



Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2950088 A1 2017/06/02

(21) **2 950 088**

(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

(22) Date de dépôt/Filing Date: 2016/11/30

(41) Mise à la disp. pub./Open to Public Insp.: 2017/06/02

(30) Priorité/Priority: 2015/12/02 (US62/262,155)

(51) Cl.Int./Int.Cl. *C07H 15/26* (2006.01),
A61K 31/7052 (2006.01)

(71) Demandeur/Applicant:
GLYCOMIMETICS, INC., US

(72) Inventeurs/Inventors:
ERNST, BEAT, CH;
WAGNER, BEATRICE, CH

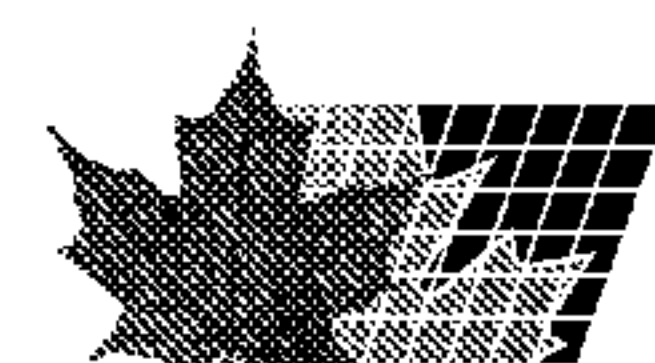
(74) Agent: SMART & BIGGAR

(54) Titre : COMPOSES HETEROBIFONCTIONNELS COMPORTANT UN LIEN TRIAZOLE ET UNE AFFINITE DE
LIAISON DE SELECTINE E OU P

(54) Title: HETEROBIFUNCTIONAL COMPOUNDS HAVING A TRIAZOLE LINKER AND E AND/OR P SELECTIN
BINDING AFFINITY

(57) **Abrégé/Abstract:**

Glycomimetics linked via a triazole linker to a member of a class of compounds termed BASAs (Benzyl Amino Sulfonic Acids) are described, and which may have E~selectin and/or P-electin binding activity.



ABSTRACT OF THE DISCLOSURE

Glycomimetics linked via a triazole linker to a member of a class of compounds termed BASAs (Benzyl Amino Sulfonic Acids) are described, and which may have E-selectin and/or P-selectin binding activity.

**HETEROBIFUNCTIONAL COMPOUNDS
HAVING A TRIAZOLE LINKER AND E AND/OR P SELECTIN BINDING AFFINITY**

RELATED APPLICATIONS

[0001] This application claims the benefit of and priority from U.S. Provisional Patent Application 62/262,155, filed December 2, 2015. The foregoing application is incorporated herein by reference in its entirety.

FIELD OF INVENTION

[0002] Compounds comprising a glycomimetic linked via a triazole linker to a member of a class of compounds termed BASAs (Benzyl Amino Sulfonic Acids) are disclosed herein. Such compounds may have selectin E and/or P selectin binding affinity.

BACKGROUND OF THE INVENTION

[0003] When a tissue is infected or damaged, the inflammatory process directs leukocytes and other immune system components to the site of infection or injury. Within this process, leukocytes play a role in the engulfment and digestion of microorganisms. Thus, the recruitment of leukocytes to infected or damaged tissue is important for mounting an effective immune defense.

[0004] Selectins are a group of structurally similar cell surface receptors that are important for mediating leukocyte binding to endothelial cells. These proteins are type 1 membrane proteins and are composed of an amino terminal lectin domain, an epidermal growth factor (EGF)-like domain, a variable number of complement receptor related repeats, a hydrophobic domain spanning region, and a cytoplasmic domain. The binding interactions appear to be mediated by contact of the lectin domain of the selectins and various carbohydrate ligands.

[0005] There are three known selectins: E-selectin, P-selectin, and L-selectin. E-selectin is found on the surface of activated endothelial cells and binds to the carbohydrate sialyl-Lewis^x (SLe^x) which is presented as a glycoprotein or glycolipid on the surface of certain leukocytes (monocytes and neutrophils) and helps these cells adhere to capillary walls in areas where

surrounding tissue is infected or damaged. E-selectin also binds to sialyl-Lewis^a (SLe^a) which is expressed on many tumor cells. P-selectin is expressed on inflamed endothelium and platelets and also recognizes SLe^x and SLe^a but also contains a second site that interacts with sulfated tyrosine. The expression of E-selectin and P-selectin is generally increased when the tissue adjacent to a capillary which is infected or damaged. L-selectin is expressed on leukocytes. Selectin-mediated intercellular adhesion and formation of new capillaries during angiogenesis are examples of selectin-mediated functions.

[0006] Modulators of selectin-mediated function include the PSGL-1 protein (and smaller peptide fragments thereof), fucoidan, glycyrrhizin (and derivatives), anti-selectin antibodies, sulfated lactose derivatives, heparin and heparin fragments, sulfated hyaluronic acid, chondroitin sulfate, sulfated dextran, sulfatides, and particular glycomimetic compounds (see, e.g., US RE44,778). All but the glycomimetics have shown to be unsuitable for drug development due to insufficient activity, toxicity, lack of specificity, poor ADME characteristics, and/or availability of material.

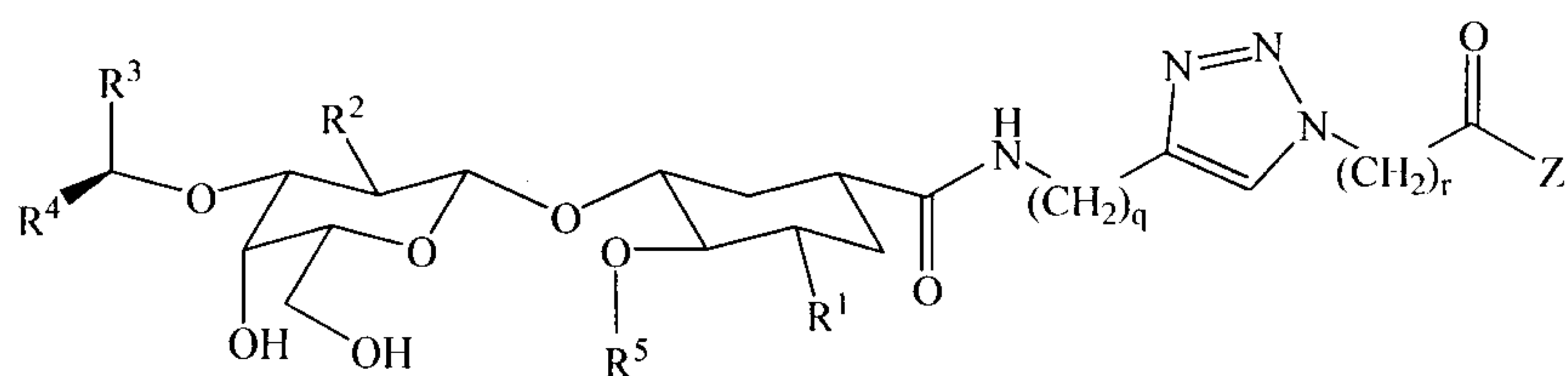
[0007] Although selectin-mediated cell adhesion is required for fighting infection and destroying foreign material, there are situations in which cell adhesion is undesirable or excessive resulting in tissue damage instead of repair. For example, pathologies that involve abnormal adhesion of white blood cells include autoimmune and inflammatory diseases, shock, and reperfusion injuries. Abnormal cell adhesion may also play a role in transplant and graft rejection. In addition, some circulating cancer cells appear to take advantage of the inflammatory mechanism to bind to activated endothelium. In these circumstances, modulation of selectin-mediated intercellular adhesion may be desirable.

[0008] There is a need in the art for identifying further compounds that may have selectin E and/or P selectin binding affinity.

SUMMARY OF THE INVENTION

[0009] Briefly stated, compounds comprising a glycomimetic linked via a triazole linker to a member of a class of compounds termed BASAs are disclosed. These compounds may have E and/or P selectin binding affinity.

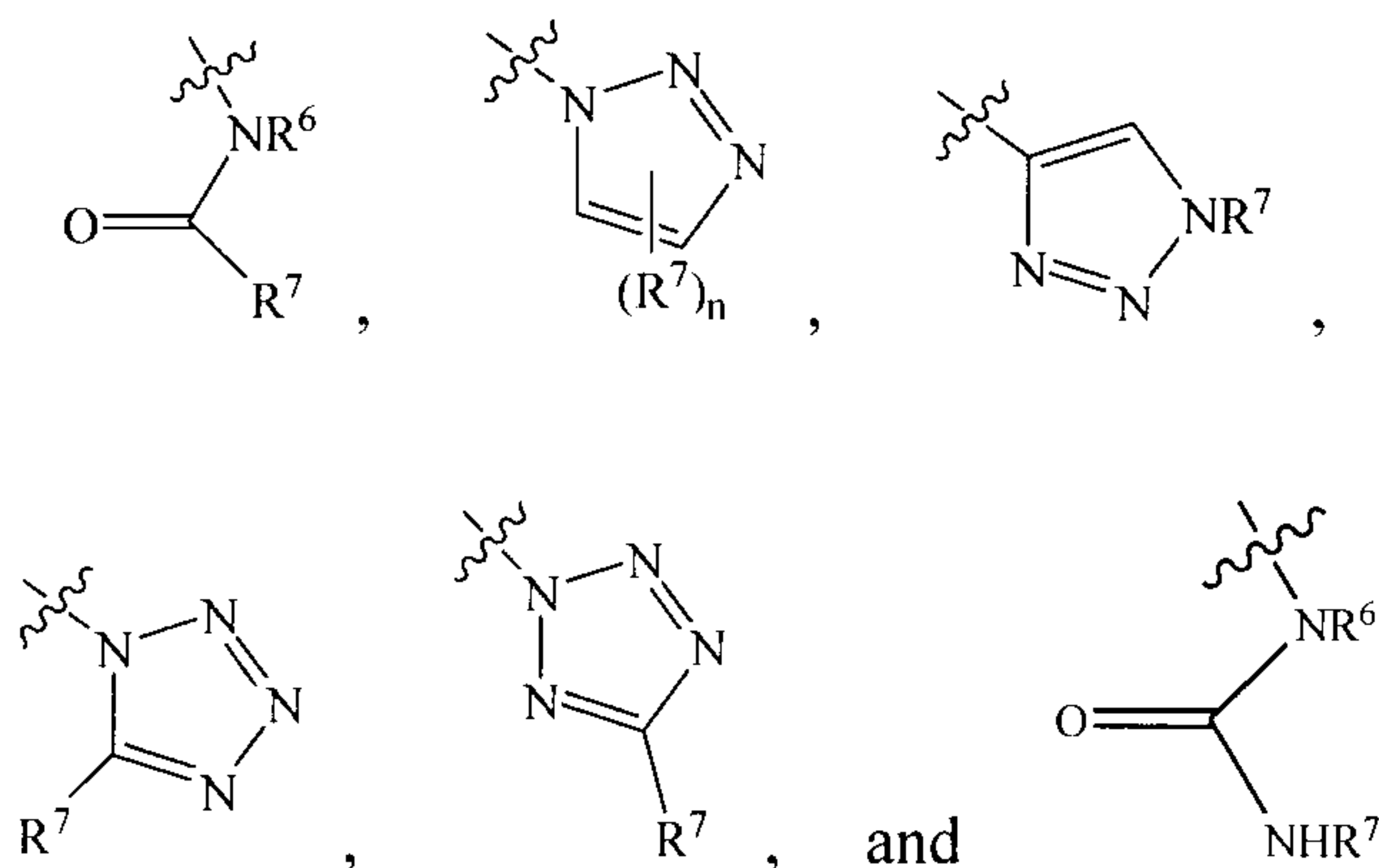
[0010] In some embodiments, there are provided compounds of Formula (I):



(I)

prodrugs thereof, and pharmaceutically acceptable salts of any of the foregoing are disclosed, wherein

R^1 is chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl



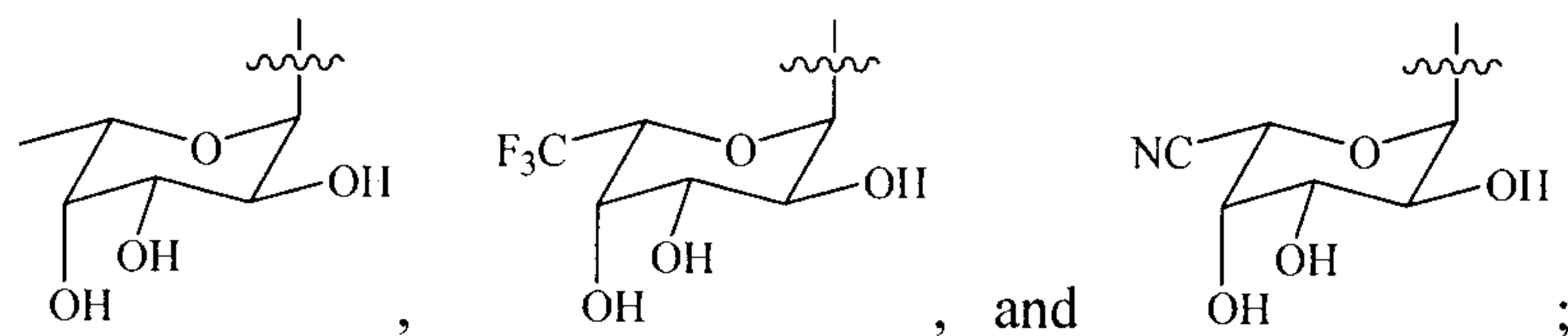
groups;

R^2 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl, $-OH$, $-OX^1$, halo, $-NH_2$, $-OC(=O)X^1$, $-NHC(=O)X^1$, and $-NHC(=O)NHX^1$ groups, wherein X^1 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl, C_{2-12} heterocyclyl, C_{6-18} aryl, and C_{1-13} heteroaryl groups;

R^3 is chosen from $-CN$, $-CH_2CN$, and $-C(=O)X^2$ groups, wherein X^2 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $-OY^2$, $-NHOH$, $-NHOCH_3$, $-NHCN$, and $-NY^2Y^3$ groups, wherein Y^2 and Y^3 , which may be identical or different, are independently chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, and C_{4-16} cycloalkylalkyl groups, wherein Y^2 and Y^3 may join together to form a ring;

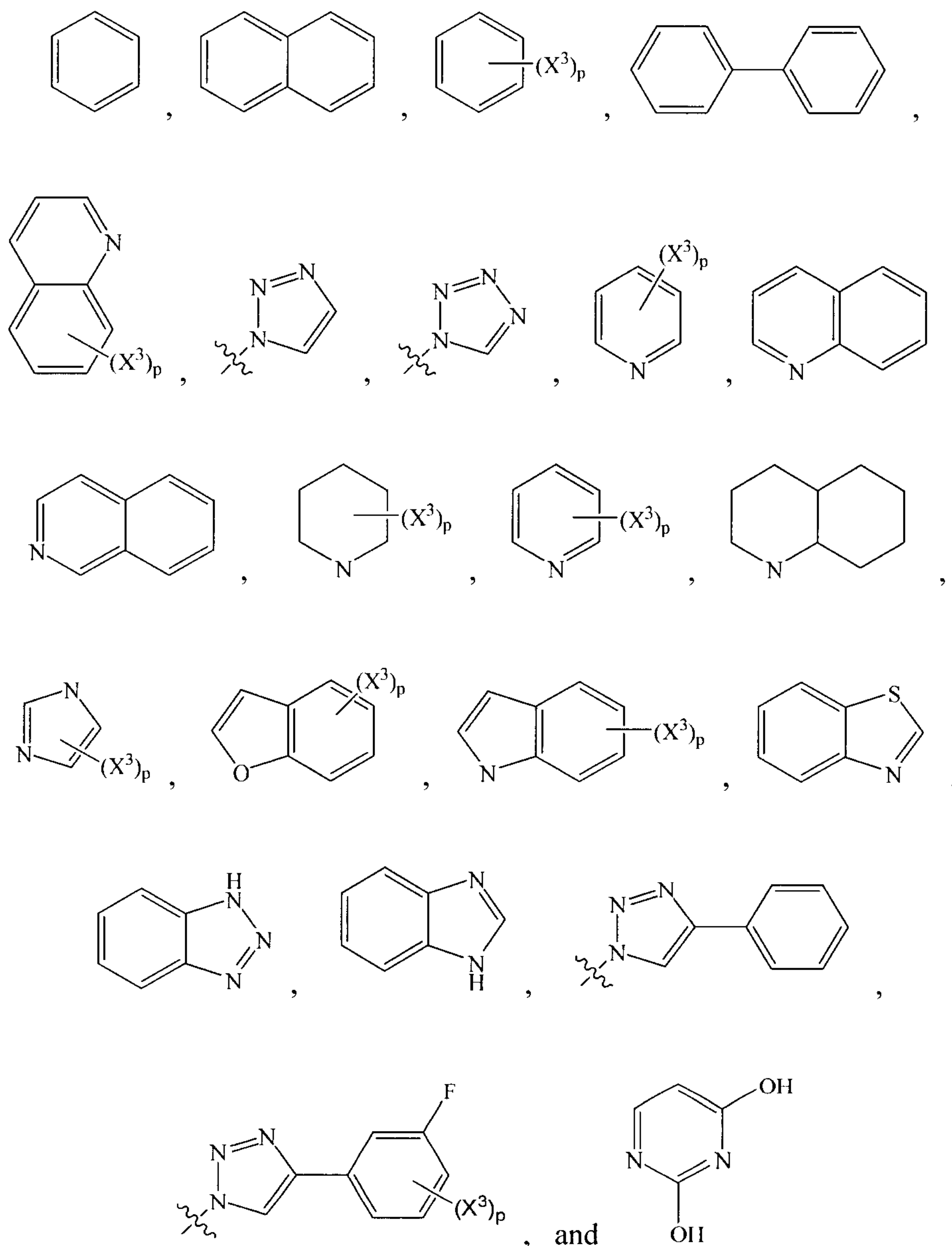
R^4 is chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl, and C_{6-18} aryl groups;

R^5 is chosen from H, mannose, arabinose, galactose, polyols,



R^6 is chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl, and $-C(=O)R^7$ groups;

each R^7 is independently chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl,



groups, wherein each X^3 is independently chosen from H, $-OH$, Cl, F, N_3 , $-NH_2$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{6-14} aryl, $-OC_{1-8}$ alkyl, $-OC_{2-8}$ alkenyl, $-OC_{2-8}$ alkynyl, and $-OC_{6-14}$ aryl groups, wherein any of the above ring compounds may be substituted with one to three groups independently chosen from Cl, F, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{6-14} aryl, and $-OY^4$ groups, wherein Y^4 is chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, and C_{6-14} aryl groups;

n is chosen from integers ranging from 0 to 2;

p is chosen from integers ranging from 0 to 3;
 q is chosen from integers ranging from 1 to 10;
 r is chosen from integers ranging from 1 to 10; and
 Z is chosen from BASA groups.

[0011] As used herein, “compound of Formula (I)” includes compounds of Formula (I), pharmaceutically acceptable salts of compounds of Formula (I), prodrugs of compounds of Formula (I), and pharmaceutically acceptable salts of prodrugs of compounds of Formula (I).

[0012] In some embodiments, there are presented compositions comprising at least one compound of Formula (I) and optionally at least one additional pharmaceutically acceptable ingredient.

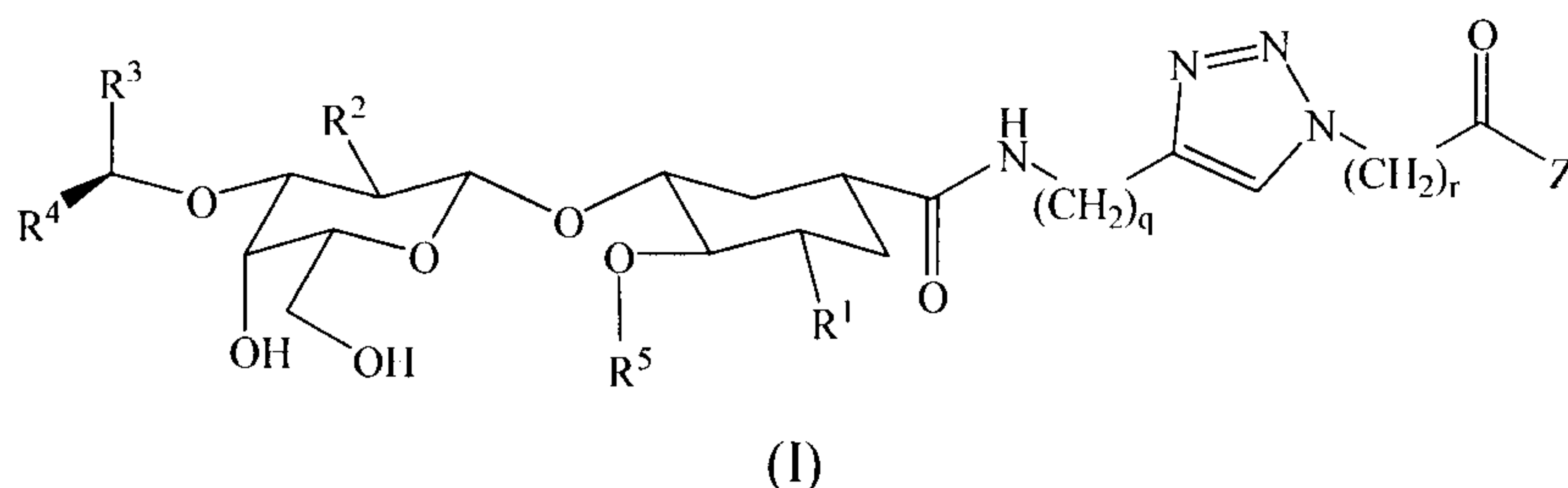
[0013] In some embodiments, a use of a compound of Formula (I) as a P-selectin antagonist is presented.

[0014] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the disclosed embodiments may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. These and other embodiments will become apparent upon reference to the following detailed description.

DETAILED DESCRIPTION

[0015] Disclosed herein are compounds that may have E and/or P selectin binding activity and compositions.

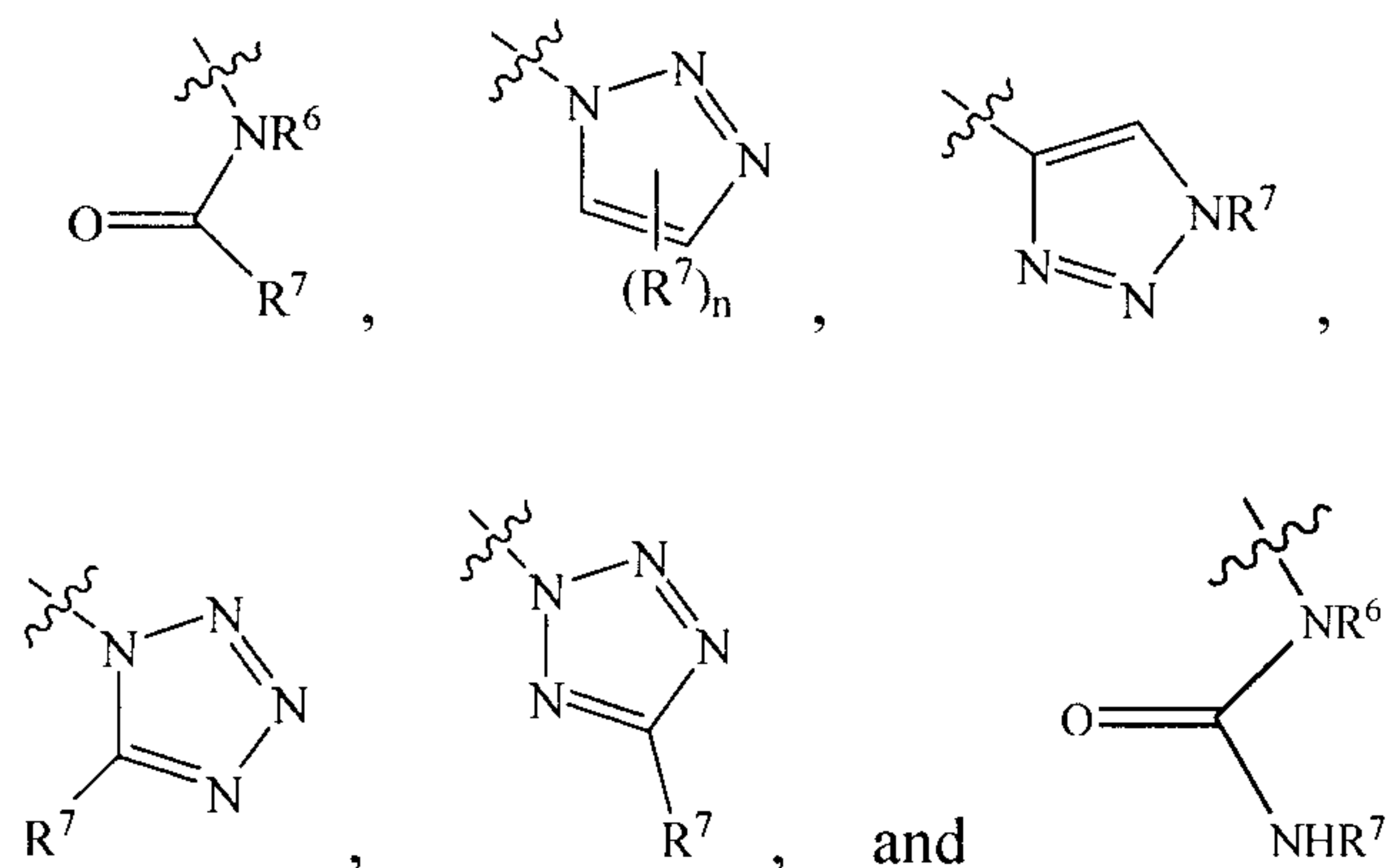
[0016] In some embodiments, presented are compounds of Formula (I):



prodrugs thereof, and pharmaceutically acceptable salts of any of the foregoing are disclosed,

wherein

R^1 is chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl



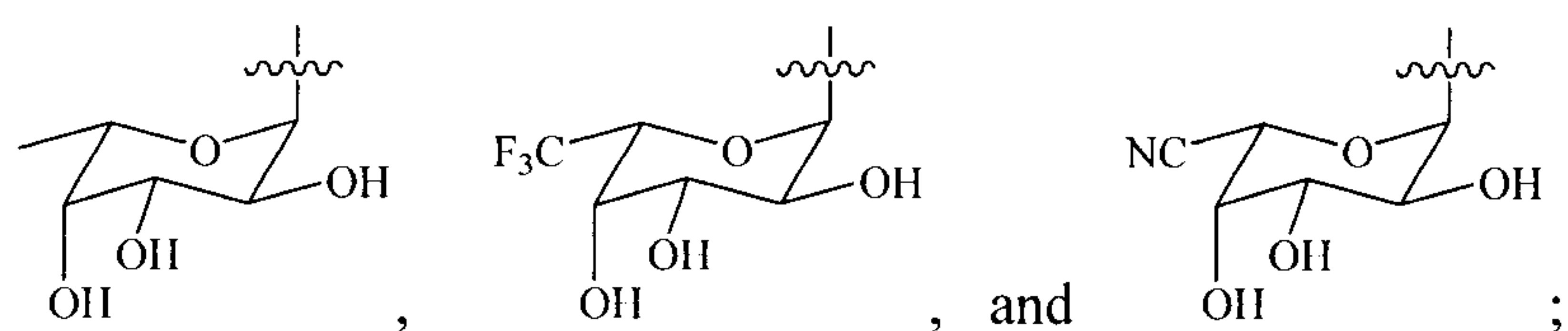
groups;

R^2 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl, $-OH$, $-OX^1$, halo, $-NH_2$, $-OC(=O)X^1$, $-NHC(=O)X^1$, and $-NHC(=O)NHX^1$ groups, wherein X^1 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl, C_{2-12} heterocyclyl, C_{6-18} aryl, and C_{1-13} heteroaryl groups;

R^3 is chosen from $-CN$, $-CH_2CN$, and $-C(=O)X^2$ groups, wherein X^2 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $-OY^2$, $-NHOH$, $-NHOCH_3$, $-NHCN$, and $-NY^2Y^3$ groups, wherein Y^2 and Y^3 , which may be identical or different, are independently chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, and C_{4-16} cycloalkylalkyl groups, wherein Y^2 and Y^3 may join together to form a ring;

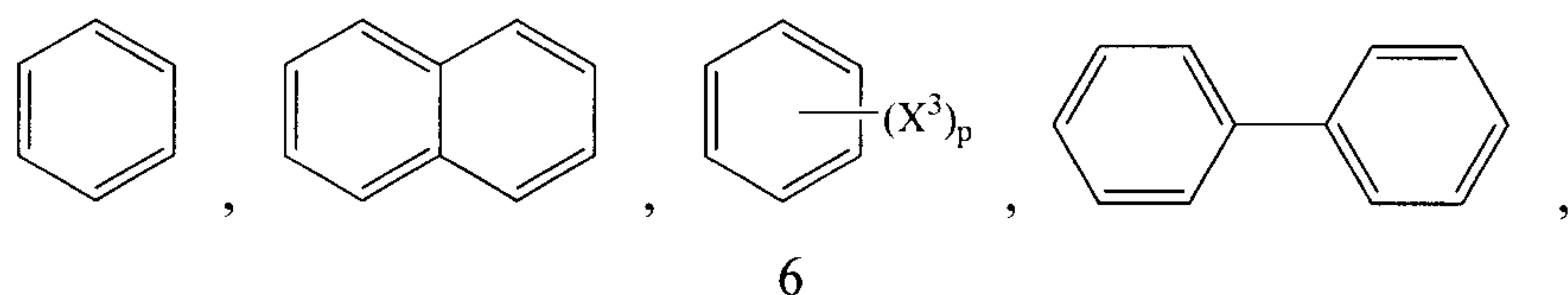
R^4 is chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl, and C_{6-18} aryl groups;

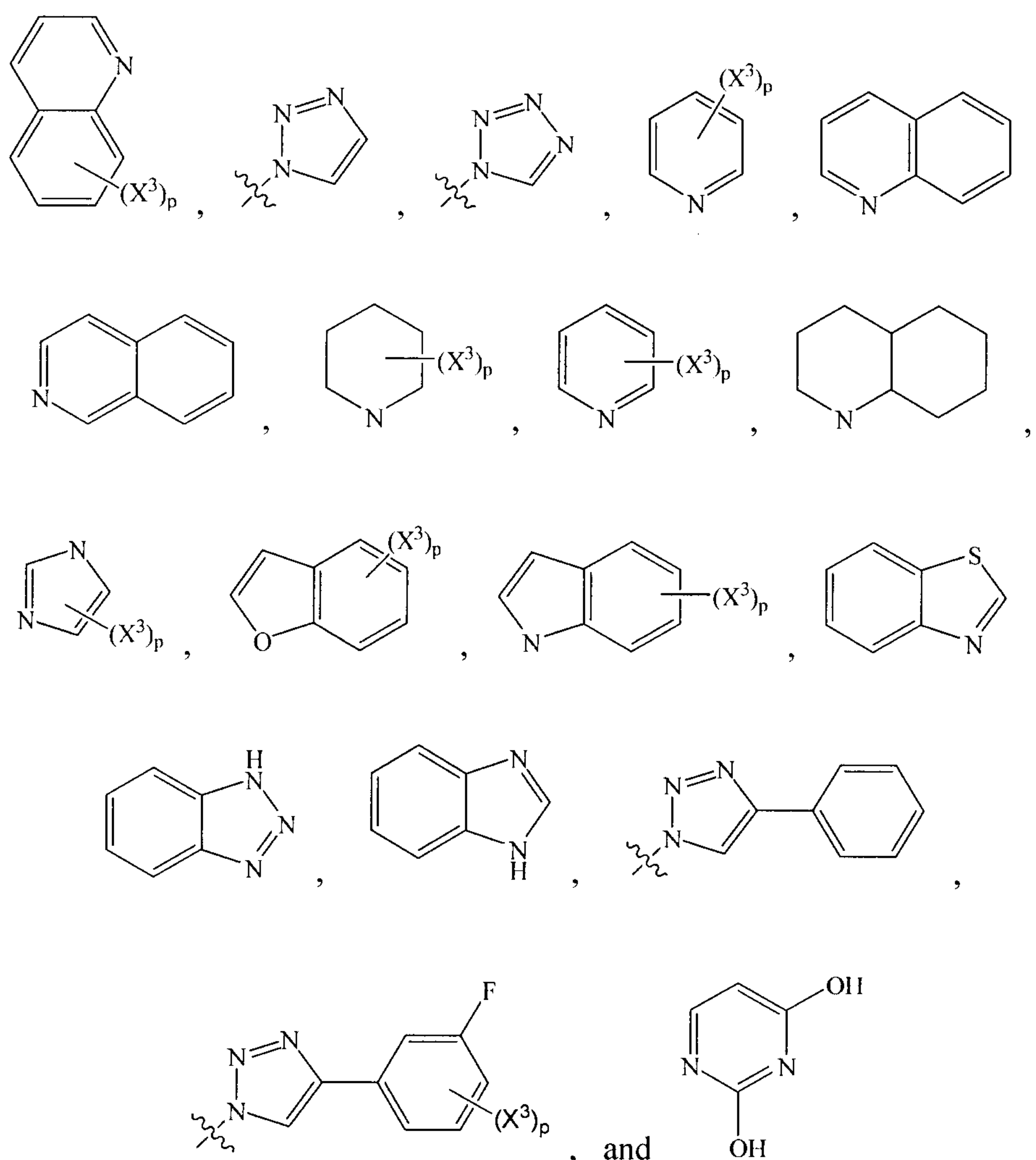
R^5 is chosen from H, mannose, arabinose, galactose, polyols,



R^6 is chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl, and $-C(=O)R^7$ groups;

each R^7 is independently chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl,





groups, wherein each X^3 is independently chosen from H, $-OH$, Cl, F, N_3 , $-NH_2$, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{6-14} aryl, $-OC_{1-8}$ alkyl, $-OC_{2-8}$ alkenyl, $-OC_{2-8}$ alkynyl, and $-OC_{6-14}$ aryl groups, wherein any of the above ring compounds may be substituted with one to three groups independently chosen from Cl, F, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{6-14} aryl, and $-OY^4$ groups, wherein Y^4 is chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, and C_{6-14} aryl groups;

n is chosen from integers ranging from 0 to 2;

p is chosen from integers ranging from 0 to 3;

q is chosen from integers ranging from 1 to 10;

r is chosen from integers ranging from 1 to 10; and

Z is chosen from BASA groups.

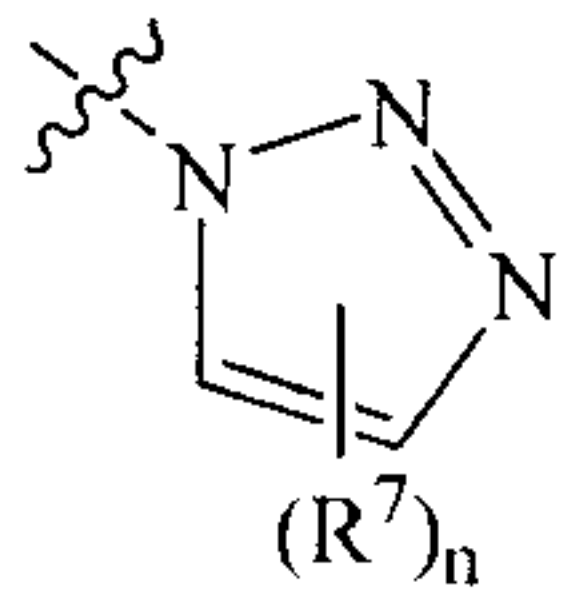
[0017] BASAs (Benzyl Amino Sulfonic Acids) are low molecular weight sulfated compounds which have the ability to interact with a selectin. They exist as either their

protonated acid form, or as a sodium salt, although sodium may be replaced with potassium or any other pharmaceutically acceptable counterion.

[0018] Portions of BASA that retain the ability to interact with a selectin are also a “BASA” as used herein. Such portions may comprise at least one aromatic ring present within the BASA structure. In some embodiments, a portion may comprise a single aromatic ring, multiple such rings, or half of a symmetrical BASA molecule.

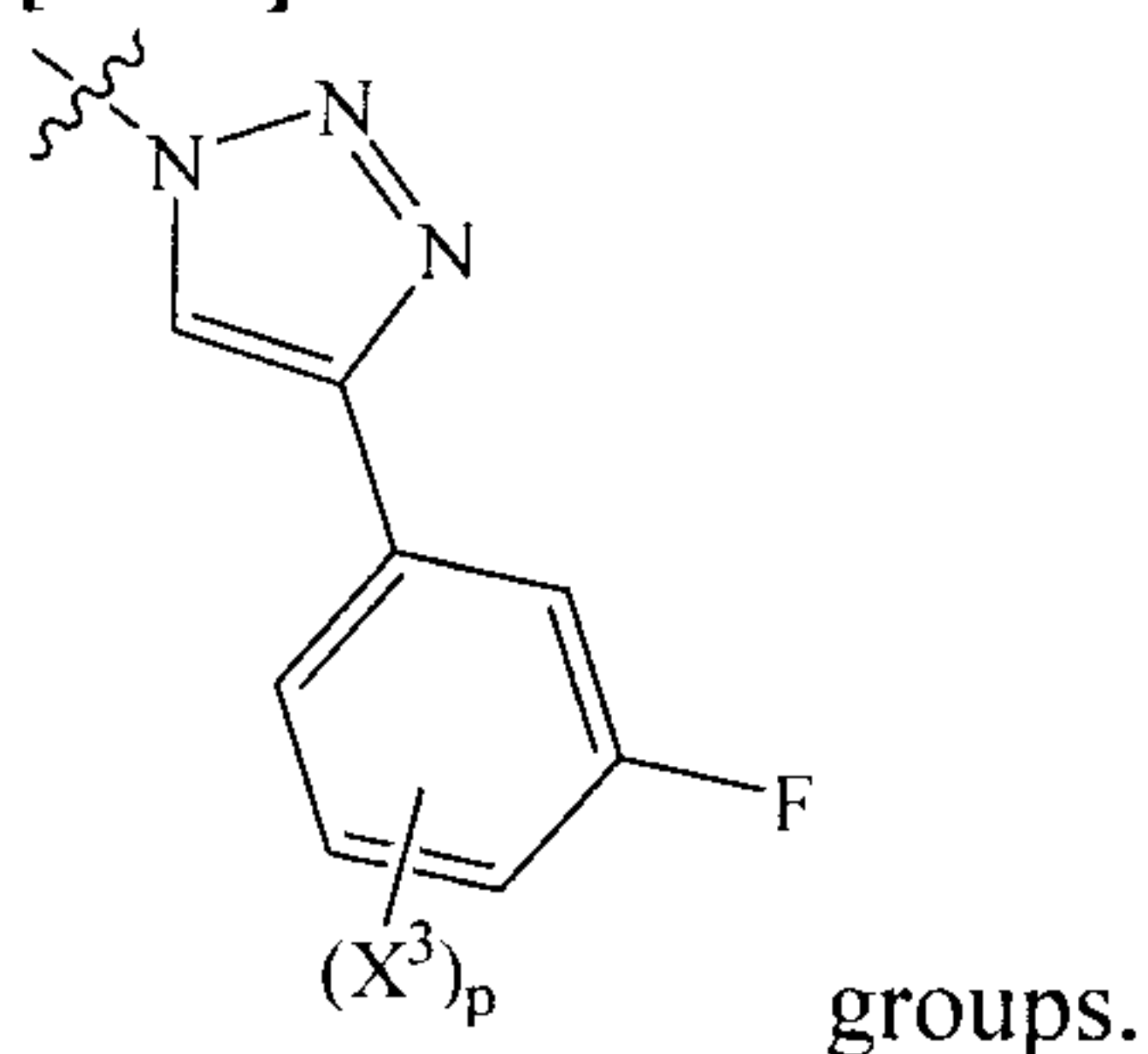
[0019] Analogues of BASA and portions thereof (both of which possess the biological characteristic set forth herein) are also encompassed, e.g., by the “BASA” group of the selectin--binding compounds within the disclosure. As used herein, an “analogue” is a compound that differs from BASA or a portion thereof because of one or more additions, deletions and/or substitutions of chemical moieties, such that the ability of the analogue to interact with a selectin is not diminished. For example, an analogue may contain S to P substitutions (e.g., a sulfate group replaced with a phosphate group). Other possible modifications include: (a) modifications to ring size (e.g., any ring may contain between 4 and 7 carbon atoms); (b) variations in the number of fused rings (e.g., a single ring may be replaced with a polycyclic moiety containing up to three fused rings, a polycyclic moiety may be replaced with a single unfused ring or the number of fused rings within a polycyclic moiety may be altered); (c) ring substitutions in which hydrogen atoms or other moieties covalently bonded to a carbon atom within an aromatic ring may be replaced with any of a variety of moieties, such as F, Cl, Br, I, OH, OC₁₋₈ alkyl, SH, NO₂, CN, NH₂, NHC₁₋₈ alkyl, N(C₁₋₈ alkyl)₂, SO₃T (wherein T is chosen from H⁺, Na⁺, K⁺, and other pharmaceutically acceptable counterions), -CO₂T, -PO₄T₂, -SO₂NH₂, C₁₋₈ alkyl, C₆₋₁₀ aryl, -C(=O)OC₁₋₈ alkyl, -CF₂Q (wherein Q is chosen from H, F, alkyl, aryl, and acyl groups) and carbohydrates; and (d) modifications to linking moieties (i.e., moieties located between rings in the BASA molecule) in which groups such as alkyl, ester, amide, anhydride, and carbamate groups may be substituted for one another.

[0020] In some embodiments, R¹ is chosen from H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl,

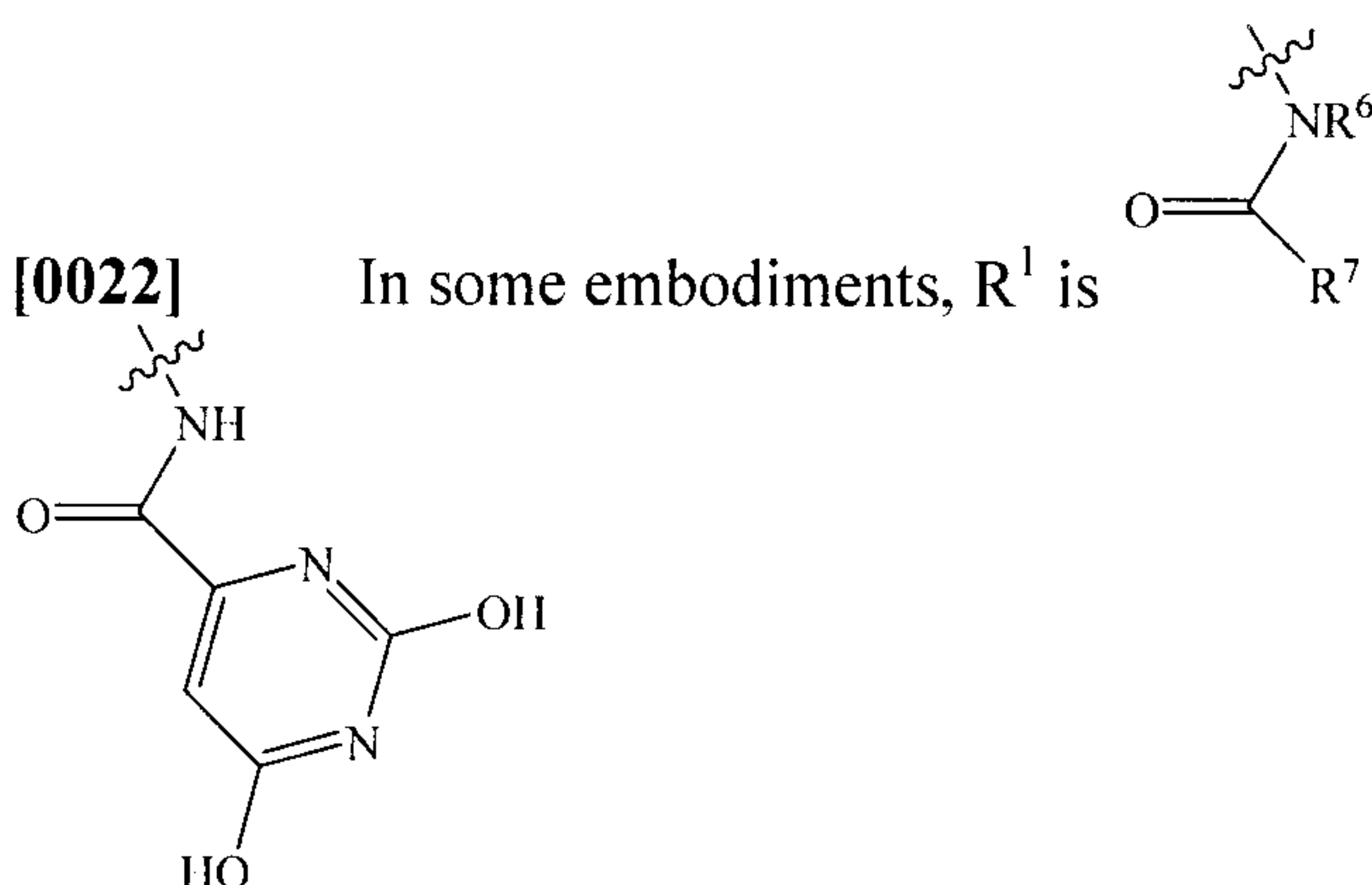


and groups. In some embodiments, R¹ is chosen from H and C₁₋₈ alkyl groups. In some embodiments, R¹ is chosen from C₁₋₈ alkyl groups. In some embodiments, R¹ is chosen from C₁₋₄ alkyl groups. In some embodiments, R¹ is methyl. In some embodiments, R¹ is ethyl.

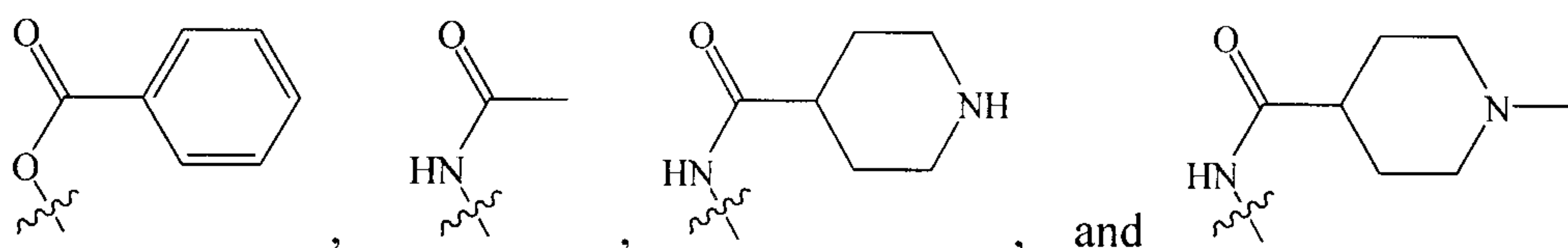
[0021] In some embodiments, R^1 is chosen from methyl, ethyl, and



[0022] In some embodiments, R^1 is



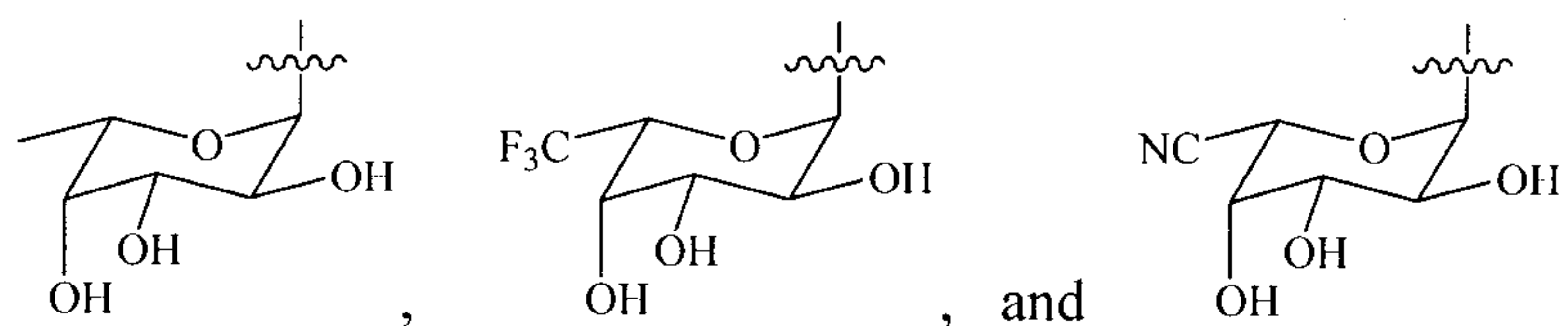
[0023] In some embodiments, R^2 is chosen from $-OC(=O)X^1$, $-NHC(=O)X^1$, and $-NHC(=O)NHX^1$ groups, wherein X^1 is chosen from C_{1-8} alkyl, C_{2-12} heterocyclyl, C_{6-18} aryl, and C_{1-13} heteroaryl groups. In some embodiments, R^2 is chosen from



[0024] In some embodiments, R^3 is chosen from $-C(=O)X^2$ groups, wherein X^2 is chosen from $-OY^2$, $-NHOH$, $-NHOCH_3$, and $-NY^2Y^3$ groups, wherein Y^2 and Y^3 , which may be identical or different, are independently chosen from H and C_{1-8} alkyl, wherein Y^2 and Y^3 may joint together to form a ring. In some embodiments, R^3 is $-C(=O)OH$.

[0025] In some embodiments, R^4 is chosen from C_{4-16} cycloalkylalkyl groups. In some embodiments, R^4 is chosen from C_{4-8} cycloalkylalkyl groups. In some embodiments, R^4 is chosen from cyclopropylmethyl and cyclohexylmethyl. In some embodiments, R^4 is cyclopropylmethyl. In some embodiments R^4 is cyclohexylmethyl.

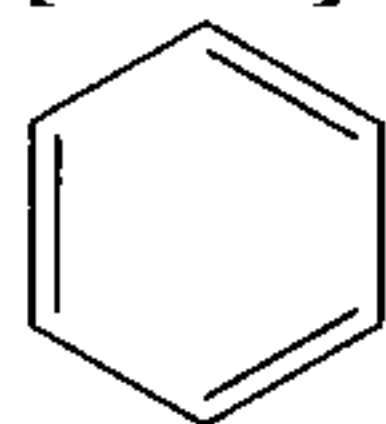
[0026] In some embodiments, R^5 is chosen from



[0027] In some embodiments, R^5 is fucose.

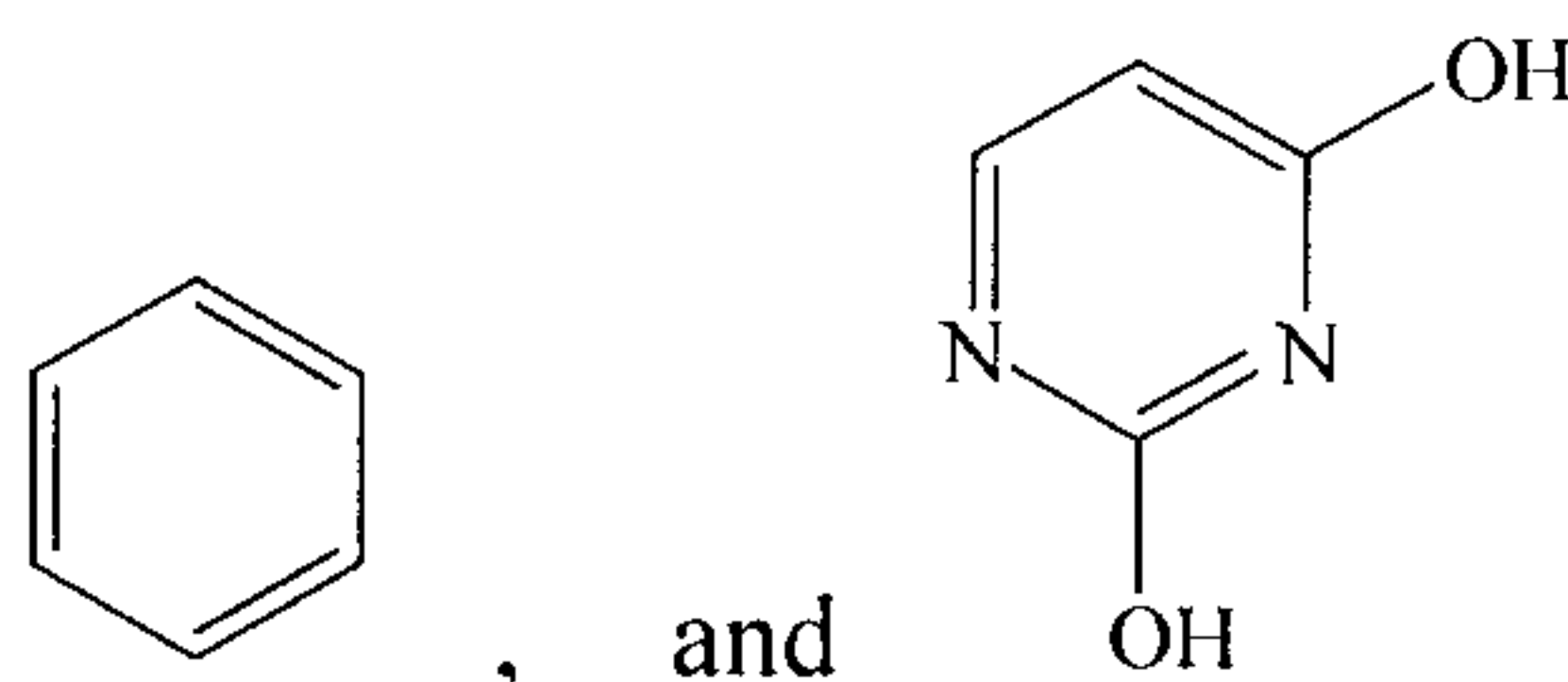
[0028] In some embodiments, R^6 is chosen from H, C_{1-8} alkyl, and $-C(=O)R^7$ groups. In some embodiments, R^6 is chosen from H and C_{1-8} alkyl groups. In some embodiments, R^6 is chosen from C_{1-4} alkyl groups. In some embodiments, R^6 is H.

[0029] In some embodiments, each R^7 is independently chosen from H, C_{1-8} alkyl, and



groups, wherein any of the above ring compounds may be substituted with one to three groups independently chosen from Cl, F, C_{1-8} alkyl, C_{6-14} aryl, and $-OY^4$ groups, wherein each Y^4 is independently chosen from H, C_{1-8} alkyl, and C_{6-14} aryl groups. In some embodiments, at least one R^7 is independently chosen from C_{1-8} alkyl groups. In some embodiments, at least one R^7 is chosen from C_{1-4} alkyl groups. In some embodiments, at least one R^7 is chosen from methyl and ethyl. In some embodiments, at least one R^7 is H. In some embodiments, at least one R^7 is methyl. In some embodiments, at least one R^7 is ethyl.

[0030] In some embodiments, each R^7 is independently chosen from H, C_{1-8} alkyl,



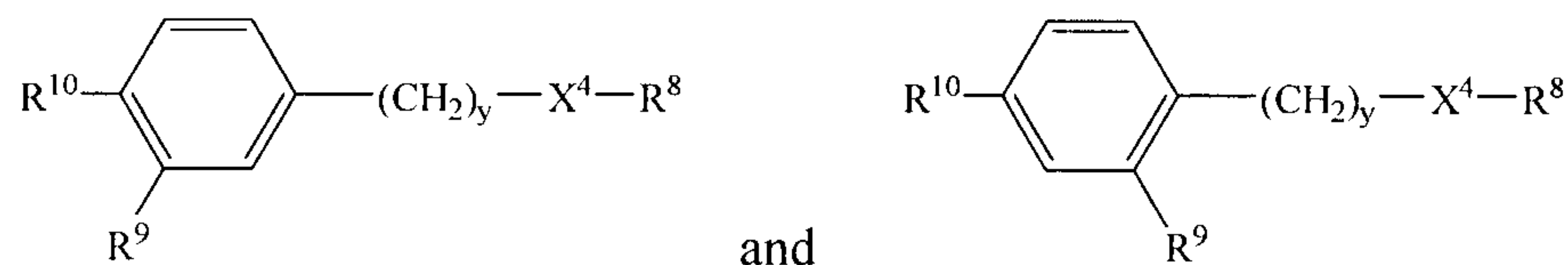
groups, wherein any of the above ring compounds may be substituted with one to three groups independently chosen from Cl, F, C_{1-8} alkyl, C_{6-14} aryl, and $-OY^4$ groups, wherein each Y^4 is independently chosen from H, C_{1-8} alkyl, and C_{6-14} aryl groups.

[0031] In some embodiments, q is chosen from integers ranging from 2 to 4. In some embodiments, q is 2. In some embodiments, q is 3. In some embodiments, q is 4.

[0032] In some embodiments, r is chosen from integers ranging from 2 to 6. In some embodiments, r is 2. In some embodiments, r is 3. In some embodiments, r is 4.

[0033] In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, p is 0. In some embodiments, p is 1.

[0034] In some embodiments, Z comprises a compound chosen from



wherein

R^8 is chosen from H, -F, and $-C(=O)OY^5$ groups;

R^9 is chosen from H, $-PO_3T_2$, $-SO_3T_2$, $-CH_2-PO_3T_2$, $-CH_2-SO_3T_2$, $-CF_3$, $-CHR^{11}R^{12}$, $-CH_2CHR^{11}R^{12}$, $-(CH_2)_2CHR^{11}R^{12}$, $-(CH_2)_3CHR^{11}R^{12}$, and $-NZ^3Z^4$ groups, wherein R^{11} and R^{12} , which may be identical or different, are independently chosen from H, $-C(=O)OY^5$, and $-NH_2$ groups, wherein Z^3 and Z^4 , which may be identical or different, are independently chosen from H and $-Y^6-(C_{6-18} \text{ aryl})$ groups, wherein Y^6 is chosen from C_{1-4} alkyl and $C(=O)$ groups;

R^{10} is chosen from H, $-PO_3T_2$, $-SO_3T_2$, $-CH_2-PO_3T_2$, $-CH_2-SO_3T_2$, $-CF_3$, $-CHR^{13}R^{14}$, $-CH_2CHR^{13}R^{14}$, $-(CH_2)_2CHR^{13}R^{14}$, $-(CH_2)_3CHR^{13}R^{14}$, and $-NZ^5Z^6$ groups, wherein R^{13} and R^{14} , which may be identical or different, are independently chosen from H, $-C(=O)OY^5$, $-NH_2$ groups, wherein Z^5 and Z^6 , which may be identical or different, are independently chosen from H and $-Y^7-(C_{6-18} \text{ aryl})$ groups, wherein Y^7 is chosen from C_{1-4} alkyl and $C(=O)$ groups;

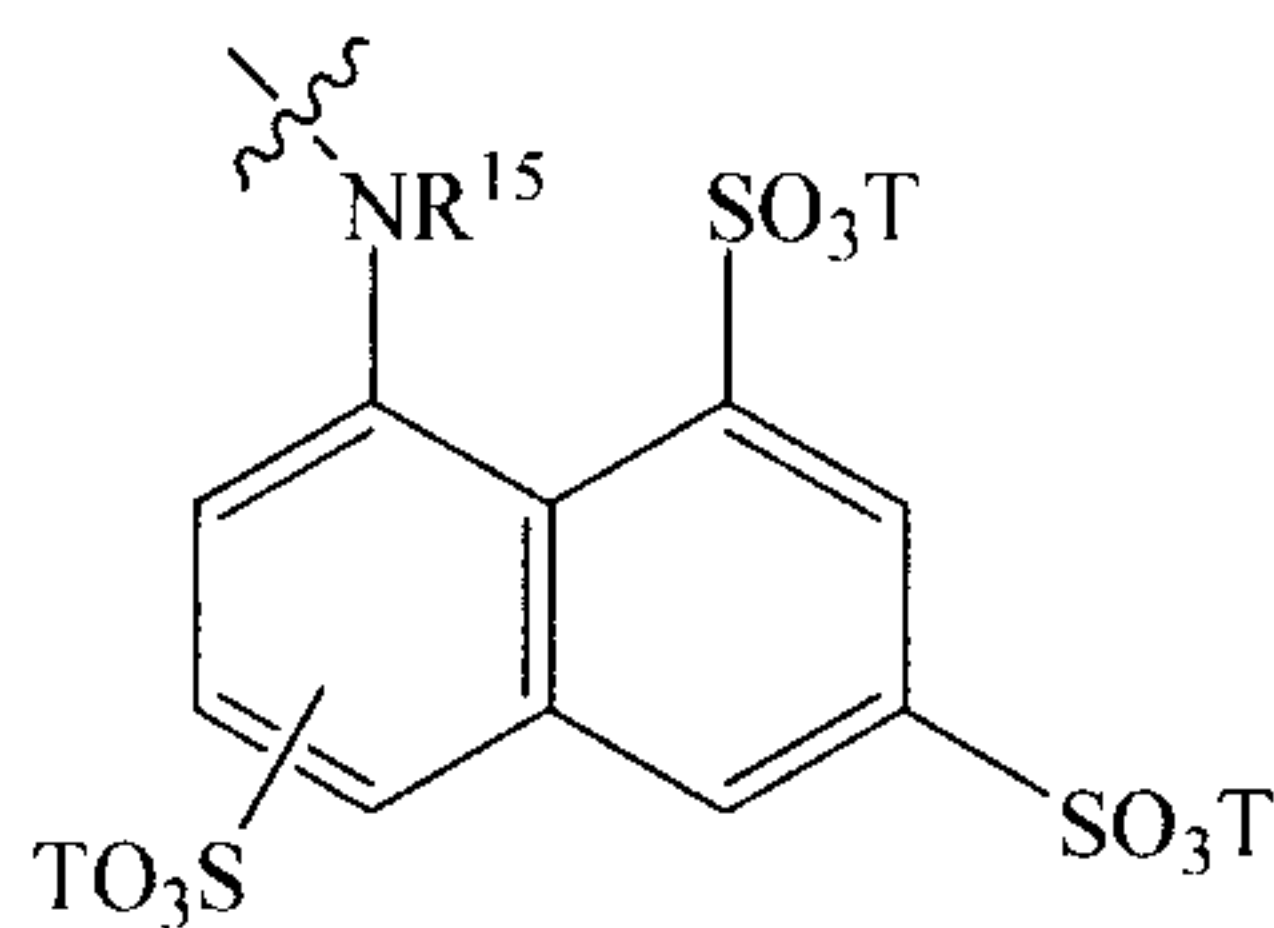
X^4 is chosen from $-PO_2T-$, $-SO_2T-$, and $-CF_2-$;

each Y^5 is independantly chosen from H, C_{1-4} alkyl, and C_{6-18} aryl groups;

each T is independantly chosen from H and pharmaceutically acceptable counterions; and

y is chosen from integers ranging from 0 to 1.

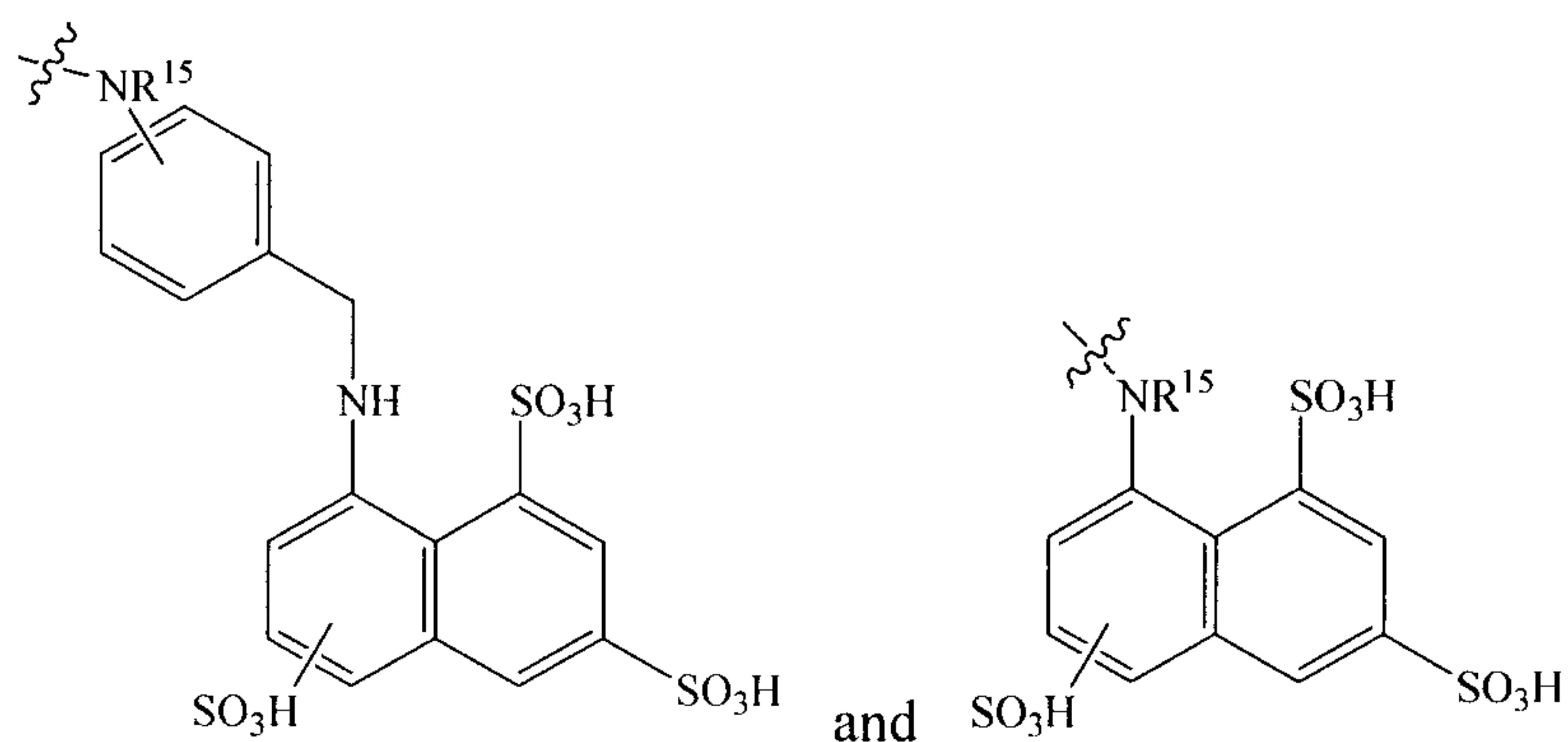
[0035] In some embodiments, Z is chosen from



wherein

R^{15} is chosen from H, C_{1-8} alkyl, $-C(=O)X^5$, and $-C(=O)NHX^5$ groups, wherein X^5 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{6-18} aryl, and C_{1-13} heteroaryl groups; and each T is independently chosen from H and pharmaceutically acceptable counterions.

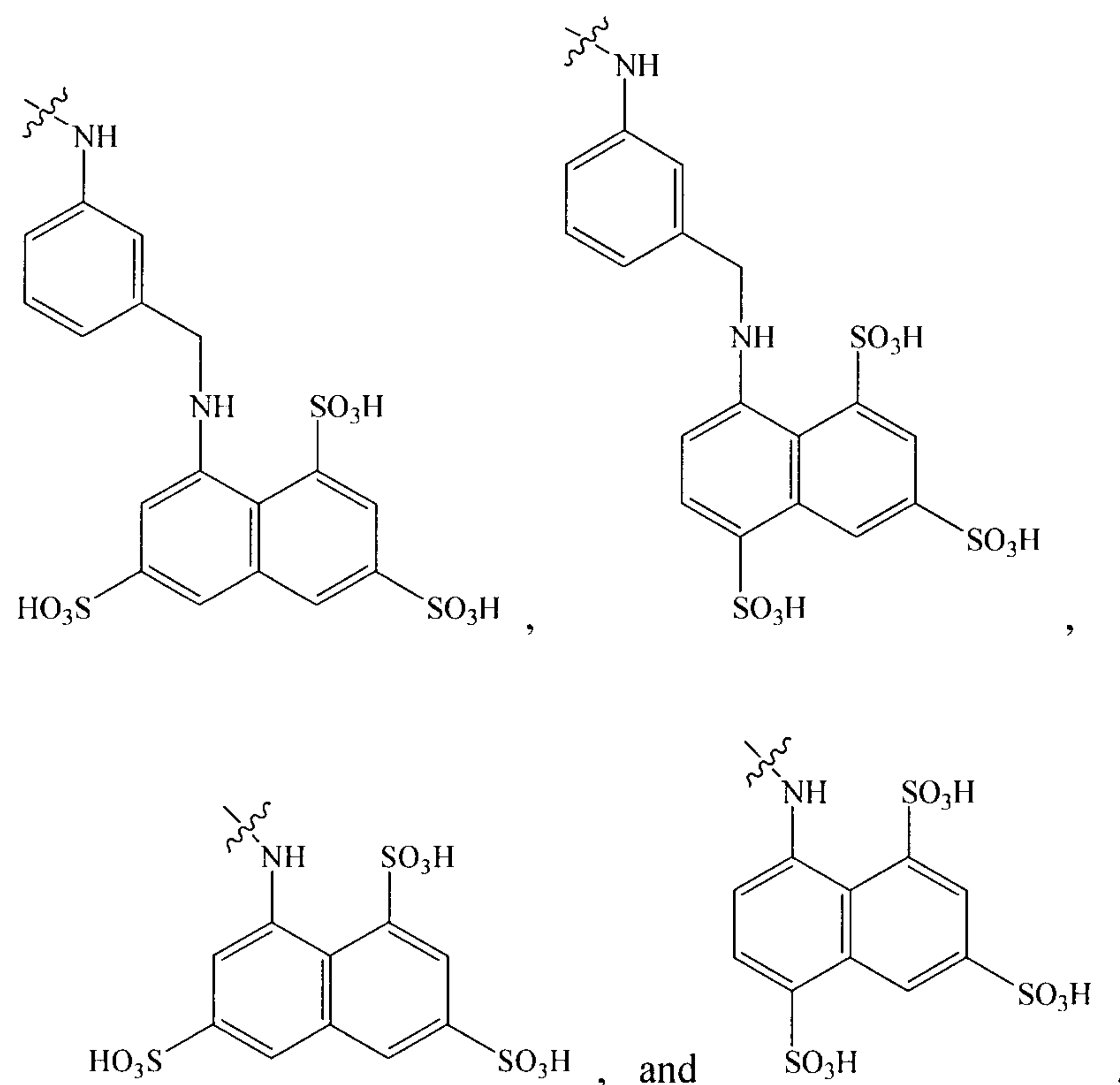
[0036] In some embodiments, Z is chosen from



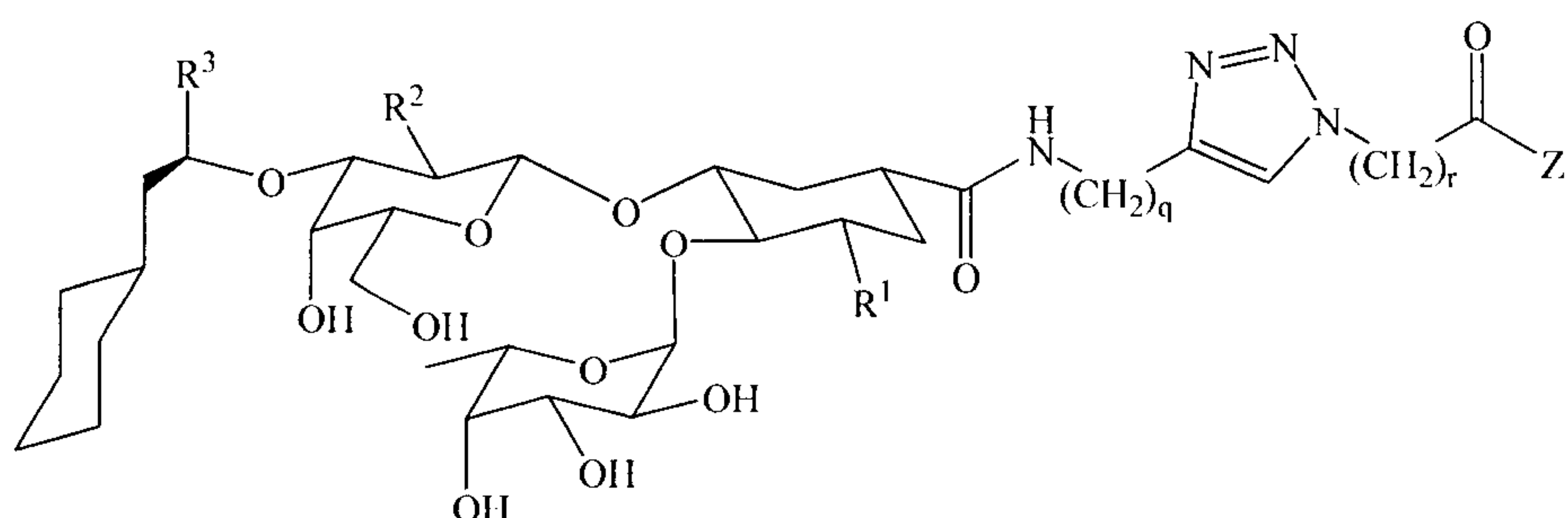
wherein

R^{15} is chosen from H, C_{1-8} alkyl, $-C(=O)X^5$, and $-C(=O)NHX^5$ groups, wherein X^5 is chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{6-18} aryl, and C_{1-13} heteroaryl groups.

[0037] In some embodiments, Z is chosen from



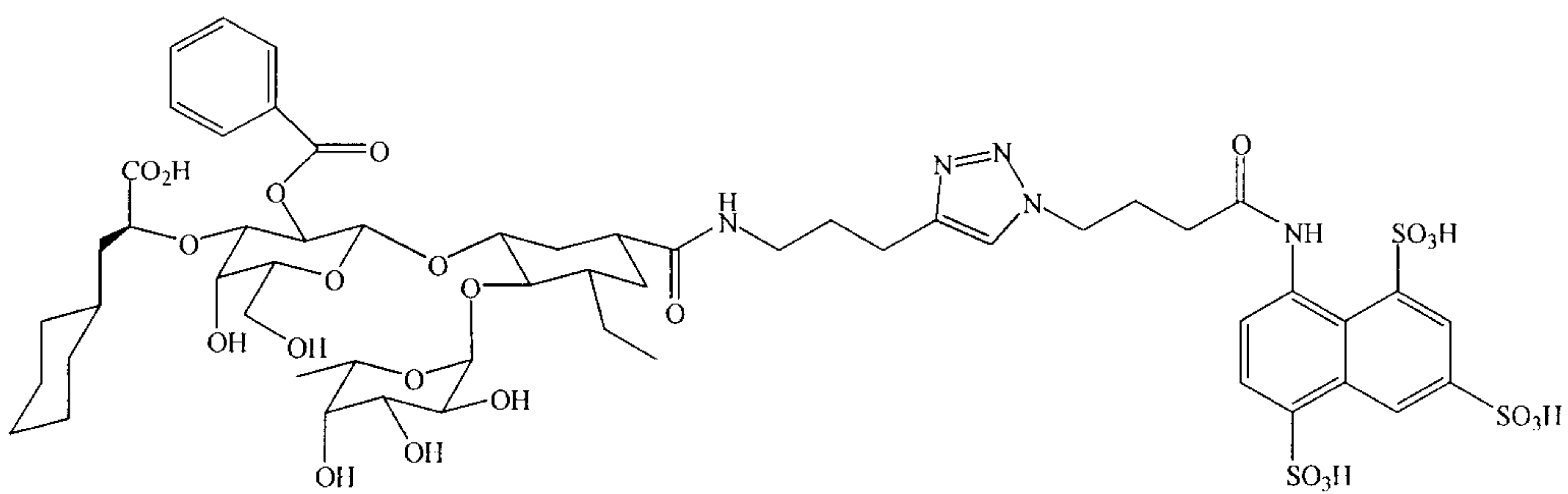
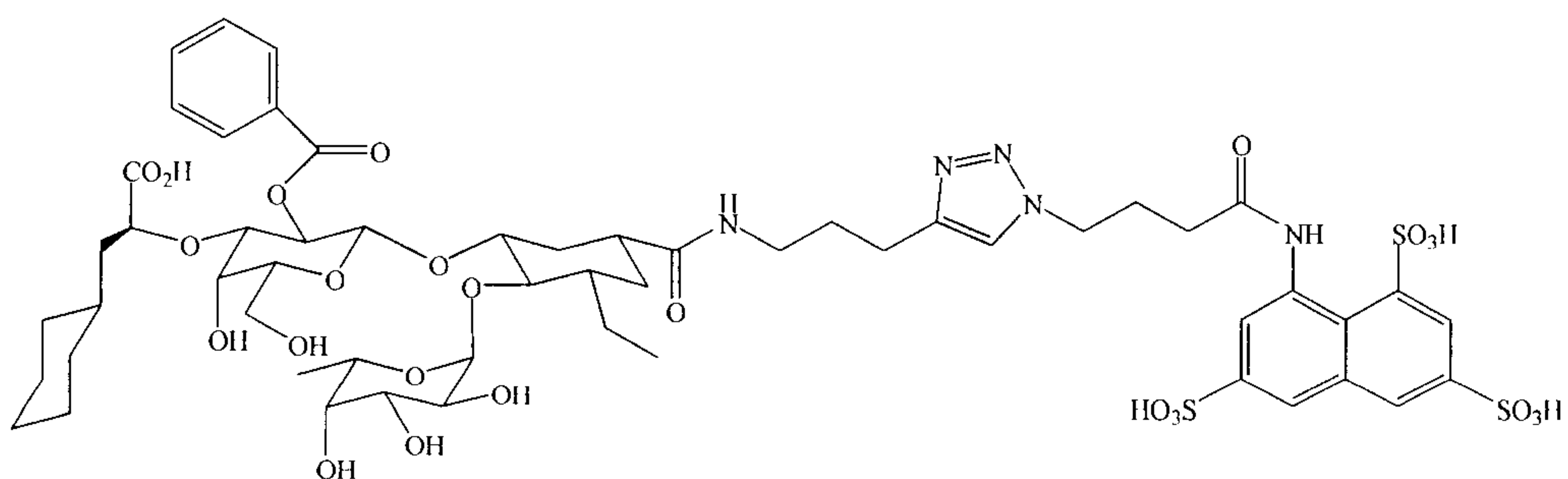
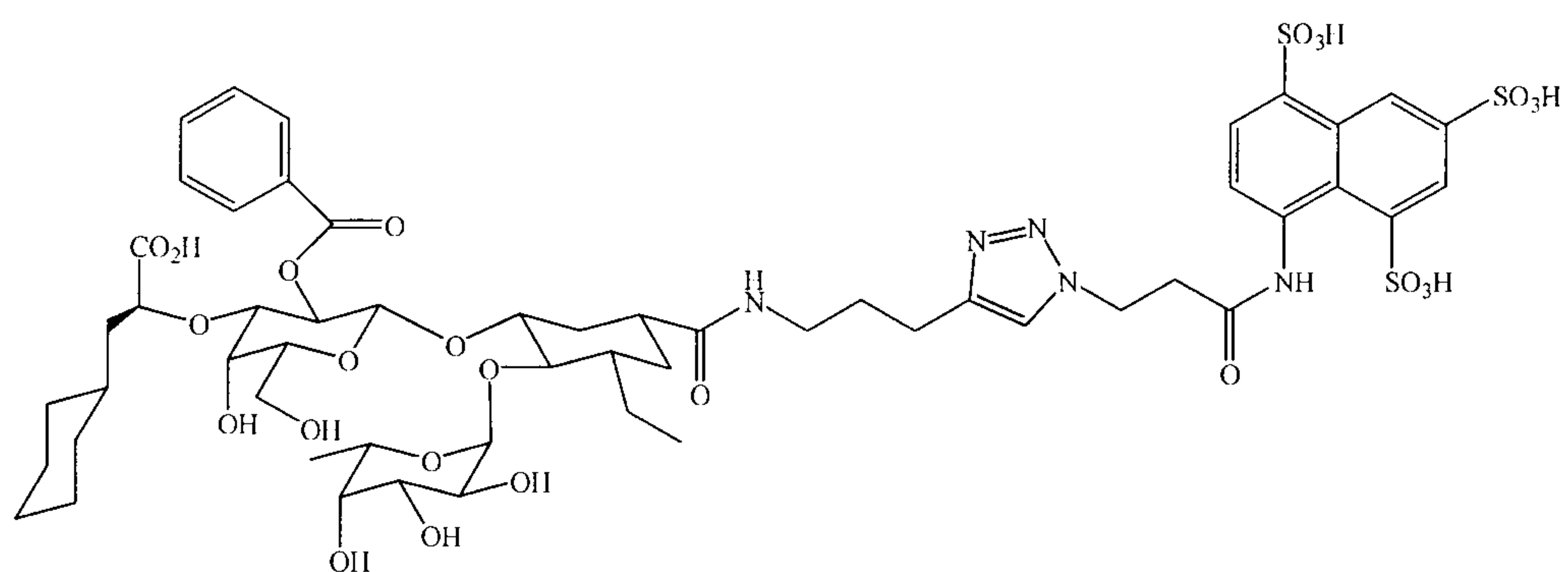
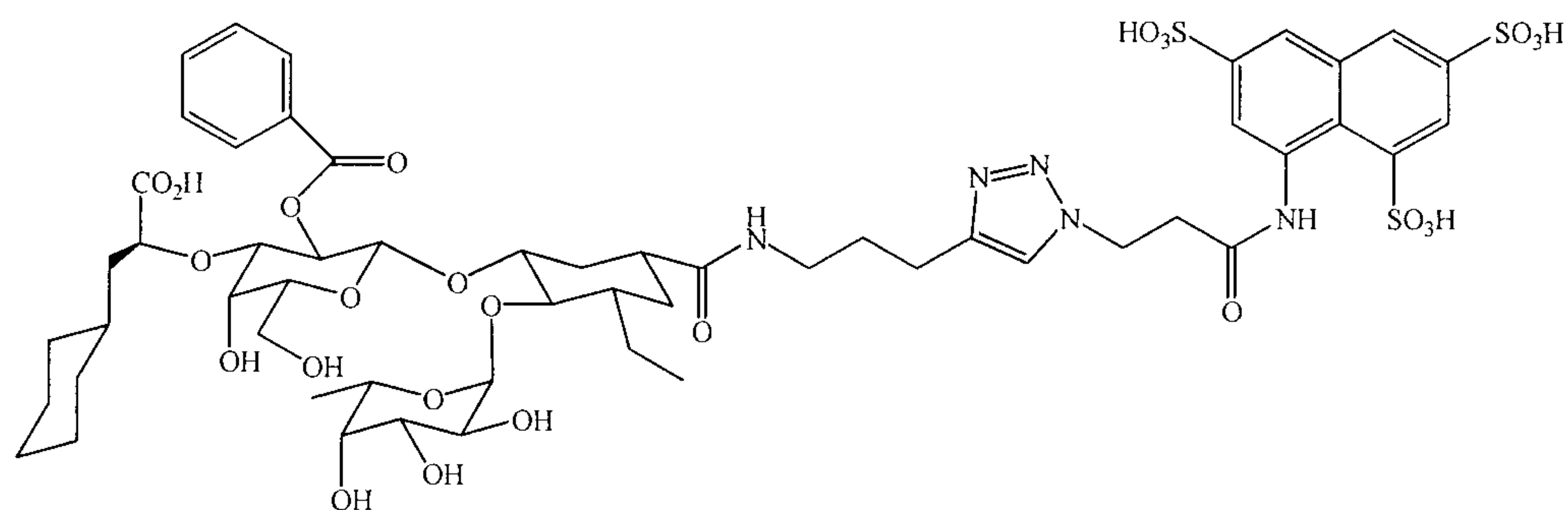
[0038] In some embodiments, the compound of Formula (I) is chosen from compounds of Formula (Ia):

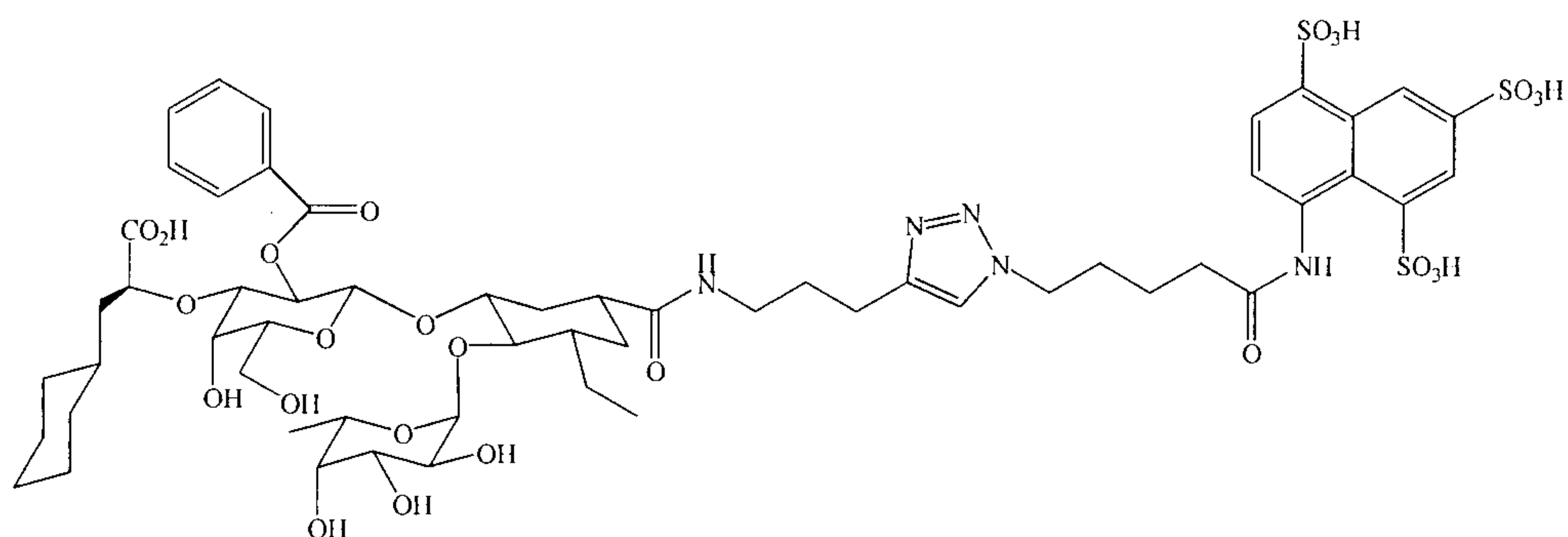
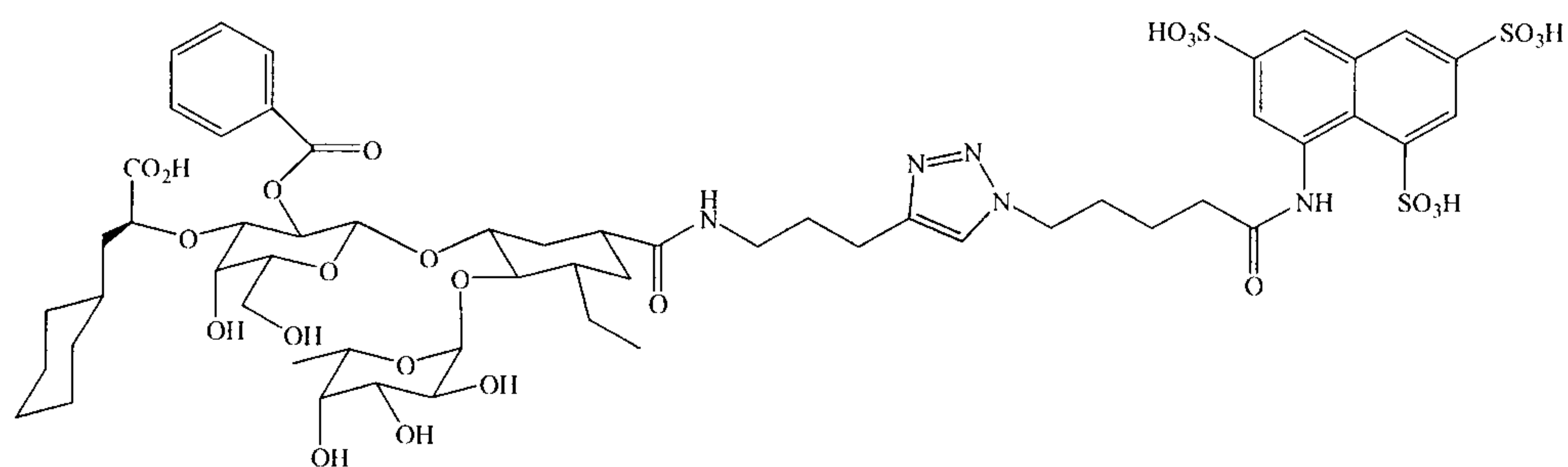


(Ia),

prodrugs thereof, and pharmaceutically acceptable salts of any of the foregoing.

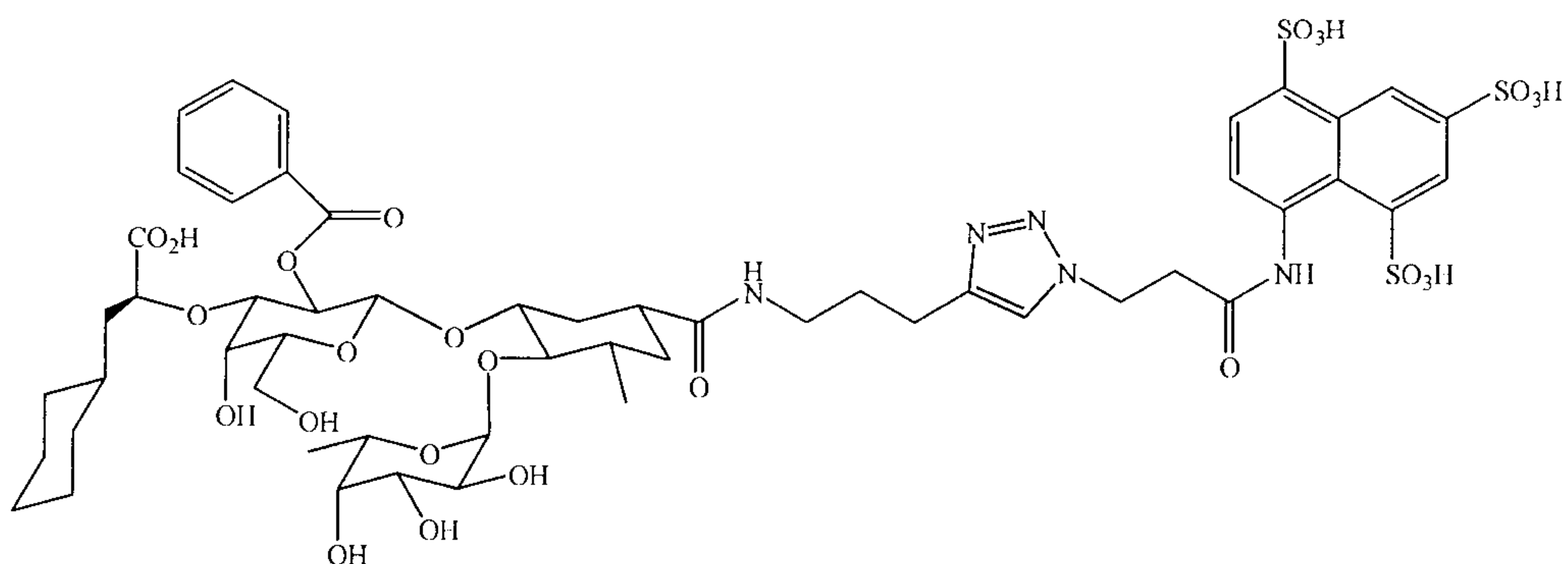
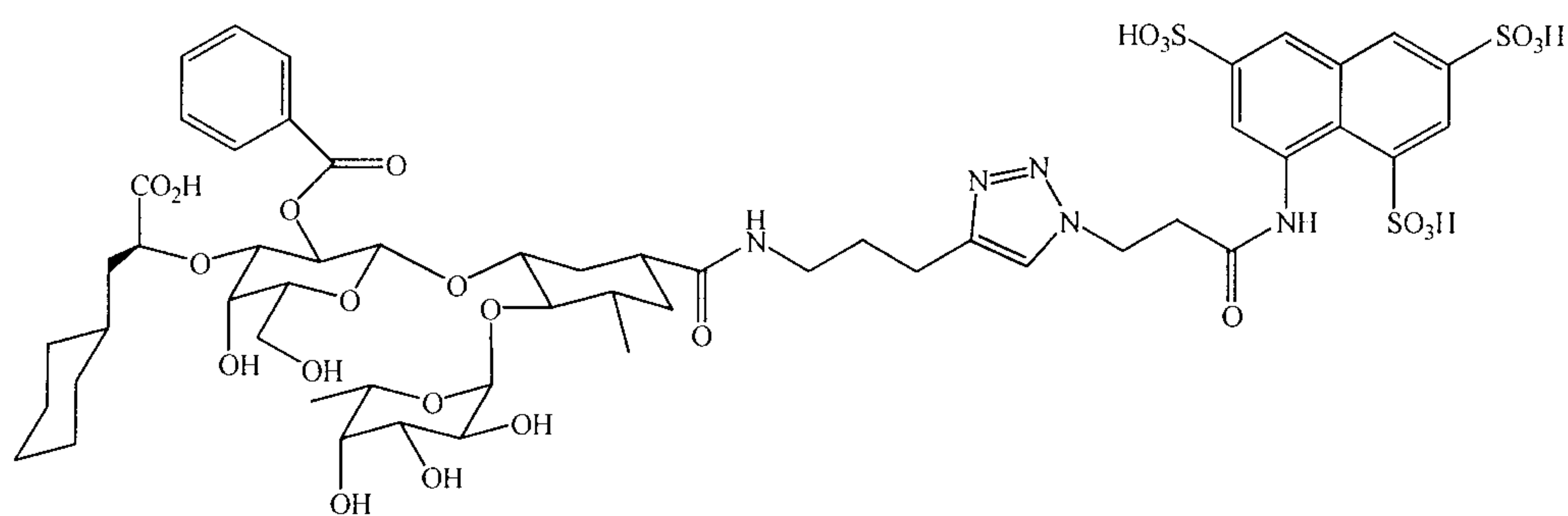
[0039] In some embodiments, the compound of Formul (I) is chosen from compounds of the following Formulae:

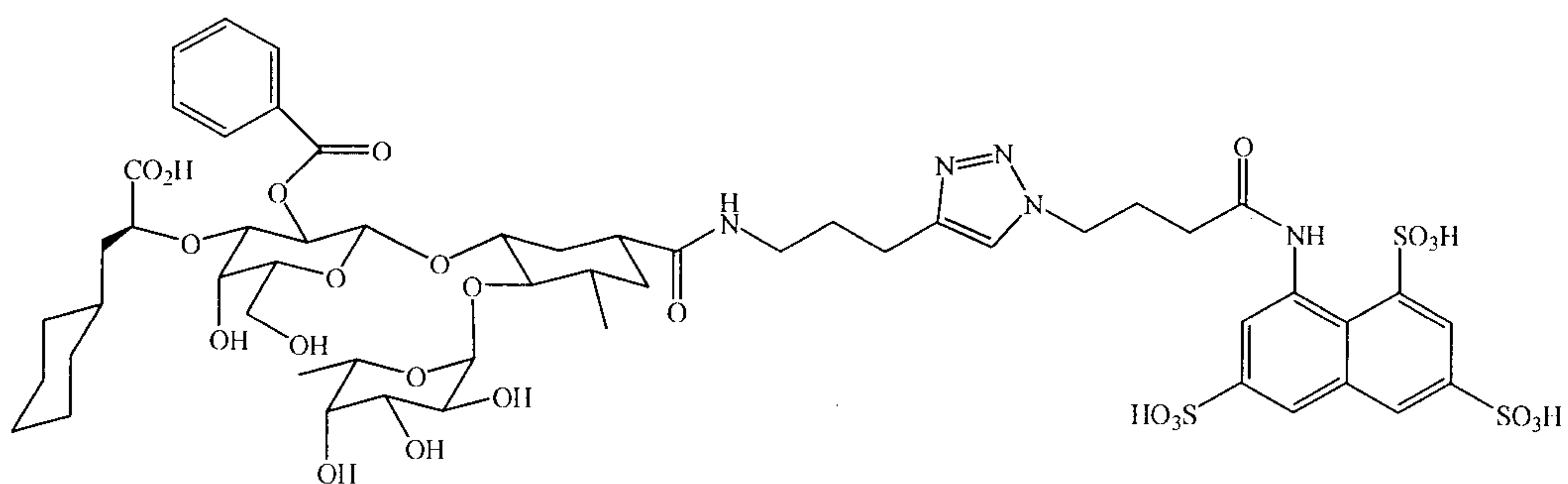




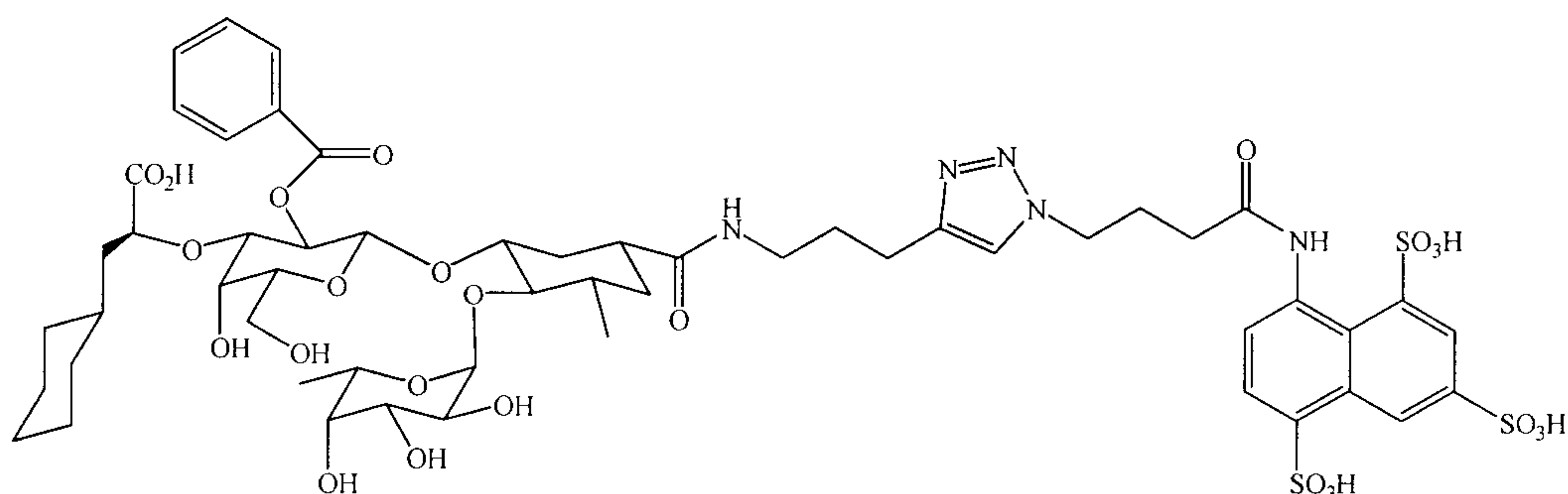
prodrugs thereof, and pharmaceutically acceptable salts of any of the foregoing.

[0040] In some embodiments, the compound of Formula (I) is chosen from compounds of the following Formulae:

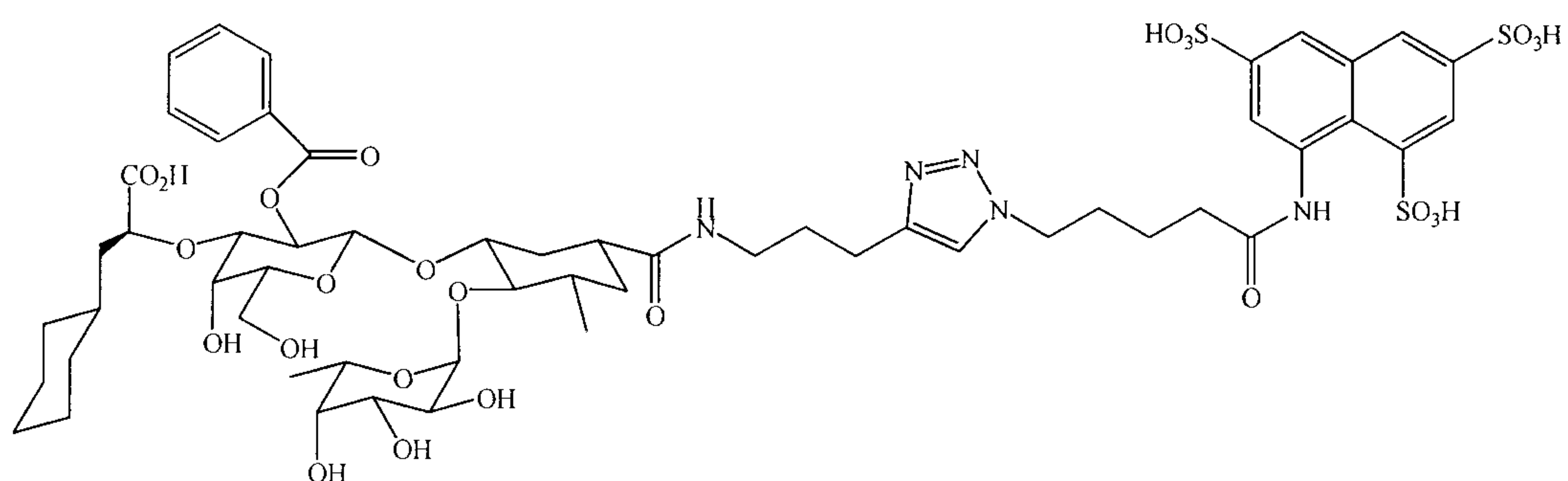




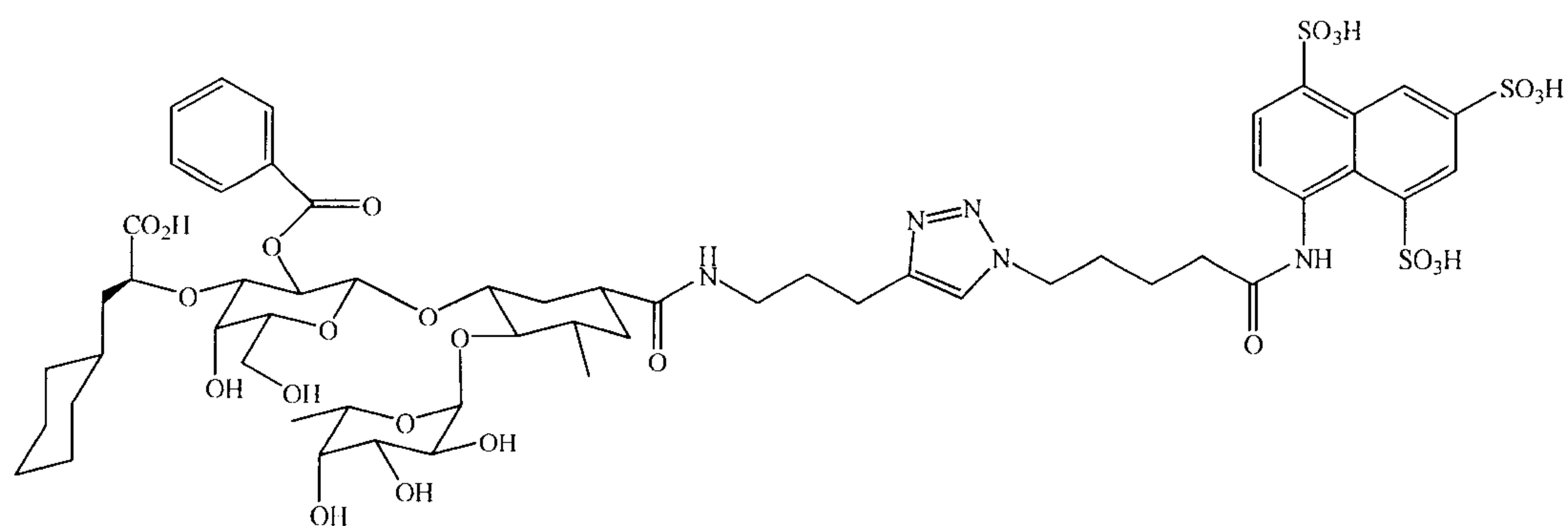
,



,



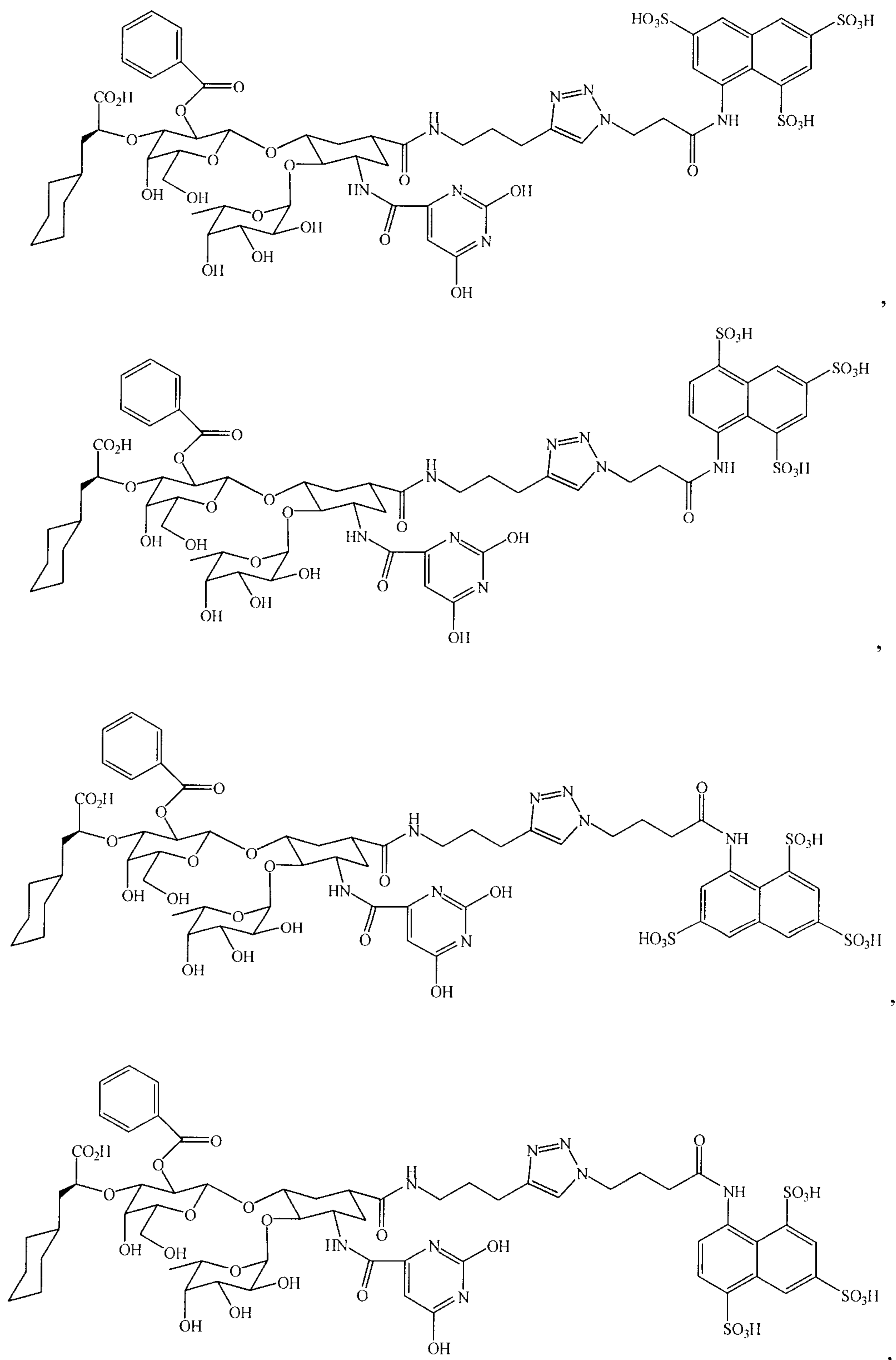
,

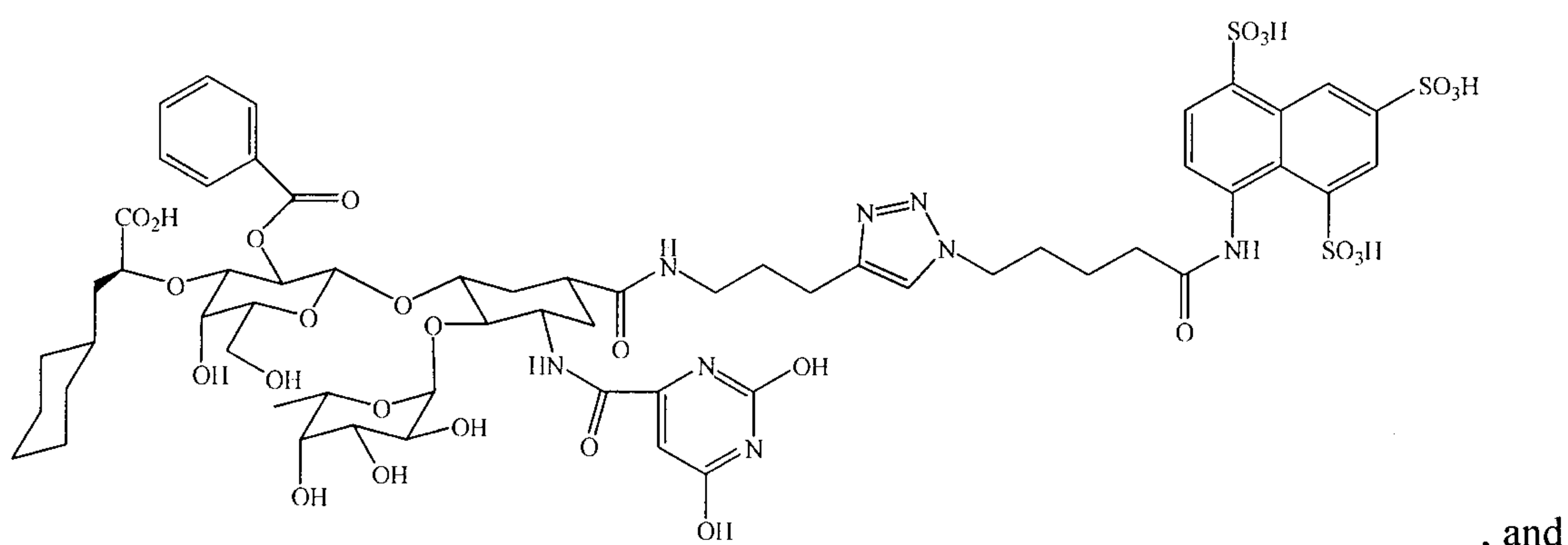
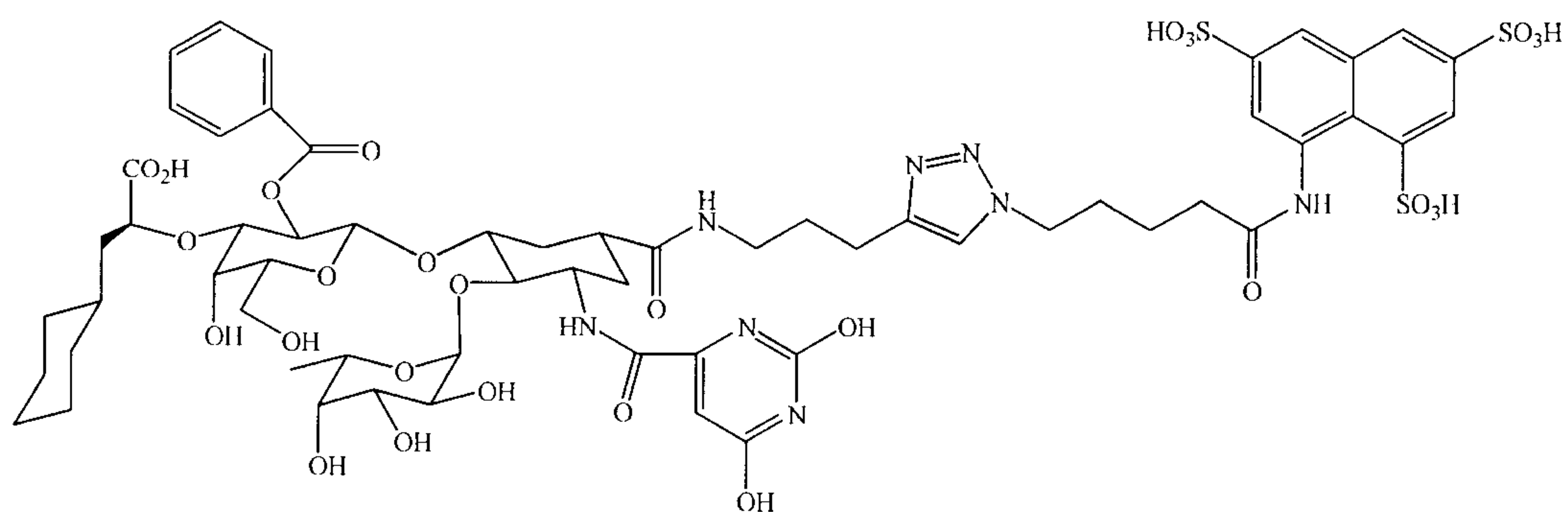


, and

prodrugs thereof, and pharmaceutically acceptable salts of any of the foregoing .

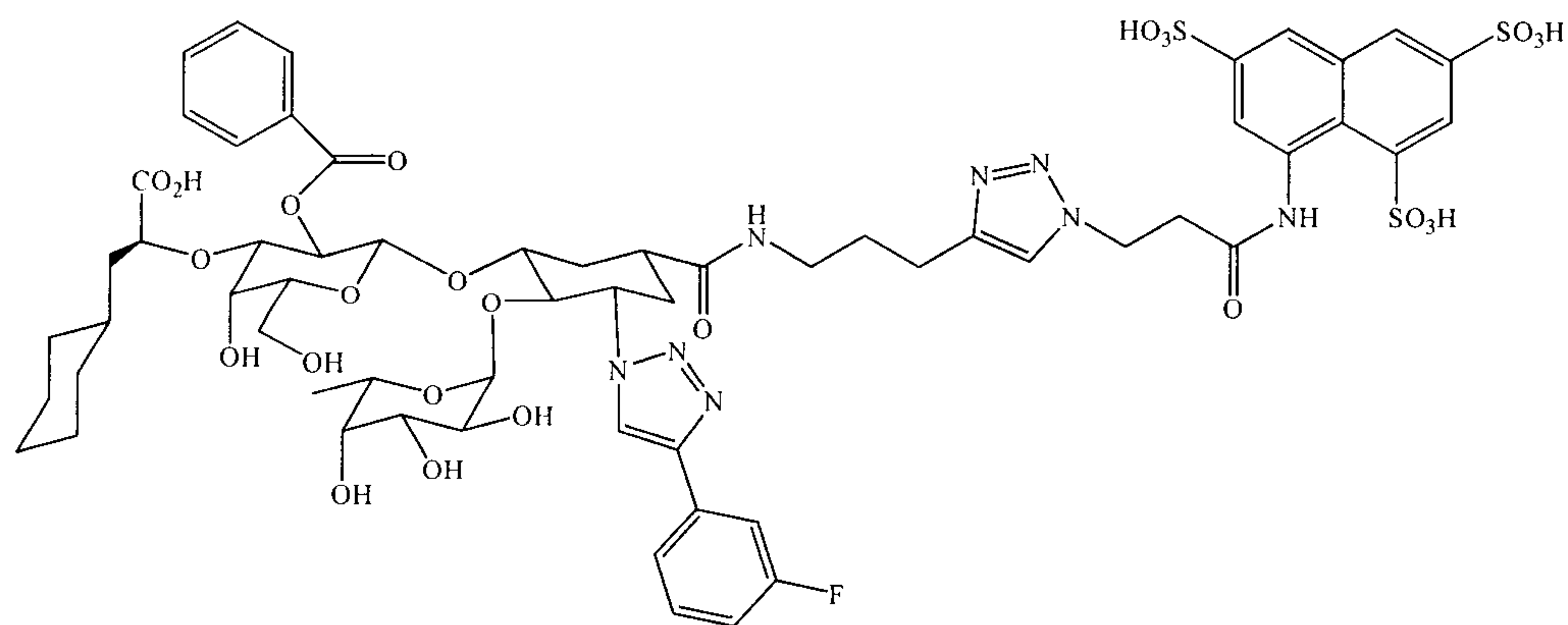
[0041] In some embodiments, the compound of Formula (I) is chosen from compounds of the following Formulae:

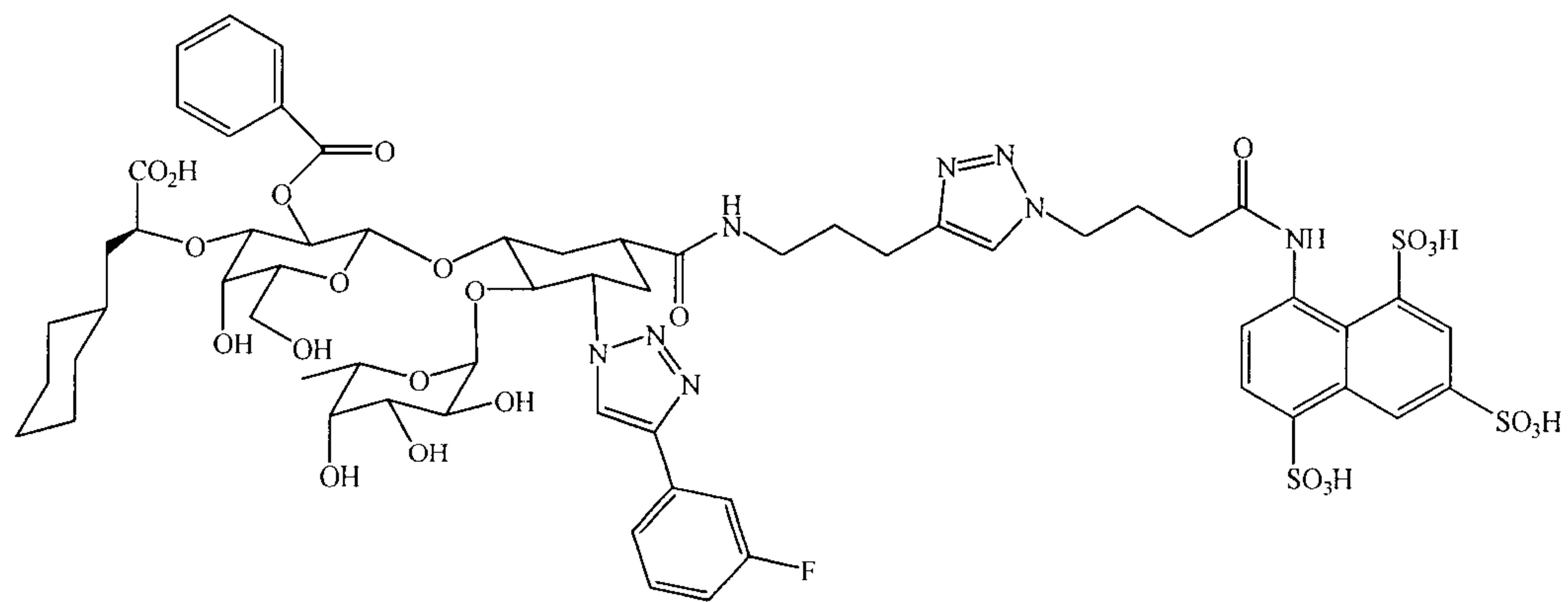
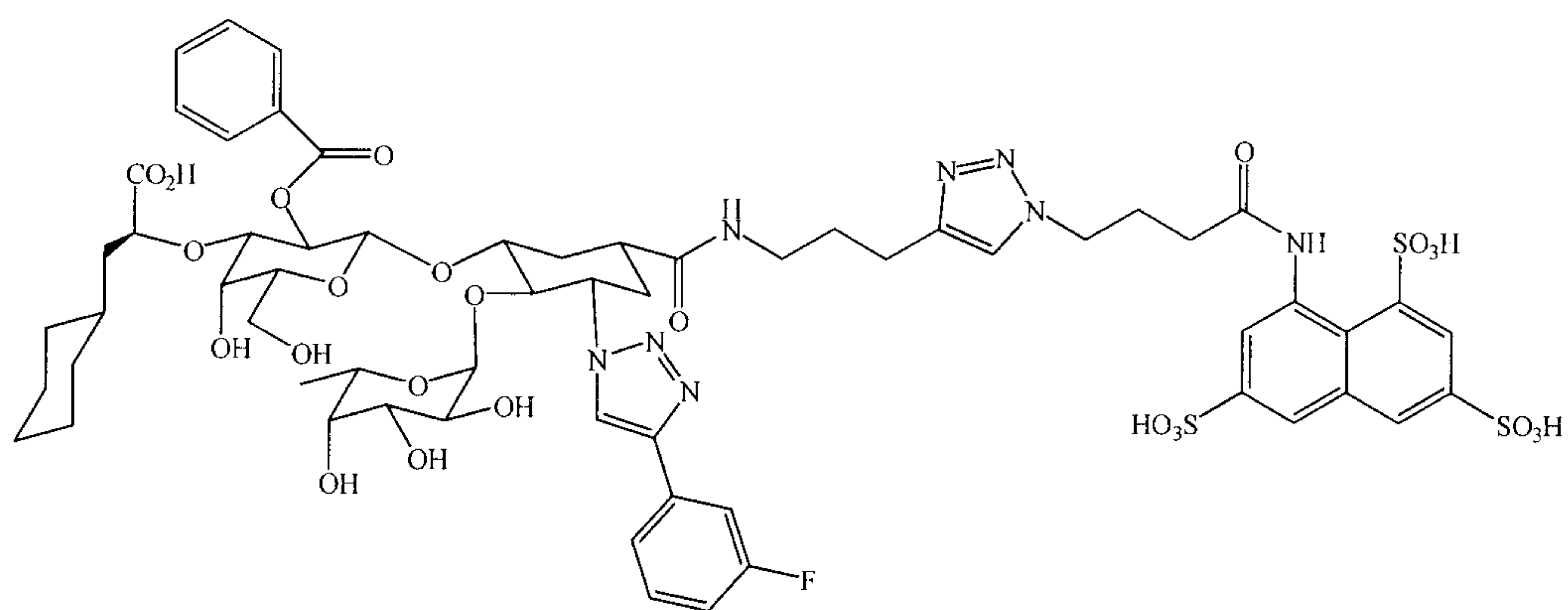
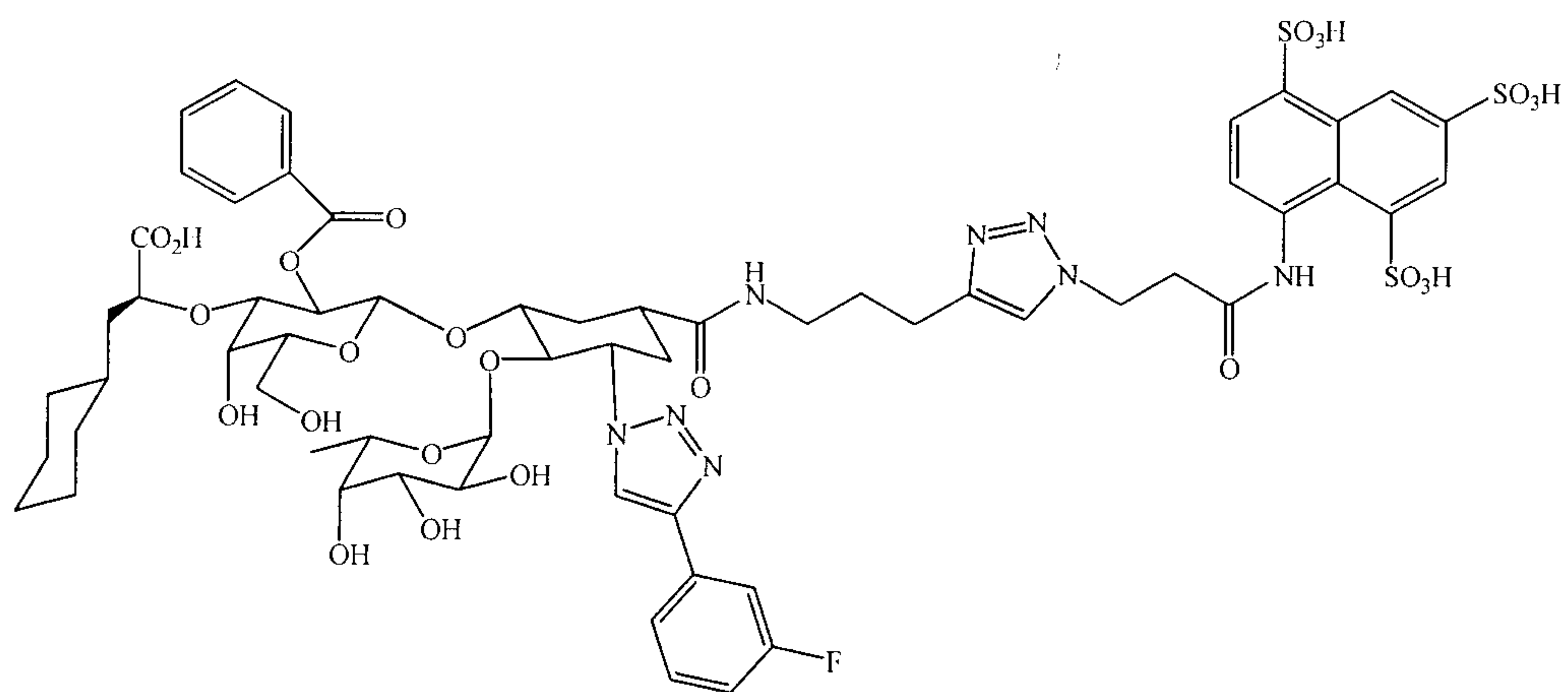


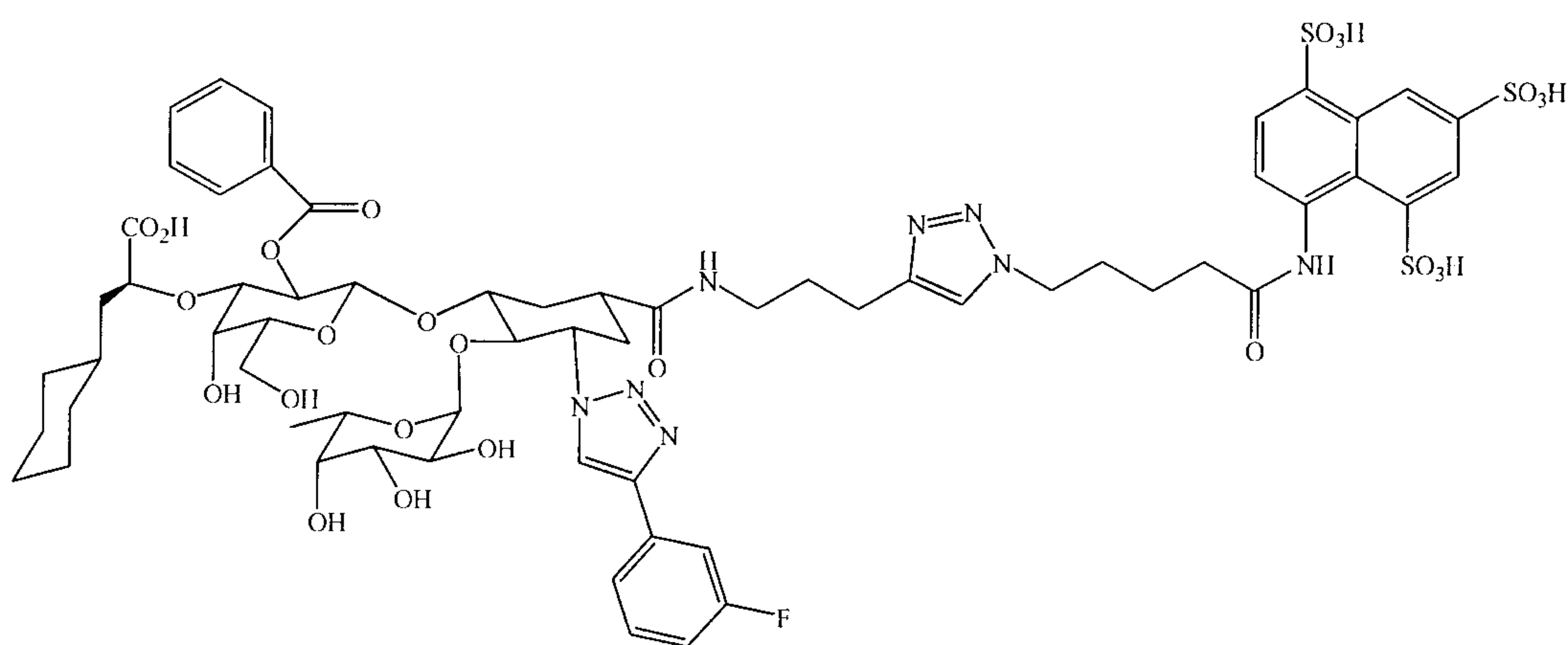
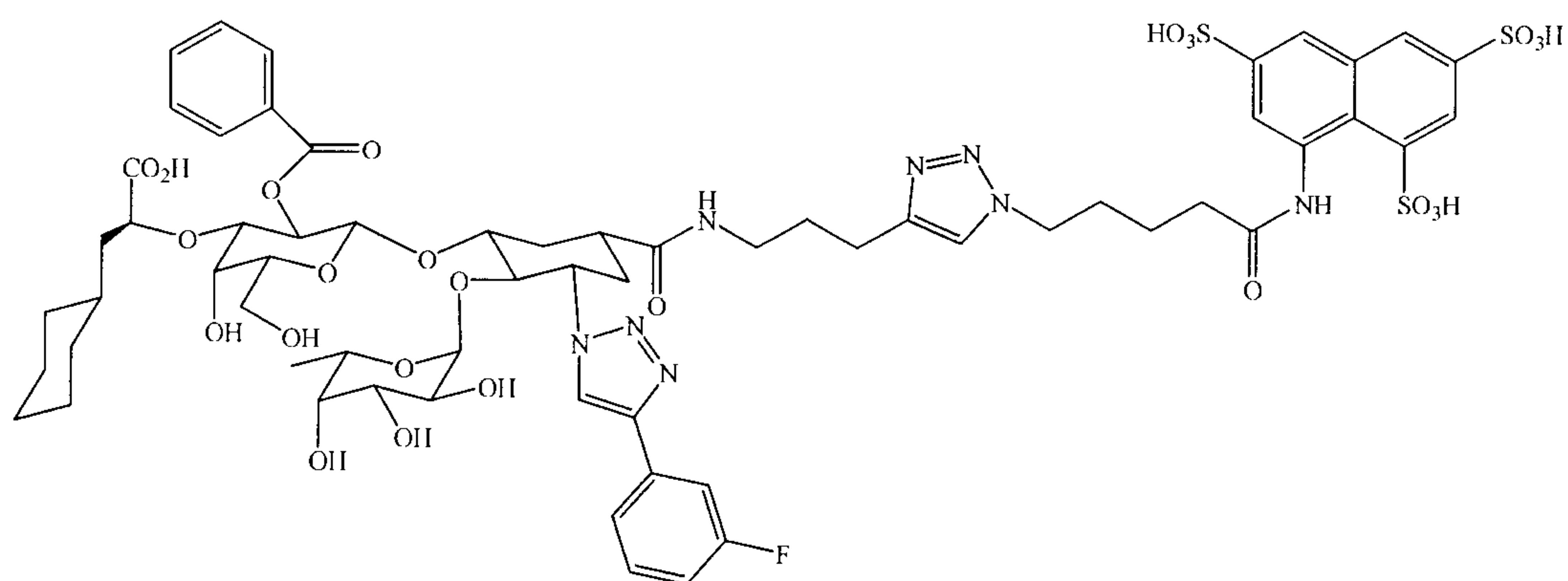


prodrugs thereof, and pharmaceutically acceptable salts of any of the foregoing.

[0042] In some embodiments, compound of Formula (I) is chosen from compounds of the following Formulae:







, and

prodrugs thereof, and pharmaceutically acceptable salts of any of the foregoing.

Also provided are compositions comprising at least one compound of Formula (I) as described herein. Such compositions are described in greater detail herein.

DEFINITIONS

[0043] Unless otherwise defined herein, scientific and technical terms used in this application shall have the meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, cell and tissue culture, molecular biology, cell and cancer biology, neurobiology, neurochemistry, virology, immunology, microbiology, pharmacology, genetics and protein and nucleic acid chemistry, described herein, are those well known and commonly used in the art.

[0044] The methods and techniques of the present invention are generally performed, unless otherwise indicated, according to conventional methods well known in the art and as

described in various general and more specific references that are cited and discussed throughout this specification.

[0045] Chemistry terms used herein are used according to conventional usage in the art, as exemplified by “The McGraw-Hill Dictionary of Chemical Terms,” Parker S., Ed., McGraw-Hill, San Francisco, C.A. (1985).

[0046] All of the publications, patents and published patent applications referred to in this application are specifically incorporated by reference herein.

[0047] Throughout this specification, the word “comprise” or variations such as “comprises” or “comprising” will be understood to imply the inclusion of a stated integer (or components) or group of integers (or components), but not the exclusion of any other integer (or components) or group of integers (or components).

[0048] The singular forms “a,” “an,” and “the” include the plurals unless the context clearly dictates otherwise.

[0049] The term “including” is used to mean “including but not limited to”. “Including” and “including but not limited to” are used interchangeably.

[0050] Whenever a term in the specification is identified as a range (*e.g.*, C₁₋₄ alkyl), the range independently discloses and includes each element of the range. As a non-limiting example, C₁₋₄ alkyls includes, independently, C₁ alkyls, C₂ alkyls, C₃ alkyls, and C₄ alkyls.

[0051] The term “at least one” refers to one or more, such as one, two, etc. For example, the term “at least one C₁₋₄ alkyl” refers to one or more C₁₋₄ alkyl groups, such as one C₁₋₄ alkyl group, two C₁₋₄ alkyl groups, etc.

[0052] The term “alkyl” includes saturated straight, branched, and cyclic (also identified as cycloalkyl), primary, secondary, and tertiary hydrocarbon groups. Non-limiting examples of alkyl groups include methyl, ethyl, propyl, *isopropyl*, cyclopropyl, butyl, *secbutyl*, *isobutyl*, *tertbutyl*, cyclobutyl, 1-methylbutyl, 1,1-dimethylpropyl, pentyl, cyclopentyl, *isopentyl*, *neopentyl*, cyclopentyl, hexyl, *isohexyl*, and cyclohexyl. Unless stated otherwise specifically in the specification, an alkyl group may be optionally substituted.

[0053] The term “alkenyl” includes straight, branched, and cyclic hydrocarbon groups comprising at least one double bond. The double bond of an alkenyl group can be unconjugated or conjugated with another unsaturated group. Non-limiting examples of alkenyl groups include vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, and cyclopent-1-en-1-yl. Unless stated otherwise specifically in the specification, an alkenyl group may be optionally substituted.

[0054] The term “alkynyl” includes straight and branched hydrocarbon groups comprising at least one triple bond. The triple bond of an alkynyl group can be unconjugated or conjugated with another unsaturated group. Non-limiting examples of alkynyl groups include ethynyl, propynyl, butynyl, pentynyl, and hexynyl. Unless stated otherwise specifically in the specification, an alkynyl group may be optionally substituted.

[0055] The term “cycloalkyl” includes saturated monocyclic or polycyclic hydrocarbon group, which may include fused or bridged ring systems. Non-limiting examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, and norbornyl. Unless otherwise stated specifically in the specification, a cycloalkyl group may be optionally substituted.

[0056] The term “cycloalkylalkyl” includes cycloalkyl groups, as described herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Non-limiting examples of cycloalkylalkyl groups include cyclopropylmethyl and cyclohexylmethyl. Unless stated otherwise specifically in the specification, a cycloalkylalkyl group may be optionally substituted.

[0057] The term “aryl” includes hydrocarbon ring system group comprising 6 to 18 carbon ring atoms and at least one aromatic ring. The aryl group may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Non-limiting examples of aryl groups include aryl groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, an aryl group may be optionally substituted.

[0058] The term “fused” includes any ring structure described herein which is fused to an existing ring structure. When the fused ring is a heterocyclyl ring or a heteroaryl ring, any carbon atom on the existing ring structure which becomes part of the fused heterocyclyl ring or the fused heteroaryl ring may be replaced with a nitrogen atom.

[0059] The term “halo” or “halogen” includes fluoro, chloro, bromo, and iodo.

[0060] The term “heterocyclyl” or “heterocyclic ring” includes 3- to 18-membered saturated or partially unsaturated non-aromatic ring groups comprising 2 to 12 ring carbon atoms and 1 to 6 ring heteroatom(s) each independently chosen from N, O, and S. Unless stated otherwise specifically in the specification, the heterocyclyl groups may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl group may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl group may be partially or fully saturated. Non-limiting examples include dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholyl, thiamorpholyl, 1-oxo-thiomorpholyl, and 1,1-dioxo-thiomorpholyl. Unless stated otherwise specifically in the specification, a heterocyclyl group may be optionally substituted.

[0061] The term “heteroaryl” includes 5- to 14-membered ring groups comprising 1 to 13 ring carbon atoms and 1 to 6 ring heteroatom(s) each independently chosen from N, O, and S, and at least one aromatic ring. Unless stated otherwise specifically in the specification, the heteroaryl group may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Non-limiting examples include azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothieryl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, carbazolyl, cinnolyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl,

indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group may be optionally substituted.

[0062] The term “pharmaceutically acceptable salts” includes both acid and base addition salts. The acid addition salt form of a compound that occurs in its free form as a base can be obtained by treating said free base form with an appropriate acid such as an inorganic acid or an organic acid. Non-limiting examples of pharmaceutically acceptable acid addition salts may include chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, methane sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, and ascorbates. Compounds containing acidic protons may be converted into their base addition salt form by treatment with appropriate organic and inorganic bases. Non-limiting examples of pharmaceutically acceptable base addition salts may include sodium, potassium, lithium, ammonium (substituted and unsubstituted), calcium, magnesium, iron, zinc, copper, manganese, aluminum salts, N-methyl-D-glucamine salts, hydrabamine salts, and salts with amino acids such as, arginine, lysine and the like. Pharmaceutically acceptable salts may, for example, be obtained using standard procedures well known in the field of pharmaceuticals.

[0063] The term “prodrug” includes compounds that may be converted, for example, under physiological conditions or by solvolysis, to a biologically active compound described herein. Thus, the term “prodrug” may therefore include metabolic precursors of compounds described herein that are biologically acceptable. A discussion of prodrugs can be found, for example, in Higuchi, T., et al., “Pro-drugs as Novel Delivery Systems,” A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987. The term “prodrug” may also include covalently bonded carriers that release the active compound(s) as described herein *in vivo*. Non-limiting examples of prodrugs may include ester and amide derivatives of hydroxy, carboxy, mercapto and amino functional groups in the compounds described herein.

[0064] The term “substituted” includes the situation where, in any of the above groups, at least one hydrogen atom is replaced by a non-hydrogen atom such as, for example, a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkylarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. “Substituted” also includes the situation where, in any of the above groups, at least one hydrogen atom is replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles.

[0065] This application contemplates all the isomers of the compounds disclosed herein. “Isomer” as used herein includes optical isomers (such as stereoisomers, e.g., enantiomers and diastereoisomers), geometric isomers (such as Z (zusammen) or E (entgegen) isomers), and tautomers. The present disclosure includes within its scope all the possible geometric isomers, e.g., Z and E isomers (*cis* and *trans* isomers), of the compounds as well as all the possible optical isomers, e.g. diastereomers and enantiomers, of the compounds. Furthermore, the present disclosure includes in its scope both the individual isomers and any mixtures thereof, e.g. racemic mixtures. The individual isomers may be obtained using the corresponding isomeric forms of the starting material or they may be separated after the preparation of the end compound according to conventional separation methods. For the separation of optical isomers, e.g., enantiomers, from the mixture thereof conventional resolution methods, e.g. fractional crystallization, may be used.

[0066] The present disclosure includes within its scope all possible tautomers. Furthermore, the present disclosure includes in its scope both the individual tautomers and any mixtures thereof. Each compound disclosed herein includes within its scope all possible tautomeric forms. Furthermore, each compound disclosed herein includes within its scope both the individual tautomeric forms and any mixtures thereof. With respect to the methods, uses and compositions of the present application, reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof. Where a

compound of the present application is depicted in one tautomeric form, that depicted structure is intended to encompass all other tautomeric forms.

Methods for Determining Selectin Binding

[0067] Selectin binding activity may be determined, for example, by performing at least one *in vitro* and/or *in vivo* study routinely practiced in the art and described herein or in the art.

[0068] *In vitro* assays include without limitation binding assays, immunoassays, competitive binding assays, and cell based activity assays. Selectin modulators are capable, for example, of inhibiting selectin-mediated cell adhesion. This ability may generally be evaluated using any of a variety of *in vitro* assays designed to measure the effect on adhesion between selectin-expressing cells (e.g., adhesion between leukocytes or tumor cells and platelets or endothelial cells). For example, such cells may be plated under standard conditions that, in the absence of modulator, permit cell adhesion. In general, a selectin modulator is an inhibitor of selectin-mediated cell adhesion if contact of the test cells with the selectin modulator results in a discernible inhibition of cell adhesion. For example, in the presence of selectin modulators (e.g., micromolar levels), disruption of adhesion between leukocytes or tumor cells and platelets or endothelial cells may be determined visually within approximately several minutes, by observing the reduction of cells interacting with one another.

[0069] Selectin modulators may also be used *in vitro*, e.g., within a variety of well-known cell culture and cell separation methods. For example, modulators may be linked to the interior surface of a tissue culture plate or other cell culture support, for use in immobilizing selectin-expressing cells for screens, assays and growth in culture. Such linkage may be performed by any suitable technique. Selectin modulators may also be used, for example, to facilitate cell identification and sorting *in vitro*, permitting the selection of cells expressing a selectin (or different selectin levels). The modulator(s) for use in such methods may be linked to a detectable marker. Suitable markers are well known in the art and include radionuclides, luminescent groups, fluorescent groups, enzymes, dyes, constant immunoglobulin domains and biotin. A selectin modulator may also be linked to a fluorescent marker, such as fluorescein, and contacted with cells, which may then be analyzed by fluorescence activated cell sorting (FACS).

[0070] Conditions for a particular assay include temperature, buffers (including salts, cations, media), and other components that maintain the integrity of any cell used in the assay and the compound, which a person of ordinary skill in the art will be familiar and/or which can be readily determined. A person of ordinary skill in the art also readily appreciates that appropriate controls can be designed and included when performing the *in vitro* methods and *in vivo* methods described herein.

[0071] The source of a compound that is characterized by at least one assay and techniques described herein and in the art may be a biological sample that is obtained from a subject who has been administered the compound. The cells that may be used in the assay may also be provided in a biological sample. A “biological sample” may include a sample from a subject, and may be a blood sample (from which serum or plasma may be prepared), a biopsy specimen, one or more body fluids (*e.g.*, lung lavage, ascites, mucosal washings, synovial fluid, urine), bone marrow, lymph nodes, tissue explant, organ culture, or any other tissue or cell preparation from the subject or a biological source. A biological sample may further include a tissue or cell preparation in which the morphological integrity or physical state has been disrupted, for example, by dissection, dissociation, solubilization, fractionation, homogenization, biochemical or chemical extraction, pulverization, lyophilization, sonication, or any other means for processing a sample derived from a subject or biological source. The subject or biological source may be a human or non-human animal, a primary cell culture (*e.g.*, immune cells), or culture adapted cell line, including but not limited to, genetically engineered cell lines that may contain chromosomally integrated or episomal recombinant nucleic acid sequences, immortalized or immortalizable cell lines, somatic cell hybrid cell lines, differentiated or differentiable cell lines, transformed cell lines, and the like.

[0072] As described herein, methods for characterizing selectin modulators include animal model studies. Non-limiting examples of animal models for liquid cancers (such as lymphomas, leukemias, and myelomas) used in the art include multiple myeloma (*see, e.g.*, DeWeerd, Nature 480:S38–S39 (15 December 2011) doi:10.1038/480S38a; Published online 14 December 2011; Mitsiades et al., *Clin. Cancer Res.* 2009 15:1210021 (2009)); acute myeloid leukemia (AML) (Zuber et al., *Genes Dev.* 2009 April 1; 23(7): 877–889). Animal models for acute lymphoblastic leukemia (ALL) have been used by persons of ordinary skill in the art for more than two decades. Numerous exemplary animal models for solid tumor cancers are routinely used and are well known to persons of ordinary skill in the art.

Exemplary Uses

[0073] In certain aspects, compounds having P-selectin binding affinity may be used as P-selectin antagonists.

Compositions

[0074] Also provided herein are compositions comprising at least one compound of Formula (I). In some embodiments, the composition further comprises at least one additional pharmaceutically acceptable ingredient.

[0075] The compositions described herein may be formulated as a topical, oral, nasal, intrathecal, enteral, buccal, sublingual, transdermal, rectal, vaginal, intraocular, subconjunctival, sublingual, and parenteral administration, including subcutaneous, intravenous, intramuscular, intrasternal, intracavernous, intrameatal, and intraurethral injection and/or infusion formulations.

[0076] The composition described herein may be sterile aqueous or sterile non-aqueous solutions, suspensions or emulsions, and may additionally comprise at least one pharmaceutically acceptable excipient (*e.g.*, a non-toxic material that does not interfere with the activity of the active ingredient). Such compositions may be in the form of a solid, liquid, or gas (aerosol). Alternatively, the compositions described herein may be formulated as a lyophilizate, or compounds described herein may be encapsulated within liposomes using technology known in the art. The compositions may further comprise at least one additional pharmaceutical acceptable ingredient, which may be biologically active or inactive. Non-limiting examples of such ingredients may include buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides, amino acids (*e.g.*, glycine), antioxidants, chelating agents (*e.g.*, EDTA and glutathione), stabilizers, dyes, flavoring agents, suspending agents, and preservatives.

[0077] Any suitable excipient or carrier known to those of ordinary skill in the art for use in pharmaceutical compositions may be employed in the compositions described herein. Excipients for such use are well known, and are described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)). For parenteral formulations, compositions may further comprise water, saline, alcohols, fats, waxes, and buffers. For oral formulations, compositions may further comprise at least one ingredient

chosen, for example, from any of the aforementioned excipients, solid excipients and carriers, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, kaolin, glycerin, starch dextrins, sodium alginate, carboxymethylcellulose, ethyl cellulose, glucose, sucrose, and magnesium carbonate.

[0078] Compositions (*e.g.*, an oral formulation or injectable formulation) may be in the form of a liquid. A liquid composition may include, for example, at least one the following: a sterile diluent such as water for injection, saline solution, *e.g.*, physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils that may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents; antioxidants; chelating agents; buffers and agents for the adjustment of tonicity such as sodium chloride or dextrose. A parenteral preparation may be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. In some embodiments, the composition may comprise physiological saline. In some embodiments, the composition may be an injectable composition, and in some embodiments, the injectable composition may be sterile.

[0079] For oral formulations, at least one of the compounds of the present disclosure may be used alone or in combination with at least one additive appropriate to make tablets, powders, granules and/or capsules, for example, those chosen from conventional additives, disintegrators, lubricants, diluents, buffering agents, moistening agents, preservatives, coloring agents, and flavoring agents. The compositions may be formulated to include at least one buffering agent, which may provide for protection of the active ingredient from low pH, such as may be present in the gastric environment, and/or an enteric coating. An oral composition may be formulated with at least one flavoring agent, *e.g.*, in a liquid, solid or semi-solid formulation and/or with an enteric coating.

[0080] Oral formulations may be gelatin capsules, which may contain the active compound along with powdered carriers. Similar carriers and diluents may be used to make compressed tablets. Tablets and capsules may be manufactured as sustained release products to provide for continuous release of active ingredients over a period of time. Compressed tablets may be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

[0081] A composition may be formulated for sustained or slow release. Such compositions may generally be prepared using well known technology and may include, for example, oral,

rectal or subcutaneous formulations, or formulations that may potentially be provided by implantation at a desired target site. Sustained-release formulations may contain the active agent dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Excipients for use within such formulations are biocompatible, and may also be biodegradable. The composition may be formulated to provide a relatively constant level of active component release.

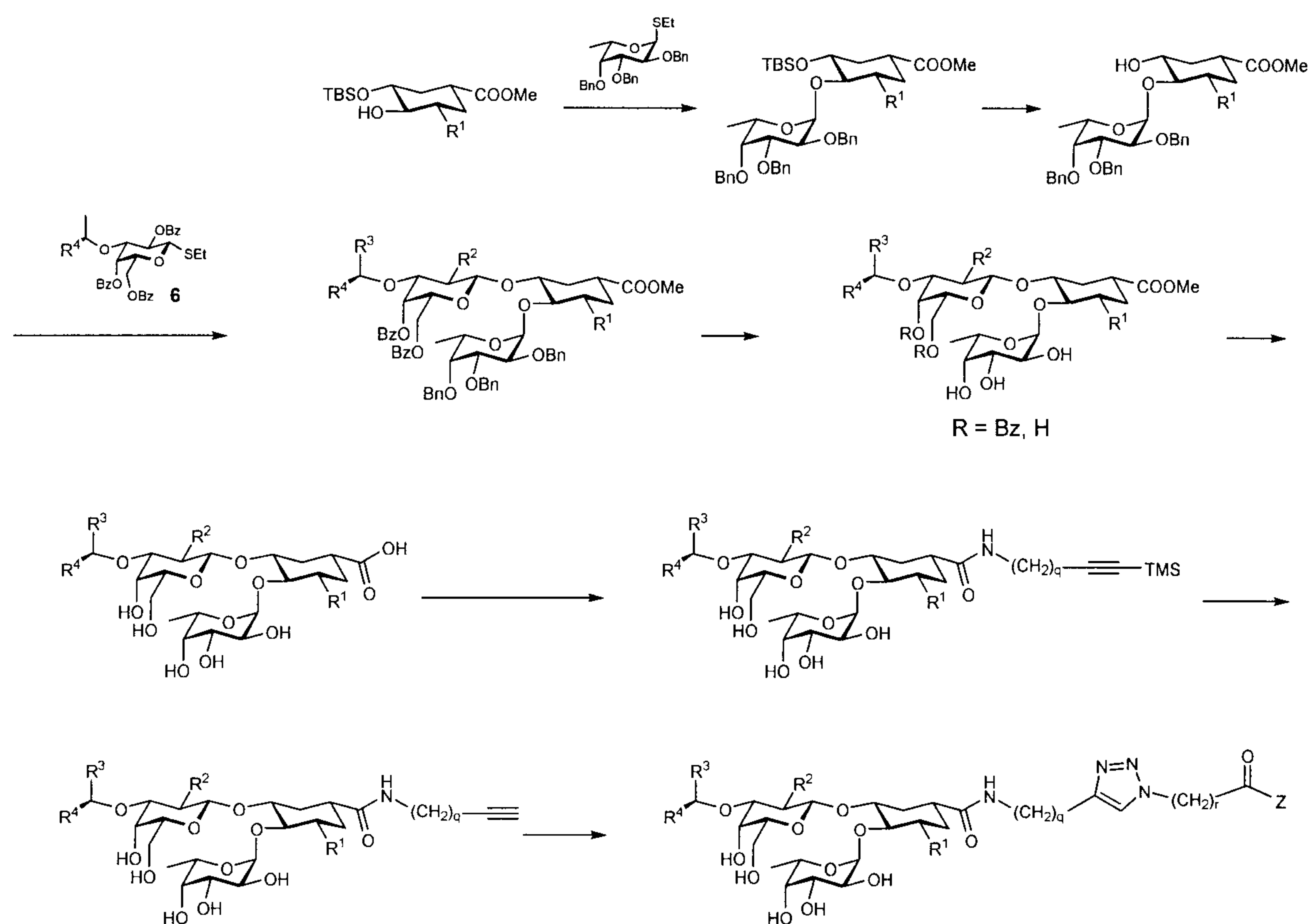
[0082] The compositions described herein may be formulated as suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. The compositions may be prepared as aerosol formulations for potential delivery via inhalation. The compositions may be formulated into pressurized acceptable propellants such as dichlorodifluoromethane, propane, nitrogen and the like.

[0083] The compositions may be formulated as topical preparations (*e.g.*, transdermal preparations). Topical formulations may be in the form of a transdermal patch, ointment, paste, lotion, cream, gel, and the like. Topical formulations may include one or more of a penetrating agent or enhancer (also call permeation enhancer), thickener, diluent, emulsifier, dispersing aid, or binder. Physical penetration enhancers may include, for example, electrophoretic techniques such as iontophoresis, use of ultrasound (or “phonophoresis”), and the like. Chemical penetration enhancers may be included to provide for enhanced skin penetration. Chemical and physical penetration enhancers are described in, for example, *Transdermal Delivery of Drugs*, A. F. Kydonieus (ED) 1987 CRL Press; *Percutaneous Penetration Enhancers*, eds. Smith et al. (CRC Press, 1995); Lenneräs et al., *J. Pharm. Pharmacol.* 54:499-508 (2002); Karande et al., *Pharm. Res.* 19:655-60 (2002); Vaddi et al., *Int. J. Pharm.* 91:1639-51 (2002); Ventura et al., *J. Drug Target* 9:379-93 (2001); Shokri et al., *Int. J. Pharm.* 228(1-2):99-107 (2001); Suzuki et al., *Biol. Pharm. Bull.* 24:698-700 (2001); Alberti et al., *J. Control Release* 71:319-27 (2001); Goldstein et al., *Urology* 57:301-5 (2001); Kijjavainen et al., *Eur. J. Pharm. Sci.* 10:97-102 (2000); and Tenjarla et al., *Int. J. Pharm.* 192:147-58 (1999).

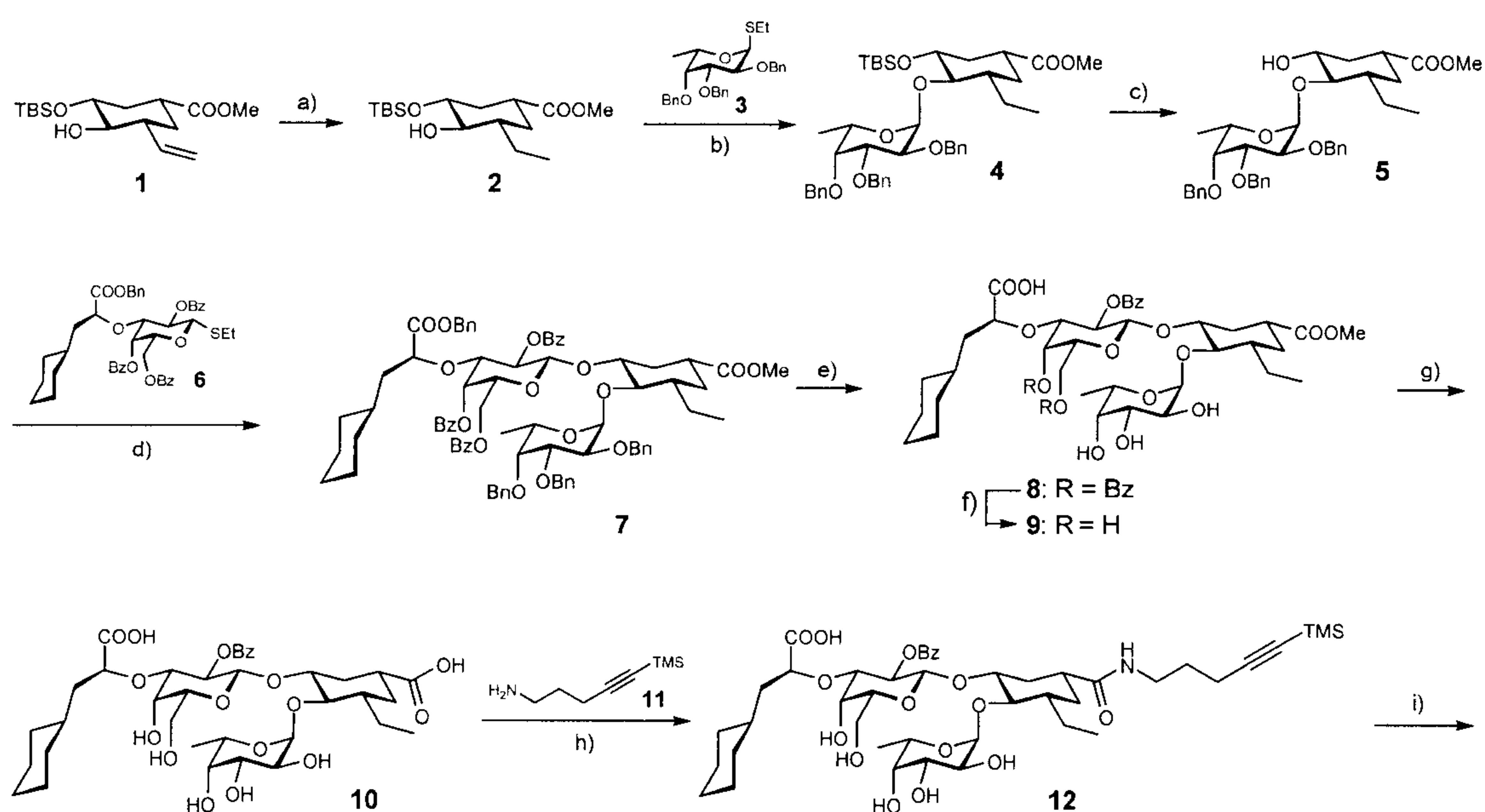
General Synthetic Methodology

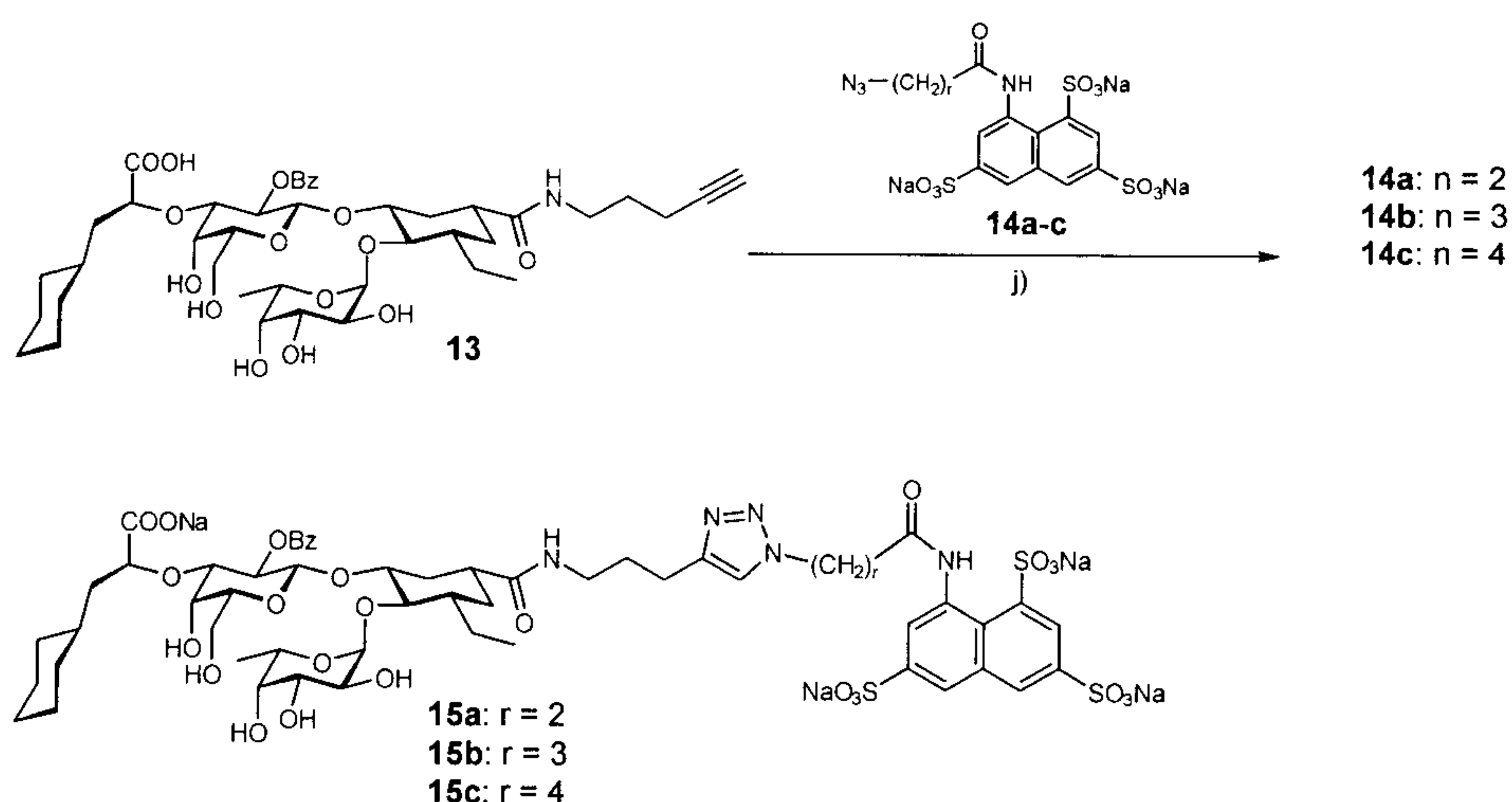
[0084] The compounds of this invention may be prepared in general by methods known to those skilled in the art. Schemes 1-5 below provide general synthetic routes for the preparation of compounds disclosed herein. Other equivalent schemes, which will be readily apparent to the

ordinary skilled organic chemist, may alternatively be used to synthesize various portions of the molecules as illustrated by the general schemes below.



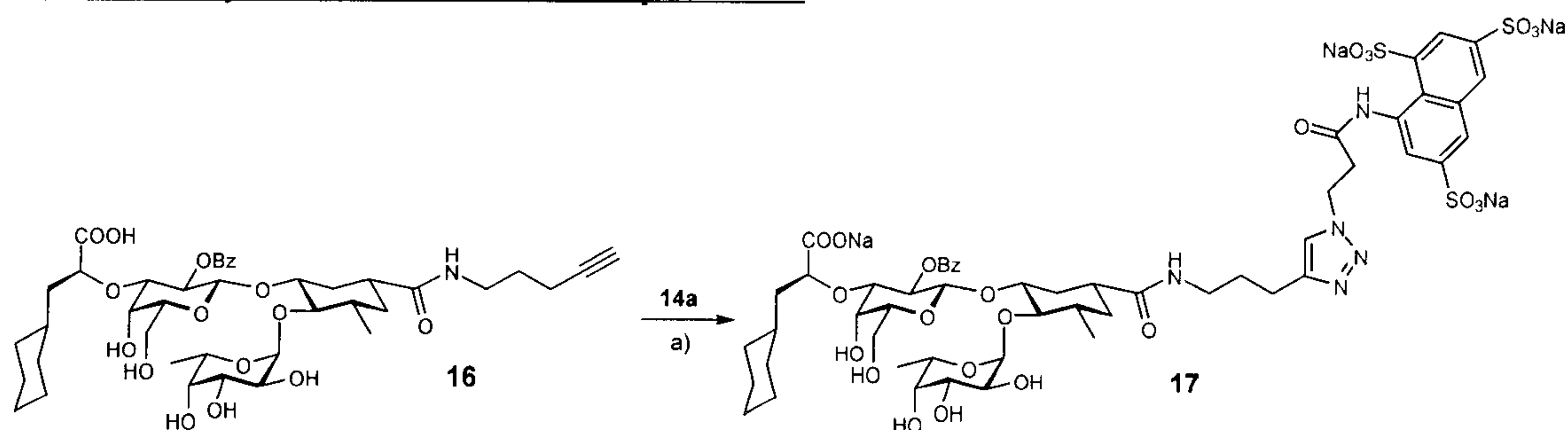
Scheme 1. Synthesis of Compounds 15a-c.





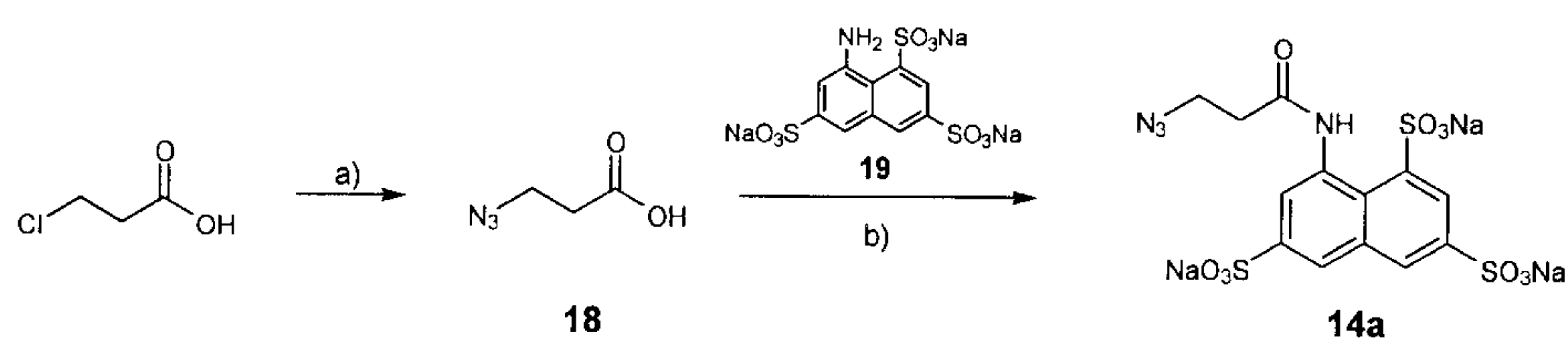
a) H_2 , 10% $\text{Pd}(\text{OH})_2$, dioxane/ H_2O , rt, 24 h, quant; b) **3**, 2,6-di-*tert*-butyl-4-methylpyridine, TBAB, Cu_2Br , MS4Å, DCM, DMF, rt, 19 h, 72%; c) TBAF/THF, THF, rt 21 h, 76%; d) **6**, DMTST, DCM, 43 h rt, 30%; e) H_2 , $\text{Pd}(\text{OH})_2$, dioxane/ H_2O , 5 h, rt, quant; f) NaOMe, MeOH, 3 h, rt, 86%; g) 0.1 M NaOH in MeOH/ H_2O , 5 h, 15 °C, 66%; h) **11**, HOBT, HBTU DMF, 66%; i) TBAF/THF, THF, 15 °C, 46 h, 95%; j) $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, Na-ascorbate, *t*-BuOH/ H_2O 1:1, rt, 1 h, 28-70%.

Scheme 2. Synthesis of Selectin Compound 17.



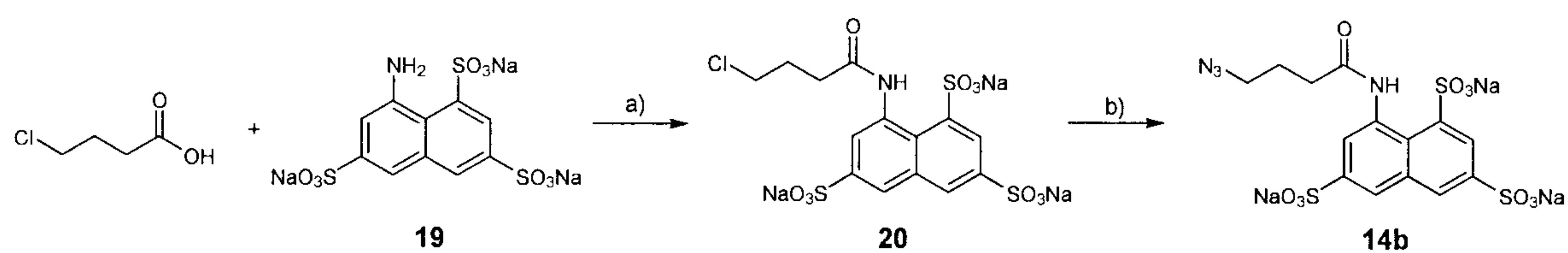
a) $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, Na-ascorbate, *t*-BuOH/ H_2O 1:1, rt, 1 h, 57%.

Scheme 3. Synthesis of Compound 14a.



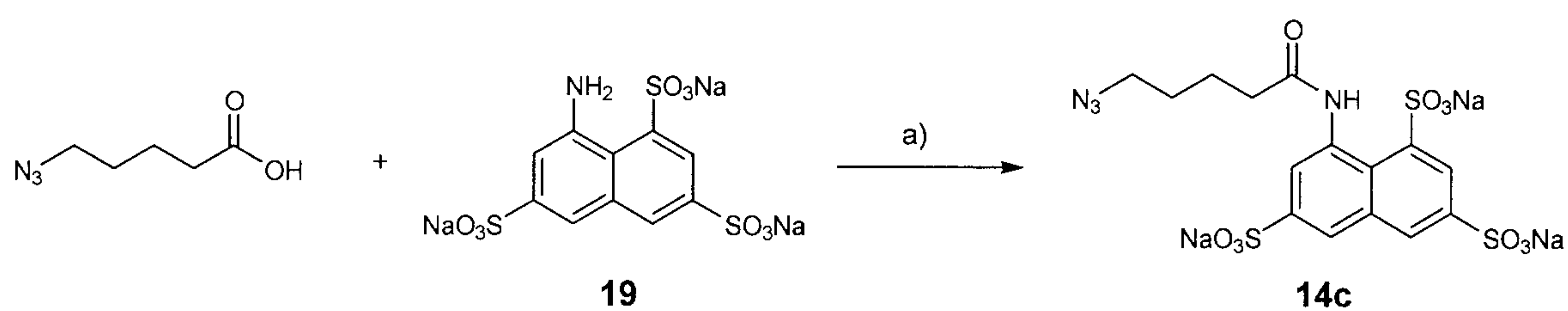
a) NaN₃, H₂O, 22 h, 100°C (81%); b) COMU, DIPEA, DMF, 21 h, 0°C – rt (26%).

Scheme 4. Synthesis of Compound 14b.



a) COMU, DIPEA, DMF, 70 h, 0 °C-rt, 48%; b) NaN₃, H₂O, 18 h, 100 °C, 29%.

Scheme 5. Synthesis of Compound 14c.



a) i. 1-Chloro-*N,N*,2-trimethylpropenylamine, DCM, 5 h, rt; ii. pyr., DMAP, 65 h, rt, 26%.

EXAMPLES**EXAMPLE 1****SYNTHESIS OF COMPOUNDS 15a-c**

[0085] Synthesis of compound 2: A suspension of compound 1 (500 mg, 1.19 mmol, purity approximately 75%; synthesized as described by Schwizer et al., Chem. Eur. J. 18:1342-1351, 2012) and Pd(OH)₂/C (10%) in dioxane/water (4:1, 5 mL) is stirred under a hydrogen atmosphere at room temperature for 24 hours. Then the reaction mixture is filtered over celite and washed with methanol. The filtrate is evaporated to dryness and the crude product is purified by column chromatography on silica gel (petroleum ether/diethyl ether, 9:1) to afford compound 2 (360 mg, quant.) as a yellowish oil. $[\alpha]_D^{20}$ -16.5 (*c* 1.14, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ = 0.10 (s, 3H, SiCH₃), 0.10 (s, 3H, SiCH₃), 0.90 (s, 9H, C(CH₃)₃), 0.89-0.93 (m, 3H, CH₃), 1.12-1.22 (m, 2H, H-6a, OH), 1.26 (m, 1H, CH₂), 1.37 (m, 1H, H-5), 1.53 (m, 1H, H-2a), 1.85 (m, 1H, CH₂), 2.01 (m, 1H, H-6b), 2.07 (ddd, *J* = 4.0, 6.2, 12.7 Hz, 1H, H-2b), 2.40 (m, 1H, H-1), 3.07 (dd, *J* = 8.6, 10.1 Hz, 1H, H-4), 3.42 (ddd, *J* = 4.5, 8.4, 11.4 Hz, 1H, H-3), 3.68 (s, 3H, OCH₃); ¹³C NMR (126 MHz, CDCl₃): δ = -4.74, -4.10 (2 SiCH₃), 10.62 (CH₃), 17.96 (C(CH₃)₃), 24.31 (CH₂), 25.77 (C(CH₃)₃), 31.81 (C-6), 35.60 (C-2), 40.66 (C-1), 41.78 (C-5), 51.79 (OCH₃), 75.82 (C-3), 78.17 (C-4), 175.00 (C=O); ESI-MS: *m/z*: Calcd for C₁₆H₃₃O₄Si [M+H]⁺: 317.21, found: 317.09.

[0086] Synthesis of compound 4: Compound 3 (1.36 g, 2.84 mmol) and (Bu)₄NBr (1.37 g, 4.27 mmol) are dried at high vacuum overnight. Then, compound 2 (450 mg, 1.42 mmol), 2,6-di-tert-butyl-4-methylpyridine (875 mg, 4.27 mmol), powdered 4Å molecular sieves (1.5 g), anhydrous DCM (10 mL) and DMF (1.5 mL) are added and the mixture is stirred at room temperature under argon for 5 hours. CuBr₂ (953 mg, 4.27 mmol), dried at 70 °C under high vacuum overnight, is added and stirring is continued for another 20 hours. The reaction mixture is then filtered through a pad of celite, the filtrate is diluted in DCM and successively washed with a solution of saturated aqueous NH₄Cl and aqueous NH₃ (9:1, v/v) (2 x 100 mL) and brine (100 mL). The aqueous layers are then extracted with DCM (2 x 100 mL), and the combined organic layers are dried (Na₂SO₄) and concentrated in vacuo. The crude product is purified by column chromatography on silica gel (petroleum ether/EtOAc, 92.5:7.5) to afford compound 4 (780 mg, 78%) as a yellowish oil. $[\alpha]_D^{20}$ -72.8 (*c* 0.70, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ = 0.02 (s, 3H, SiCH₃), 0.07 (s, 3H, SiCH₃), 0.83 (t, *J* = 7.4 Hz, 3H, CH₃), 0.87 (s, 9H, C(CH₃)₃),

1.09 (d, $J = 6.5$ Hz, 3H, H-6^F), 1.13-1.31 (m, 2H, H-6a, CH₂), 1.49 (m, 1H, H-5), 1.58 (m, 1H, H-2a), 1.83-1.98 (m, 2H, H-6b, CH₂), 2.05 (m, 1H, H-2b), 2.36 (tt, $J = 3.8, 12.2$ Hz, 1H, H-1), 3.37 (m, 1H, H-4), 3.64 (m, 1H, H-4^F), 3.67 (s, 3H, OCH₃), 3.68 (m, 1H, H-3), 4.01-4.08 (m, 2H, H-2^F, H-3^F), 4.35 (q, $J = 6.1$ Hz, 1H, H-5^F), 4.64 (A of AB, $J = 11.6$ Hz, 1H, CH₂Ph), 4.72 (A of AB, $J = 11.8$ Hz, 1H, CH₂Ph), 4.73 (A of AB, $J = 11.8$ Hz, 1H, CH₂Ph), 4.82 (B of AB, $J = 11.9$ Hz, 1H, CH₂Ph), 4.85 (B of AB, $J = 11.9$ Hz, 1H, CH₂Ph), 4.98 (B of AB, $J = 11.5$ Hz, 1H, CH₂Ph), 5.14 (d, $J = 2.8$ Hz, 1H, H-1^F), 7.22-7.43 (m, 15H, 3 C₆H₅); ¹³C NMR (126 MHz, CDCl₃): $\delta = -4.97, -3.36$ (2 SiCH₃), 10.79 (CH₃), 16.96 (C-6^F), 18.15 (C(CH₃)₃), 24.16 (CH₂), 26.15 (C(CH₃)₃), 31.52 (C-6), 37.05 (C-2), 40.40 (C-1), 43.54 (C-5), 51.72 (OCH₃), 66.36 (C-5^F), 72.81 (CH₂Ph), 74.19 (C-3), 74.42, 74.88 (CH₂Ph), 76.62 (C-2^F), 78.28 (C-4^F), 79.27 (C-3^F), 80.44 (C-4), 97.24 (C-1^F), 127.42, 127.46, 127.60, 128.14, 128.22, 128.26, 128.33, 138.57, 138.86, 138.94 (18C, 3 C₆H₅), 175.13 (C=O); ESI-MS: m/z : Calcd for C₄₃H₆₀NaO₈Si [M+Na]⁺: 755.40, found: 755.43.

[0087] Synthesis of compound 5: TBAF (1 M in THF, 5.0 mL, 5 mmol) is added to a solution of compound 4 (780 mg, 1.06 mmol) in anhydrous THF (6.4 mL). After stirring at room temperature for 20 hours, the reaction mixture is diluted with DCM (100 mL) and washed with water (2 x 100 mL) and brine (100 mL). The aqueous layers are extracted with DCM (2 x 50 mL) and the combined organic layers are dried (Na₂SO₄) and concentrated. The crude product is purified by column chromatography on silica gel (petroleum ether/EtOAc, 4:1) to afford compound 5 (500 mg, 76%) as a white solid. $[\alpha]_D^{20} -74.6$ (c 1.16, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): $\delta = 0.72$ (t, $J = 7.5$ Hz, 3H, CH₃), 1.00-1.12 (m, 2H, H-6a, CH₂), 1.09 (d, $J = 6.5$ Hz, 3H, H-6^F), 1.28-1.44 (m, 2H, H-2a, H-5), 1.92-2.02 (m, 2H, H-6b, CH₂), 2.16 (m, 1H, H-2b), 2.28 (tt, $J = 3.1, 12.6$ Hz, 1H, H-1), 2.91 (dd, $J = 8.7, 10.1$ Hz, 1H, H-4), 3.36 (ddd, $J = 4.8, 8.4, 11.6$ Hz, 1H, H-3), 3.60 (s, 3H, OCH₃), 3.63 (d, $J = 1.4$ Hz, 1H, H-4^F), 3.89 (dd, $J = 2.7, 10.2$ Hz, 1H, H-3^F), 4.00-4.07 (m, 2H, H-2^F, H-5^F), 4.58 (A of AB, $J = 11.5$ Hz, 1H, CH₂Ph), 4.62 (A of AB, $J = 11.7$ Hz, 1H, CH₂Ph), 4.67-4.79 (m, 3H, CH₂Ph), 4.89-4.94 (m, 2H, H-1^F, CH₂Ph), 7.16-7.39 (m, 15H, 3 C₆H₅); ¹³C NMR (126 MHz, CDCl₃): $\delta = 10.80$ (CH₃), 16.60 (C-6^F), 23.92 (CH₂), 32.08 (C-6), 34.68 (C-2), 40.33 (C-1), 41.52 (C-5), 51.74 (OCH₃), 67.69 (C-5^F), 72.15 (C-3), 72.85, 73.63, 74.88 (3 CH₂Ph), 76.27 (C-2^F), 77.42 (C-4^F), 78.83 (C-3^F), 90.10 (C-4), 98.64 (C-1^F), 127.41, 127.50, 127.57, 127.66, 127.83, 128.23, 128.25, 128.35, 138.27, 138.40, 138.67 (18C, 3 C₆H₅), 175.05 (C=O); ESI-MS: m/z : Calcd for C₃₇H₄₆NaO₈ [M+Na]⁺: 641.31, found: 641.23.

[0088] Synthesis of compound 7: A mixture of compound 5 (480 mg, 0.775 mmol), compound 6 (908 mg, 1.16 mmol), and activated powdered molecular sieves 4Å (400 mg) in DCM (5 mL) is stirred at room temperature under argon for 4 hours. A pre-stirred mixture (4 hours at room temperature) of DMTST (800 mg, 3.10 mmol) and activated powdered MS 4Å (200 mg) in DCM (3 mL) is added. After 43 hours, the reaction mixture is filtered over celite, diluted with DCM (100 mL), and washed with saturated aqueous NaHCO₃ (100 mL) and brine (100 mL). The aqueous layers are extracted with DCM (2 x 100 mL) and the combined organic layers are dried (Na₂SO₄) and evaporated to dryness. The crude product is purified by column chromatography on silica gel (toluene/EtOAc, 9:1) to afford compound 7 as a white solid (302 mg, 30%). $[\alpha]_D^{20}$ -66.2 (*c* 0.63, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ = 0.32-0.50, 0.55-1.34 (m, 17H, C₇H₁₃^L, CH₂, H-2a, H-5, H-6a), 0.68 (t, *J* = 7.4 Hz, 3H, CH₃) 1.36 (d, *J* = 6.5 Hz, 3H, H-6^F), 1.79 (dd, *J* = 2.5, 13.3 Hz, 1H, H-6b), 1.89 (m, 1H, CH₂), 2.05-2.14 (m, 2H, H-1, H-2b), 3.21 (t, *J* = 9.6 Hz, 1H, H-4), 3.42-3.50 (m, 2H, H-3, H-4^F), 3.46 (s, 3H, OCH₃), 3.75 (dd, *J* = 3.4, 9.9 Hz, 1H, H-3^G), 3.85 (t, *J* = 6.5 Hz, 1H, H-5^G), 3.93-3.98 (m, 2H, H-2^F, H-3^F), 4.05 (dd, *J* = 4.6, 7.9 Hz, 1H, H-2^L), 4.17-4.22 (m, 2H, H-6a^G, CH₂Ph), 4.31 (dd, *J* = 5.6, 11.5 Hz, 1H, H-6b^G), 4.45 (A of AB, *J* = 11.8 Hz, 1H, CH₂Ph), 4.49 (d, *J* = 8.2 Hz, 1H, H-1^G), 4.55 (B of AB, *J* = 11.7 Hz, 1H, CH₂Ph), 4.57 (A of AB, *J* = 11.5 Hz, 1H, CH₂Ph), 4.67 (B of AB, *J* = 11.4 Hz, 1H, CH₂Ph), 4.73 (B of AB, *J* = 11.4 Hz, 1H, CH₂Ph), 4.82 (q, *J* = 6.4 Hz, 1H, H-5^F), 4.91 (m, 1H, H-1^F), 4.97 (A of AB, *J* = 12.1 Hz, 1H, CH₂Ph), 5.05 (B of AB, *J* = 12.1 Hz, 1H, CH₂Ph), 5.54 (dd, *J* = 8.6, 9.5 Hz, 1H, H-2^G), 5.77 (d, *J* = 3.0 Hz, 1H, H-4^G), 7.07-7.28, 7.29-7.42, 7.43-7.53, 7.95-8.07 (m, 35H, 7 C₆H₅); ¹³C NMR (126 MHz, CDCl₃): δ = 10.47 (CH₃), 16.78 (C-6^F), 23.05, 23.80, 25.46, 25.70, 26.06, 30.87, 32.62, 33.20, 33.38, 40.23, 40.44, 44.05 (C₇H₁₃^L, CH₂, C-1, C-2, C-5, C-6), 51.63 (OCH₃), 62.50 (C-6^G), 66.43 (C-5^F), 66.63 (CH₂Ph), 70.20 (C-4^G), 71.61 (C-5^G), 72.00 (2C, C-2^G, CH₂Ph), 74.55, 74.89 (2 CH₂Ph), 76.32 (C-2^F), 78.07 (C-3^G), 78.44 (C-2^L), 78.67 (C-4), 79.23 (C-4^F), 79.90 (C-3^F), 80.42 (C-3), 98.23 (C-1^F), 100.17 (C-1^G), 126.92, 127.05, 127.18, 127.43, 127.69, 128.02, 128.08, 128.11, 128.40, 128.43, 128.50, 128.54, 129.61, 129.67, 129.75, 129.91, 129.94, 133.04, 133.18, 133.27, 135.41, 138.58, 138.95, 139.18 (42C, 7 C₆H₅), 164.60, 166.09, 166.14, 172.39, 174.25 (5 C=O); ESI-MS: *m/z*: Calcd for C₈₀H₈₈NaO₁₈ [M+Na]⁺: 1359.59, found: 1359.84.

[0089] Synthesis of compound 8: A mixture of 7 (204 mg, 0.153 mmol) and Pd(OH)₂/C (45 mg) in dioxane/H₂O (4:1, 3 mL) is stirred at room temperature under a hydrogen atmosphere. After 5 hours, the reaction mixture is filtered through a pad of celite and evaporated to dryness to

afford compound 8 (150 mg, quant) as a white solid. ESI-MS: m/z : Calcd for $C_{52}H_{64}NaO_{18}$ $[M+Na]^+$: 999.40, found: 999.49.

[0090] Synthesis of compound 9: To a mixture of 8 (150 mg, 0.153 mmol) in methanol (2 mL), a catalytic amount of freshly prepared sodium methoxide/methanol is added. After 3 hours, the reaction mixture is neutralized with acetic acid and evaporated to dryness. The residue is purified by column chromatography on silica gel (DCM/MeOH/H₂O, 10:3:0.5) to give compound 9 (102 mg, 86%) as a white solid. $[\alpha]_D^{20}$ -80.5 (c 0.94, MeOH); ^1H NMR (500 MHz, CD₃OD): δ = 0.42-1.15, 1.16-1.67 (m, 18H, $C_7H_{13}^L$, CH₂, H-2a, H-6a, H-5), 0.85 (t, J = 7.4 Hz, 3H, CH₃), 1.33 (d, J = 6.6 Hz, 3H, H-6^F), 1.87-2.01 (m, 2H, CH₂, H-6b), 2.27-2.41 (m, 2H, H-2b, H-1), 3.22 (dd, J = 6.3, 13.0 Hz, 1H, H-4), 3.57 (s, 3H, OCH₃), 3.60 (m, 1H, H-5^G), 3.63 (dd, J = 2.8, 9.8 Hz, 1H, H-3^G), 3.66-3.82 (m, 5H, H-3, H-2^F, H-4^F, H-6^G), 3.85-3.93 (m, 2H, H-2^L, H-3^F), 3.97 (d, J = 0.8 Hz, 1H, H-4^G), 4.72 (d, J = 8.1 Hz, 1H, H-1^G), 4.93 (d, J = 4.0 Hz, 1H, H-1^F), 4.98 (m, 1H, H-5^F), 5.42 (dd, J = 8.4, 9.4 Hz, 1H, H-2^G), 7.50 (t, J = 7.8 Hz, 2H, C₆H₅), 7.60-7.66, 8.06-8.10 (m, 3H, C₆H₅); ^{13}C NMR (126 MHz, CD₃OD): δ = 10.75 (CH₃), 16.72 (C-6^F), 24.50 (CH₂), 26.55, 26.76, 27.33, 32.56, 33.08, 34.32, 34.88, 35.29, 41.30, 43.20, 45.01 ($C_7H_{13}^L$, C-1, C-2, C-5, C-6), 52.27 (OCH₃), 62.85 (C-6^G), 67.67 (C-4^G), 67.75 (C-5^F), 70.31 (C-2^F), 71.39 (C-3^F), 73.03 (C-2^G), 73.94 (C-4^F), 75.80 (C-5^G), 79.36 (C-2^L), 80.15 (C-3), 80.64 (C-4), 83.73 (C-3^G), 100.23 (C-1^F), 100.72 (C-1^G), 129.64, 130.92, 131.61, 134.30 (6C, C₆H₅), 166.92, 176.30 (3C, C=O); ESI-MS: m/z : Calcd for $C_{38}H_{56}NaO_{16}$ $[M+Na]^+$: 791.35, found: 791.35.

[0091] Synthesis of compound 10: A solution of 1 M NaOH in H₂O/MeOH (1:1, 725 μ L) is cooled to 15 °C. Then, compound 9 (25 mg, 0.0325 mmol) is added and the mixture is stirred at 15 °C. After 4 hours, the reaction mixture is neutralized with 0.5 M aq. HCl and the solvents are removed in vacuo. The residue is purified by column chromatography on RP-18 (H₂O/MeOH, 0-10%) to afford compound 10 (16.3 mg, 66%) as a white solid. $[\alpha]_D^{20}$ -76.4 (c 0.29, MeOH); ^1H NMR (500 MHz, CD₃OD): δ = 0.41-0.54, 0.55-0.73, 0.79-0.93, 1.01-1.15, 1.15-1.43, 1.42-1.56, 1.64 (m, 20H, $C_7H_{13}^L$, CH₂, H-2a, H-5, H-6a, CH₃), 1.32 (d, J = 6.5 Hz, 3H, H-6^F), 1.87 (dp, J = 3.1, 13.5 Hz, 1H, H-6b), 1.94 (m, 1H, CH₂), 2.13 (tt, J = 3.3, 12.8 Hz, 1H, H-1), 2.31 (ddd, J = 3.1, 5.5, 12.0 Hz, 1H, H-2b), 3.27 (m, 1H, H-4), 3.57 (dd, J = 3.1, 9.7 Hz, 1H, H-3^G), 3.60 (m, 1H, H-5^G), 3.67-3.77 (m, 4H, H-2^L, H-3, H-2^F, H-6a^G), 3.77 (d, J = 3.3 Hz, 1H, H-4^F), 3.81 (dd, J = 6.8, 11.6 Hz, 1H, H-6b^G), 3.88-3.96 (m, 2H, H-3^F, H-4^G), 4.75 (d, J = 8.1 Hz, 1H, H-1^G), 4.90-4.99 (m, 2H, H-1^F, H-5^F), 5.42 (dd, J = 9.7, 8.0 Hz, 1H, H-2^G), 7.43-7.53, 7.53-7.62, 7.97-8.16 (m, 5H, C₆H₅); ^{13}C NMR (126 MHz, CD₃OD): δ = 10.86 (CH₃), 16.76

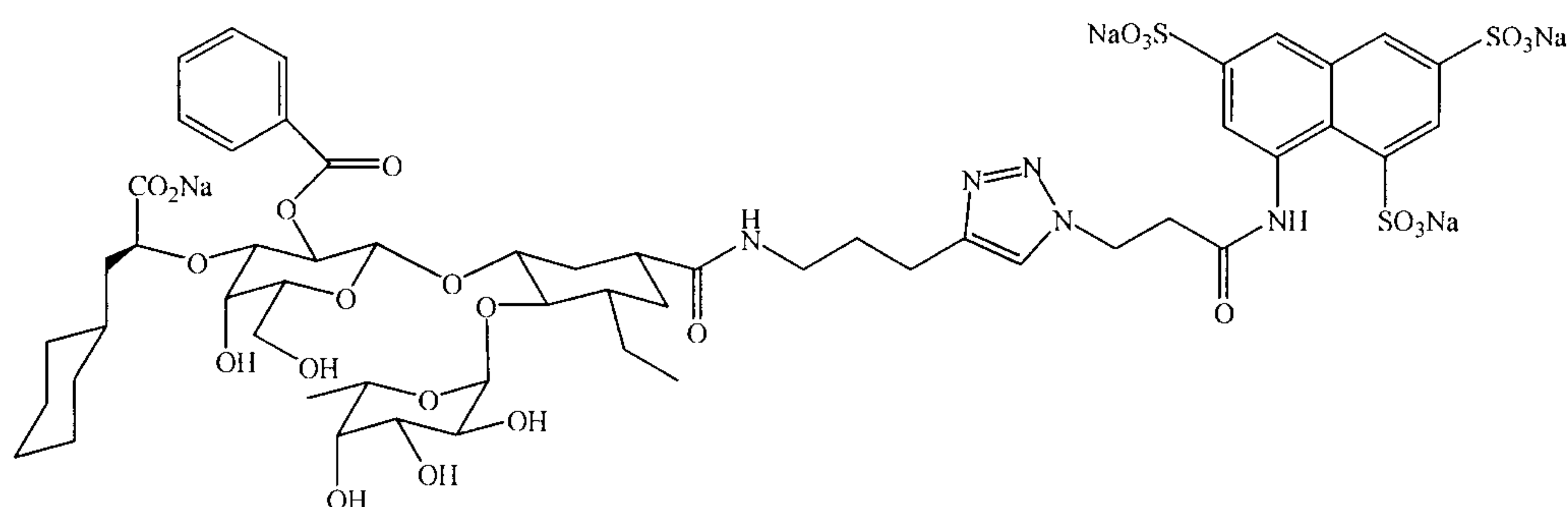
(C-6^F), 24.87 (CH₂), 26.54, 26.78, 27.44, 33.07, 33.92, 34.40, 35.43, 36.08, 43.60, 45.34, 45.47 (C₇H₁₃^L, C-1, C-2, C-5, C-6), 63.23 (C-6^G), 67.74 (C-4^G), 67.84 (C-5^F), 70.39 (C-2^F), 71.32 (C-3^F), 72.98 (C-2^G), 73.99 (C-4^F), 75.96 (C-5^G), 80.32, 80.55 (C-3, C-2^L), 81.09 (C-4), 83.96 (C-3^G), 99.95 (C-1^F), 100.31 (C-1^G), 129.68, 130.94, 131.79, 134.11 (6C, C₆H₅), 167.06, 183.27, 183.45 (3 C=O); ESI-MS: *m/z*: Calcd for C₃₇H₅₄NaO₁₆ [M+Na]⁺: 777.33, found: 777.46.

[0092] Synthesis of compound 12: To a mixture of compound 10 (11 mg, 0.0146 mmol) in dry DMF (800 μL), HOBT (5.9 mg, 0.0437 mmol) and HBTU (6.6 mg, 0.0175 mmol) are added successively at 0 °C. After stirring for 10 minutes, alkine 11 (47 μL) is added and the mixture is stirred for 1 hour at 0 °C. The solvents are evaporated in vacuo and the resulting residue is purified by column chromatography on silica gel (DCM/MeOH/H₂O, 10:3:0.5) to afford compound 12 (8.6 mg, 66%). $[\alpha]_D^{20}$ -39.3 (*c* 1.00, MeOH); ¹H NMR (500 MHz, CD₃OD): δ = 0.14 (s, 9H, Si(CH₃)₃), 0.43-0.56, 0.57-0.73, 0.81-0.95, 1.06-1.45, 1.45-1.58, 1.60-1.68, 2.11-2.26 (m, 20H, C₇H₁₃^L, H-1, H-2, H-5, H-6a, CH₂), 0.86 (t, *J* = 7.4 Hz, 3H, CH₃), 1.33 (d, *J* = 6.5 Hz, 3H, H-6^F), 1.73 (dd, *J* = 3.1, 13.4 Hz, 1H, H-6b), 1.95 (ddt, *J* = 7.3, 10.5, 15.1 Hz, 1H, CH₂CH₃), 2.23 (t, *J* = 7.2 Hz, 2H, CH₂), 3.10-3.23 (m, 2H, CH₂), 3.26 (dd, *J* = 9.1, 10.3 Hz, 1H, H-4), 3.56-3.62 (m, 2H, H-3^G, H-5^G), 3.67-3.77 (m, 4H, H-3, H-2^F, H-4^F, H-6a^G), 3.77-3.84 (m, 2H, H-2^L, H-6b^G), 3.88 (dd, *J* = 3.3, 10.3 Hz, 1H, H-3^F), 3.94 (m, 1H, H-4^G), 4.71 (d, *J* = 8.1 Hz, 1H, H-1^G), 4.94 (d, *J* = 4.0 Hz, 1H, H-1^F), 4.95-5.00 (m, 1H, H-5^F), 5.37-5.46 (m, 1H, H-2^G), 7.46-7.54, 7.58-7.65, 8.03-8.09 (m, 5H, C₆H₅), 7.80 (t, *J* = 5.7 Hz, 1H, NH); ¹³C NMR (126 MHz, CD₃OD): δ = 0.25 (Si(CH₃)₃), 10.75 (CH₃), 16.74 (C-6^F), 18.07 (CH₂), 24.56 (CH₂CH₃), 26.60, 26.79, 27.38, 27.48, 29.65, 32.89, 33.08, 34.40, 35.37, 35.57, 39.84, 43.24, 45.19 (C₇H₁₃^L, C-1, C-2, C-5, C-6, 2 CH₂), 63.03 (C-6^G), 67.63 (C-4^G), 67.82 (C-5^F), 70.31 (C-2^F), 71.34 (C-3^F), 73.00 (C-2^G), 73.96 (C-4^F), 75.98 (C-5^G), 80.16 (2C, C-3, C-2^L), 80.55 (C-4), 83.84 (C-3^G), 85.47 (CH₂CCSi), 100.24 (C-1^F), 100.63 (C-1^G), 107.65 (CH₂CCSi), 129.74, 130.86, 131.70, 134.28 (6C, C₆H₅), 166.87, 177.28 (3C, 3 C=O); ESI-MS: *m/z*: Calcd for C₄₅H₆₉NNaO₁₅Si [M+Na]⁺: 914.43, found: 914.52.

[0093] Synthesis of compound 13: TBAF (15 μL, 1M in THF) is added via syringe at 10-15 °C (waterbath) to a solution of compound 12 (9.0 mg, 0.010 mmol) in THF (500 μL). After 46 hours, the solvent is removed in vacuo, and the resulting residue is purified by column chromatography on silica gel (DCM/MeOH/water, 10:3:0.5) to give compound 13 (7.8 mg, 95%) as a white solid. $[\alpha]_D^{20}$ -64.5 (*c* 1.08, MeOH); ¹H NMR (500 MHz, CD₃OD): δ = 0.45-0.73, 0.81-0.95, 1.00-1.59, 1.59-1.69, 2.10-2.25 (m, 20H, C₇H₁₃^L, H-1, H-2, H-5, H-6a, CH₂), 0.86 (t,

$J = 7.4$ Hz, 3H, CH₃), 1.33 (d, $J = 6.5$ Hz, 3H, H-6^F), 1.74 (m, 1H, H-6b), 1.95 (m, 1H, CH₂CH₃), 2.19 (td, $J = 2.7, 7.2$ Hz, 2H, CH₂), 2.28 (t, $J = 2.7$ Hz, 1H, CH), 3.12-3.29 (m, 3H, H-4, CH₂), 3.56-3.62 (m, 2H, H-3^G, H-5^G), 3.66-3.77 (m, 4H, H-3, H-2^F, H-4^F, H-6a^G), 3.77-3.85 (m, 2H, H-6b^G, H-2^L), 3.88 (dd, $J = 3.3, 10.3$ Hz, 1H, H-3^F), 3.94 (d, $J = 2.9$ Hz, 1H, H-4^G), 4.70 (d, $J = 8.0$ Hz, 1H, H-1^G), 4.93 (d, $J = 4.0$ Hz, 1H, H-1^F), 4.97 (q, $J = 6.5$ Hz, 1H, H-5^F), 5.42 (m, 1H, H-2^G), 7.45-7.53, 7.58-7.64, 8.03-8.08 (m, 5H, C₆H₅), 7.79 (t, $J = 5.7$ Hz, 1H, NH); ¹³C NMR (126 MHz, CD₃OD): $\delta = 10.75$ (CH₃), 16.70 (CH₂), 16.74 (C-6^F), 24.55 (CH₂CH₃), 26.58, 26.79, 27.39, 29.51, 32.93, 33.11, 34.40, 35.36, 35.52, 39.45, 43.25, 43.40, 45.24 (C₇H₁₃^L, C-1, C-2, C-5, C-6, 2 CH₂), 63.04 (C-6^G), 67.66 (C-4^G), 67.83 (C-5^F), 70.09 (CH), 70.32 (C-2^F), 71.35 (C-3^F), 73.02 (C-2^G), 73.97 (C-4^F), 76.01 (C-5^G), 80.17 (2C, C-3, C-2^L), 80.54 (C-4), 83.83 (C-3^G), 84.27 (-CCH), 100.29 (C-1^F), 100.66 (C-1^G), 129.72, 130.86, 131.70, 134.31 (6C, C₆H₅), 166.85, 177.30 (3C, 3 C=O); ESI-MS: m/z : Calcd for C₄₂H₆₁NNaO₁₅ [M+Na]⁺: 842.39, found: 842.60.

[0094] Synthesis of compound 15a:



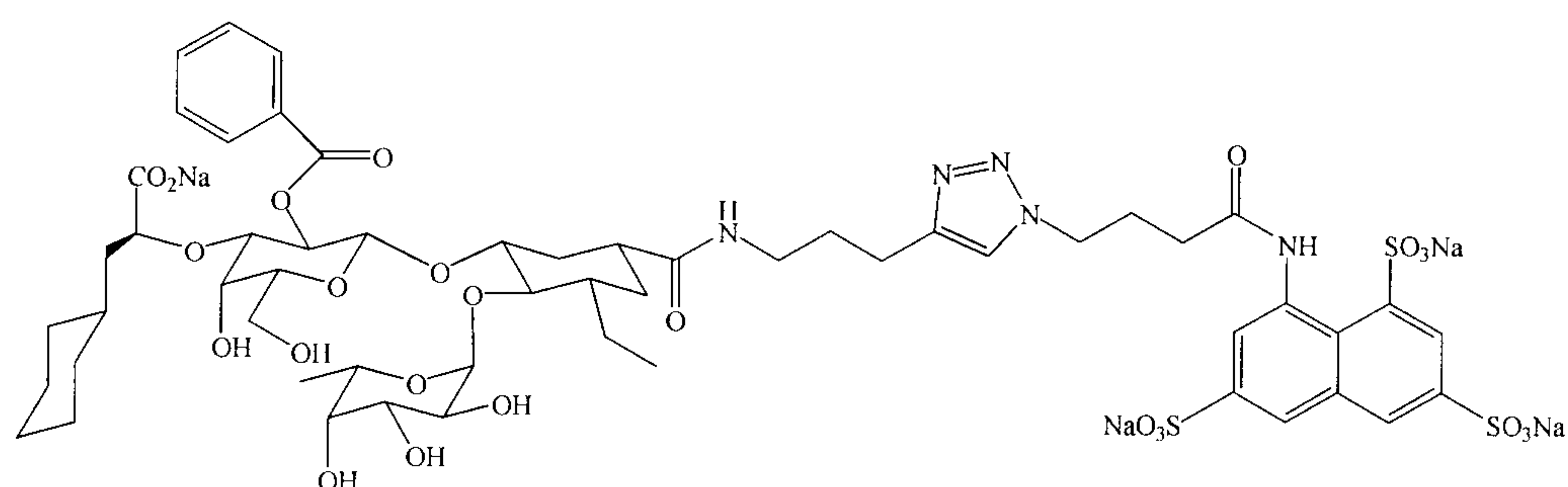
[0095] To a mixture of compound 13 (3.1 mg, 3.8 μ mol) and compound 14a (3.3 mg, 5.7 μ mol, example 3 below) in tert-BuOH/H₂O (1:1, 300 μ L), cupric sulfate pentahydrate (0.24 mg, 1.0 μ mol) and L-(+)-ascorbic acid sodium salt (0.38 mg, 1.9 μ mol) are added successively.

After 1 hour, the reaction mixture is purified by column chromatography on silica (DCM/MeOH/H₂O, 10:6:1.5) followed by ion-exchange chromatography (Na⁺ form) and RP-18 chromatography (H₂O/MeOH, 4:1) to yield compound 15a (3.2 mg, 60%) as a white solid.

$[\alpha]_D^{20} -25.1$ (c 0.35, MeOH); ¹H NMR (500 MHz, CD₃OD): $\delta = 0.42$ -0.72, 0.85-0.94, 1.04-1.42, 1.42-1.65, 1.65-1.92 (m, 23H, C₇H₁₃^L, CH₂CH₃, H-2a, H-5, H-6, 2 CH₂), 0.83 (t, $J = 7.4$ Hz, 3H, CH₃), 1.28 (d, $J = 6.7$ Hz, 3H, H-6^F), 1.97-2.11 (m, 2H, CH₂), 2.11-2.30 (m, 2H, H-1, H-2b), 2.55-2.69 (m, 2H, CH₂), 2.72 (t, $J = 7.5$ Hz, 2H, CH₂), 3.08-3.28 (m, 3H, CH₂, H-4), 3.50-3.57 (m, 2H, H-3^G, H-5^G), 3.59-3.85 (m, 6H, H-3, H-2^F, H-4^F, H-6^G, H-2^L), 3.84-3.98 (m, 2H, H-4^G, H-3^F), 4.48 (t, $J = 6.8$ Hz, 2H, CH₂), 4.69 (d, $J = 8.1$ Hz, 1H, H-1^G), 4.91-4.97 (m, 2H, H-1^F, H-

⁵F), 5.37 (t, $J = 8.9$ Hz, 1H, H-2^G), 7.40 (t, $J = 7.7$ Hz, 2H, C₆H₅), 7.55 (tt, $J = 1.2, 7.3$ Hz, 1H, C₆H₅), 7.96 (s, 1H, H^T), 8.01-8.09 (m, 2H, C₆H₅), 8.30 (d, $J = 1.9$ Hz, 1H, H^{naph}), 8.51 (d, $J = 2.0$ Hz, 1H, H^{naph}), 8.58 (t, $J = 2.5$ Hz, 1H, H^{naph}), 8.99 (d, $J = 1.9$ Hz, 1H, H^{naph}); ¹³C NMR (126 MHz, CD₃OD): $\delta = 10.59$ (CH₃), 16.67 (C-6^F), 23.03, 23.71, 26.55, 26.80, 27.40, 29.56, 30.19, 30.67, 33.07, 34.40, 35.40, 36.98, 37.31, 39.63, 42.95, 43.53, 50.81, 52.30 (19C, C₇H₁₃^L, C-1, C-2, C-5, C-6, 8 CH₂), 63.17 (C-6^G), 67.84 (2C, C-4^G, C-5^F), 70.34 (C-2^F), 71.23 (C-3^F), 72.98 (C-2^G), 73.97 (C-4^F), 75.73 (C-5^G), 80.10, 80.51 (3C, C-3, C-4, C-2^L), 83.63 (C-3^G), 99.90 (C-1^F), 100.64 (C-1^G), 101.39, 123.81, 123.95, 125.33, 128.35, 129.62, 130.89, 131.48, 131.72, 134.19, 134.55, 136.37, 142.14, 142.85, 144.34, 148.48 (19C, Ar-C), 166.96, 174.17, 177.33 (4C, 4 C=O).

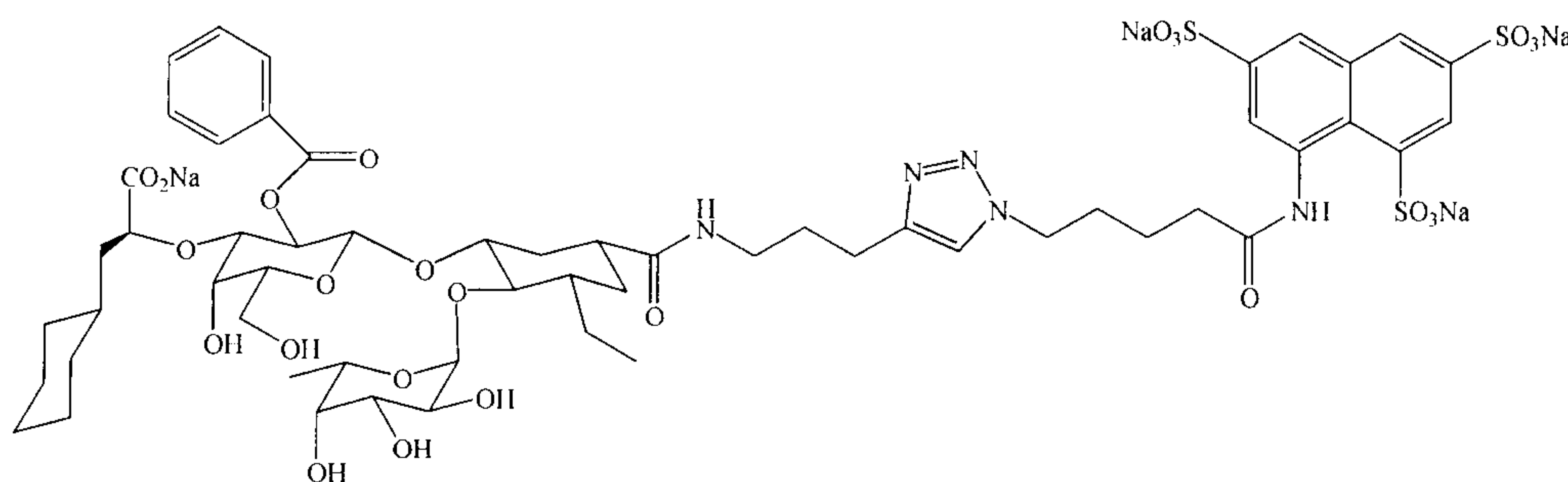
[0096] Synthesis of compound 15b:



[0097] According to the procedure for compound 15a, compound 13 (3.5 mg, 4.3 μ mol) and compound 14b (4.2 mg, 8.5 μ mol, example 3 below) were reacted in the presence of cupric sulfate pentahydrate (0.26 mg, 1.1 μ mol) and L-(+)-ascorbic acid sodium salt (0.42 mg, 2.2 μ mol) to yield compound 15b (4.2 mg, 75%) as a white solid. $[\alpha]_D^{20} -41.9$ (c 0.42, MeOH); ¹H NMR (500 MHz, CD₃OD): $\delta = 0.42$ -0.72, 0.85-0.93, 1.06-1.37, 1.37-1.42, 1.46-1.50, 1.51-1.68, 1.68-1.78, (m, 18H, C₇H₁₃^L, CH₂CH₃, H-2a, H-5, H-6) 0.82 (t, $J = 7.4$ Hz, 3H, CH₃), 1.31 (d, $J = 6.5$ Hz, 3H, H-6^F), 1.80-1.94 (m, 3H, CH₂CH₃, CH₂), 2.17 (d, $J = 12.8$ Hz, 1H, H-2b), 2.23-2.34 (m, 1H, H-1), 2.38 (p, $J = 7.0$ Hz, 2H, CH₂), 2.61 (t, $J = 7.2$ Hz, 2H, CH₂), 2.73 (t, $J = 7.5$ Hz, 2H, CH₂), 3.11-3.21 (m, 2H, CH₂), 3.28 (m, 1H, H-4), 3.51-3.61 (m, 2H, H-3^G, H-5^G), 3.68-3.84 (m, 6H, H-3, H-2^F, H-4^F, H-2^L, H-6^G), 3.90-3.92 (m, 1H, H-4^G), 3.95 (dd, $J = 3.3, 10.3$ Hz, 1H, H-3^F), 4.53 (t, $J = 6.8$ Hz, 2H, CH₂), 4.71 (d, $J = 8.1$ Hz, 1H, H-1^G), 4.93-4.97 (m, 2H, H-1^F, H-5^F), 5.39 (dd, $J = 8.0, 9.7$ Hz, 1H, H-2^G), 7.43 (t, $J = 7.8$ Hz, 2H, C₆H₅), 7.52-7.61 (m, 1H, C₆H₅), 7.99 (s, 1H, H^T), 8.05 (dd, $J = 1.4, 7.7$ Hz, 2H, C₆H₅), 8.30 (d, $J = 1.9$ Hz, 1H, H^{naph}), 8.50 (d, $J = 2.0$ Hz, 1H, H^{naph}), 8.56 (d, $J = 1.9$ Hz, 1H, H^{naph}), 8.99 (d, $J = 1.9$ Hz, 1H, H^{naph}); ¹³C NMR (126 MHz, CD₃OD): $\delta = 10.58$ (CH₃), 16.67 (C-6^F), 23.65, 24.73, 26.56, 26.71, 26.80, 27.42, 30.12,

33.06, 34.28, 34.43, 35.42, 35.52, 39.58, 43.02, 43.57, 44.89, 50.74 (18C, C₇H₁₃^L, 7 CH₂, C-1, C-2, C-5, C-6), 63.19 (C-6^G), 67.72, 67.87 (C-4^G, C-5^F), 70.33 (C-2^F), 71.22 (C-3^F), 72.98 (C-2^G), 73.96 (C-4^F), 75.85 (C-5^G), 80.04, 80.10, 80.54 (C-3, C-4, C-2^L), 83.68 (C-3^G), 99.85, 100.67 (C-1^F, C-1^G, C^T), 124.05, 124.07, 125.33, 125.43, 128.34, 129.64, 130.88, 131.43, 131.72, 134.20, 134.41, 136.36, 142.09, 142.89, 144.38, 148.44 (18C, Ar-C), 166.95, 173.24, 177.34, 183.23 (4 C=O).

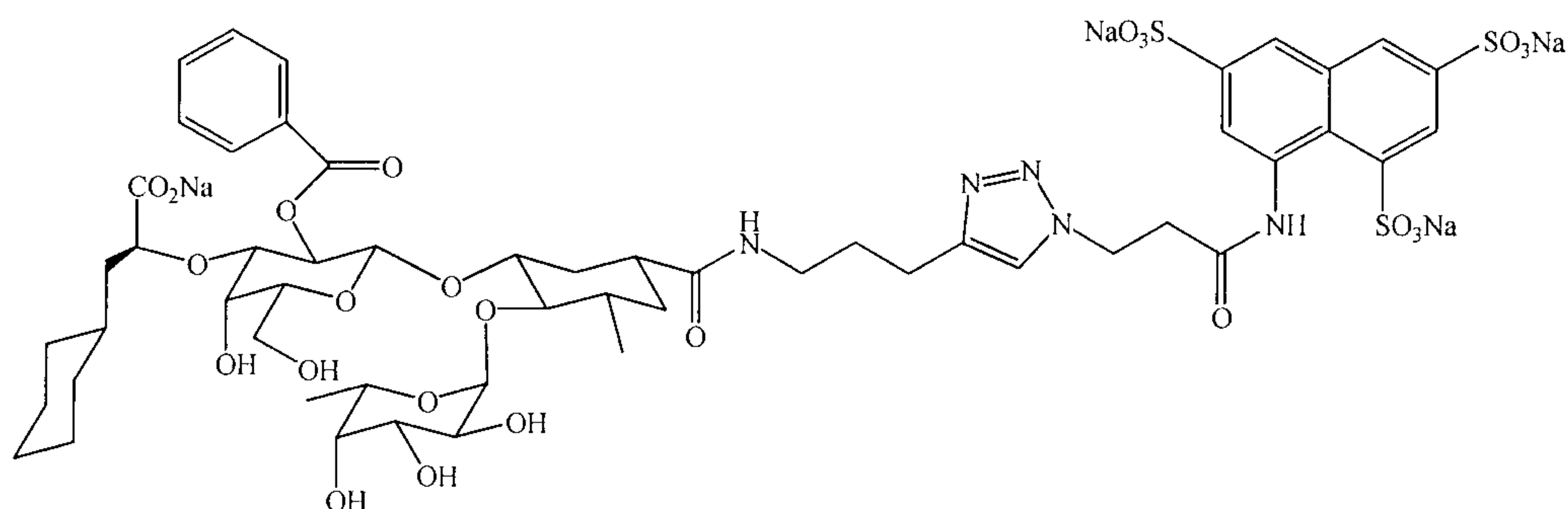
[0098] Synthesis of compound 15c:



[0099] According to the procedure for compound 15a, compound 13 (3.5 mg, 4.3 μmol) and compound 14c (3.5 mg, 6.4 μmol, example 3 below) were reacted in the presence of cupric sulfate pentahydrate (0.26 mg, 1.1 μmol) and L-(+)-ascorbic acid sodium salt (0.42 mg, 2.2 μmol) to yield compound 15c (4.2 mg, 70%) as a white solid. $[\alpha]_D^{20}$ -23.9 (*c* 0.46, MeOH); ¹H NMR (500 MHz, D₂O): δ = 0.19-0.34, 0.38-0.50, 0.54-0.77, 1.31-1.43, 1.44-1.55, 1.65-1.77 (m, 20H, C₇H₁₃^L, CH₂, CH₂CH₃, H-2a, H-5, H-6), 0.82 (t, *J* = 7.4 Hz, 3H, CH₃), 1.30 (d, *J* = 6.6 Hz, 3H, H-6^F), 1.76-1.87 (m, 1H, CH₂CH₃), 2.09-2.16 (m, 1H, H-2b), 2.16-2.26 (m, 1H, H-1), 2.67 (t, *J* = 7.5 Hz, 2H, CH₂), 2.91-3.05 (m, 2H, CH₂), 3.17-3.27 (m, 3H, CH₂, H-4), 3.72 (td, *J* = 4.5, 9.3, 10.2 Hz, 1H, H-3), 3.76-3.88 (m, 7H, H-2^L, H-2^F, H-4^F, H-3^G, H-5^G, H-6^G), 3.92 (dd, *J* = 3.4, 10.5 Hz, 1H, H-3^F), 4.00 (d, *J* = 3.2 Hz, 1H, H-4^G), 4.86-4.94 (m, 3H, CH₂, H-1^G), 4.96-5.04 (m, 2H, H-1^F, H-5^F), 5.15-5.29 (m, 1H, H-2^G), 7.28 (t, *J* = 7.7 Hz, 2H, C₆H₅), 7.46 (t, *J* = 7.3 Hz, 1H, C₆H₅), 7.94-7.99 (m, 3H, C₆H₅, H^T), 8.05 (d, *J* = 2.0 Hz, 1H, H^{naph}), 8.49 (d, *J* = 2.0 Hz, 1H, H^{naph}), 8.64 (d, *J* = 2.0 Hz, 1H, H^{naph}), 8.76 (d, *J* = 1.9 Hz, 1H, H^{naph}); ¹³C NMR (126 MHz, D₂O): δ = 9.48 (CH₃), 15.39 (C-6^F), 21.95 (CH₂), 24.83, 25.17, 25.59, 28.42, 30.64, 31.20, 32.87, 33.51, 34.68, 37.34, 38.44, 41.30, 42.85 (15C, C₇H₁₃^L, C-1, C-2, C-5, C-6, 4 CH₂), 46.49 (CH₂), 61.75 (C-6^G), 66.13 (C-4^G), 66.63 (C-5^F), 68.27 (C-2^F), 69.29 (C-3^F), 72.08, 72.26 (C-4^F, C-2^G), 74.22 (C-5^G), 78.88, 79.35 (C-3, C-2^L), 80.12 (C-4), 80.98 (C-3^G), 98.71 (C^T), 99.17 (C-1^F), 99.99 (C-1^G), 123.67, 124.75, 125.32, 126.38, 126.98, 128.63, 128.72, 129.68, 131.38, 131.52, 134.00, 135.11, 139.03, 139.79, 141.30, 147.69 (18C, Ar-C), 167.99, 171.70, 176.98, 182.71 (4 C=O).

EXAMPLE 2

SYNTHESIS OF SELETIN COMPOUND 17

[00100] Synthesis of compound 17:

[00101] According to the procedure for compound 15a, compound 16 (3.3 mg, 4.1 μ mol, synthesized as described by Egger et al., J. Am. Chem. Soc. 135:9820-9828, 2013) and compound 14a (3.4 mg, 6.2 μ mol) in the presence of cupric sulfate pentahydrate (0.25 mg, 1.0 μ mol) and L-(+)-ascorbic acid sodium salt (0.40 mg, 2.1 μ mol) to yield compound 17 (3.2 mg, 57%) as a white solid. $[\alpha]_D^{20}$ -16.5 (*c* 0.25, MeOH); ^1H NMR (500 MHz, D₂O): δ = 0.19-0.33, 0.37-0.49, 0.54-0.76, 0.92-1.04, 1.07-1.23, 1.31-1.43 (15H, C₇H₁₃^L, H-2a, H-6a), 1.06 (d, *J* = 6.5 Hz, 3H, CH₃), 1.30 (d, *J* = 6.5 Hz, 3H, H-6^F), 1.55 (d, *J* = 13.9 Hz, 1H, H-6b), 1.62 (m, 1H, H-5), 1.70 (tt, *J* = 4.3, 7.6 Hz, 2H, CH₂), 2.11 (m, 1H, H-2b), 2.24 (ddd, *J* = 3.8, 12.7, 16.5 Hz, 1H, H-1), 2.67 (dd, *J* = 6.9, 8.3 Hz, 2H, CH₂), 2.90-3.03 (m, 2H, CH₂), 3.12 (t, *J* = 9.7 Hz, 1H, H-4), 3.20 (dd, *J* = 5.3, 7.4 Hz, 2H, CH₂), 3.71 (ddd, *J* = 4.7, 9.3, 11.4 Hz, 1H, H-3), 3.77-3.85 (m, 6H, H-3^G, H-5^G, H-6^G, H-2^F, H-2^L), 3.86 (dd, *J* = 1.1, 3.5 Hz, 1H, H-4^F), 3.92 (dd, *J* = 3.4, 10.5 Hz, 1H, H-3^F), 4.00 (d, *J* = 3.2 Hz, 1H, H-4^G), 4.87 (d, *J* = 8.0 Hz, 1H, H-1^G), 4.88-4.93 (m, 2H, CH₂), 4.99 (m, 1H, H-5^F), 5.05 (d, *J* = 4.1 Hz, 1H, H-1^F), 5.21 (dd, *J* = 8.0, 9.7 Hz, 1H, H-2^G), 7.28 (t, *J* = 7.9 Hz, 2H, C₆H₅), 7.46 (m, 1H, C₆H₅), 7.88-8.02 (m, 3H, C₆H₅, H^T), 8.05 (d, *J* = 1.9 Hz, 1H, H^{naph}), 8.49 (d, *J* = 2.0 Hz, 1H, H^{naph}), 8.65 (d, *J* = 2.0 Hz, 1H, H^{naph}), 8.76 (d, *J* = 1.9 Hz, 1H, H^{naph}); ^{13}C NMR (126 MHz, D₂O): δ = 16.38 (C-6^F), 18.71 (CH₃), 22.95 (CH₂), 25.84, 26.18, 26.60, 29.41, 32.21, 33.88, 34.53, 35.72, 35.97, 38.01, 38.35, 39.43, 42.35, 42.54 (C₇H₁₃^L, 3 CH₂, C-1, C-2, C-5, C6), 47.50 (CH₂), 62.77 (C-6^G), 67.14 (C-4^G), 67.57 (C-5^F), 69.26 (C-2^F), 70.35 (C-3^F), 73.10, 73.29 (C-2^G, C-4^F), 75.23 (C-5^G), 79.89 (C-3), 80.09 (C-2^L), 81.98 (C-3^G), 83.58 (C-4), 99.85, 100.24 (3C, C-1^F, C-1^G, C^T), 124.68, 125.76, 126.32, 127.38, 127.99, 129.64, 129.73, 130.69, 132.38, 132.53, 136.12, 140.04, 140.80, 142.30, 148.69 (17C, Ar-C), 169.00, 172.70, 177.83, 183.72 (4 C=O).

EXAMPLE 3

SYNTHESIS OF COMPOUNDS 14a-c

[00102] Synthesis of compound 18: A mixture of 3-chloropropanoic acid (150 mg, 1.38 mmol) and NaN_3 (898 mg, 13.8 mmol) in water (3 mL) is stirred at reflux. After 22 hours, the reaction mixture is cooled to room temperature, acidified with aqueous HCl and extracted with diethyl ether. The organic layer is dried with Na_2SO_4 and evaporated to dryness to give 3-azidopropanoic acid, compound 18, (130 mg, 81%).

[00103] Synthesis of compound 14a: To a solution of compound 18 (16.0 mg, 0.139 mmol) in DMF (300 μL), DIPEA (40 μL) and COMU (71 mg, 0.167 mmol) are added successively at 0 °C. After 5 minutes, a pre-cooled (0 °C) mixture of sodium 8-aminonaphthalene-1,3,6-trisulfonate (19) (62.0 mg, 0.146 mmol) and DIPEA (40 μL) in DMF (300 μL) is added dropwise. After 1 hour at 0 °C, the reaction mixture is stirred for additional 21 hours at room temperature. Evaporation of the solvent and purification by chromatography on silica gel (DCM/MeOH/water, 10:5:1) yields compound 14a (48 mg, 64%) as a DIPEA complex. ^1H NMR (500 MHz, CD_3OD): δ = 1.25-1.33 (m, 30H, 10 $\text{CH}_3^{\text{DIPEA}}$), 2.85 (t, J = 6.7 Hz, 2H, CH_2), 3.12 (q, J = 7.4 Hz, 4H, 2 $\text{CH}_2^{\text{DIPEA}}$), 3.63 (h, J = 6.6 Hz, 4H, 4 CH^{DIPEA}), 3.72 (t, J = 6.7 Hz, 2H), 8.28 (d, J = 1.9 Hz, 1H, H^{naph}), 8.48 (d, J = 2.0 Hz, 1H, H^{naph}), 8.57 (d, J = 1.9 Hz, 1H, H^{naph}), 8.95 (d, J = 2.0 Hz, 1H, H^{naph}), 11.74 (s, 1H, NH); ^{13}C NMR (126 MHz, CD_3OD): δ = 11.81, 15.89, 17.35 (10C, $\text{CH}_3^{\text{DIPEA}}$), 35.95 (CH_2), 42.45 ($\text{CH}_2^{\text{DIPEA}}$), 47.04 (CH^{DIPEA}), 54.47 (CH_2), 122.70, 123.88, 123.91, 126.96, 129.81, 133.14, 134.91, 140.87, 141.74, 143.24 (10C, C^{naph}), 170.23 (C=O).

[00104] Synthesis of compound 20: To a solution of 4-chlorobutyric acid (17.6 μL , 0.178 mmol) in DMF (500 μL) at 0 °C, DIPEA (93.0 μL , 0.535 mmol) and COMU (91.0 mg, 0.214 mmol) are added successively. After 5 minutes, a pre-cooled (0 °C) mixture of compound 19 (80.0 mg, 0.187 mmol) and DIPEA (93.0 μL , 0.535 mmol) in DMF (500 μL) is added dropwise. After 1 hour at 0 °C, stirring is continued for additional 65 hours at room temperature. Evaporation of the solvent and purification of the residue by chromatography on silica gel (DCM/MeOH/water, 10:6:1.2) yields compound 20 (41 mg, 48 %) as a di-DIPEA complex. ^1H NMR (500 MHz, CD_3OD): δ = 1.26-1.33 (m, 30H, 10 $\text{CH}_3^{\text{DIPEA}}$), 2.23 (h, J = 6.3, 7.0 Hz, 2H, CH_2), 2.73 (t, J = 7.4 Hz, 2H, CH_2), 3.13 (q, J = 7.4 Hz, 4H, 2 $\text{CH}_2^{\text{DIPEA}}$), 3.63 (p, J = 6.6 Hz, 4H, 4 CH^{DIPEA}), 3.70 (t, J = 6.7 Hz, 2H, CH_2), 8.28 (d, J = 1.9 Hz 1H, H^{naph}), 8.47 (d, J = 1.9 Hz, 1H,

H^{naph}), 8.54 (d, $J = 1.9$ Hz, 1H, H^{naph}), 8.95 (d, $J = 1.9$ Hz, 1H, H^{naph}), 11.66 (s, 1H, NH); ¹³C NMR (126 MHz, CD₃OD): $\delta = 13.24, 17.32, 18.78$ (10C, CH₃^{DIPEA}), 29.71, 35.26 (CH₂), 43.87 (CH₂^{DIPEA}), 45.33 (CH₂), 55.89 (CH₂^{DIPEA}), 124.22, 125.30, 125.39, 128.34, 131.29, 134.70, 136.36, 142.26, 143.07, 144.58 (10C, C^{naph}), 173.74 (C=O).

[00105] Synthesis of compound 14b: A mixture of compound 20 (41 mg, 0.084 mmol) and NaN₃ (54 mg, 0.84 mmol) in water (1.5 mL) is stirred at reflux. After 18 hours, the reaction is cooled and lyophilized. Purification by chromatography on RP-18 (H₂O/MeOH, 4:1) gives compound 14b (12 mg, 29%) as a di-DIPEA complex. ¹H NMR (500 MHz, D₂O): $\delta = 1.23$ -1.35 (m, 30H, 10 CH₃^{DIPEA}), 2.03 (p, $J = 6.9$ Hz, 2H, CH₂), 2.68 (t, $J = 7.6$ Hz, 2H, CH₂), 3.13 (q, $J = 7.4$ Hz, 4H, 2 CH₂^{DIPEA}), 3.64 (h, $J = 6.6$ Hz, 4H, 4 CH^{DIPEA}), 3.75 (t, $J = 6.5$ Hz, 2H, CH₂), 8.24 (d, $J = 1.9$ Hz, 1H, H^{naph}), 8.50 (d, $J = 2.0$ Hz, 1H, H^{naph}), 8.69 (d, $J = 2.0$ Hz, 1H, H^{naph}), 8.80 (d, $J = 2.0$ Hz, 1H, H^{naph}); ¹³C NMR (126 MHz, D₂O): $\delta = 12.08, 16.18, 17.66$ (10C, CH₃^{DIPEA}), 27.38, 33.10 (2 CH₂), 42.49 (CH₂^{DIPEA}), 54.32 (CH^{DIPEA}), 61.06 (CH₂), 125.12, 125.66, 126.24, 126.98, 131.66, 132.03, 135.10, 139.07, 139.61, 141.11 (10C, C^{naph}), 175.60 (C=O).

[00106] Synthesis of compound 14c: To a solution of 5-azidopentanoic acid (60.0 mg, 0.419 mmol) in dry DCM (500 μ L), 1-chloro-N,N,2-trimethylpropenylamine (67.0 μ L, 0.475 mmol) is added via syringe at room temperature under argon. After 5 hours, the reaction mixture is added to a pre-stirred mixture of compound 19 (119 mg, 0.279 mmol) and DMAP (10 mg) in pyridine (750 μ L) at room temperature. After 65 hours, the solvents are removed in vacuo. Purification of the residue by chromatography on silica gel (DCM/MeOH/water, 10:6:1.2) yields compound 14c (42 mg, 26%) as a white solid. ¹H NMR (500 MHz, CD₃OD): $\delta = 1.73$ (dq, $J = 6.8, 9.9$ Hz, 2H, CH₂), 1.86 (dq, $J = 6.1, 7.7, 8.7$ Hz, 2H, CH₂), 2.62 (t, $J = 7.5$ Hz, 2H, CH₂), 3.38 (t, $J = 6.8$ Hz, 2H, CH₂), 8.30 (d, $J = 1.9, 1.1$ Hz, H^{naph}), 8.50 (d, $J = 1.9$ Hz, 1H, H^{naph}), 8.52 (d, $J = 1.8$ Hz, 1H, H^{naph}), 8.95 (d, $J = 1.9$ Hz, 1H, H^{naph}); ¹³C NMR (126 MHz, CD₃OD): $\delta = 23.66, 29.54, 37.31, 52.29$ (4 CH₂), 124.13, 125.51, 128.33, 131.51, 134.40, 136.32, 141.98 (10C, C^{naph}).

EXAMPLE 4

AFFINITY ASSAY FOR E-SELECTIN ANTAGONIST

[00107] For E-selectin, a construct consisting of the lectin domain, the EGF like domain, and the first two short consensus repeats (E-selectinLEC2) was labeled using the amine reactive protein labeling kit BLUE-NHS from NanoTemper Technologies GmbH (Munich, Germany).

[00108] The Microscale Thermophoresis (MST) experiments were carried out in a HEPES buffer adjusted to pH 7.4 containing 150 mM NaCl, 1 mM CaCl₂ and 0.05% Tween 20 at a temperature of 25° C with 50% LED power, 50% laser power, laser on time of 30 seconds, and laser off time of 5 seconds with standard treated capillaries. A fixed concentration of the labeled E-selectin_{LEC2} protein was incubated for 20 minutes with a 15-datapoint linear 1:1 dilution of ligand starting about 30 times above the expected K_D. The observed data points were fitted using the single-site binding function of Alan Cooper, *Tutorial Chemistry Texts, Vol 16: Biophysical Chemistry*; Royal Society of Chemistry: Cambridge, 2004.

Binding Affinity (K_D) of sLe^x and Test Compounds to E-Selectin Determined by MST

Compound	sLe ^x	15a	15b	15c	17
K _D	687 μM	1.5 μM	0.97 μM	1.2 μM	3 μM

EXAMPLE 5

AFFINITY ASSAY FOR P-SELECTIN ANTAGONISTS

[00109] The cell-free P-selectin ligand binding assay was adapted from Weitz-Schmidt *et al* (G. Weitz-Schmidt, D. Stokmaier, G. Scheel, N. E. Nifant'ev, A. B. Tuzikov, N. V. Bovin, *Anal Biochem* **1996**, 238, 184-190). A MaxiSorp 96-well flat bottom microtiter plate purchased from Nalge Nunc International (Penfield, NY, USA) was coated with P-selectin/IgG by incubation with 100 μL/well of the purified protein at a concentration of 3 μg/ml in 10 mM HEPES-NaOH pH 7.4, 150 mM NaCl, 1 mM CaCl₂ (HAB-Ca⁺). After an overnight incubation at 4°C, the plate was washed three times with HAB-Ca⁺ followed by a 2 hour incubation with 200 μL/well of a solution of 3% BSA in HAB-Ca⁺ at room temperature to block nonspecific binding. During this incubation, inhibitory test compounds, diluted in HAB-Ca⁺, were titrated by a twofold serial and mixed with an equal volume of 0.2 μg/ml of a preformed complex of a biotinylated sialyl Lewis^a polyacrylamide polymer (sLe^a-PAA) purchased from GlycoTech Inc. (Gaithersburg, MD, USA) and horseradish peroxidase-labeled streptavidin (streptavidin-POD) purchased from Roche (Rotkreuz, Switzerland). After blocking, the microtiter plate was washed three times with HAB-Ca⁺ and 100 μL/well of the inhibitor dilution series premixed with sLe^a-PAA streptavidin-POD complex was transferred to the different wells of the plate. The binding reaction was allowed to proceed at 25°C. After 2 hours, the plate was washed twice with HAB-Ca⁺, and 100 μL/well of ABTS (2,2'-azino-bis[3-ethylbenzthiazoline-6-sulfonic acid]) substrate reagent purchased from

Invitrogen (Paisley, UK) was added to each well. Adding 100 μ L/well of 2% oxalic acid stopped the colorimetric reaction was after 5 minutes. The optical density was determined at 450 nm (SpectraMax). The concentration of antagonist required to inhibit binding by 50% was determined and is reported as the IC₅₀ value.

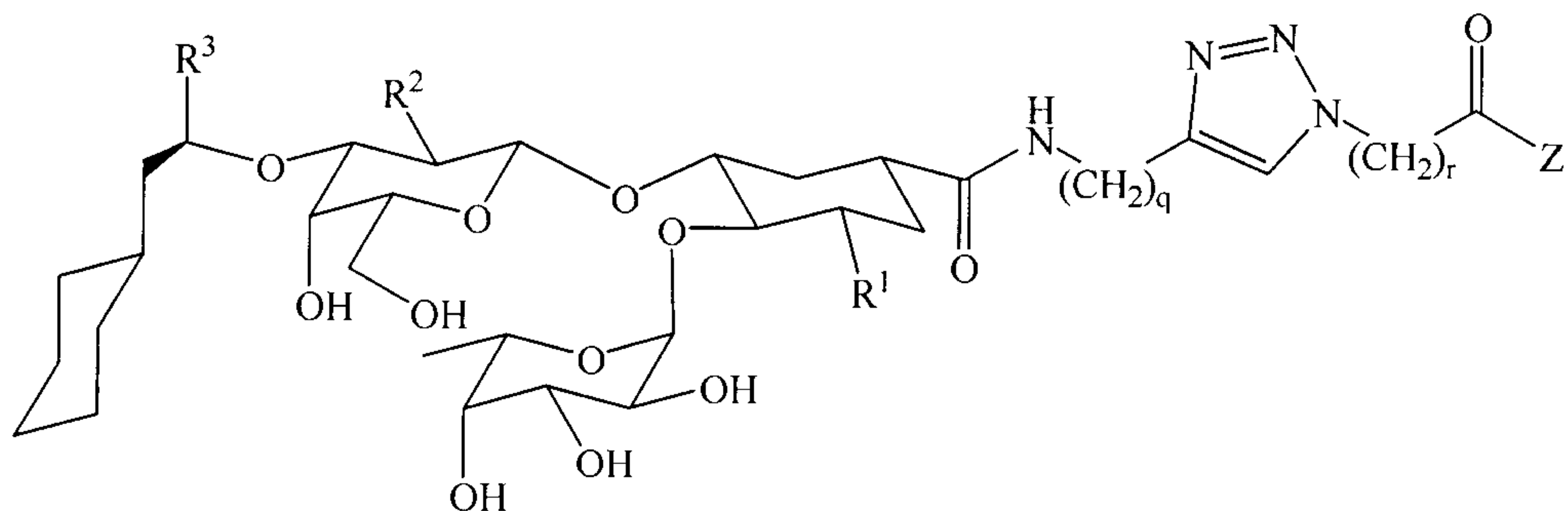
**Binding Affinity (IC) sLe^x and Test Compounds to P-Selectin
Determined by Competitive Binding Assay**

Compound	sLe ^x	15a	15b	15c	17
IC ₅₀	>7 mM	94 μ M	82 μ M	210 μ M	185 μ M

[00110] The various embodiments described above can be combined to provide further embodiments. All U.S. patents, U.S. patent application publications, U.S. patent applications, non-U.S. patents, non-U.S. patent applications, and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary, to employ concepts of the various patents, applications, and publications to provide yet further embodiments.

What is claimed is:

1. A compound chosen from compounds of Formula (Ia):

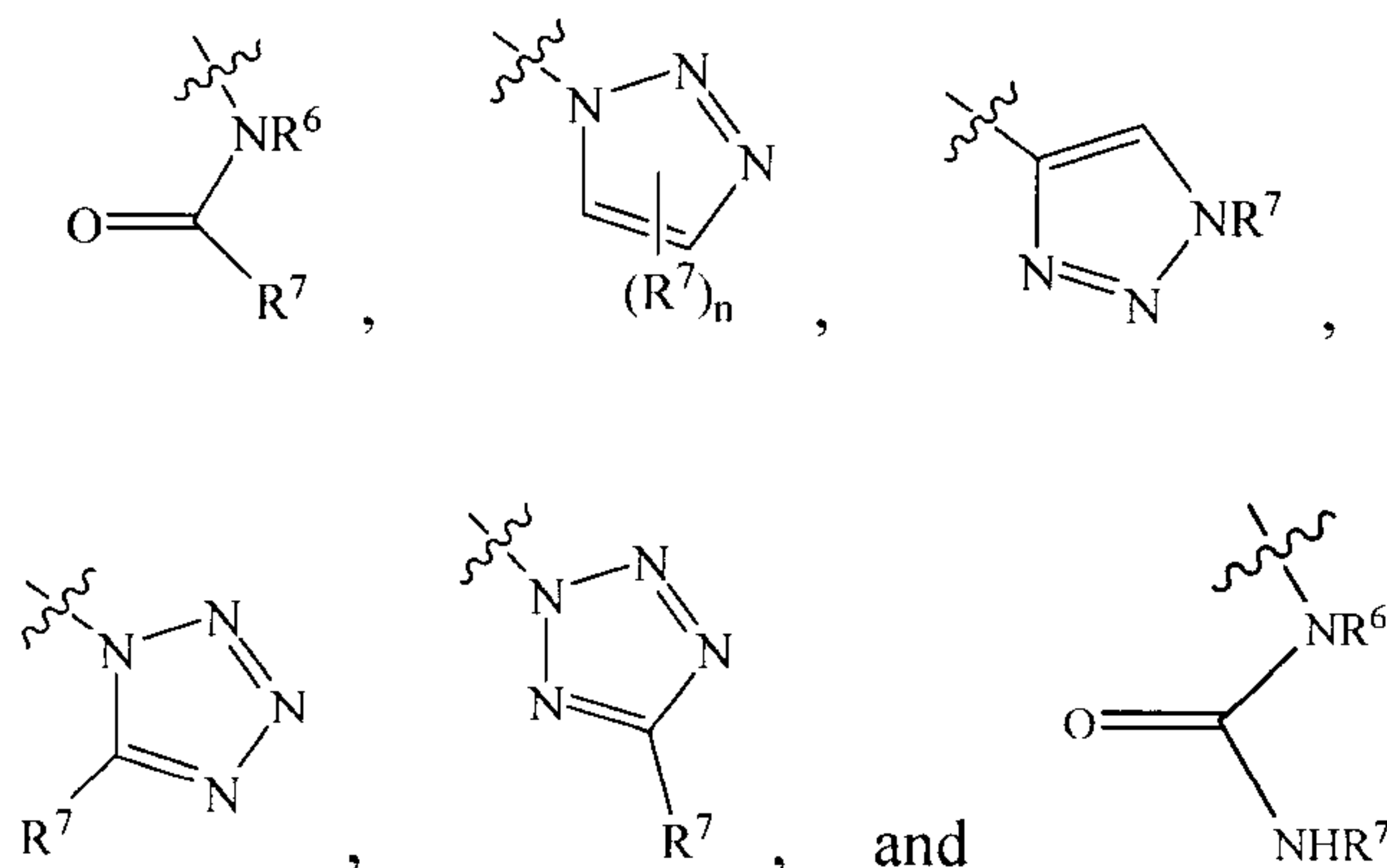


(Ia),

and pharmaceutically acceptable salts thereof,

wherein:

R^1 is chosen from H, C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl



groups;

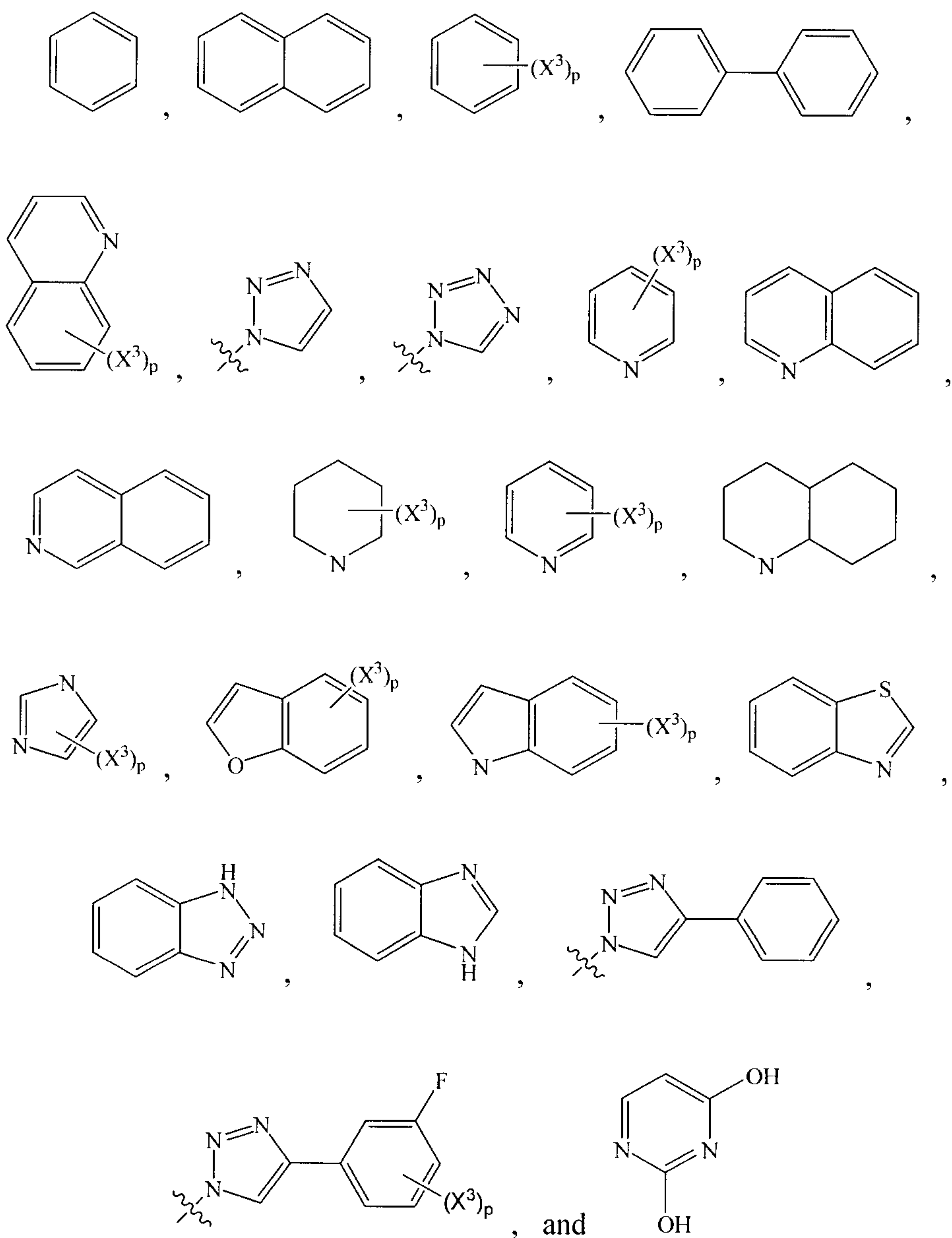
R^2 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl, $-OH$, $-OX^1$, halo, $-NH_2$, $-OC(=O)X^1$, $-NHC(=O)X^1$, and $-NHC(=O)NHX^1$ groups, wherein X^1 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{4-16} cycloalkylalkyl, C_{2-12} heterocyclyl, C_{6-18} aryl, and C_{1-13} heteroaryl groups;

R^3 is chosen from $-CN$, $-CH_2CN$, and $-C(=O)X^2$ groups, wherein X^2 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, $-OY^2$, $-NHOH$, $-NHOCH_3$, $-NHCN$, and $-NY^2Y^3$ groups, wherein Y^2 and Y^3 , which may be identical or different, are independently chosen from H, C_{1-8}

alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, and C₄₋₁₆ cycloalkylalkyl groups, wherein Y² and Y³ may join together to form a ring;

R⁶ is chosen from H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₄₋₁₆ cycloalkylalkyl, and -C(=O)R⁷ groups;

each R⁷ is independently chosen from H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₄₋₁₆ cycloalkylalkyl,



groups, wherein each X³ is independently chosen from H, -OH, Cl, F, N₃, -NH₂, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₆₋₁₄ aryl, -OC₁₋₈ alkyl, -OC₂₋₈ alkenyl, -OC₂₋₈ alkynyl, and -OC₆₋₁₄ aryl groups, wherein any of the above ring compounds may be substituted with one to three groups

independently chosen from Cl, F, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₆₋₁₄ aryl, and -OY⁴ groups, wherein Y⁴ is chosen from H, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, and C₆₋₁₄ aryl groups;

n is chosen from integers ranging from 0 to 2;

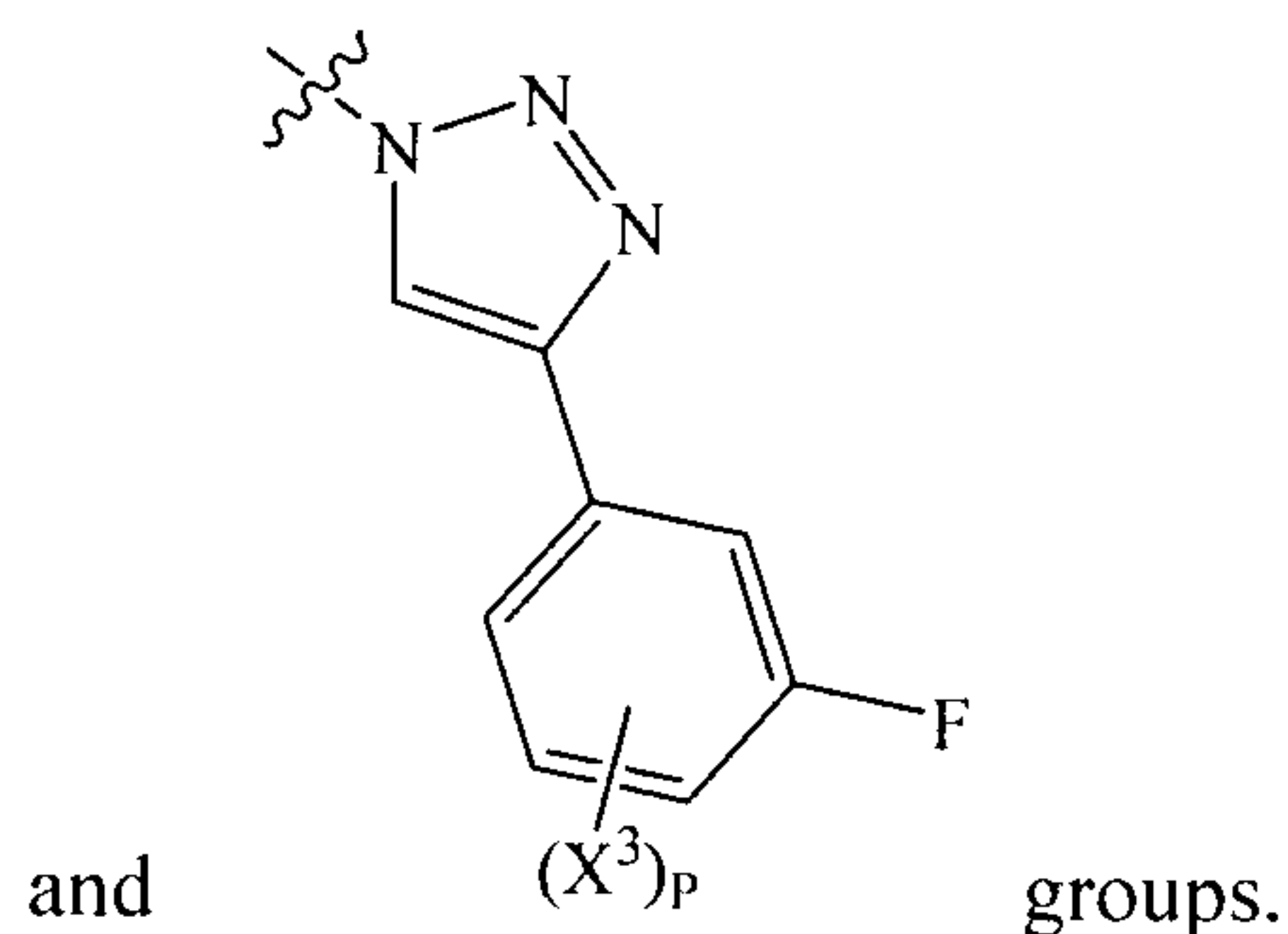
p is chosen from integers ranging from 0 to 3;

q is chosen from integers ranging from 1 to 10;

r is chosen from integers ranging from 1 to 10; and

Z is chosen from BASA groups.

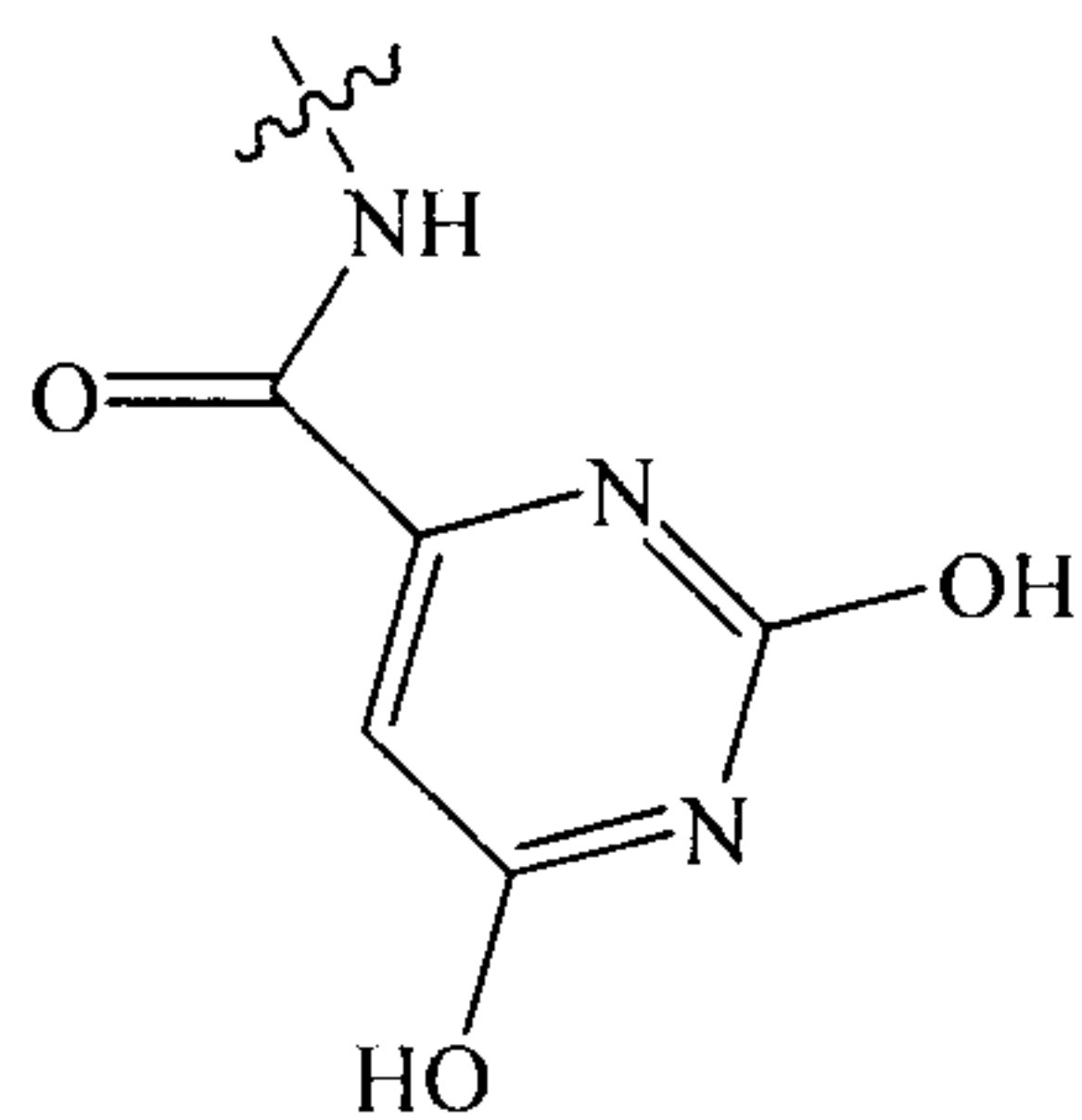
2. The compound according to claim 1, wherein R¹ is chosen from methyl, ethyl,



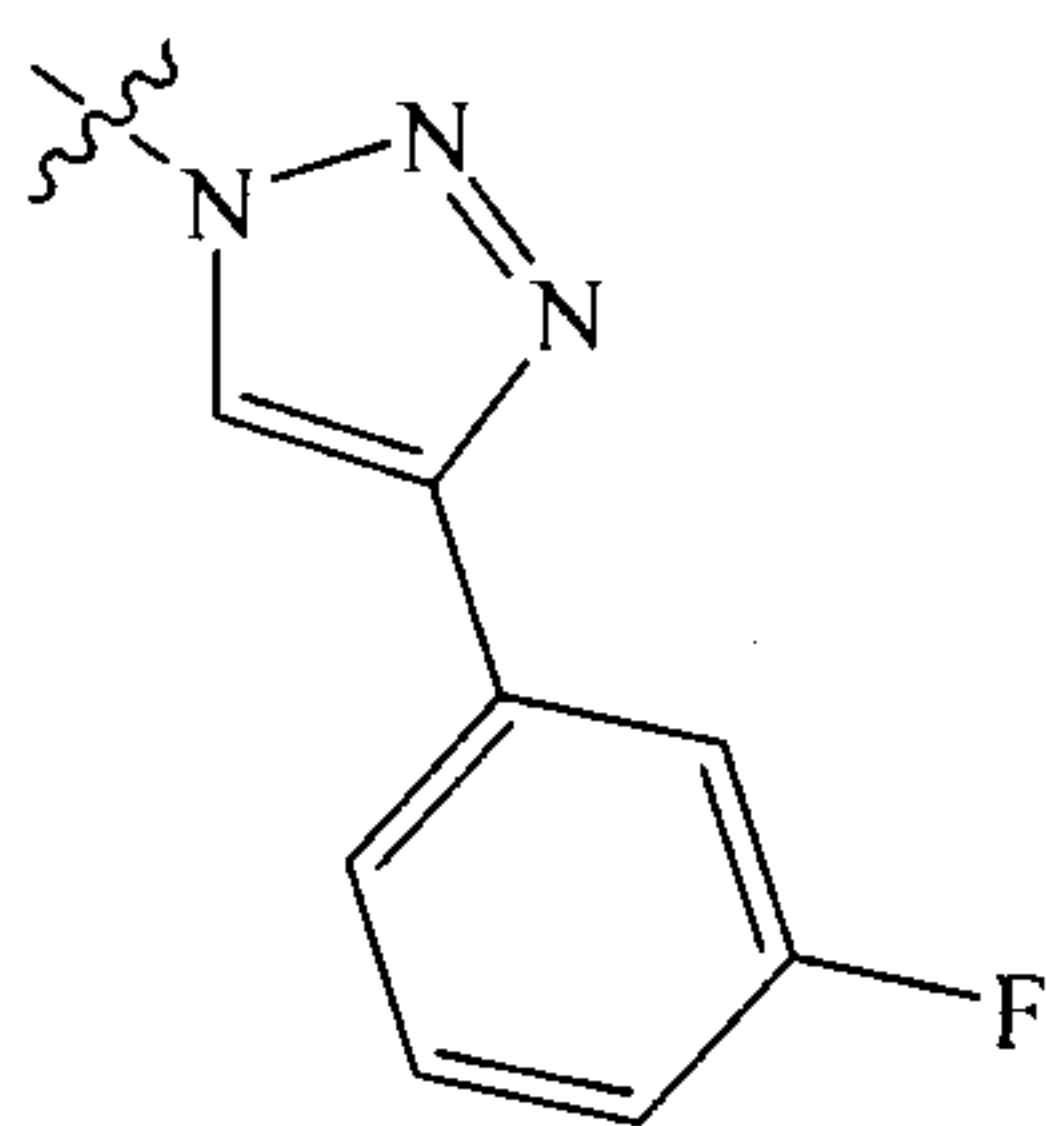
3. The compound according to claim 1 or 2, wherein R¹ is methyl.

4. The compound according to claim 1 or 2, wherein R¹ is ethyl.

5. The compound according to claim 1 or 2, wherein R¹ is

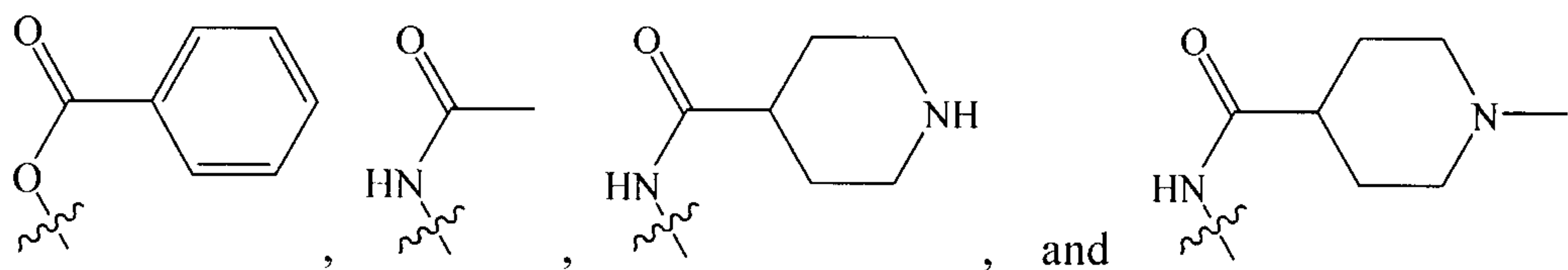


6. The compound according to claim 1 or 2, wherein R¹ is

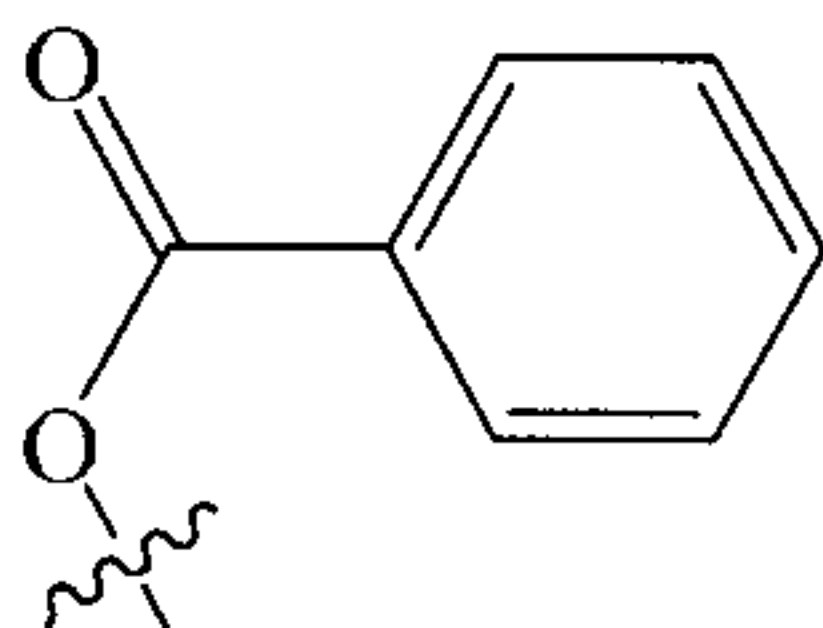


7. The compound according to any one of claims 1-6, wherein R^2 is chosen from $-OC(=O)X^1$, $-NHC(=O)X^1$, and $-NHC(=O)NHX^1$ groups, wherein X^1 is chosen from C_{1-8} alkyl, C_{2-12} heterocyclyl, C_{6-18} aryl, and C_{1-13} heteroaryl groups.

8. The compound according to any one of claims 1-6, wherein R^2 is chosen from



9. The compound according to claim 8, wherein R^2 is



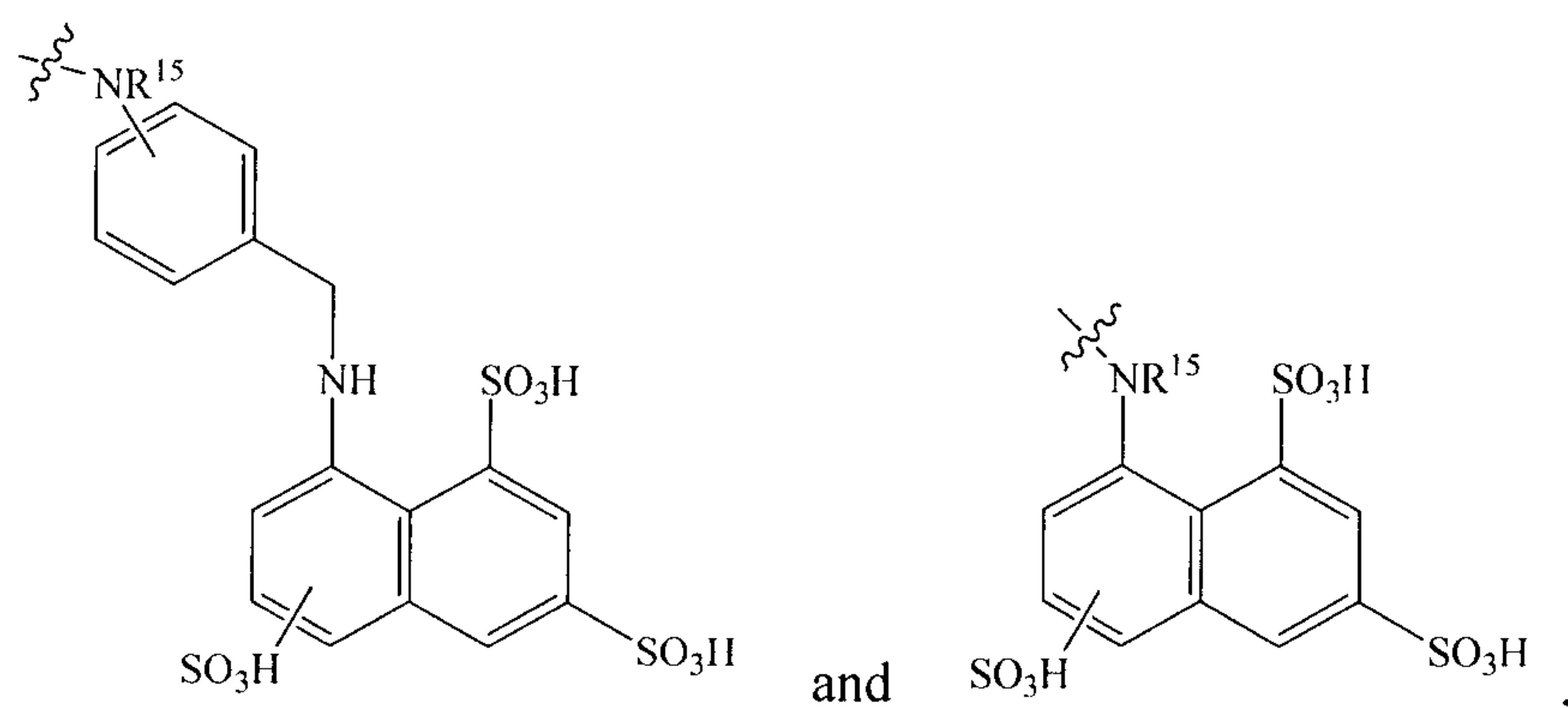
10. The compound according to any one of claims 1-9, wherein R^3 is chosen from $-C(=O)X^2$ groups, wherein X^2 is chosen from $-OY^2$, $-NHOH$, $-NHOCH_3$, and $-NY^2Y^3$ groups, wherein Y^2 and Y^3 , which may be identical or different, are independently chosen from H and C_{1-8} alkyl, wherein Y^2 and Y^3 may joint together to form a ring.

11. The compound according to claim 10, wherein R^3 is $-C(=O)OH$.

12. The compound according to any one of claims 1-11, wherein R^6 is H.

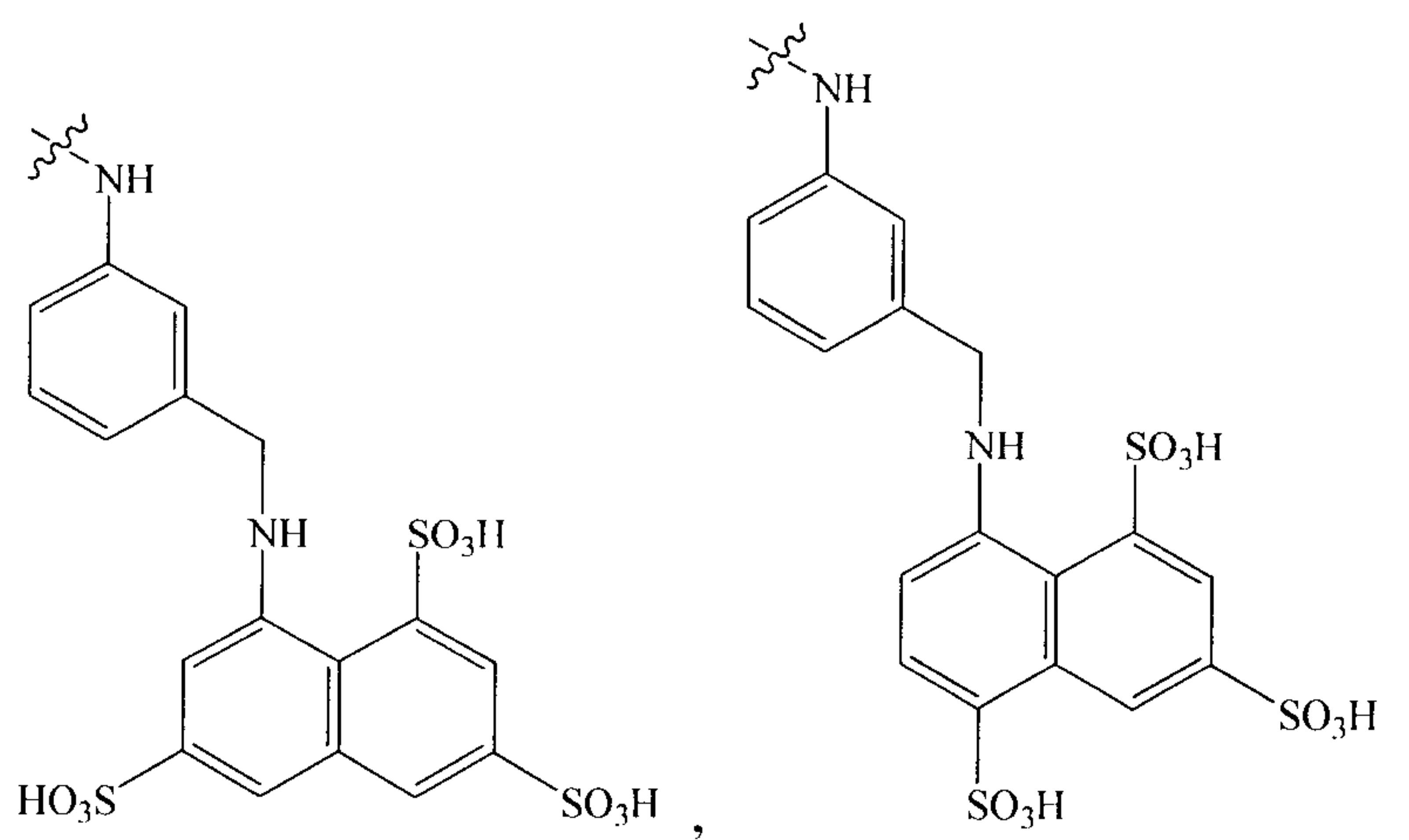
13. The compound according to any one of claims 1-12, wherein q is chosen from integers ranging from 2 to 4.

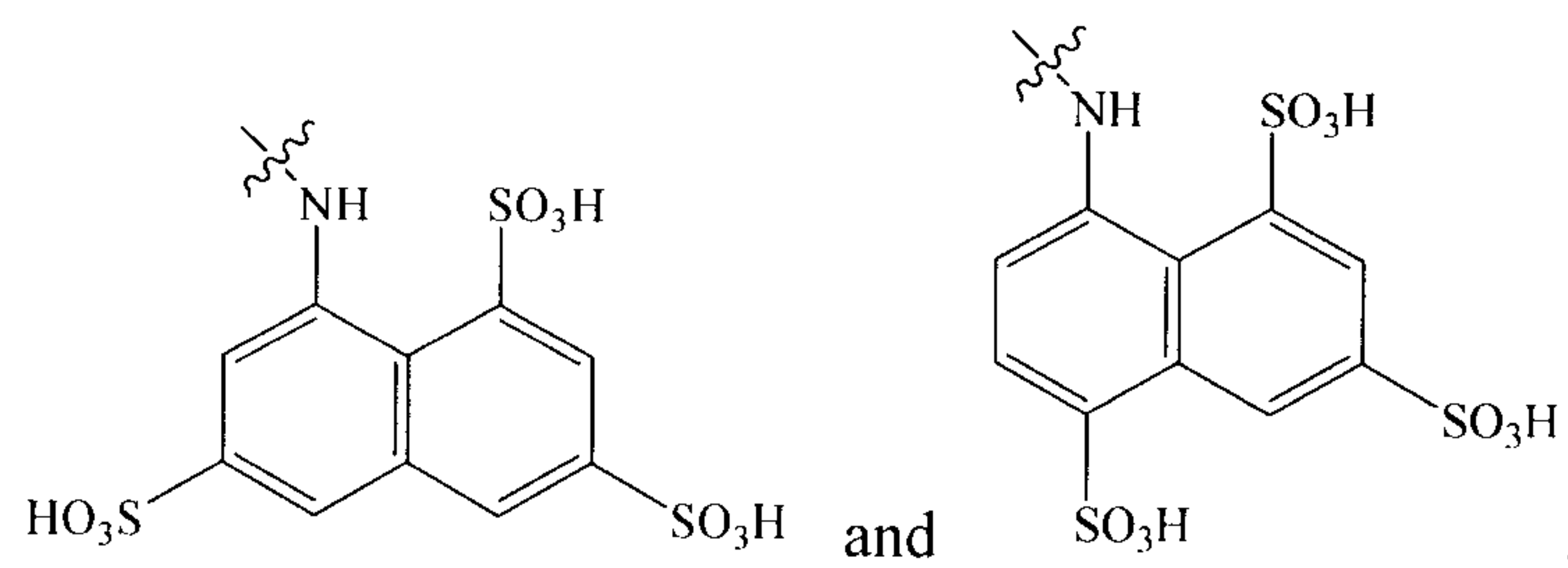
14. The compound according to claim 13, wherein q is 3.
15. The compound according to any one of claims 1 to 14, wherein r is 2.
16. The compound according to any one of claims 1-14, wherein r is 3.
17. The compound according to any one of claims 1-14, wherein r is 4.
18. The compound according to any one of claims 1-17, wherein Z is chosen from



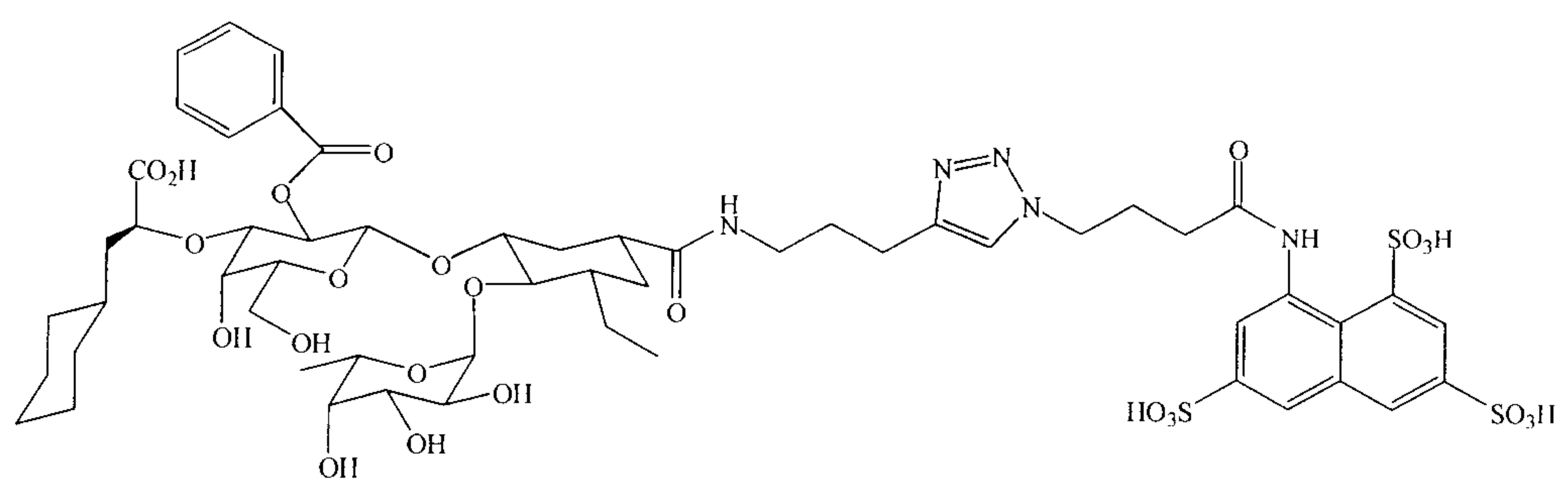
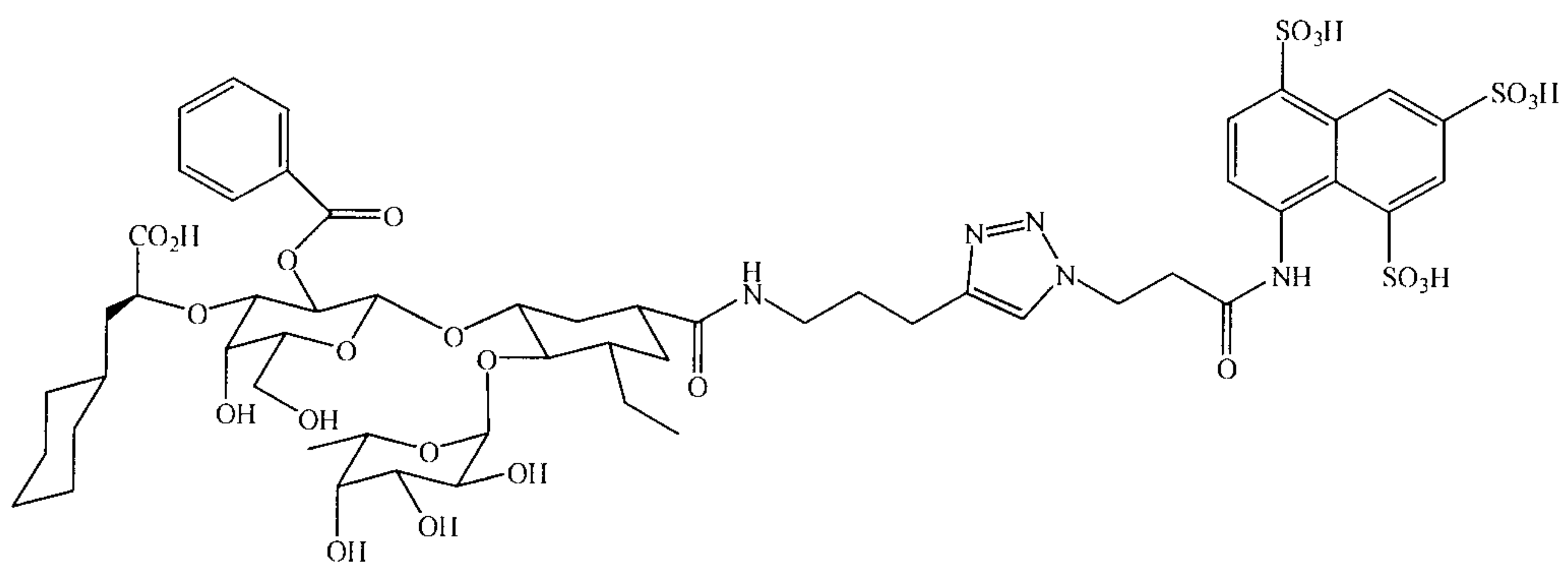
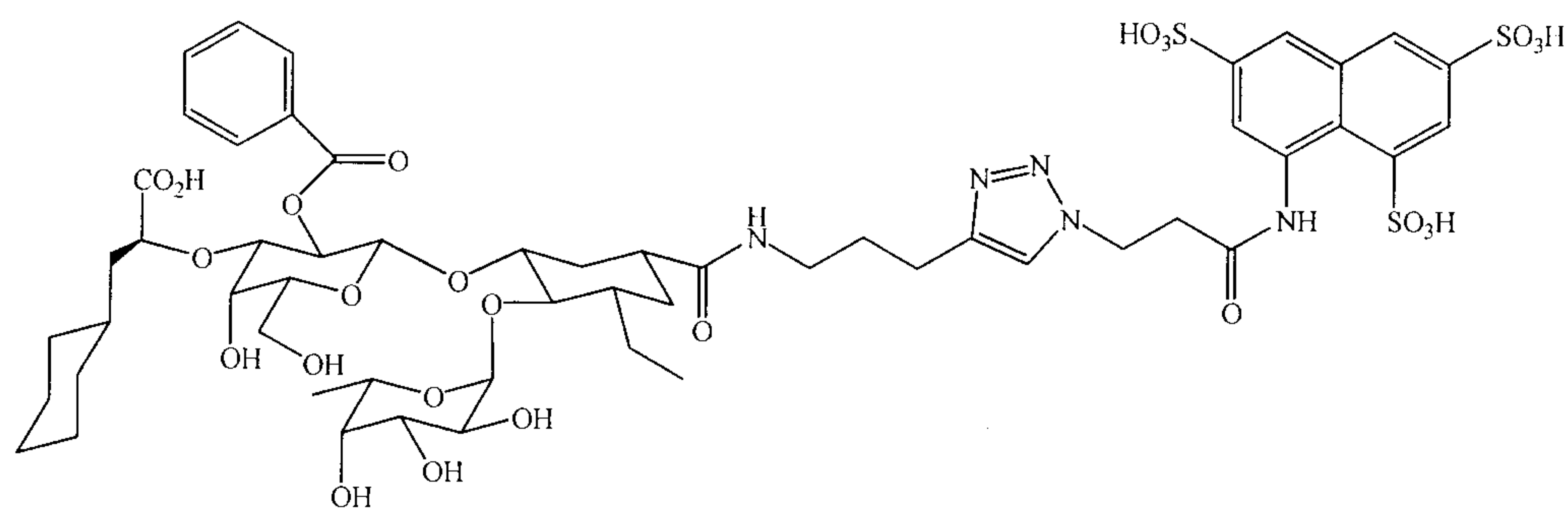
wherein R^{15} is chosen from H, C_{1-8} alkyl, $-C(=O)X^5$, and $-C(=O)NHX^5$ groups, wherein X^5 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{6-18} aryl, and C_{1-13} heteroaryl groups.

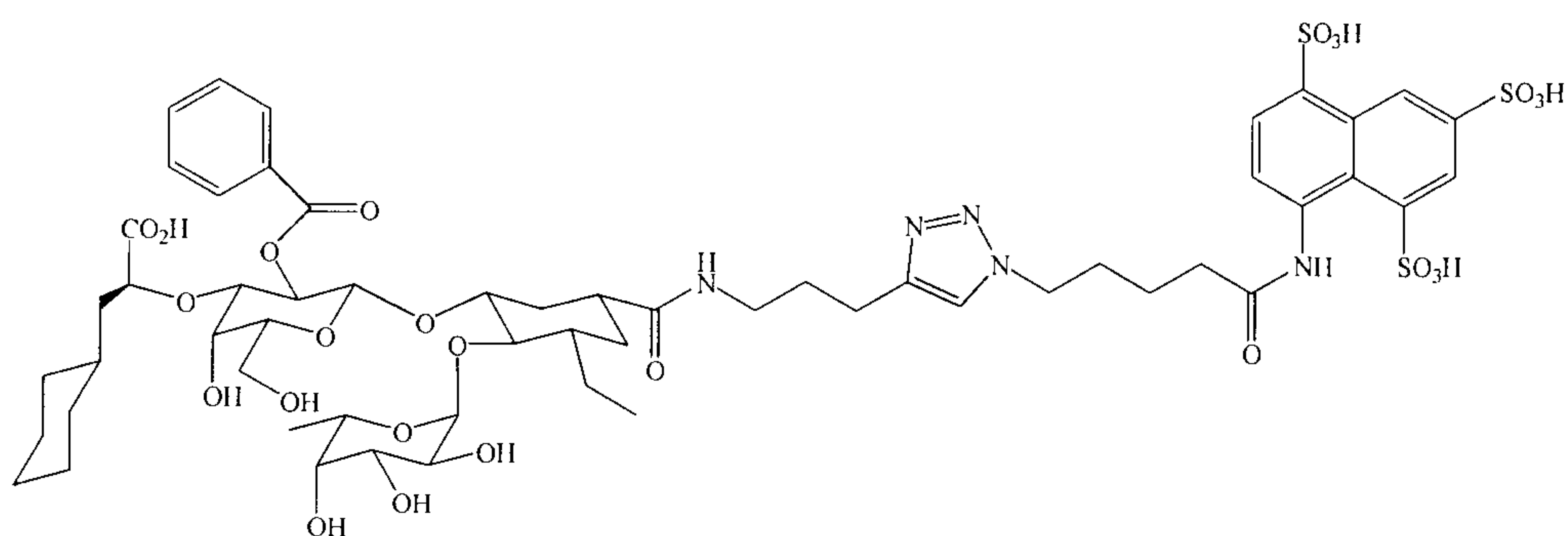
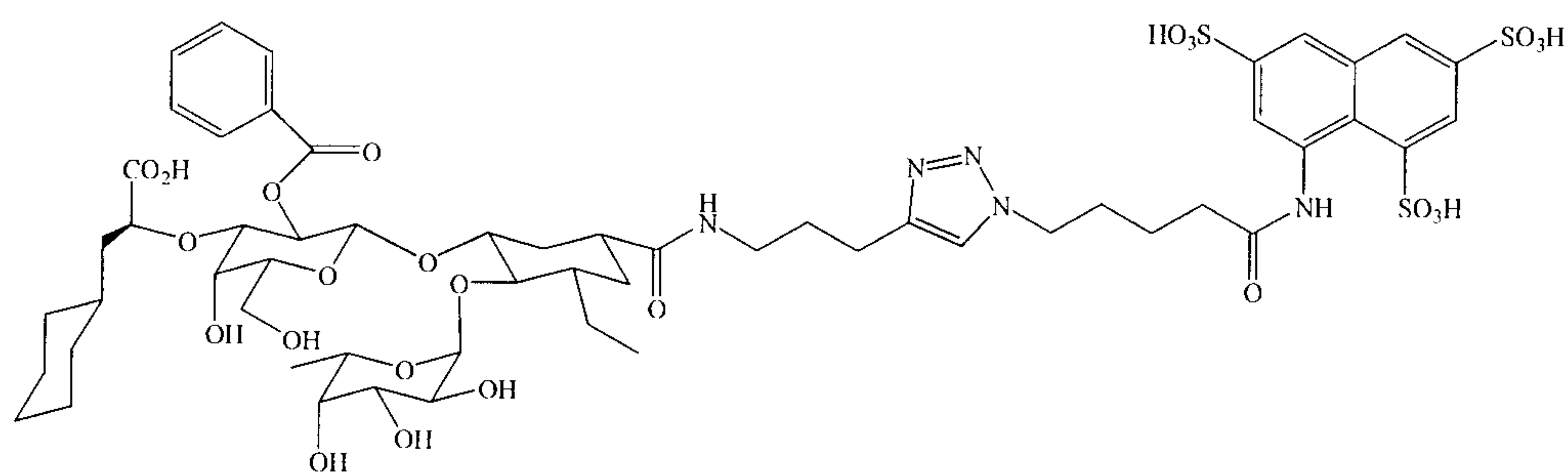
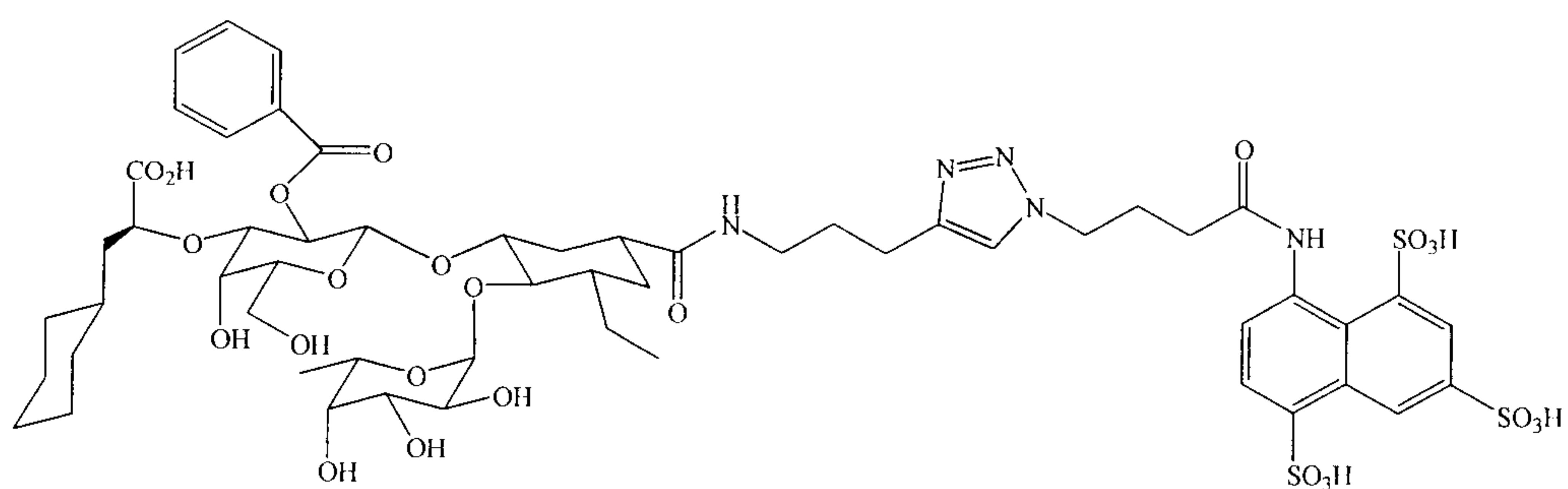
19. The compound according to claim 17, wherein Z is chosen from





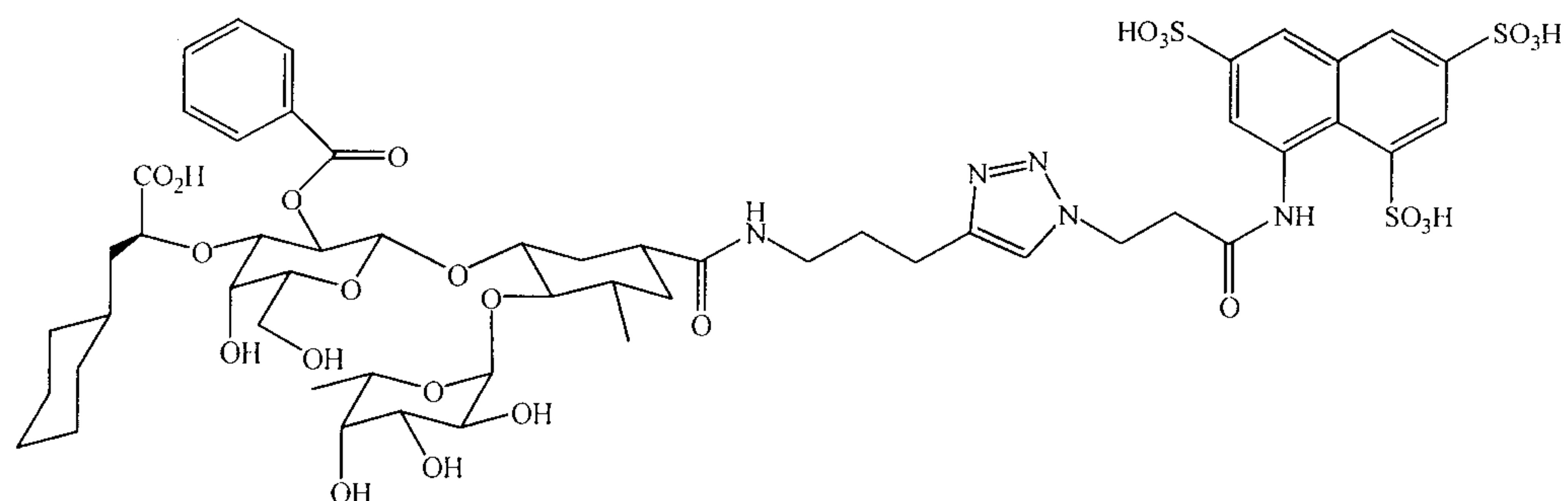
20. The compound according to claim 1, wherein the compound is chosen from

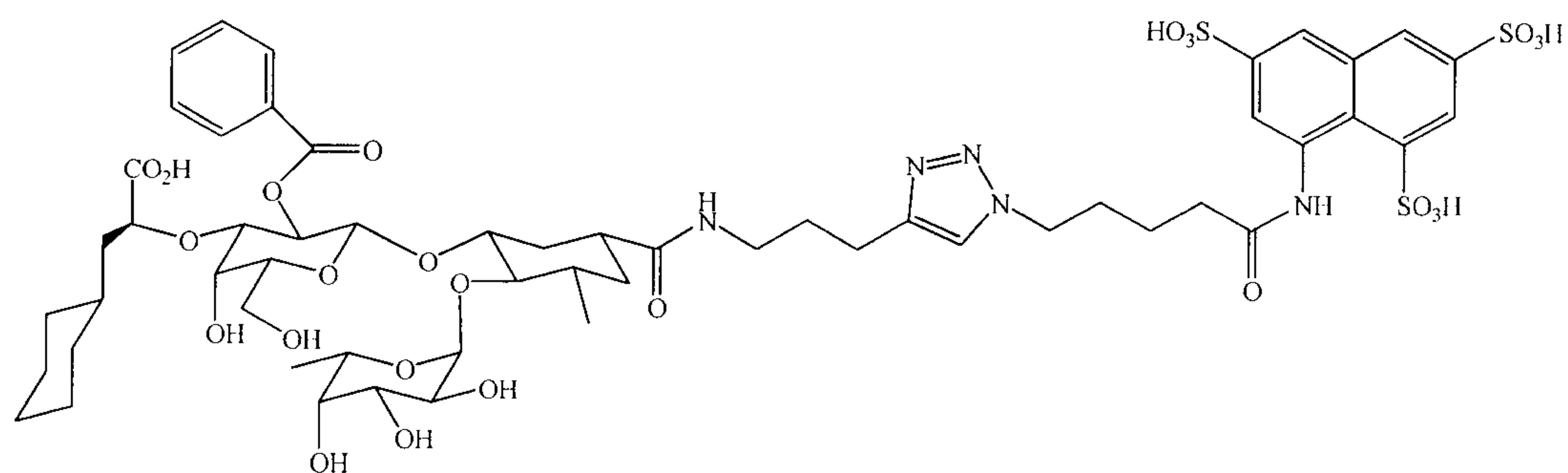
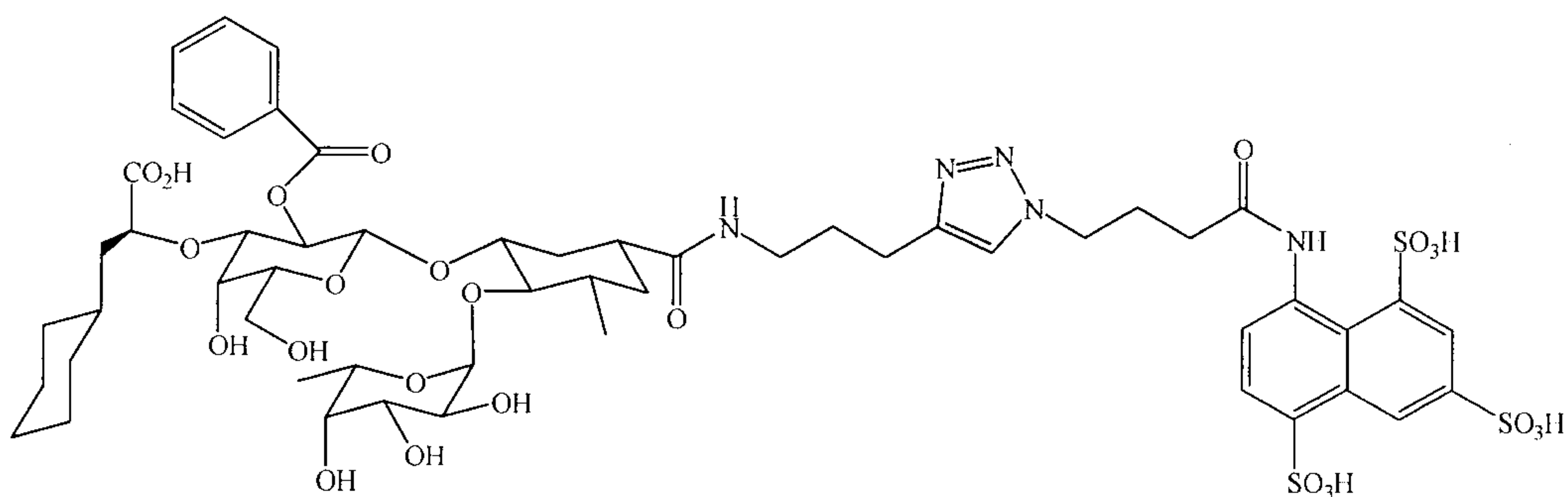
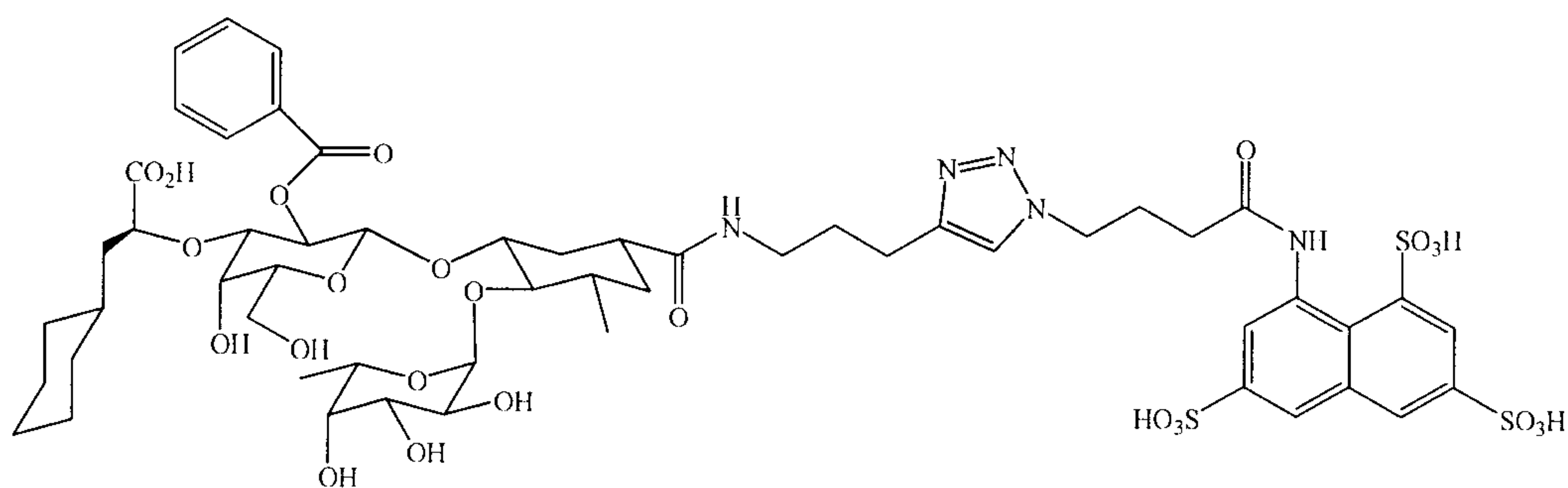
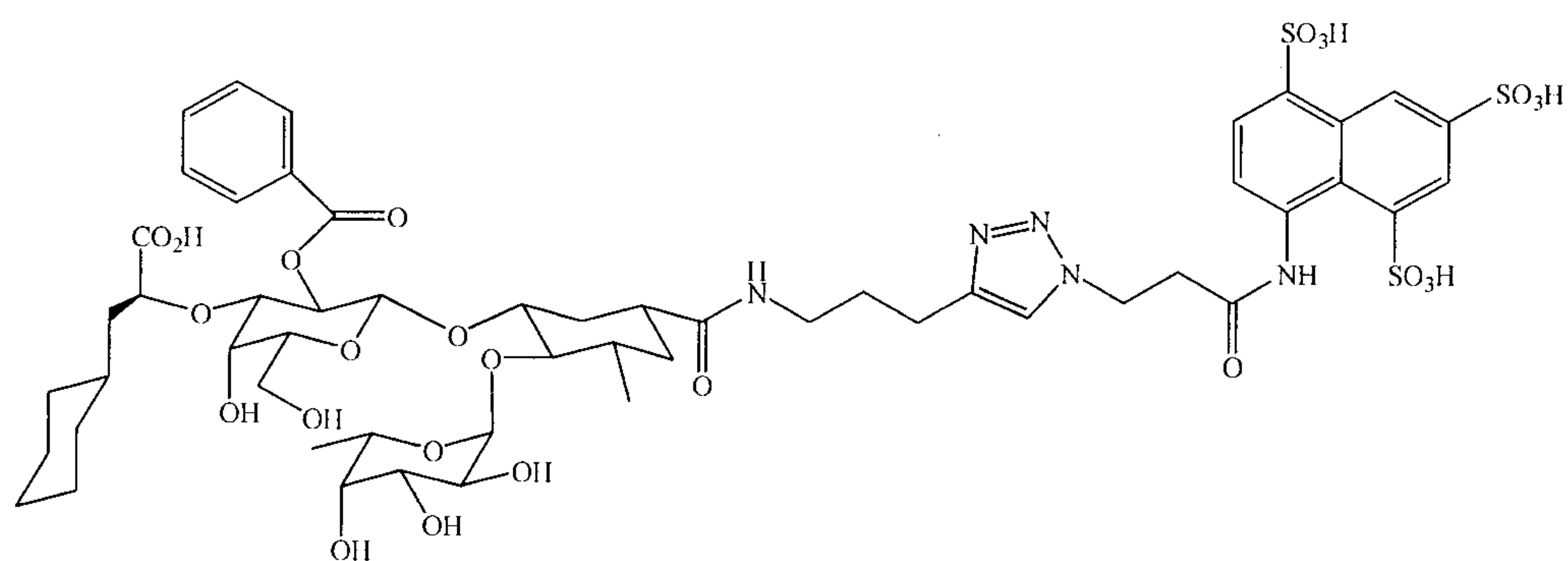


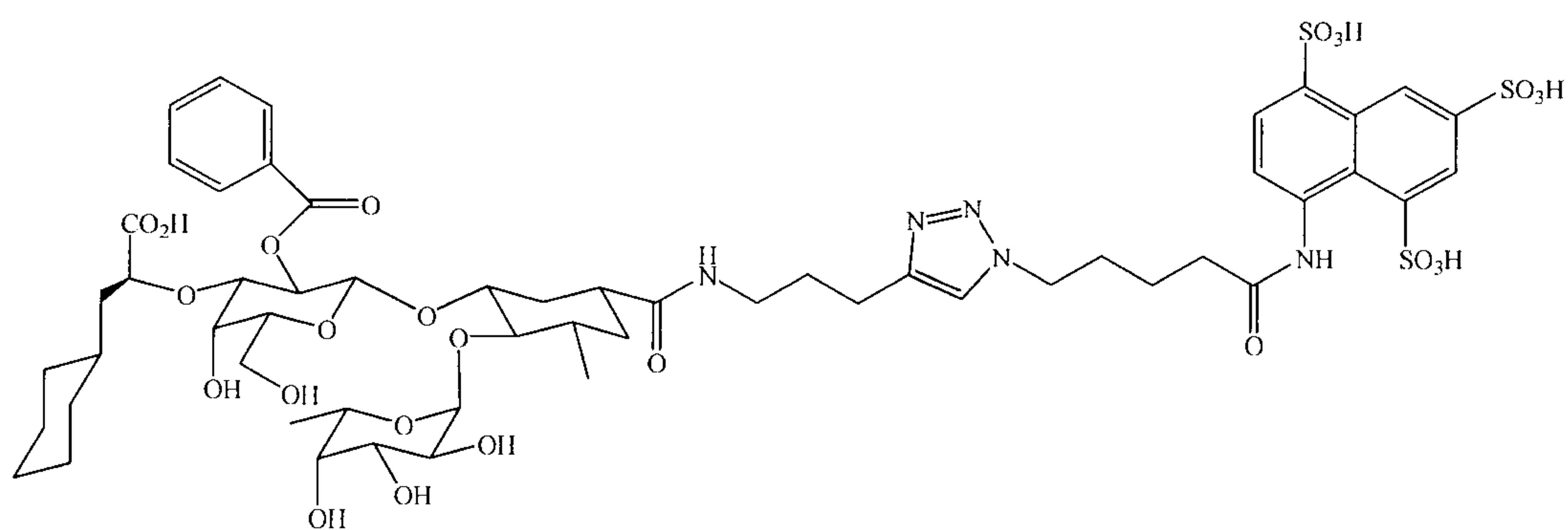


pharmaceutically acceptable salts thereof.

21. The compound according to claim 1, wherein the compound is chosen from



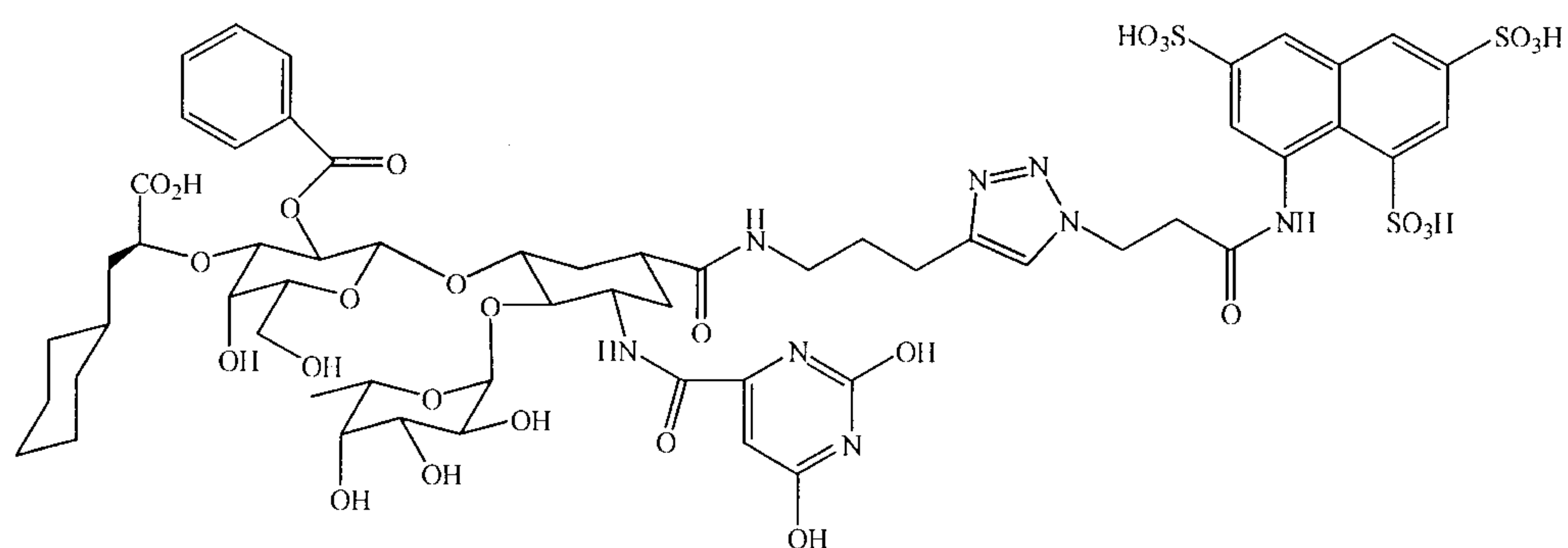




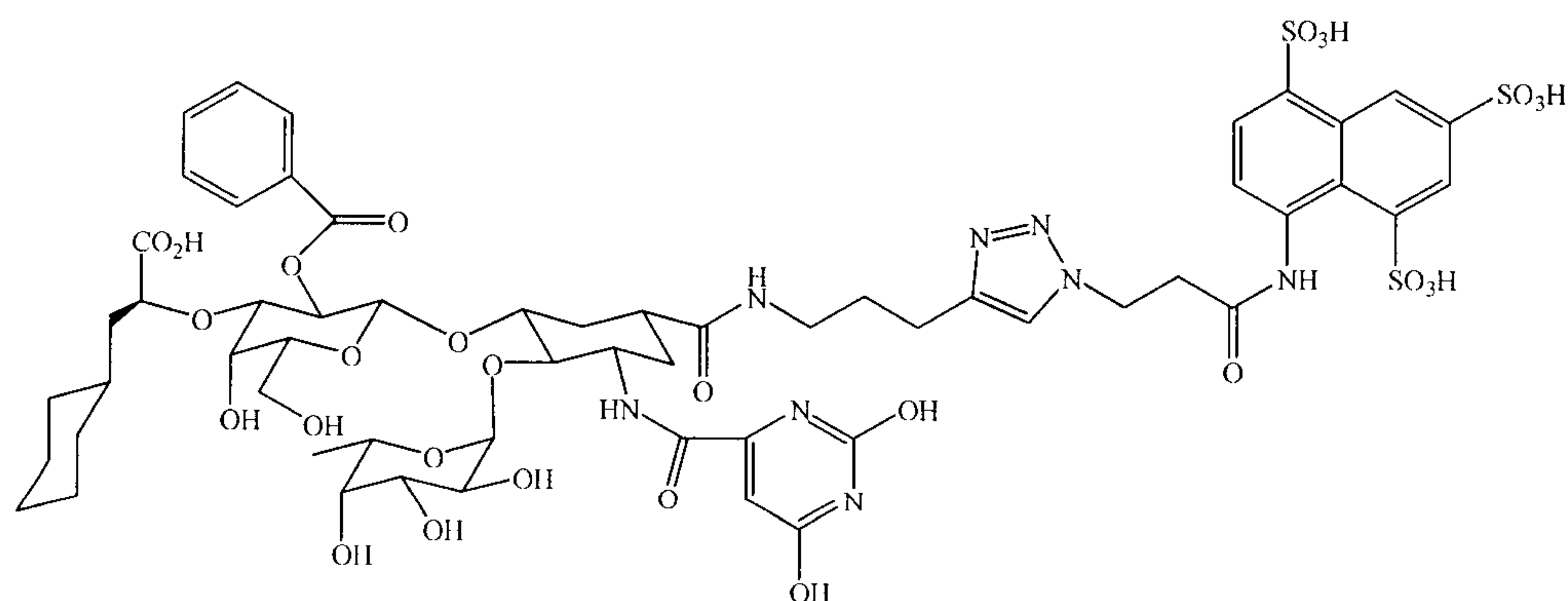
, and

pharmaceutically acceptable salts thereof.

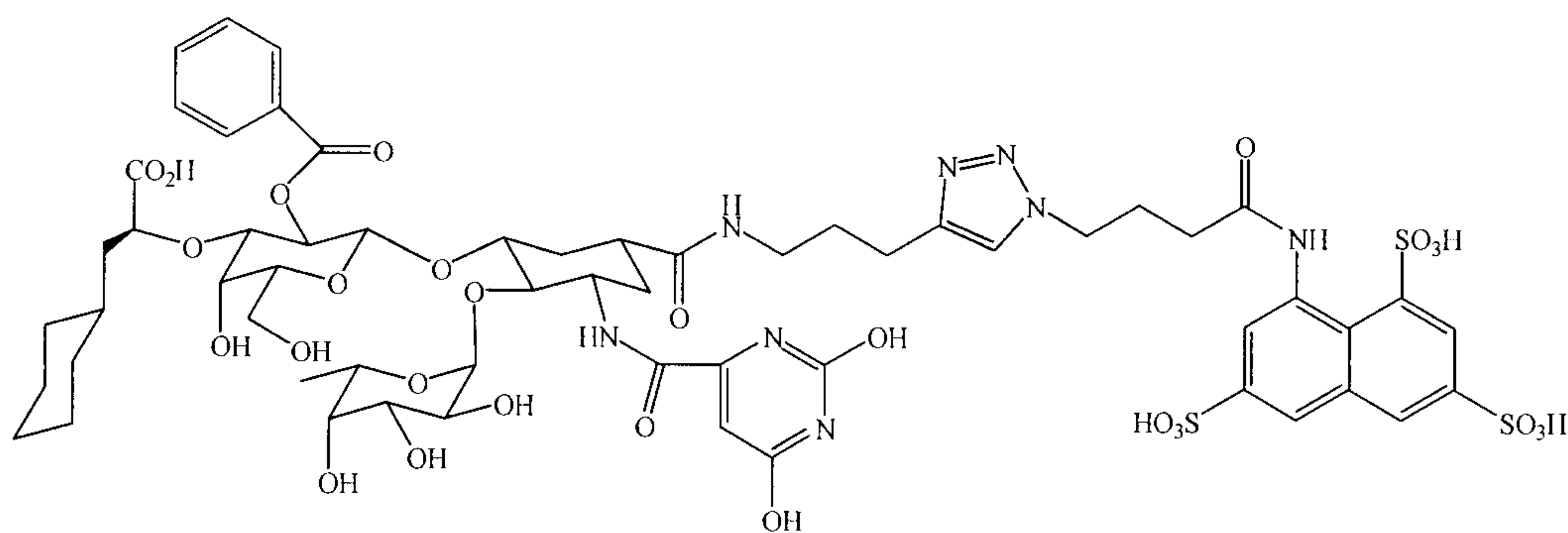
22. The compound according to claim 1, wherein the compound is chosen from



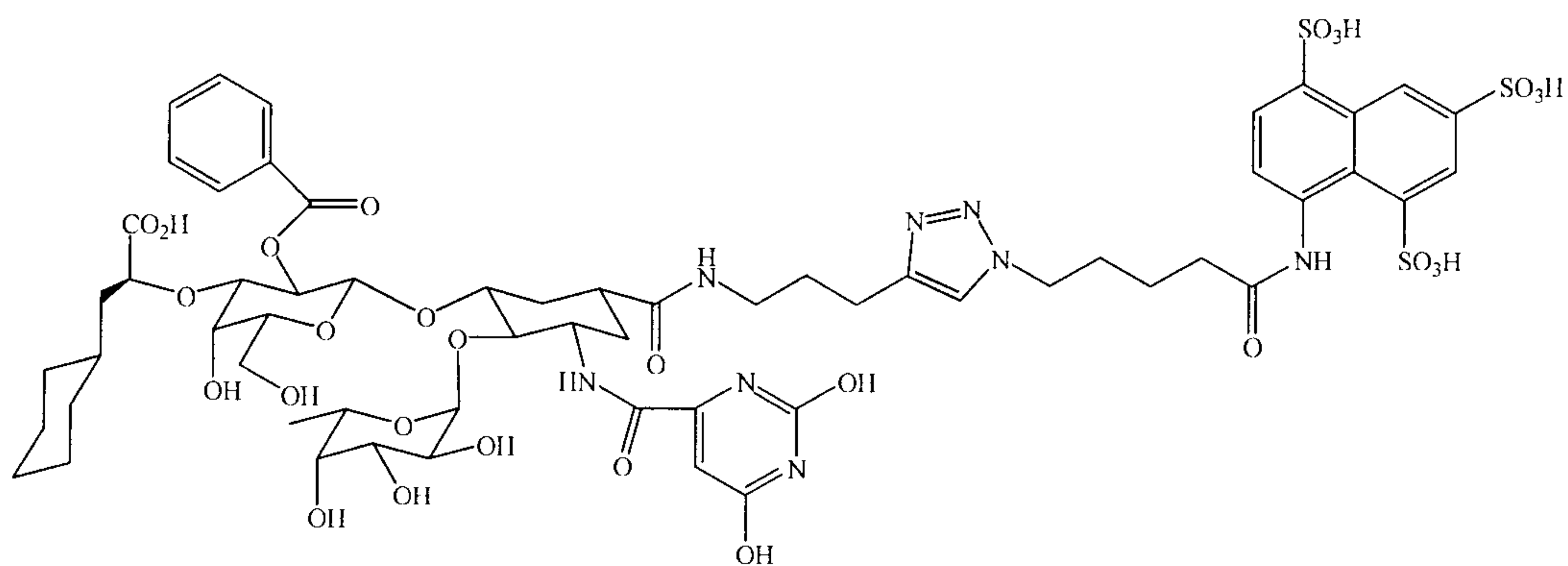
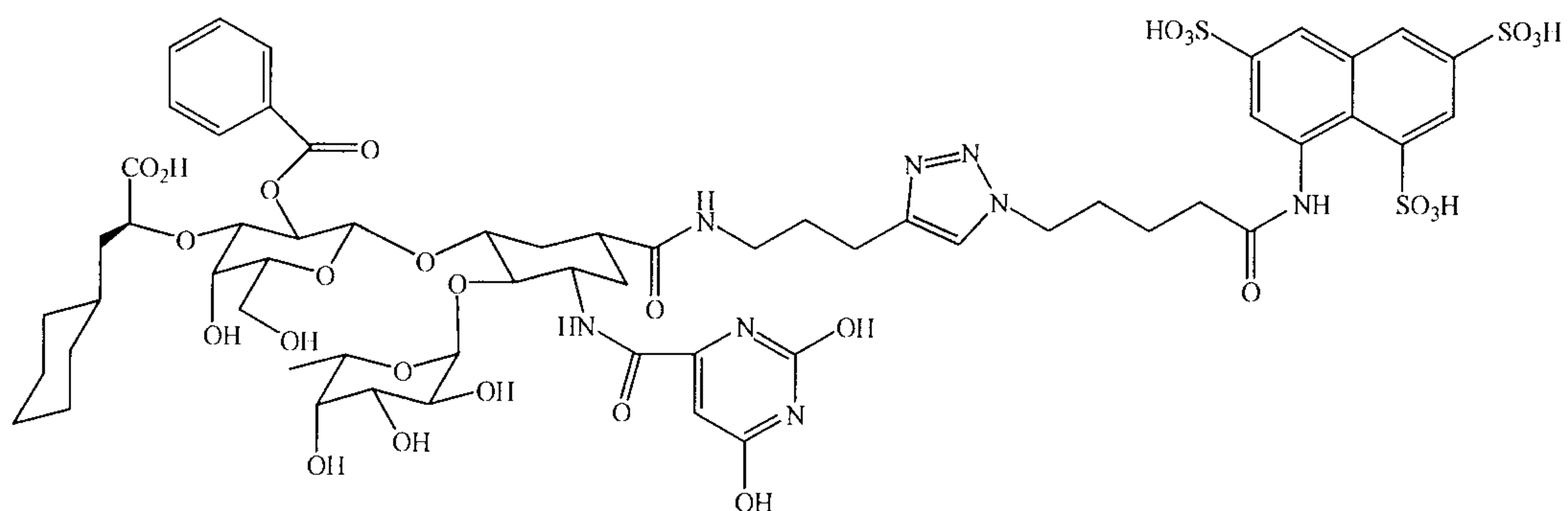
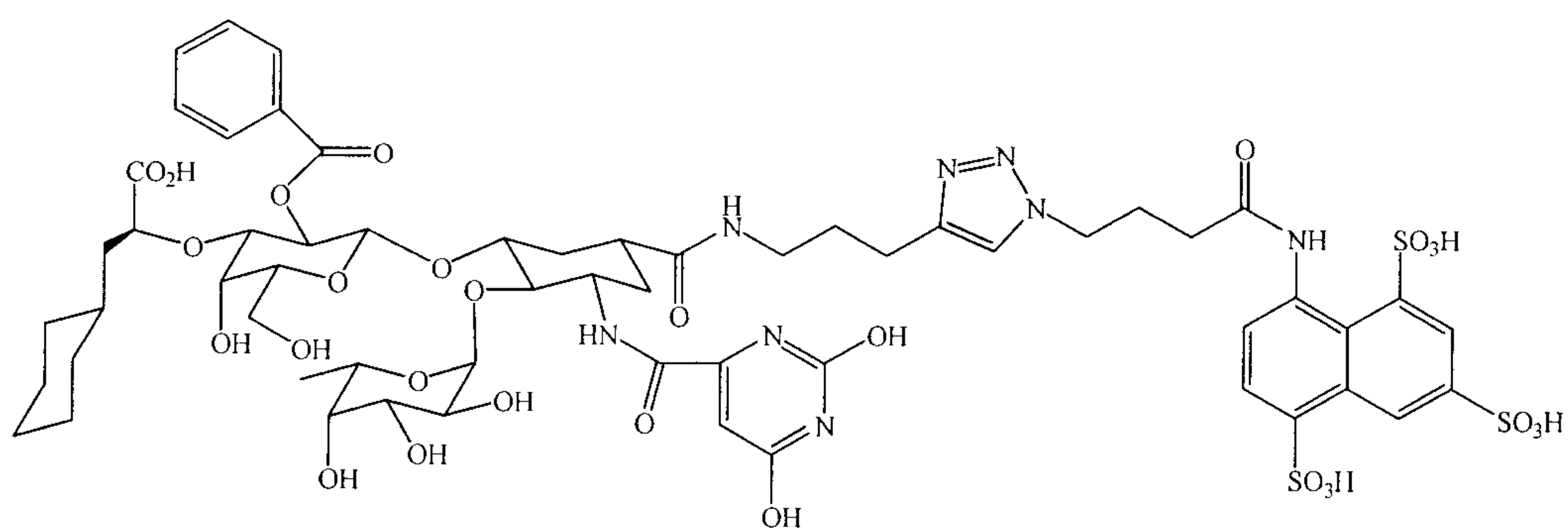
,



,

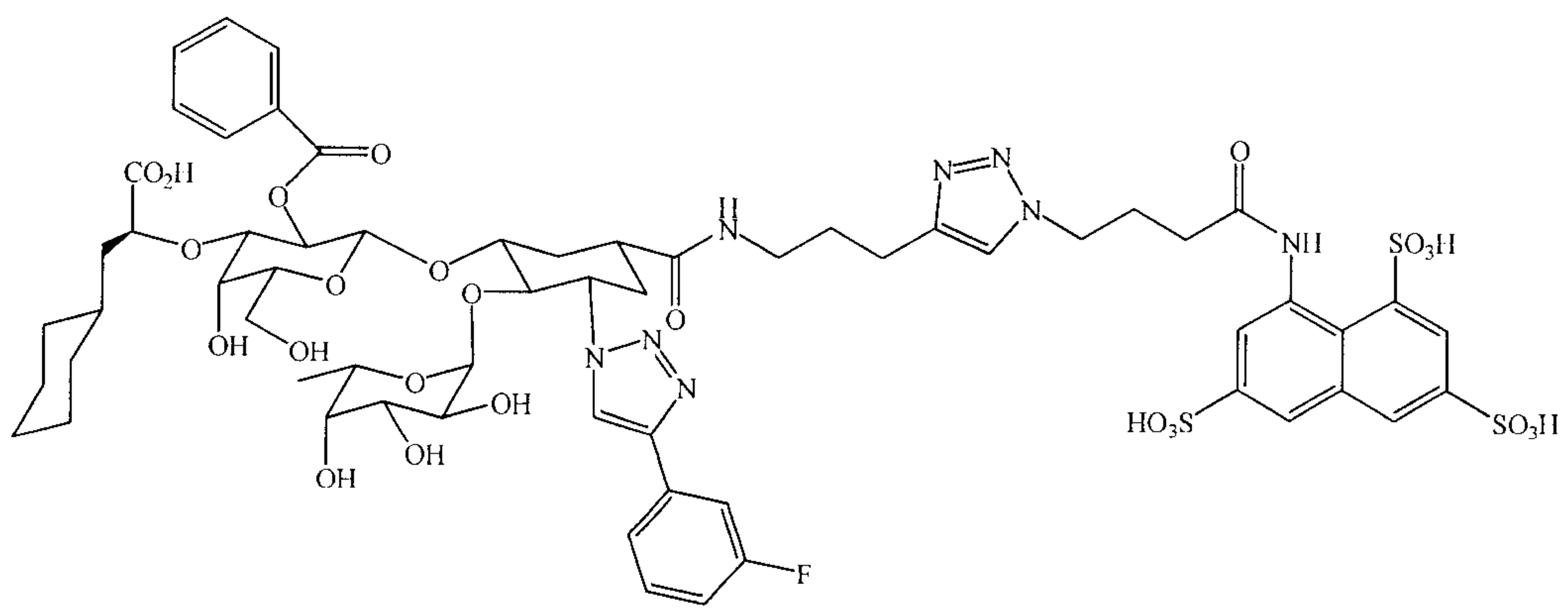
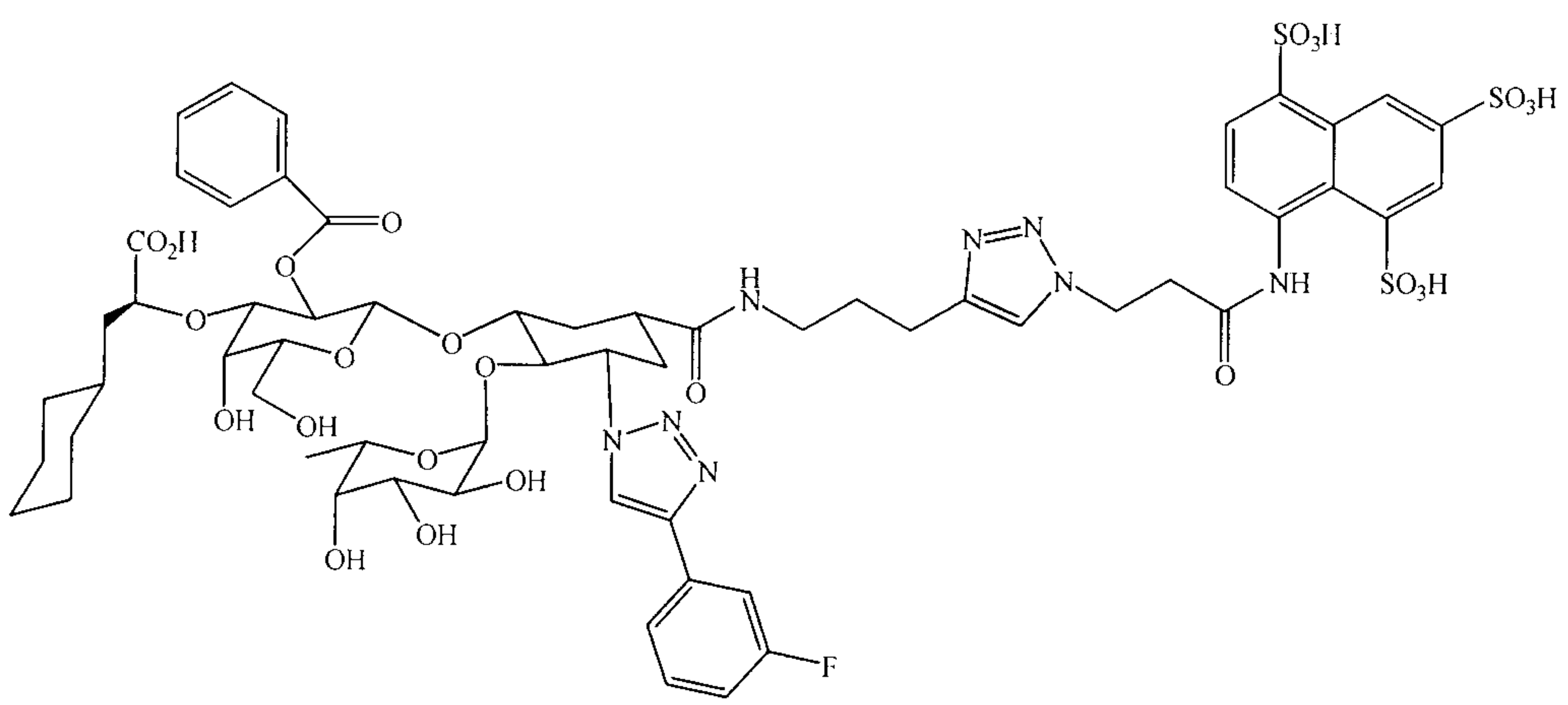
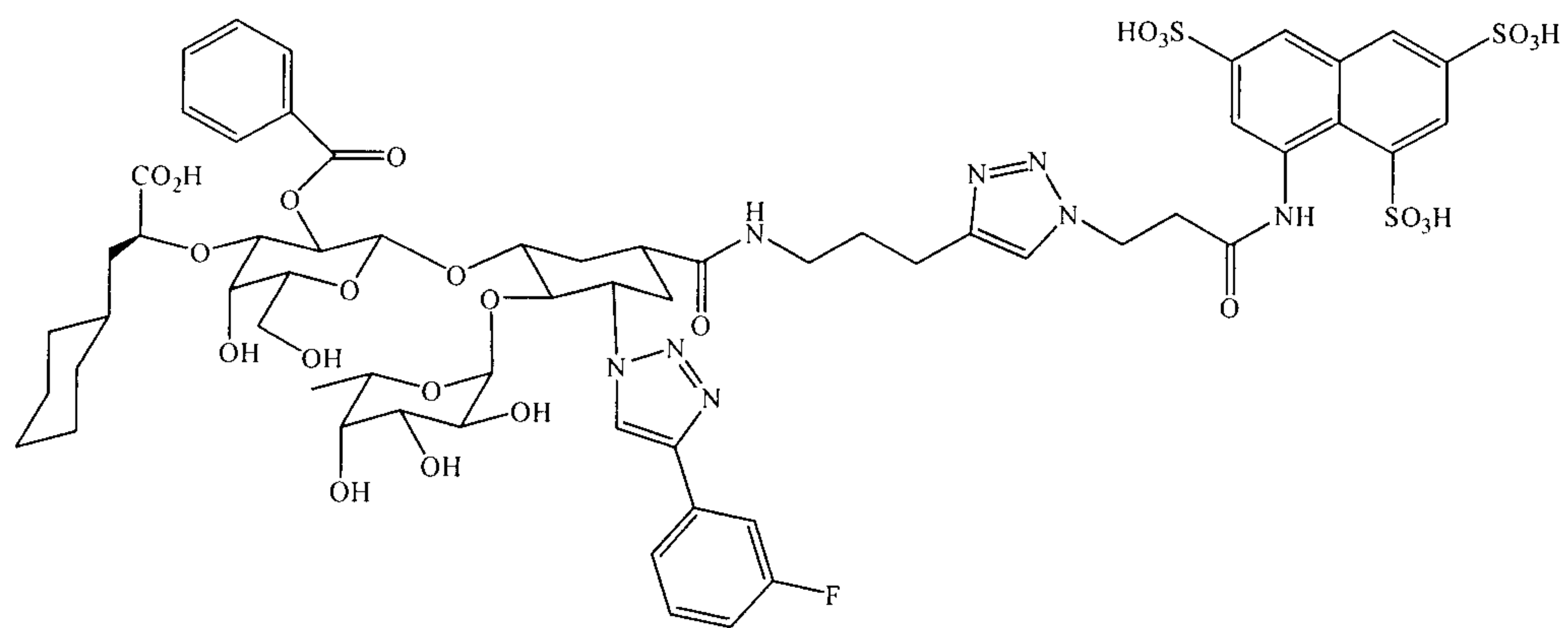


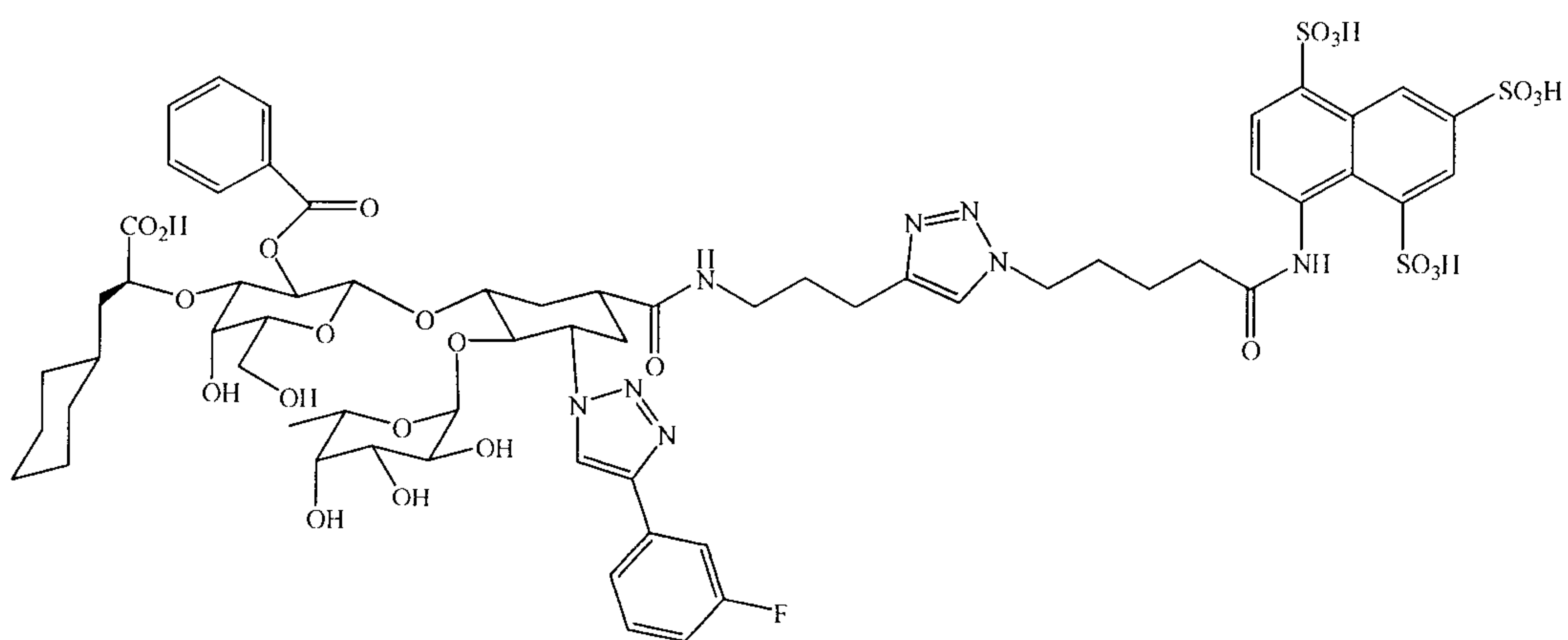
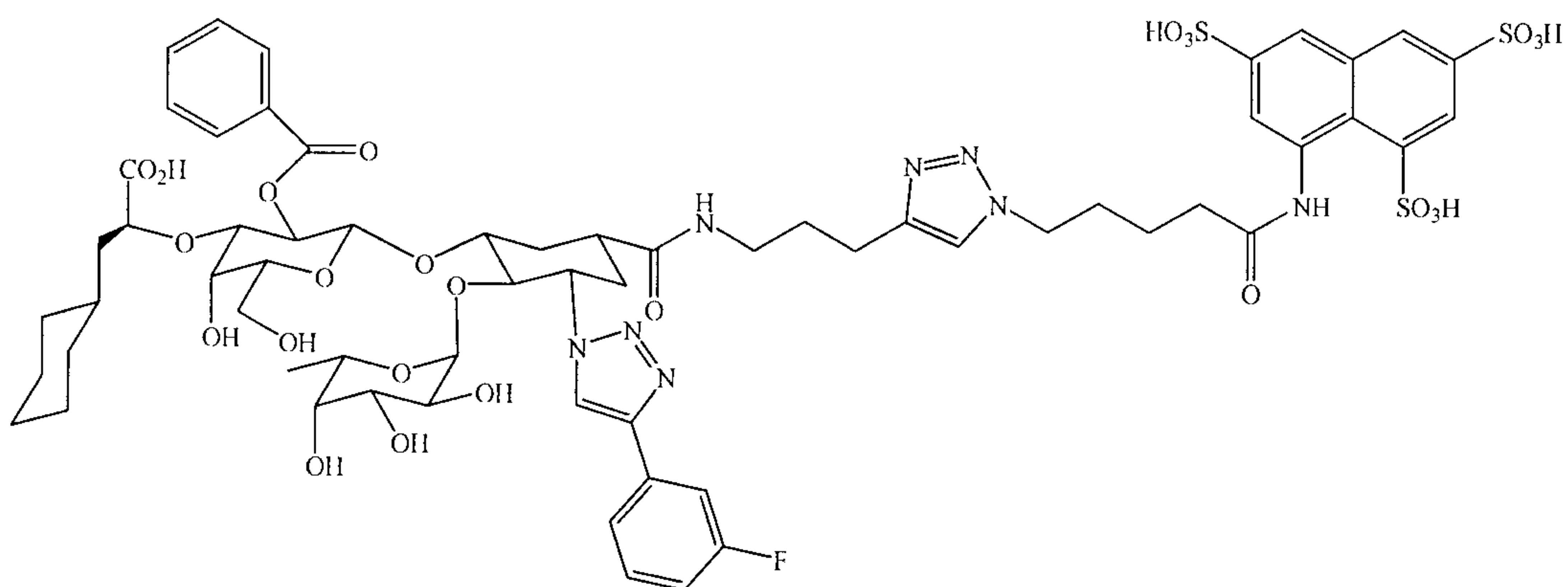
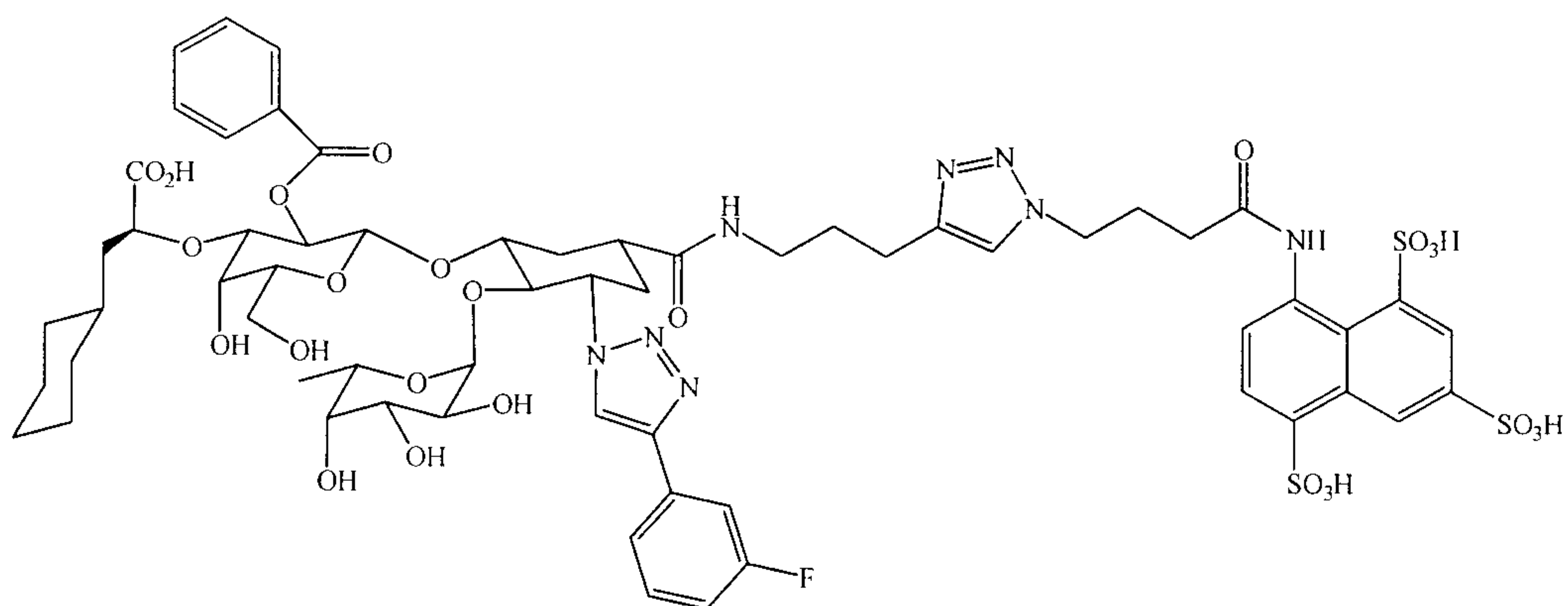
,



pharmaceutically acceptable salts thereof.

23. The compound according to claim 1, wherein the compound is chosen from





, and

pharmaceutically acceptable salts thereof.

24. A composition comprising a compound of any one of claims 1-23 and an additional pharmaceutically acceptable ingredient.

25. Use of a compound of any one of claims 1-23 for binding E and/or P selectin.

26. Use of a compound of any one of claims 1-23 as a selectin P antagonist.