pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing, managing, treating or lessening the severity of a proliferative disorder in a patient.

[025] In some embodiments, the proliferative disorder is metastatic cancer. In other embodiments, the proliferative disorder is colon cancer, gastric adenocarcinoma, bladder cancer, breast cancer, kidney cancer, liver cancer, lung cancer, skin cancer, thyroid cancer, cancer of the head and neck, prostate cancer, pancreatic cancer, cancer of the CNS, glioblastoma or a myeloproliferative disorder. In further embodiments, the proliferative disorder is atherosclerosis or lung fibrosis.

[026] In another aspect, provided hereinis a method of inhibiting or modulating PI3K and/or mTOR activity in a biological sample comprising contacting a biological sample with the compound disclosed herein, or the pharmaceutical composition disclosed herein.

[027] In some embodiments, provided herein is a method of inhibiting or modulating PI3K or mTOR, the method comprising contacting the kinase with the compound according to the present invention, or with the composition according to the present invention. In some embodiments, the invention provides a method of inhibiting or modulating PI3K or mTOR signaling, the method comprising contacting the receptor with the compound according to the present invention, or with the composition according to the present invention. In some embodiments, inhibition or modulation of PI3K or mTOR activity can be in a cell or a multicellular organism. If in a multicellular organism, the method according to this aspect of the invention comprises administering to the organism the compound according to the present invention, or the composition according to the present invention. In some embodiments, the organism is a mammal. In other embodiments is a human. In still other embodiment, the method further comprises contacting the kinase with an additional therapeutic agent.

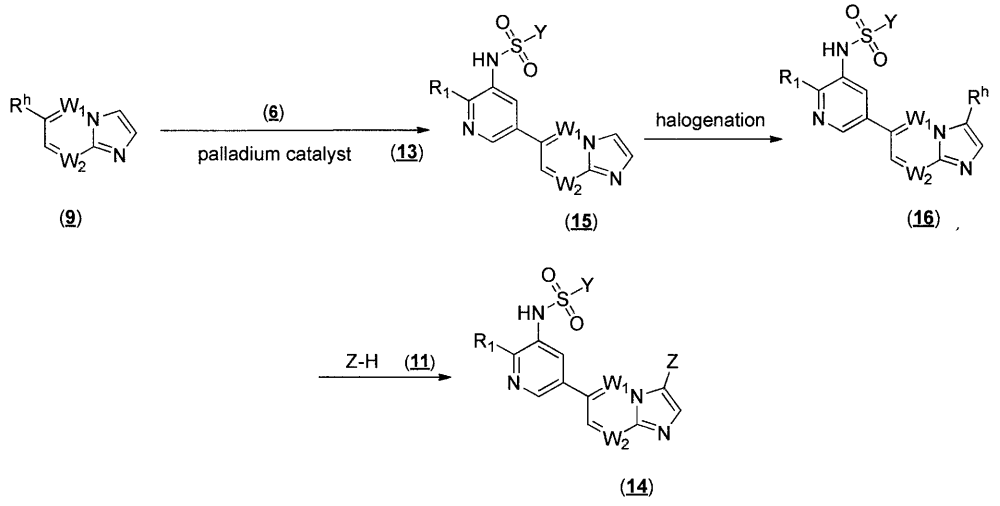
[028] In another aspect, provided herein is a method of inhibiting proliferative activity of a cell, the method comprising contacting the cell with an effective proliferative inhibiting amount of a compound according to the present invention or a composition thereof. In some embodiments, the method further comprises contacting the cell with an additional therapeutic agent.

[029] In another aspect, provided herein is a method of treating a cell proliferative

Pd/C or Fe powder in aqueous acidic conditions. Aminopyridine (**2**) is then coupled with sulfonyl chloride (**3**) to give sulfonamide (**4**) in the presence of a base such as Na_2CO_3, Et_3N, or pyridine in an aprotic solvent (for example, CH_2Cl_2, $CHCl_3$, etc.), or in pyridine with a catalytic amount of DMAP, or under the Schotten–Baumann condition. The subsequent coupling of sulfonamide (**4**) with bis(pinacolato)diboron (**5**) in the presence of an approporiate Pd catalyst leads to boronic ester (**6**).

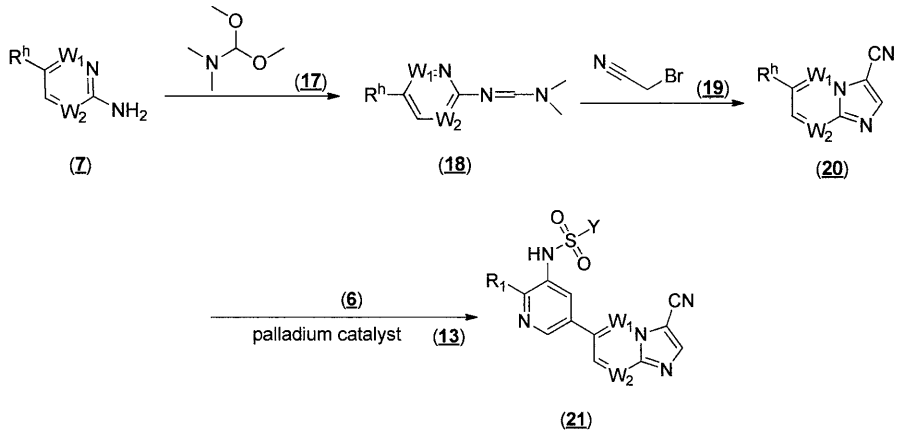
[0173] The synthesis of heteroaromatic core (**12**) having a bromo group is shown in Scheme 1. Bromo heteroaryl compound (**7**) is first condensed with acetal (**8**) to furnish bicyclic heteroaromatic compound (**9**) in an alcoholic solvent such as MeOH or EtOH. The subsequent iodination of (**9**) with N-iodosuccinimide at room temperature affords iodo compound (**10**). Compound (**10**) is then coupled with acetylene, cyanide or azide Z (**11**) to give heteroaromatic compound (**12**) under either basic conditions or in the presence of a Pd catalyst. The desired kinase inhibitors having formula (**14**) are obtained by the coupling of bromo heteroaromatic compound (**12**) with boronic ester (**6**) in the presence of an appropriate Pd catalyst.

Scheme 2



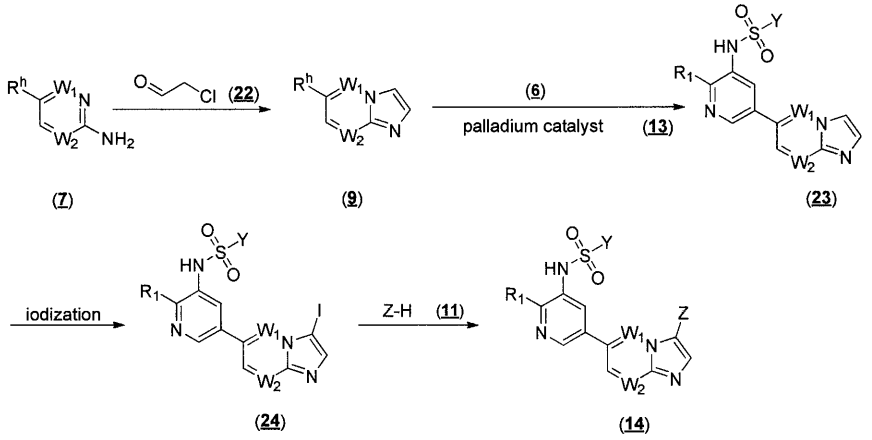
[0174] Alternatively, the compounds disclosed herein may be prepared by the method as described in Scheme 2. Bromo compound (**9**) is first coupled with boronic ester (**6**) to give biaryl compound (**15**) using an appropriate Pd complex as catalyst. Biaryl compound (**15**) is then treated with a halogenating agent (such as NIS) to afford compound (**16**). Coupling of compound (**16**) with compound (**11**) (i.e., acetylene deterivatives, cyanide or azide) under either basic conditions or in the presence of a Pd catalyst affords the desired kinase inhibitors (**14**).

Scheme 3



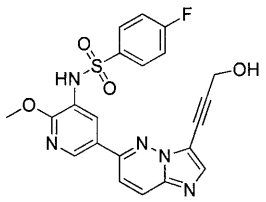
[0175] Scheme 3 shows another method to prepare the kinase inhibitors disclosed herein. Thus, substituted heteroaryl compound (**7**) having a bromo group can react with 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (**17**) at an elevated temperature to provide enamine intermediate (**18**), which is further cyclized with alkyl halides (**19**) leading to nitrile (**20**). Coupling of nitrile (**20**) with boronic ester (**6**) in the presence of an appropriate Pd catalyst furnishes the desired kinase inhibitors (**21**).

Scheme 4



[0176] The compounds disclosed herein can also be prepared using the synthetic route as shown in Scheme 4. Thus, bromo substituted heteroaryl compound (**7**) is first cyclized with 2-chloroacetaldehyde (**22**) at an elevated temperature to give compound (**9**). The coupling of compound (**9**) with boronic ester (**6**) in the presence of an appropriate Pd catalyst furnishes compound (**23**). The iodination of compound (**23**) with N-iodosuccinimide affords compound (**24**). Coupling of compound (**24**) with compound (**11**) (i.e., acetylene deterivatives, cyanide or azide) under either

Example 2 4-fluoro-N-(5-(3-(3-hydroxyprop-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step1) 3-(6-bromoimidazo[1,2-b]pyridazin-3-yl)prop-2-yn-1-ol

[0183] To a suspension of 6-bromo-3-iodoimidazo[1,2-b]pyridazine (1.48 g, 4.6 mmol), $Pd(PPh_3)_2Cl_2$ (322 mg, 0.46 mmol), CuI (87 mg, 0.46 mmol) and triethylamine (2.33 g, 23 mmol) in DMF (65 mL) was added prop-2-yn-1-ol (235 mg, 4.2 mmol). The mixture was stirred at rt under N_2 atmosphere for 4 hours and concentrated *in vacuo*. The residue was diluted with brine (150 mL) and extracted with EtOAc (60 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 4/1) to give the title compound as a yellow solid (580 mg, 50%).

MS (ESI, pos. ion) m/z: 252.1 $[M+H]^+$.

Step 2) 4-fluoro-N-(5-(3-(3-hydroxyprop-1-yn-1-yl)imidazo[1,2-*b*]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

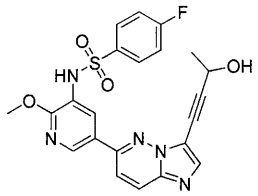
[0184] To a suspension of 3-(6-bromoimidazo[1,2-b]pyridazin-3-yl)prop-2-yn-1-ol (500 mg,2mmol), 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (900 mg, 2.2 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (164 mg, 0.2 mmol) in DME (40 mL) was added a solution of Na_2CO_3 (530 mg, 5 mmol) in H_2O (4 mL). The mixture was stirred at 70 °C under N_2 atmosphere for 4 hours, then cooled to rt, quenched with water (50 mL), and extracted with EtOAc (100 mL x 3). The combined organic phases were washed with brine (80 mL x 3), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (PE/EtOAc (v/v) = 30/1) to give the title compound as a yellow solid (110 mg, 12%).

MS (ESI, pos. ion) m/z: 454.0 $[M+H]^+$;

^1H NMR (400 MHz, DMSO-d_6): δ 3.74 (s, 3H), 4.49 (d, J = 5.9 Hz, 2H), 5.55 (t, J = 5.9 Hz, 1H),

7.42 (t, J = 8.8 Hz, 2H), 7.87-7.92 (m, 3H), 8.09 (s,1H), 8.27 (d, J = 9.6 Hz, 1H), 8.33 (d, J = 2.2 Hz, 1H), 8.68 (d, J = 2.2 Hz, 1H), 10.19 (s, 1H).

Example 3 4-fluoro-N-(5-(3-(3-hydroxybut-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide



Step1) 4-(6-bromoimidazo[1,2-b]pyridazin-3-yl)but-3-yn-2-ol

[0185] To a suspension of 6-bromo-3-iodoimidazo[1,2-b]pyridazine (520 mg, 1.6 mmol), $Pd(PPh_3)_2Cl_2$ (112 mg, 0.16 mmol), CuI (30 mg, 0.16 mmol) and DIPEA (1.04 g, 4.0 mmol) in DMF (24 mL) was added but-3-yn-2-ol (112 mg, 1.6 mmol). The resulted mixture was stirred at rt under N_2 atmosphere for 2 hours and then concentrated *in vacuo*. The residue was purified by a flash silica gel column chromatography (PE/DCM (v/v) = 1/50) to give the title compound as a yellow solid (210 mg, 50%).

MS (ESI, pos. ion) m/z: 266.0 $[M+H]^+$.

Step 2) 4-fluoro-N-(5-(3-(3-hydroxybut-1-yn-1-yl)imidazo[1,2-b]pyridazin-6-yl)-2-methoxypyridin-3-yl)benzenesulfonamide

[0186] To a suspension of 4-fluoro-N-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)benzenesulfonamide (354 mg, 0.87 mmol), 4-(6-bromoimidazo[1,2-b]pyridazin-3-yl)but-3-yn-2-ol (210 mg, 0.79 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (58 mg, 0.08 mmol) in DMF (21 mL) was added a solution of Na_2CO_3 (210 mg, 1.97 mmol) in water (4 mL). The mixture was stirred at 70 °C under N_2 atmosphere for 4 hours, then cooled to rt, quenched with H_2O (100 mL), and extracted with EtOAc (100 mL x 3). The combined organic phases were concentrated *in vacuo*. The residue was purified by a silica gel column chromatography (DCM/MeOH (v/v) = 100/1) to give the title compound as a light brown solid (149 mg, 40%).

MS (ESI, pos. ion) m/z: 468.0 $[M+H]^+$;

MRM	490.2→383.1
Fragmentor	230 V
CE	55 V
Drying Gas Temp	350 °C
Nebulize	40 psi
Drying Gas Flow	10 L/min

[0239] An Agilent XDB-C18, 2.1 x 30 mm, 3.5 μM column was used for the analysis. 5 μL of the samples were injected. Analysis condition: The mobile phase was 0.1% formic acid in water (A) and 0.1% formic acidin methanol (B). The flow rate was 0.4 mL/min. And the gradient of Mobile phase was in the Table B.

Table B

Time	Gradient of Mobile Phase B
0.5 min	5%
1.0 min	95%
2.2 min	95%
2.3 min	5%
5.0 min	stop

[0240] Alternatively, an Agilent 6330 series LC/MS/MS spectrometer equipped with G1312A binary pumps, a G1367A autosampler and a G1314C UV detector were used in the analysis. An ESI source was used on the LC/MS/MS spectrometer. The analysis was done in positive ion mode as appropriate and the MRM transition for each analyte was optimized using standard solution. A Capcell MP-C18 100 x 4.6 mm I.D., 5 μM column (Phenomenex, Torrance, California, USA) was used during the analysis. The mobile phase was 5 mM ammonia acetate, 0.1% MeOH in water (A): 5 mM ammonia acetate, 0.1% MeOH in acetonitrile (B) (70/30, v/v). The flow rate was 0.6 mL/min. Column was maintained at ambient temperature. 20 μL of the samples were injected.

Example A: Compound Stability In Human and Rat Liver Microsomes

[0241] Human or rat liver microsomes incubations were conducted in duplicate in

Table 2 Human and rat liver microsomes stability

Example #	Human		Rat	
	$T_{1/2}$ (min)	CL_{int} (mL/min/kg)	$T_{1/2}$ (min)	CL_{int} (mL/min/kg)
Ex. 1	161.6	10.76	97.36	25.51
Ex. 3	144	12.07	50.6	49.09
Ex. 4	112.1	15.51	39.97	62.14
Ex. 5	68.37	25.43	35.71	69.55
Ex. 8	242.6	7.17	74.89	33.16
Ex. 9	∞	N/A	∞	N/A
Ex. 10	527.3	3.30	279.3	8.89
Ex. 13	1129	1.54	95.23	26.08
Ex. 15	503.5	3.45	120.6	20.59
Ex. 16	313.4	5.55	53.67	46.28
Ex. 17	511.8	3.40	279.9	8.87
Ex. 18	212.5	8.18	43.86	56.63
Ex. 19	424.4	4.10	∞	N/A
Ex. 23	∞	N/A	∞	N/A
Ex. 24	∞	N/A	∞	N/A

Example B: Evaluation of Pharmacokinetics After Intravenous and Oral Administration of The Compounds Disclosed Herein In Mice, Rats, Dogs And Monkeys

[0246] The compounds disclosed herein are assessed in pharmacokinetic studies in mice, rats, dogs or monkeys. The compounds are administered as a water solution, 2% HPMC + 1% TWEEN®80 in water solution, 5% DMSO + 5% solutol in saline, 4% MC suspension or capsule. For the intravenous administration, the animals are generally given at 1 or 2 mg/kg dose. For the oral (p.o.) dosing, mice and rats are generally given 5 or 10 mg/kg dose, and dogs and monkeys are generally given 10 mg/kg dose. The blood samples (0.3 mL) are drawn at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12 and 24 h time points or 0.083, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 24 h time points and centrifuged at 3,000 or 4000 rpm for 2 to 10 min. The plasma solutions are collected, stored at -20 °C or -70 °C until analyzed by LC/MS/MS as described above.

Table 3 Pharmacokinetic profiles in rats

Example #	iv dosing					F (%)
	dose (mg/kg)	$T_{1/2}$ (h)	AUC_{last} (ng.h/mL)	Cl/F (L/h/kg)	Vss (L/kg)	
Ex. 1	1	6.39	6541	0.14	1.00	96.0
Ex. 2	2	3.42	20712	0.10	0.22	56.1
Ex. 3	2	3.11	28956	0.07	0.16	61.5
Ex. 5	1	8.74	2551	0.37	2.29	95.6
Ex. 6	1	3.70	2659	0.33	1.25	123.7
Ex. 7	2	3.19	48059	0.04	0.17	95.4
Ex. 8	2	3.02	16596	0.13	0.37	115.1
Ex. 9	1	4.10	7490	0.14	0.37	104.2
Ex. 10	2	4.27	67010	0.03	0.14	79.88
Ex. 11	1	4.92	40399	0.02	0.15	115.8
Ex. 12	2	4.71	411	4.67	18.42	1.3
Ex. 13	1	3.08	11271	0.09	0.32	95.8
Ex. 15	2	3.14	25551	0.08	0.22	97.0
Ex. 16	1	2.65	19399	0.10	0.35	99.77
Ex. 17	1	5.30	38738	0.03	0.17	123.1
Ex. 18	1	2.33	10253	0.10	0.35	97.16
Ex. 19	2	2.58	10075	0.23	0.55	54.66
Ex. 23	1	0.15	561	1.81	0.19	5.9
Ex. 24	2	3.06	8404	0.24	0.55	108

Table 4 Pharmacokinetic profiles in Mice, Dogs and Monkeys

Example #	Species	iv dosing					F (%)
		dose (mg/kg)	$T_{1/2}$ (h)	AUC_{last} (ng.h/mL)	Cl/F (L/h/kg)	Vss (L/kg)	
Ex. 9	Mouse	2	4.02	5329	0.37	0.57	118.7
	Dog	1	0.73	2754	0.37	0.31	44.2
	Monkey	1	3.59	2368	0.45	0.39	27.3

by preparing a 10 point curve using a ½ log dilution series (for example, a typical curve may be prepared using the following compound concentrations: 10 μM, 3 μM, 1 μM, 0.3 μM, 0.1 μM, 0.03 μM, 0.01 μM, 0.003 μM, 0.001 μM and 0 μM).

PI3 KINASE GENERAL ASSAY PROTOCOL

PI3K (p110α/p85α) (h) [Non-radioactive assay]

[0250] PI3K (p110α/p85α) (h) is incubated in assay buffer containing 10 μM phosphatidylinositol 4,5-bisphosphate and MgATP (concentration as required). The reaction is initiated by the addition of the ATP solution. After incubation for 30 minutes at room temperature, the reaction is stopped by the addition of stop solution containing EDTA and biotinylated phosphatidylinositol-3,4,5-trisphosphate. Finally, detection buffer is added, which contains europium-labelled anti-GST monoclonal antibody, GST-tagged GRP1 PH domain and streptavidin allophycocyanin. The plate is then read in timeresolved fluorescence mode and the homogenous time-resolved fluorescence (HTRF) signal is determined according to the formula HTRF = 10000 x (Em665nm/Em620nm).

PI3K (p110β/p85α) (h) [Non-radioactive assay]

[0251] PI3K (p110β/p85α) (h) is incubated in assay buffer containing 10 μM phosphatidylinositol-4, 5-bisphosphate and MgATP (concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 30 minutes at room temperature, the reaction is stopped by the addition of stop solution containing EDTA and biotinylated phosphatidylinositol-3,4,5-trisphosphate. Finally, detection buffer is added, which contains europium-labelled anti-GST monoclonal antibody, GST-tagged GRP1 PH domain and streptavidin-allophycocyanin. The plate is then read in timeresolved fluorescence mode and the homogenous time-resolved fluorescence (HTRF) signal is determined according to the formula HTRF = 10000 x (Em665nm/Em620nm).

PI3K (p110δ/p85α) (h) [Non-radioactive assay]

[0252] PI3K (p110δ/p85α) (h) is incubated in assay buffer containing 10 μM phosphatidylinositol-4, 5-bisphosphate and MgATP (concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation for 30 minutes at room

with calipers twice weekly, and the tumor volume (TV) calculated as (L x W^2)/2). TGI was calculated from the difference between the median tumor volumes of vehicle-treated and drug-treated mice, expressed as a percentage of the median tumor volume of the vehicle-treated control group, by the following relation:

$$\%TGI = \left(\frac{\text{Median Tumor Volume}_{control} - \text{Median Tumor Volume}_{drug\text{-}treated}}{\text{Median Tumor Volume}_{control}} \right) \times 100$$

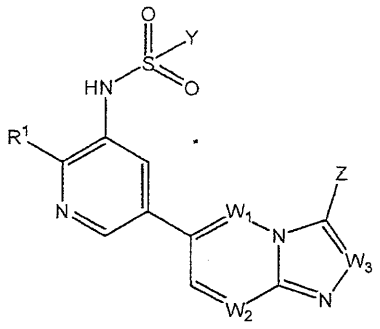
[0262] Initial statistical analysis is done by repeated measures analysis of variance (RMANOVA), followed by Scheffe psot hoc testing for multiple comparisons. Vehicle alone (5% DMSO+70% Captisol® (30%), 7% HCl (pH1), 18% Captisol® (30%); or 7% DMSO, 7% HCl (pH1), 70% Captisol® (30%), 16% Captisol® (30%), or the like) is the negative control.

Table 6 Selected results from tumor xenograft model (U87MG) studies

Example #	**Dosing (mg/kg)**	**TGI (%)**
		U87MG
Ex. 2 14 days	1	6
	3	21
	10	35
Ex. 6 12 days	0.3	14
	1	41
	3	71
Ex. 9 12 days	1	23
	3	26
	10	62
Ex. 10 12 days	1	32
	3	44
	10	65
Ex. 15 12 days	3	28
	10	51
Ex. 16 12 days	3	14
	10	43

What Is Claimed IS:

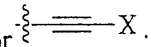
1. A compound of Formula (I):



(I),

or a stereoisomer, a geometric isomer, a tautomer, an *N*-oxide, a solvate, a pharmaceutically acceptable salt or a prodrug thereof, wherein:

each of W_1, W_2 and W_3 is independently N or CR^c;

Z is CN, N_3 or ;

X is H, D, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl or -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$heterocyclyl, -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$cycloalkyl and -$(C_1$-$C_4)$alkylene-$(C_3$-$C_6)$heterocyclyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkenyl and $(C_2$-$C_6)$alkynyl;

Y is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl or 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, wherein each of the $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, Br, CN, N_3, OR^a, SR^a, NR^aR^b, $-C(=O)NR^aR^b$, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_2$-$C_6)$alkynyl, $(C_6$-$C_{10})$aryl and 5-10 membered heteroaryl;

R^1 is H, D, Cl, OR^a, NR^aR^b, $(C_1$-$C_6)$aliphatic or $(C_3$-$C_6)$cycloalkyl, wherein each of the $(C_1$-$C_6)$aliphatic and $(C_3$-$C_6)$cycloalkyl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3, OR^a, SR^a and NR^aR^b, provided that when each of

W_1, W_2 and W_3 is CH, R^1 is not H or NH_2;

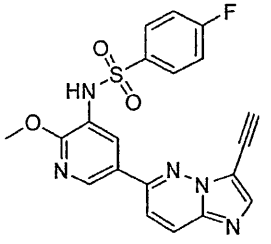
each R^a and R^b is independently H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$heterocyclyl, $(C_6\text{-}C_{10})$aryl, 5-10 membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms independently selected from O, S and N, -$(C_1\text{-}C_4)$alkylene-$(C_6\text{-}C_{10})$aryl or -$(C_1\text{-}C_4)$alkylene-(5-10 membered heteroaryl); or when R^a and R^b are bonded to the same nitrogen atom, R^a and R^b, together with the nitrogen atom they are attached to, optionally form a substituted or unsubstituted 3-8 membered heterocyclic ring, wherein each of the $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$heterocyclyl, $(C_6\text{-}C_{10})$aryl and 5-10 membered heteroaryl is optionally substituted with 1, 2, 3 or 4 substituents independently selected from D, F, Cl, CN, N_3, OH, NH_2, $(C_1\text{-}C_6)$alkoxy, and $(C_1\text{-}C_6)$alkylamino; and

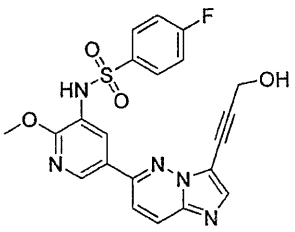
each R^c is independently H.

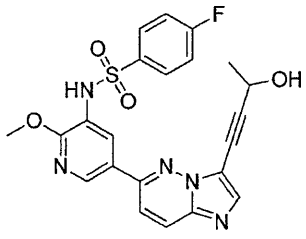
2. The compound according to claim 1, wherein each of W_1 and W_2 is independently N or CR^c, W_3 is CR^c.

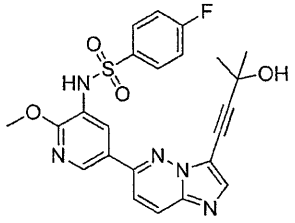
3. The compound according to claim 1, wherein R^1 is H, D, Cl, CH_3, CH_2CH_3, CF_3, CH_2CF_3, OCH_3, OCH_2CH_3, NH_2, $NHCH_3$ or $N(CH_3)_2$, provided that when each of W_1, W_2 and W_3 is CH, R^1 is not H or NH_2.

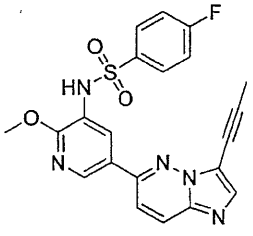
4. The compound according to claim 1 having one of the following structures:

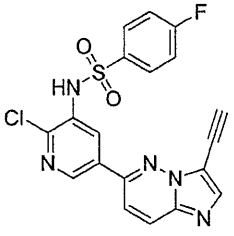

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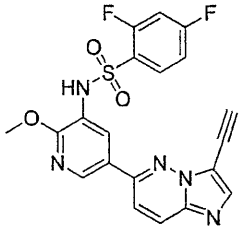

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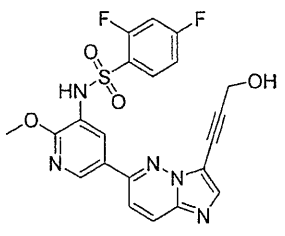

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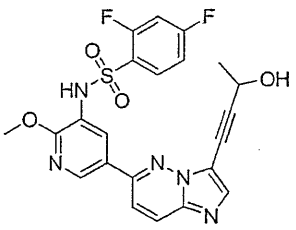

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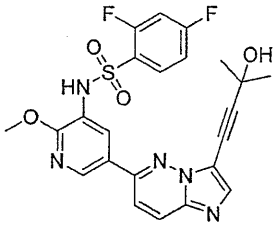

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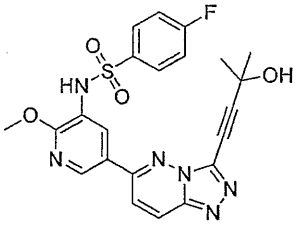

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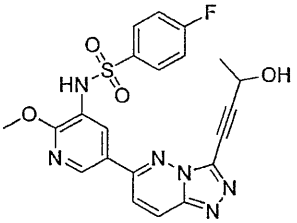
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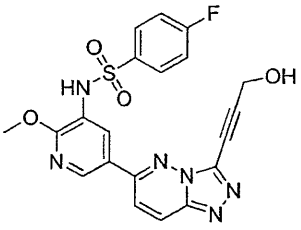
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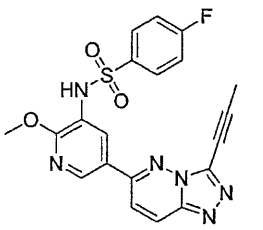
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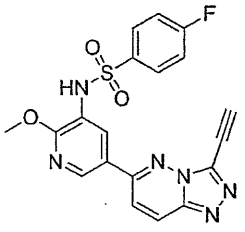
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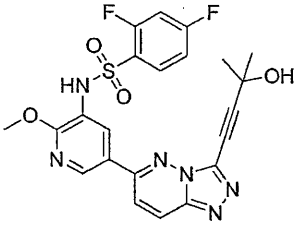
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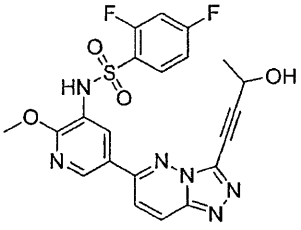
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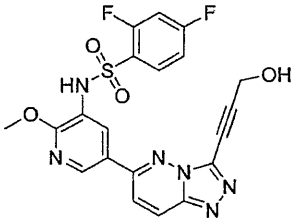
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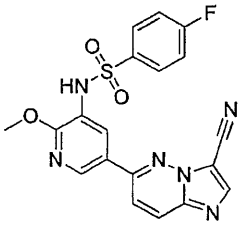
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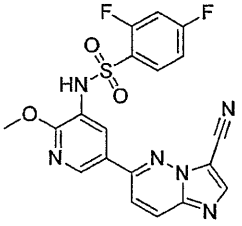
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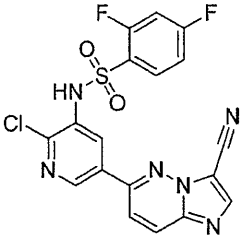
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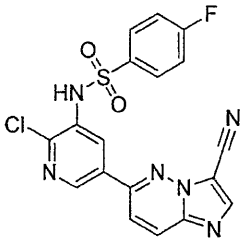
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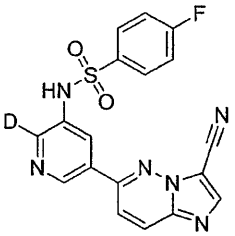
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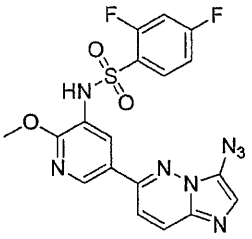
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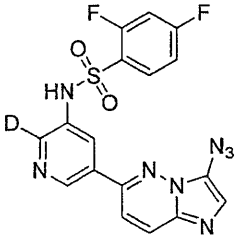
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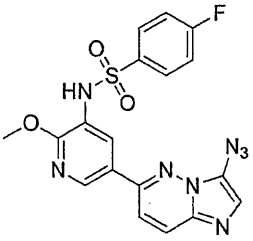
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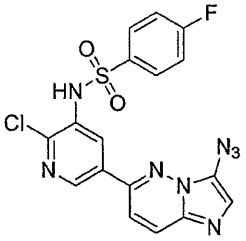
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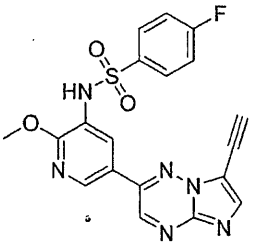
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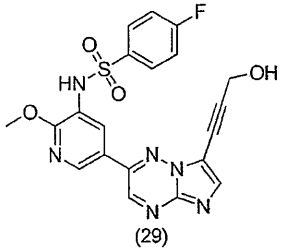
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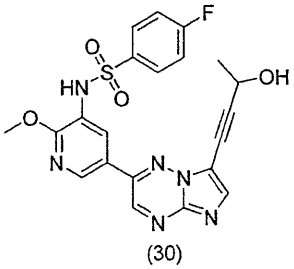
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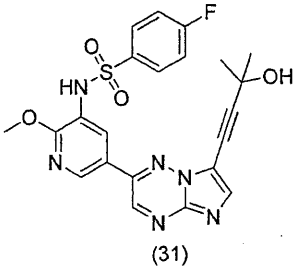
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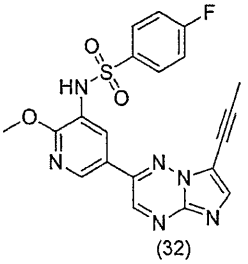
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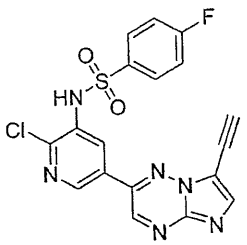
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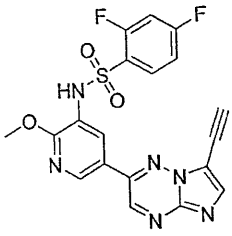


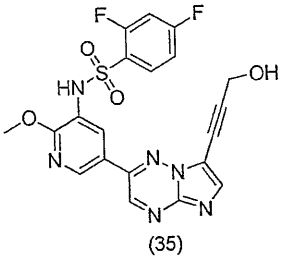
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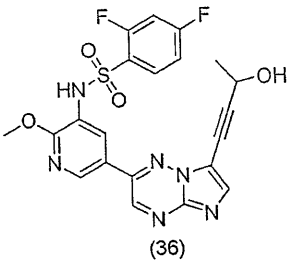


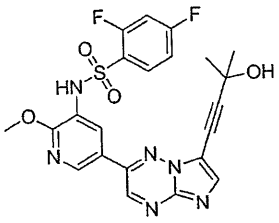
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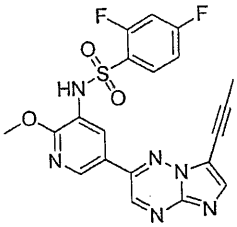

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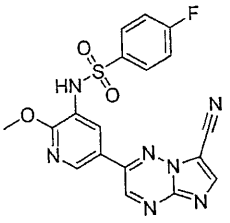

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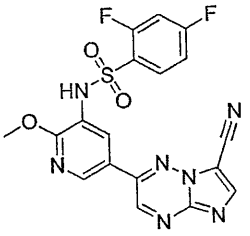

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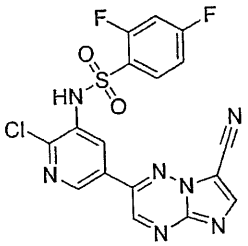

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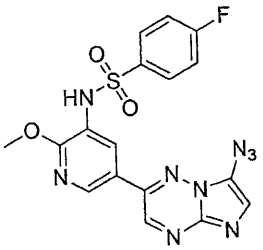

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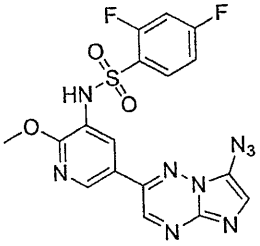

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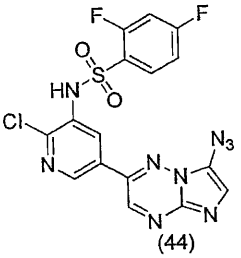

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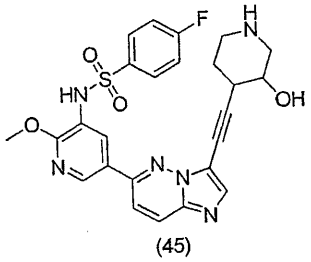

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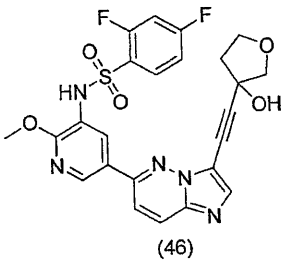

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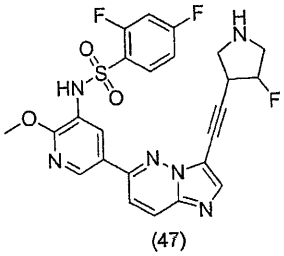

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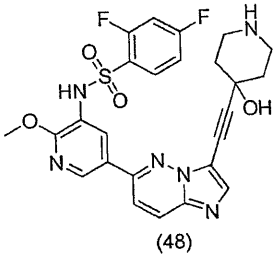

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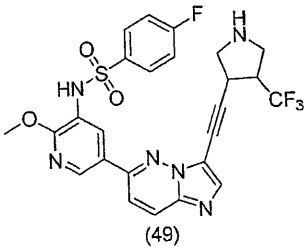

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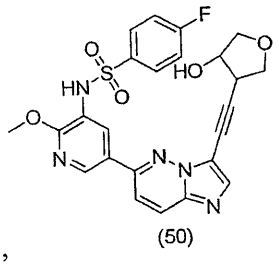

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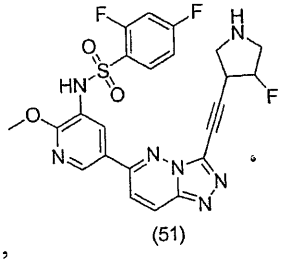

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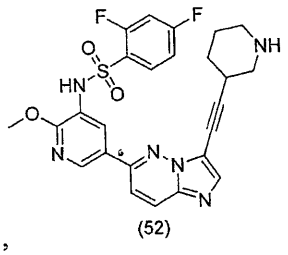

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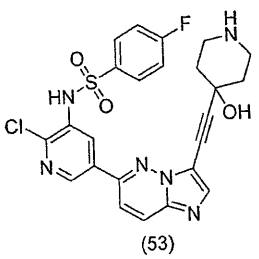

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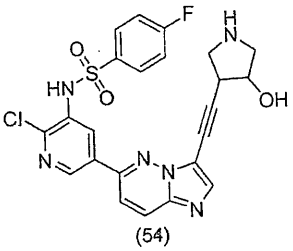

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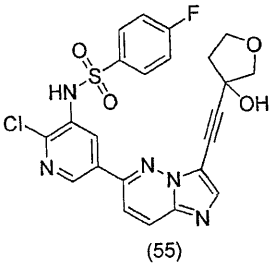

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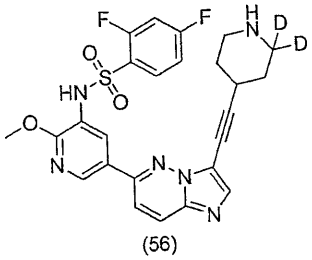

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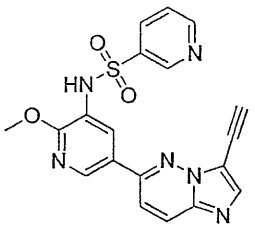
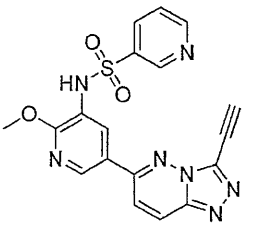
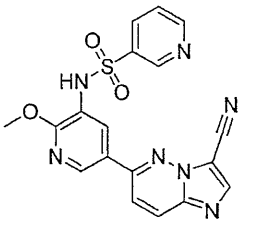
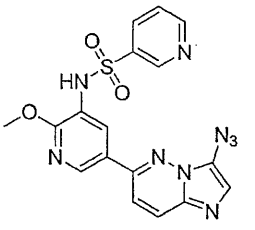
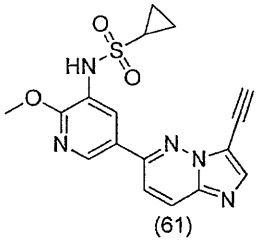
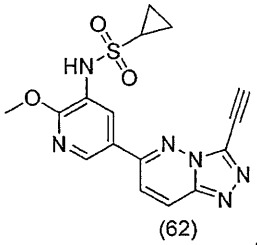
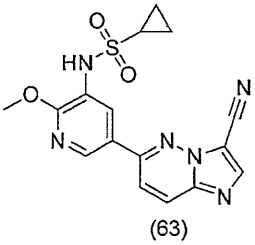
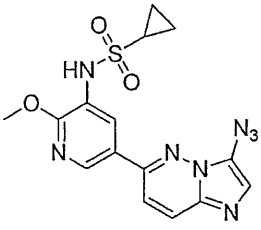
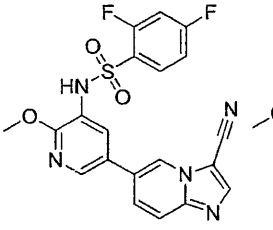
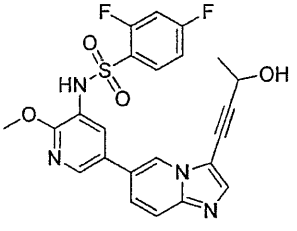
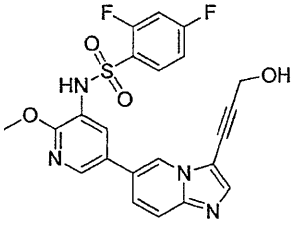
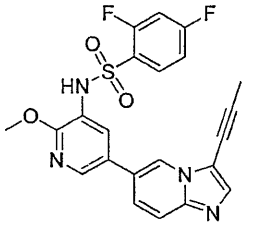
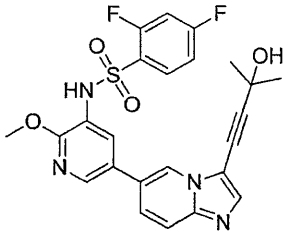
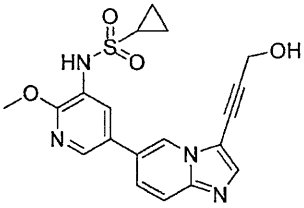
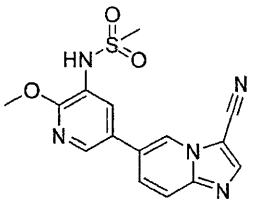
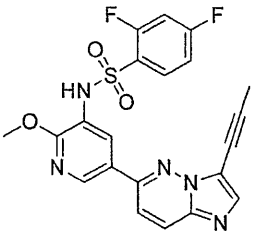
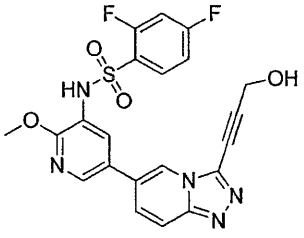
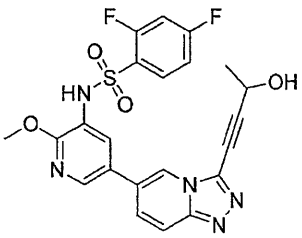

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(74).

5. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4, and a pharmaceutically acceptable carrier, excipient, diluent, adjuvant, vehicle or a combination thereof.

6. The pharmaceutical composition according to claim 5, further comprising an additional therapeutic agent selected from a chemotherapeutic agent, an anti-proliferative agent, an agent for treating atherosclerosis, an agent for treating lung fibrosis or a combination thereof.

7. The pharmaceutical composition according to claim 6, wherein the additional therapeutic agent is chlorambucil, melphalan, cyclophosphamide, ifosfamide, busulfan, carmustine, lomustine, streptozocin, cisplatin, carboplatin, oxaliplatin, dacarbazine, temozolomide, procarbazine, methotrexate, fluorouracil, cytarabine, gemcitabine, mercaptopurine, fludarabine, vinblastine, vincristine, vinorelbine, paclitaxel, docetaxel, topotecan, irinotecan, etoposide, trabectedin, dactinomycin, doxorubicin, epirubicin, daunorubicin, mitoxantrone, bleomycin, mitomycin, ixabepilone, tamoxifen, flutamide, gonadorelin analogues, megestrol, prednidone, dexamethasone, methylprednisolone, thalidomide, interferon alfa, leucovorin, sirolimus, temsirolimus, everolimus, afatinib, alisertib, amuvatinib, apatinib, axitinib, bortezomib, bosutinib, brivanib, cabozantinib, cediranib, crenolanib, crizotinib, dabrafenib, dacomitinib, danusertib, dasatinib, dovitinib, erlotinib, foretinib, ganetespib, gefitinib, ibrutinib, icotinib, imatinib, iniparib, lapatinib, lenvatinib, linifanib, linsitinib, masitinib, momelotinib, motesanib, neratinib, nilotinib, niraparib, oprozomib, olaparib, pazopanib, pictilisib, ponatinib, quizartinib, regorafenib, rigosertib, rucaparib, ruxolitinib, saracatinib, saridegib, sorafenib, sunitinib, tasocitinib, telatinib, tivantinib, tivozanib, tofacitinib, trametinib, vandetanib, veliparib, vemurafenib, vismodegib, volasertib, alemtuzumab, bevacizumab, brentuximab vedotin, catumaxomab, cetuximab, denosumab, gemtuzumab, ipilimumab, nimotuzumab, ofatumumab, panitumumab, ramucirumab, rituximab, tositumomab, trastuzumab, or a combination thereof.

8. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for preventing, managing, treating or lessening the severity of a proliferative disorder, wherein the proliferative disorder is modulated by PI3K, mTOR, or a combination thereof.

9. The use according to claim 8, wherein the proliferative disorder is colon cancer, breast cancer, lung cancer, or prostate cancer.