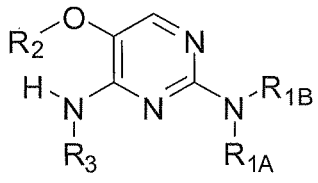
ACYLAMINOPYRIMIDINE DERIVATIVES FOR THE TREATMENT OF VIRAL INFECTIONS AND FURTHER DISEASES.

This invention relates to acylaminopyrimidine derivatives, processes for their preparation, pharmaceutical compositions, and their use in therapy.

The present invention relates to the use of acylaminopyrimidine derivatives in the treatment of viral infections, immune disorders, and cancer, or as a vaccine adjuvant, whereby the induction of interferon is desired. In the treatment of certain viral infections, regular injections of interferon (IFN-type 1) can be administered, as is the case for hepatitis C virus (HCV), For more information see reference Fried et. al. Peginterferon-alfa plus ribavirin for chronic hepatitis C virus infection, *N Engl J Med* 2002; 347: 975-82. Orally available small molecule IFN inducers offer the potential advantages of reduced immunogenicity and convenience of administration. Thus, novel IFN inducers are a potentially effective new class of drugs for treating virus infections. For an example in the literature of a small molecule IFN inducer having antiviral effect see De Clercq, E.; Descamps, J.; De Somer, P. *Science* **1978**, *200*, 563-565.

However there exists a strong need for novel interferon inducers having an improved safety profile compared to the compounds currently known.

In ~~one aspect of~~ the present disclosure, a compound of formula (I) is provided



(I)

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

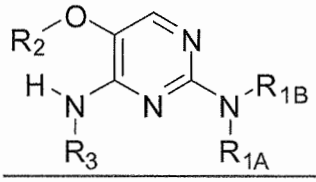
R_{1A} is selected from the group hydrogen, a substituted or unsubstituted acyl, or acyloxy group,

R_{1B} is selected from the group hydrogen, a substituted or unsubstituted acyl, or acyloxy group,
with the proviso that R_{1A} and R_{1B} are not both hydrogen,

R_2 is C_{1-6}alkyl, C_{1-6} alkoxy, arylalkyl or heteroarylalkyl, each of which is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, amino, di-(C_{1-6})alkylamino, C_{1-6} alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, carboxylic acid, carboxylic ester, carboxylic amide, heterocycle, bicyclic heterocycle, aryl, alkenyl, alkynyl, arylalkyl, heteroaryl, heteroarylalkyl, or nitrile and

R_3 is a C_{1-8} alkyl, or arylalkyl each of which is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, amino, C_{1-6} alkyl, di-(C_{1-6})alkylamino, C_{1-6} alkylamino, C_{1-6} alkoxy, C_{3-6} cycloalkyl, carboxylic acid, aromatic or aliphatic carboxylic ester, carboxylic amide, heterocycle, aryl, alkenyl, alkynyl, arylalkyl, heteroaryl, heteroarylalkyl, or nitrile.

In one aspect of the present disclosure, a compound of formula (I) is provided



(I)

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

R_{1A} is selected from the group hydrogen, a substituted or unsubstituted acyl, or acyloxy group,

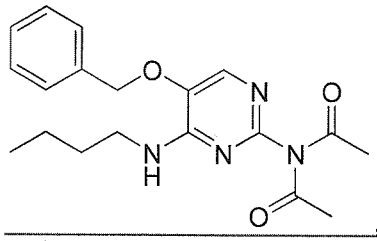
R_{1B} is selected from the group hydrogen, a substituted or unsubstituted acyl, or acyloxy group,

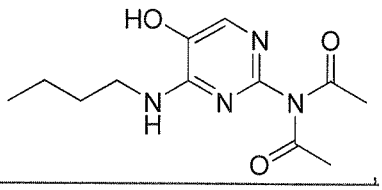
with the proviso that R_{1A} and R_{1B} are not both hydrogen,

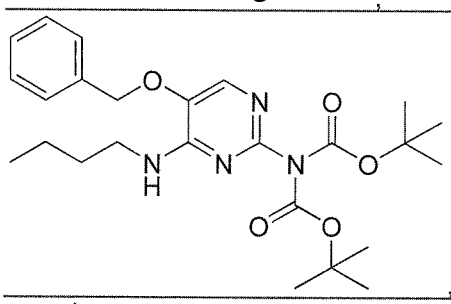
R_2 is C_{1-6}alkyl, C_{1-6} alkoxy, arylalkyl or heteroarylalkyl, each of which is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, amino, di-(C_{1-6})alkylamino, C_{1-6} alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, carboxylic acid, carboxylic ester, carboxylic amide, heterocycle, bicyclic heterocycle, aryl, alkenyl, alkynyl, arylalkyl, heteroaryl, heteroarylalkyl, or nitrile and

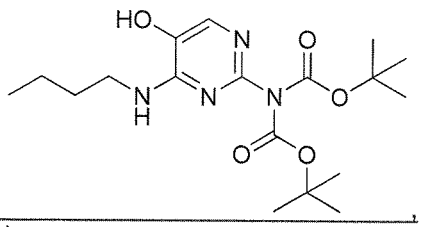
R_3 is a C_{1-8} alkyl, or arylalkyl each of which is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, amino, C_{1-6} alkyl, di-(C_{1-6})alkylamino, C_{1-6} alkylamino, C_{1-6} alkoxy, C_{3-6} cycloalkyl, carboxylic acid, aromatic or aliphatic carboxylic ester, carboxylic amide, heterocycle, aryl, alkenyl, alkynyl, arylalkyl, heteroaryl, heteroarylalkyl, or nitrile,

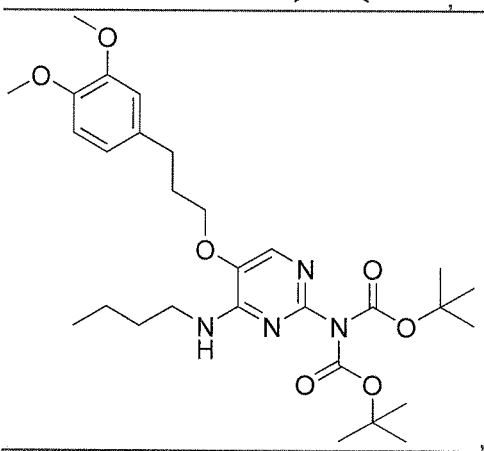
with the proviso that said compound is not

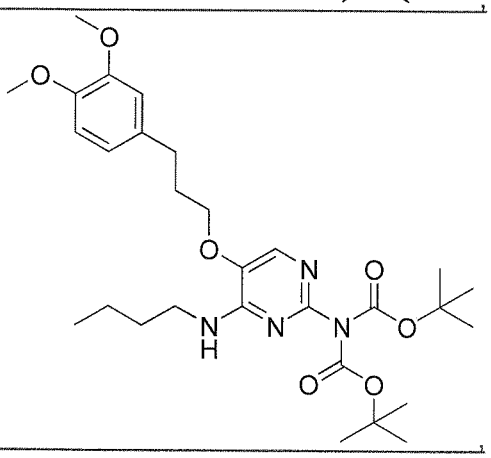


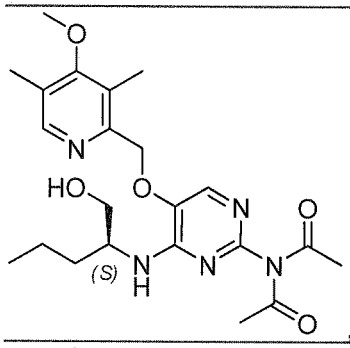


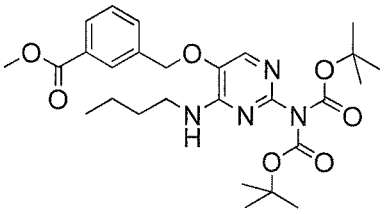


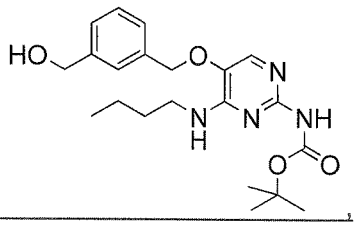


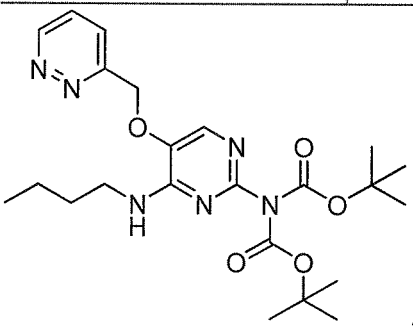


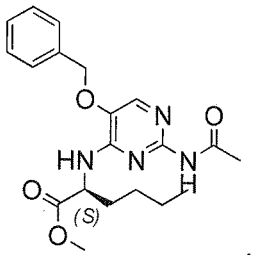


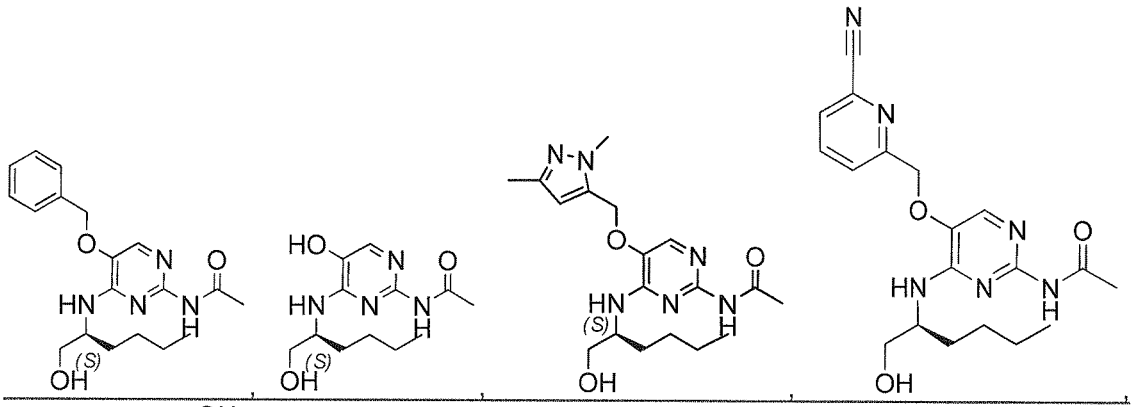


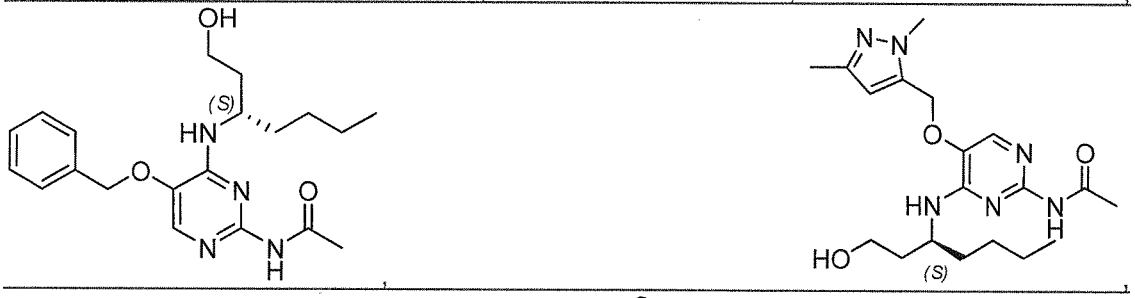


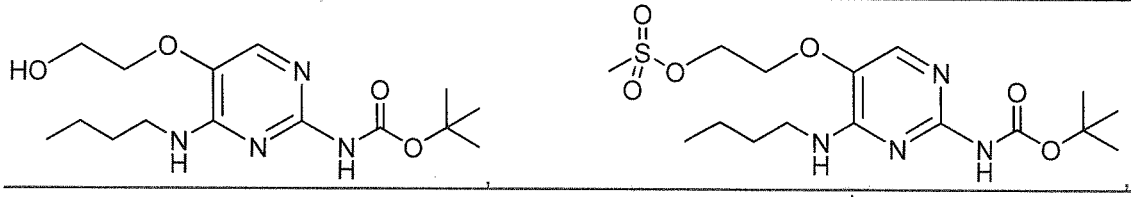


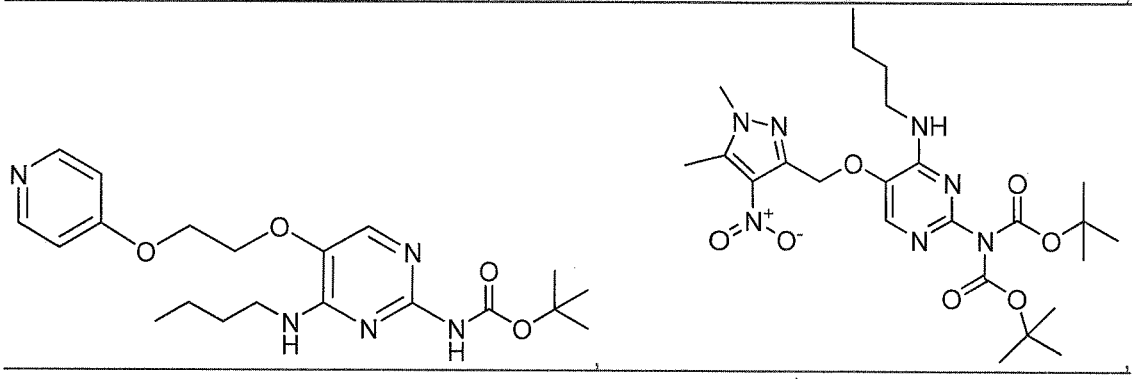


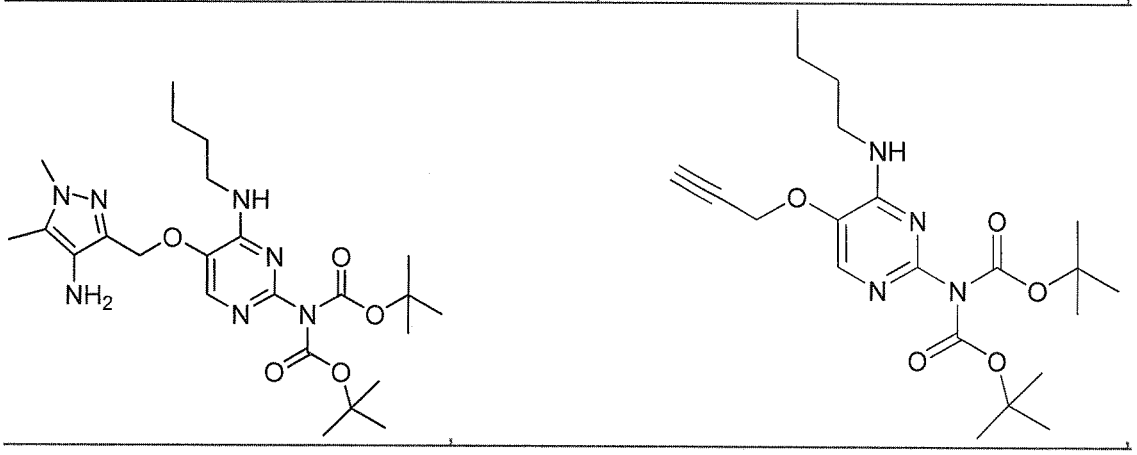


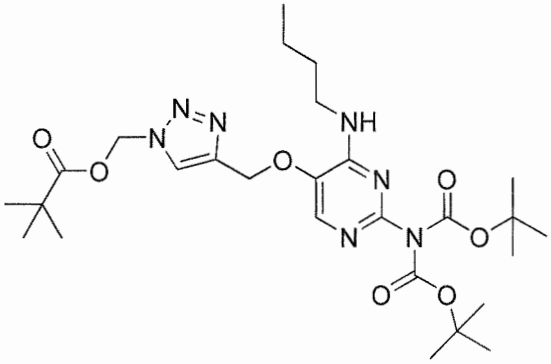


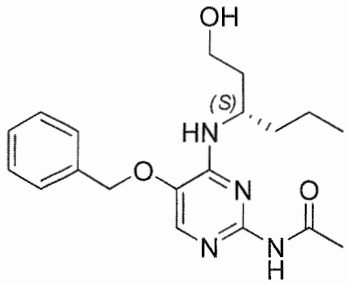












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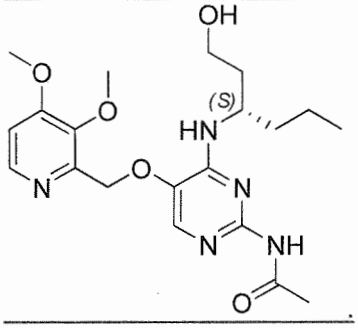


In a first embodiment the present disclosure provides compounds of formula (I) wherein R_{1A} and/ or R_{1B} are substituted or unsubstituted acyl and wherein R_2 is C_{1-6} alkyl preferably $-CH_3$ and R_3 is C_{1-8} alkyl substituted with an alkylester.

In a second embodiment the present disclosure provides compounds of formula (I) wherein R_{1A} and/or R_{1B} are isobutyryl and wherein R_2 is $-CH_3$, and R_3 is heptan-3-yl isobutyrate.

The compounds of formula (I) in any stereochemical form and their pharmaceutically acceptable salt, solvate or polymorph thereof have activity as pharmaceuticals, in particular as inducers of interferon.

So, in a further aspect the present disclosure provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

Furthermore, in a further aspect the present disclosure provides a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to the current disclosure, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof for use as a medicament.

Another aspect of the disclosure provides for a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof, or said pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate

or polymorph thereof for use in the treatment of a disorder in which the induction of interferon is involved.

Another aspect of the disclosure provides for use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof, or said pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof in the manufacture of a medicament for the treatment of a disorder in which the induction of interferon is involved, wherein said disorder is selected from the group consisting of a viral infection, an immune disorder and cancer.

The term "alkyl" refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon containing the specified number of carbon atoms.

The term "halogen" refers to fluorine, chlorine, bromine or iodine.

The term "acyl" refers to the group defined as –(C=O)R, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heteroaryl.

The term "acyloxy" refers to the group defined as –(C=O)OR, where R is a substituted or unsubstituted alkyl, cycloalkyl, aryl, heteroaryl.

The term "alkenyl" refers to an alkyl as defined above consisting of at least two carbon atoms and at least one carbon-carbon double bond.

The term "alkynyl" refers to an alkyl as defined above consisting of at least two carbon atoms and at least one carbon-carbon triple bond.

The term "cycloalkyl" refers to a carbocyclic ring containing the specified number of carbon atoms.

The term "alkoxy" refers to an alkyl (carbon and hydrogen chain) group singular bonded to oxygen (e.g. methoxy group or ethoxy group).

The term "aryl" means an aromatic ring structure optionally comprising one or two heteroatoms selected from N, O and S, in particular from N and O. Said aromatic ring structure may have 5, 6 or 7 ring atoms. In particular, said aromatic ring structure may have 5 or 6 ring atoms.

The term "bicyclic heterocycle" means an aromatic ring structure, as defined for the term "aryl" comprised of two fused aromatic rings. Each ring is optionally comprised of heteroatoms selected from N, O and S, in particular from N and O.

The term "arylalkyl" means an aromatic ring structure as defined for the term "aryl" optionally substituted with an alkyl group.

Claims

1. A compound of formula (I)

(I)

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

R_{1A} is selected from the group hydrogen, a substituted or unsubstituted acyl, or acyloxy group,

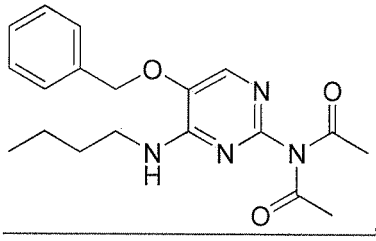
R_{1B} is selected from the group hydrogen, a substituted or unsubstituted acyl, or acyloxy group,

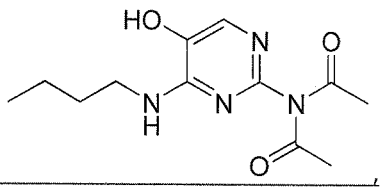
with the proviso that R_{1A} and R_{1B} are not both hydrogen,

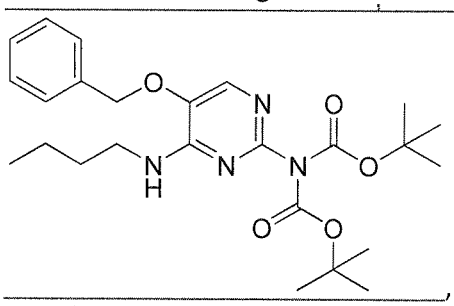
R_2 is $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$ alkoxy, arylalkyl or heteroarylalkyl, each of which is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, amino, di-($C_{1\text{-}6}$)alkylamino, $C_{1\text{-}6}$ alkylamino, $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$ alkoxy, $C_{3\text{-}6}$ cycloalkyl, carboxylic acid, carboxylic ester, carboxylic amide, heterocycle, bicyclic heterocycle, aryl, alkenyl, alkynyl, arylalkyl, heteroaryl, heteroarylalkyl, or nitrile and

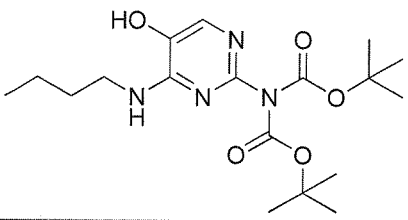
R_3 is a $C_{1\text{-}8}$ alkyl, or arylalkyl each of which is optionally substituted by one or more substituents independently selected from halogen, hydroxyl, amino, $C_{1\text{-}6}$ alkyl, di-($C_{1\text{-}6}$)alkylamino, $C_{1\text{-}6}$ alkylamino, $C_{1\text{-}6}$ alkoxy, $C_{3\text{-}6}$ cycloalkyl, carboxylic acid, aromatic or aliphatic carboxylic ester, carboxylic amide, heterocycle, aryl, alkenyl, alkynyl, arylalkyl, heteroaryl, heteroarylalkyl, or nitrile,

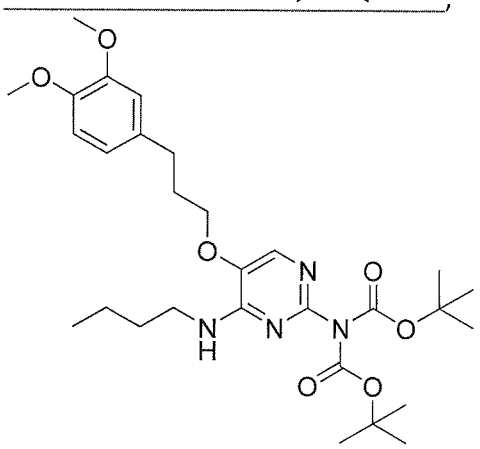
with the proviso that said compound is not

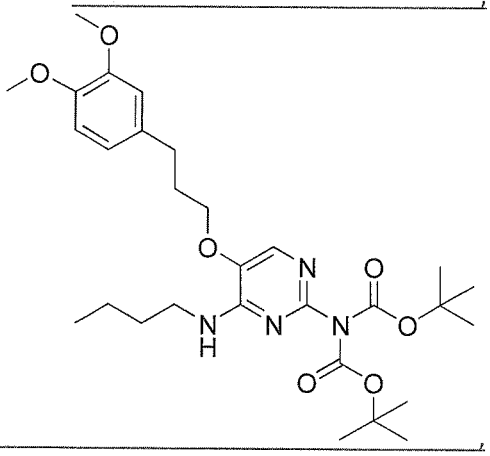


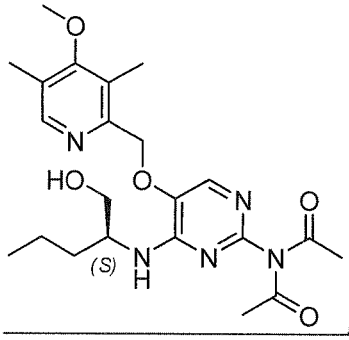


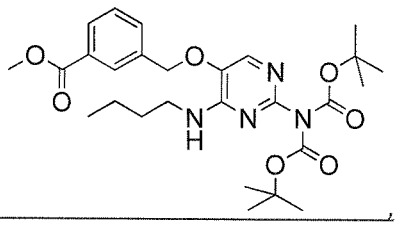


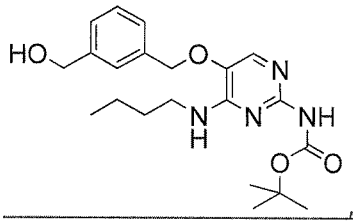


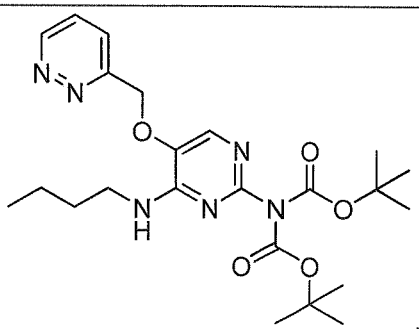


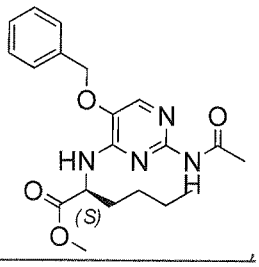


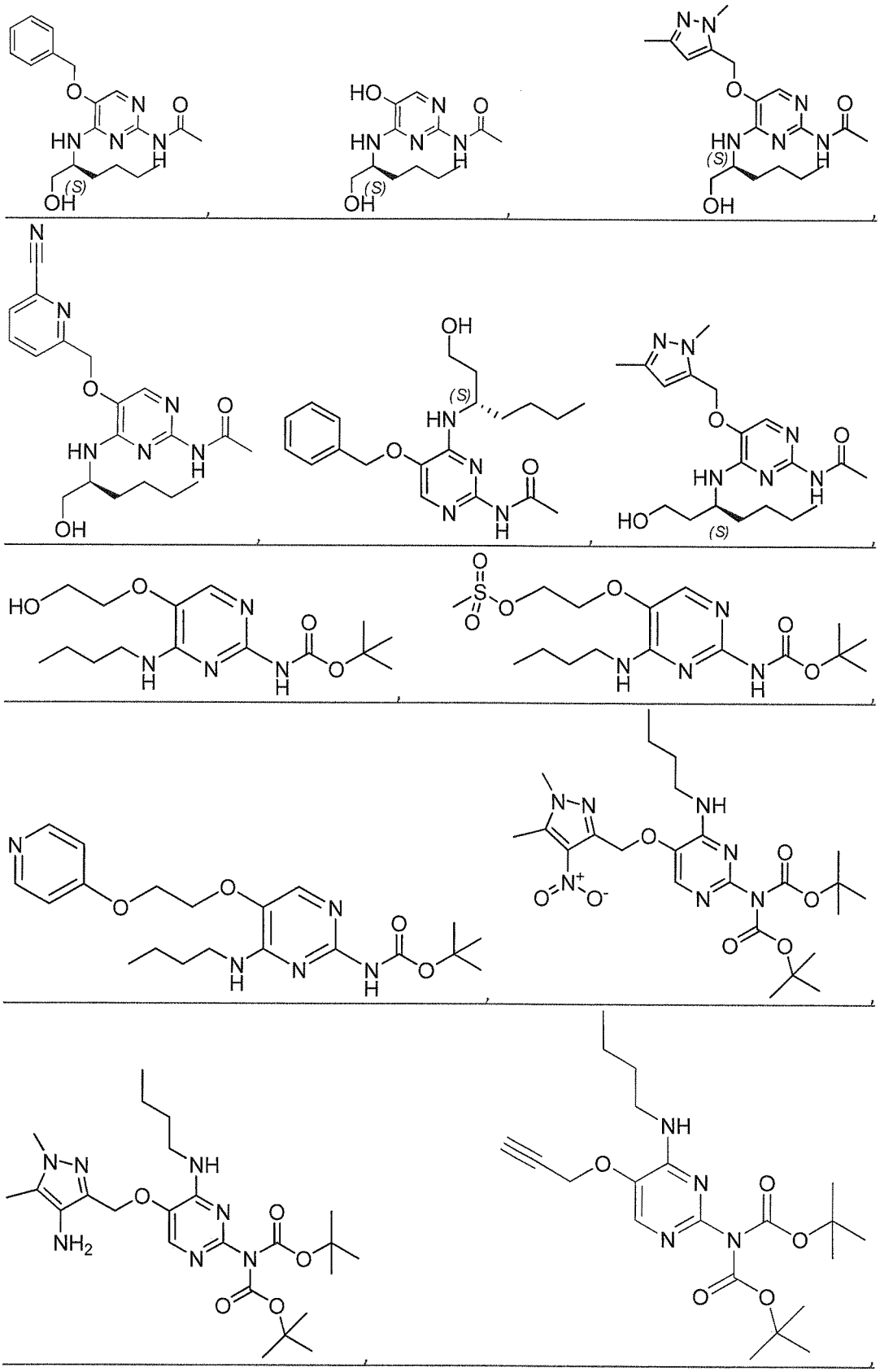


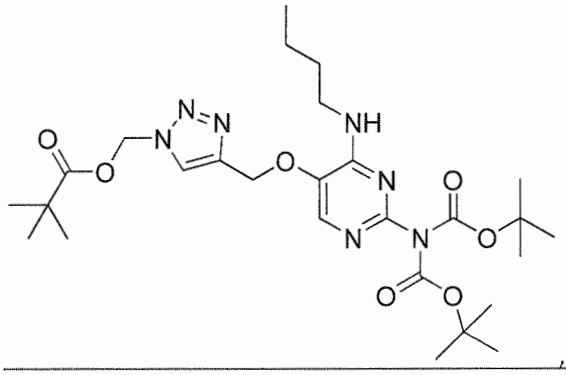


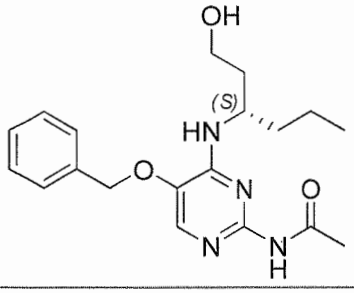












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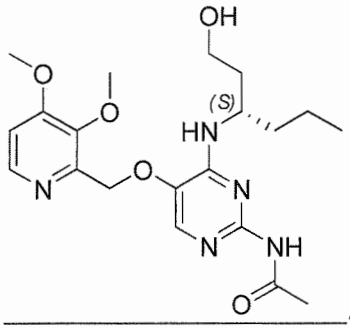

2. A compound according to claim 1 wherein R_{1A} and/ or R_{1B} are substituted or unsubstituted acyl and wherein R_2 is C_{1-6} alkyl preferably -CH_3 and R_3 is C_{1-8} alkyl substituted with an alkylester.

3. A compound according to claim 1 wherein R_{1A} and/or R_{1B} are isobutyryl and wherein R_2 is $-CH_3$, and R_3 is heptan-3-yl isobutyrate.

4. The compounds according to claims 1-3 in any stereo chemical form and their pharmaceutically acceptable salt, solvate or polymorph thereof with activity as a pharmaceutical, in particular as inducers of interferon.

5. A pharmaceutical composition comprising a compound of formula (I) according to claim 1-3 or a pharmaceutically acceptable salt, solvate or polymorph thereof together with one or more pharmaceutically acceptable excipients, diluents or carriers.

6. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1-3, or a pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 5 for use as a medicament.

7. A compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1-3, or said pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 5 for use in the treatment of a disorder in which the induction of interferon is involved.

8. Use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 1-3, or said pharmaceutical composition comprising said compound of formula (I) or a pharmaceutically acceptable salt, solvate or polymorph thereof according to claim 5 in the manufacture of a medicament for the treatment of a disorder in which the induction of interferon is involved, wherein said disorder is selected from the group consisting of a viral infection, an immune disorder and cancer.