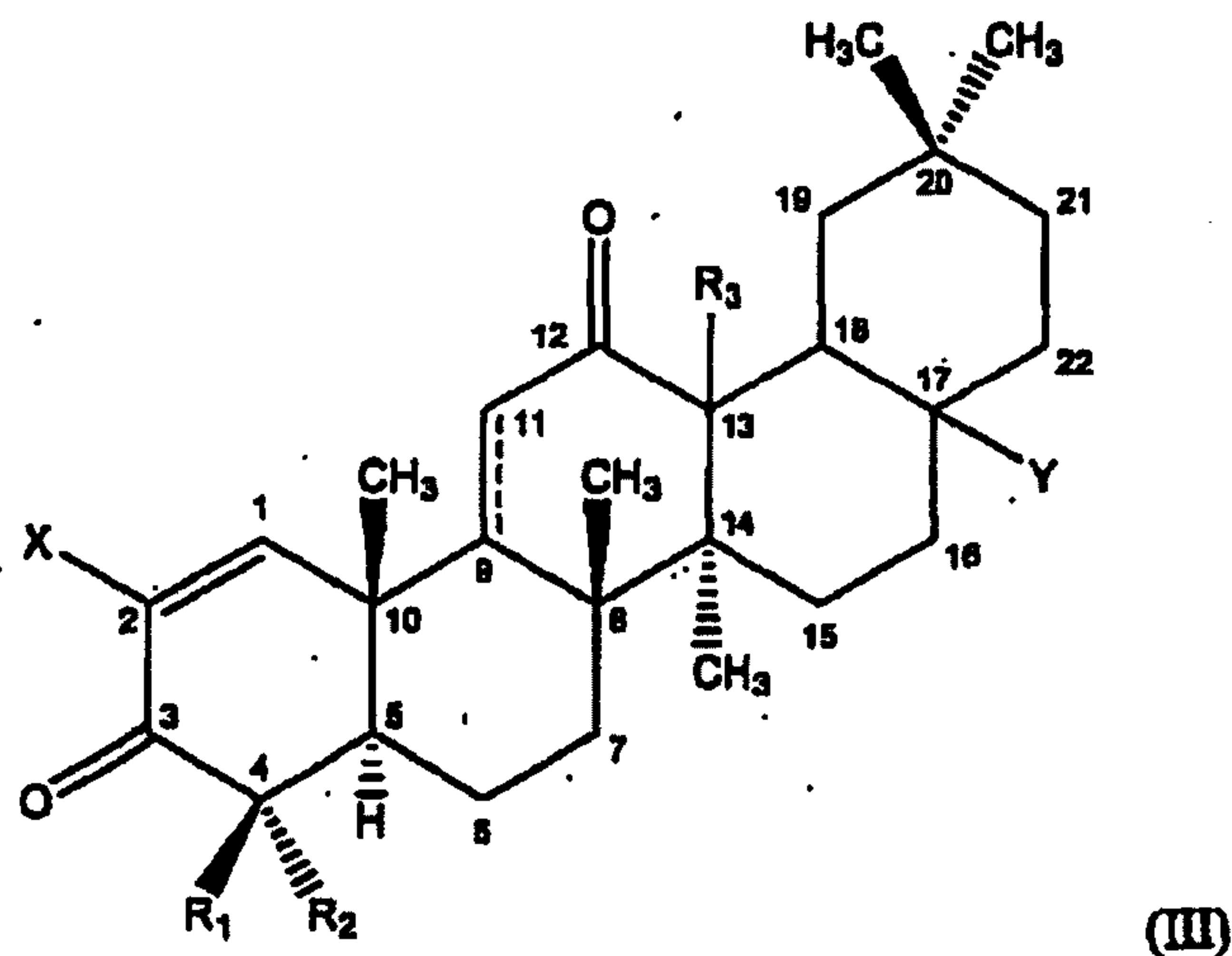
p is 0-6; and

R_f is $-O-$ or $-NR_7-$; wherein:

R_7 is hydrogen, alkyl(csa), substituted alkyl(csa), acyl(csa), or
substituted acyl(csa);

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 2 further defined as:



wherein:

the bond between atoms 9 and 11 is a single bond or a double bond;

X is cyano, heteroaryl(csa), substituted heteroaryl(csa), $-CF_3$, or $-C(O)-R_4$;

wherein

R_4 is hydroxy, amino, or alkoxy(csa), alkylamino(csa), dialkylamino(csa),
alkylsulfonylamino(csa), or a substituted version of any of these
groups;

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R_1 is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R_2 is amino,

heteroaryl_(C₁₋₈), substituted heteroaryl_(C₁₋₈), acyl_(C₁₋₈), substituted acyl_(C₁₋₈), amido_(C₁₋₈), substituted amido_(C₁₋₈), alkylamino_(C₁₋₈), substituted alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), or dialkylamino_(C₁₋₈);

-OR₄, wherein:

R_4 is hydrogen or alkyl_(C₁₋₈), acyl_(C₁₋₈), or a substituted version of either of these groups;

-(CH₂)_sNR₅'(R₆), wherein:

s is 0, 1, 2, 3, or 4;

R_5' is hydrogen, alkyl_(C₁₋₈), alkoxy_(C₁₋₈), substituted alkoxy_(C₁₋₈), acyl_(C₁₋₈), substituted acyl_(C₁₋₈), -C(O)-alkoxy_(C₁₋₈), substituted -C(O)-alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), substituted acyloxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or substituted alkylsilyloxy_(C₁₋₈); and

R_6 is hydrogen, alkyl_(C₁₋₈), or substituted alkyl_(C₁₋₈); or

-(CH₂)_q-C(O)-R₅", wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy_(C₁₋₈), alkylthio_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), alkenyl_(C₂₋₈), alkynyl_(C₂₋₈), aryl_(C₆₋₁₂), heteroaryl_(C₁₋₈), heterocycloalkyl_(C₃₋₁₂), alkoxy_(C₁₋₈), cycloalkoxy_(C₃₋₈), aryloxy_(C₆₋₁₂), acyloxy_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), alkenylamino_(C₂₋₈), arylamino_(C₆₋₁₂), aralkylamino_(C₁₋₈), alkylthio_(C₁₋₈), acylthio_(C₁₋₈), alkylsulfonylamino_(C₁₋₈), or substituted versions of any of these groups;

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-alkanediyl_(CS)-R_b, -alkenediyl_(CS)-R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

aryl_(CS), heteroaryl_(CS), alkoxy_(CS), cycloalkoxy_(CS), alkenyloxy_(CS), aryloxy_(CS), aralkoxy_(CS), heteroaryloxy_(CS), acyloxy_(CS), alkylamino_(CS), dialkylamino_(CS), alkenylamino_(CS), arylamino_(CS), aralkylamino_(CS), heteroarylamino_(CS), alkylsulfonylamino_(CS), amido_(CS), -OC(O)NH-alkyl_(CS), -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio_(CS), or a substituted version of any of these groups;

-(CH₂)_pC(O)R_c, wherein p is 0-6 and R_c is:

hydrogen, halo, hydroxy, amino, -NHOH, or mercapto; or

alkyl_(CS), cycloalkyl_(CS), alkenyl_(CS), alkynyl_(CS), aryl_(CS), aralkyl_(CS), heteroaryl_(CS), heterocycloalkyl_(CS), alkoxy_(CS), cycloalkoxy_(CS), alkenyloxy_(CS), aryloxy_(CS), aralkoxy_(CS), heteroaryloxy_(CS), acyloxy_(CS), alkylamino_(CS), dialkylamino_(CS), arylamino_(CS), alkylsulfonylamino_(CS), amido_(CS), alkoxyamino_(CS), heterocycloalkylamino_(CS), -NHC(NO₂)-alkyl_(CS), -NH-amido_(CS), or a substituted version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(CS), or substituted alkyl_(CS);

R_e is hydrogen, hydroxy, amino; or

alkyl_(CS), cycloalkyl_(CS), alkenyl_(CS), alkynyl_(CS), aryl_(CS), aralkyl_(CS), heteroaryl_(CS), heterocycloalkyl_(CS), alkoxy_(CS), cycloalkoxy_(CS), aryloxy_(CS), aralkoxy_(CS), heteroaryloxy_(CS), acyloxy_(CS), alkylamino_(CS), dialkylamino_(CS), arylamino_(CS), or a substituted version of any of these groups; or

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Y is taken together with R_3 and is $-(CH_2)_pC(O)R_f$, wherein

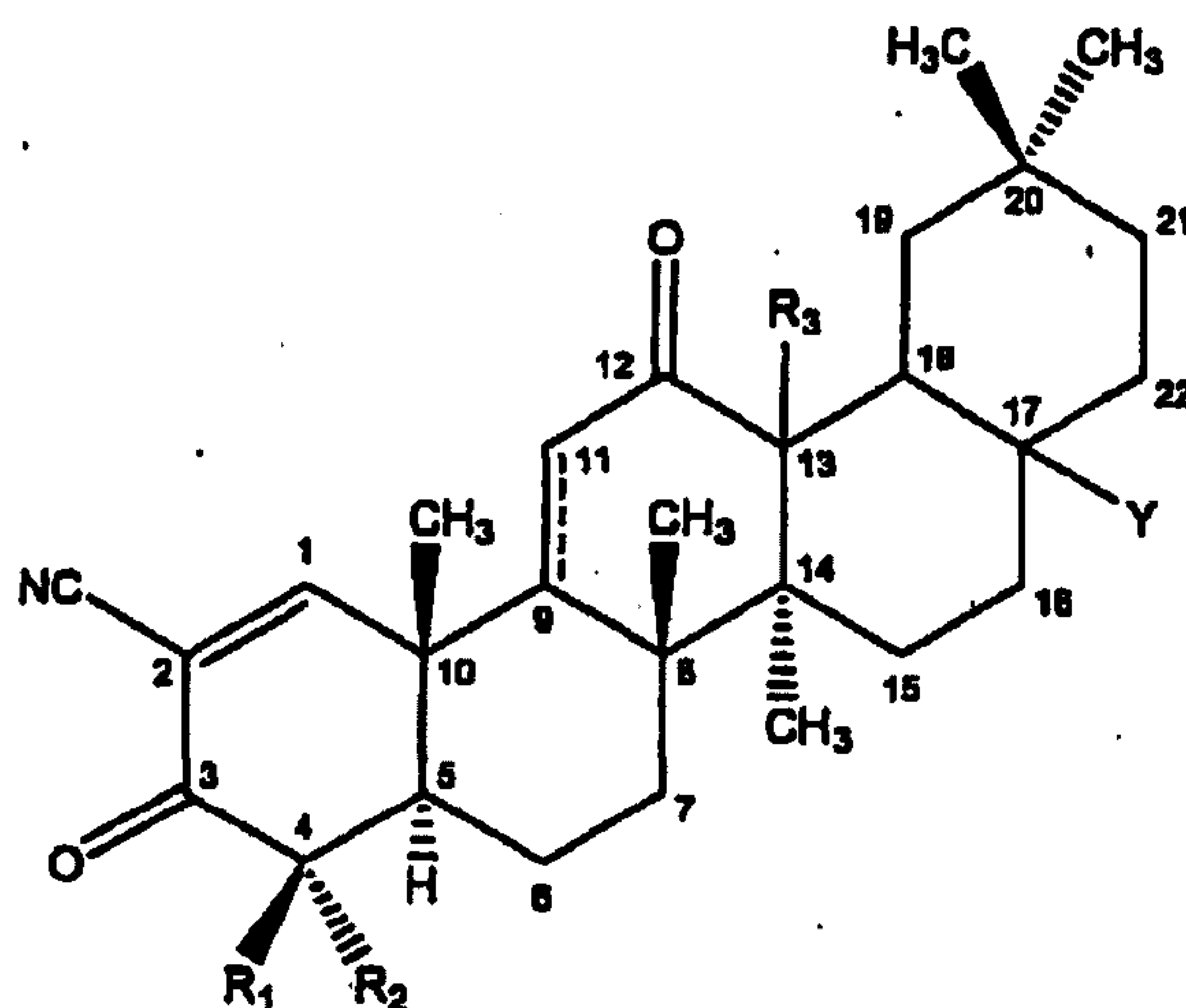
p is 0-6; and

R_f is $-O-$ or $-NR_7-$; wherein:

R_7 is hydrogen, alkyl(C_{1-6}), substituted alkyl(C_{1-6}), acyl(C_{1-6}), or substituted acyl(C_{1-6});

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3 further defined as:



(IV)

wherein:

the bond between atoms 9 and 11 is a single bond or a double bond;

R_1 is hydrogen, alkyl(C_{1-6}), cycloalkyl(C_{3-6}), substituted alkyl(C_{1-6}), or substituted cycloalkyl(C_{3-6});

R_2 is amino,

heteroaryl(C_{1-6}), substituted heteroaryl(C_{1-6}), acyl(C_{1-6}), substituted acyl(C_{1-6}), amido(C_{1-6}), substituted amido(C_{1-6}), alkylamino(C_{1-6}), substituted alkylamino(C_{1-6}), dialkylamino(C_{1-6}), or dialkylamino(C_{1-6});

$-OR_a$, wherein:

R_a is hydrogen or alkyl(C_{1-6}), acyl(C_{1-6}), or a substituted version of either of these groups;

$-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

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R_5' is hydrogen, alkyl(C_{1-8}), alkoxy(C_{1-8}), substituted alkoxy(C_{1-8}), acyl(C_{1-8}), substituted acyl(C_{1-8}), $-C(O)-$ alkoxy(C_{1-8}), substituted $-C(O)-$ alkoxy(C_{1-8}), acyloxy(C_{1-8}), substituted acyloxy(C_{1-8}), alkylsilyloxy(C_{1-8}), or substituted alkylsilyloxy(C_{1-8}); and

R_6 is hydrogen, alkyl(C_{1-8}), or substituted alkyl(C_{1-8}); or $-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy(C_{1-8}), alkylthio(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{1-12}), heteroaryl(C_{1-8}), heterocycloalkyl(C_{3-12}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), aryloxy(C_{1-12}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenylamino(C_{2-8}), arylamino(C_{1-8}), aralkylamino(C_{1-8}), alkylthio(C_{1-8}), acylthio(C_{1-8}), alkylsulfonylamino(C_{1-8}), or substituted versions of any of these groups;

$-alkanediy l(C_{1-8})-R_b$, $-alkenediy l(C_{2-8})-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

aryl(C_{1-8}), heteroaryl(C_{1-8}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), alkenyloxy(C_{2-8}), aryloxy(C_{1-12}), aralkoxy(C_{1-8}), heteroaryloxy(C_{1-8}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenylamino(C_{2-8}), arylamino(C_{1-8}), aralkylamino(C_{1-8}), heteroarylamino(C_{1-8}), alkylsulfonylamino(C_{1-8}), amido(C_{1-8}), $-OC(O)NH-alkyl(C_{1-8})$, $-OC(O)CH_2NHC(O)O-t-butyl$, $-OCH_2-alkylthio(C_{1-8})$, or a substituted version of any of these groups;

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$-(CH_2)_pC(O)R_e$, wherein p is 0-6 and R_e is:

hydrogen, halo, hydroxy, amino, $-NHOH$, or mercapto; or

alkyl(csa), cycloalkyl(csa), alkenyl(csa), alkynyl(csa),

aryl(csa), aralkyl(csa), heteroaryl(csa), hetero-

cycloalkyl(csa), alkoxy(csa), cycloalkoxy(csa),

alkenyloxy(csa), aryloxy(csa), aralkoxy(csa),

heteroaryloxy(csa), acyloxy(csa), alkylamino(csa),

dialkylamino(csa), arylamino(csa), alkylsulfonyl-

amino(csa), amido(csa), alkoxyamino(csa),

heterocycloalkylamino(csa),

$-NHC(NOH)-alkyl(csa)$, $-NH-amido(csa)$, or a

substituted version of any of these groups;

$-NR_dC(O)R_e$, wherein

R_d is hydrogen, alkyl(csa), or substituted alkyl(csa);

R_e is hydrogen, hydroxy, amino; or

alkyl(csa), cycloalkyl(csa), alkenyl(csa), alkynyl(csa), aryl(csa),

aralkyl(csa), heteroaryl(csa), heterocycloalkyl(csa),

alkoxy(csa), cycloalkoxy(csa), aryloxy(csa), aralkoxy(csa),

heteroaryloxy(csa), acyloxy(csa), alkylamino(csa),

dialkylamino(csa), arylamino(csa), or a substituted version

of any of these groups; or

Y is taken together with R_3 and is $-(CH_2)_pC(O)R_f-$, wherein

p is 0-6; and

R_f is $-O-$ or $-NR_7-$; wherein:

R_7 is hydrogen, alkyl(csa), substituted alkyl(csa), acyl(csa), or

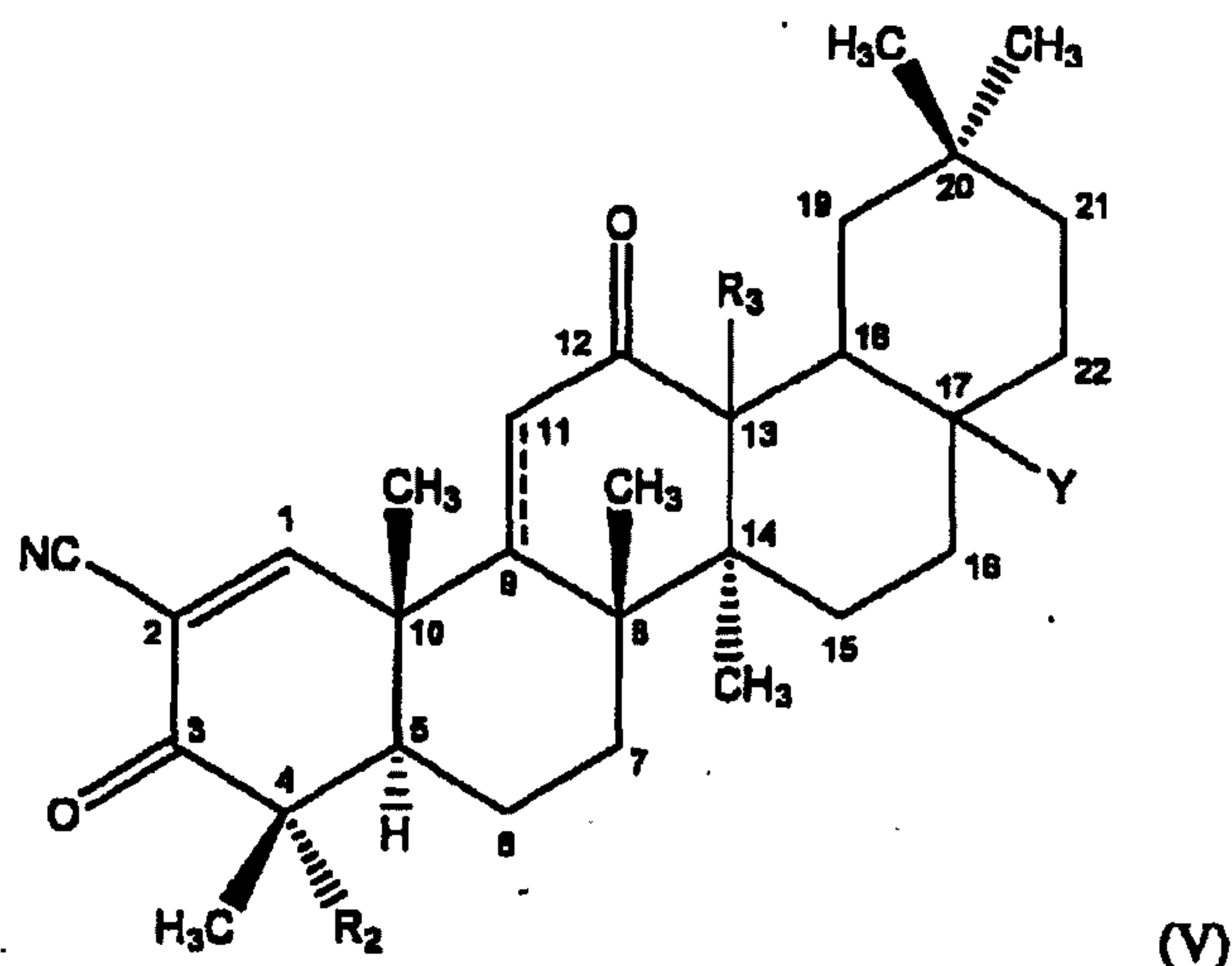
substituted acyl(csa);

or a pharmaceutically acceptable salt thereof.

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5. The compound of claim 3 further defined as:



wherein:

the bond between atoms 9 and 11 is a single bond or a double bond;

R_2 is amino,

heteroaryl_(C₁₋₈), substituted heteroaryl_(C₁₋₈), acyl_(C₁₋₈), substituted acyl_(C₁₋₈),
amido_(C₁₋₈), substituted amido_(C₁₋₈), alkylamino_(C₁₋₈), substituted
alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), or dialkylamino_(C₁₋₈);

$-OR_4$, wherein:

R_4 is hydrogen or alkyl_(C₁₋₈), acyl_(C₁₋₈), or a substituted version of
either of these groups;

$-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R_5' is hydrogen, alkyl_(C₁₋₈), alkoxy_(C₁₋₈), substituted alkoxy_(C₁₋₈),
acyl_(C₁₋₈), substituted acyl_(C₁₋₈), $-C(O)-$ alkoxy_(C₁₋₈),
substituted $-C(O)-$ alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), substituted
acyloxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or substituted
alkylsilyloxy_(C₁₋₈); and

R_6 is hydrogen, alkyl_(C₁₋₈), or substituted alkyl_(C₁₋₈); or

$-(CH_2)_4-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

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alkoxy(C₁₋₈), alkylthio(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy(C₁₋₈), acyloxy(C₁₋₈), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₁₂), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₁₂), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), aryloxy(C₁₋₁₂), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), alkylthio(C₁₋₈), acylthio(C₁₋₈), alkylsulfonylamino(C₁₋₈), or substituted versions of any of these groups;

—alkanediyl(C₁₋₈)—R_b, —alkenediyl(C₁₋₈)—R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

aryl(C₁₋₈), heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), heteroarylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), —OC(O)NH—alkyl(C₁₋₈), —OC(O)CH₂NHC(O)O—*t*-butyl, —OCH₂—alkylthio(C₁₋₈), or a substituted version of any of these groups;

—(CH₂)_pC(O)R_c, wherein p is 0–6 and R_c is:

hydrogen, halo, hydroxy, amino, —NHOH, or mercapto; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈),

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dialkylamino(C₁₋₈), arylamino(C₁₋₈), alkylsulfonyl-
amino(C₁₋₈), amido(C₁₋₈), alkoxyamino(C₁₋₈),
heterocycloalkylamino(C₁₋₈),
-NHC(NO₂)-alkyl(C₁₋₈), -NH-amido(C₁₋₈), or a
substituted version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(C₁₋₈), or substituted alkyl(C₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈),
aralkyl(C₁₋₈), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈),
alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈),
heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkyl-
amino(C₁₋₈), arylamino(C₁₋₈), or a substituted version of any
of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f-, wherein

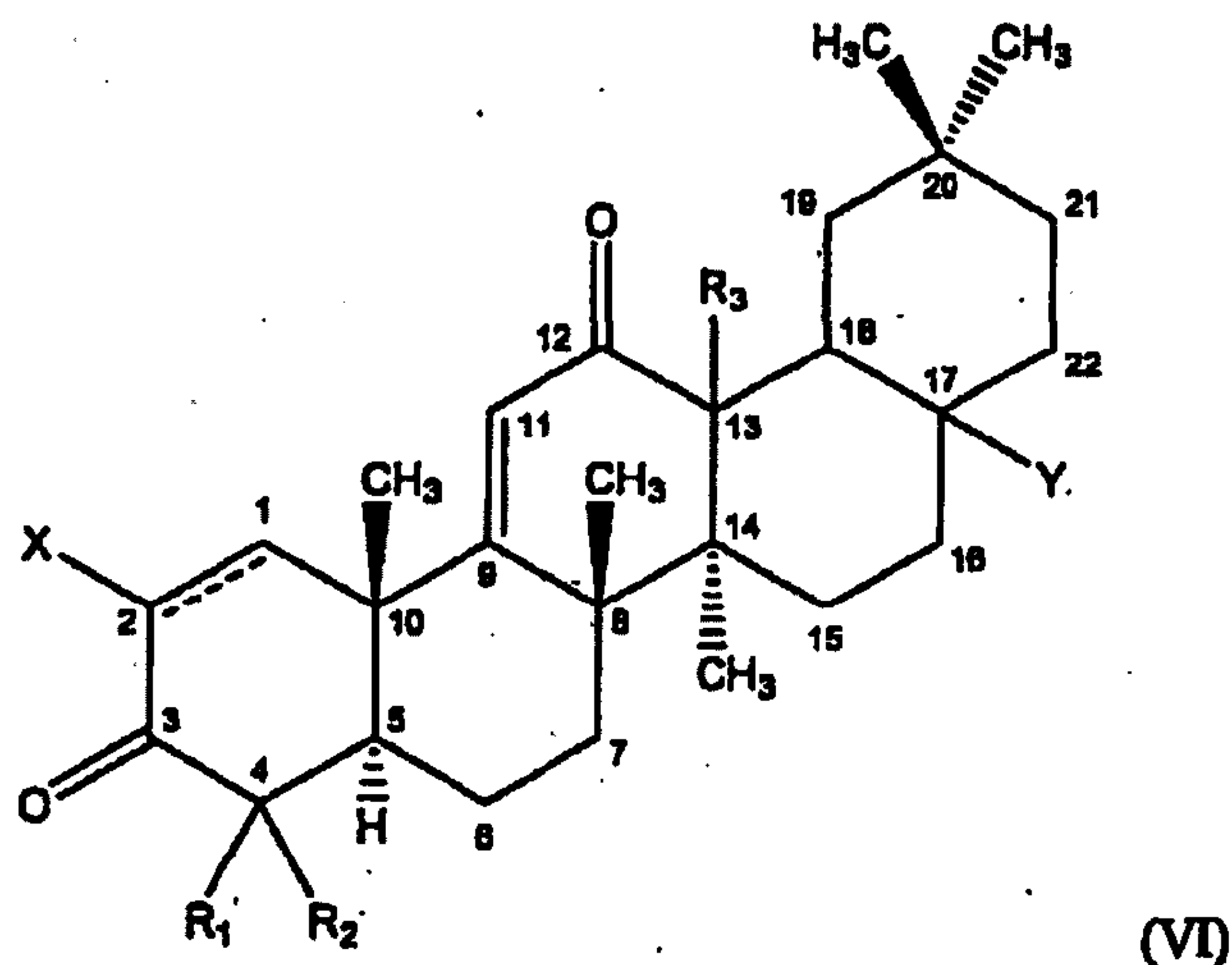
p is 0-6; and

R_f is -O- or -NR₇-; wherein:

R₇ is hydrogen, alkyl(C₁₋₈), substituted alkyl(C₁₋₈), acyl(C₁₋₈), or
substituted acyl(C₁₋₈);

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, wherein the compound is further defined as:



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wherein:

the bond between atoms 1 and 2 is a single bond, an epoxidized double bond,
or a double bond;

X is cyano, heteroaryl_(C≤8), substituted heteroaryl_(C≤8), -CF₃, or -C(O)-R₄;
wherein

R₄ is hydroxy, amino, or alkoxy_(C≤8), alkylamino_(C≤8), dialkylamino_(C≤8),
alkylsulfonylamino_(C≤8), or a substituted version of any of these
groups;

R₁ is hydrogen, alkyl_(C≤8), cycloalkyl_(C≤8), substituted alkyl_(C≤8), or substituted
cycloalkyl_(C≤8);

R₂ is amino, cyano, halo, or hydroxy,
substituted alkyl_(C≤8), heteroaryl_(C≤8), substituted heteroaryl_(C≤8), acyl_(C≤8),
substituted acyl_(C≤8), amido_(C≤8), substituted amido_(C≤8), alkylamino_(C≤8),
substituted alkylamino_(C≤8), dialkylamino_(C≤8), or dialkylamino_(C≤8); or
-OR₆, wherein:

R₆ is hydrogen or alkyl_(C≤8), alkenyl_(C≤8), alkynyl_(C≤8), aryl_(C≤12),
aralkyl_(C≤12), heteroaryl_(C≤12), heterocycloalkyl_(C≤8),
acyl_(C≤8), or a substituted version of any of these groups;

-(CH₂)_m-(OCH₂)_n-R₅, wherein:

R₅ is hydroxy or acyl_(C≤8), alkoxy_(C≤8), acyloxy_(C≤8),
alkylsilyloxy_(C≤8), or a substituted version of any of these
groups;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

-(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

R_{5'} is hydrogen, alkyl_(C≤8), alkoxy_(C≤8), substituted alkoxy_(C≤8),
acyl_(C≤8), substituted acyl_(C≤8), -C(O)-alkoxy_(C≤8),
substituted -C(O)-alkoxy_(C≤8), acyloxy_(C≤8), substituted
acyloxy_(C≤8), alkylsilyloxy_(C≤8), or substituted
alkylsilyloxy_(C≤8); and

R₆ is hydrogen, alkyl_(C≤8), or substituted alkyl_(C≤8); or

-(CH₂)_q-C(O)-R_{5''}, wherein:

R_{5''} is amino, hydroxy, or mercapto; or

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alkoxy(C₁₋₈), alkylthio(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy(C₁₋₈), acyloxy(C₁₋₈), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₂), aralkyl(C₁₋₂), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₂), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), aryloxy(C₁₋₂), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), alkylthio(C₁₋₈), acylthio(C₁₋₈), alkylsulfonylamino(C₁₋₈), or substituted versions of any of these groups;

-alkanediyl(C₁₋₈)-R_b, -alkenediyl(C₁₋₈)-R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), heteroarylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), -OC(O)NH-alkyl(C₁₋₈), -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(C₁₋₈), or a substituted version of any of these groups;

-(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), alkoxyamino(C₁₋₈), heterocycloalkylamino(C₁₋₈), -NHC(NOH)-alkyl(C₁₋₈), -NH-amido(C₁₋₈), or a substituted version of any of these groups;

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$-\text{NR}_d\text{C}(\text{O})\text{R}_e$, wherein

R_d is hydrogen, alkyl(C_{1-8}), or substituted alkyl(C_{1-8});

R_e is hydrogen, hydroxy, amino; or

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{6-10}), aralkyl(C_{1-10}),
heteroaryl(C_{3-10}), heterocycloalkyl(C_{3-8}), alkoxy(C_{1-8}),
cycloalkoxy(C_{3-8}), aryloxy(C_{6-10}), aralkoxy(C_{1-10}), heteroaryloxy(C_{3-10}),
acyloxy(C_{2-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), arylamino(C_{6-10}),
or a substituted version of any of these groups; or

Y is taken together with R_3 and is $-(\text{CH}_2)_p\text{C}(\text{O})\text{R}_f-$, wherein

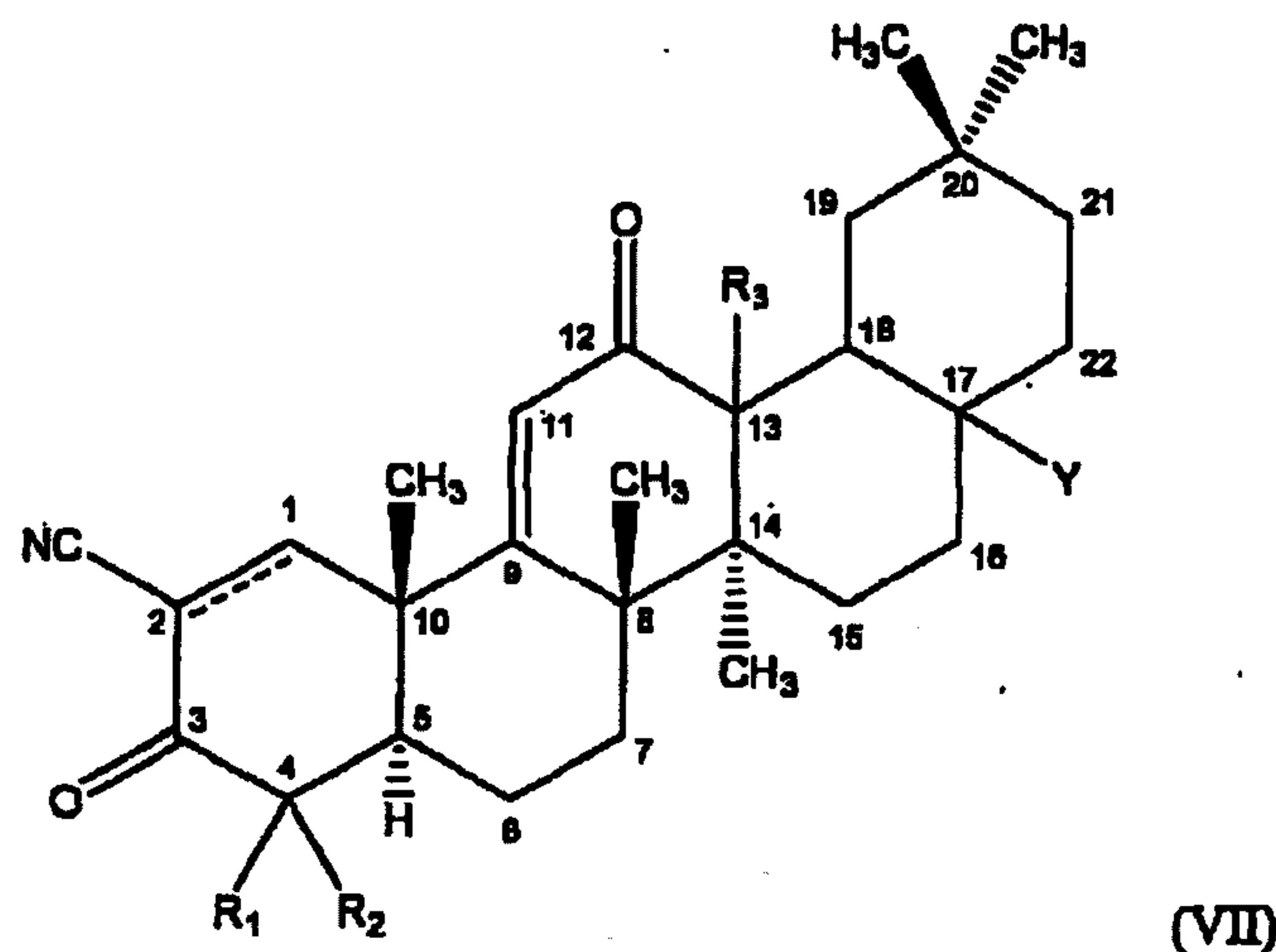
p is 0-6; and

R_f is $-\text{O}-$ or $-\text{NR}_7-$; wherein:

R_7 is hydrogen, alkyl(C_{1-8}), substituted alkyl(C_{1-8}), acyl(C_{1-8}), or
substituted acyl(C_{1-8});

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

7. The compound of either claim 1 or claim 6, wherein the compound is further defined as:



wherein:

the bond between atoms 1 and 2 is a single bond, an epoxidized double bond,
or a double bond;

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted
cycloalkyl(C_{3-8});

R_2 is amino, cyano, halo, or hydroxy,

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substituted alkyl_(C₁₋₈), heteroaryl_(C₁₋₈), substituted heteroaryl_(C₁₋₈), acyl_(C₁₋₈),
substituted acyl_(C₁₋₈), amido_(C₁₋₈), substituted amido_(C₁₋₈),
alkylamino_(C₁₋₈), substituted alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈),
or dialkylamino_(C₁₋₈); or

-OR_a, wherein:

R_a is hydrogen or alkyl_(C₁₋₈), alkenyl_(C₁₋₈), alkynyl_(C₁₋₈), aryl_(C₁₋₁₂),
aralkyl_(C₁₋₁₂), heteroaryl_(C₁₋₁₂), heterocycloalkyl_(C₁₋₈),
acyl_(C₁₋₈), or a substituted version of any of these groups;

-(CH₂)_m-(OCH₂)_n-R₅, wherein:

R₅ is hydroxy or acyl_(C₁₋₈), alkoxy_(C₁₋₈), acyloxy_(C₁₋₈),
alkylsilyloxy_(C₁₋₈), or a substituted version of any of these
groups;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

-(CH₂)_sNR_{5'}(R₆), wherein:

s is 0, 1, 2, 3, or 4;

R_{5'} is hydrogen, alkyl_(C₁₋₈), alkoxy_(C₁₋₈), substituted alkoxy_(C₁₋₈),
acyl_(C₁₋₈), substituted acyl_(C₁₋₈), -C(O)-alkoxy_(C₁₋₈),
substituted -C(O)-alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), substituted
acyloxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or substituted alkyl-
silyloxy_(C₁₋₈); and

R₆ is hydrogen, alkyl_(C₁₋₈), or substituted alkyl_(C₁₋₈); or

-(CH₂)_q-C(O)-R_{5''}, wherein:

R_{5''} is amino, hydroxy, or mercapto; or

alkoxy_(C₁₋₈), alkylthio_(C₁₋₈), alkylamino_(C₁₋₈), dialkyl-
amino_(C₁₋₈), or a substituted version of any of these
groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of
either of these groups; or R₃ is taken together with Y as described below;

and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

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alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₁₂), aralkyl(C₁₋₁₂), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₁₂), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), aryloxy(C₁₋₁₂), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), alkylthio(C₁₋₈), acylthio(C₁₋₈), alkylsulfonylamino(C₁₋₈), or substituted versions of any of these groups;

-alkanediyl(C₁₋₈)-R_b, -alkenediyl(C₁₋₈)-R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), heteroarylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), -OC(O)NH-alkyl(C₁₋₈), -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(C₁₋₈), or a substituted version of any of these groups;

-(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), alkoxyamino(C₁₋₈), heterocycloalkylamino(C₁₋₈), -NHC(NO₂)-alkyl(C₁₋₈), -NH-amido(C₁₋₈), or a substituted version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(C₁₋₈), or substituted alkyl(C₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈), or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

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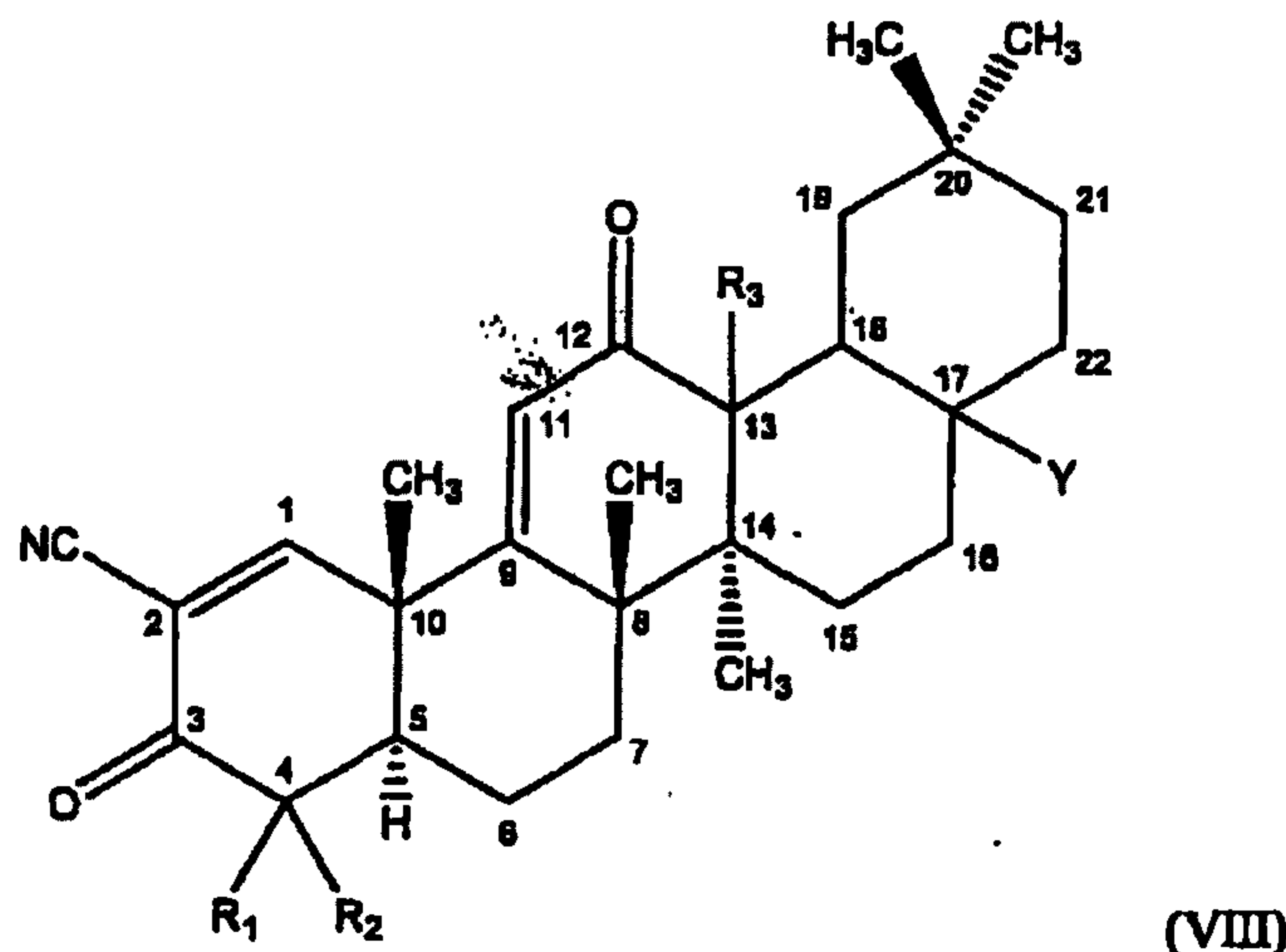
p is 0-6; and

R_f is -O- or -NR_f-; wherein:

R_f is hydrogen, alkyl(C₁₋₈), substituted alkyl(C₁₋₈), acyl(C₁₋₈), or substituted acyl(C₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

8. The compound according to any one of claims 1-7, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C₁₋₈), cycloalkyl(C₃₋₈), substituted alkyl(C₁₋₈), or substituted cycloalkyl(C₃₋₈);

R_2 is amino, cyano, halo, or hydroxy,

substituted alkyl(C₁₋₈), heteroaryl(C₁₋₈), substituted heteroaryl(C₁₋₈), acyl(C₁₋₈), substituted acyl(C₁₋₈), amido(C₁₋₈), substituted amido(C₁₋₈), alkylamino(C₁₋₈), substituted alkylamino(C₁₋₈), dialkylamino(C₁₋₈), or dialkylamino(C₁₋₈); or -OR_a, wherein:

R_a is hydrogen or alkyl(C₁₋₈), alkenyl(C₂₋₈), alkynyl(C₁₋₈), aryl(C₆₋₁₂), aralkyl(C₁₋₁₂), heteroaryl(C₁₋₁₂), heterocycloalkyl(C₃₋₈), acyl(C₁₋₈), or a substituted version of any of these groups;

-(CH₂)_m-(OCH₂)_n-R₅, wherein:

R_5 is hydroxy or acyl(C₁₋₈), alkoxy(C₁₋₈), acyloxy(C₁₋₈), alkylsilyloxy(C₁₋₈), or a substituted version of any of these groups;

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m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

-(CH₂)_sNR₅'(R₆), wherein:

s is 0, 1, 2, 3, or 4;

R₅' is hydrogen, alkyl(C₁₋₈), alkoxy(C₁₋₈), substituted alkoxy(C₁₋₈), acyl(C₁₋₈), substituted acyl(C₁₋₈), -C(O)-alkoxy(C₁₋₈), substituted -C(O)-alkoxy(C₁₋₈), acyloxy(C₁₋₈), substituted acyloxy(C₁₋₈), alkylsilyloxy(C₁₋₈), or substituted alkylsilyloxy(C₁₋₈); and

R₆ is hydrogen, alkyl(C₁₋₈), or substituted alkyl(C₁₋₈); or

-(CH₂)_q-C(O)-R₅'', wherein:

R₅'' is amino, hydroxy, or mercapto; or

alkoxy(C₁₋₈), alkylthio(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R₃ is hydrogen, hydroxy, or alkoxy(C₁₋₈), acyloxy(C₁₋₈), or substituted version of either of these groups; or R₃ is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₁₂), aralkyl(C₁₋₁₂), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₁₂), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), aryloxy(C₁₋₁₂), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), alkylthio(C₁₋₈), acylthio(C₁₋₈), alkylsulfonylamino(C₁₋₈), or substituted versions of any of these groups;

-alkanediyl(C₁₋₈)-R_b, -alkenediyl(C₁₋₈)-R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), aryl-

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amino_(C₁₋₈), aralkylamino_(C₁₋₈), heteroaryl_(C₁₋₈), alkyl-sulfonylamino_(C₁₋₈), amido_(C₁₋₈), -OC(O)NH-alkyl_(C₁₋₈), -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio_(C₁₋₈), or a substituted version of any of these groups;

-(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), alkenyl_(C₂₋₈), alkynyl_(C₂₋₈), aryl_(C₆₋₁₀), aralkyl_(C₁₋₈), heteroaryl_(C₁₋₈), heterocycloalkyl_(C₃₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), arylamino_(C₁₋₈), alkylsulfonylamino_(C₁₋₈), amido_(C₁₋₈), alkoxyamino_(C₁₋₈), heterocycloalkylamino_(C₁₋₈), -NHC(NO₂)-alkyl_(C₁₋₈), -NH-amido_(C₁₋₈), or a substituted version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C₁₋₈), or substituted alkyl_(C₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), alkenyl_(C₂₋₈), alkynyl_(C₂₋₈), aryl_(C₆₋₁₀), aralkyl_(C₁₋₈), heteroaryl_(C₁₋₈), heterocycloalkyl_(C₃₋₈), alkoxy_(C₁₋₈), cycloalkoxy_(C₃₋₈), aryloxy_(C₆₋₁₀), aralkoxy_(C₁₋₈), heteroaryloxy_(C₁₋₈), acyloxy_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), arylamino_(C₁₋₈), or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

p is 0-6; and

R_f is -O- or -NR₇-; wherein:

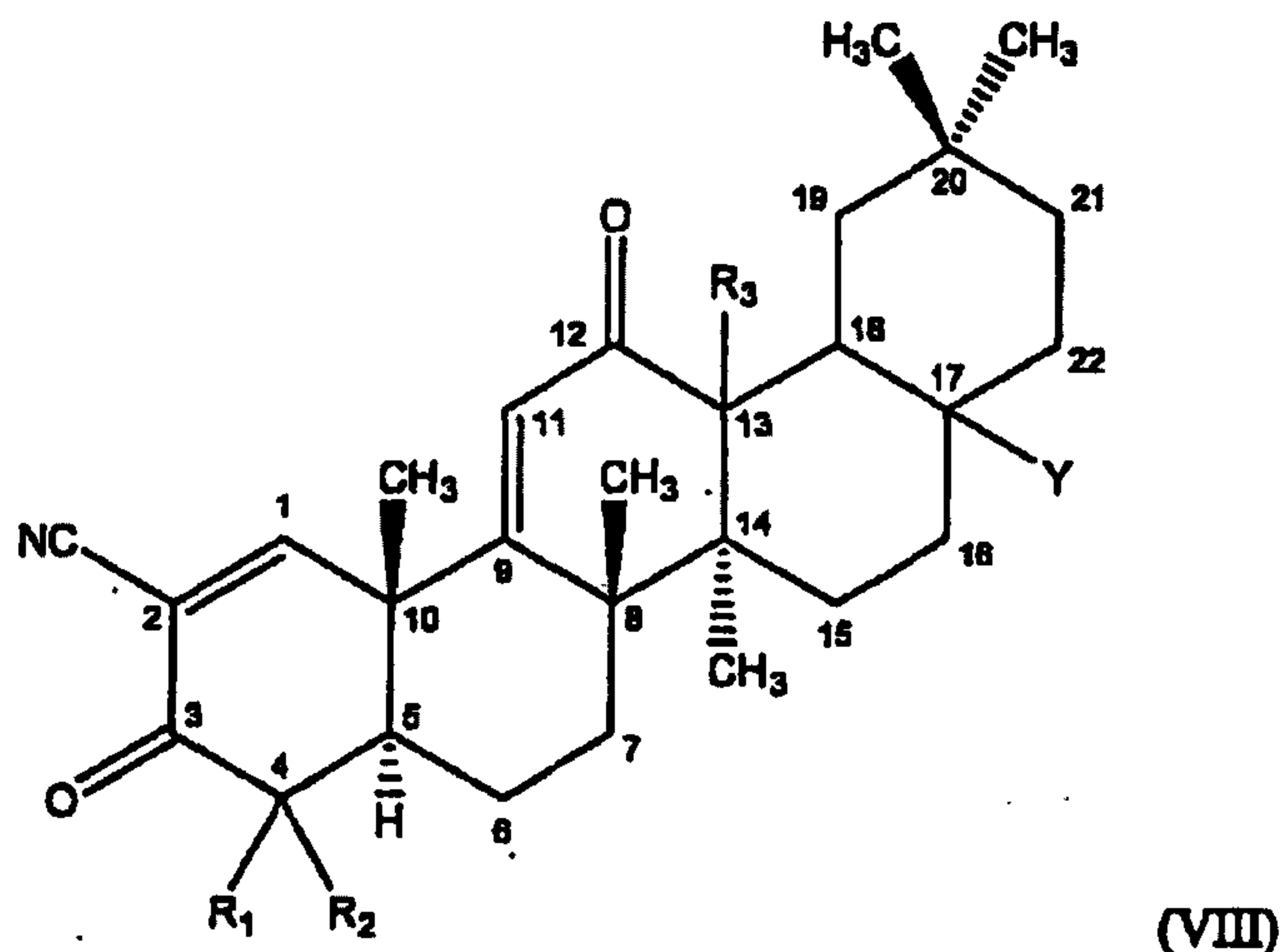
R₇ is hydrogen, alkyl_(C₁₋₈), substituted alkyl_(C₁₋₈), acyl_(C₁₋₈), or substituted acyl_(C₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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9. The compound according to any one of claims 1-8, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is amino, cyano, halo, hydroxy, substituted alkyl(C_{1-8}), heteroaryl(C_{1-8}), substituted heteroaryl(C_{1-8}), acyl(C_{1-8}), substituted acyl(C_{1-8}), amido(C_{1-8}), substituted amido(C_{1-8}), alkylamino(C_{1-8}), substituted alkylamino(C_{1-8}), dialkylamino(C_{1-8}), or dialkylamino(C_{1-8});

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{1-12}), aralkyl(C_{1-12}), heteroaryl(C_{1-8}), heterocycloalkyl(C_{3-12}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), aryloxy(C_{1-12}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenylamino(C_{1-8}), arylamino(C_{1-8}), aralkylamino(C_{1-8}), alkylthio(C_{1-8}), acylthio(C_{1-8}), alkylsulfonylamino(C_{1-8}), or substituted versions of any of these groups;

—alkanediyl(C_{2-8})— R_b , —alkenediyl(C_{2-8})— R_b , or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

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heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈),
 aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈),
 alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈),
 arylamino(C₁₋₈), aralkylamino(C₁₋₈), heteroarylamino(C₁₋₈),
 alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), -OC(O)NH-alkyl(C₁₋₈),
 -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(C₁₋₈), or a
 substituted version of any of these groups;

-(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈),
 heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkylamino(C₁₋₈),
 dialkylamino(C₁₋₈), arylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈),
 amido(C₁₋₈), alkoxyamino(C₁₋₈), heterocycloalkylamino(C₁₋₈),
 -NHC(NO₂)-alkyl(C₁₋₈), -NH-amido(C₁₋₈), or a substituted
 version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(C₁₋₈), or substituted alkyl(C₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈),
 heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkoxy(C₁₋₈),
 cycloalkoxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈),
 acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈),
 or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

p is 0-6; and

R_f is -O- or -NR₇-; wherein:

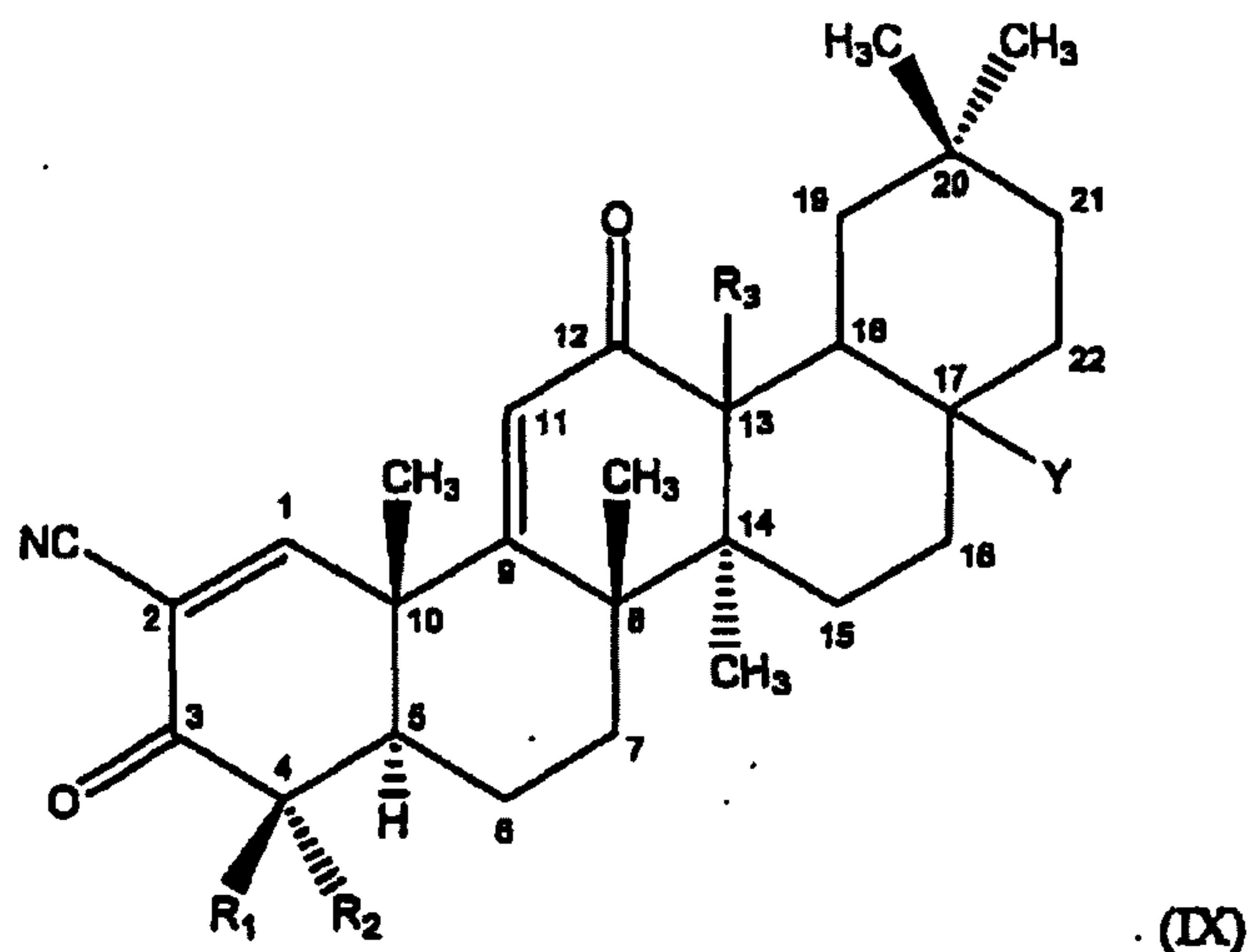
R₇ is hydrogen, alkyl(C₁₋₈), substituted alkyl(C₁₋₈), acyl(C₁₋₈), or
 substituted acyl(C₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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10. The compound according to any one of claims 1-9, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is amino, cyano, halo, hydroxy, substituted alkyl(C_{1-8}), heteroaryl(C_{1-8}), substituted heteroaryl(C_{1-8}), acyl(C_{1-8}), substituted acyl(C_{1-8}), amido(C_{1-8}), substituted amido(C_{1-8}), alkylamino(C_{1-8}), substituted alkylamino(C_{1-8}), dialkylamino(C_{1-8}), or dialkylamino(C_{1-8});

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{1-8}), alkynyl(C_{1-8}), aryl(C_{1-12}), aralkyl(C_{1-12}), heteroaryl(C_{1-8}), heterocycloalkyl(C_{1-12}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), aryloxy(C_{1-12}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenylamino(C_{1-8}), arylamino(C_{1-8}), aralkylamino(C_{1-8}), alkylthio(C_{1-8}), acylthio(C_{1-8}), alkylsulfonylamino(C_{1-8}), or substituted versions of any of these groups;

—alkanediyl(C_{1-8})— R_b , —alkenediyl(C_{1-8})— R_b , or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

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heteroaryl(c₁₋₈), alkoxy(c₁₋₈), cycloalkoxy(c₁₋₈), alkenyloxy(c₁₋₈),
 aryloxy(c₁₋₈), aralkoxy(c₁₋₈), heteroaryloxy(c₁₋₈), acyloxy(c₁₋₈),
 alkylamino(c₁₋₈), dialkylamino(c₁₋₈), alkenylamino(c₁₋₈), aryl-
 amino(c₁₋₈), aralkylamino(c₁₋₈), heteroarylamino(c₁₋₈), alkyl-
 sulfonylamino(c₁₋₈), amido(c₁₋₈), -OC(O)NH-alkyl(c₁₋₈),
 -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(c₁₋₈), or a
 substituted version of any of these groups;

-(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl(c₁₋₈), cycloalkyl(c₁₋₈), alkenyl(c₁₋₈), alkynyl(c₁₋₈), aryl(c₁₋₈), aralkyl(c₁₋₈),
 heteroaryl(c₁₋₈), heterocycloalkyl(c₁₋₈), alkylamino(c₁₋₈),
 dialkylamino(c₁₋₈), arylamino(c₁₋₈), alkylsulfonylamino(c₁₋₈),
 amido(c₁₋₈), alkoxyamino(c₁₋₈), heterocycloalkylamino(c₁₋₈),
 -NHC(NO₂)-alkyl(c₁₋₈), -NH-amido(c₁₋₈), or a substituted
 version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(c₁₋₈), or substituted alkyl(c₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(c₁₋₈), cycloalkyl(c₁₋₈), alkenyl(c₁₋₈), alkynyl(c₁₋₈), aryl(c₁₋₈), aralkyl(c₁₋₈),
 heteroaryl(c₁₋₈), heterocycloalkyl(c₁₋₈), alkoxy(c₁₋₈),
 cycloalkoxy(c₁₋₈), aryloxy(c₁₋₈), aralkoxy(c₁₋₈), heteroaryloxy(c₁₋₈),
 acyloxy(c₁₋₈), alkylamino(c₁₋₈), dialkylamino(c₁₋₈), arylamino(c₁₋₈),
 or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

p is 0-6; and

R_f is -O- or -NR₇-; wherein:

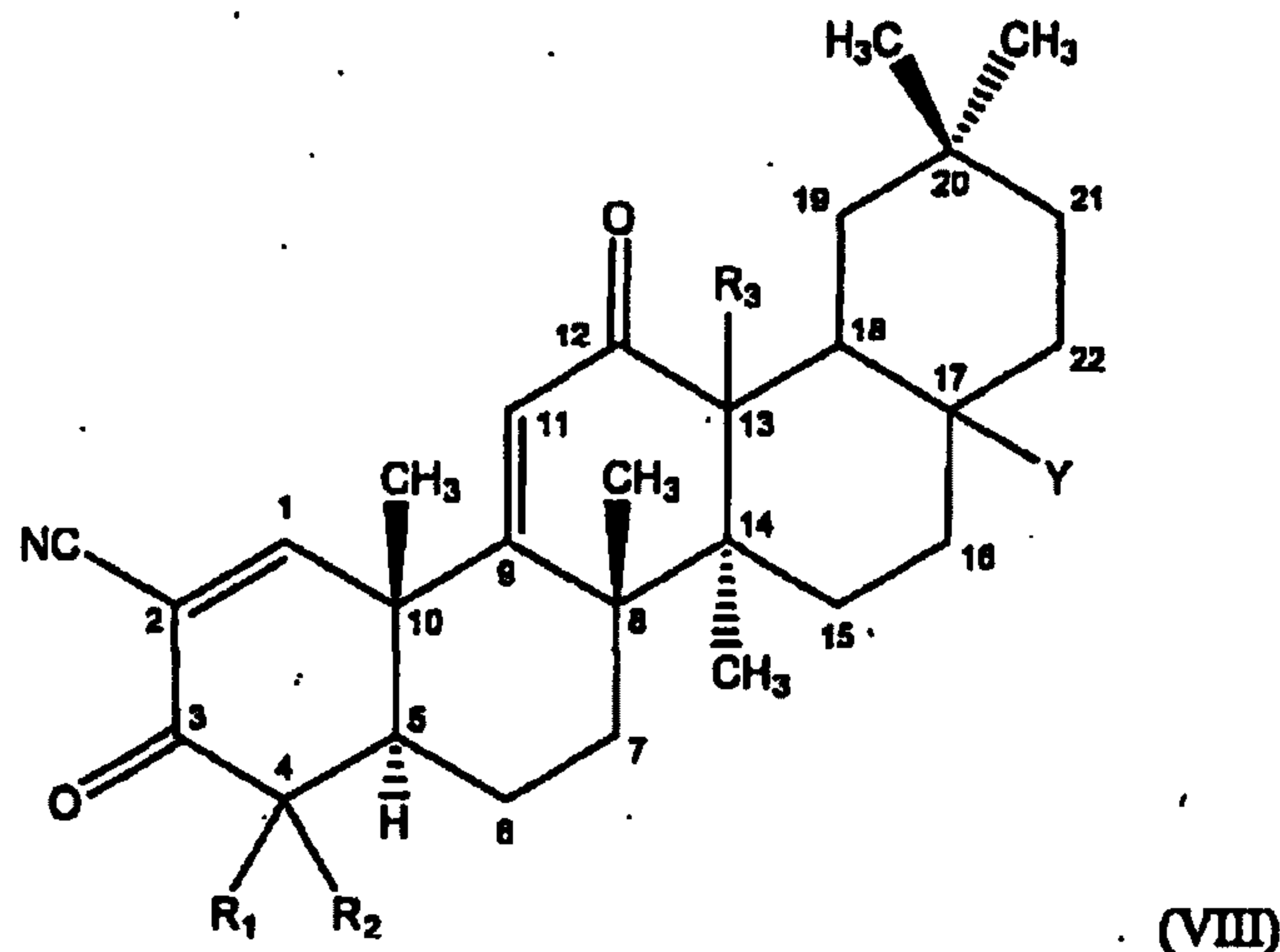
R₇ is hydrogen, alkyl(c₁₋₈), substituted alkyl(c₁₋₈), acyl(c₁₋₈), or
 substituted acyl(c₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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11. The compound according to any one of claims 1-8, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is $-OR_a$, wherein:

R_a is hydrogen or alkyl(C_{1-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{6-12}), aralkyl(C_{1-12}), heteroaryl(C_{6-12}), heterocycloalkyl(C_{3-8}), acyl(C_{1-8}), or a substituted version of any of these groups;

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{6-12}), aralkyl(C_{1-12}), heteroaryl(C_{6-12}), heterocycloalkyl(C_{3-8}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), aryloxy(C_{6-12}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenylamino(C_{2-8}), arylamino(C_{6-12}), aralkylamino(C_{1-12}), alkylthio(C_{1-8}), acylthio(C_{1-8}), alkylsulfonylamino(C_{1-8}), or substituted versions of any of these groups;

$-alkanediy(C_{1-8})-R_b$, $-alkenediy(C_{2-8})-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

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heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈),
 aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈),
 alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), aryl-
 amino(C₁₋₈), aralkylamino(C₁₋₈), heteroarylamino(C₁₋₈), alkyl-
 sulfonylamino(C₁₋₈), amido(C₁₋₈), -OC(O)NH-alkyl(C₁₋₈),
 -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(C₁₋₈), or a
 substituted version of any of these groups;

-(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈),
 heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkylamino(C₁₋₈),
 dialkylamino(C₁₋₈), arylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈),
 amido(C₁₋₈), alkoxyamino(C₁₋₈), heterocycloalkylamino(C₁₋₈),
 -NHC(NO₂)-alkyl(C₁₋₈), -NH-amido(C₁₋₈), or a substituted
 version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(C₁₋₈), or substituted alkyl(C₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈),
 heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkoxy(C₁₋₈),
 cycloalkoxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈),
 acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈),
 or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

p is 0-6; and

R_f is -O- or -NR₇-; wherein:

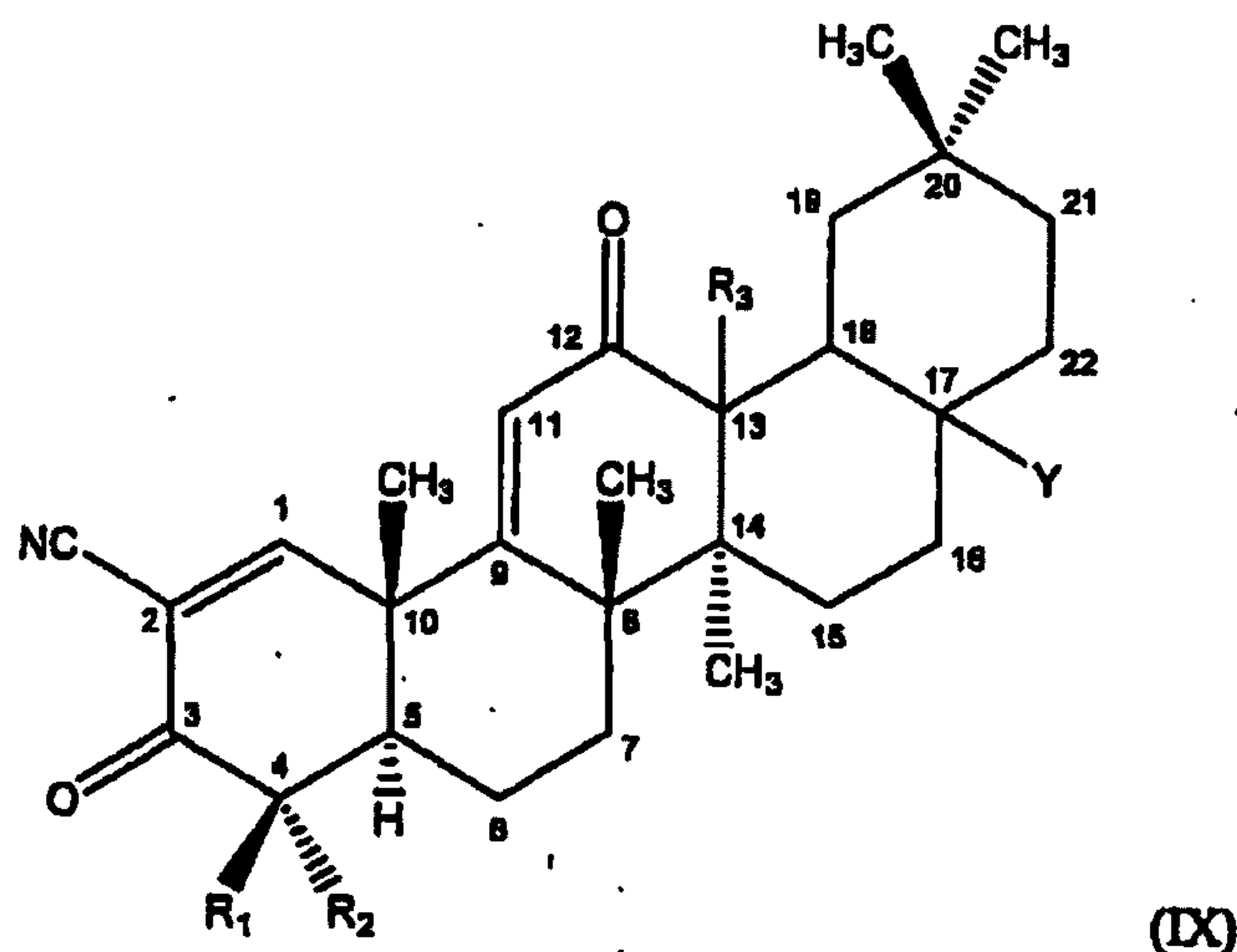
R₇ is hydrogen, alkyl(C₁₋₈), substituted alkyl(C₁₋₈), acyl(C₁₋₈), or
 substituted acyl(C₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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12. The compound according to any one of claims 1-8 and 11, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is $-OR_a$, wherein:

R_a is hydrogen or alkyl(C_{1-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{6-12}), aralkyl(C_{7-12}), heteroaryl(C_{6-12}), heterocycloalkyl(C_{3-8}), acyl(C_{1-8}), or a substituted version of any of these groups;

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{6-12}), aralkyl(C_{7-12}), heteroaryl(C_{6-12}), heterocycloalkyl(C_{3-8}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), aryloxy(C_{6-12}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenylamino(C_{2-8}), arylamino(C_{6-12}), aralkylamino(C_{7-12}), alkylthio(C_{1-8}), acylthio(C_{1-8}), alkylsulfonylamino(C_{1-8}), or substituted versions of any of these groups;

$-alkanediy(C_{1-8})-R_b$, $-alkenediy(C_{2-8})-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

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heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₃₋₈), alkenyloxy(C₂₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), heteroarylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), -OC(O)NH-alkyl(C₁₋₈), -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(C₁₋₈), or a substituted version of any of these groups;

-(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl(C₁₋₈), cycloalkyl(C₃₋₈), alkenyl(C₂₋₈), alkynyl(C₂₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈), heteroaryl(C₁₋₈), heterocycloalkyl(C₃₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), alkoxyamino(C₁₋₈), heterocycloalkylamino(C₃₋₈), -NHC(NO₂)-alkyl(C₁₋₈), -NH-amido(C₁₋₈), or a substituted version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(C₁₋₈), or substituted alkyl(C₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(C₁₋₈), cycloalkyl(C₃₋₈), alkenyl(C₂₋₈), alkynyl(C₂₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈), heteroaryl(C₁₋₈), heterocycloalkyl(C₃₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₃₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈), or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

p is 0-6; and

R_f is -O- or -NR₇-; wherein:

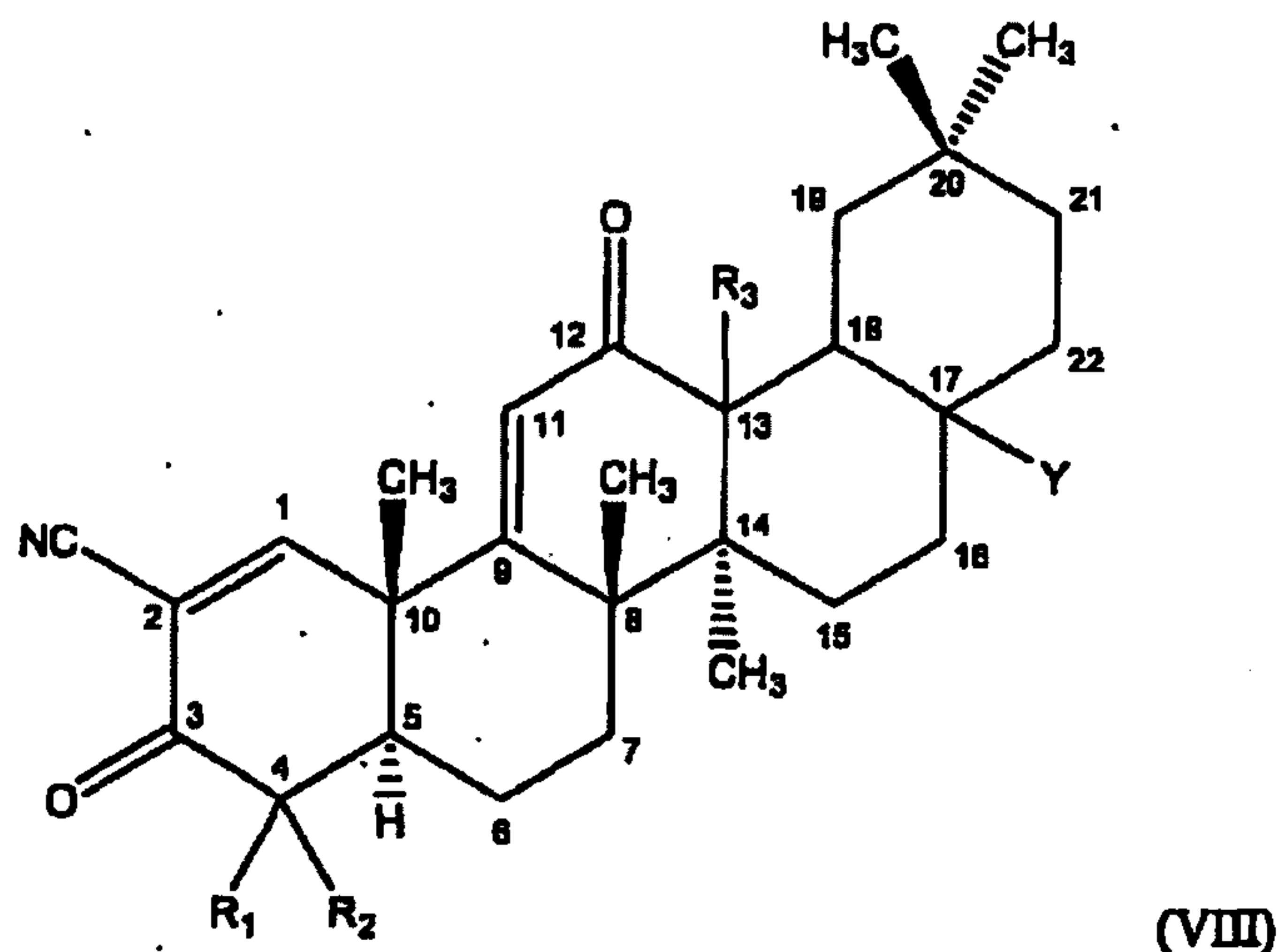
R₇ is hydrogen, alkyl(C₁₋₈), substituted alkyl(C₁₋₈), acyl(C₁₋₈), or substituted acyl(C₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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13. The compound according to any one of claims 1-8, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is $-(CH_2)_m-(OCH_2)_n-R_5$, wherein:

R_5 is hydroxy or acyl(C_{1-8}), alkoxy(C_{1-8}), acyloxy(C_{1-8}), alkylsilyloxy(C_{1-8}), or a substituted version of any of these groups;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{6-12}), aralkyl(C_{7-12}),

heteroaryl(C_{6-12}), heterocycloalkyl(C_{3-12}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}),

aryloxy(C_{6-12}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenyl-

amino(C_{2-8}), arylamino(C_{6-12}), aralkylamino(C_{7-12}), alkylthio(C_{1-8}), acylthio(C_{1-8}),

alkylsulfonylamino(C_{1-8}), or substituted versions of any of these groups;

$-alkanediy(C_{1-8})-R_6$, $-alkenediy(C_{1-8})-R_6$, or a substituted version of any of these groups, wherein R_6 is:

hydrogen, hydroxy, halo, amino or mercapto; or

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heteroaryl(c₁₋₈), alkoxy(c₁₋₈), cycloalkoxy(c₁₋₈), alkenyloxy(c₁₋₈),
 aryloxy(c₁₋₈), aralkoxy(c₁₋₈), heteroaryloxy(c₁₋₈), acyloxy(c₁₋₈),
 alkylamino(c₁₋₈), dialkylamino(c₁₋₈), alkenylamino(c₁₋₈), aryl-
 amino(c₁₋₈), aralkylamino(c₁₋₈), heteroarylamino(c₁₋₈), alkyl-
 sulfonylamino(c₁₋₈), amido(c₁₋₈), -OC(O)NH-alkyl(c₁₋₈),
 -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(c₁₋₈), or a
 substituted version of any of these groups;

-(CH₂)_oC(O)R_c, wherein o is 0-6 and R_c is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl(c₁₋₈), cycloalkyl(c₁₋₈), alkenyl(c₁₋₈), alkynyl(c₁₋₈), aryl(c₁₋₈), aralkyl(c₁₋₈),
 heteroaryl(c₁₋₈), heterocycloalkyl(c₁₋₈), alkylamino(c₁₋₈),
 dialkylamino(c₁₋₈), arylamino(c₁₋₈), alkylsulfonylamino(c₁₋₈),
 amido(c₁₋₈), alkoxyamino(c₁₋₈), heterocycloalkylamino(c₁₋₈),
 -NHC(NOH)-alkyl(c₁₋₈), -NH-amido(c₁₋₈), or a substituted
 version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(c₁₋₈), or substituted alkyl(c₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(c₁₋₈), cycloalkyl(c₁₋₈), alkenyl(c₁₋₈), alkynyl(c₁₋₈), aryl(c₁₋₈), aralkyl(c₁₋₈),
 heteroaryl(c₁₋₈), heterocycloalkyl(c₁₋₈), alkoxy(c₁₋₈),
 cycloalkoxy(c₁₋₈), aryloxy(c₁₋₈), aralkoxy(c₁₋₈), heteroaryloxy(c₁₋₈),
 acyloxy(c₁₋₈), alkylamino(c₁₋₈), dialkylamino(c₁₋₈), arylamino(c₁₋₈),
 or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

p is 0-6; and

R_f is -O- or -NR₇-; wherein:

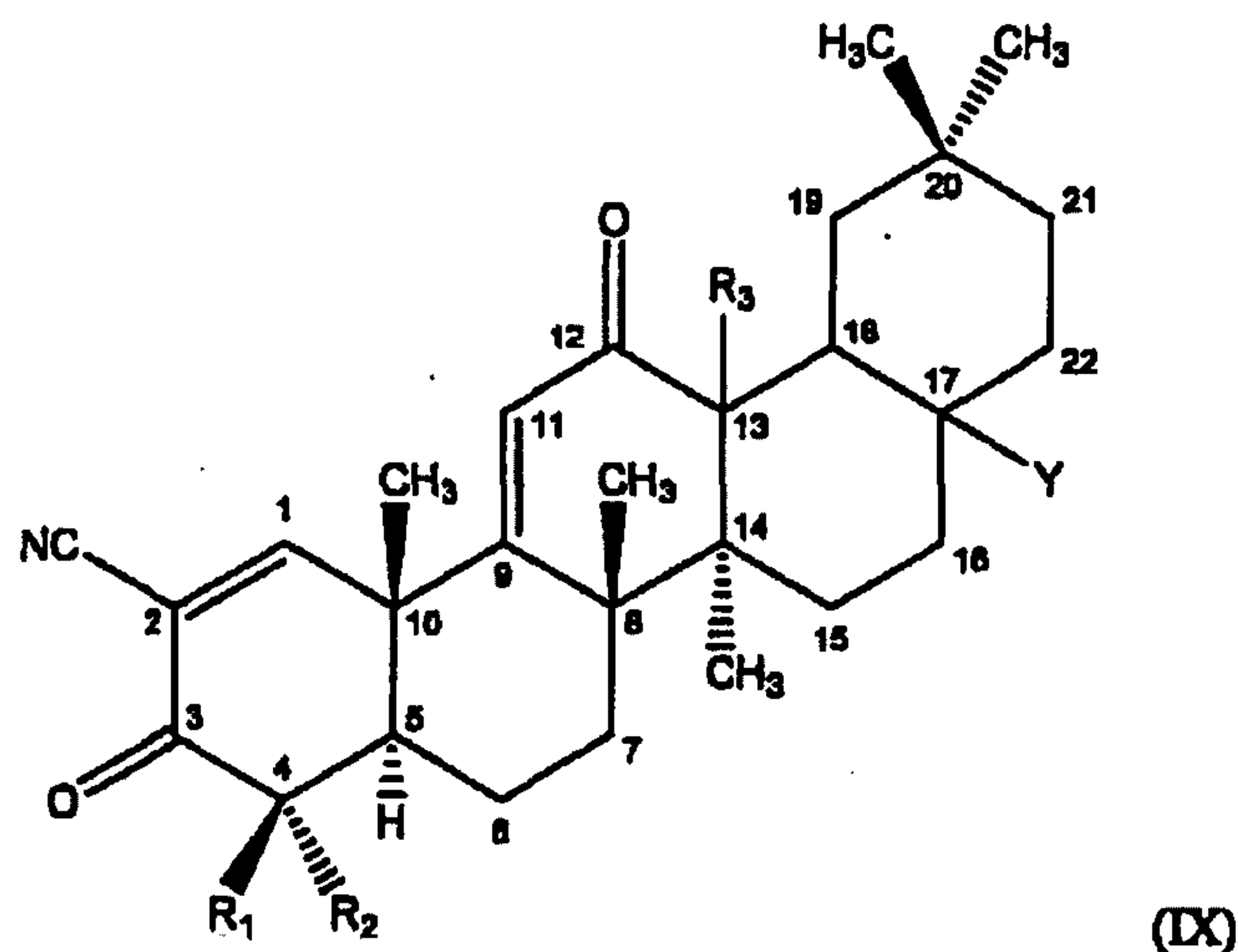
R₇ is hydrogen, alkyl(c₁₋₈), substituted alkyl(c₁₋₈), acyl(c₁₋₈), or
 substituted acyl(c₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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14. The compound according to any one of claims 1-8 and 13, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R_2 is $-(CH_2)_m-(OCH_2)_n-R_5$, wherein:

R_5 is hydroxy or acyl_(C₁₋₈), alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or a substituted version of any of these groups;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3;

R_3 is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), alkenyl_(C₂₋₈), alkynyl_(C₂₋₈), aryl_(C₆₋₁₂), aralkyl_(C₇₋₁₂), heteroaryl_(C₆₋₁₂), heterocycloalkyl_(C₃₋₁₂), alkoxy_(C₁₋₈), cycloalkoxy_(C₃₋₈), aryloxy_(C₆₋₁₂), acyloxy_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), alkenylamino_(C₂₋₈), arylamino_(C₆₋₁₂), aralkylamino_(C₇₋₁₂), alkylthio_(C₁₋₈), acylthio_(C₁₋₈), alkylsulfonylamino_(C₁₋₈), or substituted versions of any of these groups;

$-alkanediy l_{(C_{1-8})}-R_b$, $-alkenediy l_{(C_{2-8})}-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

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heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈),
 aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈),
 alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), aryl-
 amino(C₁₋₈), aralkylamino(C₁₋₈), heteroarylamino(C₁₋₈), alkyl-
 sulfonylamino(C₁₋₈), amido(C₁₋₈), -OC(O)NH-alkyl(C₁₋₈),
 -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(C₁₋₈), or a
 substituted version of any of these groups;

-(CH₂)_oC(O)R_e, wherein o is 0-6 and R_e is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈),
 heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkylamino(C₁₋₈),
 dialkylamino(C₁₋₈), arylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈),
 amido(C₁₋₈), alkoxyamino(C₁₋₈), heterocycloalkylamino(C₁₋₈),
 -NHC(NO₂)-alkyl(C₁₋₈), -NH-amido(C₁₋₈), or a substituted
 version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(C₁₋₈), or substituted alkyl(C₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈),
 heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkoxy(C₁₋₈),
 cycloalkoxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈),
 acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈),
 or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

p is 0-6; and

R_f is -O- or -NR₇-; wherein:

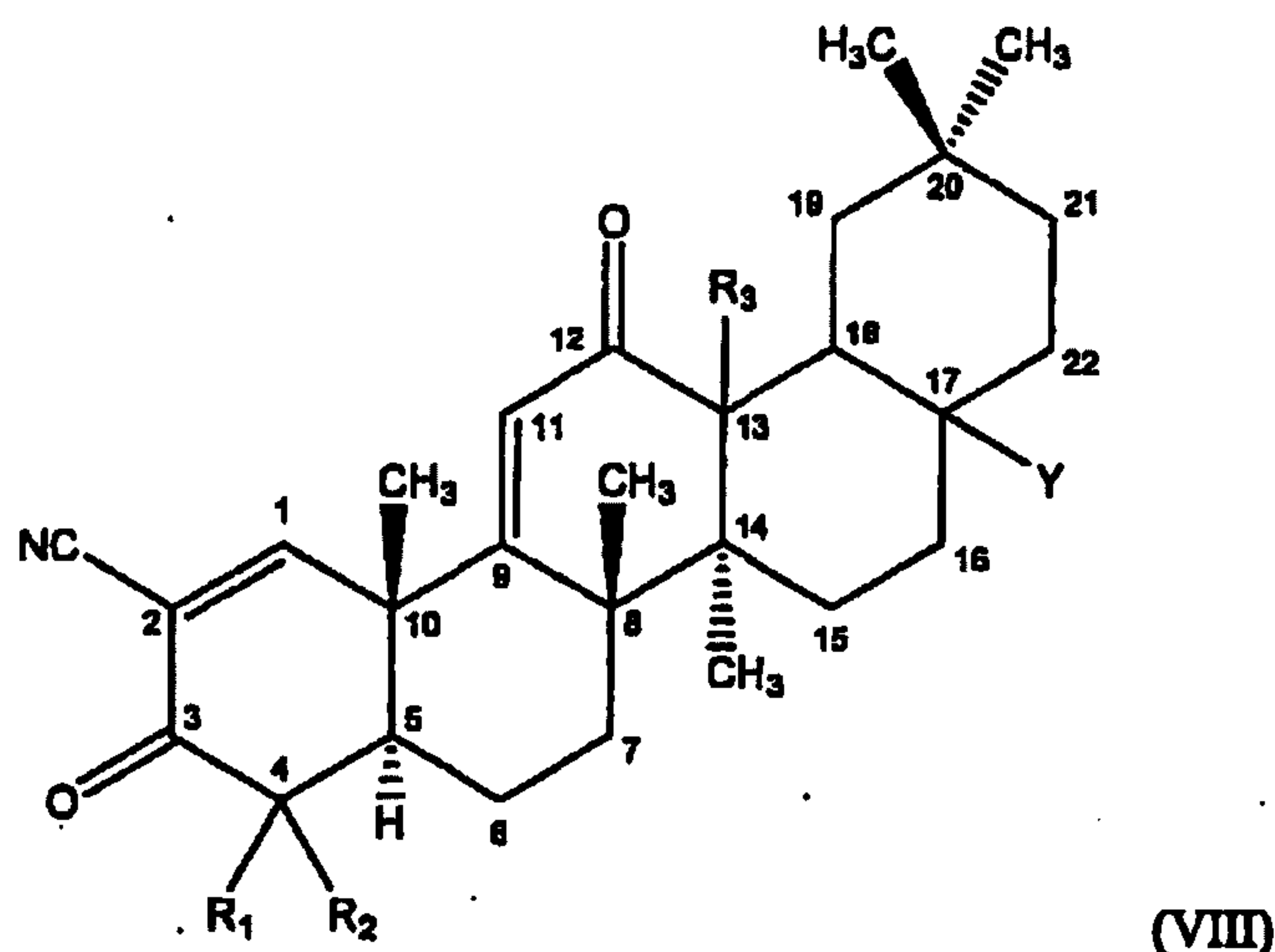
R₇ is hydrogen, alkyl(C₁₋₈), substituted alkyl(C₁₋₈), acyl(C₁₋₈), or
 substituted acyl(C₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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15. The compound according to any one of claims 1-8, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is $-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R_5' is hydrogen, alkyl(C_{1-8}), alkoxy(C_{1-8}), substituted alkoxy(C_{1-8}), acyl(C_{1-8}), substituted acyl(C_{1-8}), $-C(O)-$ alkoxy(C_{1-8}), substituted $-C(O)-$ alkoxy(C_{1-8}), acyloxy(C_{1-8}), substituted acyloxy(C_{1-8}), alkylsilyloxy(C_{1-8}), or substituted alkylsilyloxy(C_{1-8}); and

R_6 is hydrogen, alkyl(C_{1-8}), or substituted alkyl(C_{1-8});

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{1-12}), aralkyl(C_{1-12}), heteroaryl(C_{1-8}), heterocycloalkyl(C_{1-12}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), aryloxy(C_{1-12}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenylamino(C_{2-8}), arylamino(C_{1-8}), aralkylamino(C_{1-8}), alkylthio(C_{1-8}), acylthio(C_{1-8}), alkylsulfonylamino(C_{1-8}), or substituted versions of any of these groups;

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—alkanediyl_(C₁₋₈)—R_b, —alkenediyl_(C₁₋₈)—R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl_(C₁₋₈), alkoxy_(C₁₋₈), cycloalkoxy_(C₁₋₈), alkenyloxy_(C₁₋₈), aryloxy_(C₁₋₈), aralkoxy_(C₁₋₈), heteroaryloxy_(C₁₋₈), acyloxy_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), alkenylamino_(C₁₋₈), arylamino_(C₁₋₈), aralkylamino_(C₁₋₈), heteroarylamino_(C₁₋₈), alkylsulfonylamino_(C₁₋₈), amido_(C₁₋₈), —OC(O)NH—alkyl_(C₁₋₈), —OC(O)CH₂NHC(O)O—*t*-butyl, —OCH₂—alkylthio_(C₁₋₈), or a substituted version of any of these groups;

—(CH₂)_oC(O)R_c, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, —NHOH, or mercapto; or

alkyl_(C₁₋₈), cycloalkyl_(C₁₋₈), alkenyl_(C₁₋₈), alkynyl_(C₁₋₈), aryl_(C₁₋₈), aralkyl_(C₁₋₈), heteroaryl_(C₁₋₈), heterocycloalkyl_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), arylamino_(C₁₋₈), alkylsulfonylamino_(C₁₋₈), amido_(C₁₋₈), alkoxyamino_(C₁₋₈), heterocycloalkylamino_(C₁₋₈), —NHC(NOH)—alkyl_(C₁₋₈), —NH—amido_(C₁₋₈), or a substituted version of any of these groups;

—NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl_(C₁₋₈), or substituted alkyl_(C₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl_(C₁₋₈), cycloalkyl_(C₁₋₈), alkenyl_(C₁₋₈), alkynyl_(C₁₋₈), aryl_(C₁₋₈), aralkyl_(C₁₋₈), heteroaryl_(C₁₋₈), heterocycloalkyl_(C₁₋₈), alkoxy_(C₁₋₈), cycloalkoxy_(C₁₋₈), aryloxy_(C₁₋₈), aralkoxy_(C₁₋₈), heteroaryloxy_(C₁₋₈), acyloxy_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), arylamino_(C₁₋₈), or a substituted version of any of these groups; or

Y is taken together with R₃ and is —(CH₂)_pC(O)R_f—, wherein

p is 0–6; and

R_f is —O— or —NR₇—, wherein:

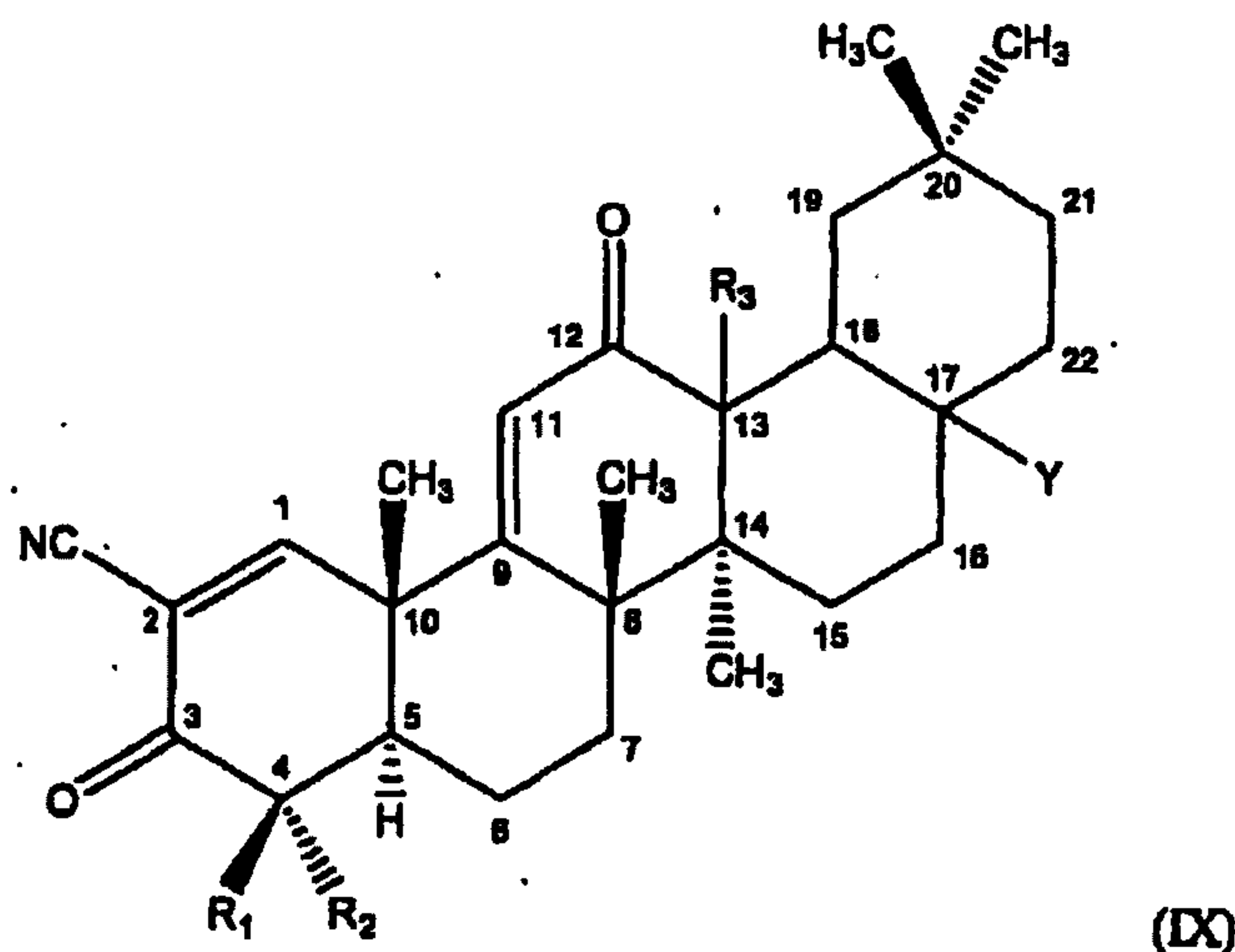
R₇ is hydrogen, alkyl_(C₁₋₈), substituted alkyl_(C₁₋₈), acyl_(C₁₋₈), or substituted acyl_(C₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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16. The compound according to any one of claims 1-8 and 15, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is $-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R_5' is hydrogen, alkyl(C_{1-8}), alkoxy(C_{1-8}), substituted alkoxy(C_{1-8}), acyl(C_{1-8}), substituted acyl(C_{1-8}), $-C(O)-$ alkoxy(C_{1-8}), substituted $-C(O)-$ alkoxy(C_{1-8}), acyloxy(C_{1-8}), substituted acyloxy(C_{1-8}), alkylsilyloxy(C_{1-8}), or substituted alkylsilyloxy(C_{1-8}); and

R_6 is hydrogen, alkyl(C_{1-8}), or substituted alkyl(C_{1-8});

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{6-12}), aralkyl(C_{7-12}), heteroaryl(C_{6-12}), heterocycloalkyl(C_{3-12}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), aryloxy(C_{6-12}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenylamino(C_{2-8}), arylamino(C_{6-12}), aralkylamino(C_{7-12}), alkylthio(C_{1-8}), acylthio(C_{1-8}), alkylsulfonylamino(C_{1-8}), or substituted versions of any of these groups;

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—alkanediyl(C₁₋₈)—R_b, —alkenediyl(C₁₋₈)—R_b, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), arylamino(C₁₋₈), aralkylamino(C₁₋₈), heteroarylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), —OC(O)NH—alkyl(C₁₋₈), —OC(O)CH₂NHC(O)O-*t*-butyl, —OCH₂—alkylthio(C₁₋₈), or a substituted version of any of these groups;

—(CH₂)_oC(O)R_c, wherein o is 0–6 and R_c is:

hydrogen, halo, amino, —NHOH, or mercapto; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈), amido(C₁₋₈), alkoxyamino(C₁₋₈), heterocycloalkylamino(C₁₋₈), —NHC(NOH)—alkyl(C₁₋₈), —NH—amido(C₁₋₈), or a substituted version of any of these groups;

—NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(C₁₋₈), or substituted alkyl(C₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈), heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈), or a substituted version of any of these groups; or

Y is taken together with R₃ and is —(CH₂)_pC(O)R_f—, wherein

p is 0–6; and

R_f is —O— or —NR₇—; wherein:

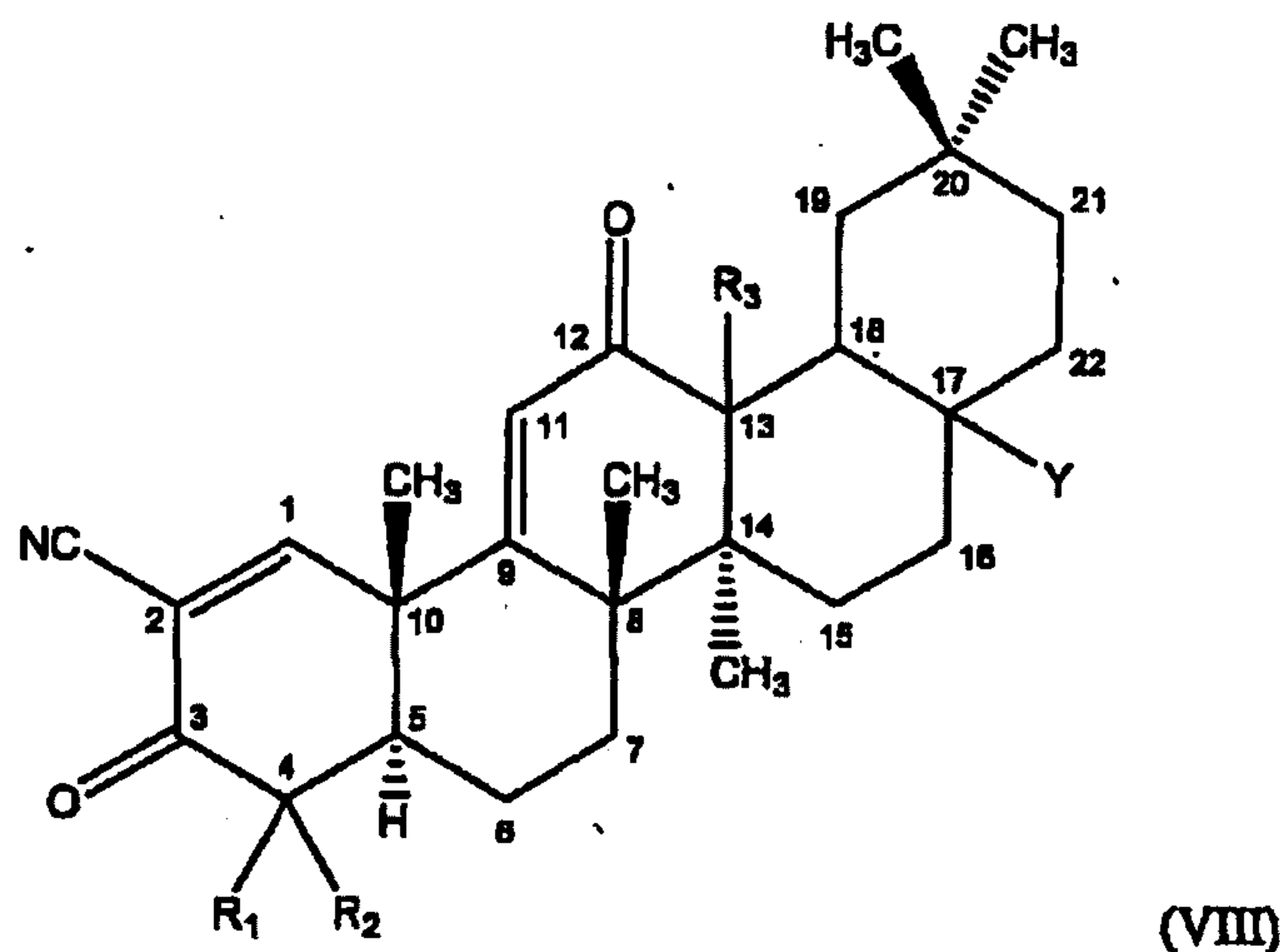
R₇ is hydrogen, alkyl(C₁₋₈), substituted alkyl(C₁₋₈), acyl(C₁₋₈), or substituted acyl(C₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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17. The compound according to any one of claims 1-8, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is $-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy(C_{1-8}), alkylthio(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{1-12}), aralkyl(C_{1-12}),

heteroaryl(C_{1-8}), heterocycloalkyl(C_{3-12}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}),

aryloxy(C_{1-12}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenyl-

amino(C_{1-8}), arylamino(C_{1-8}), aralkylamino(C_{1-8}), alkylthio(C_{1-8}), acylthio(C_{1-8}),

alkylsulfonylamino(C_{1-8}), or substituted versions of any of these groups;

$-alkanediy(C_{1-8})-R_b$, $-alkenediy(C_{1-8})-R_b$, or a substituted version of any of these groups, wherein R_b is:

hydrogen, hydroxy, halo, amino or mercapto; or

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heteroaryl(C₁₋₈), alkoxy(C₁₋₈), cycloalkoxy(C₁₋₈), alkenyloxy(C₁₋₈),
 aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈), acyloxy(C₁₋₈),
 alkylamino(C₁₋₈), dialkylamino(C₁₋₈), alkenylamino(C₁₋₈), aryl-
 amino(C₁₋₈), aralkylamino(C₁₋₈), heteroarylamino(C₁₋₈), alkyl-
 sulfonylamino(C₁₋₈), amido(C₁₋₈), -OC(O)NH-alkyl(C₁₋₈),
 -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(C₁₋₈), or a
 substituted version of any of these groups;

-(CH₂)_oC(O)R_e, wherein o is 0-6 and R_e is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈),
 heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkylamino(C₁₋₈),
 dialkylamino(C₁₋₈), arylamino(C₁₋₈), alkylsulfonylamino(C₁₋₈),
 amido(C₁₋₈), alkoxyamino(C₁₋₈), heterocycloalkylamino(C₁₋₈),
 -NHC(NO₂)-alkyl(C₁₋₈), -NH-amido(C₁₋₈), or a substituted
 version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(C₁₋₈), or substituted alkyl(C₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(C₁₋₈), cycloalkyl(C₁₋₈), alkenyl(C₁₋₈), alkynyl(C₁₋₈), aryl(C₁₋₈), aralkyl(C₁₋₈),
 heteroaryl(C₁₋₈), heterocycloalkyl(C₁₋₈), alkoxy(C₁₋₈),
 cycloalkoxy(C₁₋₈), aryloxy(C₁₋₈), aralkoxy(C₁₋₈), heteroaryloxy(C₁₋₈),
 acyloxy(C₁₋₈), alkylamino(C₁₋₈), dialkylamino(C₁₋₈), arylamino(C₁₋₈),
 or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

p is 0-6; and

R_f is -O- or -NR₇-; wherein:

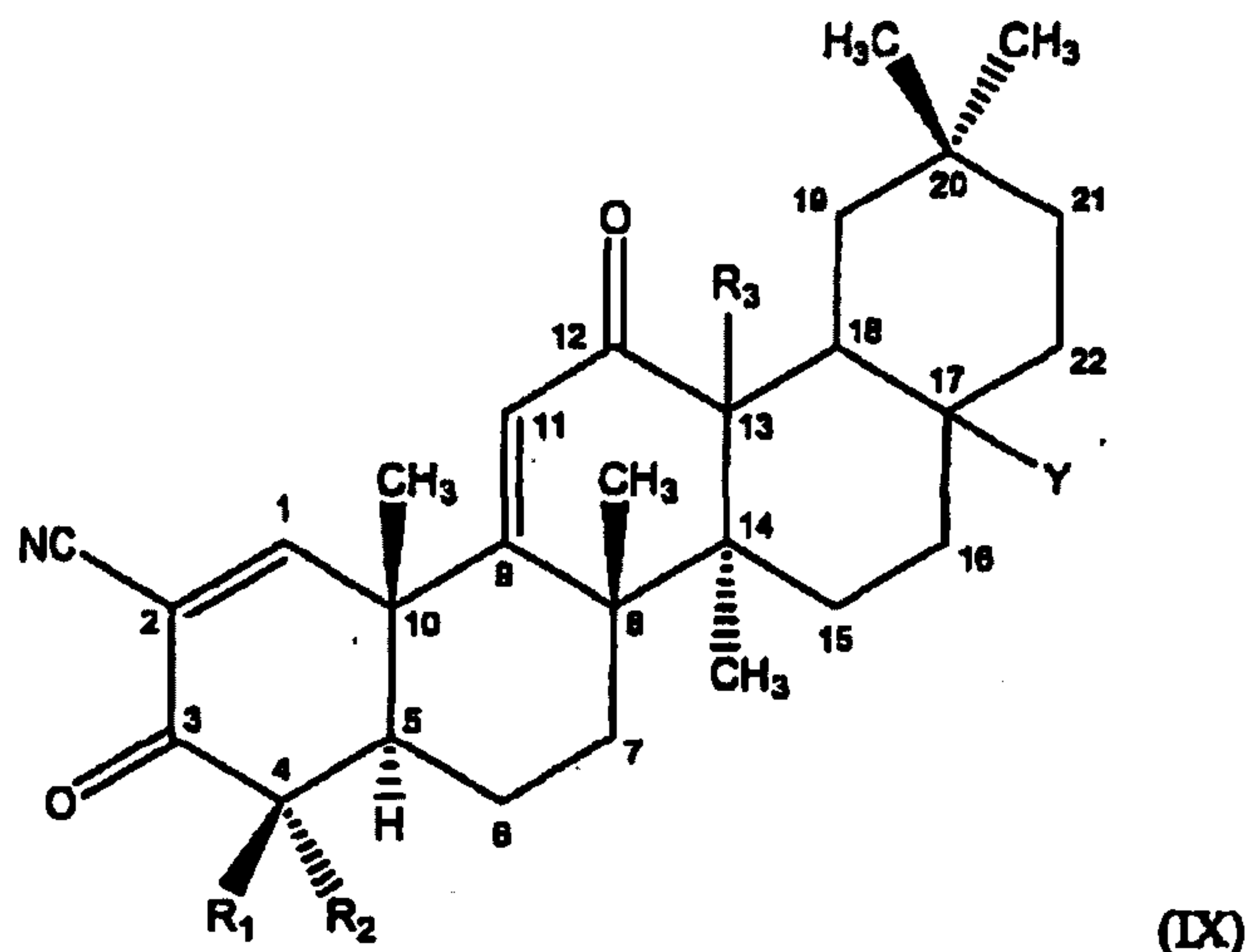
R₇ is hydrogen, alkyl(C₁₋₈), substituted alkyl(C₁₋₈), acyl(C₁₋₈), or
 substituted acyl(C₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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18. The compound according to any one of claims 1-8 and 17, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is $-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy(C_{1-8}), alkylthio(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; or R_3 is taken together with Y as described below; and

Y is hydrogen, hydroxy, halo, amino, cyano, isocyanate, or mercapto;

alkyl(C_{1-8}), cycloalkyl(C_{3-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{1-12}), aralkyl(C_{1-12}),

heteroaryl(C_{3-8}), heterocycloalkyl(C_{3-12}), alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}),

aryloxy(C_{1-12}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), alkenyl-

amino(C_{2-8}), arylamino(C_{1-8}), aralkylamino(C_{1-8}), alkylthio(C_{1-8}), acylthio(C_{1-8}),

alkylsulfonylamino(C_{1-8}), or substituted versions of any of these groups;

$-alkanediy(C_{1-8})-R_6$, $-alkenediy(C_{1-8})-R_6$, or a substituted version of any of these groups, wherein R_6 is:

hydrogen, hydroxy, halo, amino or mercapto; or

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heteroaryl(c₁₋₈), alkoxy(c₁₋₈), cycloalkoxy(c₁₋₈), alkenyloxy(c₁₋₈), aryloxy(c₁₋₈), aralkoxy(c₁₋₈), heteroaryloxy(c₁₋₈), acyloxy(c₁₋₈), alkylamino(c₁₋₈), dialkylamino(c₁₋₈), alkenylamino(c₁₋₈), arylamino(c₁₋₈), aralkylamino(c₁₋₈), heteroarylamino(c₁₋₈), alkylsulfonylamino(c₁₋₈), amido(c₁₋₈), -OC(O)NH-alkyl(c₁₋₈), -OC(O)CH₂NHC(O)O-*t*-butyl, -OCH₂-alkylthio(c₁₋₈), or a substituted version of any of these groups;

-(CH₂)_oC(O)R_e, wherein o is 0-6 and R_e is:

hydrogen, halo, amino, -NHOH, or mercapto; or

alkyl(c₁₋₈), cycloalkyl(c₁₋₈), alkenyl(c₁₋₈), alkynyl(c₁₋₈), aryl(c₁₋₈), aralkyl(c₁₋₈), heteroaryl(c₁₋₈), heterocycloalkyl(c₁₋₈), alkylamino(c₁₋₈), dialkylamino(c₁₋₈), arylamino(c₁₋₈), alkylsulfonylamino(c₁₋₈), amido(c₁₋₈), alkoxyamino(c₁₋₈), heterocycloalkylamino(c₁₋₈), -NHC(NO₂)-alkyl(c₁₋₈), -NH-amido(c₁₋₈), or a substituted version of any of these groups;

-NR_dC(O)R_e, wherein

R_d is hydrogen, alkyl(c₁₋₈), or substituted alkyl(c₁₋₈);

R_e is hydrogen, hydroxy, amino; or

alkyl(c₁₋₈), cycloalkyl(c₁₋₈), alkenyl(c₁₋₈), alkynyl(c₁₋₈), aryl(c₁₋₈), aralkyl(c₁₋₈), heteroaryl(c₁₋₈), heterocycloalkyl(c₁₋₈), alkoxy(c₁₋₈), cycloalkoxy(c₁₋₈), aryloxy(c₁₋₈), aralkoxy(c₁₋₈), heteroaryloxy(c₁₋₈), acyloxy(c₁₋₈), alkylamino(c₁₋₈), dialkylamino(c₁₋₈), arylamino(c₁₋₈), or a substituted version of any of these groups; or

Y is taken together with R₃ and is -(CH₂)_pC(O)R_f, wherein

p is 0-6; and

R_f is -O- or -NR₇-; wherein:

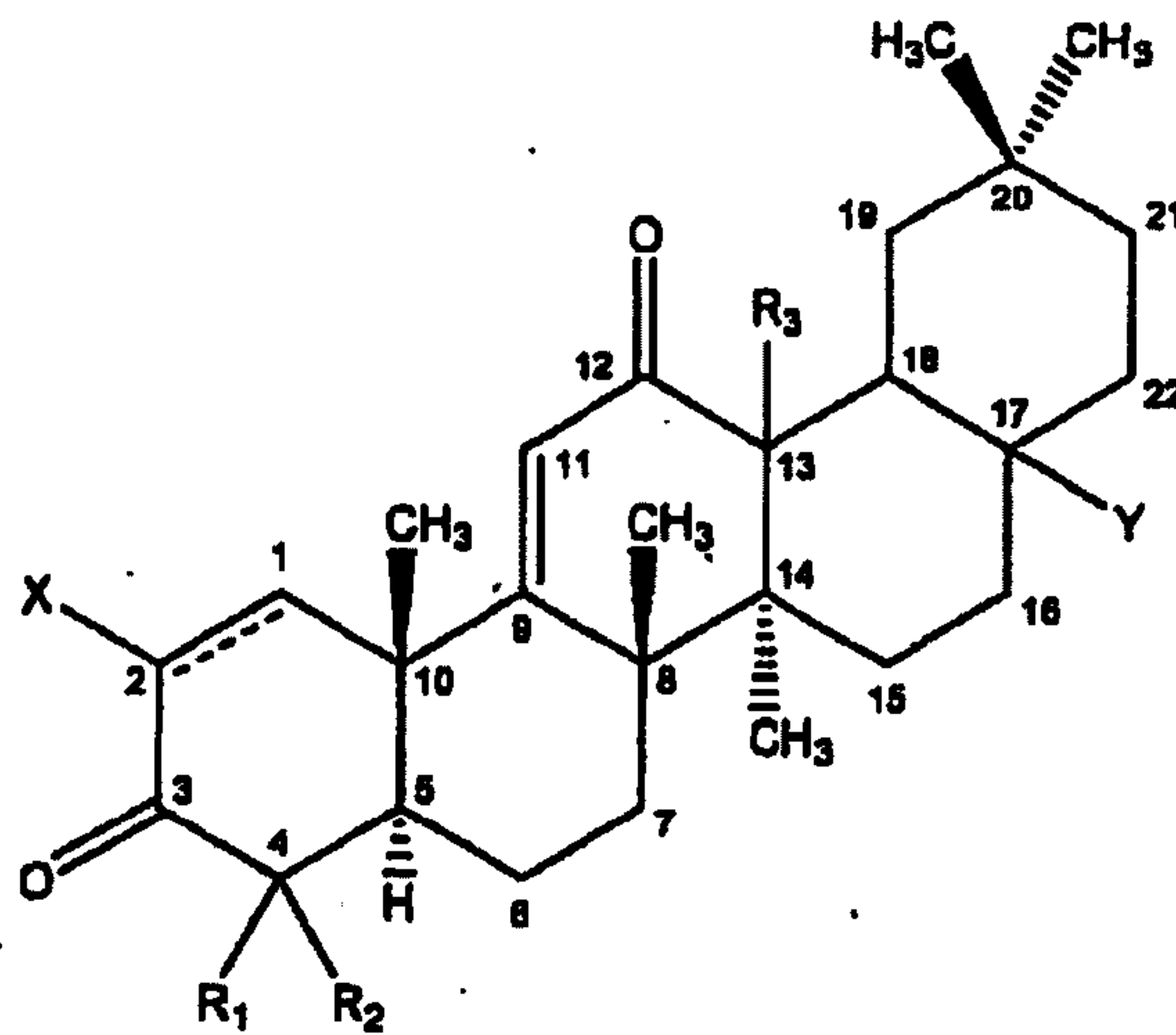
R₇ is hydrogen, alkyl(c₁₋₈), substituted alkyl(c₁₋₈), acyl(c₁₋₈), or substituted acyl(c₁₋₈);

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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19. The compound of claim 1, wherein the compound is further defined as:



wherein:

the bond between atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

X is cyano, heteroaryl_(C₁₋₈), substituted heteroaryl_(C₁₋₈), -CF₃, or -C(O)-R₄; wherein

R₄ is hydroxy, amino, or alkoxy_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), alkylsulfonylamino_(C₁₋₈), or a substituted version of any of these groups;

R₁ is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R₂ is amino, cyano, halo, or hydroxy,

haloalkyl_(C₁₋₈), substituted cycloalkyl_(C₃₋₈), heteroaryl_(C₁₋₈), substituted heteroaryl_(C₁₋₈), acyl_(C₁₋₈), substituted acyl_(C₁₋₈), amido_(C₁₋₈), substituted amido_(C₁₋₈), alkylamino_(C₁₋₈), substituted alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), or dialkylamino_(C₁₋₈); or

-OR₅, wherein:

R₅ is hydrogen or alkyl_(C₁₋₈), alkenyl_(C₂₋₈), alkynyl_(C₂₋₈), aryl_(C₆₋₁₂), aralkyl_(C₁₋₁₂), heteroaryl_(C₁₋₁₂), heterocycloalkyl_(C₃₋₈), acyl_(C₁₋₈), or a substituted version of any of these groups;

-(CH₂)_m-R₅'', wherein:

R₅'' is alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), substituted acyloxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or substituted alkylsilyloxy_(C₁₋₈); and

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m is 0, 1, 2, 3, or 4;

$-(CH_2)_{m2}-R_5'''$, wherein:

R_5''' is hydroxy; and

m_2 is 2, 3, or 4;

$-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R_5' is hydrogen, alkyl($C_{\leq 8}$), alkoxy($C_{\leq 8}$), substituted alkoxy($C_{\leq 8}$),

acyl($C_{\leq 8}$), substituted acyl($C_{\leq 8}$), $-C(O)-$ alkoxy($C_{\leq 8}$),

substituted $-C(O)-$ alkoxy($C_{\leq 8}$), acyloxy($C_{\leq 8}$), substituted

acyloxy($C_{\leq 8}$), alkylsilyloxy($C_{\leq 8}$), or substituted

alkylsilyloxy($C_{\leq 8}$); and

R_6 is hydrogen, alkyl($C_{\leq 8}$), or substituted alkyl($C_{\leq 8}$); or

$-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy($C_{\leq 8}$), alkylthio($C_{\leq 8}$), alkylamino($C_{\leq 8}$), dialkyl-

amino($C_{\leq 8}$), or a substituted version of any of these

groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy($C_{\leq 8}$), acyloxy($C_{\leq 8}$), or substituted version of

either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

alkoxy($C_{\leq 8}$), cycloalkoxy($C_{\leq 8}$), alkenyloxy($C_{\leq 8}$), aryloxy($C_{\leq 8}$), aralkoxy($C_{\leq 8}$),

heteroaryloxy($C_{\leq 8}$), acyloxy($C_{\leq 8}$), or a substituted version of any

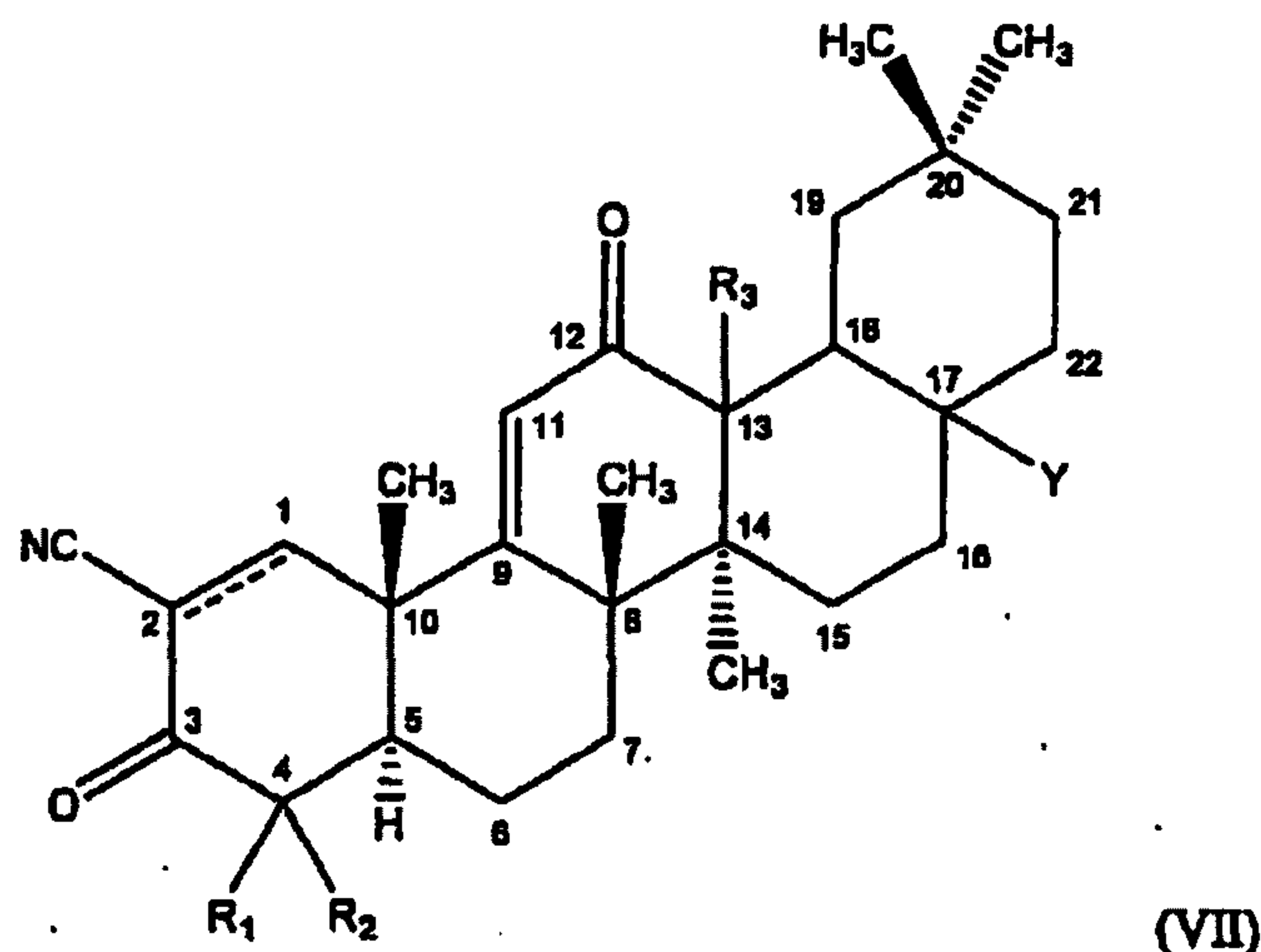
of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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20. The compound of either claim 1 or claim 19, wherein the compound is further defined as:



wherein:

the bond between atoms 1 and 2 is a single bond, an epoxidized double bond, or a double bond;

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is amino, cyano, halo, or hydroxy,

haloalkyl(C_{1-8}), substituted cycloalkyl(C_{3-8}), heteroaryl(C_{1-8}), substituted heteroaryl(C_{1-8}), acyl(C_{1-8}), substituted acyl(C_{1-8}), amido(C_{1-8}), substituted amido(C_{1-8}), alkylamino(C_{1-8}), substituted alkylamino(C_{1-8}), dialkylamino(C_{1-8}), or dialkylamino(C_{1-8}); or

$-OR_a$, wherein:

R_a is hydrogen or alkyl(C_{1-8}), alkenyl(C_{2-8}), alkynyl(C_{2-8}), aryl(C_{1-12}), aralkyl(C_{1-12}), heteroaryl(C_{1-12}), heterocycloalkyl(C_{3-8}), acyl(C_{1-8}), or a substituted version of any of these groups;

$-(CH_2)_m-R_5'''$, wherein:

R_5''' is alkoxy(C_{1-8}), acyloxy(C_{1-8}), substituted alkoxy(C_{1-8}), alkylsilyloxy(C_{1-8}), or substituted alkylsilyloxy(C_{1-8}); and

m is 0, 1, 2, 3, or 4; or

$-(CH_2)_{m_2}-R_5'''$, wherein:

R_5''' is hydroxy; and

m_2 is 2, 3, or 4;

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$-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R_5' is hydrogen, alkyl_(C₁₋₈), alkoxy_(C₁₋₈), substituted alkoxy_(C₁₋₈), acyl_(C₁₋₈), substituted acyl_(C₁₋₈), $-C(O)-$ alkoxy_(C₁₋₈), substituted $-C(O)-$ alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), substituted acyloxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or substituted alkylsilyloxy_(C₁₋₈); and

R_6 is hydrogen, alkyl_(C₁₋₈), or substituted alkyl_(C₁₋₈); or

$-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy_(C₁₋₈), alkylthio_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

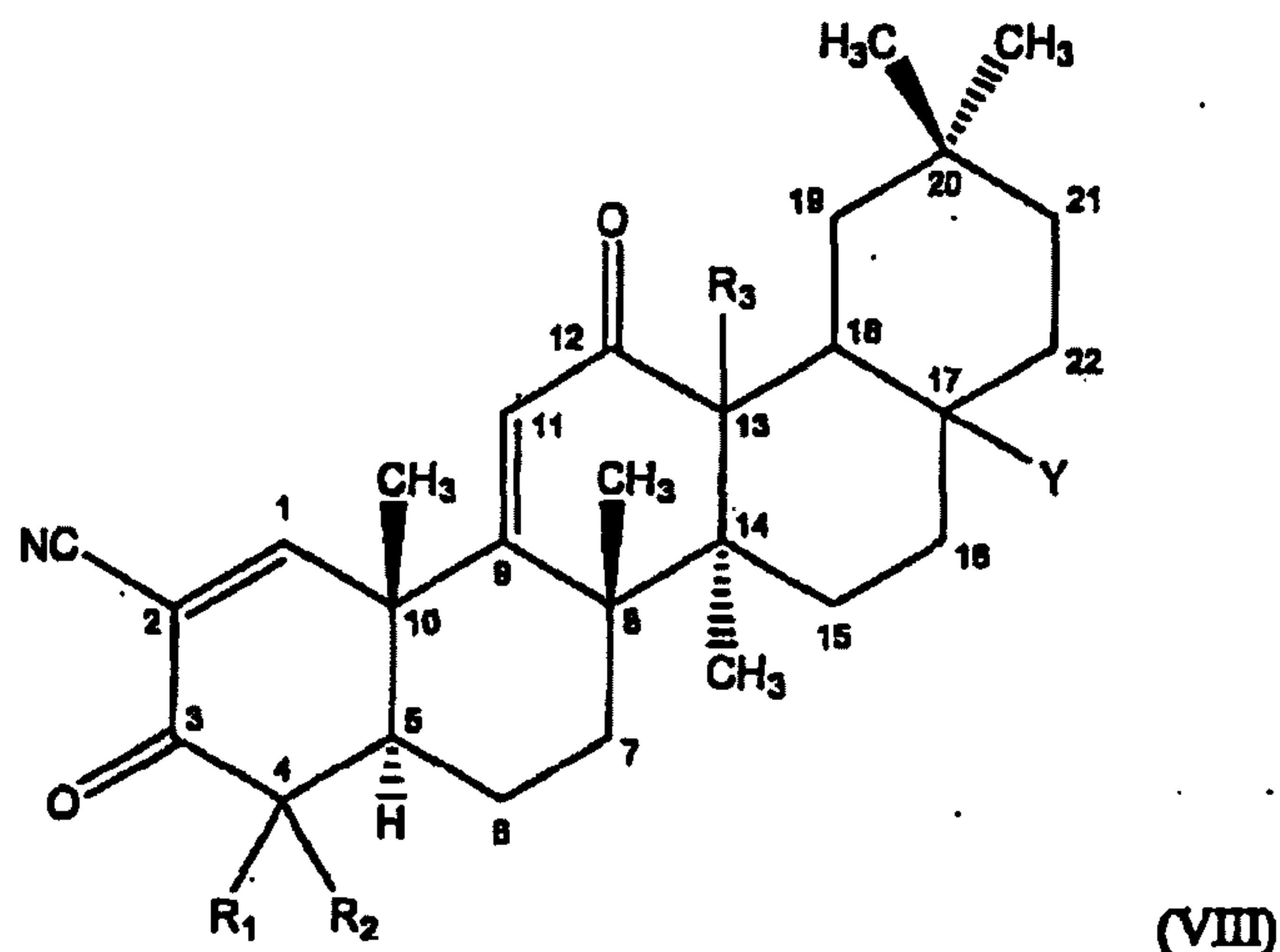
alkoxy_(C₁₋₈), cycloalkoxy_(C₁₋₈), alkenyloxy_(C₁₋₈), aryloxy_(C₁₋₈), aralkoxy_(C₁₋₈), heteroaryloxy_(C₁₋₈), acyloxy_(C₁₋₈), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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21. The compound according to any one of claims 1, 19, and 20, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R_2 is amino, cyano, halo, or hydroxy,

haloalkyl_(C₁₋₈), substituted cycloalkyl_(C₃₋₈), heteroaryl_(C₁₋₈), substituted heteroaryl_(C₁₋₈), acyl_(C₁₋₈), substituted acyl_(C₁₋₈), amido_(C₁₋₈), substituted amido_(C₁₋₈), alkylamino_(C₁₋₈), substituted alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), or dialkylamino_(C₁₋₈); or

$-OR_a$, wherein:

R_a is hydrogen or alkyl_(C₁₋₈), alkenyl_(C₂₋₈), alkynyl_(C₂₋₈), aryl_(C₆₋₁₂), aralkyl_(C₇₋₁₂), heteroaryl_(C₆₋₁₂), heterocycloalkyl_(C₃₋₈), acyl_(C₁₋₈), or a substituted version of any of these groups;

$-(CH_2)_m-R_5'''$, wherein:

R_5''' is alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), substituted alkoxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or substituted alkylsilyloxy_(C₁₋₈); and

m is 0, 1, 2, 3, or 4; or

$-(CH_2)_{m2}-R_5'''$, wherein:

R_5''' is hydroxy; and

m_2 is 2, 3, or 4;

$-(CH_2)_s-NR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

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R_5' is hydrogen, alkyl(C_{1-8}), alkoxy(C_{1-8}), substituted alkoxy(C_{1-8}), acyl(C_{1-8}), substituted acyl(C_{1-8}), $-C(O)-$ alkoxy(C_{1-8}), substituted $-C(O)-$ alkoxy(C_{1-8}), acyloxy(C_{1-8}), substituted acyloxy(C_{1-8}), alkylsilyloxy(C_{1-8}), or substituted alkylsilyloxy(C_{1-8}); and

R_6 is hydrogen, alkyl(C_{1-8}), or substituted alkyl(C_{1-8}); or $-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy(C_{1-8}), alkylthio(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

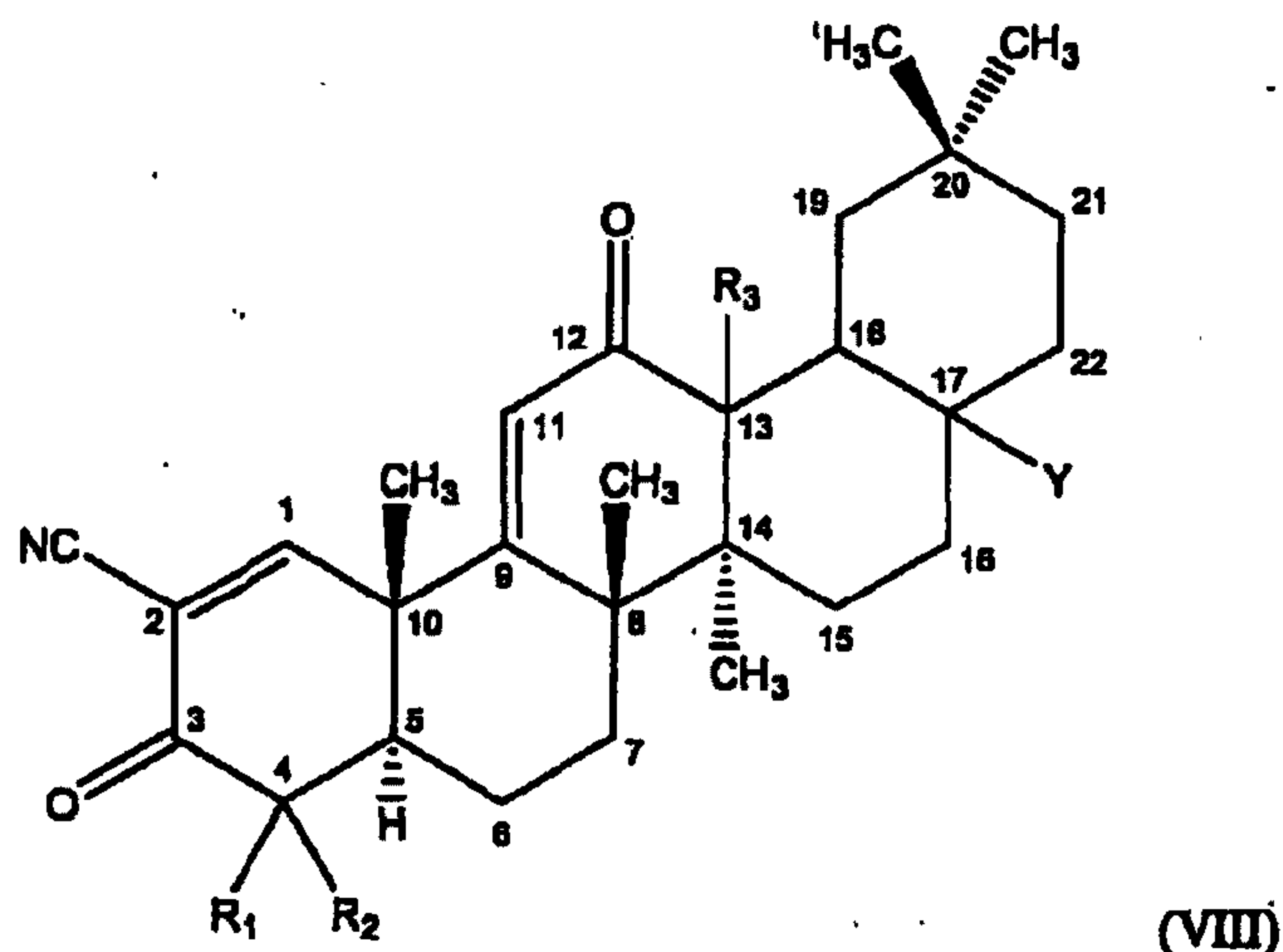
alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), alkenyloxy(C_{2-8}), aryloxy(C_{6-8}), aralkoxy(C_{1-8}), heteroaryloxy(C_{6-8}), acyloxy(C_{1-8}), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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22. The compound according to any one of claims 1 and 19-21, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-6}), cycloalkyl(C_{3-6}), substituted alkyl(C_{1-6}), or substituted cycloalkyl(C_{3-6});

R_2 is amino, cyano, halo, or hydroxy, haloalkyl(C_{1-6}), heteroaryl(C_{1-6}), substituted heteroaryl(C_{1-6}), acyl(C_{1-6}), substituted acyl(C_{1-6}), amido(C_{1-6}), substituted amido(C_{1-6}), alkylamino(C_{1-6}), substituted alkylamino(C_{1-6}), dialkylamino(C_{1-6}), or dialkylamino(C_{1-6});

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-6}), acyloxy(C_{1-6}), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

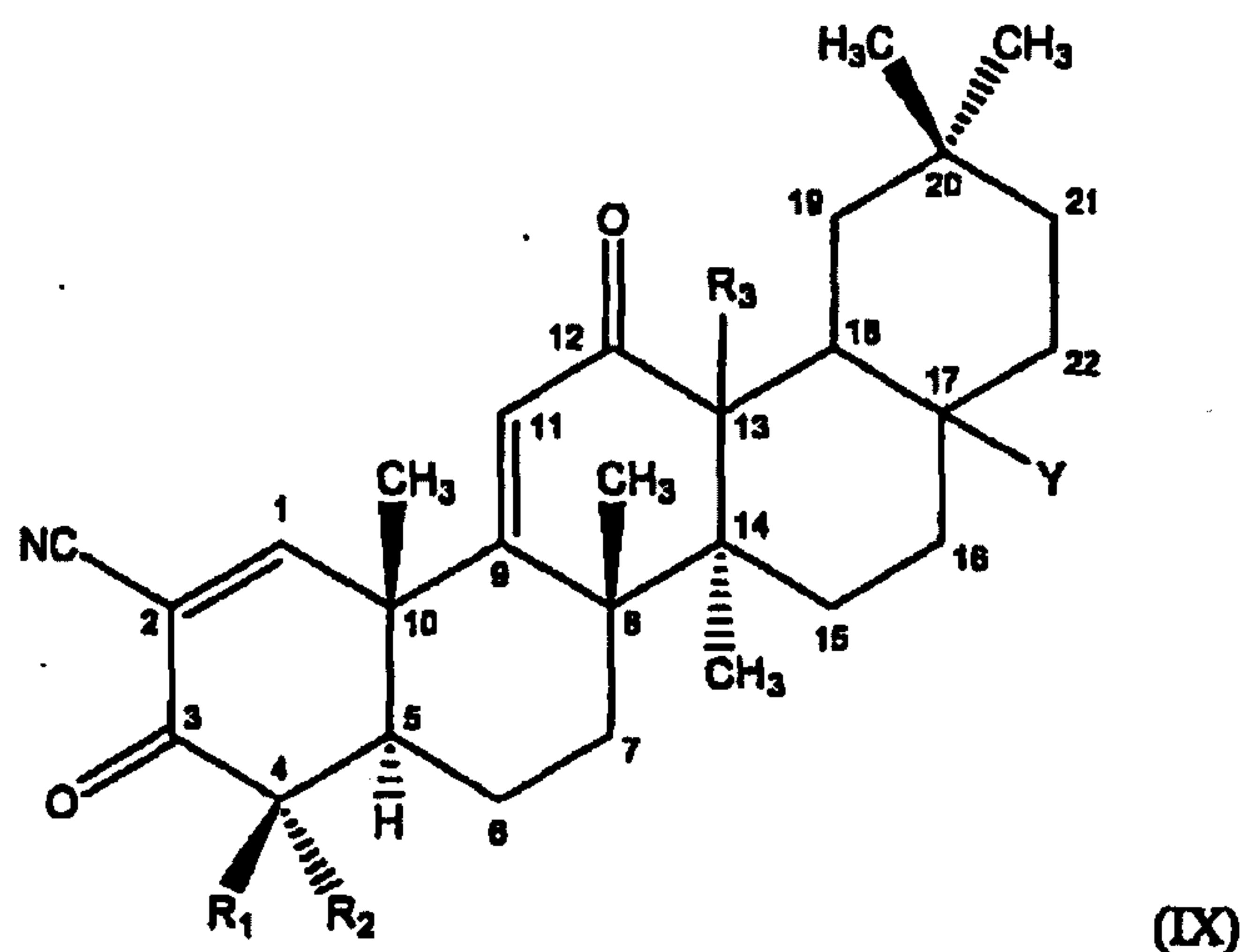
alkoxy(C_{1-6}), cycloalkoxy(C_{3-6}), alkenyloxy(C_{1-6}), aryloxy(C_{1-6}), aralkoxy(C_{1-6}), heteroaryloxy(C_{1-6}), acyloxy(C_{1-6}), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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23. The compound according to any one of claims 1 and 19-22, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is amino, cyano, halo, or hydroxy, haloalkyl(C_{1-8}), heteroaryl(C_{1-8}), substituted heteroaryl(C_{1-8}), acyl(C_{1-8}), substituted acyl(C_{1-8}), amido(C_{1-8}), substituted amido(C_{1-8}), alkylamino(C_{1-8}), substituted alkylamino(C_{1-8}), dialkylamino(C_{1-8}), or dialkylamino(C_{1-8});

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

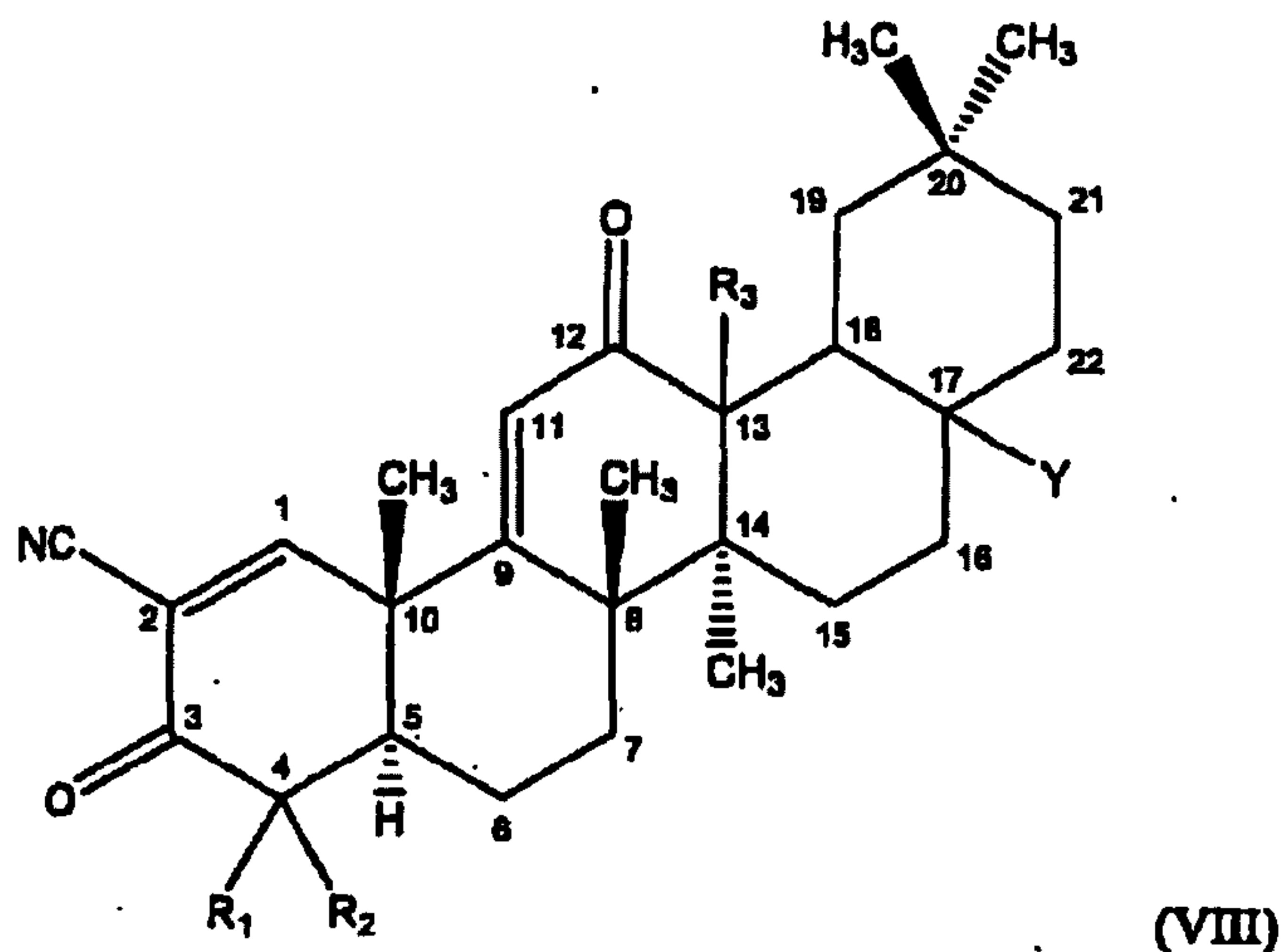
alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), alkenyloxy(C_{1-8}), aryloxy(C_{1-8}), aralkoxy(C_{1-8}), heteroaryloxy(C_{1-8}), acyloxy(C_{1-8}), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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24. The compound according to any one of claims 1 and 19-21, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R_2 is $-(CH_2)_m-R_5'''$, wherein:

R_5''' is alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), ~~substituted alkoxy_(C₁₋₈)~~, alkylsilyloxy_(C₁₋₈), or substituted alkylsilyloxy_(C₁₋₈); and

m is 0, 1, 2, 3, or 4; or

R_2 is $-(CH_2)_{m2}-R_5'''$, wherein:

R_5''' is hydroxy; and

m_2 is 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

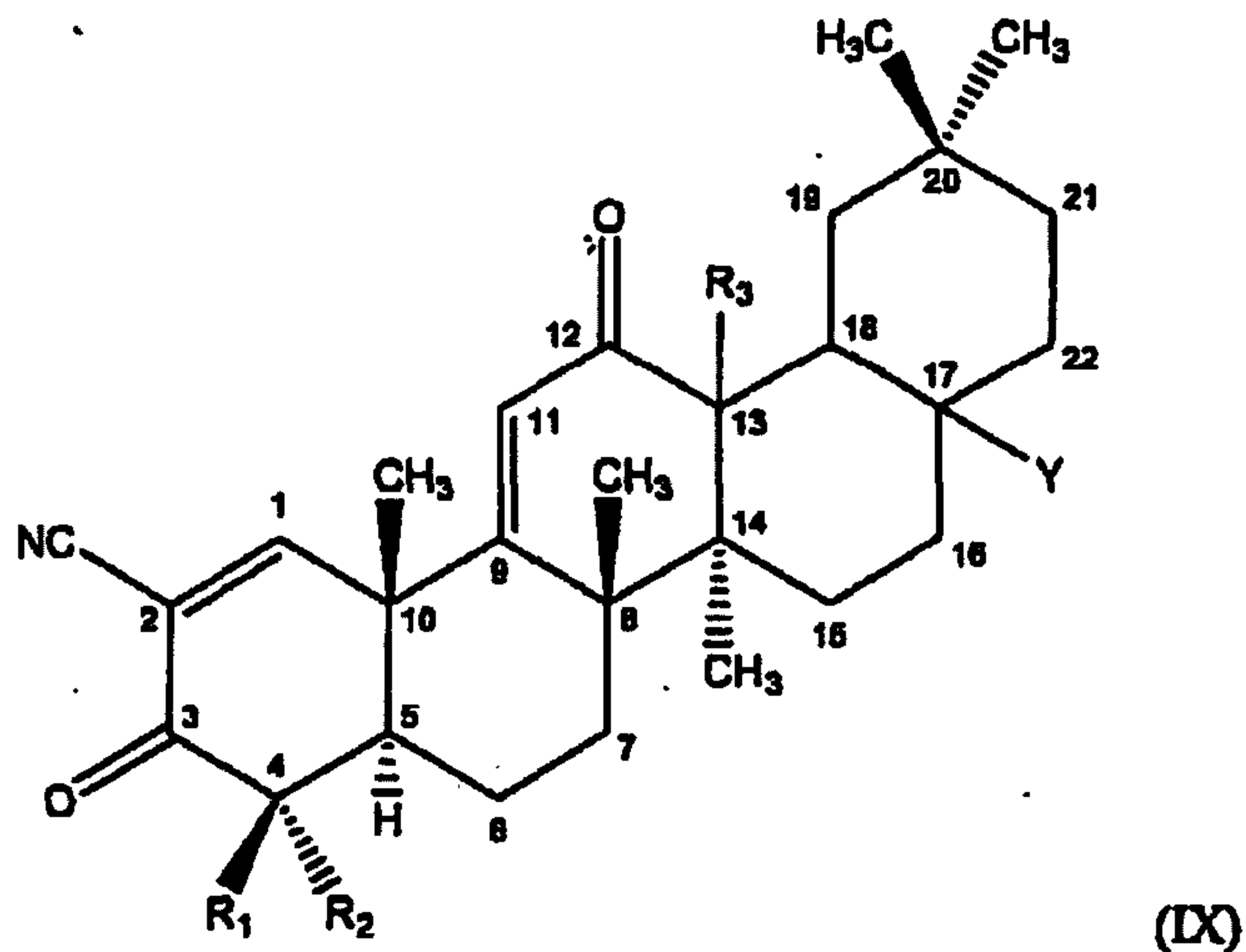
alkoxy_(C₁₋₈), cycloalkoxy_(C₃₋₈), alkenyloxy_(C₁₋₈), aryloxy_(C₁₋₈), aralkoxy_(C₁₋₈), heteroaryloxy_(C₁₋₈), acyloxy_(C₁₋₈), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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25. The compound according to any one of claims 1, 19-21, and 24, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is $-(CH_2)_m-R_5'''$, wherein:

R_5''' is alkoxy(C_{1-8}), acyloxy(C_{1-8}), ~~substituted~~ ~~acyloxy~~(C_{1-8}), alkylsilyloxy(C_{1-8}), or substituted alkylsilyloxy(C_{1-8}); and

m is 0, 1, 2, 3, or 4; or

R_2 is $-(CH_2)_{m2}-R_5'''$, wherein:

R_5''' is hydroxy; and

m_2 is 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

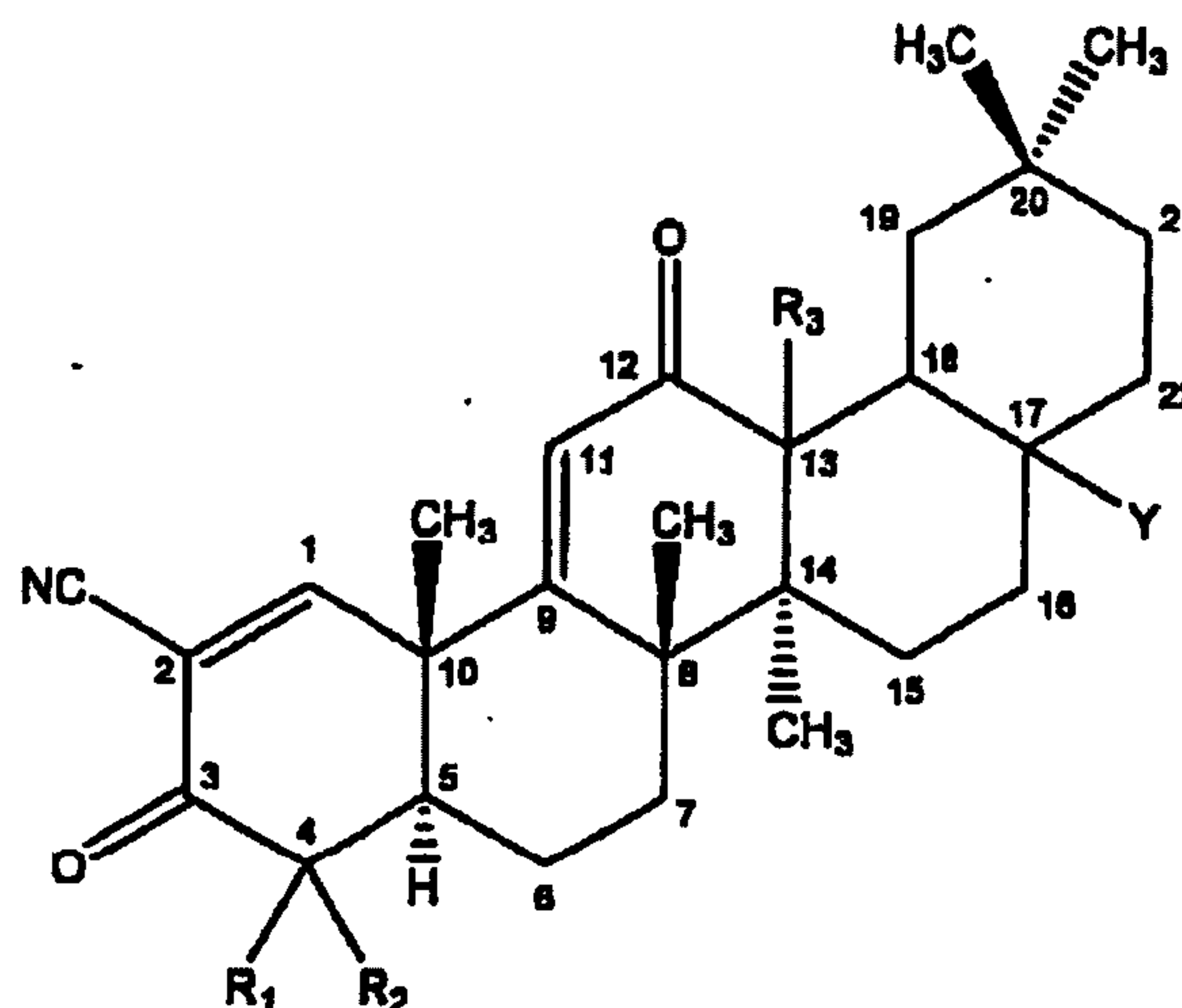
alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), alkenyloxy(C_{1-8}), aryloxy(C_{1-8}), aralkoxy(C_{1-8}), heteroaryloxy(C_{1-8}), acyloxy(C_{1-8}), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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26. The compound according to any one of claims 1 and 19-21, wherein the compound is further defined as:



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wherein:

R_1 is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R_2 is $-OR_a$, wherein:

R_a is hydrogen or alkyl_(C₁₋₈), alkenyl_(C₂₋₈), alkynyl_(C₂₋₈), aryl_(C₆₋₁₂), aralkyl_(C₁₋₁₂), heteroaryl_(C₆₋₁₂), heterocycloalkyl_(C₃₋₈), acyl_(C₁₋₈), or a substituted version of any of these groups;

R_3 is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

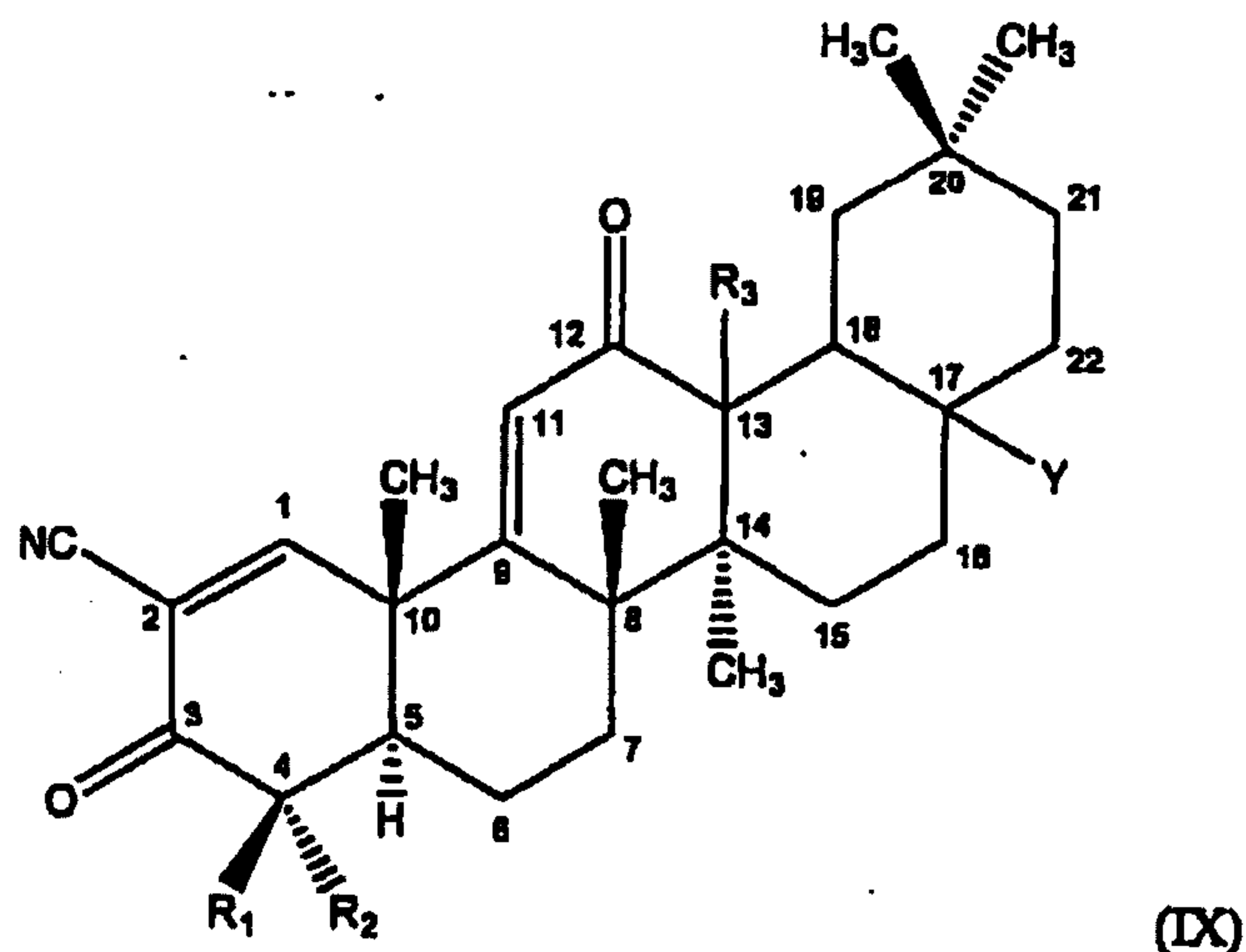
alkoxy_(C₁₋₈), cycloalkoxy_(C₃₋₈), alkenyloxy_(C₂₋₈), aryloxy_(C₆₋₁₂), aralkoxy_(C₁₋₁₂), heteroaryloxy_(C₆₋₁₂), acyloxy_(C₁₋₈), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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27. The compound according to any one of claims 1, 19-21, and 26, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R_2 is $-OR_a$, wherein:

R_a is hydrogen or alkyl_(C₁₋₈), alkenyl_(C₂₋₈), alkynyl_(C₂₋₈), aryl_(C₆₋₁₂), aralkyl_(C₇₋₁₂), heteroaryl_(C₆₋₁₂), heterocycloalkyl_(C₃₋₈), acyl_(C₁₋₈), or a substituted version of any of these groups;

R_3 is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

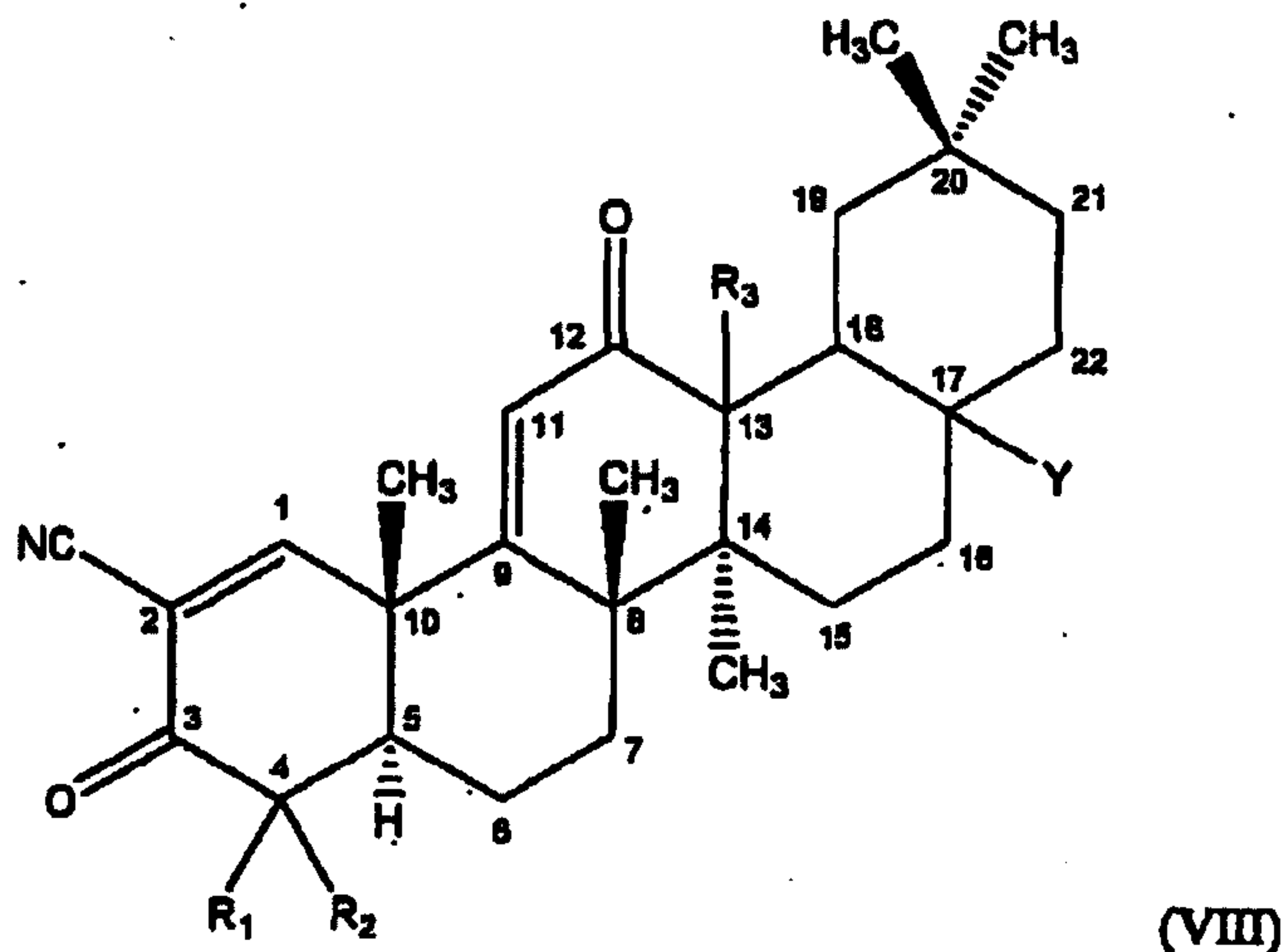
alkoxy_(C₁₋₈), cycloalkoxy_(C₃₋₈), alkenyloxy_(C₂₋₈), aryloxy_(C₆₋₁₂), aralkoxy_(C₇₋₁₂), heteroaryloxy_(C₆₋₁₂), acyloxy_(C₁₋₈), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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28. The compound according to any one of claims 1 and 19-21, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R_2 is $-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R_5' is hydrogen, alkyl_(C₁₋₈), alkoxy_(C₁₋₈), substituted alkoxy_(C₁₋₈), acyl_(C₁₋₈), substituted acyl_(C₁₋₈), $-C(O)-$ alkoxy_(C₁₋₈), substituted $-C(O)-$ alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), substituted acyloxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or substituted alkylsilyloxy_(C₁₋₈); and

R_6 is hydrogen, alkyl_(C₁₋₈), or substituted alkyl_(C₁₋₈);

R_3 is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

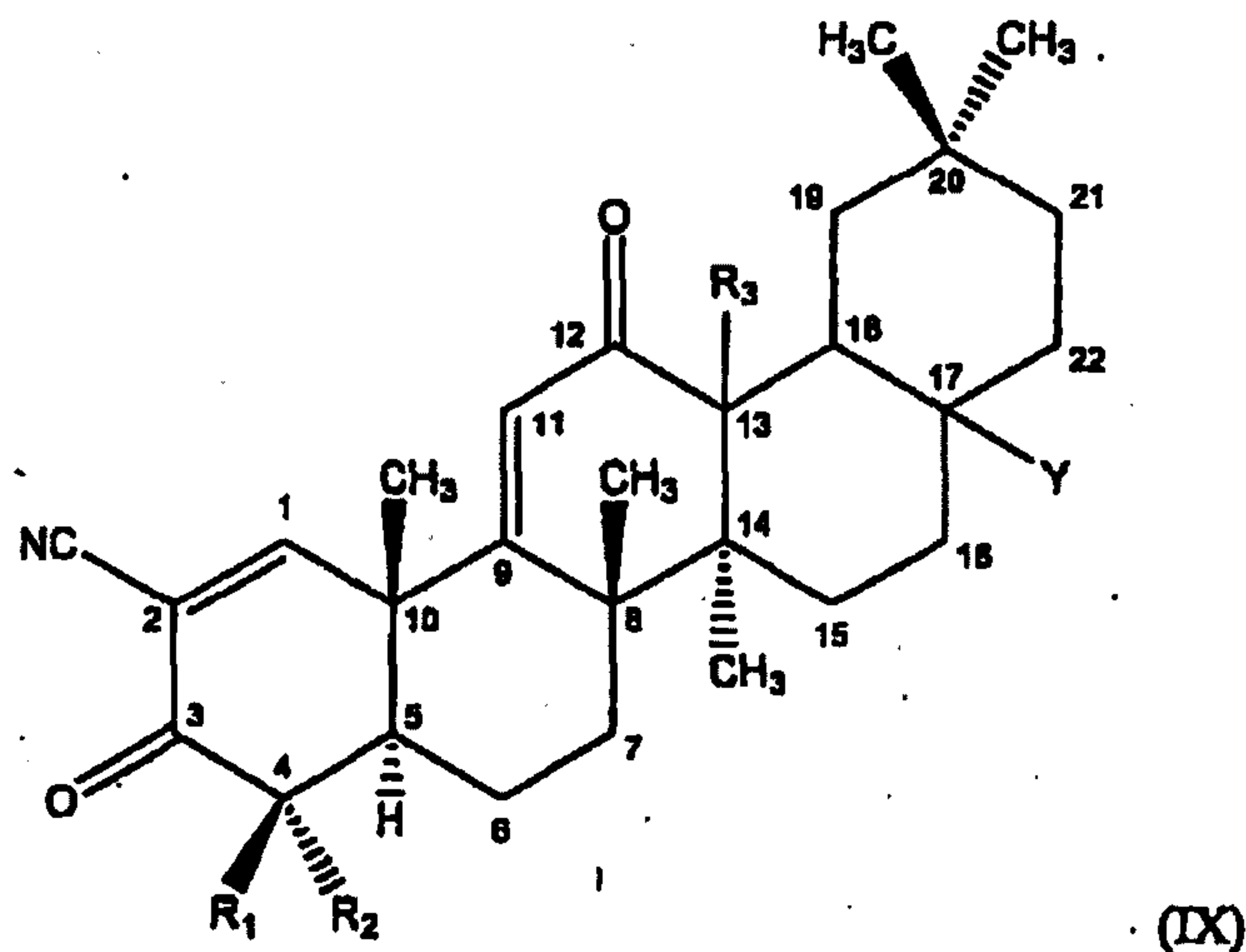
alkoxy_(C₁₋₈), cycloalkoxy_(C₃₋₈), alkenyloxy_(C₁₋₈), aryloxy_(C₁₋₈), aralkoxy_(C₁₋₈), heteroaryloxy_(C₁₋₈), acyloxy_(C₁₋₈), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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29. The compound according to any one of claims 1, 19-21, and 28, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl(C_{1-8}), cycloalkyl(C_{3-8}), substituted alkyl(C_{1-8}), or substituted cycloalkyl(C_{3-8});

R_2 is $-(CH_2)_sNR_5'(R_6)$, wherein:

s is 0, 1, 2, 3, or 4;

R_5' is hydrogen, alkyl(C_{1-8}), alkoxy(C_{1-8}), substituted alkoxy(C_{1-8}), acyl(C_{1-8}), substituted acyl(C_{1-8}), $-C(O)-$ alkoxy(C_{1-8}), substituted $-C(O)-$ alkoxy(C_{1-8}), acyloxy(C_{1-8}), substituted acyloxy(C_{1-8}), alkylsilyloxy(C_{1-8}), or substituted alkylsilyloxy(C_{1-8}); and

R_6 is hydrogen, alkyl(C_{1-8}), or substituted alkyl(C_{1-8});

R_3 is hydrogen, hydroxy, or alkoxy(C_{1-8}), acyloxy(C_{1-8}), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

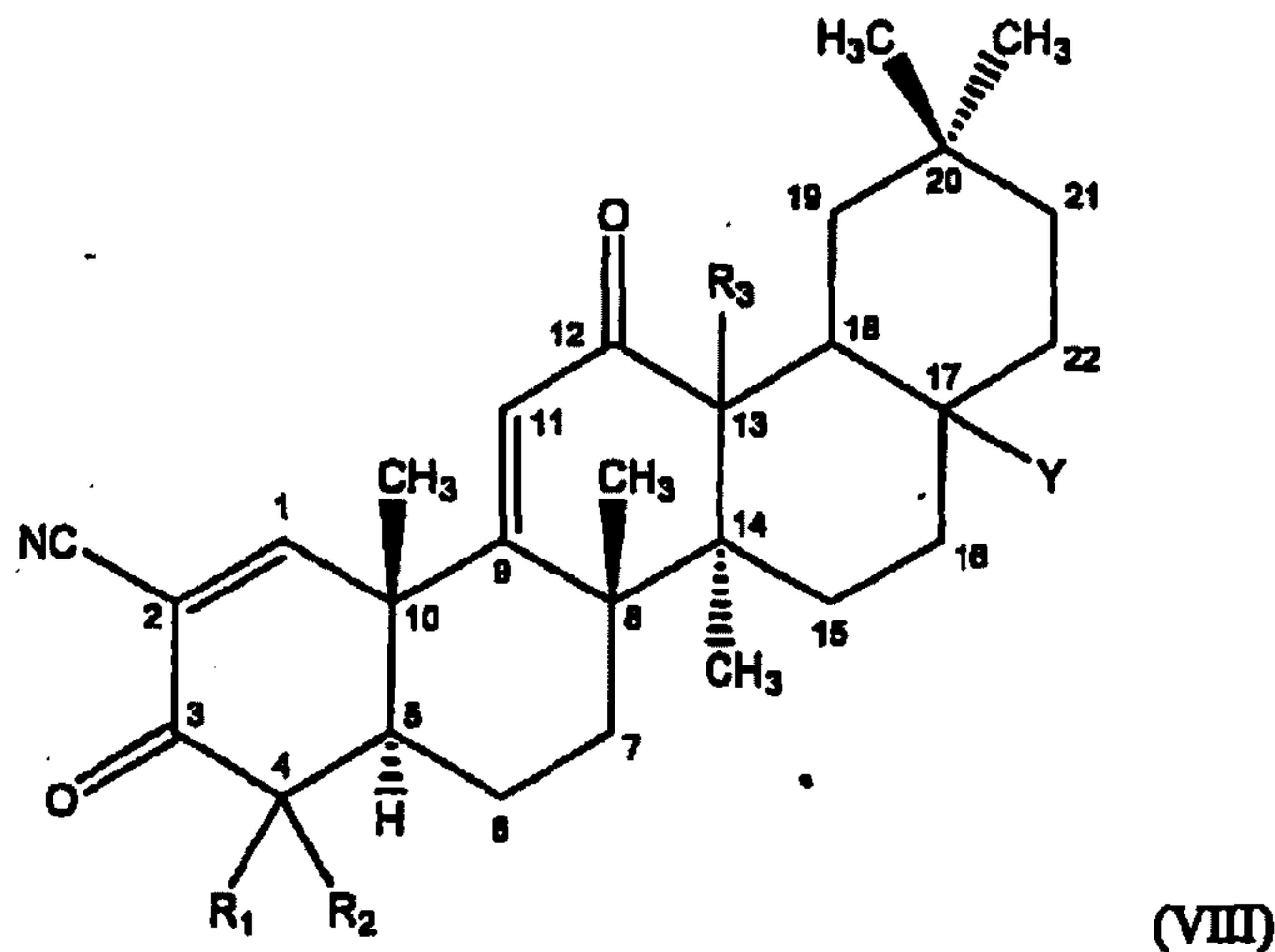
alkoxy(C_{1-8}), cycloalkoxy(C_{3-8}), alkenyloxy(C_{1-8}), aryloxy(C_{1-8}), aralkoxy(C_{1-8}), heteroaryloxy(C_{1-8}), acyloxy(C_{1-8}), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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30. The compound according to any one of claims 1 and 19-21, wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R_2 is $-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy_(C₁₋₈), alkylthio_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

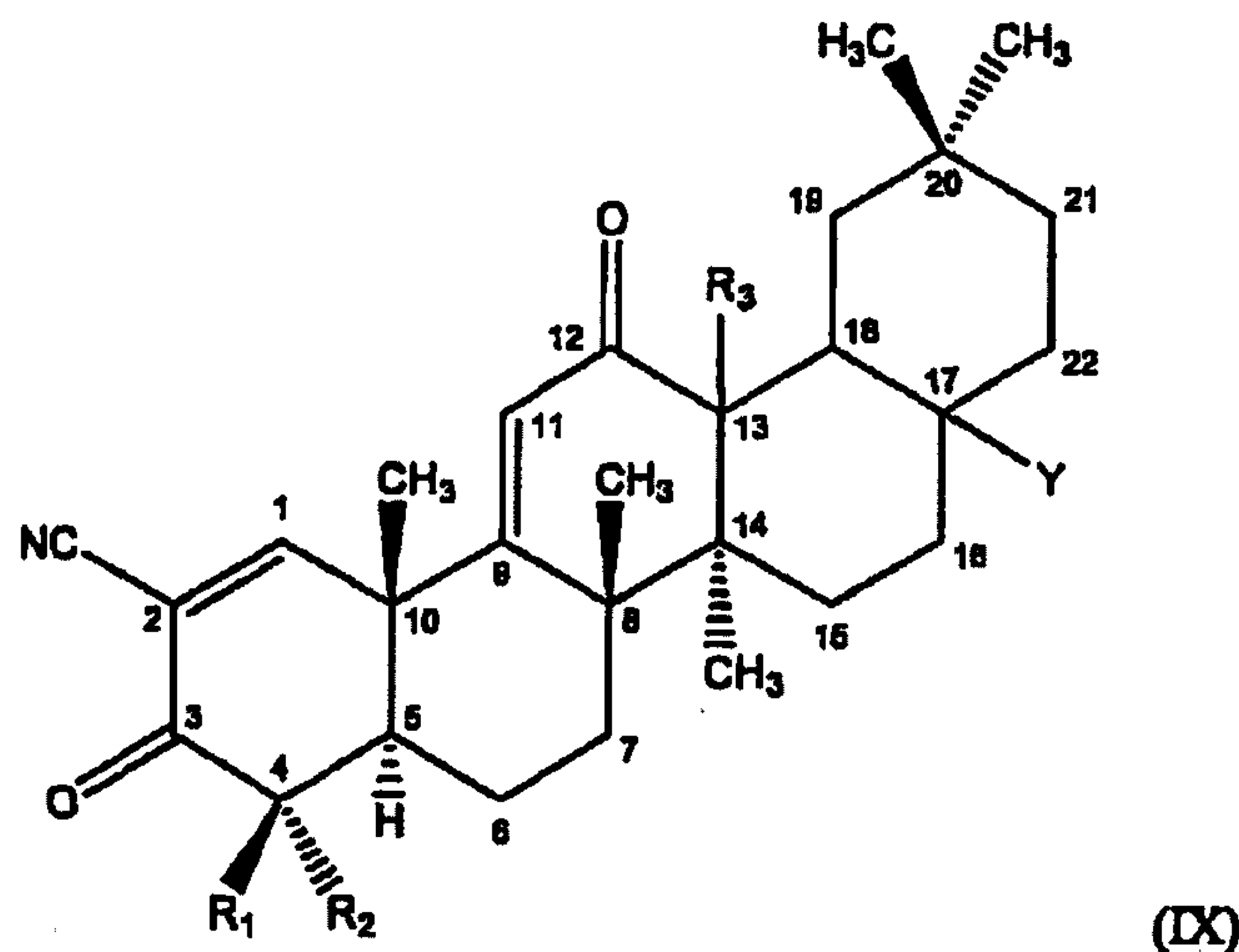
alkoxy_(C₁₋₈), cycloalkoxy_(C₃₋₈), alkenyloxy_(C₁₋₈), aryloxy_(C₁₋₈), aralkoxy_(C₁₋₈), heteroaryloxy_(C₁₋₈), acyloxy_(C₁₋₈), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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31. The compound according to any one of claims 1, 19-21, and 30 wherein the compound is further defined as:



wherein:

R_1 is hydrogen, alkyl_(C₁₋₈), cycloalkyl_(C₃₋₈), substituted alkyl_(C₁₋₈), or substituted cycloalkyl_(C₃₋₈);

R_2 is $-(CH_2)_q-C(O)-R_5''$, wherein:

R_5'' is amino, hydroxy, or mercapto; or

alkoxy_(C₁₋₈), alkylthio_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), or a substituted version of any of these groups; and

q is 0, 1, 2, 3, or 4;

R_3 is hydrogen, hydroxy, or alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), or substituted version of either of these groups; and

Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:

hydroxy; or

alkoxy_(C₁₋₈), cycloalkoxy_(C₃₋₈), alkenyloxy_(C₁₋₈), aryloxy_(C₁₋₈), aralkoxy_(C₁₋₈), heteroaryloxy_(C₁₋₈), acyloxy_(C₁₋₈), or a substituted version of any of these groups;

or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

32. The compound according to any one of claims 1-6 and 19, wherein X is cyano.
33. The compound according to any one of claims 1-7, 19, 20, and 32, wherein the bond between atoms 1 and 2 are an epoxidized double bond.

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34. The compound according to any one of claims 1-7, 19, 20, and 32, wherein the bond between atoms 1 and 2 are a double bond.
35. The compound according to any one of claims 1-34, wherein R_1 is hydrogen.
36. The compound according to any one of claims 1-34, wherein R_1 is alkyl(C_{1-8}) or substituted alkyl(C_{1-8}).
37. The compound of claim 36, wherein R_1 is alkyl(C_{1-8}).
38. The compound of claim 37, wherein R_1 is methyl.
39. The compound according to any one of claims 1-10, 19-23, and 32-38, wherein R_2 is amino.
40. The compound according to any one of claims 1, 6-10, and 32-38, wherein R_2 is substituted alkyl(C_{1-8}).
41. The compound of claim 40, wherein R_2 is hydroxymethyl, difluoromethyl, acetoxymethyl, methoxyethyl, methoxymethyl, methyl carboxymethyl, 2-hydroxyethyl, or 1-hydroxyethyl.
42. The compound according to any one of claims 1, 6-10, 19-23, and 32-38, wherein R_2 is haloalkyl(C_{1-8}).
43. The compound of claim 42, wherein R_2 is difluoromethyl.
44. The compound according to any one of claims 1-10, 19-23, and 32-38 wherein R_2 is heteroaryl(C_{1-8}) or substituted heteroaryl(C_{1-8}).
45. The compound of claim 44, wherein R_2 is 2-methyloxadiazole.
46. The compound according to any one of claims 1-10, 19-23, and 32-38, wherein R_2 is amido(C_{1-8}) or substituted amido(C_{1-8}).
47. The compound of claim 46, wherein R_2 is *N*-acetamide.
48. The compound according to any one of claims 1, 6-8, 13, 14, and 32-38, wherein R_2 is $-(CH_2)_m-(OCH_2)_n-R_5$, wherein:

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R_3 is hydroxy or acyl($C_{\leq 8}$), alkoxy($C_{\leq 8}$), acyloxy($C_{\leq 8}$), alkylsilyloxy($C_{\leq 8}$), or a substituted version of any of these groups;

m is 0, 1, 2, 3, or 4; and

n is 0, 1, 2, or 3.

49. The compound of claim 48, wherein R_3 is alkoxy($C_{\leq 8}$) or substituted alkoxy($C_{\leq 8}$).
50. The compound of claim 49, wherein R_3 is methoxy.
51. The compound of claim 48, wherein R_3 is acyloxy($C_{\leq 8}$) or substituted acyloxy($C_{\leq 8}$).
52. The compound of claim 51, wherein R_3 is $-OC(O)C_6H_5$.
53. The compound of claim 48, wherein R_3 is alkylsilyloxy($C_{\leq 8}$) or substituted alkylsilyloxy($C_{\leq 8}$).
54. The compound of claim 53, wherein R_3 is *t*-butyldimethylsiloxy.
55. The compound according to any one of claims 48-54, wherein m is 1 or 2.
56. The compound of claim 55, wherein m is 1.
57. The compound of claim 55, wherein m is 2.
58. The compound according to any one of claims 48-57, wherein n is 0 or 1.
59. The compound of claim 57, wherein n is 0.
60. The compound of claim 57, wherein n is 1.
61. The compound according to any one of claims 1, 19-21, 24, 25, and 32-38, wherein R_2 is $-(CH_2)_m-R_5'''$, wherein:

R_5''' is alkoxy($C_{\leq 8}$), acyloxy($C_{\leq 8}$), ~~substituted acyloxy($C_{\leq 8}$)~~, alkylsilyloxy($C_{\leq 8}$), or substituted alkylsilyloxy($C_{\leq 8}$); and

m is 0, 1, 2, 3, or 4.
62. The compound according to any one of claims 1, 19-21, 24, 25, and 32-38, wherein R_2 is $-(CH_2)_{m_2}-R_5'''$, wherein:

R_5''' is hydroxy; and

m_2 is 2, 3, or 4.

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63. The compound of claim 61, wherein R_5''' is alkoxy_(C₁₋₈) or substituted alkoxy_(C₁₋₈).
64. The compound of claim 63, wherein R_5''' is methoxy.
65. The compound of claim 61, wherein R_5''' is acyloxy_(C₁₋₈) or substituted acyloxy_(C₁₋₈).
66. The compound of claim 65, wherein R_5''' is $-\text{OC}(\text{O})\text{C}_6\text{H}_5$.
67. The compound of claim 61, wherein R_5''' is alkylsilyloxy_(C₁₋₈) or allylsilyloxy_(C₁₋₈).
68. The compound of claim 67, wherein R_5''' is *t*-butyldimethylsiloxy.
69. The compound according to any one of claims 61 and 63-68, wherein *m* is 1 or 2.
70. The compound of claim 69, wherein *m* is 1.
71. The compound of claim 69, wherein *m* is 2.
72. The compound of claim 62, wherein *m*₂ is 2 or 3.
73. The compound according to any one of claims 1-8, 15, 16, 19-21, 28, 29, and 32-38, wherein R_2 is $-(\text{CH}_2)_s\text{NR}_5'(\text{R}_6)$, wherein:
 - s* is 0, 1, 2, 3, or 4;
 - R_5' is hydrogen, alkyl_(C₁₋₈), alkoxy_(C₁₋₈), substituted alkoxy_(C₁₋₈), acyl_(C₁₋₈), substituted acyl_(C₁₋₈), $-\text{C}(\text{O})$ -alkoxy_(C₁₋₈), substituted $-\text{C}(\text{O})$ -alkoxy_(C₁₋₈), acyloxy_(C₁₋₈), substituted acyloxy_(C₁₋₈), alkylsilyloxy_(C₁₋₈), or substituted alkylsilyloxy_(C₁₋₈); and
 - R_6 is hydrogen, alkyl_(C₁₋₈), or substituted alkyl_(C₁₋₈).
74. The compound of claim 73, wherein *s* is 0 or 1.
75. The compound of either claim 73 or claim 74, wherein *s* is 0.
76. The compound of either claim 73 or claim 74, wherein *s* is 1.
77. The compound of claim 73, wherein R_5' is hydrogen.
78. The compound of claim 73, wherein R_5' is acyl_(C₁₋₈).
79. The compound of claim 78, wherein R_5' is acetyl.

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80. The compound of claim 73, wherein R_5' is $-C(O)-alkoxy(C_{1-8})$.
81. The compound of claim 80, wherein R_5' is *tert*-butyloxycarbonyl.
82. The compound according to any one of claims 73-81, wherein R_6 is hydrogen.
83. The compound according to any one of claims 1-8, 17-21, and 30-38, wherein R_2 is $-(CH_2)_q-C(O)-R_5''$, wherein:
 R_5'' is amino, hydroxy, or mercapto; or
 $alkoxy(C_{1-8})$, $alkylthio(C_{1-8})$, $alkylamino(C_{1-8})$, $dialkylamino(C_{1-8})$, or a substituted version of any of these groups; and
 q is 0, 1, 2, 3, or 4.
84. The compound of claim 83, wherein R_5'' is amino.
85. The compound of claim 83, wherein R_5'' is $alkylamino(C_{1-8})$.
86. The compound of claim 85, wherein R_5'' is methylamino.
87. The compound of claim 83, wherein R_5'' is $dialkylamino(C_{1-8})$.
88. The compound of claim 87, wherein R_5'' is dimethylamino.
89. The compound of claim 83, wherein R_5'' is hydroxy.
90. The compound of claim 83, wherein R_5'' is $alkoxy(C_{1-8})$.
91. The compound of claim 90, wherein R_5'' is methoxy.
92. The compound according to any one of claims 83-91, wherein q is 0.
93. The compound according to any one of claims 83-91, wherein q is 1.
94. The compound according to any one of claims 1-8, 11, 12, 19-21, 26, 27, and 32-38, wherein R_2 is $-OR_a$, wherein:
 R_a is hydrogen or $alkyl(C_{1-8})$, $acyl(C_{1-8})$, or a substituted version of either of these groups.
95. The compound of claim 94, wherein R_a is hydrogen.

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96. The compound of claim 94, wherein R_a is alkyl_(C₁₋₈) or substituted alkyl_(C₁₋₈).
97. The compound of claim 94, wherein R_a is acyl_(C₁₋₈) or substituted acyl_(C₁₋₈).
98. The compound according to any one of claims 1-18 and 32-97, wherein Y is heteroaryl_(C₁₋₈) or substituted heteroaryl_(C₁₋₈).
99. The compound of claim 98, wherein Y is 3-methyl-1,2,4-oxadiazole or 2-methyl-1,3,4-oxadiazole.
100. The compound according to any one of claims 1-18 and 32-97, wherein Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:
hydrogen, halo, amino, -NHOH, or mercapto; or
alkyl_(C₁₋₈), alkenyl_(C₁₋₈), alkynyl_(C₁₋₈), aryl_(C₁₋₈), aralkyl_(C₁₋₈), heteroaryl_(C₁₋₈),
heterocycloalkyl_(C₁₋₈), alkylamino_(C₁₋₈), dialkylamino_(C₁₋₈), arylamino_(C₁₋₈),
alkylsulfonylamino_(C₁₋₈), amido_(C₁₋₈), alkoxyamino_(C₁₋₈),
heterocycloalkylamino_(C₁₋₈), -NHC(NO₂)-alkyl_(C₁₋₈), -NH-amido_(C₁₋₈),
or a substituted version of any of these groups.
101. The compound of claim 100, wherein o is 0, 1, or 2.
102. The compound of claim 101, wherein o is 0.
103. The compound according to any one of claims 100-102, wherein R_c is alkylamino_(C₁₋₈) or substituted alkylamino_(C₁₋₈).
104. The compound of claim 103, wherein R_c is alkylamino_(C₁₋₈).
105. The compound of claim 104, wherein R_c is ethylamino.
106. The compound of claim 103, wherein R_c is substituted alkylamino_(C₁₋₈).
107. The compound of claim 106, wherein R_c is 2,2,2-trifluoroethylamino.
108. The compound according to any one of claims 100-102, wherein R_c is dialkylamino_(C₁₋₈) or substituted dialkylamino_(C₁₋₈).
109. The compound of claim 108, wherein R_c is dialkylamino_(C₁₋₈).

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110. The compound of claim 109, wherein R_c is dimethylamino.
111. The compound according to any one of claims 1-5, 19-31, and 32-97, wherein Y is $-(CH_2)_oC(O)R_c$, wherein o is 0-6 and R_c is:
hydroxy; or
alkoxy(C_{1-8}), alkenyloxy(C_{1-8}), aryloxy(C_{1-8}), aralkoxy(C_{1-8}), heteroaryloxy(C_{1-8}),
acyloxy(C_{1-8}), or a substituted version of any of these groups.
112. The compound of claim 111, wherein o is 0, 1, or 2.
113. The compound of claim 112, wherein o is 0.
114. The compound according to any one of claims 111-113, wherein R_c is alkoxy(C_{1-8}) or substituted alkoxy(C_{1-8}).
115. The compound of claim 114, wherein R_c is alkoxy(C_{1-8}).
116. The compound of claim 115, wherein R_c is methoxy.
117. The compound according to any one of claims 1-18 and 32-97, wherein Y is $-NR_dC(O)R_c$, wherein
 R_d is hydrogen, alkyl(C_{1-8}), or substituted alkyl(C_{1-8}); and
 R_c is hydrogen, hydroxy, amino; or
alkyl(C_{1-8}), alkenyl(C_{1-8}), alkynyl(C_{1-8}), aryl(C_{1-8}), aralkyl(C_{1-8}), heteroaryl(C_{1-8}),
heterocycloalkyl(C_{1-8}), alkoxy(C_{1-8}), aryloxy(C_{1-8}), aralkoxy(C_{1-8}),
heteroaryloxy(C_{1-8}), acyloxy(C_{1-8}), alkylamino(C_{1-8}), dialkylamino(C_{1-8}),
arylamino(C_{1-8}), or a substituted version of any of these groups.
118. The compound of claim 117, wherein R_d is hydrogen.
119. The compound of either claim 117 or claim 118, wherein R_c is alkyl(C_{1-8}) or substituted alkyl(C_{1-8}).
120. The compound of claim 119, wherein R_c is substituted alkyl(C_{1-8}).
121. The compound of claim 120, wherein R_c is 1,1-difluoroethyl.

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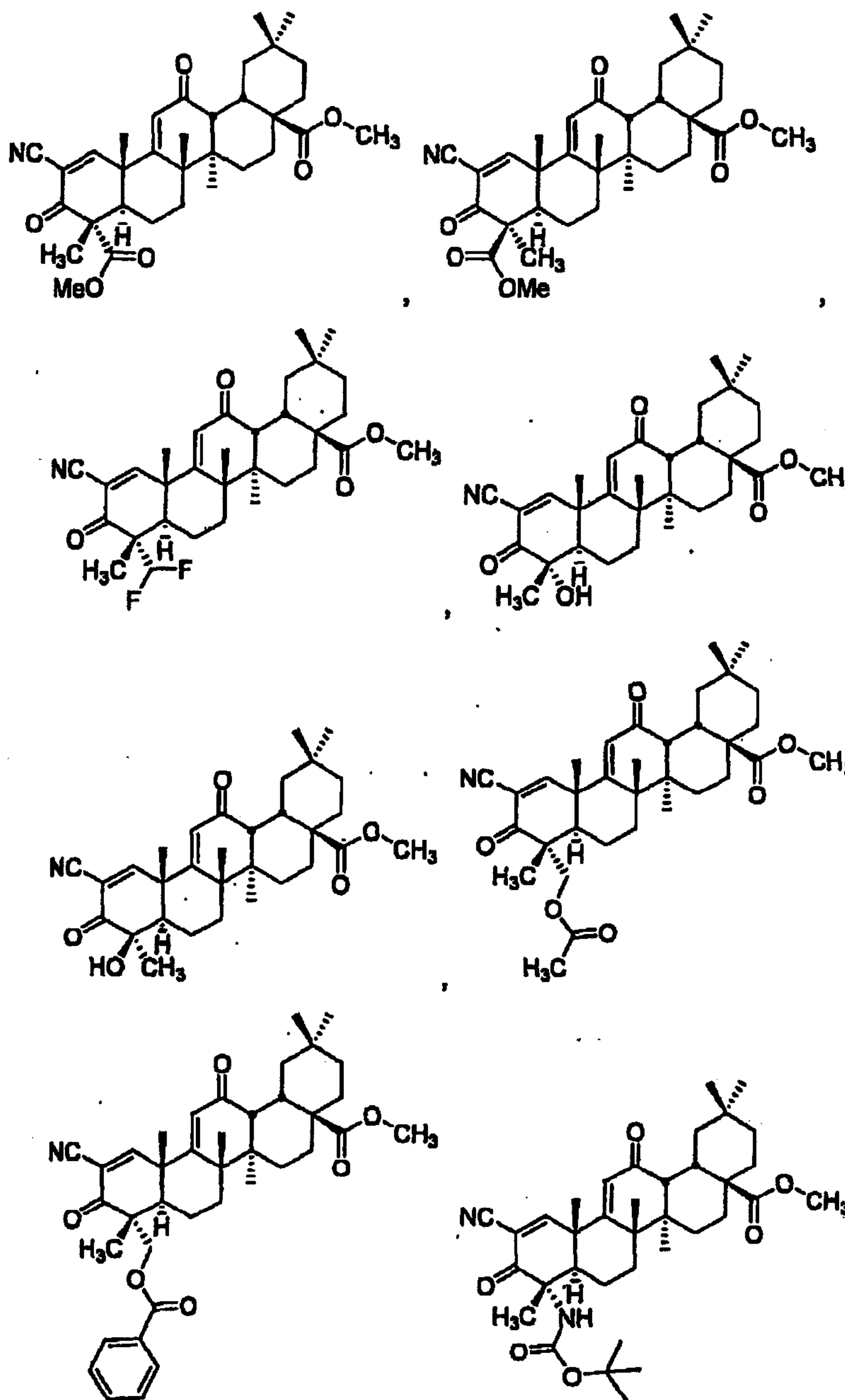
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122. The compound of either claim 117 or claim 118, wherein R_e is alkoxy($C_{\leq 8}$) or substituted alkoxy($C_{\leq 8}$).
123. The compound of claim 122, wherein R_e is alkoxy($C_{\leq 8}$).
124. The compound of claim 123, wherein R_e is methoxy.
125. The compound according to any one of claims 1-97, wherein Y is taken together with R_3 and is $-(CH_2)_pC(O)R_f-$, wherein
p is 0-6; and
 R_f is $-O-$ or $-NR_7-$; wherein:
 R_7 is hydrogen, alkyl($C_{\leq 8}$), substituted alkyl($C_{\leq 8}$), acyl($C_{\leq 8}$), or substituted acyl($C_{\leq 8}$).
126. The compound of claim 125, wherein p is 0 or 1.
127. The compound of claim 126, wherein p is 0.
128. The compound according to any one of claims 125-127, wherein R_f is $-O-$.
129. The compound according to any one of claims 1-128, wherein R_3 is hydrogen.
130. The compound according to any one of claims 1-128, wherein R_3 is hydroxy.
131. The compound according to any one of claims 1-130, wherein the carbon atom 4 is in the α orientation.
132. The compound according to any one of claims 1-130, wherein the carbon atom 4 is in the β orientation.
133. The compound according to any one of claims 1-132, wherein the carbon atom 4 is in the S configuration.
134. The compound according to any one of claims 1-132, wherein the carbon atom 4 is in the R configuration.

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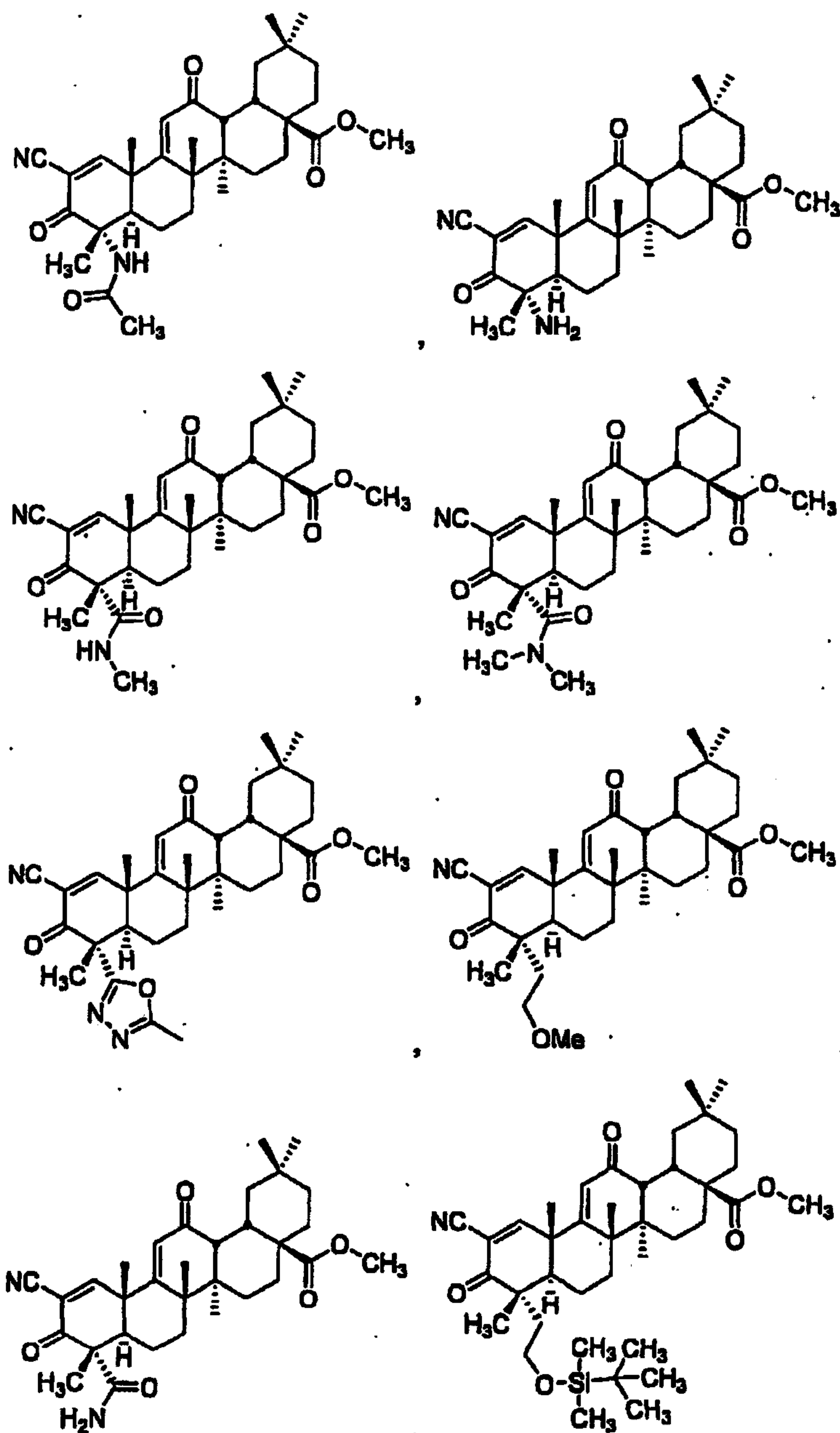
135. The compound according to any one of claims 1-132, wherein the compound is further defined as:



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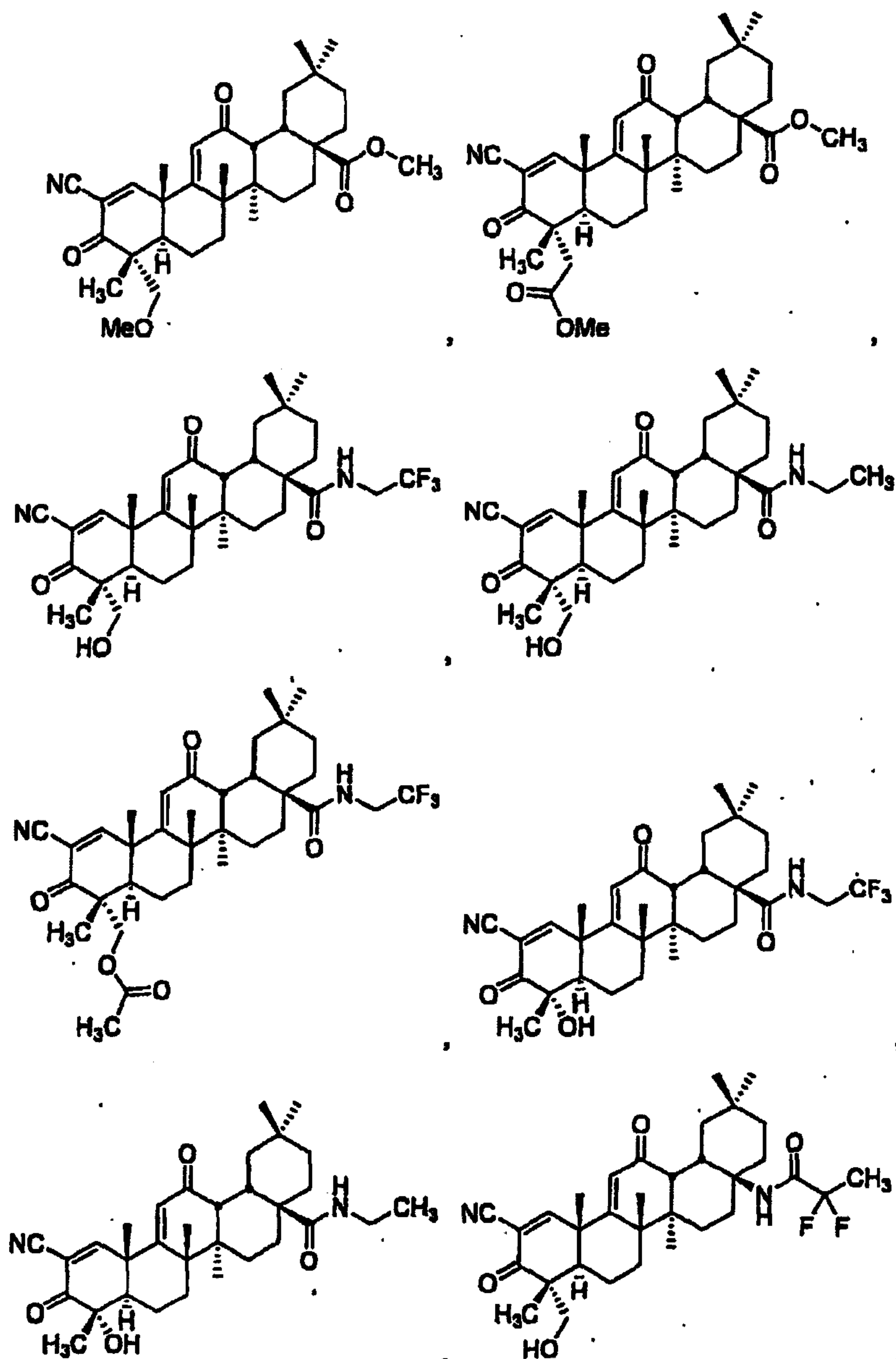


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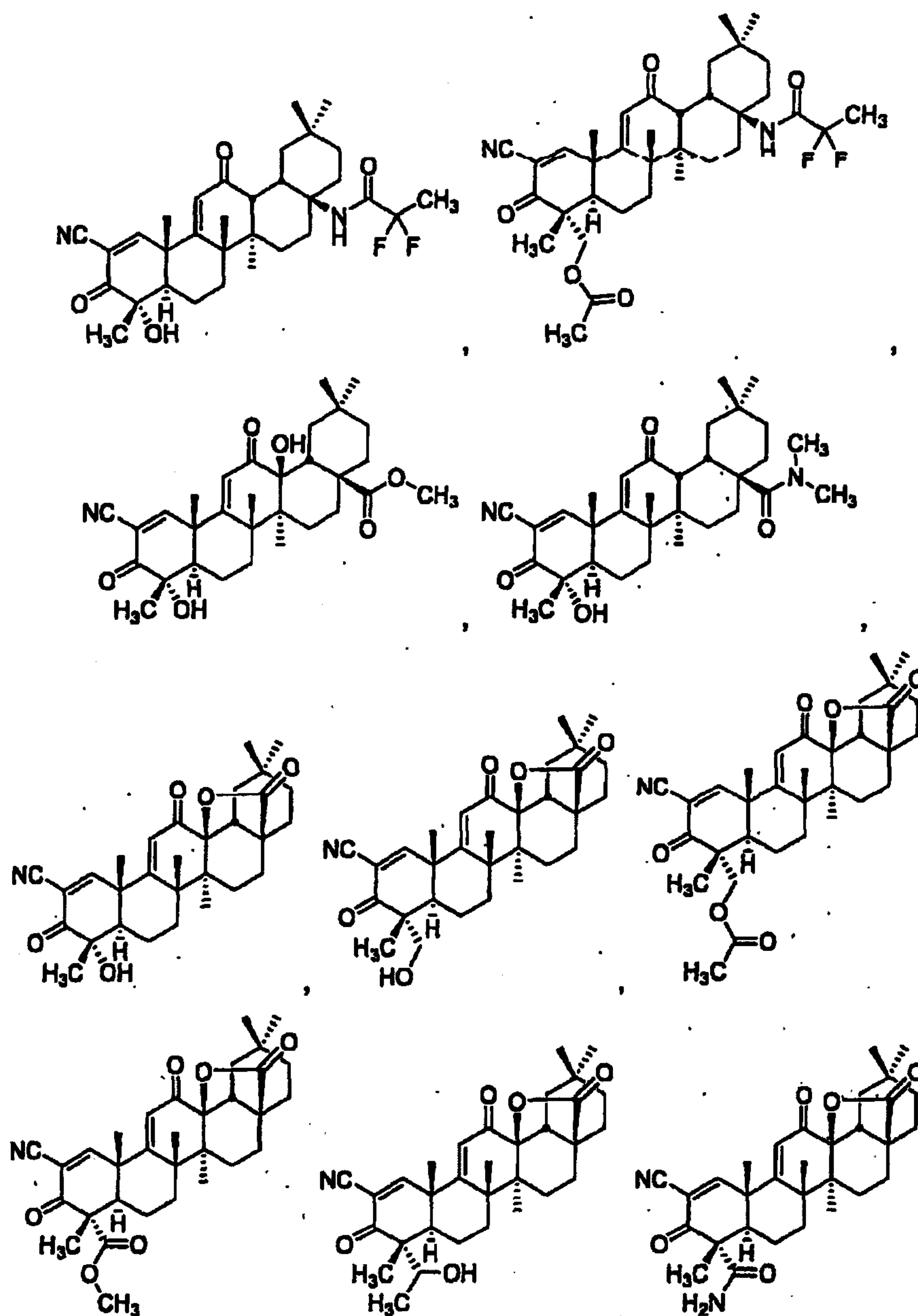


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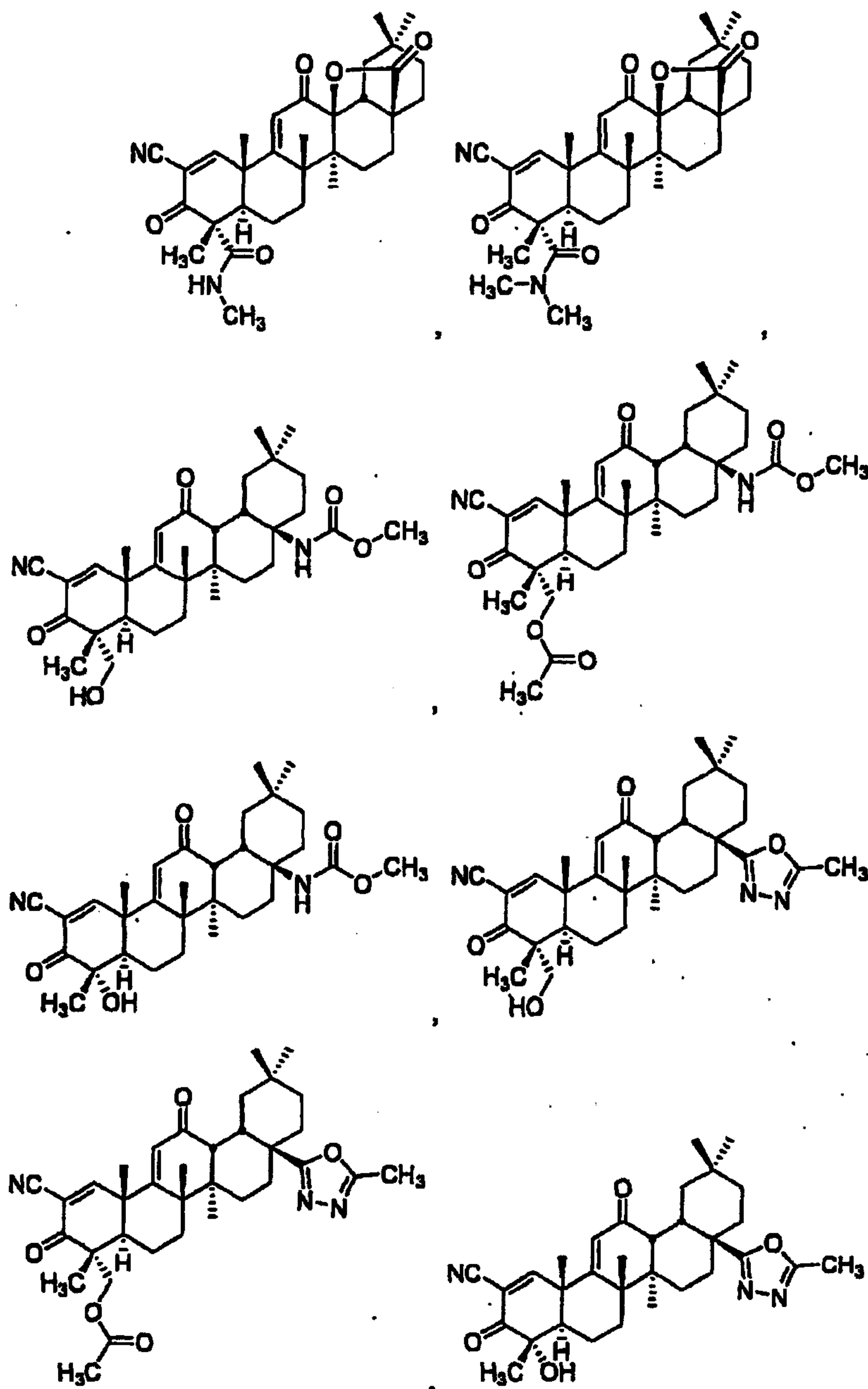
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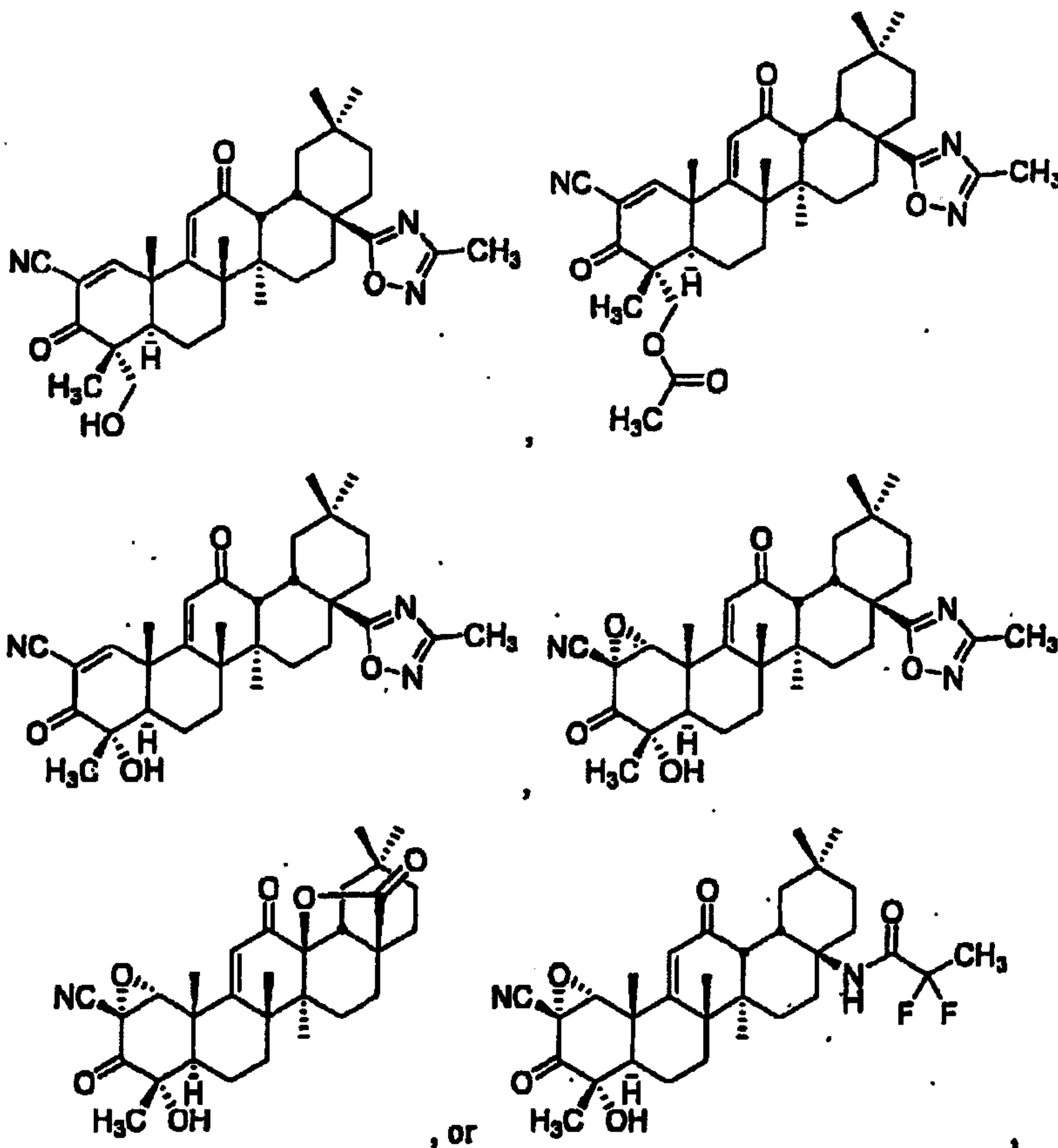
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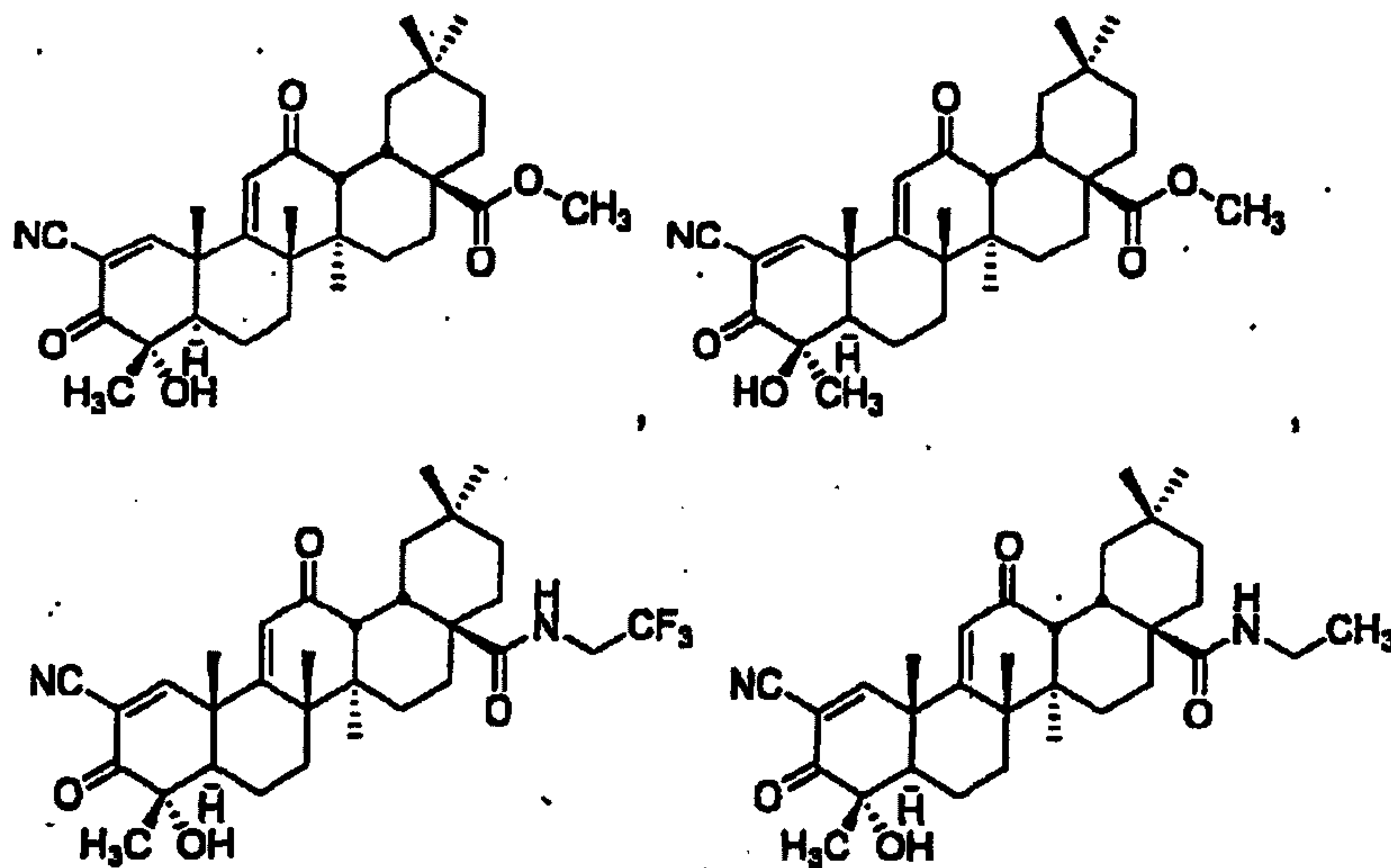
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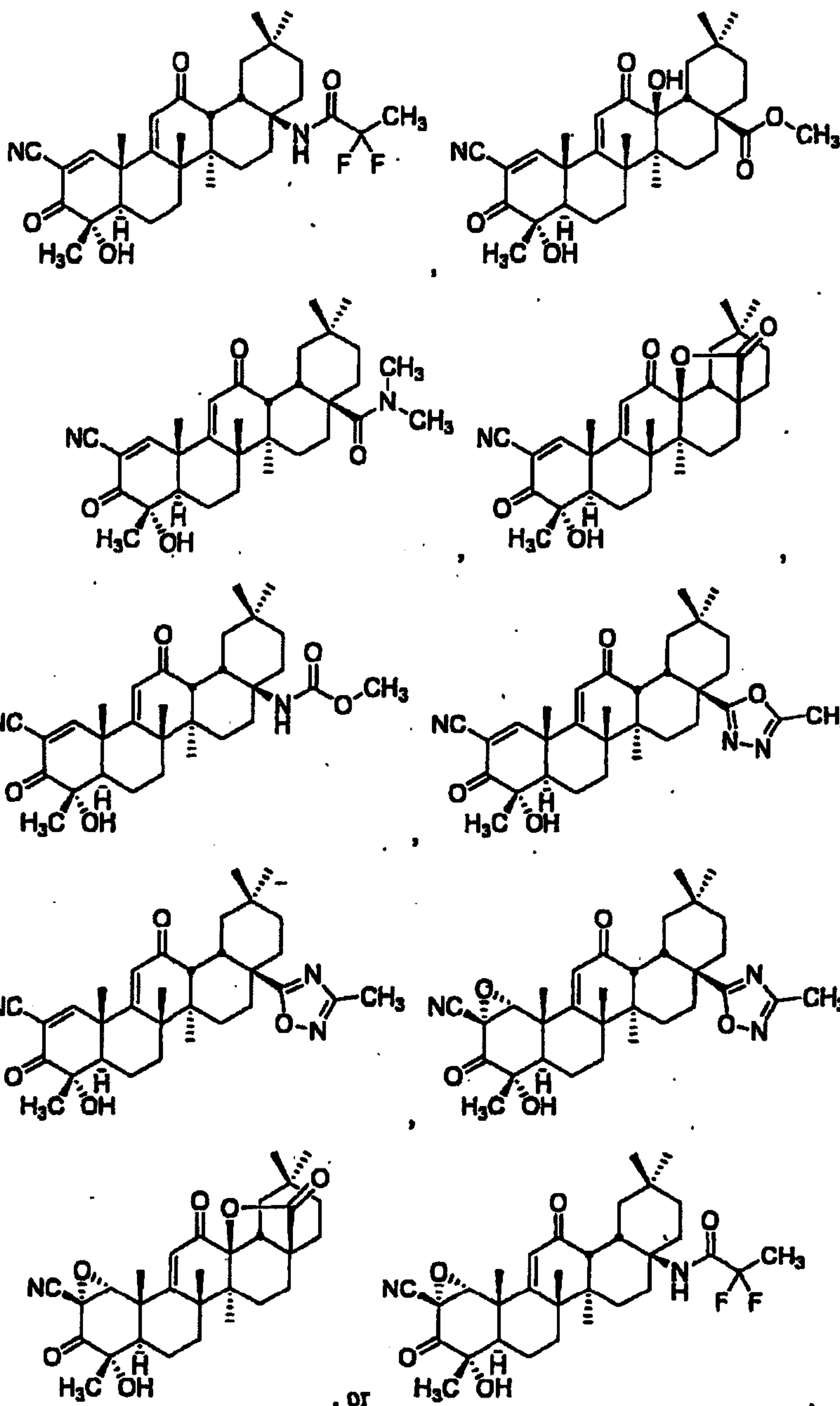
or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

136. The compound according to any one of claims 1-135, wherein the compound is further defined as:



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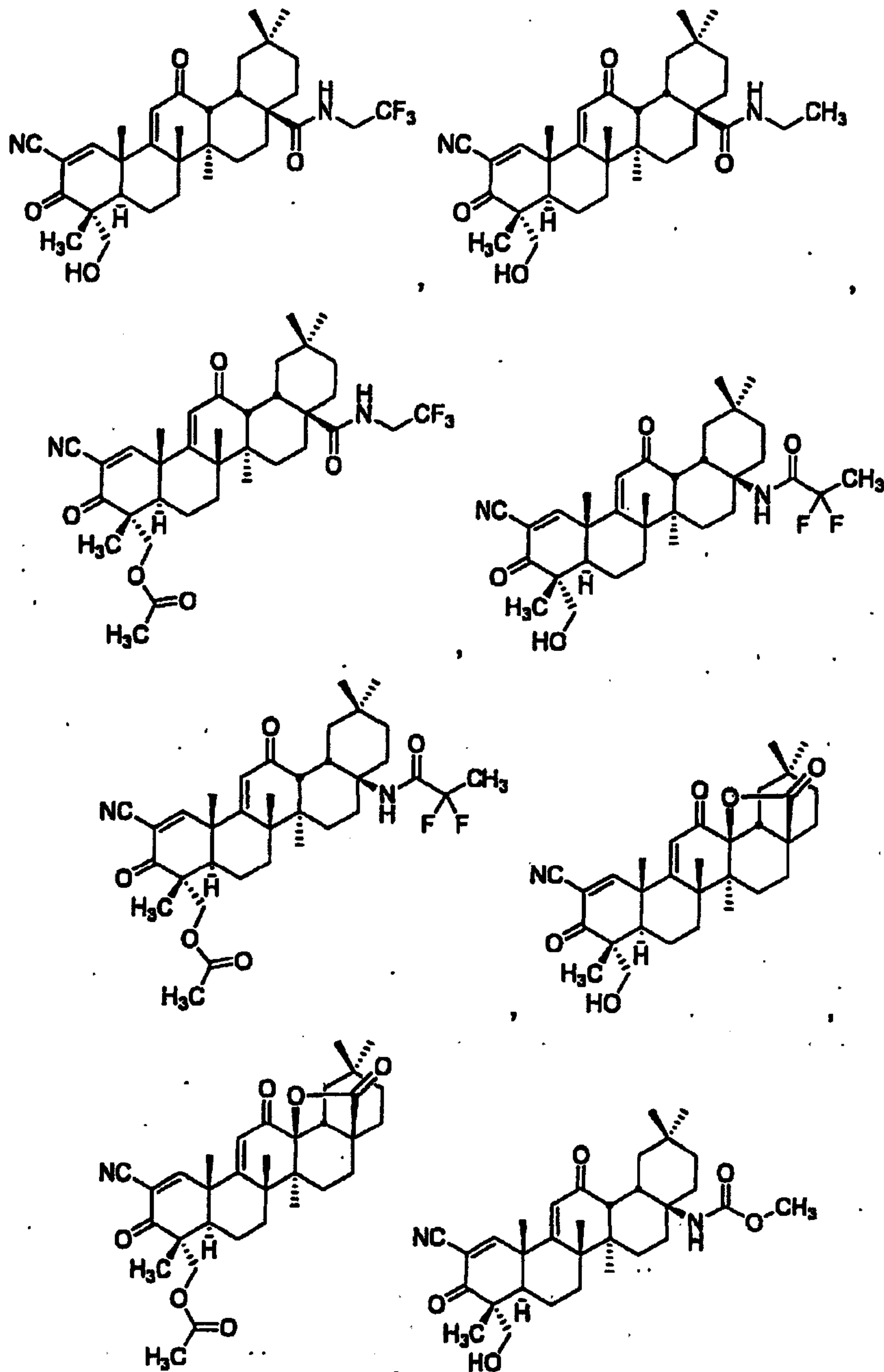


or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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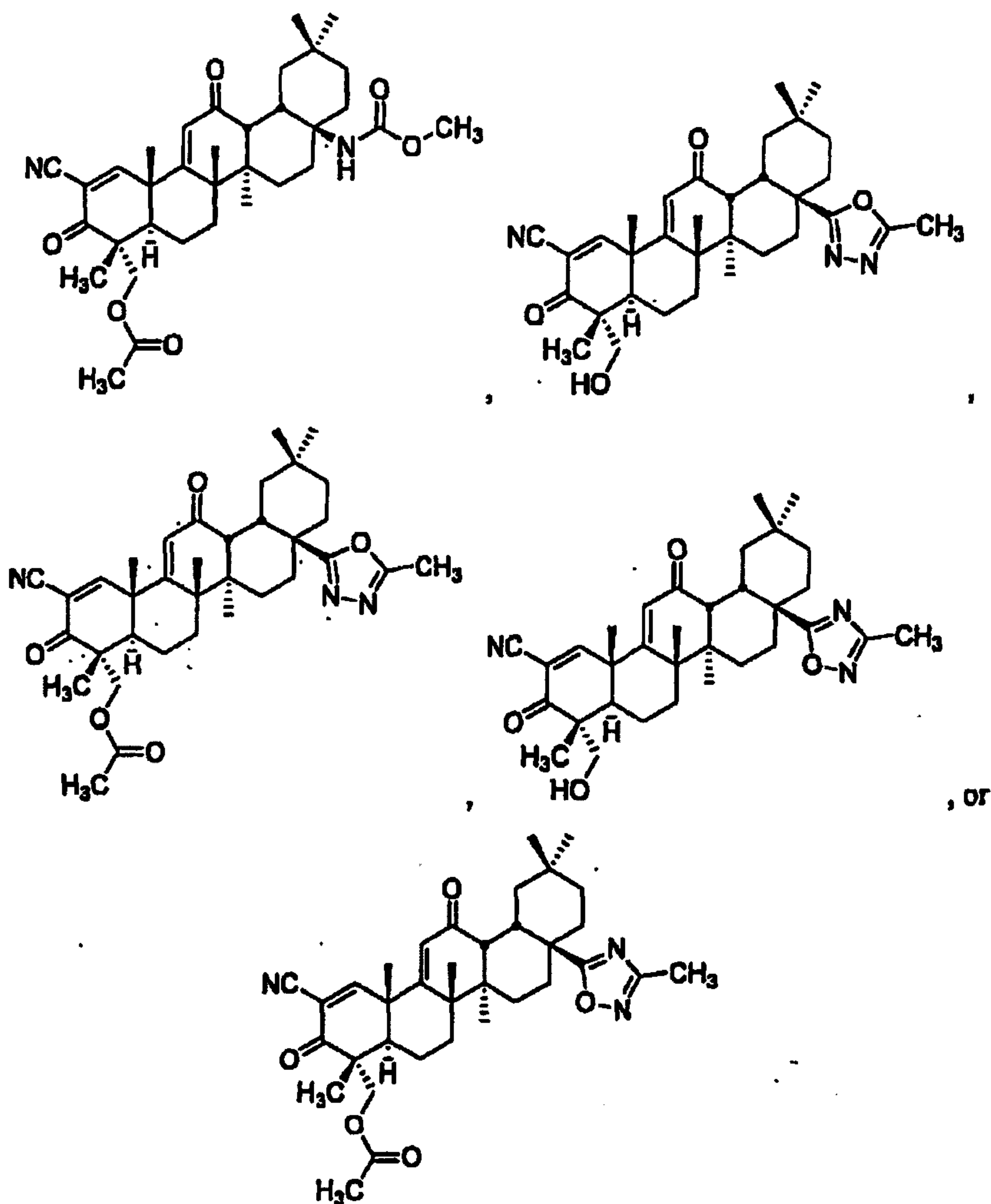
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137. The compound according to any one of claims 1-135, wherein the compound is further defined as:



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or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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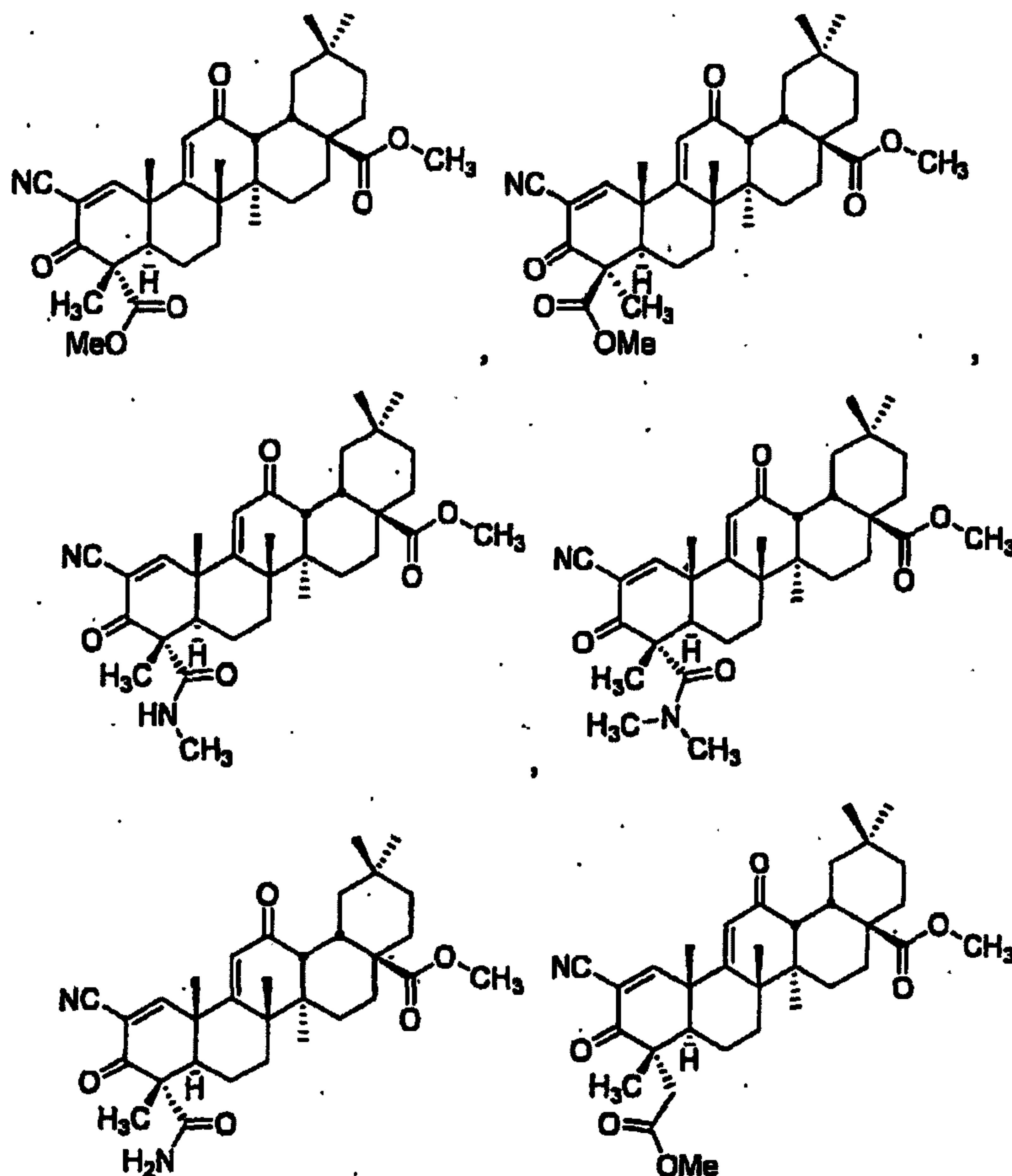
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138. The compound according to any one of claims 1-135, wherein the compound is further defined as:



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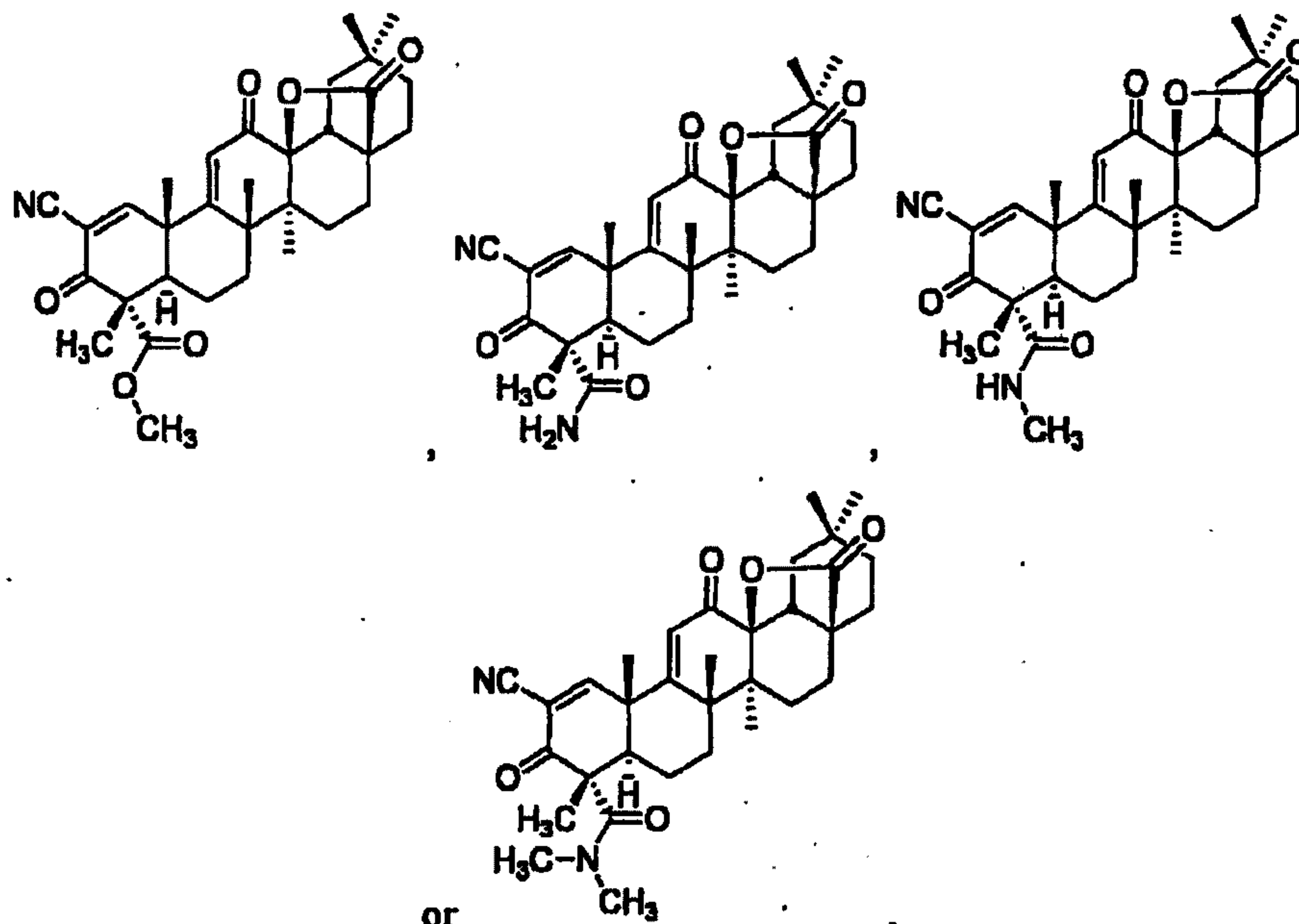
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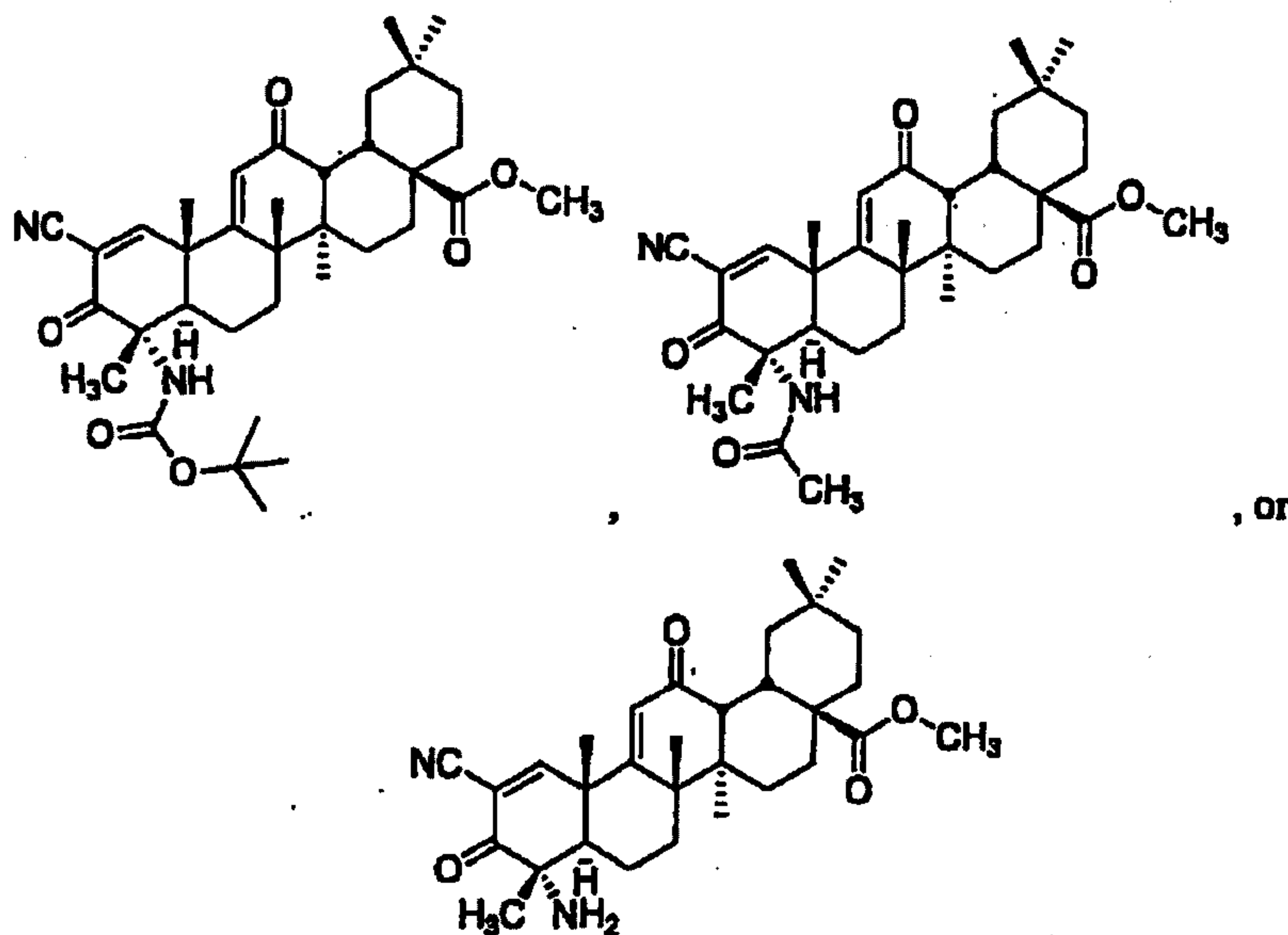
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or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

139. The compound according to any one of claims 1-135, wherein the compound is further defined as:

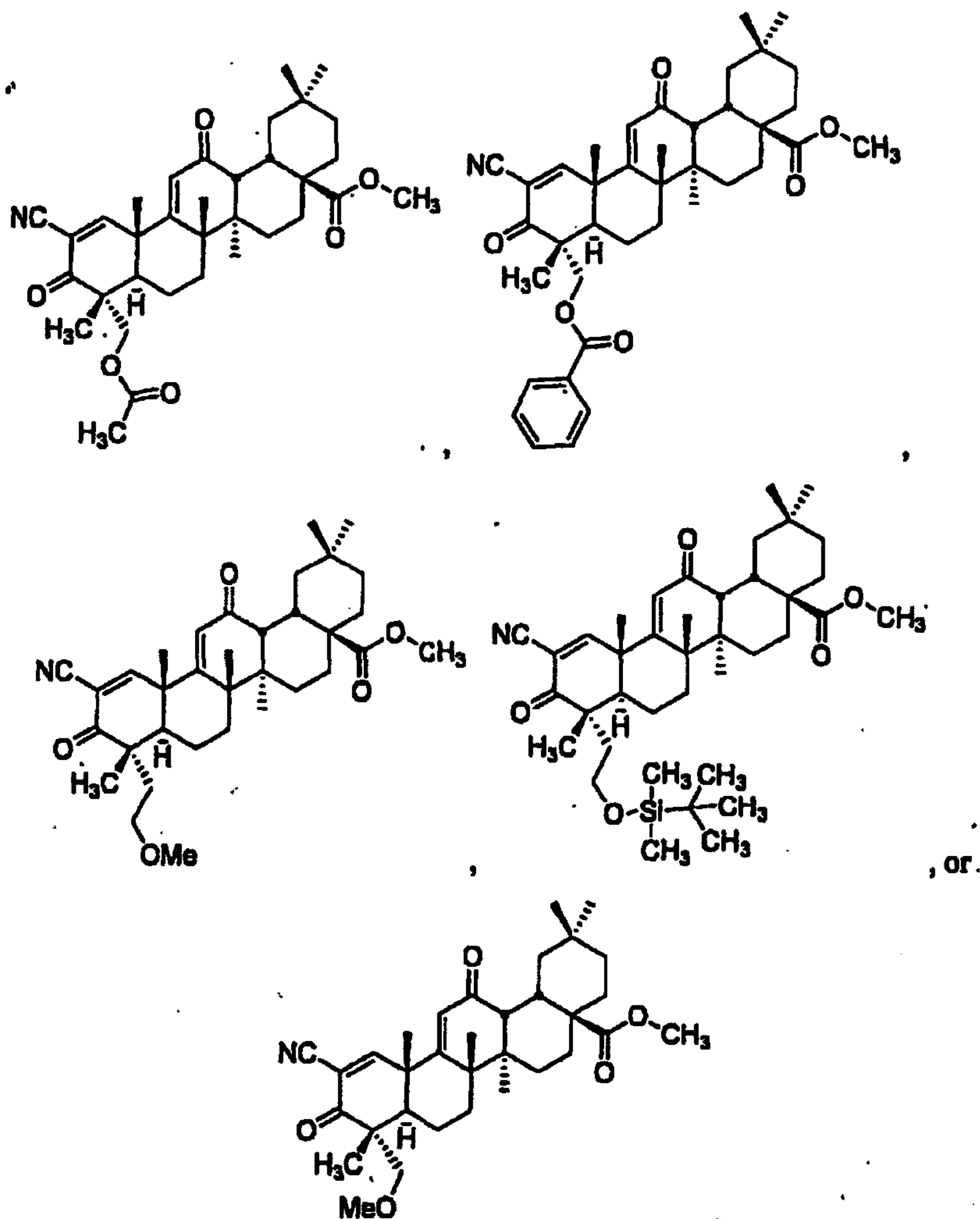


or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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140. The compound according to any one of claims 1-135, wherein the compound is further defined as:

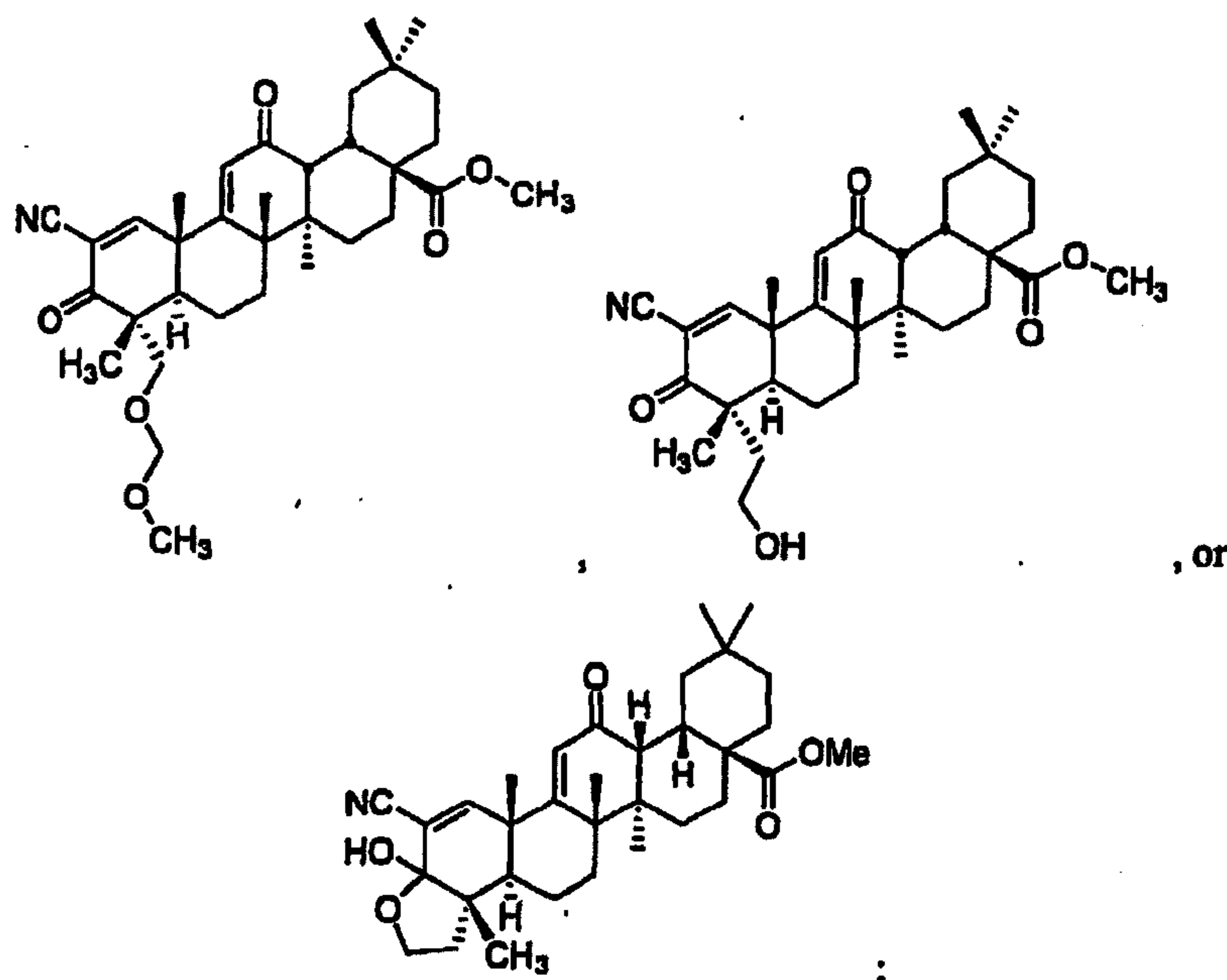


or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

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141. A compound of the formula:



or a pharmaceutically acceptable salt, acetal, or hemiacetal thereof.

142. A compound further defined as:

dimethyl (4S,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-4,4a,5,6,6a,6b,7,8,9,10,11,12,12a,12b,13,14b-hexadecahydricene-4,8a(3H)-dicarboxylate;

dimethyl (4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-4,4a,5,6,6a,6b,7,8,9,10,11,12,12a,12b,13,14b-hexadecahydricene-4,8a(3H)-dicarboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-(difluoromethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-hydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

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methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-hydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-9-(acetoxymethyl)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-9-((benzoyloxy)methyl)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-9-((tert-butoxycarbonyl)amino)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-9-acetamido-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-9-amino-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-9-(methylcarbamoyl)-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-(dimethylcarbamoyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

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methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-9-(5-methyl-1,3,4-oxadiazol-2-yl)-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-(2-methoxyethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-9-carbamoyl-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-9-(2-((tert-butyl)dimethylsilyl)oxy)ethyl)-11-cyano-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-(methoxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-(2-methoxy-2-oxoethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

(4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-N-(2,2,2-trifluoroethyl)-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxamide;

(4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-N-ethyl-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxamide;

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((4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-8a-((2,2,2-trifluoroethyl)carbamoyl)-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydricen-4-yl)methyl acetate;

(4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-hydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-N-(2,2,2-trifluoroethyl)-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxamide;

(4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-N-ethyl-9-hydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxamide;

N-((4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricen-4a(2H)-yl)-2,2-difluoropropanamide;

N-((4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-hydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricen-4a(2H)-yl)-2,2-difluoropropanamide;

((4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-8a-(2,2-difluoropropanamido)-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydricen-4-yl)methyl acetate;

methyl (4aS,6aS,6bR,8aR,9S,12aS,14aS,14bR)-11-cyano-9,14a-dihydroxy-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxylate;

(4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-hydroxy-N,N,2,2,6a,6b,9,12a-octamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydricene-4a(2H)-carboxamide;

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(4S,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-4-hydroxy-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-2-carbonitrile;

(4R,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-4-(hydroxymethyl)-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-2-carbonitrile;

((4R,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picen-4-yl)methyl acetate;

methyl (4S,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-4-carboxylate;

(4R,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-4-((S)-1-hydroxyethyl)-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-2-carbonitrile;

(4S,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-4-carboxamide;

(4S,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-2-cyano-N,4,6a,6b,11,11,14b-heptamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-4-carboxamide;

(4S,4aR,6aR,6bS,8aS,12aR,12bS,14bS)-2-cyano-N,N,4,6a,6b,11,11,14b-octamethyl-3,13,16-trioxo-4,4a,5,6,6a,6b,7,8,10,11,12,12a,13,14b-tetradecahydro-3H,9H-12b,8a-(epoxymethano)picene-4-carboxamide;

methyl ((4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-(hydroxymethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicen-4a(2H)-yl)carbamate;

((4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-8a-((methoxycarbonyl)amino)-4,6a,6b,11,11,14b-hexamethyl-3,13-dioxo-

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3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicen-4-yl)methyl acetate;

methyl ((4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-hydroxy-

2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-

1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicen-4a(2H)-

yl)carbamate;

(4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-4-(hydroxymethyl)-4,6a,6b,11,11,14b-

hexamethyl-8a-(5-methyl-1,3,4-oxadiazol-2-yl)-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-

carbonitrile;

((4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-8a-

(5-methyl-1,3,4-oxadiazol-2-yl)-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicen-4-

yl)methyl acetate;

(4S,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-4-hydroxy-4,6a,6b,11,11,14b-hexamethyl-8a-

(5-methyl-1,3,4-oxadiazol-2-yl)-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-

carbonitrile;

(4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-4-(hydroxymethyl)-4,6a,6b,11,11,14b-

hexamethyl-8a-(3-methyl-1,2,4-oxadiazol-5-yl)-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-

carbonitrile;

((4R,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-2-cyano-4,6a,6b,11,11,14b-hexamethyl-8a-

(3-methyl-1,2,4-oxadiazol-5-yl)-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicen-4-

yl)methyl acetate;

(4S,4aR,6aS,6bR,8aS,12aS,12bR,14bS)-4-hydroxy-4,6a,6b,11,11,14b-hexamethyl-8a-

(3-methyl-1,2,4-oxadiazol-5-yl)-3,13-dioxo-

3,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,12b,13,14b-octadecahydropicene-2-

carbonitrile;

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(1aR,3S,3aR,5aS,5bR,7aS,11aS,11bR,13bS,13cR)-3-hydroxy-3,5a,5b,10,10,13b-hexamethyl-7a-(3-methyl-1,2,4-oxadiazol-5-yl)-2,12-dioxo-3,3a,4,5,5a,5b,6,7,7a,8,9,10,11,11a,11b,12,13b,13c-octadecahydropiceno[1,2-b]oxirene-1a(2H)-carbonitrile;

(1aR,3S,3aR,5aR,5bS,7aS,11aR,11bS,13bS,13cR)-3-hydroxy-3,5a,5b,10,10,13b-hexamethyl-2,12,15-trioxo-3,3a,4,5,5a,6,7,9,10,11,11a,12,13b,13c-tetradecahydro-2H,8H-11b,7a-(epoxymethano)piceno[1,2-b]oxirene-1a(5bH)-carbonitrile; and

N-((1aR,3S,3aR,5aS,5bR,7aS,11aS,11bR,13bS,13cR)-1a-cyano-3-hydroxy-3,5a,5b,10,10,13b-hexamethyl-2,12-dioxo-1a,3,3a,4,5,5a,5b,6,7,8,9,10,11,11a,11b,12,13b,13c-octadecahydropiceno[1,2-b]oxiren-7a(2H)-yl)-2,2-difluoropropanamide.

143. A compound further defined as:

methyl (4aS,6aR,6bS,8aR,9R,12aS,14aR,14bS)-11-cyano-9-((methoxymethoxy)methyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate;

methyl (4aS,6aR,6bS,8aR,9S,12aS,14aR,14bS)-11-cyano-9-(2-hydroxyethyl)-2,2,6a,6b,9,12a-hexamethyl-10,14-dioxo-1,3,4,5,6,6a,6b,7,8,8a,9,10,12a,14,14a,14b-hexadecahydropicene-4a(2H)-carboxylate; and

methyl (3aS,3bR,5aS,5bR,7aS,11aS,11bR,13bS)-15-cyano-15a-hydroxy-3a,5a,5b,10,10,13b-hexamethyl-12-oxo-2,3,3a,4,5,5a,5b,6,7,8,9,10,11,11a,11b,12,13b,15a-octadecahydropiceno[3,4-b]furan-7a(3bH)-carboxylate.

144. A pharmaceutical composition comprising:

- (A) a compound according to any one of claims 1-143; and
- (B) an excipient or a pharmaceutically acceptable carrier.

145. The pharmaceutical composition of claim 144, wherein the composition is formulated for administration: orally, intraadiposally, intraarterially, intraarticularly, intracranially,

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intradermally, intralesionally, intramuscularly, intranasally, intraocularly, intrapericardially, intraperitoneally, intrapleurally, intraprostatically, intrarectally, intrathecally, intratracheally, intratumorally, intraumbilically, intravaginally, intravenously, intravesicularly, intravitreally, liposomally, locally, mucosally, parenterally, rectally, subconjunctival, subcutaneously, sublingually, topically, transbuccally, transdermally, vaginally, in crèmes, in lipid compositions, via a catheter, via a lavage, via continuous infusion, via infusion, via inhalation, via injection, via local delivery, or via localized perfusion.

146. A method of treating or preventing a disease or disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound or composition according to any one of claims 1-145.
147. The method of claim 146, wherein the patient is a mammal.
148. The method of claim 147, wherein the patient is a human.
149. The method according to any one of claims 146-148, wherein the disease or disorder is associated with increased production of cytokine IL-17.
150. The method according to any one of claims 146-149, wherein the disease or disorder is associated with dysregulated angiogenesis.
151. The method according to any one of claims 146-150, wherein the disease or disorder is an autoimmune disease, organ rejection, asthma, cancer, a neurological disorder, a psychiatric disorder, a neuropsychiatric disorder, chronic pain syndrome, an inflammatory condition, or a cardiovascular disease.
152. The method of claim 151, wherein the autoimmune disease is psoriasis, multiple sclerosis, scleroderma, rheumatoid arthritis, lupus, psoriatic arthritis, ankylosing spondylitis, Sjögren syndrome, vitiligo, uveitis, systemic sclerosis, type 1 diabetes, myasthenia gravis, and inflammatory bowel disease.
153. The method of claim 151, wherein the cardiovascular disease is vasculitis, atherosclerosis, myocardial infarction, myocarditis, heart failure, pulmonary hypertension, or stroke.

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154. The method of claim 151, wherein the neurological disorder is epilepsy, multiple sclerosis, spinal cord injury, Guillain-Barre syndrome, or a neurological disorder.
155. The method of claim 154, wherein the neurodegenerative disorder is Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or Huntington's disease.
156. The method of claim 151, wherein the inflammatory condition is pancreatitis, hepatitis, pulmonary fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, asthma, dermatitis, gastritis, esophagitis, irritable bowel syndrome, inflammatory bowel disease, nephritis, muscle wasting, or osteoarthritis.
157. The method of claim 151, wherein the chronic pain syndrome is fibromyalgia or neuropathic pain.
158. The method of claim 151, wherein the disease or disorder is a severe inflammatory response to a pathogen.
159. The method of claim 158, wherein the severe inflammatory response to a pathogen is from encephalitis, meningitis, *H. pylori*, *Toxoplasma gondii*, or *Leishmania spp.*
160. The method of claim 151, wherein the disease or disorder is obesity or a condition associated with obesity.
161. The method of claim 160, wherein the condition associated with obesity are insulin resistance or fatty liver disease.
162. The method according to any one of claims 146-159, wherein the method comprises administering the compound once.
163. The method according to any one of claims 146-159, wherein the method comprises administering the compound two or more times.
164. A method of inhibiting the activity of an interleukin 17 comprising contacting the interleukin 17 with an effective amount of a compound or composition according to any one of claims 1-145.
165. The method of claim 164, wherein the method comprises inhibiting the activity of interleukin 17 *in vivo*.

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166. The method of claim 165, wherein contacting the interleukin comprises administering the compound to a patient in need thereof.
167. The method according to any one of claims 164-166, wherein the compound also inhibits the production of nitric oxide *in vivo*.
168. The method according to any one of claims 164-167, wherein inhibition of interleukin 17 activity is sufficient to treat a disease or disorder.
169. The method of claim 168, wherein the disease or disorder is associated with the misregulation of interleukin 17.
170. The method of claim 168, wherein the disease or disorder is associated with inflammation.
171. The method of claim 168, wherein the disease or disorder is associated with the misregulation of nitric oxide production.

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