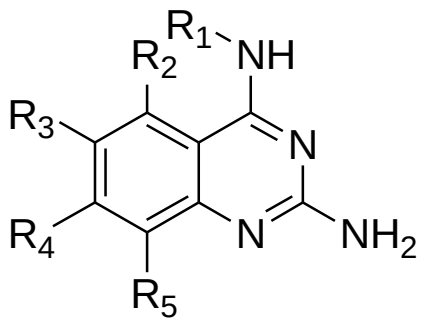
and

- R_5 is hydrogen, deuterium, fluorine, chlorine, methyl, or methoxy,

provided that at least one of R_2, R_3, R_4 and R_5 is not hydrogen.

In one aspect the application provides a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

- R_1 is a C_{4-8} alkyl substituted with a hydroxyl
- the carbon of R_1 bonded to the amine in the 4-position of the quinazoline is in (*R*)-configuration,
- R_2 is hydrogen, deuterium, fluorine, chlorine, methyl, methoxy, cyclopropyl, trifluoromethyl, or carboxylic amide, wherein each of methyl, methoxy and cyclopropyl is optionally substituted by one or more substituents independently selected from fluorine and nitrile,
- R_3 is hydrogen or deuterium,
- R_4 is hydrogen, deuterium, fluorine, methyl, carboxylic ester, carboxylic amide, nitrile, cyclopropyl, C_{4-7}heterocycle, or 5-membered heteroaryl group, wherein each of methyl, cyclopropyl, C_{4-7}heterocycle and 5-membered heteroaryl group is optionally substituted by one or more substituents independently selected from fluorine, hydroxyl, or methyl,

and

- R_5 is hydrogen, deuterium, fluorine, chlorine, methyl, or methoxy,

provided that at least one of R_2, R_3, R_4 and R_5 is not hydrogen.

The products of the application may advantageously display improved TLR8 agonism (or selectivity) over TLR7.

The application also provides means, which comprise or contains the compound of the application, such as pharmaceutical composition, immunological compositions and kits.

In another aspect the application provides a pharmaceutical composition, which comprises the compound as defined herein or a pharmaceutically acceptable salt, solvate or polymorph thereof, together with one or more pharmaceutically acceptable excipients, diluents or carriers.

The products and means of the application may be useful in the activation or stimulation of TLR8.

The products and means of the application may be useful in the activation or stimulation of a Th1 immune response and/or of the production of cytokines, such as IL12.

The products and means of the application are notably useful in the treatment or prevention of virus infection or of a virus-induced disease, more particularly of an HBV infection or of an HBV-induced disease, as well as in other indications, more particularly the treatment or prevention of malignant tumor, cancer or allergy.

In another aspect the application provides the compound as defined herein, or the pharmaceutical composition as defined herein, for use as medicament.

In another aspect the application provides the compound as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment or prevention of viral infection, of cancer or of allergy, more particularly in the treatment or prevention of viral infection or of cancer, more particularly in the treatment or prevention of viral infection.

In another aspect the application provides the compound as defined herein, or the pharmaceutical composition as defined herein, for use in the treatment or prevention of chronic viral infection, more particularly for use in the treatment or prevention of HBV infection or of an HBV-induced disease, more particularly for use in the treatment or prevention of chronic HBV infection or of one or several diseases chosen from among liver fibrosis, liver inflammation, liver necrosis, cirrhosis, liver disease and hepatocellular carcinoma.

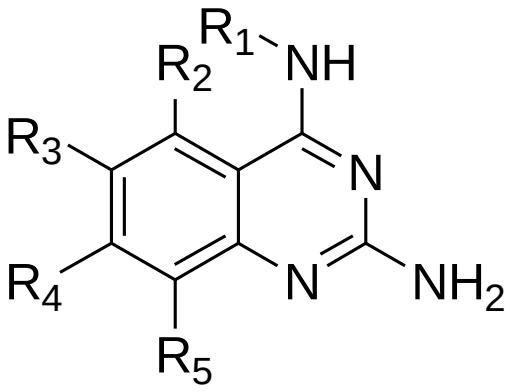
In another aspect the application provides use of the compound as defined herein, or the pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment or prevention of viral infection, of cancer or of allergy, more particularly in the treatment or prevention of viral infection or of cancer, more particularly in the treatment or prevention of viral infection or of a virus-induced disease.

In another aspect the application provides use of the compound as defined herein, or the pharmaceutical composition as defined herein, in the manufacture of a medicament for the treatment or prevention of chronic viral infection, more particularly for use in the treatment or prevention of HBV infection or of an HBV-induced disease, more particularly for use in the treatment or prevention of chronic HBV infection or of one or several diseases chosen from among liver fibrosis, liver inflammation, liver necrosis, cirrhosis, liver disease and hepatocellular carcinoma.

DETAILED DESCRIPTION

The application describes the subject matter described below, the subject illustrated below as well the subject matter defined in the claims as filed, which are herein incorporated by reference.

The application provides a compound of formula (I)



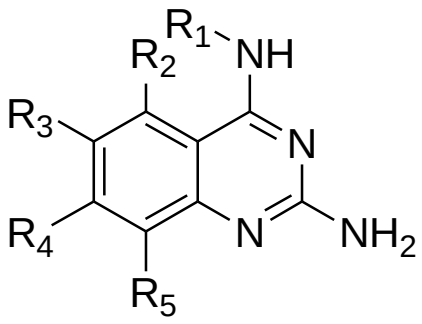
(I)

or a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

- R_1 is a C_{3-8}alkyl, optionally substituted by one or more substituents (more particularly 1, 2 or 3 substituents, more particularly 1 or 2 substituents, more

CLAIMS

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate or polymorph thereof, wherein

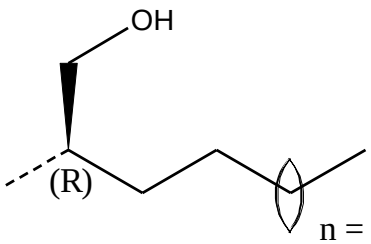
- R_1 is a C_{4-8} alkyl substituted with a hydroxyl,
- the carbon of R_1 bonded to the amine in the 4-position of the quinazoline is in (*R*)-configuration,
- R_2 is hydrogen, deuterium, fluorine, chlorine, methyl, methoxy, cyclopropyl, trifluoromethyl, or carboxylic amide, wherein each of methyl, methoxy and cyclopropyl is optionally substituted by one or more substituents independently selected from fluorine and nitrile,
- R_3 is hydrogen or deuterium,
- R_4 is hydrogen, deuterium, fluorine, methyl, carboxylic ester, carboxylic amide, nitrile, cyclopropyl, C_{4-7}heterocycle, or 5-membered heteroaryl group, wherein each of methyl, cyclopropyl, C_{4-7}heterocycle and 5-membered heteroaryl group is optionally substituted by one or more substituents independently selected from fluorine, hydroxyl, or methyl,

and

- R_5 is hydrogen, deuterium, fluorine, chlorine, methyl, or methoxy,

provided that at least one of R_2, R_3, R_4 and R_5 is not hydrogen.

2. The compound of claim 1, wherein R_1 is of formula (II):

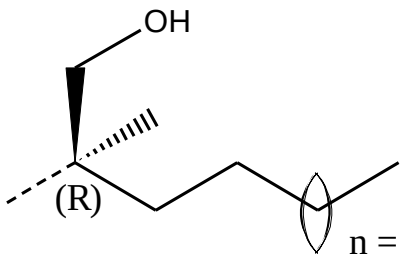


n = 0, 1 or 2
more particularly 1

formula (II)

,

or of formula (III):



n = 0, 1 or 2,
more particularly 1

formula (III)

.

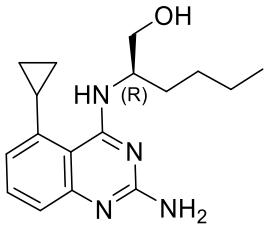
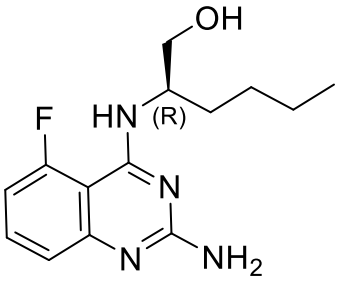
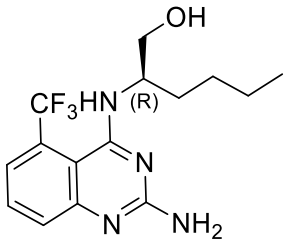
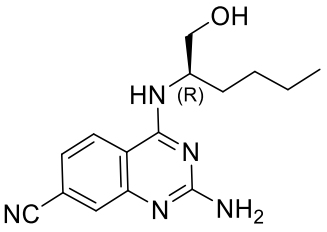
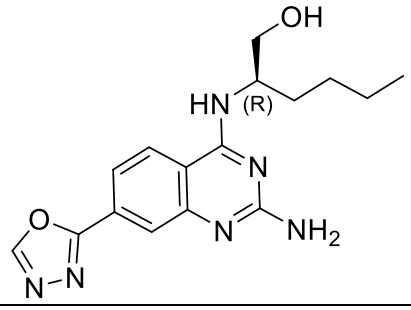
3. The compound of claim 1 or 2, wherein R_2 is fluorine, chlorine or methyl, and wherein methyl is optionally substituted by one or more substituents independently selected from fluorine and nitrile.

4. The compound of any one of claims 1-3, wherein R_2 is fluorine or chlorine or methyl, more particularly fluorine or chlorine, more particularly fluorine.

5. The compound of any one of claims 1-4, wherein R_4 is fluorine or methyl, and wherein methyl is optionally substituted by one or more substituents independently selected from fluorine, hydroxyl, or methyl.

6. The compound of claim 1 or 2, which is chosen from among compounds 1-10, 12-19 and 21-26:

Compound number	

1	
2	
3	
4	
5	

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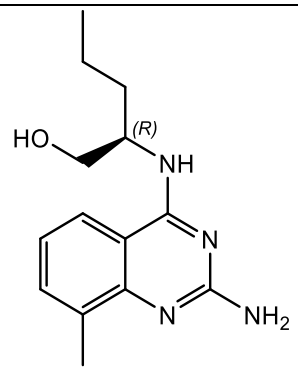
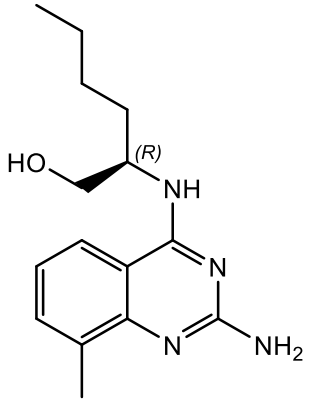
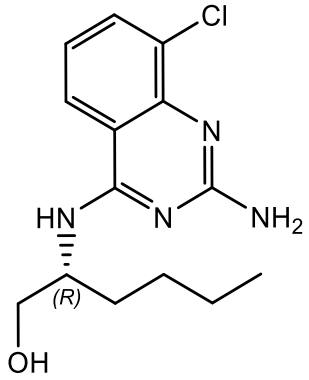
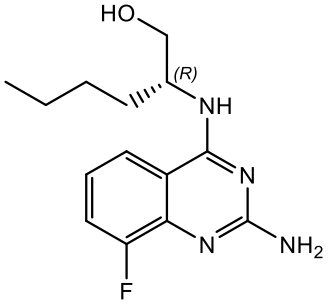
6	
7	
8	
9	

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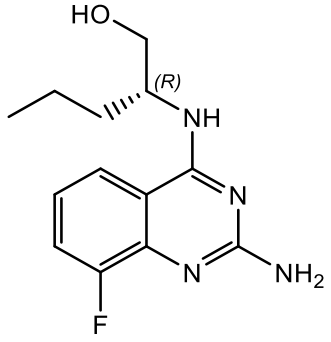
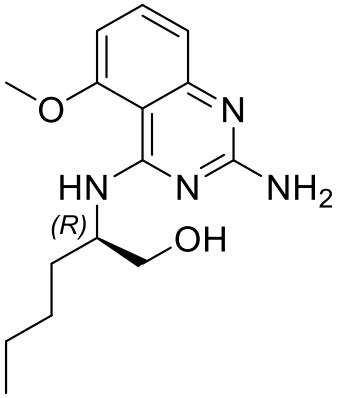
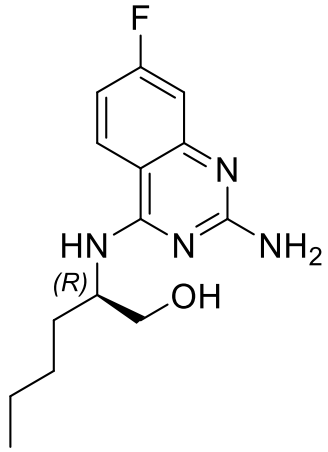
10	
12	
13	

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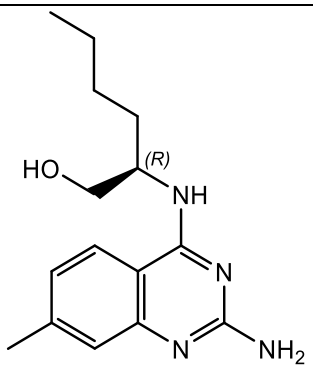
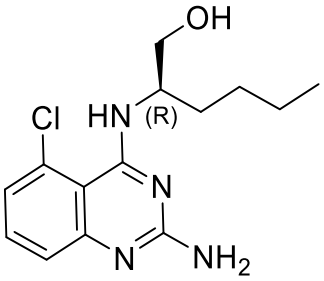
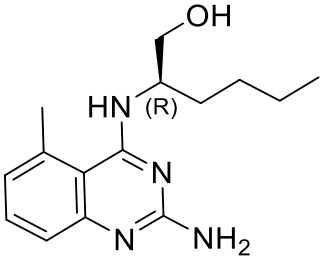
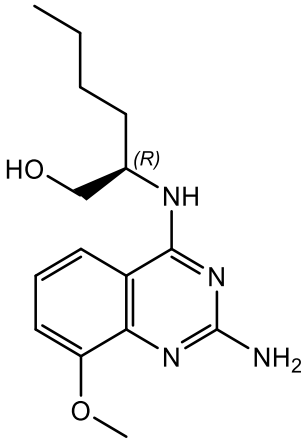
14	
15	
16	
17	

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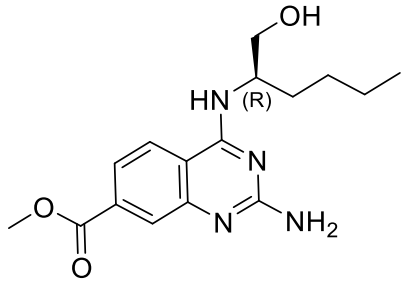
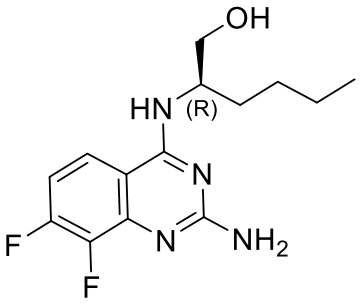
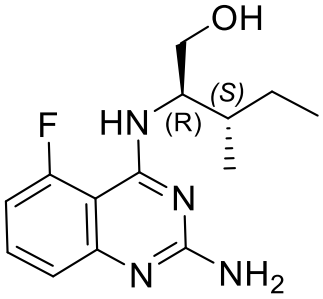
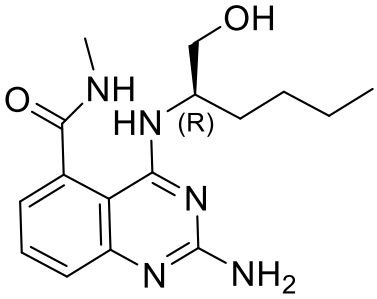
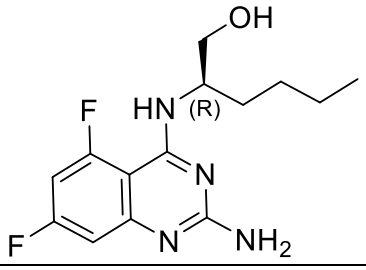
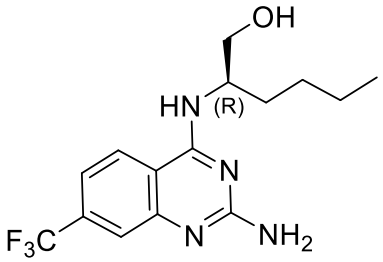
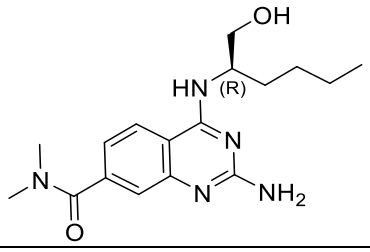
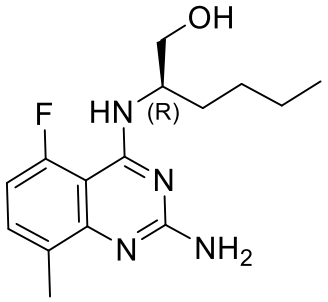
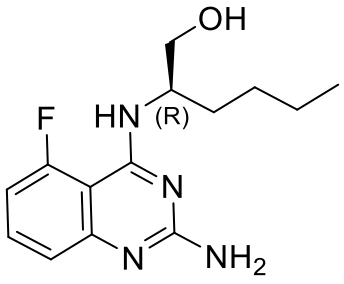
18	
19	
21	
22	
23	

Compound number	
24	
25	
26	

7. The compound of claim 6, which is chosen from among compounds 1, 2, 3, 4, 5, 7, 9, 12, 13, 14, 15, 16, 18, 19, 21, 22, 23, 24 and 26.

8. The compound of claim 6 or 7, which is chosen from among compounds 2, 13, 14, 15, 16, 21 and 23.

9. The compound of claim 8, which is compound 2 having the structural formula:



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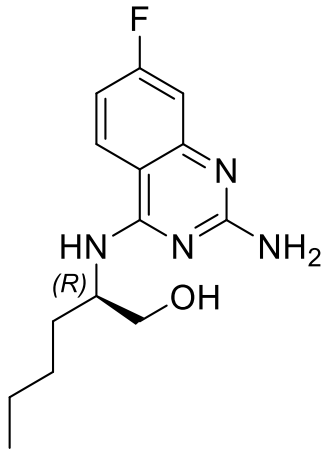
10. The compound of claim 8, which is compound 13 having the structural formula: 

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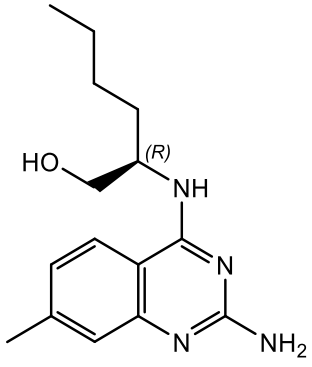
11. The compound of claim 8, which is compound 14 having the structural formula: 

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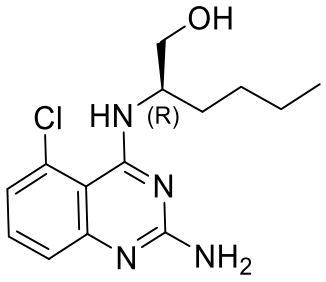
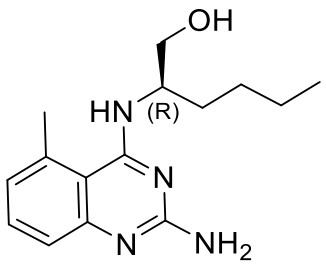
12. The compound of claim 8, which is compound 15 having the structural formula:



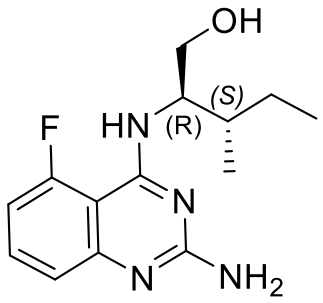
.

13. The compound of claim 8, which is compound 16 having the structural formula:



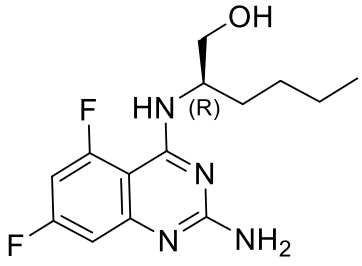
.

14. The compound of claim 8, which is compound 21 having the structural formula:



.

15. The compound of claim 8, which is compound 23 having the structural formula:



.

16. The compound of any one of claims 1-15, which is a TLR8 agonist, and which displays improved TLR8 agonism over TLR7.

17. The compound of any one of claims 1-15, which stimulate or activate a Th1 immune response, and/or which stimulate or activate cytokine production, more particularly the production of IL12.

18. A pharmaceutical composition, which comprises the compound of any one of claims 1-17 or a pharmaceutically acceptable salt, solvate or polymorph thereof, together with one or more pharmaceutically acceptable excipients, diluents or carriers.

19. The compound of any one of claims 1-17, or the pharmaceutical composition of claim 18, for use as medicament.

20. The compound of any one of claims 1-17, or the pharmaceutical composition of claim 18, for use in the treatment or prevention of viral infection, of cancer or of allergy, more particularly in the treatment or prevention of viral infection or of cancer, more particularly in the treatment or prevention of viral infection.

21. The compound of any one of claims 1-17, or the pharmaceutical composition of claim 18, for use in the treatment or prevention of chronic viral infection, more particularly for use in the treatment or prevention of HBV infection or of an HBV-induced disease, more particularly for use in the treatment or prevention of chronic HBV infection or of one or several diseases chosen from among liver fibrosis, liver inflammation, liver necrosis, cirrhosis, liver disease and hepatocellular carcinoma.

22. Use of the compound of any one of claims 1-17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for the treatment or prevention of viral infection, of cancer or of allergy, more particularly in the treatment or prevention of viral infection or of cancer, more particularly in the treatment or prevention of viral infection or of a virus-induced disease.

23. Use of the compound of any one of claims 1-17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for the treatment or prevention of chronic viral infection, more particularly for use in the treatment or prevention of HBV infection or of an HBV-induced disease, more particularly for use in the treatment or prevention of chronic HBV infection or of one or several diseases chosen from among liver fibrosis, liver inflammation, liver necrosis, cirrhosis, liver disease and hepatocellular carcinoma.