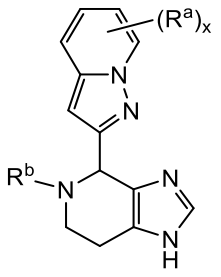
medical guidelines currently recommend maintaining blood Phe concentration in the range of 120 to 360 μM in both adults and children under the age of 12 years. European medical guidelines currently recommend maintaining blood Phe concentration below 360 μM in children under the age of 12 years and in pregnant women and below 600 μM in non-pregnant patients older than 12 years.

[0005] A standard of care for treating PKU is a Phe-restricted diet that severely limits the intake of natural protein, supplemented with medical foods to provide protein equivalents and prevent nutritional deficiencies. Such diets are very strict diets and challenging to adhere to. Two medications are currently approved for treating PKU, each having its own challenges. Kuvan (sapropterin dihydrochloride) is a synthetic BH4 cofactor approved in 2007 for use in infants to adults. Kuvan is not effective for all PKU patients, and the current guidelines suggest response testing in patients unless the patient is known to have two null mutations. Pegvaliase is an enzyme substitution therapy approved in 2018 for adults with a blood Phe concentration greater than 600 μM, despite prior management with available treatment options. Pegvaliase typically involves injection of a purified PEGylated form of phenylalanine ammonia lyase that reduces Phe by converting it to ammonia and trans-cinnamic acid instead of tyrosine. One of the main complications with enzyme substitution therapy is the attainment and maintenance of therapeutically effective amounts of protein in vivo due to rapid degradation or inactivation of the infused protein. A current approach to overcome this problem is to perform numerous costly high dose injections.

[0006] Pharmaceutical agents that enable PKU patients to increase their intake of natural protein are desired.

SUMMARY

[0006a] In one aspect, the disclosure provides a compound of Formula **I**:

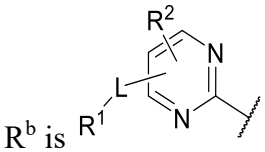
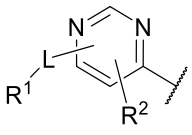
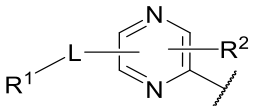
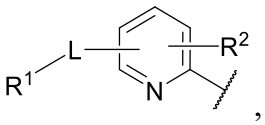
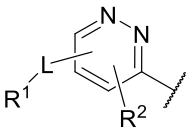
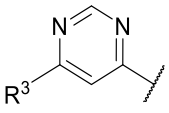


I,

or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein:

x is 0 to 5;

each R^a independently is halo, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy or C_{1-6}haloalkoxy;

R^b is , , , , , or ;

L is -C(O)-, -CH(OH)-, or -C(O)NH-;

R^1 is optionally substituted phenyl, optionally substituted 4-, 5-, or 6-membered heterocyclyl, $-NR^4R^5$, or optionally substituted C_{3-6}cycloalkyl;

R^2 is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

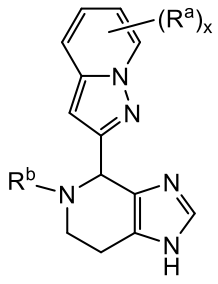
R^3 is optionally substituted 5- or 6-membered heterocyclyl; and

R^4 and R^5 are each independently hydrogen or C_{1-6}alkyl.

[0007] In some examples, the disclosure provides compounds as disclosed in Tables 1 and 2 herein, or a pharmaceutically acceptable salt thereof.

[0008] In further examples, the disclosure provides racemates of compounds disclosed in Tables 1 and 2 herein, or a pharmaceutically acceptable salt thereof.

[0009] In other examples, the disclosure provides compounds of Formula **I**:

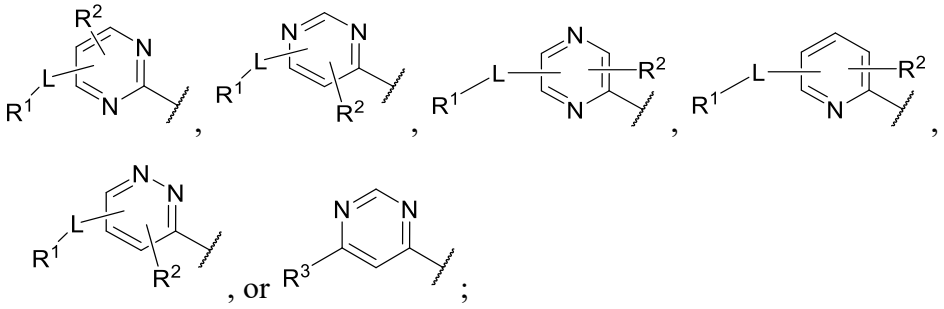


I

or a pharmaceutically acceptable salt thereof, wherein:

x is 0 to 5;

each R^a independently is halo, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy or C_{1-6}haloalkoxy;

R^b is 

L is -C(O)-, -CH(OH)-, or -C(O)NH-;

R^1 is optionally substituted phenyl, optionally substituted 4-, 5-, or 6-membered heterocyclyl, $-NR^4R^5$, or optionally substituted C_{3-6}cycloalkyl;

R^2 is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

R^3 is optionally substituted 5- or 6-membered heterocyclyl; and

R^4 and R^5 are each independently hydrogen or C_{1-6}alkyl.

[0010] In further examples, the disclosure provides pharmaceutical compositions comprising one or more compound described herein or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0010a] In another aspect, the disclosure provides a pharmaceutical composition comprising a compound as described herein, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, and a pharmaceutically acceptable excipient.

[0011] In yet other examples, the disclosure provides methods for stabilizing a mutant PAH protein, comprising contacting the protein with one or more compound as described herein or a pharmaceutically acceptable salt thereof. In some examples, the mutant PAH protein contains at least one R408W, R261Q, R243Q, Y414C, L48S, A403V, I65T, R241C, L348V, R408Q, or V388M mutation. In other

examples, the mutant PAH protein contains at least one R408W, Y414C, I65T, F39L, R408Q, L348V, R261Q, A300S, or L48S mutation.

[0011a] In another aspect, the disclosure provides a compound as described herein, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition as described herein, for use in stabilizing a mutant phenylalanine hydroxylase (PAH) protein in a subject suffering from phenylketonuria, comprising contacting the protein with a compound as described herein, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition as described herein.

[0011b] In another aspect, the disclosure provides a compound as described herein, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition as described herein, for use in reducing blood phenylalanine concentration in a subject suffering from phenylketonuria, optionally wherein:

i) the blood phenylalanine concentration is reduced to a concentration less than or equal to 600 μM or the blood phenylalanine concentration is reduced to a concentration less than or equal to 360 μM; and/or

ii) the subject has a blood phenylalanine concentration greater than 600 μM prior to administration of the compound, or wherein the subject has a blood phenylalanine concentration greater than 1200 μM prior to administration of the compound.

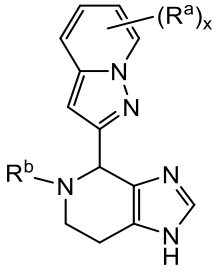
[0011c] In another aspect, the disclosure provides a compound as described herein, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition as described herein, for use in treating phenylketonuria in a subject.

[0011d] In another aspect, the disclosure provides use of the compound as described herein, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition as described herein, in the manufacture of a medicament for treating phenylketonuria in a subject.

[0012] In still further examples, the disclosure provides methods for reducing phenylalanine levels in a subject suffering from phenylketonuria comprising administering a

What is Claimed Is:

1. A compound of Formula **I**:

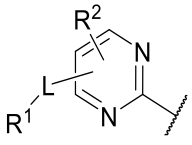
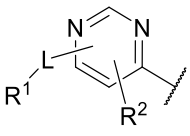
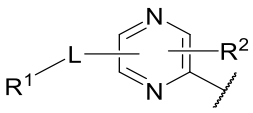
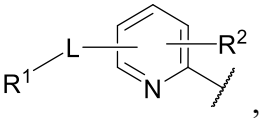
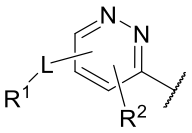
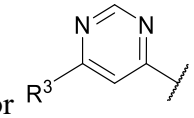


I,

or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein:

x is 0 to 5;

each R^a independently is halo, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy or C_{1-6}haloalkoxy;

R^b is , , , , , or ;

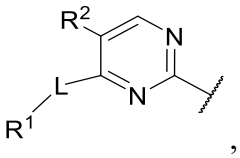
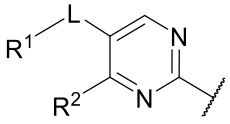
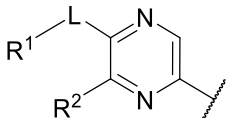
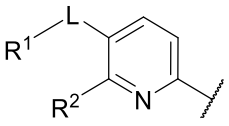
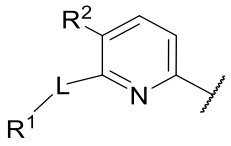
L is -C(O)-, -CH(OH)-, or -C(O)NH-;

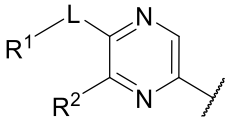
R^1 is optionally substituted phenyl, optionally substituted 4-, 5-, or 6-membered heterocyclyl, $-NR^4R^5$, or optionally substituted C_{3-6}cycloalkyl;

R^2 is hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, or halo;

R^3 is optionally substituted 5- or 6-membered heterocyclyl; and

R^4 and R^5 are each independently hydrogen or C_{1-6}alkyl.

2. The compound of claim 1, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein R^b is , , , , or .

3. The compound of claim 2, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein R^b is .

4. The compound of any one of claims 1 to 3, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein L is -C(O)-.

5. The compound of any one of claims 1 to 3, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein L is -C(O)NH-.

6. The compound of any one of claims 1 to 5, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein R^1 is:

(i) phenyl, optionally substituted with one or more of C_{1-6}alkoxy, halo, C_{1-6}alkyl, or C_{1-6}haloalkyl;

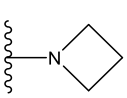
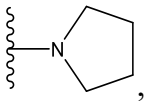
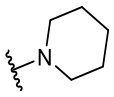
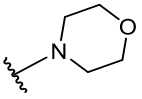
(ii) 4-, 5-, or 6-membered heterocyclyl, optionally substituted with one or more of halo, C_{1-6}alkyl, OH, C_{1-6}hydroxyalkyl, or C_{3-6}cycloalkyl; or

(iii) C_{3-6}cycloalkyl, optionally substituted with one or more of halo, OH, C_{1-6}alkyl, or C_{1-6}haloalkyl.

7. The compound of any one of claims 1 to 6, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein:

(i) R^1 is optionally substituted 4-, 5-, or 6-membered heterocyclyl wherein the 4-, 5-, or 6-membered heterocyclyl is optionally substituted azetidinyl, optionally

substituted pyrrolidinyl, optionally substituted piperidinyl, optionally substituted piperazinyl, or optionally substituted morpholinyl; or

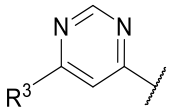
(ii) R^1 is unsubstituted 4-, 5-, or 6-membered heterocyclyl, optionally wherein the 4-, 5-, or 6-membered heterocyclyl is , , , or .

8. The compound of any one of claims 1 to 6, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein R^1 is optionally substituted cyclopropyl or optionally substituted cyclobutyl.

9. The compound of any one of claims 1 to 6, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein R^1 is unsubstituted C_{3-6}cycloalkyl.

10. The compound of any one of claims 1 to 4, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein R^1 is $-NR_4R_5$.

11. The compound of any one of claims 1 to 10, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein R^2 is hydrogen.

12. The compound of claim 1, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein R^b is , and R^3 is optionally substituted with one or more of halo, C_{1-6}alkyl, OH, C_{1-6}hydroxyalkyl, or optionally substituted phenyl, wherein the optional substitution on the phenyl group is one or more of halo, C_{1-6}alkyl, C_{1-6}haloalkyl, or cyano.

13. The compound of any one of claims 1 to 12, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein x is 0 or 1, and R^a is one of the following:

i) halo such as F, Br, or Cl;

ii) C_{1-6}alkyl such as methyl, ethyl, or isopropyl;

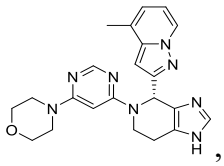
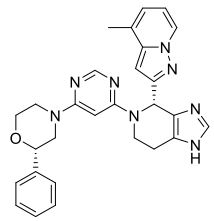
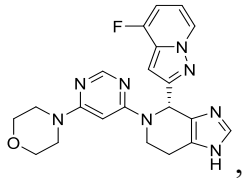
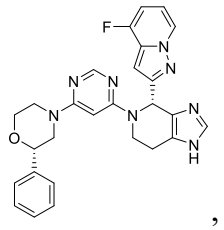
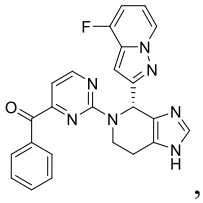
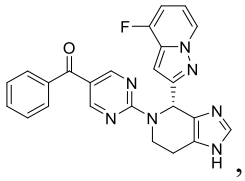
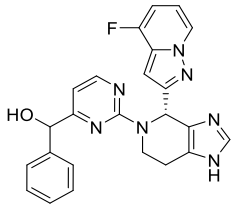
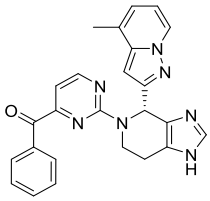
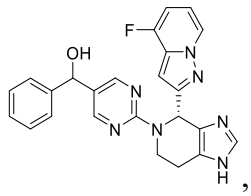
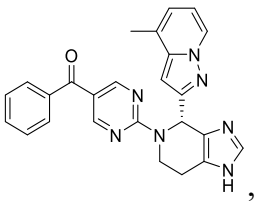
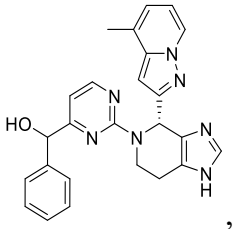
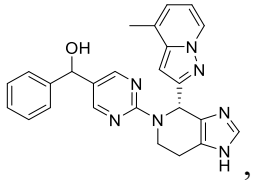
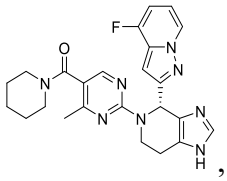
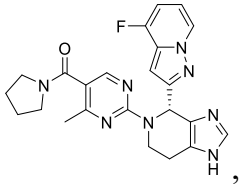
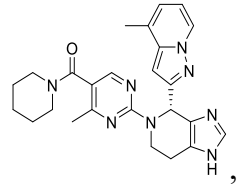
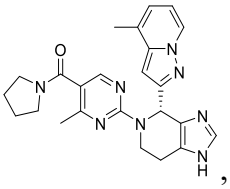
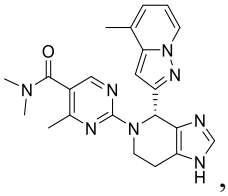
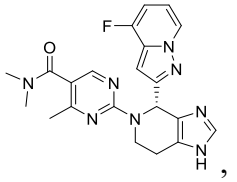
iii) C_{1-6}alkoxy such as methoxy or ethoxy;

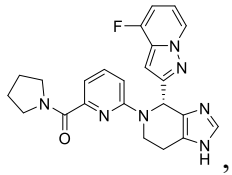
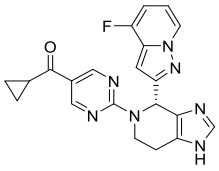
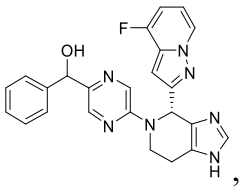
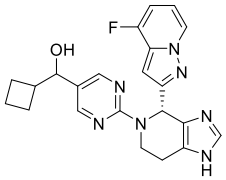
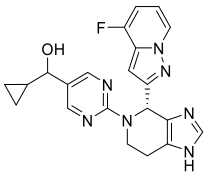
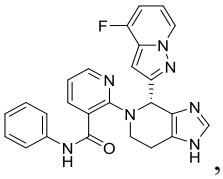
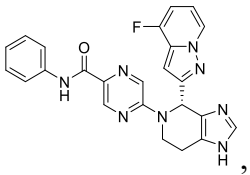
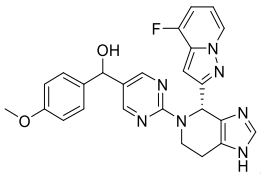
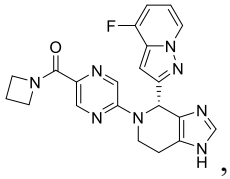
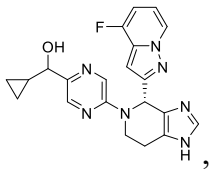
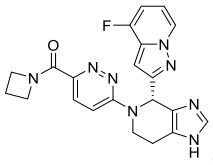
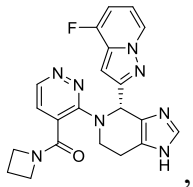
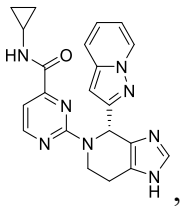
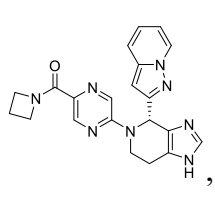
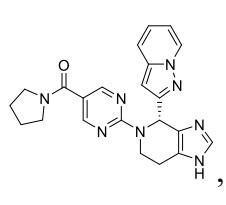
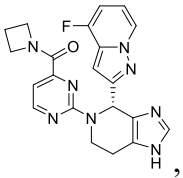
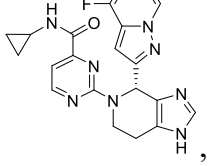
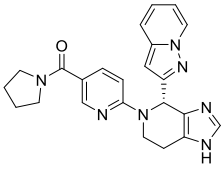
iv) C_{1-6}haloalkyl such as CF_3 or CHF_2;

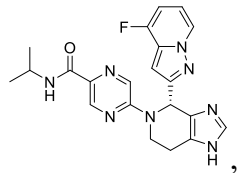
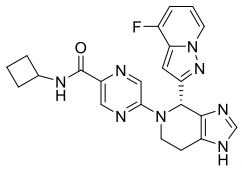
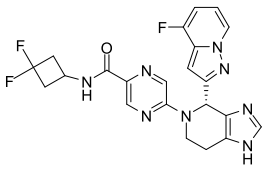
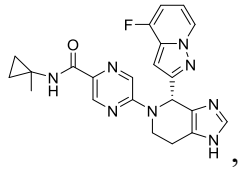
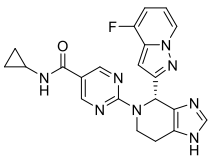
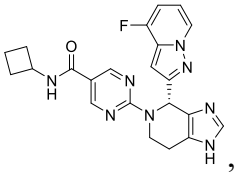
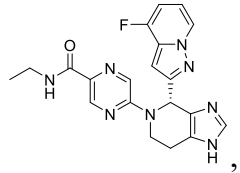
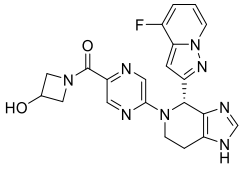
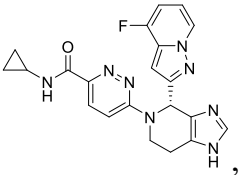
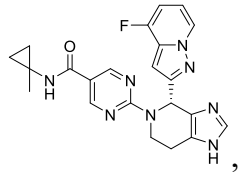
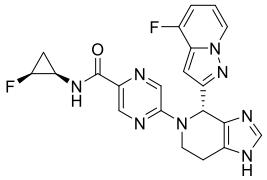
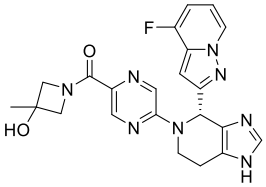
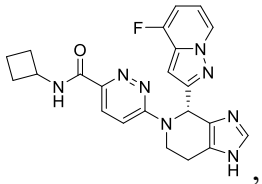
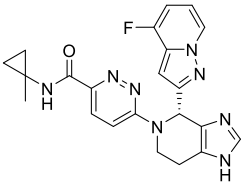
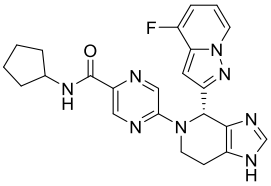
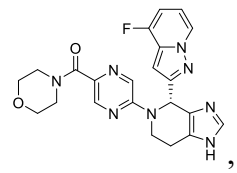
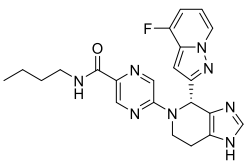
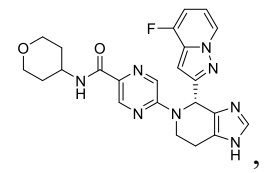
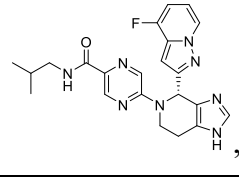
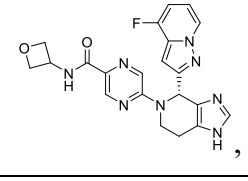
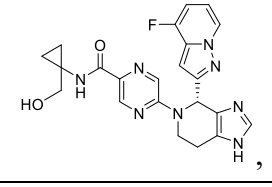
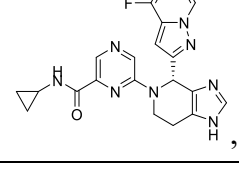
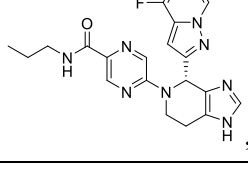
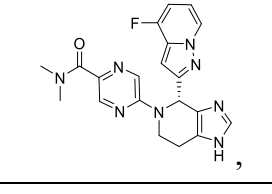
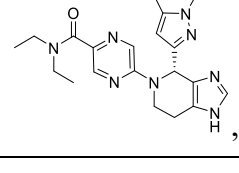
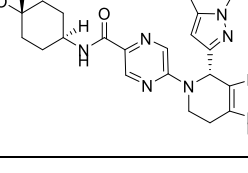
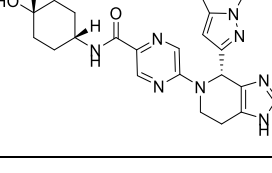
v) C_{1-6}haloalkoxy such as OCF_3 or $OCHF_2$; or

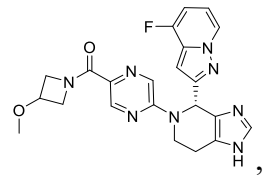
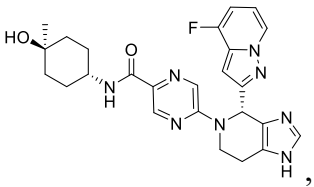
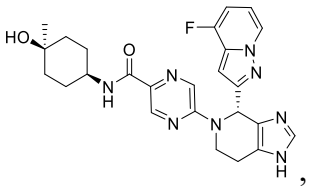
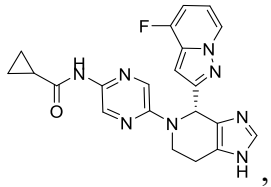
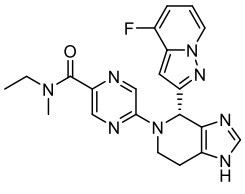
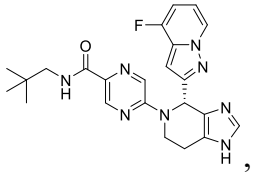
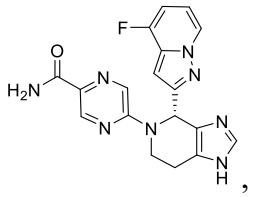
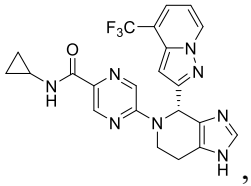
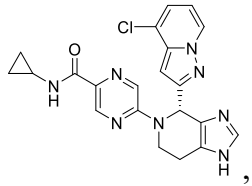
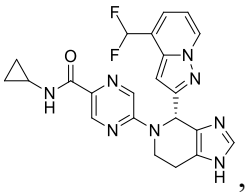
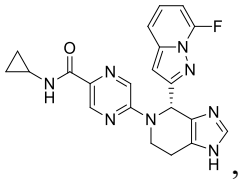
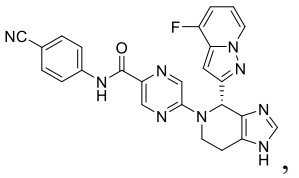
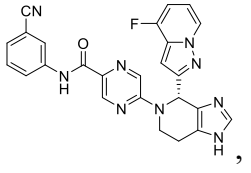
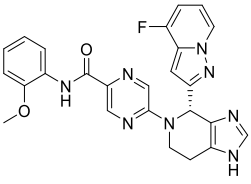
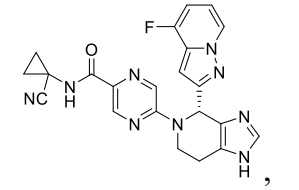
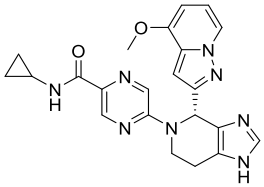
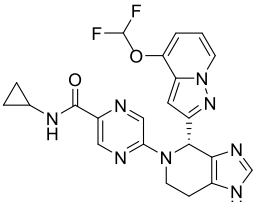
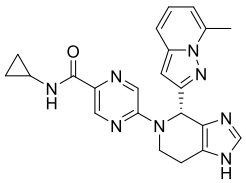
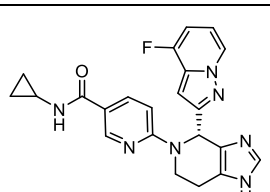
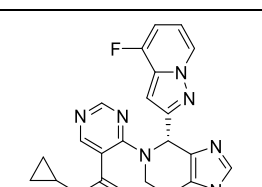
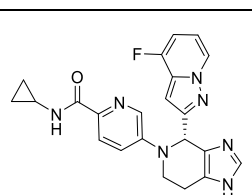
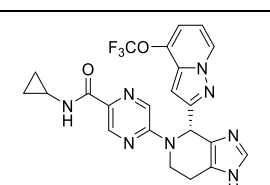
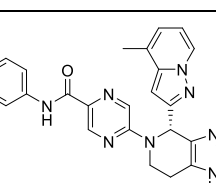
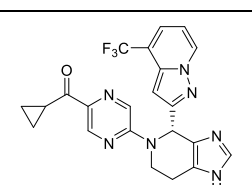
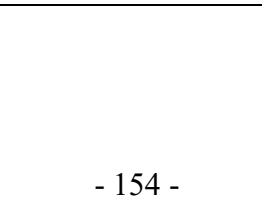
vi) C_{3-6}cycloalkyl such as cyclopropyl.

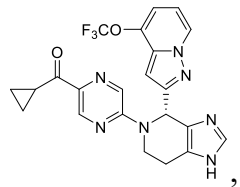
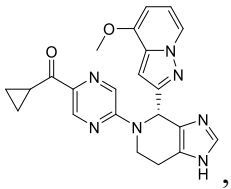
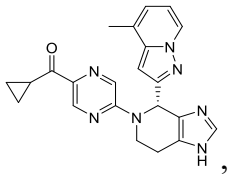
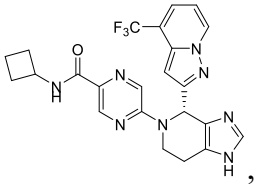
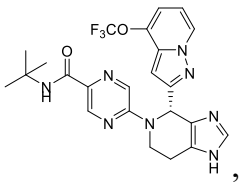
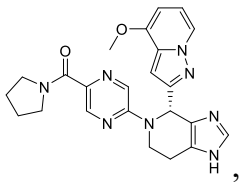
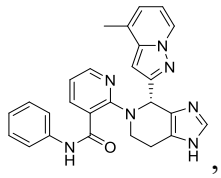
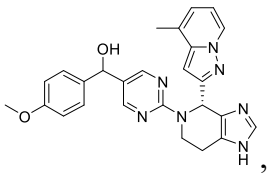
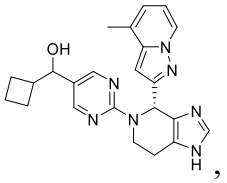
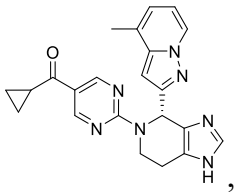
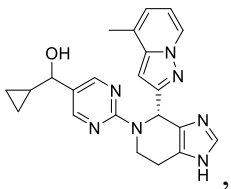
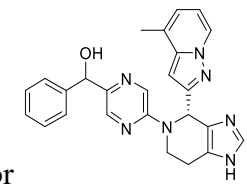
14. The compound of claim 1, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, wherein the compound is selected from the following:

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15. The compound of any one of claims 1 to 13, wherein the compound is an S-enantiomer, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer.

16. A pharmaceutical composition comprising a compound of any one of claims 1 to 15, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or the tautomer, and a pharmaceutically acceptable excipient.

17. A compound of any one of claims 1 to 15, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition of claim 16, for use in stabilizing a mutant phenylalanine hydroxylase (PAH) protein in a subject suffering from phenylketonuria, comprising contacting the protein with a compound of any one of claims 1 to 15, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition of claim 16.

18. The compound, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition, for use of claim 17, wherein:

i) the mutant phenylalanine hydroxylase (PAH) protein contains at least one R408W, R261Q, R243Q, Y414C, L48S, A403V, I65T, R241C, L348V, R408Q, or V388M mutation; or

ii) the mutant phenylalanine hydroxylase (PAH) protein contains at least one R408W, Y414C, I65T, F39L, R408Q, L348V, R261Q, A300S, or L48S mutation; or

iii) the mutant phenylalanine hydroxylase (PAH) protein contains at least one R408W mutation; or

iv) the mutant phenylalanine hydroxylase (PAH) protein contains two R408W mutations.

19. A compound of any one of claims 1 to 15, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition of claim 16, for use in reducing blood phenylalanine concentration in a subject suffering from phenylketonuria, optionally wherein:

i) the blood phenylalanine concentration is reduced to a concentration less than or equal to 600 μM or the blood phenylalanine concentration is reduced to a concentration less than or equal to 360 μM; and/or

ii) the subject has a blood phenylalanine concentration greater than 600 μM prior to administration of the compound, or wherein the subject has a blood phenylalanine concentration greater than 1200 μM prior to administration of the compound.

20. A compound of any one of claims 1 to 15, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition of claim 16, for use in treating phenylketonuria in a subject.

21. Use of the compound of any one of claims 1 to 15, or tautomer thereof, or a pharmaceutically acceptable salt of the compound or tautomer, or the pharmaceutical composition of claim 16, in the manufacture of a medicament for treating phenylketonuria in a subject.