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(54) **METHODS OF TREATING CANCER IN BIOMARKER-IDENTIFIED PATIENTS WITH NON-COVALENT INHIBITORS OF CYCLIN-DEPENDENT KINASE 7 (CDK7)**

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(57) **ABSTRACT**

The present invention relates to methods of identifying patients suffering from various types of cancer who are more likely to respond to treatment with a CDK7 inhibitor conforming to structural Formula (I), (Ia), a species thereof, or a specified form thereof (as described herein), either when administered or used alone or in combination with a second therapeutic agent (e.g., another anti-cancer therapy). Patients are identified based on one or more features (e.g., gene copy number or expression level) of certain biomarkers (e.g., RB1 or another member of the E2F pathway). In addition, the present invention relates to methods of treating an identified patient with a compound conforming to structural Formula (I), (Ia), a species thereof, or a specified form thereof, either alone or in combination with a second therapeutic agent. In another aspect, the present invention features kits including instructions for treating a patient identified as described herein.

Specification includes a Sequence Listing.

FIG. 1

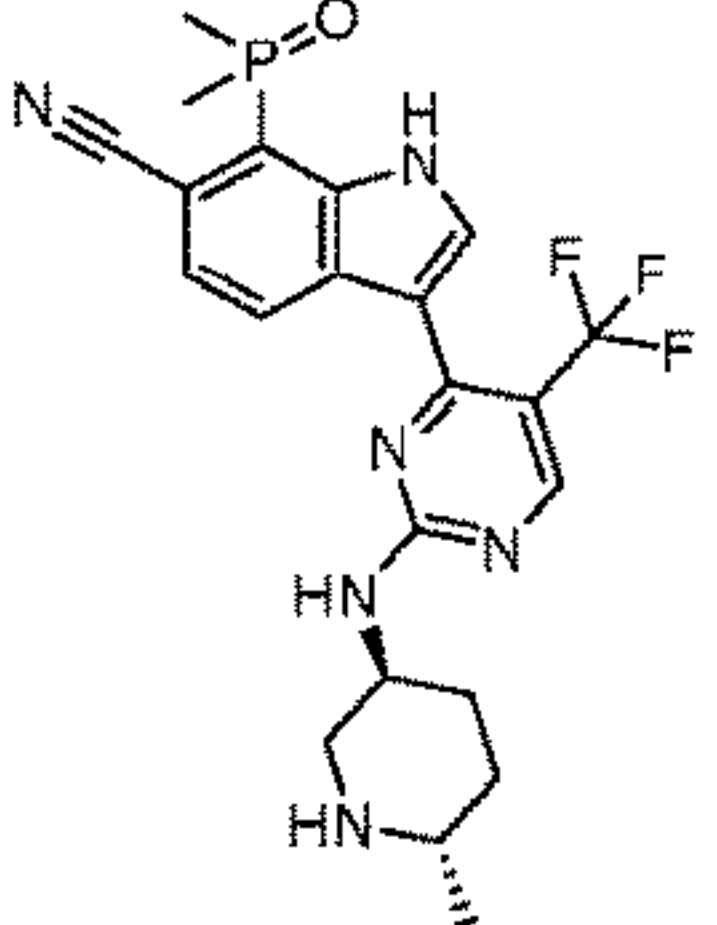
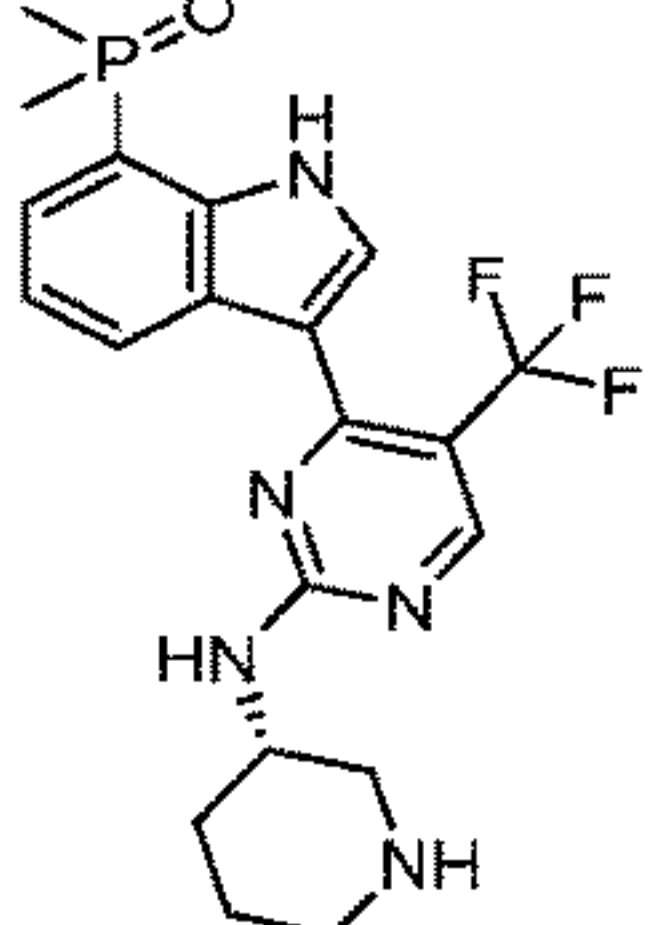
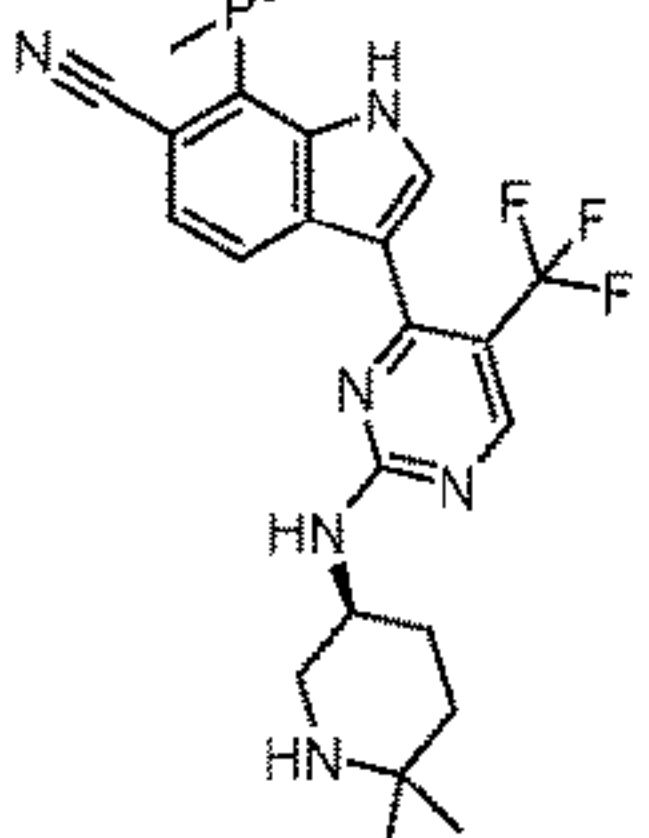
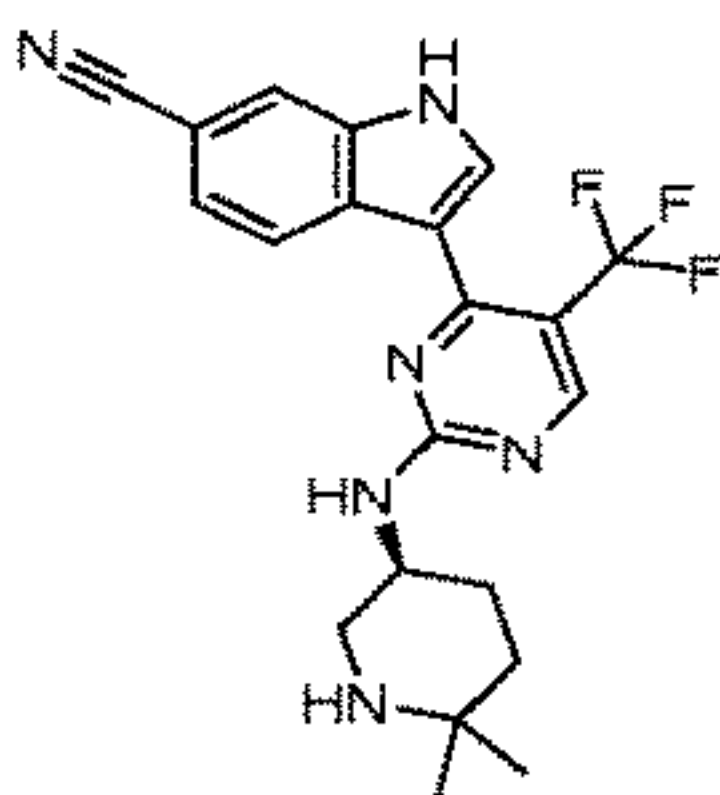
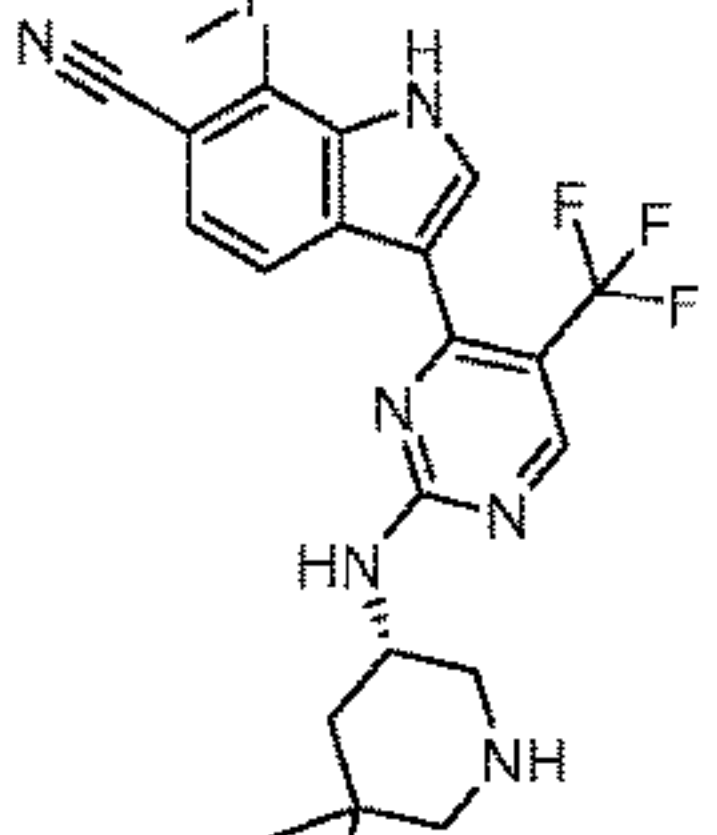
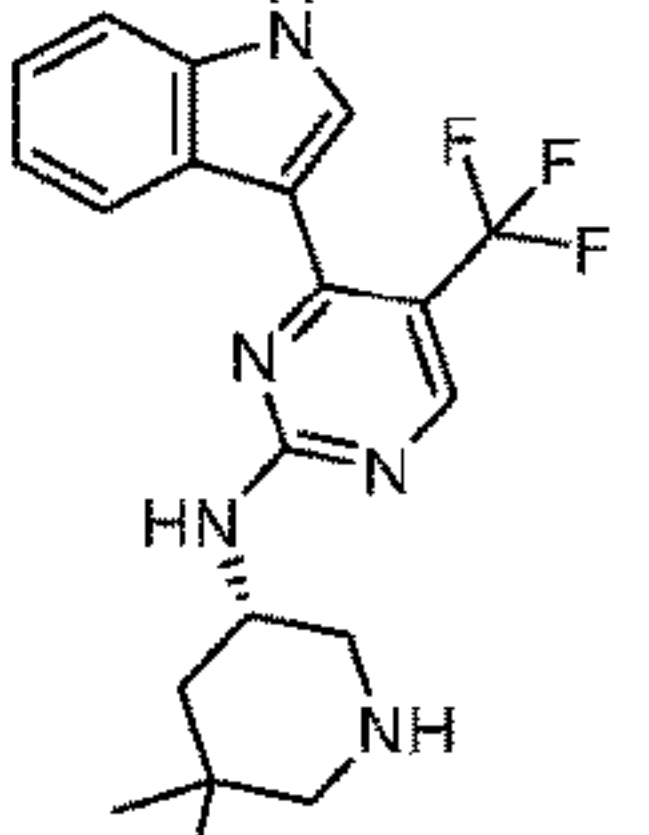
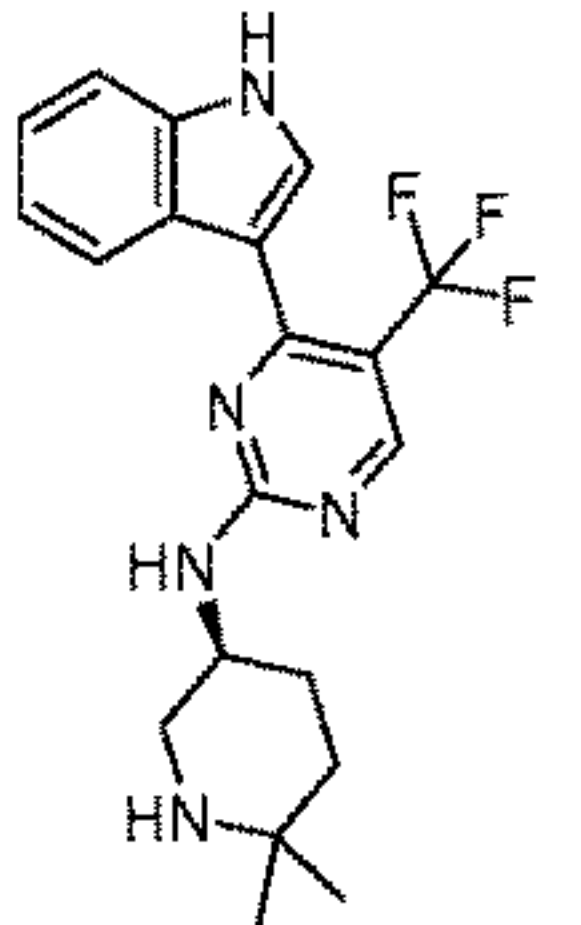
Compound 100 	CDK7 K _D (nM) = 0.057		Comparator 1 	CDK7 K _D (nM) = 0.18		
	CDK12 K _i (nM) 230	(K _i /K _D CDK7) 4100		CDK12 K _i (nM) 51	(K _i /K _D CDK7) 280	
	CDK2 K _i (nM) 1500	(K _i /K _D CDK7) 26000		CDK2 K _i (nM) 210	(K _i /K _D CDK7) 1100	
	CDK9 K _i (nM) 800	(K _i /K _D CDK7) 14000		CDK9 K _i (nM) 140	(K _i /K _D CDK7) 790	
Compound 101 	CDK7 K _D (nM) =0.065		Comparator 2 	CDK7 K _D (nM) = 0.45		
	CDK12 K _i (nM) 870	(K _i /K _D CDK7) 13000		CDK12 K _i (nM) 140	(K _i /K _D CDK7) 320	
	CDK2 K _i (nM) 2600	(K _i /K _D CDK7) 40000		CDK2 K _i (nM) 810	(K _i /K _D CDK7) 1800	
	CDK9 K _i (nM) 960	(K _i /K _D CDK7) 15000		CDK9 K _i (nM) 130	(K _i /K _D CDK7) 280	
Compound 102 	CDK7 K _D (nM) = 0.059		Comparator 3 	CDK7 K _D (nM) = 0.21		
	CDK12 K _i (nM) 78	(K _i /K _D CDK7) 1300		CDK12 K _i (nM) 18	(K _i /K _D CDK7) 89	
	CDK2 K _i (nM) 390	(K _i /K _D CDK7) 6800		CDK2 K _i (nM) 26	(K _i /K _D CDK7) 130	
	CDK9 K _i (nM) 290	(K _i /K _D CDK7) 4900		CDK9 K _i (nM) 20	(K _i /K _D CDK7) 99	
			Comparator 4 	CDK7 K _D (nM) = 0.34		
				CDK12 K _i (nM) 48	(K _i /K _D CDK7) 140	
				CDK2 K _i (nM) 64	(K _i /K _D CDK7) 190	
				CDK9 K _i (nM) 36	(K _i /K _D CDK7) 100	

FIG. 2

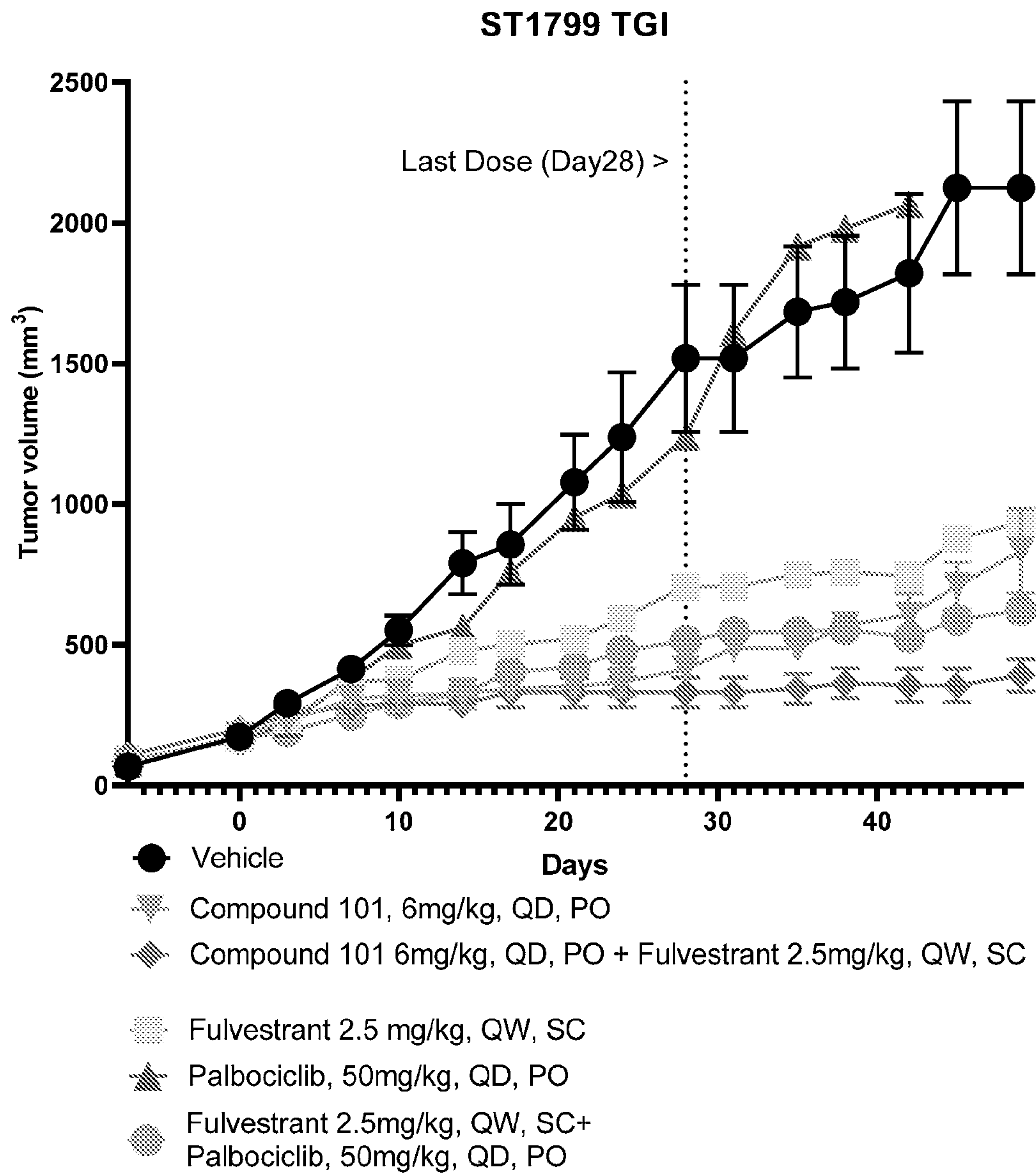


FIG. 3

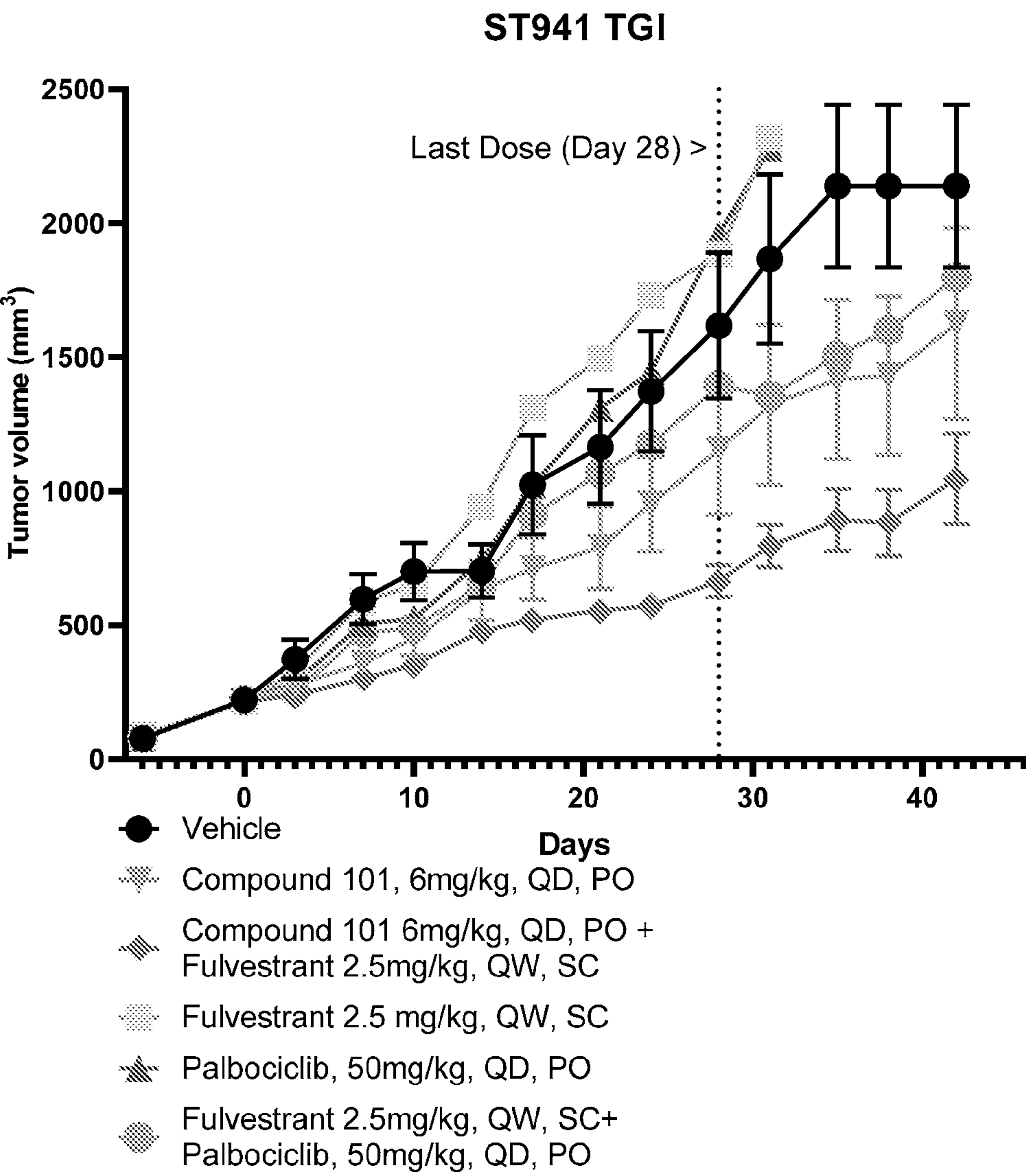


FIG. 4

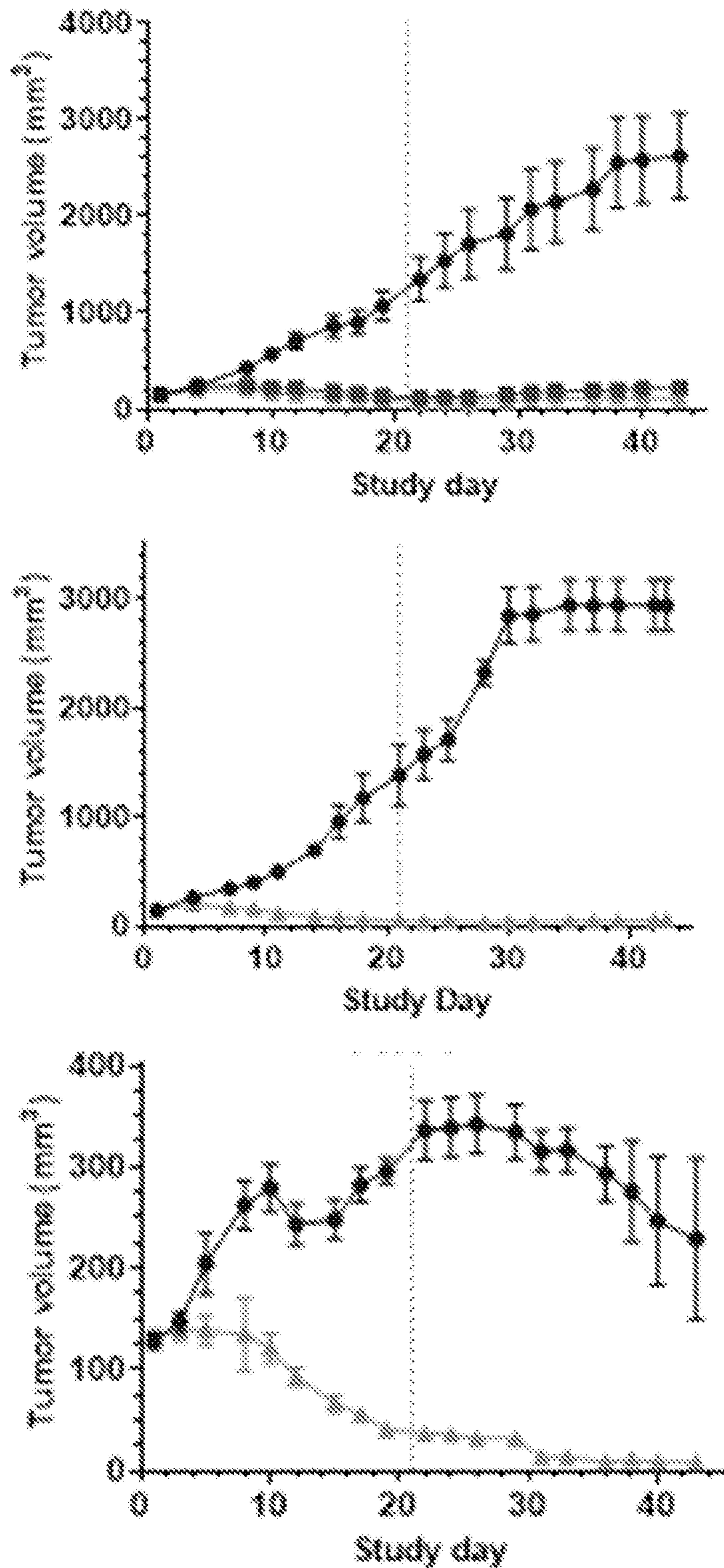


FIG. 5

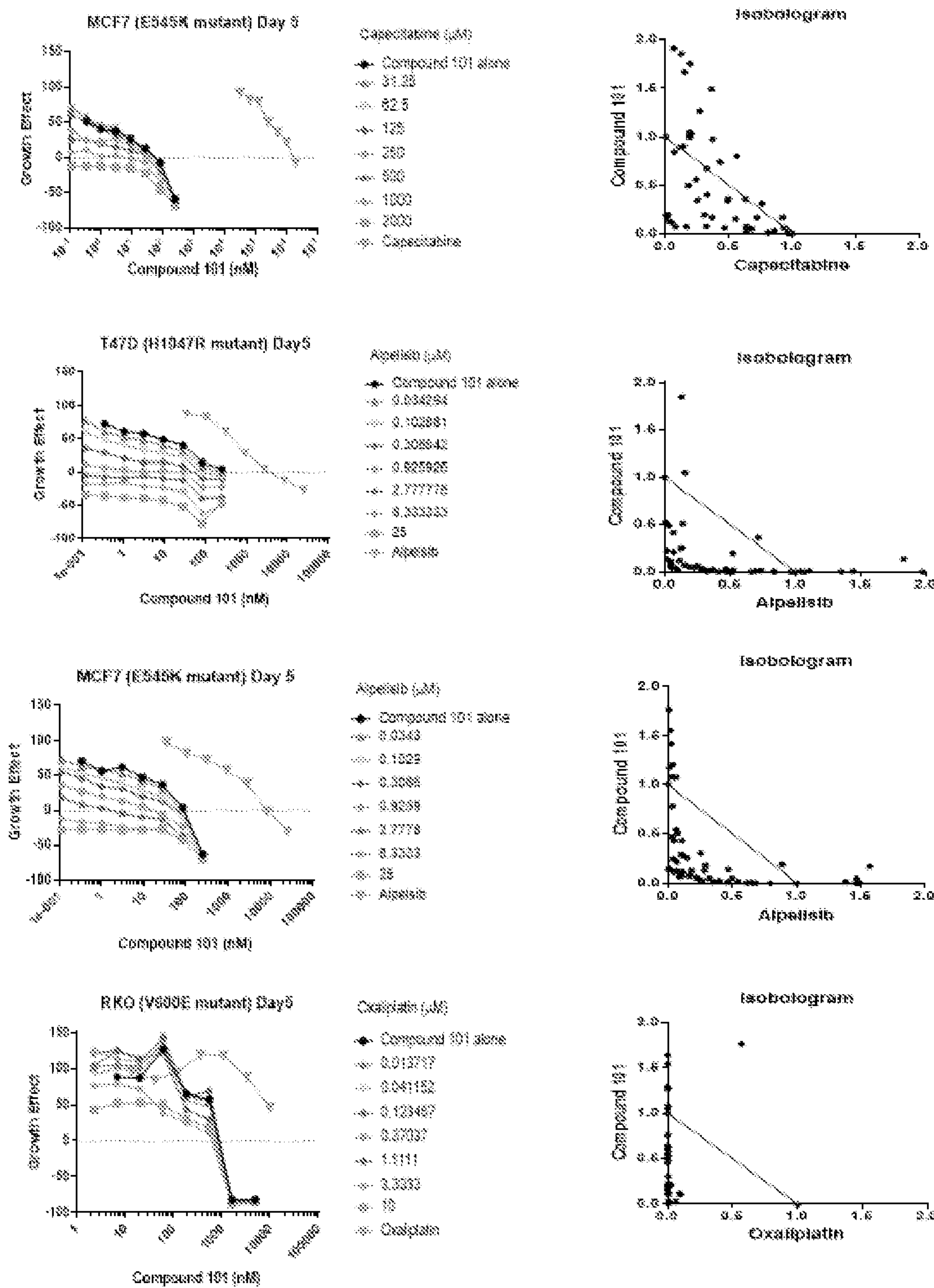


FIG. 5 (cont.)

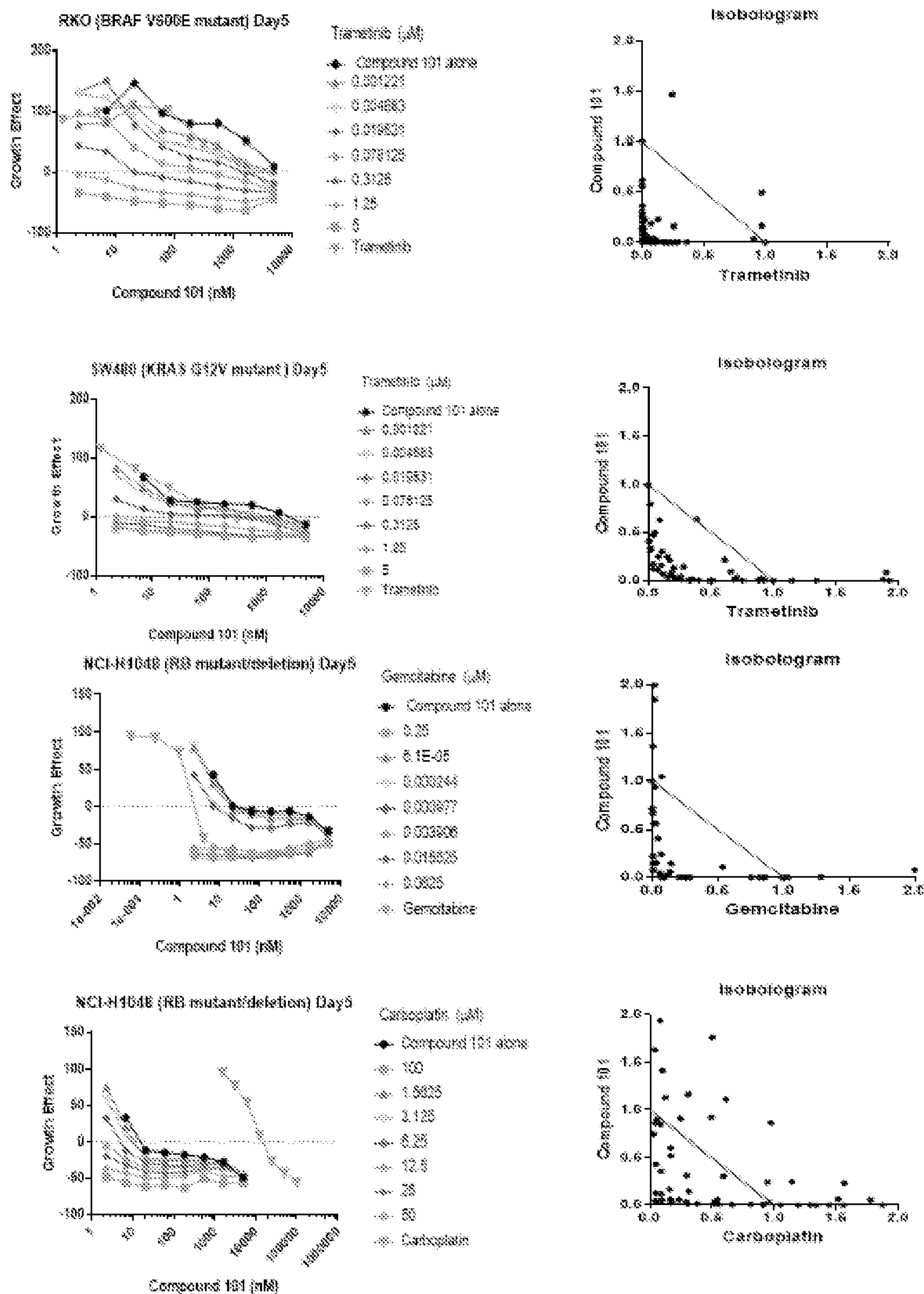


FIG. 6

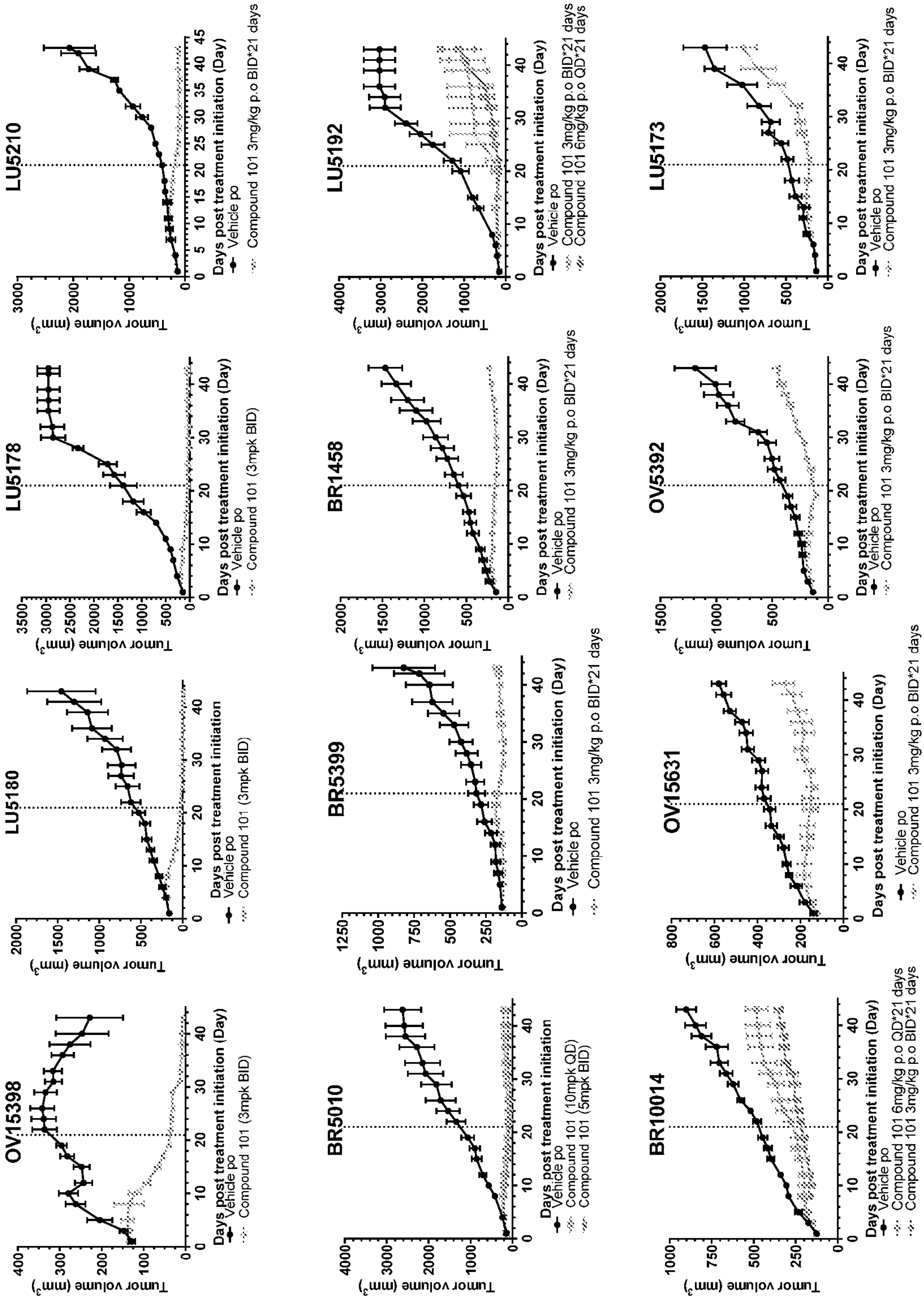
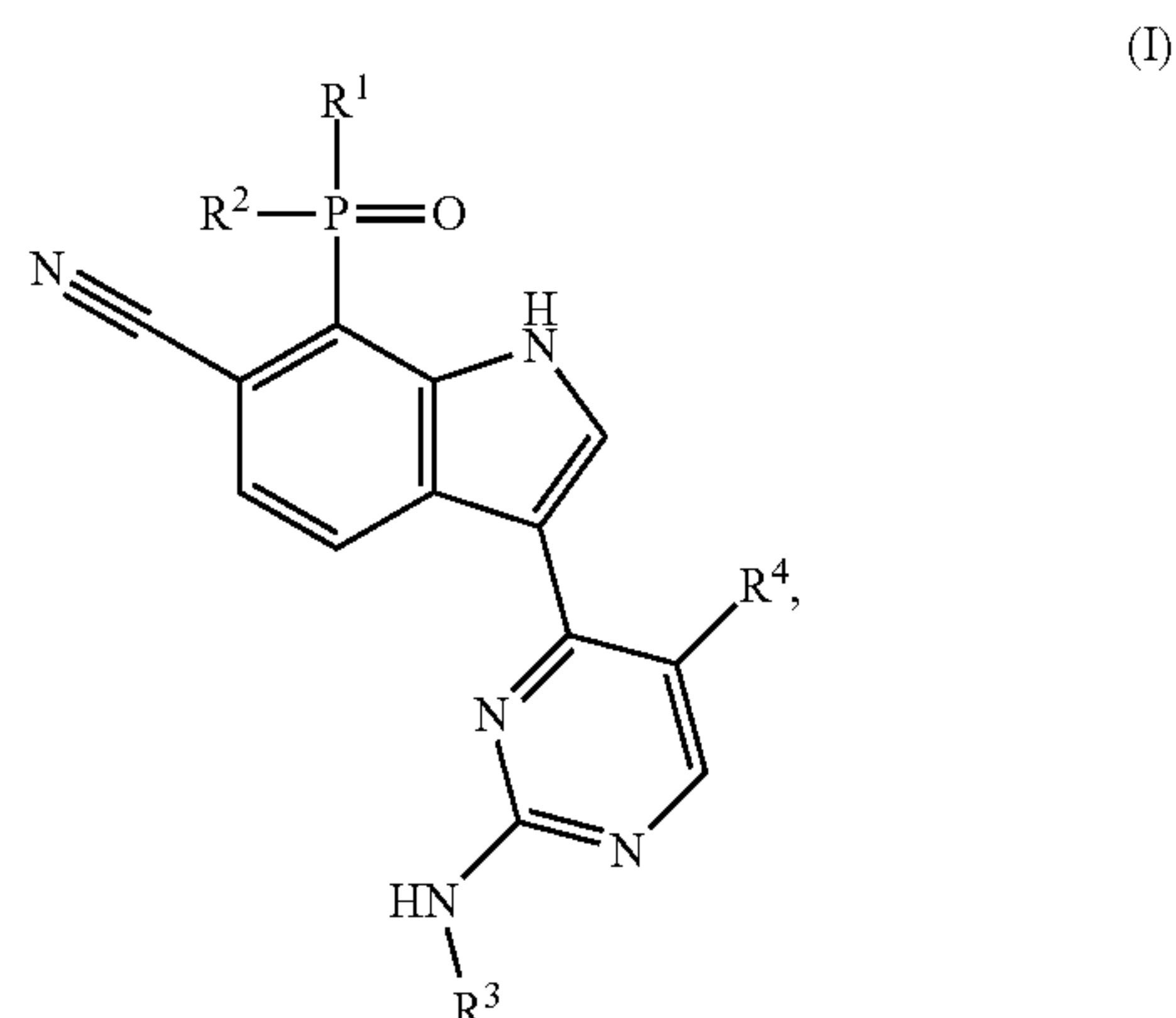


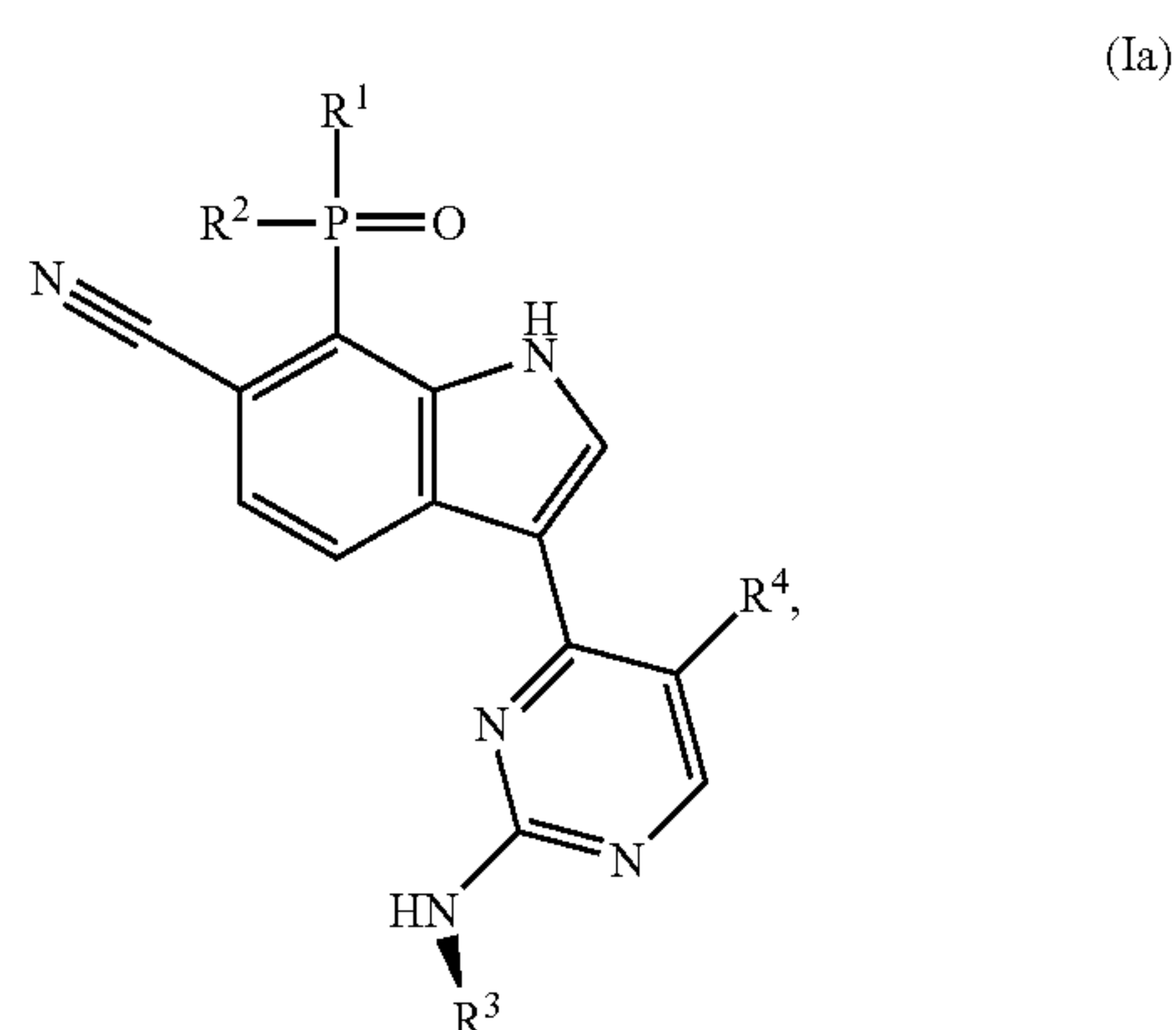
FIG. 7

PDX model	End of Treatment Day 21		Post-treatment Day 42		RB pathway genetics
	% TGI	% Regression	% TGI	% Regression	
OV15398	>100	80	>100	98	RB1 (CN=1, p.Q637*)
LU5180	>100	72	>100	93	CDKN2A (CN=1)
LU5178	>100	64	>100	73	RB1 (CN=0)
BR5010	>100	55	>100	27	CCNE1 (CN=21)
LU5210	82	0	>100	8	RB1 (p.L343SfsTer3)
BR1458	90	0	95	0	CDKN2A (CN=0)
					RB1 (CN=1, p.Y155C)
BR5399	82	0	95	0	RB1 (CN=1)
LU5192	94	0	69	0	None
BR10014	91	0	67	0	None
OV5392	92	0	64	0	None
OV15631	70	0	71	0	None
LU5173	74	0	33	0	None

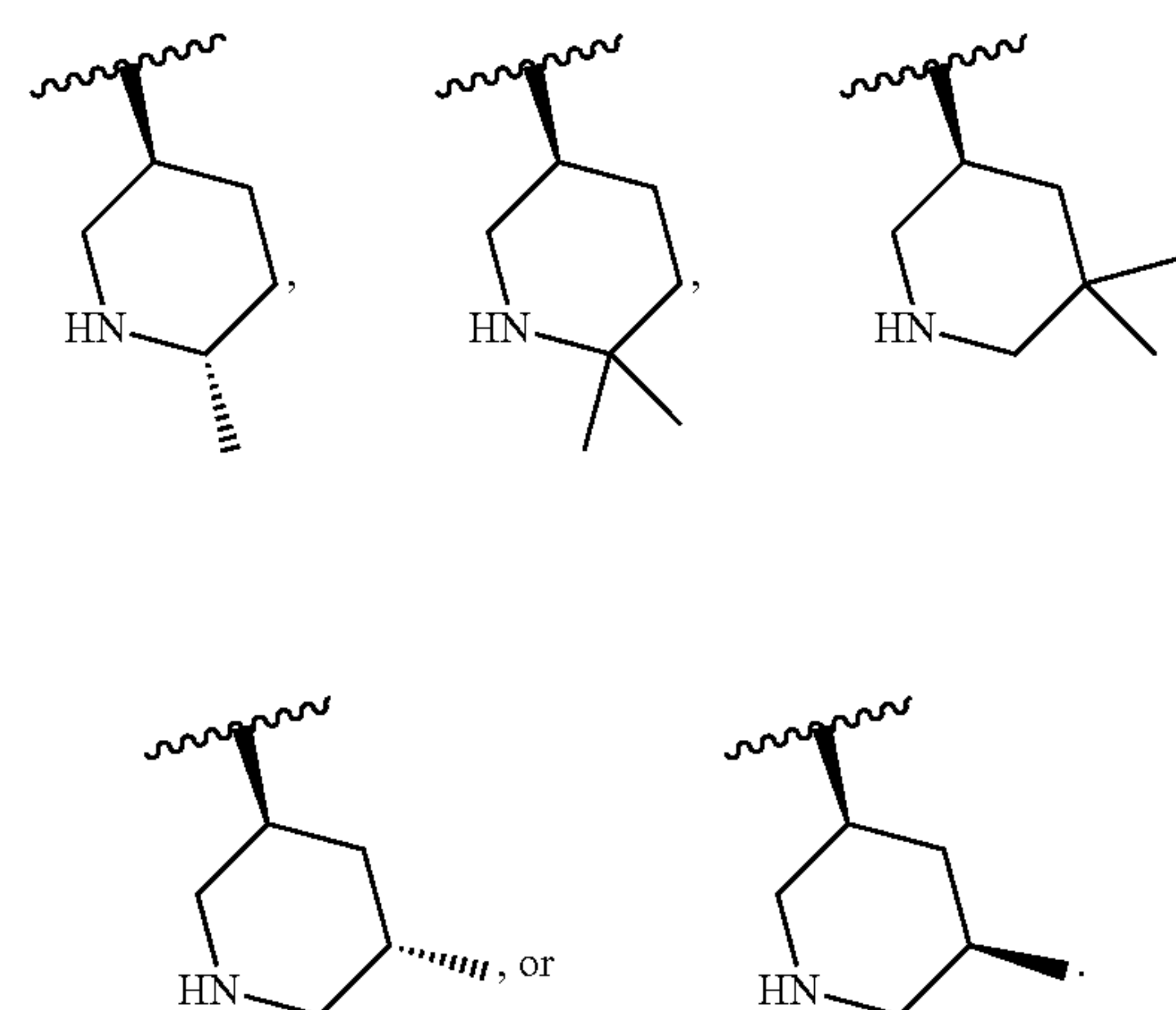
[0004] The treatment methods of the invention and corresponding “uses” include administering, or the use of, a compound of Formula (I), any of which may be included in a pharmaceutically acceptable composition and administered, e.g., by a route and regimen described herein, to a patient identified as described herein. Compounds useful in the present methods have structural Formula (I):



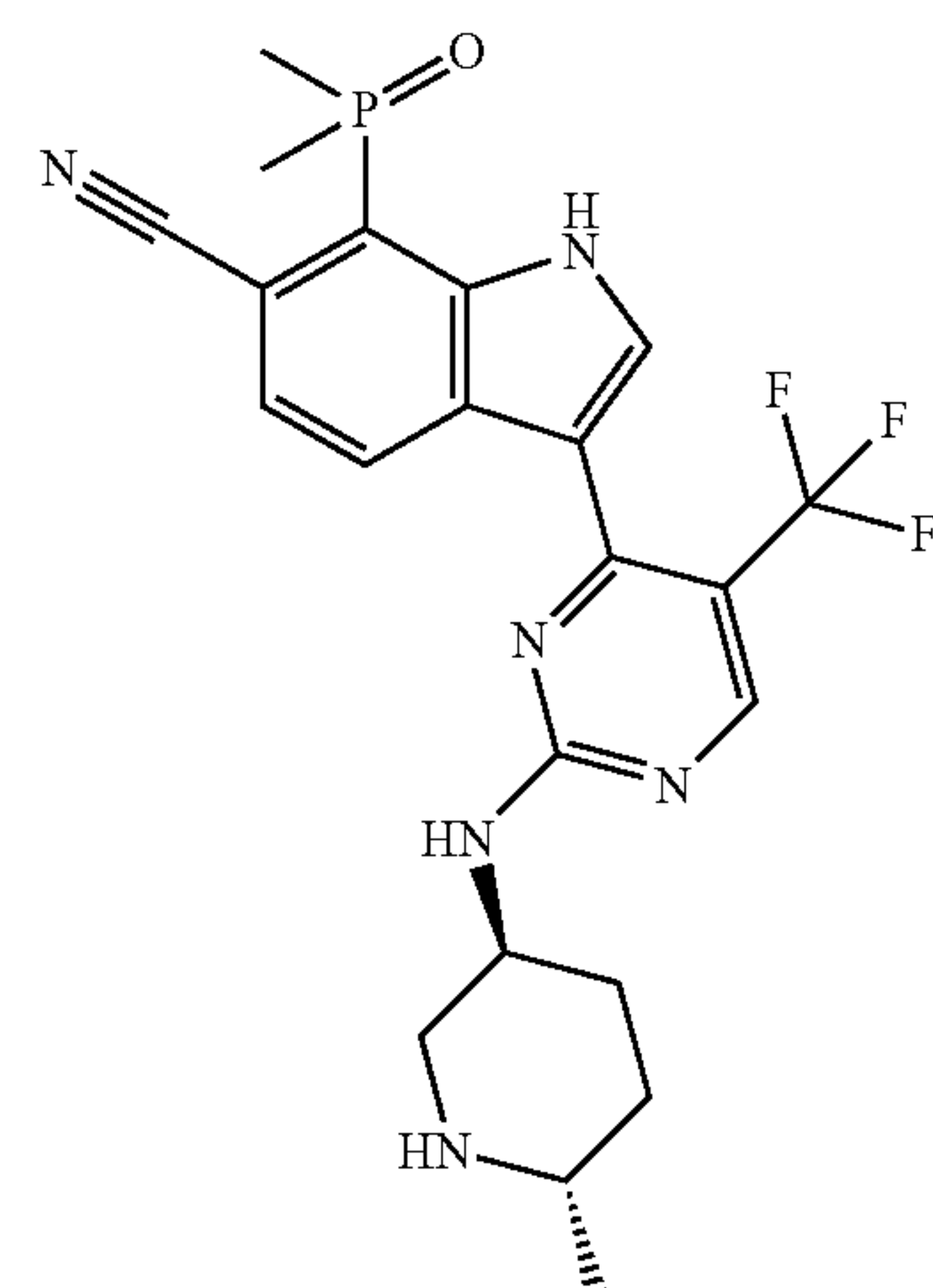
or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, or isotopic form thereof, wherein R^1 is methyl or ethyl; R^2 is methyl or ethyl; R^3 is 5-methylpiperidin-3-yl, 5,5-dimethylpiperidin-3-yl, 6-methylpiperidin-3-yl, or 6,6-dimethylpiperidin-3-yl, wherein one or more hydrogen atoms in R^3 is optionally replaced by deuterium; and R^4 is $-\text{CF}_3$ or chloro. More specifically, in a compound of Formula (I) or in the pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, isotopic form, or other specified form thereof (i) R^1 is methyl and R^2 is methyl or (ii) R^1 is methyl and R^2 is ethyl. In other embodiments, R^1 is ethyl and R^2 is ethyl. In some aspects of any one of these embodiments, R^4 is $-\text{CF}_3$. In other aspects of any one of these embodiments, R^4 is chloro. In various aspects of any of the preceding embodiments, R^3 is 5-methylpiperidin-3-yl, R^3 is 5,5-dimethylpiperidin-3-yl, R^3 is 6-methylpiperidin-3-yl, or R^3 is 6,6-dimethylpiperidin-3-yl, wherein one or more hydrogen atoms in R^3 is optionally replaced by deuterium. A compound of Formula (I) can have structural Formula (Ia):

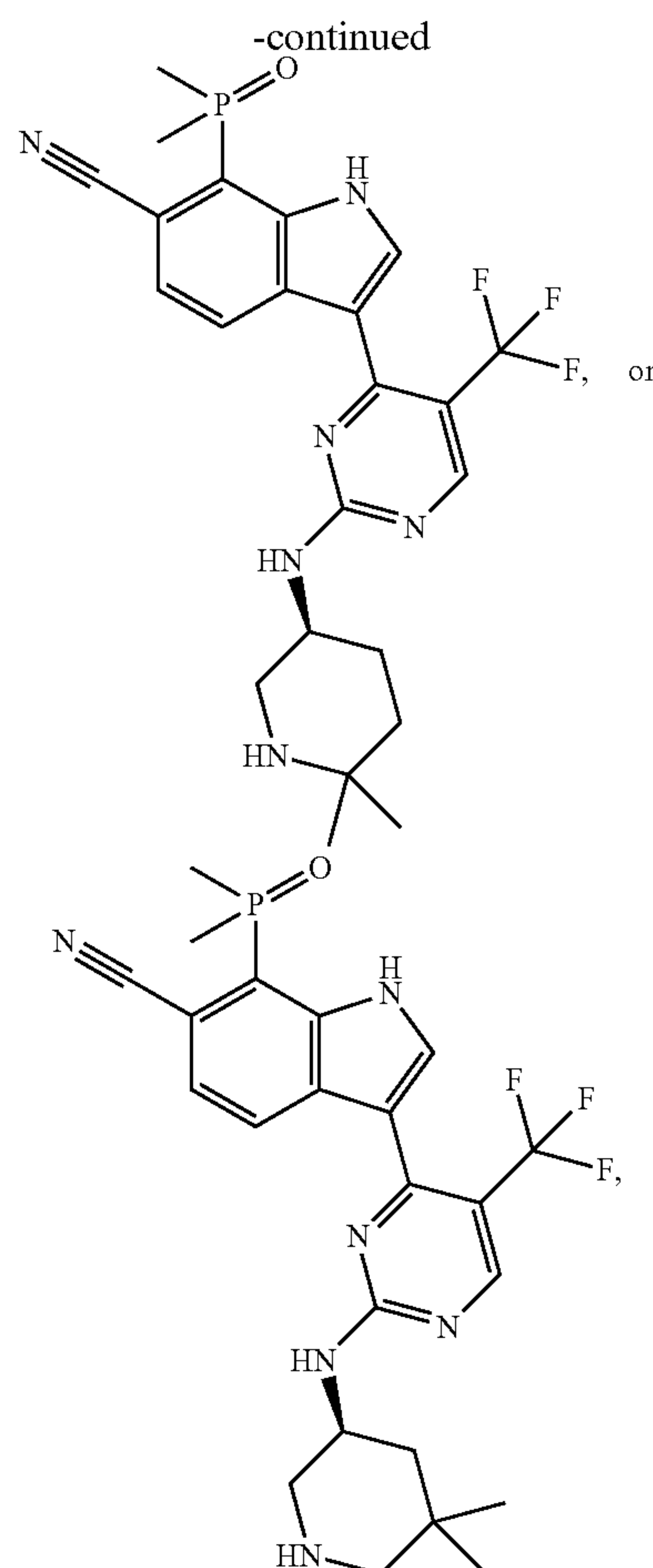


and the invention encompasses pharmaceutically acceptable salts, solvates (e.g., hydrates), tautomers, isotopic forms, or other specified forms of a compound of Formula (Ia), wherein R^3 is

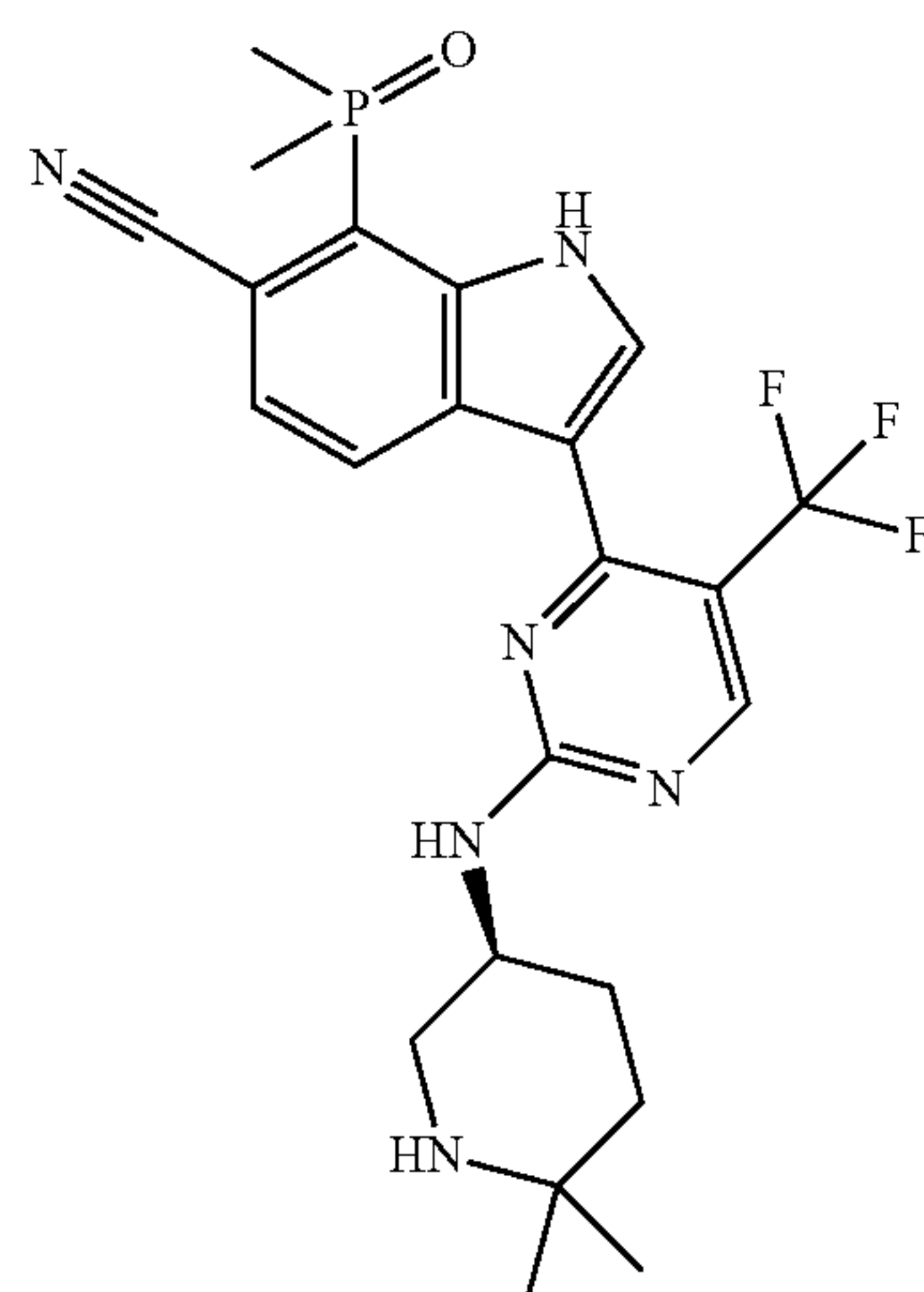


[0005] More specifically, in a compound of Formula (Ia) or a pharmaceutically acceptable salt, solvate, tautomer, isotopic form, or other specified form thereof (i) R^1 is methyl and R^2 is methyl or (ii) R^1 is methyl and R^2 is ethyl. In other embodiments, R^1 is ethyl and R^2 is ethyl. In some embodiments, in a compound of Formula (Ia) or a specified form thereof, R^4 is $-\text{CF}_3$. In other embodiments, in a compound of Formula (Ia) or a specified form thereof, R^4 is chloro. In some embodiments, a compound of Formula (I) or (Ia) is:





and the invention encompasses methods and the use of pharmaceutically acceptable salts, solvates (e.g., hydrates), tautomers, isotopic forms or other specified forms of any one of the three foregoing compounds. In one embodiment, the compound is



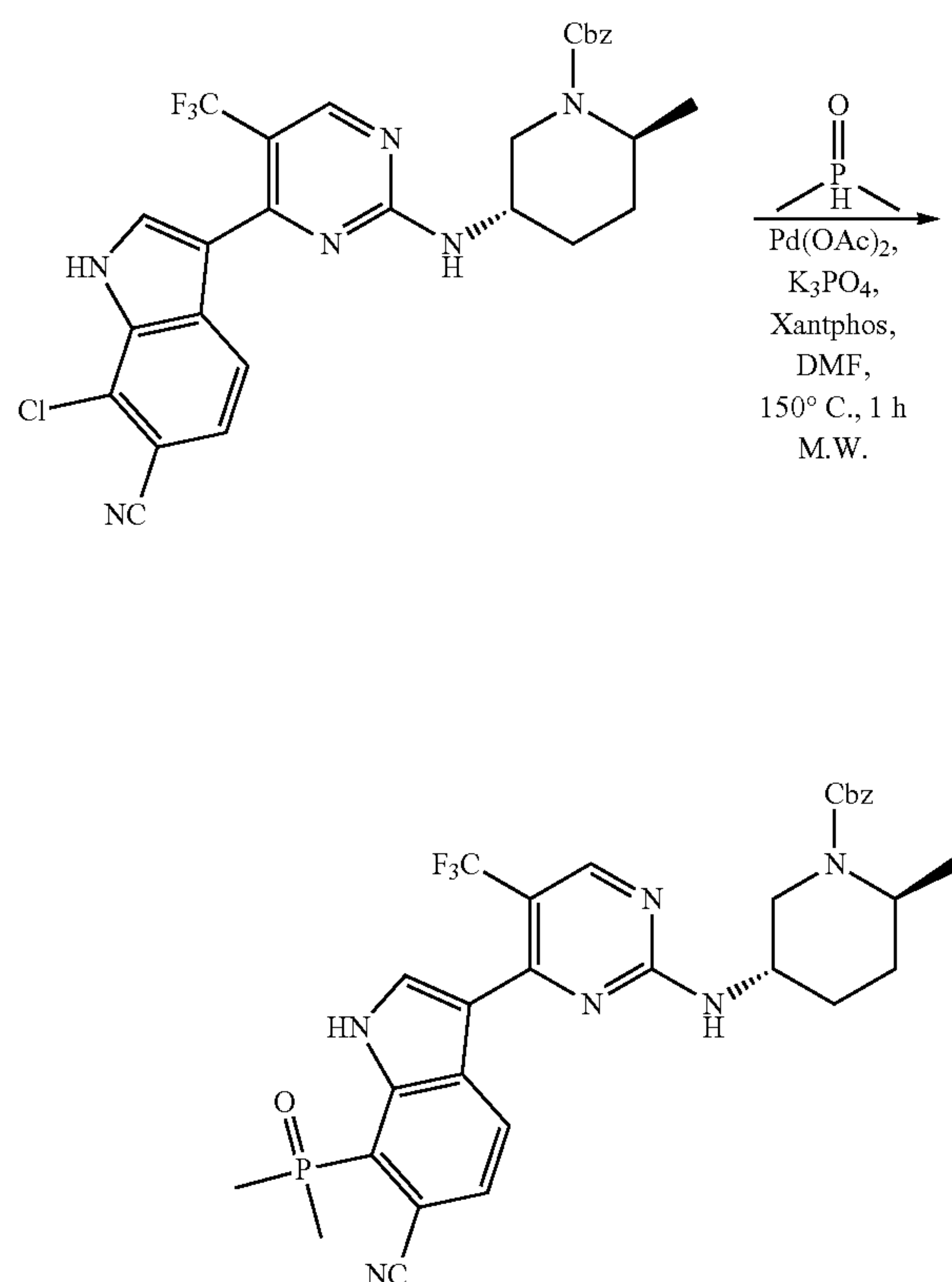
or a pharmaceutically acceptable salt thereof. The invention also encompasses solvates (e.g., hydrates), tautomers, isotopic forms or other specified forms of the foregoing com-

pound. In isotopic forms, one or more hydrogen atoms in R^3 is replaced with deuterium. In other embodiments, none of the hydrogen atoms of a compound (e.g., none of the hydrogen atoms in R^3) are replaced with deuterium. Any compound of Formula (I), (Ia), or a species thereof can be of a “specified form,” by which we mean a salt, solvate (e.g., hydrate), stereoisomer (or mixture thereof), tautomer, or isotopic form of a compound of Formula (I), (Ia), or a species thereof. Also within the meaning of “specified form” are forms of a compound that manifest a combination of the attributes, features, or properties of a salt, solvate, stereoisomer, tautomer, or isotopic form. For example, the methods and uses of the invention can be carried out with a salt that has been solvated (e.g., a hydrated) or a salt of a stereoisomer, tautomer, or isotopic form of a compound of Formula I, I(a), or a species thereof; with a solvate (e.g., hydrate) containing a salt, stereoisomer, tautomer, or isotopic form of a compound of Formula I, I(a), or a species thereof; with a stereoisomer of a compound of Formula I, I(a), or a species thereof that is in the form of a salt or solvate (e.g., hydrate) or is a tautomer or isotopic form of a compound of Formula I, I(a), or a species thereof, with a tautomer of a compound of Formula I, I(a), or a species thereof that is in the form of a salt or solvate (e.g., hydrate) or that is a stereoisomer or isotopic form of a compound of Formula I, I(a), or a species thereof; or with an isotopic form of a compound of Formula I, I(a), or a species thereof that is a salt, solvate (e.g., hydrate), stereoisomer, or tautomer of a compound of Formula I, I(a), or a species thereof. Any of these specified forms can be pharmaceutically acceptable and/or contained within a pharmaceutically acceptable composition (e.g., formulated for oral administration) for use in a method described herein.

[0006] Accordingly, the invention features treatment methods including a step of administering a compound of structural Formula (I), or a pharmaceutically acceptable salt, solvate, stereoisomer or mixture of stereoisomers, tautomer, or isotopic form thereof, optionally within a pharmaceutical composition, wherein R^1 , R^2 , R^3 , and R^4 are as defined herein, in treating cancer in a selected patient, wherein the patient has been determined to have a cancer in which: (a) a gene selected from RB1, RBL1, RBL2, CDKN2A, CDKN2B, CDKN2C, CDKN2D, CDKN1A, CDKN1B, CDKN1C, and FBWX7 is mutated, is genetically deleted, contains an epigenetic alteration, is translocated, is transcribed at a level equal to or below a pre-determined threshold, or encodes a protein that is translated at a level equal to or below a pre-determined threshold or has decreased activity relative to a reference standard; (b) a gene selected from E2F1, E2F2, E2F3, E2F4, E2F5, E2F6, E2F7, E2F8, CDK1, CDK2, CDK4, CDK6, CCNA1, CCNB1, CCND1, CCND2, CCND3, CCNE1, CCNE2, and BRAF is mutated, is genetically gained or amplified, contains an epigenetic alteration, is translocated, transcribed at a level equal to or above a pre-determined threshold, or encodes a protein that is translated at a level equal to or above a pre-determined threshold or has increased activity relative to a reference standard; or (c) the gene Bcl2-like 1 is mutated, contains an epigenetic alteration, is translocated, is transcribed at a level equal to or below a pre-determined threshold, or encodes a BCL-xL protein that is translated at a level equal to or below a pre-determined threshold or has decreased activity relative to a reference standard. In any embodiment of this method, the cancer is a blood cancer,

Step 2: Benzyl (2S, 5S)-5-[[4-(6-cyano-7-dimethylphosphoryl-1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]amino]-2-methyl-piperidine-1-carboxylate

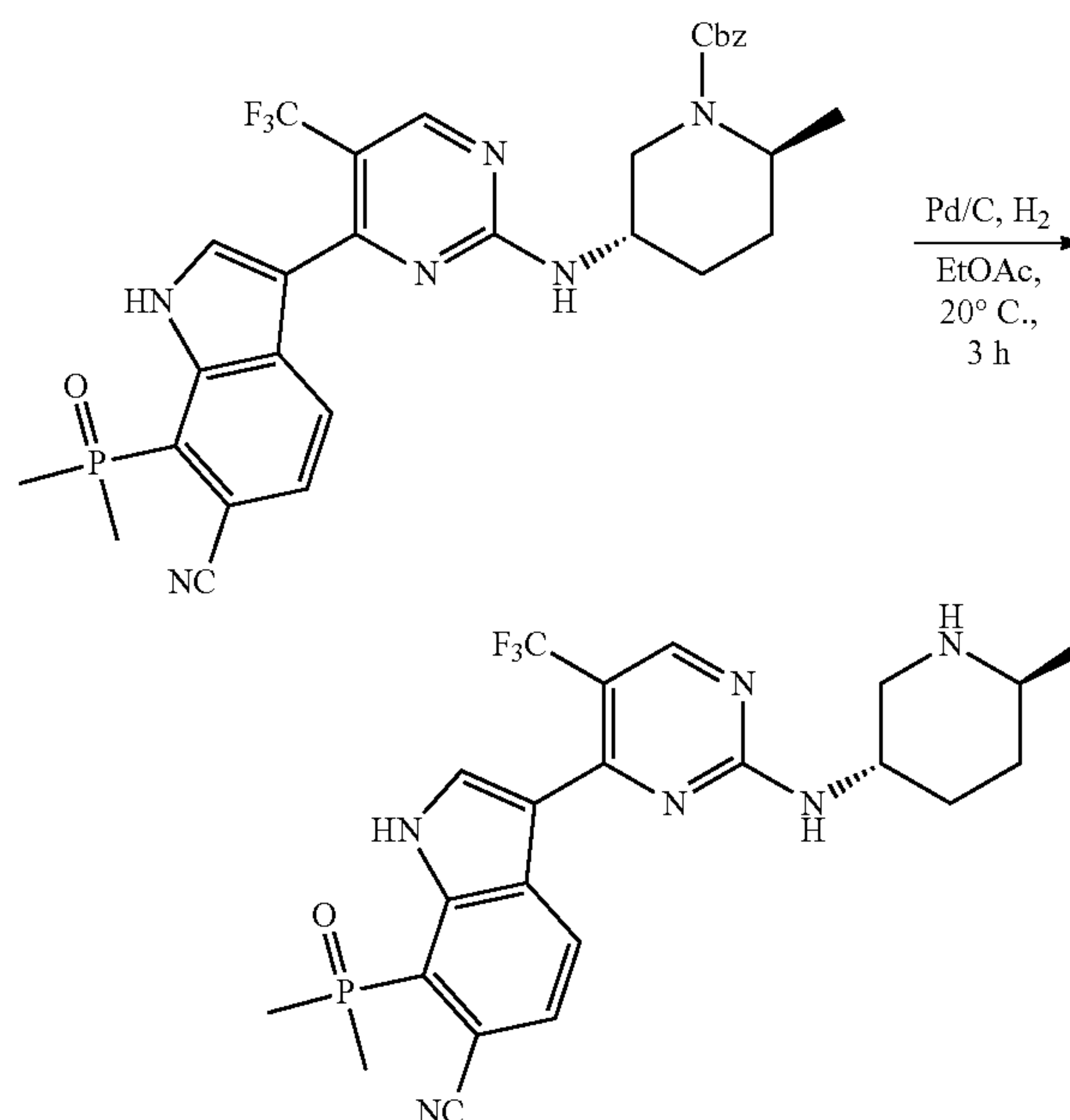
[0109]



[0110] We prepared a mixture of benzyl (2S,5S)-5-[[4-(7-chloro-6-cyano-1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]amino]-2-methyl-piperidine-1-carboxylate (1.05 g, 1.85 mmol, 1 eq), methylphosphonoylmethane (720.17 mg, 9.23 mmol, 5 eq), K_3PO_4 (783.45 mg, 3.69 mmol, 2 eq), $Pd(OAc)_2$ (41.43 mg, 184.54 μ mol, 0.1 eq), xantphos ($C_{39}H_{32}OP_2$; 106.78 mg, 184.54 μ mol, 0.1 eq) and dimethylformamide (DMF; 10 mL) in a microwave sealed tube, degassed it, and purged it with N_2 ($\times 3$). The mixture was then stirred at 150° C. for 1 hour in microwave. The reaction mixture was diluted with H_2O (100 mL) and extracted with ethyl acetate (EtOAc; 50 mL $\times 3$). The combined organic layers were washed with brine (150 mL $\times 2$), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure to give a residue that we purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=10:1 to 1:1) to afford the title compound as a yellow oil (490 mg).

Step 3: 7-dimethylphosphoryl-3-[2-[[[(3S, 6S)-6-methyl-3-piperidyl]amino]-5-(trifluoromethyl)pyrimidin-4-yl]-1H-indole-6-carbonitrile

[0111]

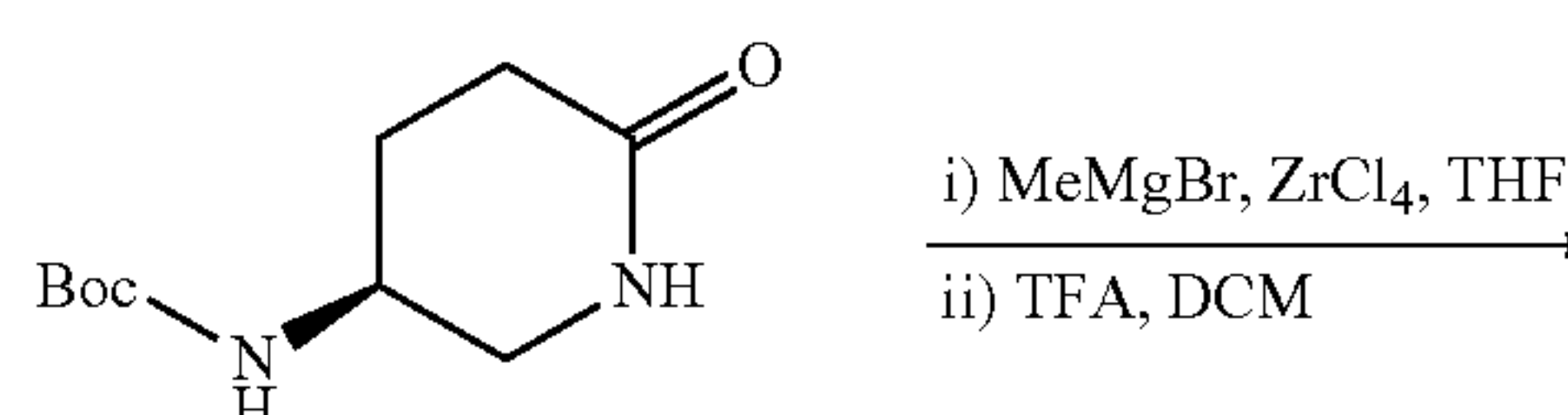


[0112] To a solution of benzyl(2S,5S)-5-[[4-(6-cyano-7-dimethylphosphoryl-1H-indol-3-yl)-5-(trifluoromethyl)pyrimidin-2-yl]amino]-2-methyl-piperidine-1-carboxylate (440 mg, 720.64 μ mol, 1 eq) in EtOAc (5 mL), we added Pd/C (200 mg, 10% purity) under N_2 . We degassed the suspension under vacuum, purged it with H_2 several times, then stirred the mixture under H_2 (15 psi) at 20° C. for 3 hours before filtering it. The filtrate was concentrated to give a residue we purified by prep-HPLC (high performance liquid chromatography; neutral condition) to yield the title compound as a white solid (142.2 mg).

[0113] The reaction was combined with another reaction in 50 mg scale for purification by liquid chromatography mass spectrometry (LCMS). LCMS: ET6034-1492-P1C: ($M+H^+$): 477.1 @2.572 (10-80% ACN (acetonitrile) in H_2O 4.5 minutes). 1H NMR (400 MHz, DMSO (d_6)) δ 8.74 (br d, $J=7.89$ Hz, 1H), 8.65-8.44 (m, 2H), 8.17 (br d, $J=15.35$ Hz, 1H), 7.84 (brt, $J=8.11$ Hz, 1H), 7.67 (brt, $J=7.02$ Hz, 1H), 3.81 (br s, 1H), 3.10 (br d, $J=11.40$ Hz, 1H), 2.45-2.38 (m, 1H), 2.02 (d, $J=13.59$ Hz, 8H), 1.64 (br d, $J=11.40$ Hz, 1H), 1.49-1.34 (m, 1H), 1.11 (br d, $J=10.96$ Hz, 1H), 0.97 (br d, $J=5.70$ Hz, 3H).

Example 3: Synthesis of (S)-6,6-dimethylpiperidin-3-amine

[0114]



SEQUENCE LISTING

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<210> SEQ ID NO 1

<211> LENGTH: 25

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 1

Tyr Ser Pro Thr Ser Pro Ser Tyr Ser Pro Thr Ser Pro Ser Tyr Ser
1 5 10 15

Pro Thr Ser Pro Ser Lys Lys Lys Lys
20 25

<210> SEQ ID NO 2

<211> LENGTH: 7

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

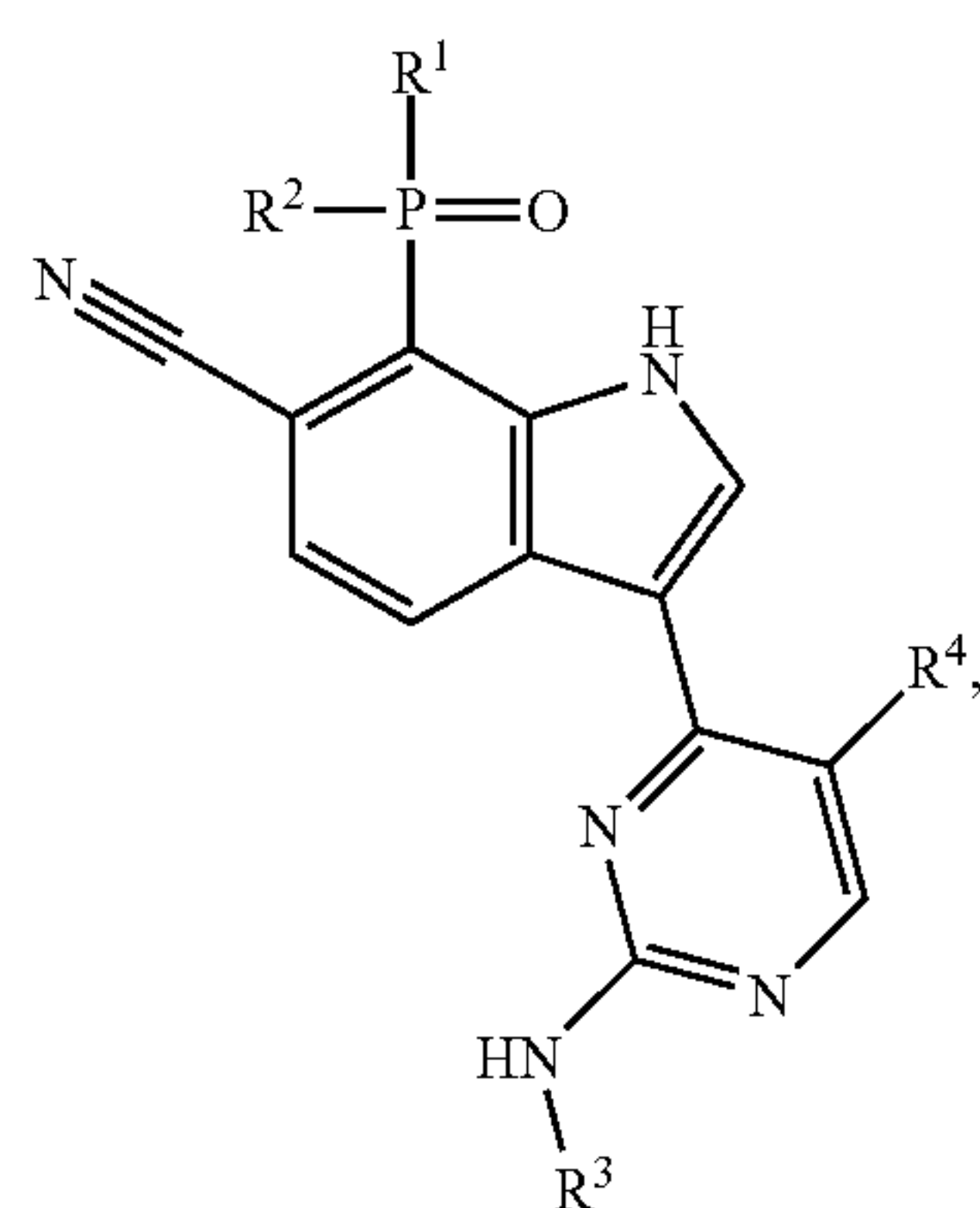
<220> FEATURE:

<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide

<400> SEQUENCE: 2

Gly Ser Arg Thr Pro Met Tyr
1 5

1. A method of treating a selected patient, the method comprising administering a therapeutically effective amount of a compound of structural Formula (I):



or a pharmaceutically acceptable salt thereof, wherein the compound or the pharmaceutically acceptable salt thereof is optionally within a pharmaceutical composition;

R¹ is methyl or ethyl;

R² is methyl or ethyl;

R³ is 5-methylpiperidin-3-yl, 5,5-dimethylpiperidin-3-yl, 6-methylpiperidin-3-yl, or 6,6-dimethylpiperidin-3-yl, wherein one or more hydrogen atoms in R³ is optionally replaced by deuterium;

R⁴ is —CF₃ or chloro;

and the selected patient has been determined to have a cancer in which

(a) a gene selected from RB1, RBL1, RBL2, CDKN2A, CDKN2B, CDKN2C, CDKN2D, CDKN1A, CDKN1B, CDKN1C, and FBWX7 is mutated, is genetically deleted, contains an epigenetic alteration, is translocated, is transcribed at a level equal to or below a pre-determined threshold, or encodes a protein that is translated at a level equal to or below a pre-determined threshold or has decreased activity relative to a reference standard;

(b) a gene selected from E2F1, E2F2, E2F3, E2F4, E2F5, E2F6, E2F7, E2F8, CDK1, CDK2, CDK4, CDK6, CCNA1, CCNB1, CCND1, CCND2, CCND3, CCNE1, CCNE2, and BRAF is mutated, is genetically gained or amplified, contains an epigenetic alteration, is translocated, transcribed at a level equal to or above a pre-determined threshold, or encodes a protein that is translated at a level equal to or above a pre-determined threshold or has increased activity relative to a reference standard; or

(c) the gene Bcl2-like 1 is mutated, contains an epigenetic alteration, is translocated, is transcribed at a level equal to or below a pre-determined threshold, or encodes a BCL-xL protein that is translated at a level equal to or below a pre-determined threshold or has decreased activity relative to a reference standard.

2. The method of claim 1, wherein (i) R¹ is methyl and R² is methyl or (ii) R¹ is methyl and R² is ethyl.

3. The method of claim 1, wherein (i) R¹ is ethyl and R² is ethyl or (ii) R⁴ is —CF₃.

4. The method of claim 1, wherein R⁴ is chloro.

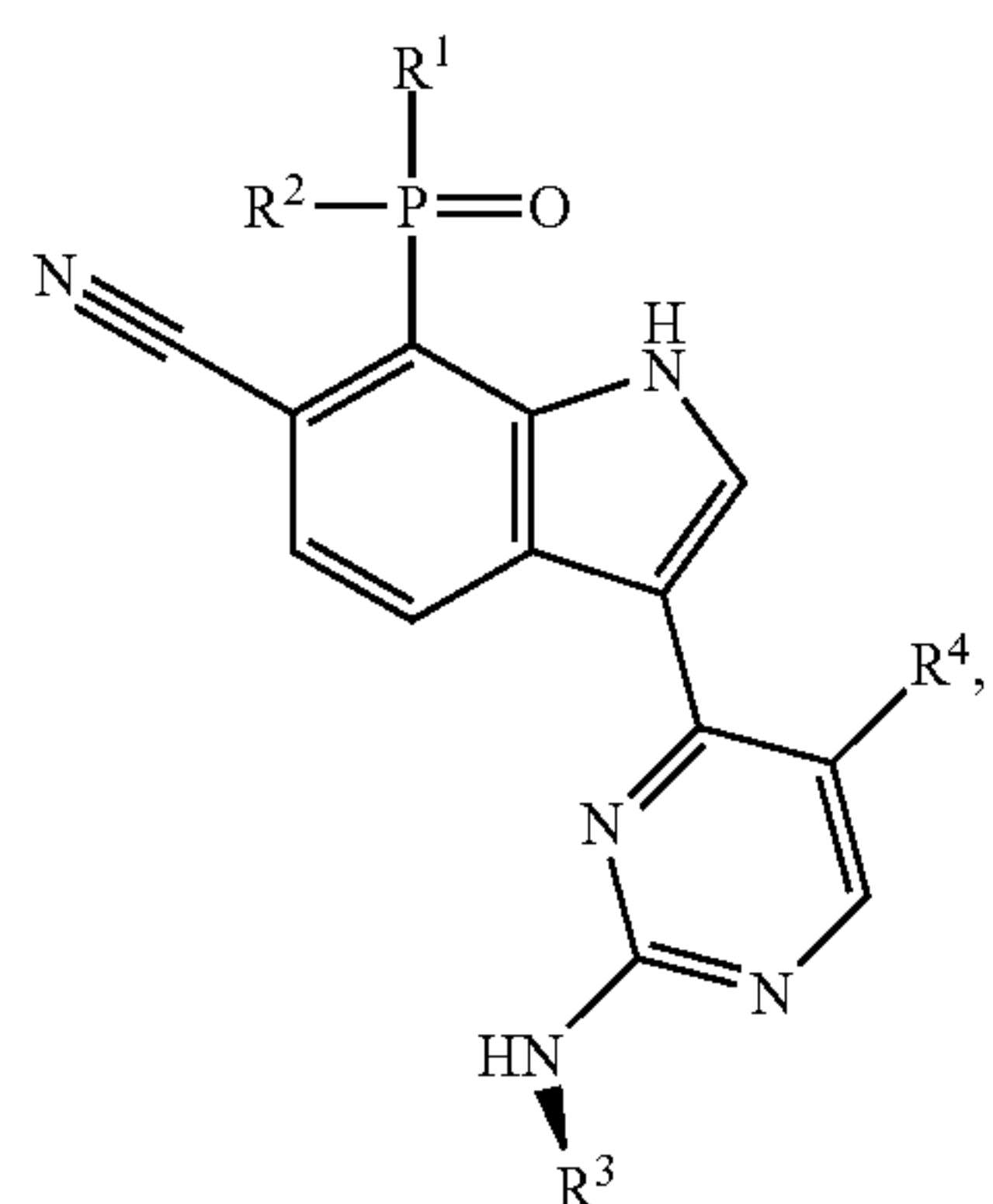
5. The method of claim 1, wherein R³ is 5-methylpiperidin-3-yl.

6. The method of claim 1, wherein R³ is 5,5-dimethylpiperidin-3-yl.

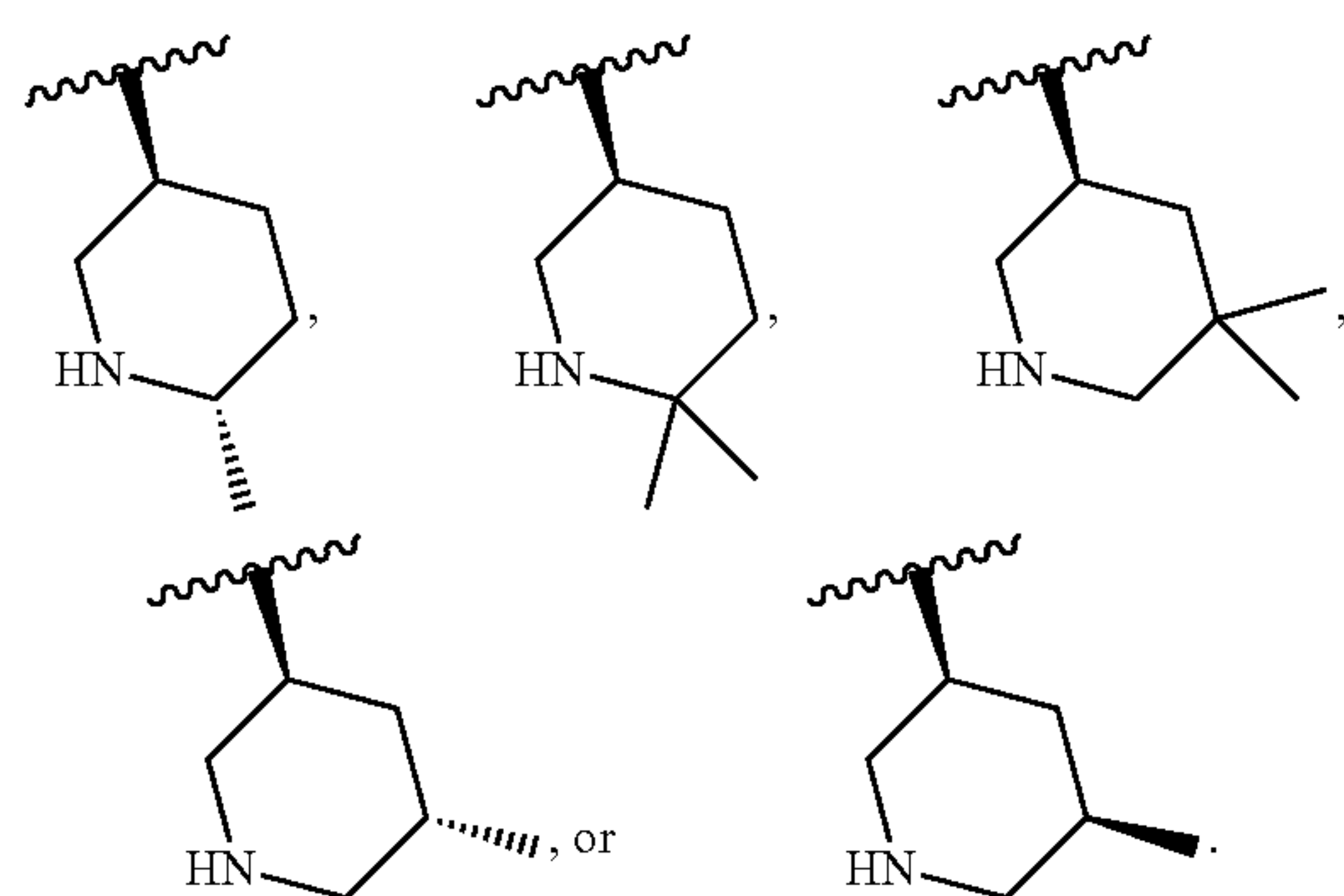
7. The method of claim 1, wherein R^3 is 6-methylpiperidin-3-yl.

8. The method of claim 1, wherein R^3 is 6,6-dimethylpiperidin-3-yl.

9. The method of claim 1, wherein the compound has structural Formula (Ia):

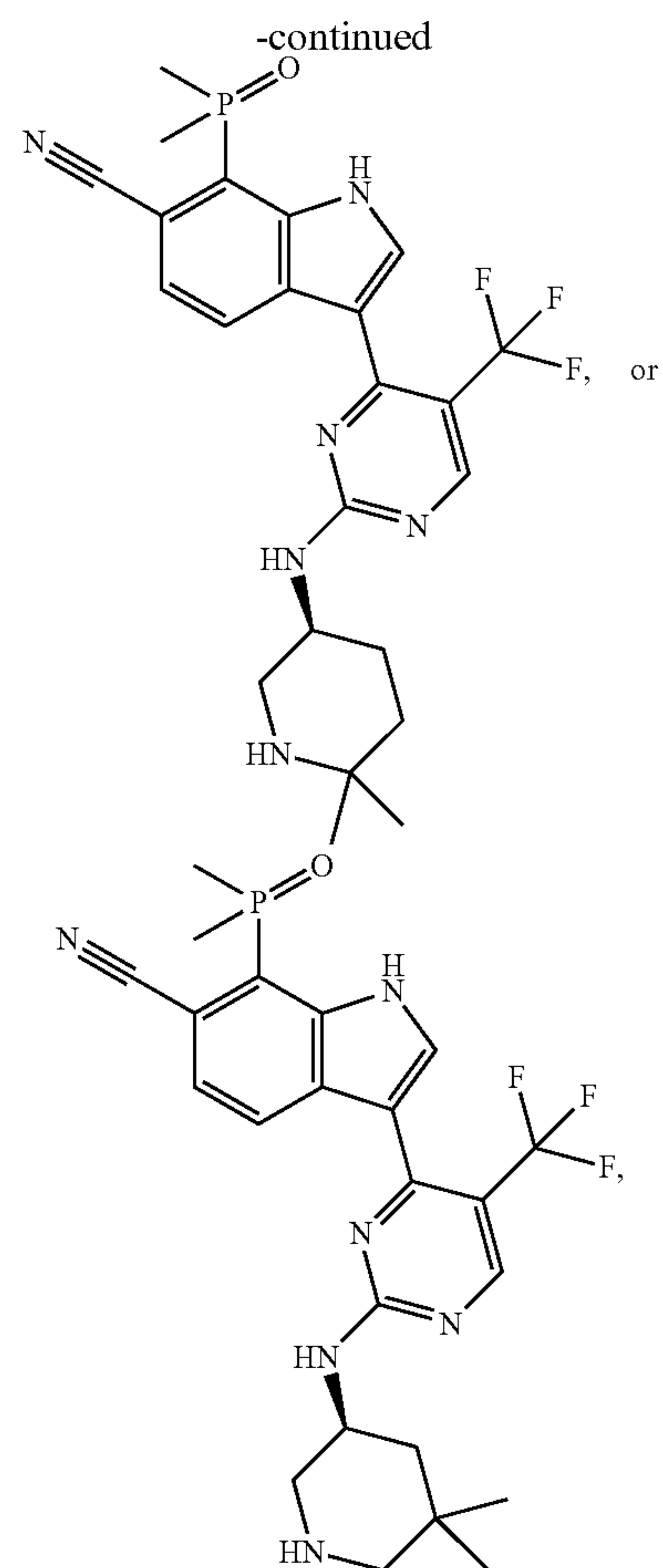
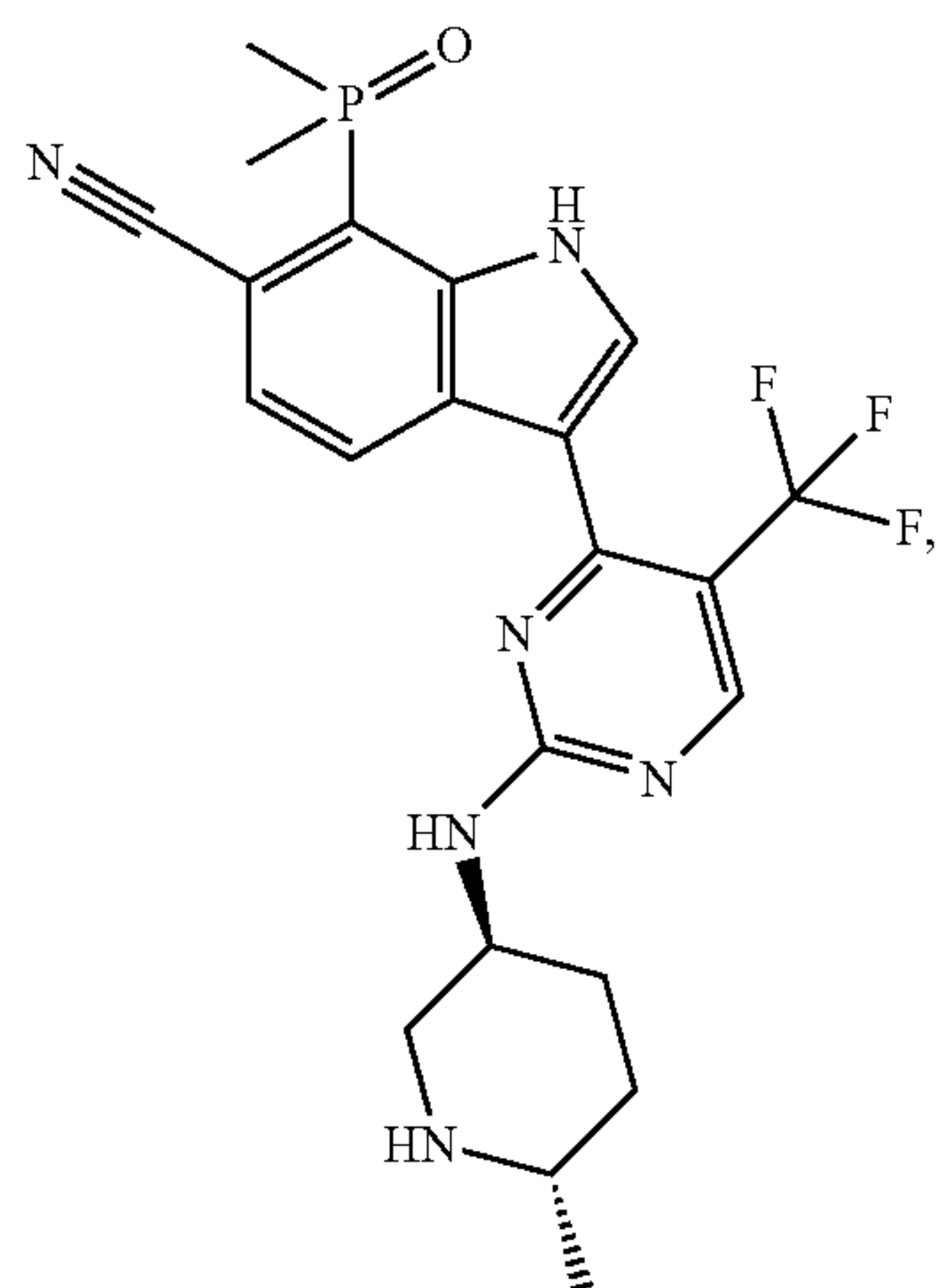


is a pharmaceutically acceptable salt thereof, wherein R^3 is



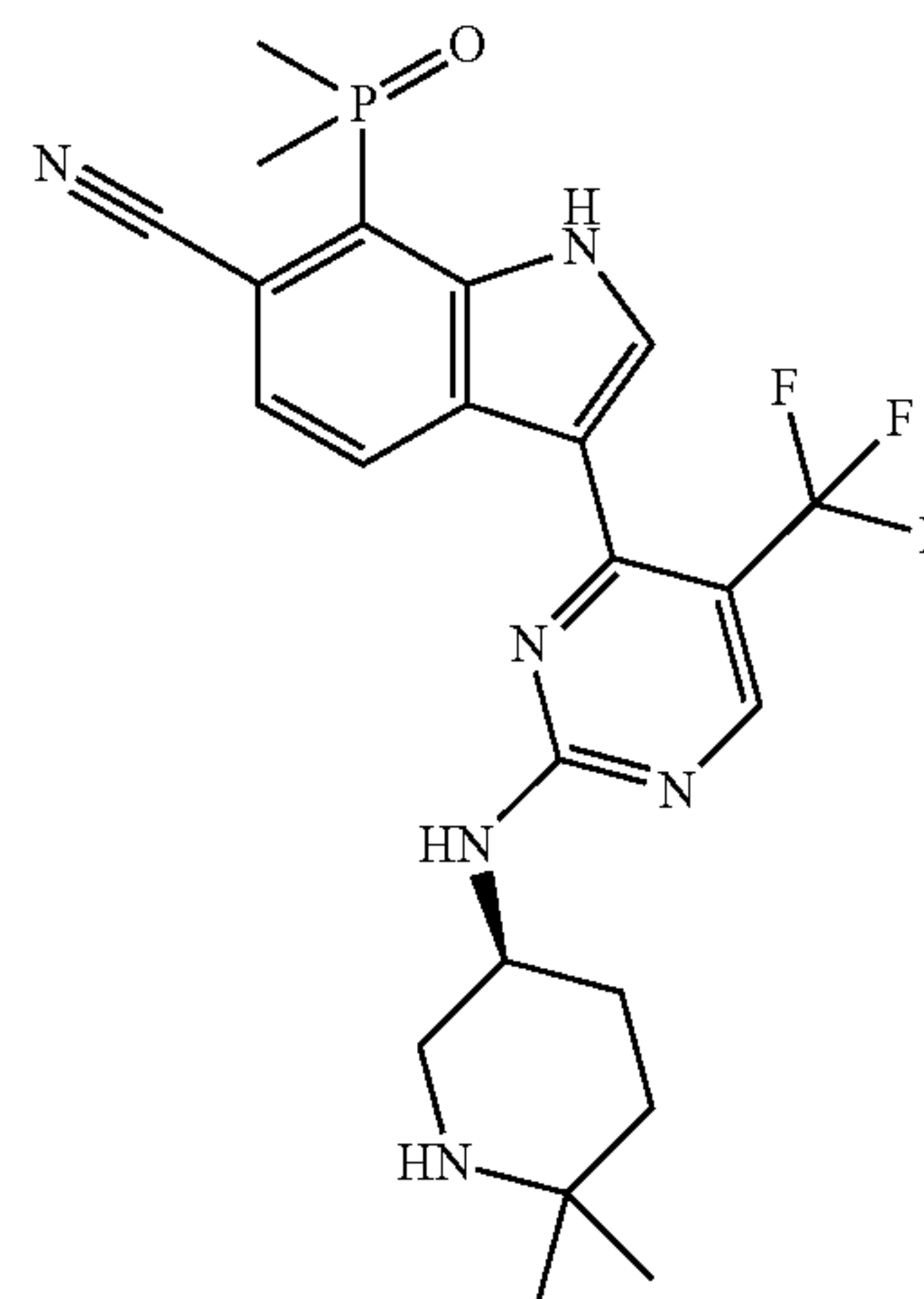
10.-12. (canceled)

13. The method of claim 9, wherein the compound is:



or is a pharmaceutically acceptable salt of any one of the foregoing compounds.

14. The method of claim 13, wherein the compound is



or a pharmaceutically acceptable salt thereof.

15.-18. (canceled)

19. The method of claim 1, wherein the cancer is a blood cancer, a breast cancer, Ewing's sarcoma, fallopian tube cancer, a GI tract cancer, a glioma, a lung cancer, melanoma,

