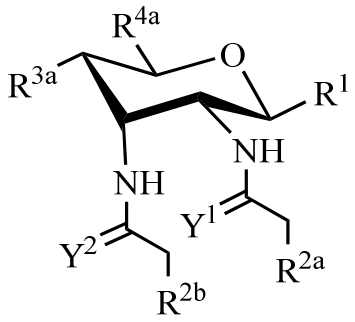
[0006] Thus, there is a need for improved TLR ligands with improved potency, stability, and/or purity.

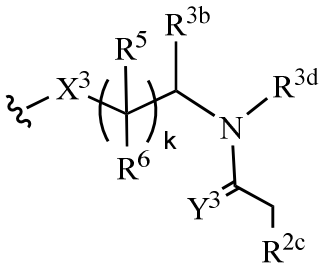
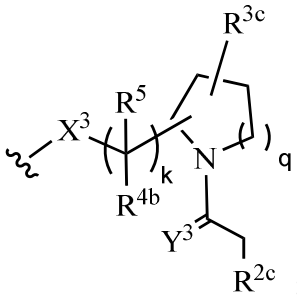
SUMMARY

[0007] The present disclosure describes compounds or a pharmaceutically acceptable salt thereof and the methods, compositions and kits disclosed herein for treating or preventing a disease or condition mediated by Toll-like receptors. The TLR ligands of the disclosure have a novel allose-based scaffold with remarkable stability in aqueous formulation. In one example, the disclosure refers to a compound of formula (I), or a pharmaceutically acceptable salt thereof,



(I)

[0008] wherein:

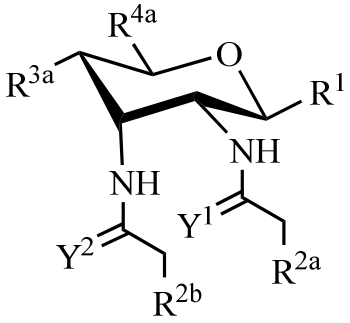
[0009] R^1 is  or  ;

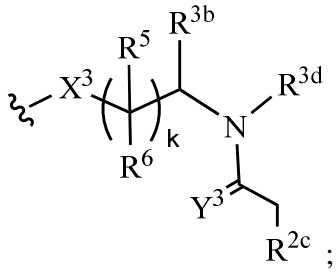
[0010] R^{2a}, R^{2b}, and R^{2c} are each independently C_{4-22}alkyl, $–X^1–C_{3-21}$alkyl, $–CH_2–X^1–C_{2-20}$alkyl, or $–CH(R^{10})(R^{11})$;

[0011] R^{10}, at each occurrence, is independently C_{1-21}alkyl, $–X^1–C_{2-20}$alkyl, or $–CH_2–X^1–C_{1-19}$alkyl;

[0012] R^{11}, at each occurrence, is independently C_{3-17}alkyl, $–X^2–C_{2-16}$alkyl, $–CH_2–X^2–C_{1-15}$alkyl, $–X^2–C(=Y^4)C_{1-15}$alkyl, $–CH_2–C(=Y^4)C_{1-15}$alkyl, $–X^2–C(=Y^4)C_{1-15}$alkylene$–Z^1–C_{1-15}$alkyl, $–CH_2–C(=Y^4)C_{1-15}$alkylene$–Z^1–C_{1-15}$alkyl, $–C_{3-17}$alkylene$–Z^1–C_{1-15}$alkyl, $–X^2–C_{2-16}$alkylene$–Z^1–$

[0024] k and q are each independently an integer from 0-4. In one aspect, the present disclosure refers to a compound of formula (I), or a pharmaceutically acceptable salt thereof,





(I) wherein: R^1 is ; R^{2a}, R^{2b}, and R^{2c} are each independently $–CH(R^{10})(R^{11})$; R^{10}, at each occurrence, is independently C_{1-21}alkyl, $–X^1–C_{2-20}$alkyl, or $–CH_2–X^1–C_{1-19}$alkyl; R^{11}, at each occurrence, is independently C_{3-17}alkyl, $–X^2–C_{2-16}$alkyl, $–CH_2–X^2–C_{1-15}$alkyl, $–X^2–C(=Y^4)C_{1-15}$alkyl, $–CH_2–C(=Y^4)C_{1-15}$alkyl, $–X^2–C(=Y^4)C_{1-15}$alkylene$–Z^1–C_{1-15}$alkyl, $–CH_2–C(=Y^4)C_{1-15}$alkylene$–Z^1–C_{1-15}$alkyl, $–C_{3-17}$alkylene$–Z^1–C_{1-15}$alkyl, $–X^2–C_{2-16}$alkylene$–Z^1–C_{1-15}$alkyl, $–CH_2–X^2–C_{1-15}$alkylene$–Z^1–C_{1-15}$alkyl, $–X^2–C(=Y^4)C_{1-15}$alkylene$–Z^2$, or $–X^2–C_{2-16}$alkylene$–Z^2$; R^{3a} is $–OP(O)(OH)_2$, $–OSO_3H$, or $–OCH_2P(O)(OH)_2$; R^{3b} is hydrogen or COOH, or an ester thereof; R^{3d} is HR^{4a} is CH_2OH; R^5 and R^6 are H; X^1 and X^2 are O; X^3 is O; Y^1, Y^2, and Y^3 are O; Y^4 is O; Z^1, at each occurrence, is independently phenylene or 5- to 6-membered heteroarylene, the phenylene and heteroarylene being optionally substituted with 1-4 substituents independently selected from C_{1-4}alkyl, C_{1-4}haloalkyl, $–OC_{1-4}$alkyl, $–OC_{1-4}$haloalkyl, cyano, and halogen; Z^2, at each occurrence, is independently phenyl or a 5- to 6-membered heteroaryl, wherein Z^2 is optionally substituted with 1-5 substituents independently selected from C_{1-4}alkyl, C_{1-4}haloalkyl, $–OC_{1-4}$alkyl, $–OC_{1-4}$haloalkyl, cyano, and halogen; and k is 1.

[0025] Another example of the present disclosure describes pharmaceutical compositions comprising a pharmaceutically acceptable carrier and the compound of formula (I), or a pharmaceutically acceptable salt thereof. In another aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0026] Another example of the disclosure describes a method of treating, preventing, or reducing the susceptibility to a disease or condition mediated by a Toll-like receptor comprising administering to a subject, in need thereof, a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

[0027] Another example of the disclosure describes a method of eliciting or enhancing, or modifying an immune response in a subject comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In yet another aspect, the present disclosure refers to use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for eliciting or enhancing, or modifying an immune response against a cancer, an infectious disease, or an allergy in a subject

[0028] Another example of the disclosure describes a method of treating, preventing, or reducing the susceptibility to cancer in a subject comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In yet another aspect, the present disclosure refers to use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating, preventing, or reducing the susceptibility to cancer or an infectious disease in a subject.

[0029] Another example of the disclosure describes a method of treating, preventing, or reducing the susceptibility to an infectious disease in a subject comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

[0030] Another example of the disclosure describes a method of treating, preventing, or reducing the susceptibility to an allergy in a subject comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

[0031] Another example of the disclosure describes a method of treating, preventing, or reducing the susceptibility to an autoimmune condition in a subject comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

[0032] Another example of the disclosure describes a method of treating, preventing, or reducing the susceptibility in a subject to bacterial, viral, prion infection, autoimmunity, cancer or allergy comprising administering to a subject in need thereof a therapeutically effective amount of the

compound of formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof.

[0033] Another example of the disclosure describes a method of treating or preventing or reducing the susceptibility to autoimmunity, allergy, ischemia reperfusion or sepsis in a subject comprising administering to a subject in need thereof a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt or a pharmaceutical composition thereof. In yet another aspect, the present disclosure refers to use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating, preventing, or reducing the susceptibility to an allergy, an autoimmune condition, bacterial, viral, or prion infection, cancer, ischemia reperfusion, sepsis, or ocular diseases such as macular degeneration, ocular hypertension, and ocular infection in a subject. In yet another aspect, the present disclosure refers to use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating or preventing or reducing the severity of epileptic seizures.

[0034] In another example, the disclosure describes compounds of formula (I), or a pharmaceutically acceptable salt thereof, for use in treating a disease or condition mediated by a Toll-like receptor.

[0035] In another example, the disclosure describes the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment a disease or condition mediated by a Toll-like receptor.

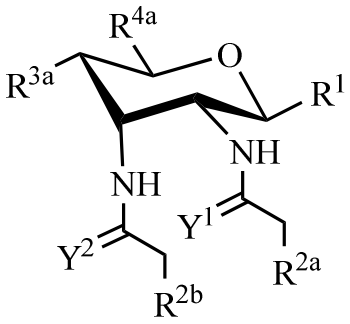
[0036] The disclosure also describes kits comprising compounds of formula (I). In yet another aspect, the present disclosure refers to a kit comprising: the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein; and instructions for use.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] FIG. 1A, 1B, and 1C show hTLR4 activation by representative compounds. Hek hTLR4-expressing cells also containing an NF-κB driven SEAP reporter were stimulated with the indicated concentration of the indicated compound for 18 hours followed by assessment of the cellular supernatant for SEAP. Results depict the average OD values over the average OD value for vehicle treated cells (± SD) of technical duplicates.

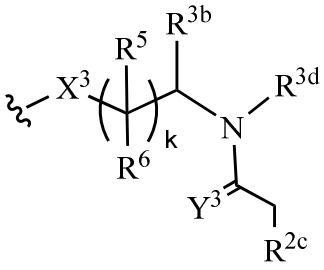
WE CLAIM:

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein:



R^1 is ;

R^{2a}, R^{2b}, and R^{2c} are each independently $–CH(R^{10})(R^{11})$;

R^{10}, at each occurrence, is independently $C_{1\text{-}21}$alkyl, $–X^1–C_{2\text{-}20}$alkyl, or $–CH_2–X^1–C_{1\text{-}19}$alkyl;

R^{11}, at each occurrence, is independently $C_{3\text{-}17}$alkyl, $–X^2–C_{2\text{-}16}$alkyl, $–CH_2–X^2–C_{1\text{-}15}$alkyl, $–X^2–C(=Y^4)C_{1\text{-}15}$alkyl, $–CH_2–C(=Y^4)C_{1\text{-}15}$alkyl, $–X^2–C(=Y^4)C_{1\text{-}15}$alkylene$–Z^1–C_{1\text{-}15}$alkyl, $–CH_2–C(=Y^4)C_{1\text{-}15}$alkylene$–Z^1–C_{1\text{-}15}$alkyl, $–C_{3\text{-}17}$alkylene$–Z^1–C_{1\text{-}15}$alkyl, $–X^2–C_{2\text{-}16}$alkylene$–Z^1–C_{1\text{-}15}$alkyl, $–CH_2–X^2–C_{1\text{-}15}$alkylene$–Z^1–C_{1\text{-}15}$alkyl, $–X^2–C(=Y^4)C_{1\text{-}15}$alkylene$–Z^2$, or $–X^2–C_{2\text{-}16}$alkylene$–Z^2$;

R^{3a} is $–OP(O)(OH)_2$, $–OSO_3H$, or $–OCH_2P(O)(OH)_2$;

R^{3b} is hydrogen or COOH, or an ester thereof;

R^{3d} is HR^{4a} is CH_2OH;

R^5 and R^6 are H;

X^1 and X^2 are O;

X^3 is O;

Y^1, Y^2, and Y^3 are O;

Y^4 is O;

Z^1, at each occurrence, is independently phenylene or 5- to 6-membered heteroarylene, the phenylene and heteroarylene being optionally substituted with 1-4 substituents independently selected from C_{1-4}alkyl, C_{1-4}haloalkyl, –OC_{1-4}alkyl, –OC_{1-4}haloalkyl, cyano, and halogen;

Z^2, at each occurrence, is independently phenyl or a 5- to 6-membered heteroaryl, wherein Z^2 is optionally substituted with 1-5 substituents independently selected from C_{1-4}alkyl, C_{1-4}haloalkyl, –OC_{1-4}alkyl, –OC_{1-4}haloalkyl, cyano, and halogen; and

k is 1.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

R^{11} is C_{3-17}alkyl, –X^2–C_{2-16}alkyl, –CH_2–X^2–C_{1-15}alkyl, –X^2–$C(=Y^4)C_{1-15}$alkyl, –CH_2–$C(=Y^4)C_{1-15}$alkyl, –X^2–$C(=Y^4)C_{1-15}$alkylene–Z^1–C_{1-15}alkyl, –CH_2–$C(=Y^4)C_{1-15}$alkylene–Z^1–C_{1-15}alkyl, –C_{3-17}alkylene–Z^1–C_{1-15}alkyl, –X^2–C_{2-16}alkylene–Z^1–C_{1-15}alkyl, or –CH_2–X^2–C_{1-15}alkylene–Z^1–C_{1-15}alkyl.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein at least one occurrence of R^{10} is C_{1-21}alkyl.

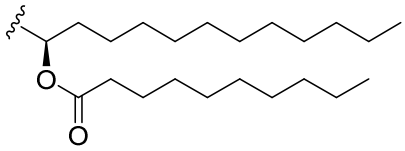
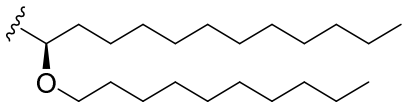
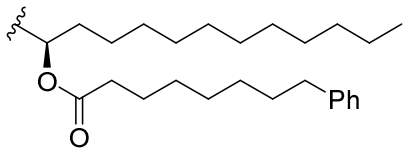
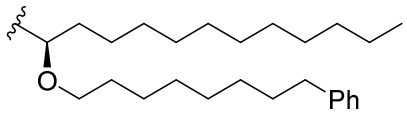
4. The compound of any of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein at least one occurrence of R^{11} is –X^2–$C(=Y^4)C_{1-15}$alkyl, –X^2–$C(=Y^4)C_{1-15}$alkylene–Z^2, –X^2–C_{2-16}alkylene–Z^2, –X^2–C_{2-16}alkyl, or –CH_2–X^2–C_{1-15}alkyl.

5. The compound of any of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R^{10}, at each occurrence, is independently C_{8-14}alkyl.

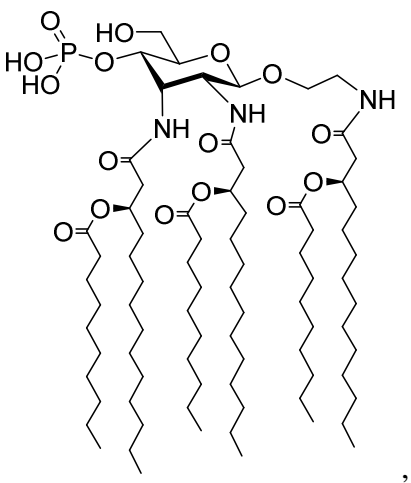
6. The compound of claim 5, or a pharmaceutically acceptable salt thereof, wherein R^{10}, at each occurrence, is independently C_{11}alkyl.

7. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein R^{10}, at each occurrence, is independently straight chain C_{11}alkyl.

8. The compound of any of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein R^{11}, at each occurrence, is independently –O–C(=O)C_9alkyl, –O–C_{10}alkyl, –O–C(=O)C_7alkylene–Z^2, or –O–$C_{8\text{-}9}$alkylene–Z^2.

9. The compound of any of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein –CH(R^{10})(R^{11}) is , , , or .

10. The compound of claim 1, selected from the group consisting of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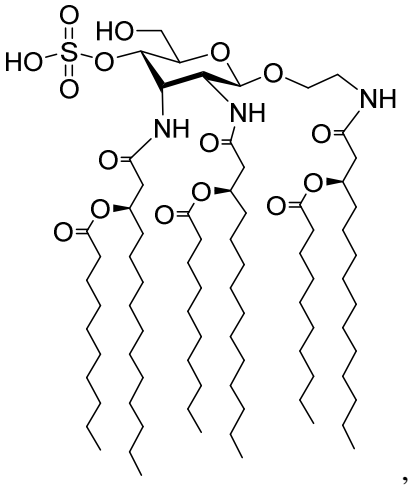
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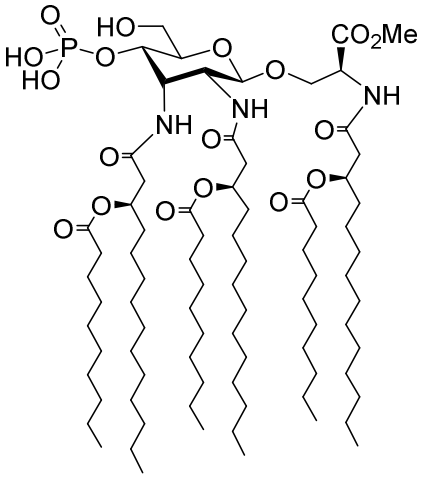
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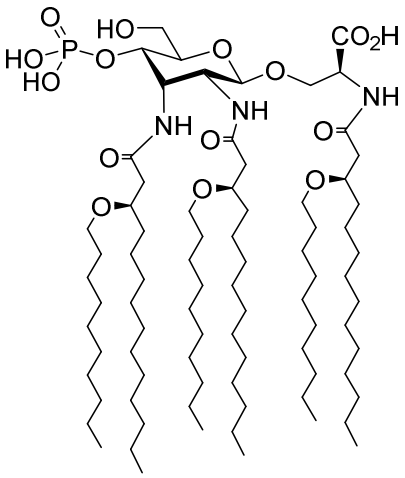
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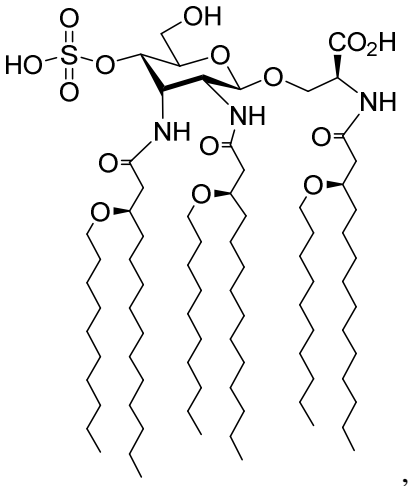
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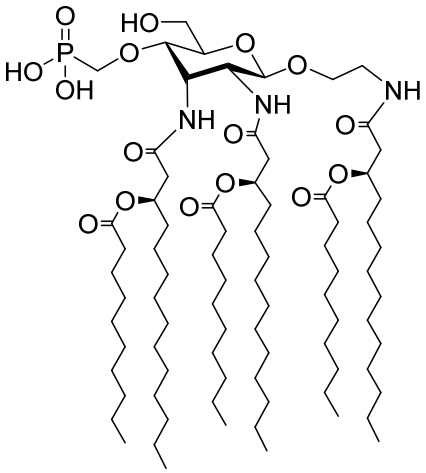
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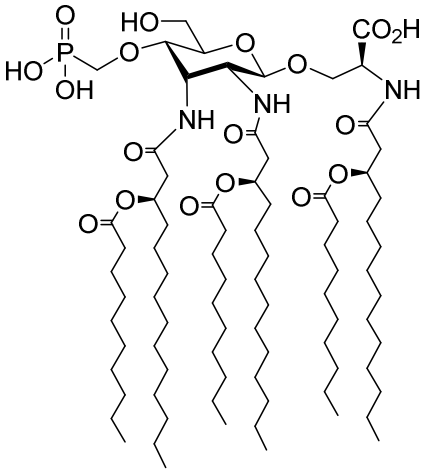
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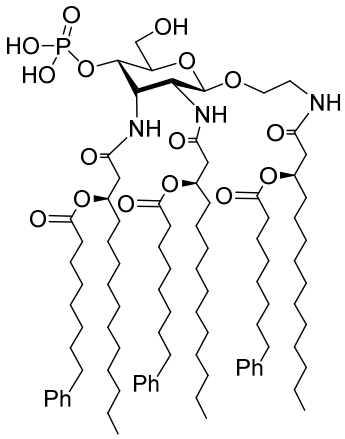
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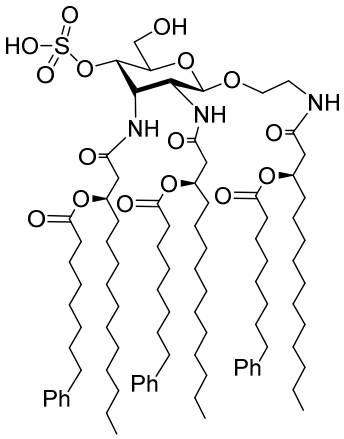
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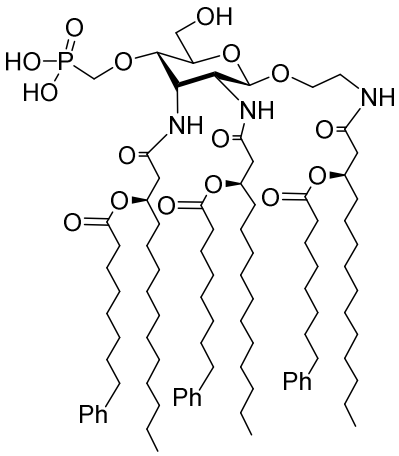
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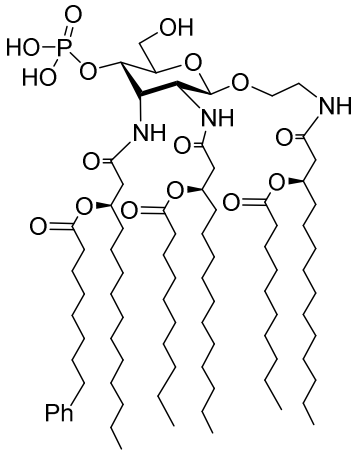
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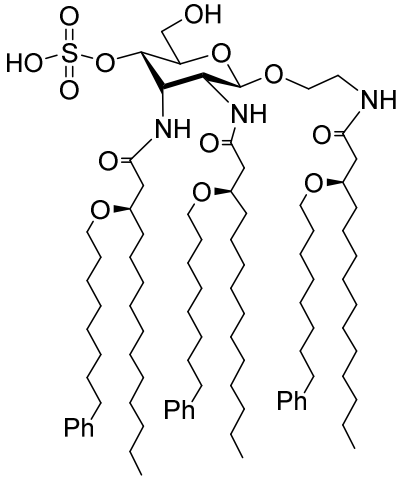
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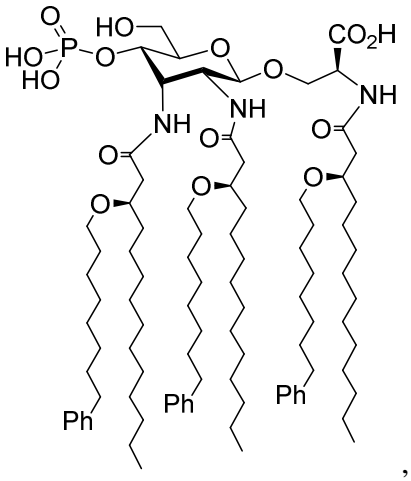
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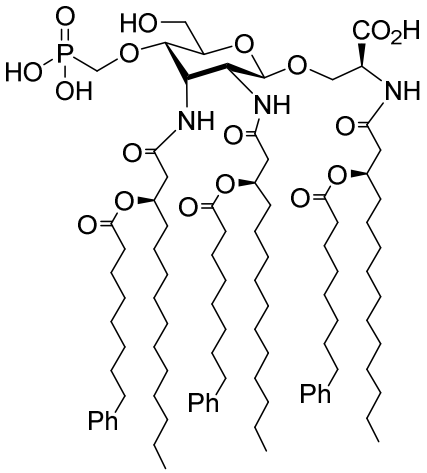
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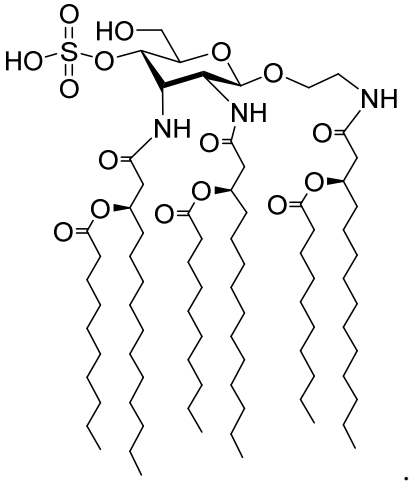
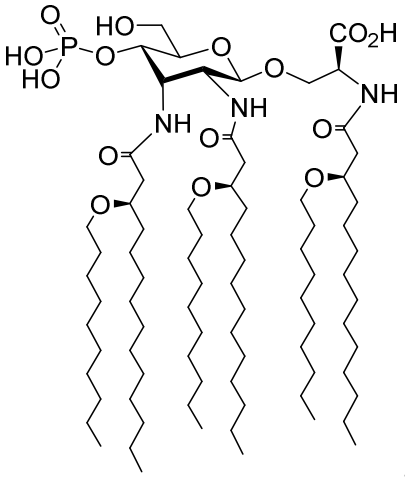
or a pharmaceutically acceptable salt thereof.

11. The compound or pharmaceutically acceptable salt thereof, of claim 10, wherein the compound is  .

12. The compound, or pharmaceutically acceptable salt thereof, of claim 10, wherein the compound is  .

13. A pharmaceutical composition comprising the compound of any of claims 1-12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 13, further comprising an antigen.

15. The pharmaceutical composition of claim 13 or 14 for intranasal administration.

16. Use of the compound of any of claims 1-12, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of any of claims 13-15 in the manufacture of a medicament for eliciting or enhancing, or modifying an immune response against a cancer, an infectious disease, or an allergy in a subject.

17. Use of the compound of any of claims 1-12, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of any of claims 13-15 in the manufacture of a medicament for treating, preventing, or reducing the susceptibility to cancer or an infectious disease in a subject.

18. Use of the compound of any of claims 1-12, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of any of claims 13-15 in the manufacture of a medicament for treating, preventing, or reducing the susceptibility to an allergy, an autoimmune condition, bacterial, viral, or prion infection, cancer, ischemia reperfusion, sepsis, or ocular diseases such as macular degeneration, ocular hypertension, and ocular infection in a subject.

19. Use of the compound of any of claims 1-12, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of any of claims 13-15 in the manufacture of a medicament for treating or preventing or reducing the severity of epileptic seizures.

20. The use of any of claims 16-19 wherein the medicament is to be administered intramuscularly, intradermally, subcutaneous, topically, intravenously or mucosally.

21. The use of claim 20, for intranasal administration.

22. A kit comprising:
the compound of any of claims 1-12, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of any of claims 13-15; and
instructions for use.