Supporting Information

Optimization of 3-Pyrimidin-4-yl-oxazolidin-2-ones as Allosteric and Mutant Specific Inhibitors of IDH1

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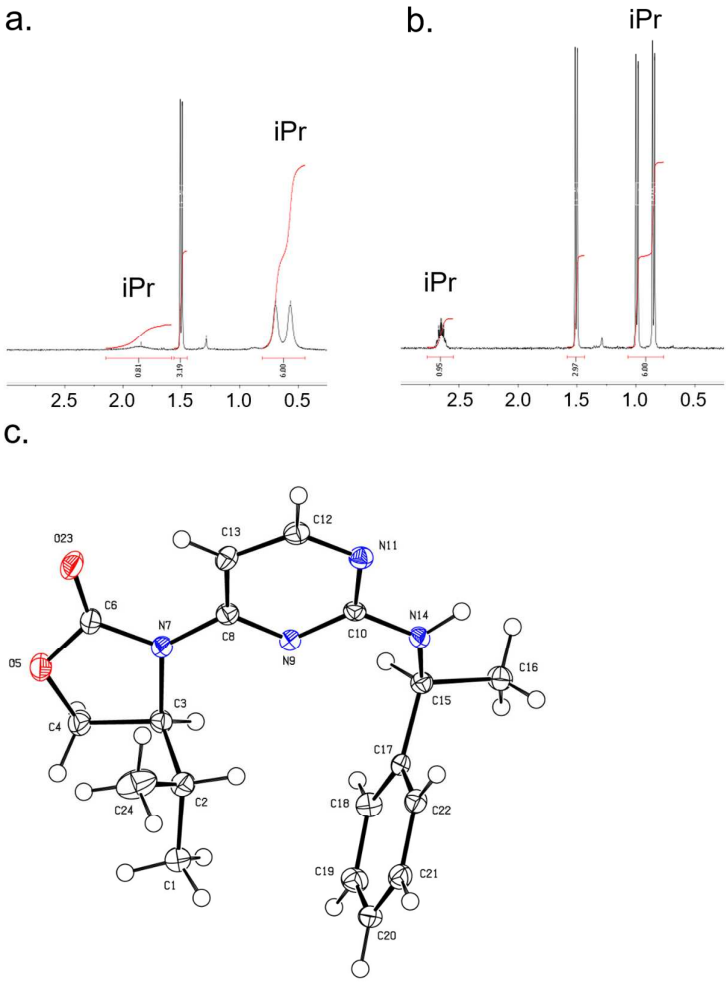
General Comment on Synthesis for Compounds 1c-f

An interesting analytical observation of the ^{1}H-NMR spectra for **1c-f** was a peak broadening and shift of ~0.4 ppm for the isopropyl (iPr) signals in the *R,R*- and *S,S*-isomers, relative to the *R,S*- and *S,R*-isomers (Figure SI-1a vs. b for **IDH125** vs. **1e**). Small-molecule X-ray crystallography of **IDH125** (Figure SI-1c) shows the molecule undergoes hydrophobic collapse to place the iPr and phenyl on the same side of the plane within van-der-Waals contact with each other, which could explain both the broadening (restricted rotation) as well as the upfield shift (shielding) of the iPr signals. The conformation is the same for the enantiomer (**1c)**, albeit with both phenyl and iPr on the opposite side of the plane of the pyrimidine. However, both the R,S (**1e**) and S,R (**1d**) have one substituent on each side of the plane leading to sharp iPr signals in the ^{1}H-NMR

Figure SI-1. Partial NMR for IDH125 (a) and 1e (b) showing restricted rotation and shielding effects of hydrophobic collapse, and small molecule x-ray structure of IDH125 (c)



Experimental details for the synthetic procedures and characterization data

All starting materials were commercially available from Sigma Aldrich, VWR, Oakwood, Chembridge, Ryan Scientific and Anichem. All chiral ethylamines were commercially available as racemates, and were either used as such (with separation of the final compounds), separated prior to the final coupling reactions, or synthesized as pure enantiomers using Ellman chiral sulfinamides as chiral auxiliaries. Commerically available chiral building blocks were purchased as >97% ee, and assumed to have the chiral identity and purity as claimed; for example (R)-(+)-4-isopropyl-2-oxazolidinone was purchased from Aldrich (Cat #339946), with ee: 99% (GLC) and (S)-(−)-4-isopropyl-2-oxazolidinone was purchased from Aldrich (Cat # 298883), with ee: 98% (GLC).

(*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one

A solution of 2,4-dichloropyrimidine (3.86g, 25.9mmol) and (S)-4-isopropyloxazolidin-2-one (3.03g, 23.46mmol) in DMF (30mL) was stirred at room temperature and treated slowly with NaH. The resulting reaction mixture was stirred at room temperature for 2 h, diluted with EtOAc (200 mL), washed with 4% aqueous NaCl (3 x 75 mL), dried over Na2SO4, filtered and concentrated to dryness. The crude product was purified on silica gel with gradient dilution of ethyl acetate/heptane from 5 to 70% to give (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (3.507g, 14.5mmol, 62%). 1H-NMR (400 MHz, CD3OD) δ8.50 (d, J = 5.9 Hz, 1 H), 8.17 (d, J = 5.8 Hz, 1 H), 4.83 – 4.76 (m, 1 H), 4.48 – 4.43 (m, 2 H), 2.56 (dtd, J = 14, 7.0, 3.8 Hz, 1 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.87 (d, J = 7.1 Hz, 3 H); LCMS *m/z* 242.6 $(M+H)^+$**.**

(S)-3-(2-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one

A solution of 2,4-difluoropyrimidine (3.5 mL, 41 mmol) and (S)-4-isopropyloxazolidin-2-one (5.3 g 41 mmol) in 30 mL DMF was cooled to 0 °C under N_2 atmosphere. NaH (2.1 g of 60% suspension, 53 mmol) was slowly added. A bubbling exotherm was observed. Internal temp was kept below 5 °C. After 5 minutes, the cold bath was removed. Reaction mixture (a sandy suspension) was allowed to warm to room temp and stir for 18 h. The reaction mixture was diluted with water (100 mL) and extracted with (3 x 75 mL) EtOAc. Organic layer was washed with water (50mL), and brine (50mL). Dried over Na_2SO_4, and concentrated on silica gel in vacuo. Column chromatography (EtOAc/heptane 10 to 100% gradient) gave 3.1 g (S)-3-(2-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (IV) as a crystalline white solid (33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

8.50 (dd, J = 5.8, 2.2 Hz, 1H), 8.19 (dd, J = 5.8, 3.8 Hz, 1H), 4.79 (dt, J = 8.1, 3.5 Hz, 1H), 4.48 – 4.34 (m, 2H), 2.64 (heptd, J = 7.0, 3.6 Hz, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H). MS m/z 471.8 and 471.8 (M + H)+. [CAUTION : HF byproduct]

1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethanone

1-(5-Bromopyrimidin-2-yl)ethanone (200 mg, 0.995 mmol), 4-fluoro-3-methylphenylboronic acid (306 mg, 1.99 mmol), K_3PO_4 (634 mg, 2.98 mmol), and [2-(Di-tert-butylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl)]palladium (II) chloride (34 mg, 0.05 mmol) in toluene (6mL) was heated at 110ºC for 1 h. The reaction mixture was cooled to room temperature, and filtered through Celite. Filter cake was rinsed with EtOAc (30mL). The filtrate was poured into water (30mL). Layers were separated, and the aqueous was further extracted with EtOAc (2x20 mL). Combined organics were washed with water (20mL) and brine (20mL), dried over Na_2SO_4, filtered and concentrated directly onto silica gel. Column chromatography (10 - 50% EtOAc/heptane) gave 1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethanone (68mg, 30%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 2H), 7.52 – 7.41 (m, 2H), 7.24 – 7.16 (m, 1H), 2.85 (s, 3H), 2.41 (d, J = 2.0 Hz, 3H). MS m/z 231.0 (M+H)+.

1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethanamine

1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethanone (65 mg, 0.282 mmol), NH4OAc (0.326 g, 4.23 mmol), and NaBH3CN (71 mg, 1.13 mmol) were taken up in 200 proof EtOH (6mL), and heated at 130ºC for 3 minutes in a microwave apparatus. The mixture was concentrated to remove the EtOH. Crude was taken up in water (30mL) + EtOAc (25mL). 6N NaOH was added until aqueous pH was ~10. Separated layers, and extracted aqueous with EtOAc (25 mL). The combined organic layer was washed with brine (25mL) and dried with Na_2SO_4. Filtered and concentrated with reduced pressure to give crude product as a colorless oil (60mg), which was carried forward without further purification. MS m/z 231.9 (M+H)+.

(*S*)-3-(2-chloropyrimidin-4-yl)-4-phenyloxazolidin-2-one

A solution of (*S*)-4-phenyloxazolidin-2-one (2.99 g, 18.3 mmol) and 2,4-dichloropyrimidine (3 g, 20.2 mmol, 1.1 equiv) in DMF (30 mL) was treated with NaH (95 %, 0.48 g, 19 mmol, 1.04 equiv), and the resulting mixture (yellow to red cloudy) was stirred at room temperature for 4 h. The reaction mixture was diluted with EtOAc (200 mL), washed with sat. NH_4Cl (75 mL) and 4% aqueous NaCl (2 x 100 mL), dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 0 to 50%) provided (*S*)-3-(2-chloropyrimidin-4-yl)-4-

phenyloxazolidin-2-one as a tacky white solid (2 g, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 6.1 Hz, 1 H), 8.18 (d, J = 5.7 Hz, 1 H), 7.39 – 7.27 (m, 5 H), 5.80 (dd, J = 8.6, 3.5 Hz, 1 H), 4.87 (t, J = 8.8 Hz, 1 H), 4.37 (dd, J = 8.8, 3.8 Hz, 1 H); MS *m/z* 276.5 $(M + H)^+$.

Table SI-1: Chemical name, NMR chemical shifts and LCMS signal for each compound synthesized by the same methods as described for (S)-3-(2-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one, (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one or (*S*)-3-(2-chloropyrimidin-4-yl)-4-phenyloxazolidin-2-one

Intermediate: Name	**^{1}H NMR (400 MHz) δ ppm**	**LCMS**
3-(2-chloropyrimidin-4-yl)oxazolidin-2-one	(Methanol-d_4) 8.48 (d, J = 6.1 Hz, 1 H), 8.16 (d, J = 6.1 Hz, 1 H), 4.54 (t, J = 7.8 Hz, 2 H), 4.22 (t, J = 8.1 Hz, 2 H)	MS *m/z* 200.4 $(M + H)^+$
(*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(Methanol-d_4) 8.50 (d, J = 5.9 Hz, 1 H), 8.17 (d, J = 5.8 Hz, 1 H), 4.83 – 4.76 (m, 1 H), 4.48 – 4.43 (m, 2 H), 2.56 (dtd, J = 14, 7.0, 3.8 Hz, 1 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.87 (d, J = 7.1 Hz, 3 H)	MS *m/z* 242.6 $(M + H)^+$
(*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyl-5,5-dimethyloxazolidin-2-one	(Methanol-d_4) 8.48 (d, J = 5.8 Hz, 1 H), 8.20 (d, J = 5.8 Hz, 1 H), 4.63 (d, J = 3.1 Hz, 1 H), 2.29 (dtd, J = 14, 7.0, 3.1, 1 H), 1.60 (s, 3 H), 1.47 (s, 3 H), 1.05 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H)	MS *m/z* 270.1 $(M + H)^+$
(*S*)-3-(2-chloro-6-methylpyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) 8.06 (s, 1 H), 4.83 – 4.77 (m, 1 H), 4.44 – 4.34 (m, 2 H), 2.65 – 2.55 (m, 1 H), 2.53 (s, 3 H), 1.00 (d, J = 8 Hz, 3 H), 0.88 (d, J = 8 Hz, 3 H)	MS *m/z* 255.8 $(M + H)^+$
(*S*)-3-(2-chloro-5-methylpyrimidin-4-yl)-4-isopropyloxazolidin-2-one	($CDCl_3$) 8.50 (s, 1 H), 5.01 – 4.96 (m, 1 H), 4.53 (t, J = 9.0 Hz, 1 H), 4.28 (t, J = 8.8 Hz, 1 H), 2.35 (s, 3 H), 2.16 (td, J = 7.0 Hz, J = 4.5 Hz, 1 H), 0.93 (d, J = 7.0 Hz, 3 H), 0.84 (d, J = 6.5 Hz, 3 H)	MS *m/z* 255.9 $(M + H)^+$
3-(2-chloropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one	($CDCl_3$) 8.47 (d, J = 5. 8 Hz, 1 H), 8.06 (d, J = 5.8 Hz, 1 H), 4.17 (s, 2 H), 1.77 (s, 6 H)	MS *m/z* 228.3 $(M + H)^+$
3-(2-fluoropyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.51 (dd, J = 5.8, 2.0 Hz, 1 H), 8.17 (dd, J = 5.8, 2.0 Hz, 1 H), 4.61 - 4.57 (m, 2 H), 4.31 - 4.27 (m, 2 H)	MS *m/z* 184.0 (M + H)
3-(2-chloropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one		MS m/z (M + H)+ 228.0, Rt 0.73 min

(S)-3-(2-chloropyrimidin-4-yl)-4-ethyloxazolidin-2-one

Step 1: A solution of 2,4-dichloropyrimidine (500mg, 3.36mmol) and (S)-2-aminobutan-1-ol (299mg, 3.36mmol) was dissolved in DMF (6mL), heated at 65°C for 2h, cooled to rt and poured into water (30mL). Extracted with EtOAc (2x25mL), washed organics with water and brine, dried over Na_2SO_4, and concentrated onto silica. Silica-gel column chromatography (EtOAc / heptane,

10-100%) gave (S)-2-((2-chloropyrimidin-4-yl)amino)butan-1-ol (310mg, 46%). MS m/z 202.4 (M + H)+.

Step 2: (S)-2-((2-chloropyrimidin-4-yl)amino)butan-1-ol (200mg, 0.992mmol) was dissolved in THF (6mL) and added *N,N*-diisopropylethylamine (260µL, 1.488mmol, 1.5eq). Triphosgene (300mg, 1mmol) was added and rm heated at 50°C for 4h. Added water (30mL), extracted into EtOAc (2x30mL), washed organics with water and brine, dried over Na_2SO_4, and concentrated onto silica. Silica-gel column chromatography (EtOAc / heptane, 10-100%) gave (S)-3-(2-chloropyrimidin-4-yl)-4-ethyloxazolidin-2-one

(155mg, 69%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, H), 8.07 (d, H), 4.68-4.74 (m, H), 4,53 (t, H), 4,32 (dd, H), 1.79-1.86 (m, 2H), 0.85 (t, 3H). MS m/z 228.0 (M + H)+.

1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethanamine

Step 1: A solution of 1-(5-fluoropyrimidin-2-yl)ethanone (700 mg, 5.0 mmol) and 4-fluorophenol (616 mg, 5.50 mmol) in DMF (6mL) was treated with potassium carbonate (829 mg, 6.0 mmol) and heated to 50ºC for 3.5 h. The reaction mixture was poured into water (20mL), and extracted with EtOAc (2 x 20 mL). Organics were washed with water (20mL), brine (20mL), and dried over Na_2SO_4, filtered and concentrated on silica gel. Column chromatography (10-100% EtOAc / heptane) gave 1-(5-(4-fluorophenoxy) pyrimidin-2-yl)ethanone (295mg, 25%) as a white solid used directly in the following step. MS m/z 233.2 (M + H)+. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 2H), 7.23 – 7.07 (m, 4H), 2.78 (s, 3H).

Step 2: 1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethanone (290 mg, 1.25 mmol), NH_4OAc (1.9 g, 24.6 mmol), and $NaBH_3CN$ (314 mg, 5.00 mmol) were taken up in 200 proof EtOH (20mL), and heated at 130°C for 3 minutes in a microwave apparatus. The mixture was concentrated to remove the EtOH. Crude was taken up in water (30mL) + EtOAc (25 mL). 6N NaOH was added until aqueous pH was ~10. Separated layers, and extracted aqueous with EtOAc (25 mL). The combined organic layer was washed with brine (25 mL) and dried with Na_2SO_4. Filtered and concentrated with reduced pressure to give 275 mg crude tan oil, which was carried forward without further purification. MS m/z 234.1 (M+H)+.

(*S*)-4-isopropyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one (**1e**)

A solution of (S)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (96 mg, 0.395 mmol) and (*R*)-(-)-1-phenylethanamine (0.3 mL, 2.4 mmol, 6 equiv) in DMSO (1.5 mL) was heated at 110 °C for 2 hours. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics

were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 50%) provided (*S*)-4-isopropyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one (98 mg, 76%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 5.8 Hz, 1 H), 7.35 – 7.27 (m, 5 H), 7.23 – 7.15 (m, 1 H), 4.96 (q, J = 6.9 Hz, 1 H), 4.44 (br s, 1 H), 4.34 – 4.23 (m, 2 H), 2.72 – 2.58 (m, 1 H), 1.51 (d, J = 6.6 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H); HRMS *m/z* 326.1746 M^+.

1c, 1d, and 1f were synthesized by the same method described for 1e above, but using the appropriate chiral starting materials. 1a and 1b were also synthesized using the same methodology but using a racemic mixture of 1-phenylethanamine with the chirally pure oxazolidinone starting material. Chiral analysis with SFC chromatography on chiralpak IA 4.6 x 100mm 5µm column, 5-55% MeOH with 10mM NH4OH/CO2 at 5mL/min flow rate gave the following analysis:

Compound	Major Isomer Retention time (%)	Minor Isomer Retention time (%)	% de
1a	1.68min, 2.06min	NA	NA
1b	1.74min, 1,86min	NA	NA
1c	1.82min (99.68%)	1.72min (0.32%)	99.36%
1d	1.73min (100%)	---	100%
1e	1.65min (99.1%)	2.03 (0.9%)	98.2%
IDH125, 1f	2.05min (99.48%)	1.68min (0.52%)	98.96%

(*S*)-3-(2-((*S*)-1-(biphenyl-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (**5r**)
A solution of (*S*)-3-(2-chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (90 mg, 0.37 mmol), *N,N*-diisopropylethylamine (0.455 mL, 2.61 mmol, 7.0 equiv) and racemic 1-(biphenyl-4-yl)ethanamine hydrochloride (87 mg, 0.37 mmol) in DMSO (1 mL) was heated at 110 °C for 2 h. The reaction mixture was diluted with EtOAc (8 mL) and washed with water (30 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 8 mL). Combined organics were dried over Na_2SO_4, filtered and concentrated. Silica gel column chromatography (EtOAc/Heptane 10 to 50%) provided (*S*)-3-(2-((*S*)-1-(biphenyl-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one as the second eluted product (21 mg, 14%) ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 5.8 Hz, 1 H), 7.58 – 7.52 (m, 4 H), 7.42 – 7.28 (m, 6 H), 5.06 (q, J = 7.1 Hz, 1 H), 4.63

(br s, 1 H), 4.34 – 4.25 (m, 2 H), 1.79 (br s, 1 H), 1.55 (d, J = 7.1 Hz, 3 H), 0.65 (br s, 3 H), 0.53 (br s, 3 H); HRMS *m/z* 403.2139 $(M + H)^+$.

(S)-3-(2-((S)-1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (**IDH889, 5x**).

A solution of (*S*)-3-(2-fluoropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (1055 mg, 4.68 mmol), 1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethanamine (1300 mg, 5.62 mmol, 1.2 equiv) and diisopropylethylamine (908mg, 7.03mmol, 1.5 equiv) in DMSO (20 mL) was heated at 110 °C for 1 h. The reaction mixture was poured into water (60 mL) and extracted with EtOAc (2x50 mL). Combined organics were washed with water (40mL), brine (40mL), dried over Na_2SO_4, filtered and concentrated directly onto silica gel. Silica gel chromatography provided the mixed distereomers of (S)-3-(2-(1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethylamino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (560mg). Chiral separation was carried out with SFC (ID, 5µm, 20 x 250 mm) using 35% MeOH in CO2 to give (S)-3-(2-((S)-1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one as the first eluted product (302 mg, 15%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 2H), 8.23 (d, J = 5.8 Hz, 1H), 7.49 (d, J = 5.7 Hz, 1H), 7.43 – 7.30 (m, 2H), 7.21 – 7.11 (m, 1H), 6.26 (br s, 1H), 5.31 (br s, 1H), 4.75 (dt, J = 7.9, 3.3 Hz, 1H), 4.39 – 4.24 (m, 2H), 2.38 (s, 3H), 2.09 (br s, 1H), 1.66-1.62 (m, 3H), 0.90 (dd, J = 9.8, 6.0 Hz, 3H), 0.78 (br s, 3H). HRMS m/z 437.2093 (M + H)+. [CAUTION : HF byproduct]

Chiral analysis with SFC chromatography on chiralpak IA 4.6 x 100mm 5µm column, 5-55% MeOH with 20mM NH4OH/CO2 at 5mL/min flow rate gave the following analysis:

Compound	Major Isomer Retention time (%)	Minor Isomer Retention time (%)	% de
Diastereomeric mixture prior to chiral separation	2.74min, 3.36min	NA	NA
IDH889, 5x	2.73min (100%)	-----	100%

Table SI-2 . Chemical name, NMR chemical shifts and LCMS signal for each compound synthesized by the same methods as described for (*S*)-4-isopropyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one (**1e**) and (*S*)-3-(2-((*S*)-1-(biphenyl-4-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (**5r**)

Name	**^{1}H NMR (400 MHz, methanol-d_4) δ ppm (other solvents described)**	**LCMS**
1c: (*R*)-4-isopropyl-3-(2-((*R*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.37 – 7.25 (m, 5 H), 7.19 – 7.16 (m, 1H), 5.04 (q, J = 6.9 Hz, 1 H), 4.64 (br s, 1 H), 4.35 – 4.26 (m, 2 H), 1.88 (br s, 1 H), 1.50 (d, J = 6.6 Hz, 3 H), 0.70 (br s, 3 H), 0.57 (br s, 3 H)	HRMS *m/z* 327.1821 $(M + H)^+$
1d: (*R*)-4-isopropyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.10 (d, J = 5.8 Hz, 1 H), 7.35 – 7.27 (m, 5 H), 7.20 – 7.17 (m, 1 H), 4.96 (q, J = 6.7 Hz, 1 H), 4.44 (br s, 1 H), 4.32 (dd, J = 9.1, 2.5 Hz, 1 H), 4.25 (t, J = 8.6 Hz, 1 H), 2.65 (dtd, J = 14, 7.0, 3.5 Hz, 1 H), 1.51 (d, J = 7.1 Hz, 3 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.85 (d, J = 7.1 Hz, 3 H)	HRMS *m/z* 327.1824 $(M + H)^+$
1f: (*S*)-4-isopropyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.6 Hz, 1 H), 7.34 – 7.26 (m, 5 H), 7.22 – 7.13 (m, 1 H), 5.04 (q, J = 7.1 Hz, 1 H), 4.64 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.85 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.70 (br s, 3 H), 0.57 (br s, 3 H)	HRMS *m/z* 326.1745 M^+
2a: (*S*)-3-(2-(benzylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.13 (d, J = 5.8 Hz, 1 H), 7.37 (d, J = 5.8 Hz, 1 H), 7.28 (d, J = 4.6 Hz, 4 H), 7.20 (dq, J = 8.5, 4.2 Hz, 1 H), 4.64 (br s, 1 H), 4.56 (dd, J = 51, 16 Hz, 2 H), 4.35 – 4.29 (m, 2 H), 2.31 (br s, 1 H), 0.77 (br s, 3 H), 0.72 (br d, J = 6.6 Hz, 3 H)	HRMS *m/z* 312.1584 M^+
2b: (S)-4-isopropyl-3-(2-((2-phenylpropan-2-yl)amino)pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, *J* = 5.8 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 5.8 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 4.29 – 4.03 (m, 3H), 1.81 (s, 3H), 1.71 (br s, 1H),1.65 (s, 3H), 0.66 (d, *J* = 7.0 Hz, 3H), 0.57 (d, *J* = 6.9 Hz, 3H).	HRMS *m/z* 341.1964 $(M + H)^+$
2c: (*S*)-4-isopropyl-3-(2-((*S*)-1-phenylpropylamino)pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.6 Hz, 1 H), 7.33 – 7.26 (m, 5 H), 7.22 – 7.15 (m, 1 H), 4.83 – 4.79 (m, 1 H), 4.68 (br s, 1 H), 4.36 – 4.28 (m, 2 H), 1.84 (quin, J = 7.3 Hz, 2 H), 0.99 (t, J = 7.3 Hz, 3 H), 0.76 (br s, 3 H), 0.59 (br s, 3 H)	HRMS *m/z* 341.1974 $(M + H)^+$
2d: (S)-4-isopropyl-3-(2-((1-phenylcyclopropyl)amino)pyrimidin-4-yl)oxazolidin-2-one	8.14 (br d, *J* = 5.4 Hz, 1H), 7.40 (d, *J* = 5.8 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.16 – 7.08 (m, 3H), 4.42 (br s, 1 H), 4.25 (br s, 2H), 2.10 (br s, 1 H), 1.46 – 1.19 (m, 4H), 0.59 (br s, 6H).	HRMS *m/z* 339.1830 $(M + H)^+$
3a: 3-(2-((1-phenylethyl)amino)pyrimidin-4-yl)oxazolidin-2-one ***(racemic)***	8.07 (d, *J* = 5.8 Hz, 1H), 7.37 (d, *J* = 7.4 Hz, 2H), 7.33 – 7.24 (m, 3H), 7.18 (t, *J* = 7.2 Hz, 1H), 5.04 (q, *J* = 6.9 Hz, 1H), 4.44 (h, *J* = 8.5 Hz, 2H), 4.18 (td, *J* = 9.8, 7.0 Hz, 1H), 3.93 (br s, 1H), 1.51 (d, *J* = 7.0 Hz, 3H).	HRMS *m/z* 285.1347 $(M + H)^+$
3b: (*S*)-4,4-dimethyl-3-(2-(1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.08 (d, J = 5.8 Hz, 1 H), 7.27 – 7.20 (m, 4 H), 7.17 (d, J = 5.6 Hz, 1 H), 7.15 – 7.11 (m, 1 H), 5.42 (br s, 1 H), 4.94 – 4.87 (m, 1 H), 3.92 –	HRMS *m/z* 313.1668 $(M + H)^+$

	3.86 (m, 2 H), 1.58 (s, 3 H), 1.47 (d, J = 6.9 Hz, 3 H), 1.06 (br s, 3 H)	
3c: (*S*)-4-ethyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.19 (d, *J* = 5.9 Hz, 1H), 7.44 (d, *J* = 5.6 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.27 – 7.19 (m, 1H), 5.44 (br s, 1 H), 5.07 (p, *J* = 7.0 Hz, 1H), 4.64 – 4.57 (m, 1H), 4.40 (t, *J* = 8.4 Hz, 1H), 4.14 (dd, *J* = 8.6, 3.1 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H), 1.57 – 1.40 (m, 2H), 0.74 (t, *J* = 7.5 Hz, 3H).	LCMS *m/z* 313.1 $(M + H)^+$
3d: (*S*)-4-phenyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.07 (d, J = 5.6 Hz, 1 H), 7.38 (d, J = 5.6 Hz, 1 H), 7.28 – 7.05 (m, 10 H), 5.84 (dd, J = 8.6, 3.5 Hz, 2 H), 4.88 (q, J = 6.8 Hz, 1 H), 4.83 – 4.79 (m, 1 H), 4.24 (dd, J = 8.6, 3.5 Hz, 1 H), 1.44 (d, J = 6.8 Hz, 3 H)	HRMS *m/z* 361.1666 $(M + H)^+$
3e: (*S*)-4-isopropyl-3-(5-methyl-2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 8.13 (s, 1 H), 7.35 – 7.28 (m, 4 H), 7.24 – 7.20 (m, 1 H), 5.73 (br s, 1 H), 5.00 – 4.92 (m, 1 H), 4.59 – 4.51 (m, 1 H), 4.38 (t, J = 8.8 Hz, 1 H), 4.12 (t, J = 8.8 Hz, 1 H), 2.14 (s, 3 H), 1.55 (d, J = 6.5 Hz, 3 H), 1.44 (br s, 1 H), 0.59 (d, J = 6.5 Hz, 3 H), 0.53 (d, J = 5.0 Hz, 3 H)	HRMS *m/z* 341.1974 $(M + H)^+$
3f: (*S*)-4-isopropyl-3-(6-methyl-2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	($CDCl_3$) 7.57 – 7.19 (m, 6 H), 5.05 – 4.86 (m, 1 H), 4.63 – 4.09 (m, 3 H), 2.56 / 2.49 (2 x s, 3 H), 1.91 – 1.70 (m, 1 H), 1.62 / 1.54 (2 x d, 3 H), 0.75 – 0.45 (m, 6 H)	HRMS *m/z* 341.1982 $(M + H)^+$
4a: (*S*)-4-isopropyl-5,5-dimethyl-3-(2-((*S*)-1-phenylethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.13 (d, J = 5.8 Hz, 1 H), 7.35 – 7.26 (m, 5 H), 7.19 – 7.16 (m, 1H), 5.08 – 5.03 (m, 1 H), 4.45 (br s, 1 H), 1.99 (br s, 1 H), 1.52 (s, 3 H), 1.50 (d, J = 7.1 Hz, 3 H), 1.41 (s, 3 H), 0.73 (br s, 3 H), 0.58 (br s, 3 H)	HRMS *m/z* 355.2132 $(M + H)^+$
4d: (S)-4-isopropyl-3-(2-(methyl((S)-1-phenylethyl)amino)pyrimidin-4-yl)oxazolidin-2-one	8.25 (d, *J* = 5.8 Hz, 1H), 7.39 (d, *J* = 5.8 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.29 – 7.21 (m, 3H), 6.12 (q, *J* = 7.0 Hz, 1H), 4.77 (dt, *J* = 7.4, 3.6 Hz, 1H), 4.43 – 4.30 (m, 2H), 2.87 (s, 3H), 2.44 (br s, 1H), 1.60 (d, *J* = 7.1 Hz, 3H), 0.88 – 0.72 (m, 6H).	HRMS *m/z* 341.1976 $(M + H)^+$
5a: (*S*)-3-(2-(((*S*)-1-cyclohexylethyl)amino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	(DMSO-d_6) 8.13 (d, *J* = 5.8 Hz, 1 H), 7.19 – 7.09 (m, 2 H), 4.68 (br s, 1 H), 4.41 – 4.33 (m, 2 H), 3.77 (br s, 1 H), 2.47 (br s, 1 H), 1.76 – 1.58 (m, 5 H), 1.43 – 1.35 (m, 1 H), 1.15 – 1.04 (m, 6 H), 0.97 – 0.88 (m, 5 H), 0.77 (d, *J* = 6.8 Hz, 3 H);	HRMS *m/z* 333.2288 $(M + H)^+$
5b: (S)-3-(2-((S)-1-(2-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.51 (d, J = 5.7 Hz, 1H), 7.76 – 7.51 (m, 3H), 7.48 – 7.37 (m, 2H), 5.71 (q, J = 7.0 Hz, 1H), 5.06 – 5.02 (m, 1H), 4.75 – 4.61 (m, 2H), 2.30 (br s, 1H), 1.89 (d, J = 7.0, 3H), 1.10 (d, J = 7.1 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H).	HRMS (M+H) 393.2026
5c: (*S*)-3-(2-((*S*)-1-(3-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.13 (d, J = 5.7 Hz, 1 H), 7.36 (d, J = 5.8 Hz, 1 H), 7.29 (td, J = 8.1, 6.1 Hz, 1 H), 7.13 (d, J = 7.6 Hz, 1 H), 7.06 – 7.04 (m, 1 H), 6.94 – 6.87 (m, 1 H), 5.03 (q, J = 7.1 Hz, 1 H), 4.64 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.79 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.70 (br s, 3 H), 0.58 (br s, 3 H)	HRMS *m/z* 345.1727 $(M + H)^+$.

5d: (*S*)-3-(2-((*S*)-1-(4-fluorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.35 – 7.31 (m, 3 H), 7.03 – 6.97 (m, 2 H), 5.03 (q, J = 7.1 Hz, 1 H), 4.66 – 4.63 (br m, 1 H), 4.35 – 4.27 (m, 2 H), 1.85 (br s, 1 H), 1.49 (d, J = 7.0 Hz, 3 H), 0.71 (br s, 3 H), 0.60 (br s, 3 H)	HRMS *m/z* 345.1724 $(M + H)^+$
5e: (*S*)-3-(2-((*S*)-1-(3-chlorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.14 (d, J = 5.8 Hz, 1 H), 7.36 (d, J = 5.8 Hz, 1 H), 7.32 (br s, 1 H), 7.29 – 7.23 (m, 2 H), 7.20 – 7.17 (m, 1 H), 5.02 (q, J = 6.9 Hz, 1 H), 4,63 (br s, 1 H), 4.34 – 4.27 (m, 2 H), 1.82 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.70 (br s, 3 H), 0.59 (br s, 3 H)	HRMS *m/z* 361.1424 $(M + H)^+$
5f: (*S*)-3-(2-((*S*)-1-(4-chlorophenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.	8.13 (d, J = 5.7 Hz, 1 H), 7.36 – 7.26 (m, 5 H), 5.00 (q, J = 7.1 Hz, 1 H), 4,62 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.77 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.68 (br s, 3 H), 0.59 (br s, 3 H)	HRMS *m/z* 361.1431 $(M + H)^+$.
5g: (*S*)-3-(2-((*S*)-1-(3,4-dichlorophenyl)ethylamino) pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.15 (d, J = 5.8 Hz, 1 H), 7.47 – 7.42 (m, 2 H), 7.37 (d, J = 5.8 Hz, 1 H), 7.25 (dd, J = 8.1, 2.0 Hz, 1 H), 5.01 – 4.96 (m, 1 H), 4.61 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.72 (br s, 1 H), 1.50 (d, J = 7.1 Hz, 3 H), 0.67 (br s, 3 H), 0.60 (br s, 3 H)	HRMS *m/z* 395.1044 $(M + H)^+$.
5h: (*S*)-4-isopropyl-3-(2-((*S*)-1-(2-methoxyphenyl)ethylamino) pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.8 Hz, 3 H), 7.20 – 7.16 (m, 2 H), 6.95 (d, J = 8.1 Hz, 1 H), 6.86 – 6.82 (m, 1 H), 5.28 (q, J = 7.1 Hz, 1 H), 4.63 (br s, 1 H), 4.35 – 4.26 (m, 2 H), 3.87 (s, 3 H), 1.86 (br s, 1 H), 1.46 (d, J = 6.9 Hz, 3 H), 0.69 (br s, 3 H), 0.56 (br s, 3 H)	HRMS *m/z* 357.1924 $(M + H)^+$
5i: (*S*)-4-isopropyl-3-(2-((*S*)-1-(3-methoxyphenyl)ethylamino) pyrimidin-4-yl)oxazolidin-2-one	8.12 (d, J = 5.8 Hz, 1 H), 7.34 (d, J = 6.0 Hz, 1 H), 7.20 – 7.16 (m, 1 H), 6.89 – 6.87 (m, 2 H), 6.75 – 6.73 (m, 1 H), 4.99 (q, J = 6.7 Hz, 1 H), 4.63 (br s, 1 H), 4.34 – 4.25 (m, 2 H), 3.74 (s, 3 H), 1.84 (br s, 1 H), 1.49 (d, J = 7.1 Hz, 3 H), 0.68 (br s, 3 H), 0.57 (br s, 3 H)	HRMS *m/z* 357.1918 $(M + H)^+$
5k: (*S*)-4-isopropyl-3-(2-((*S*)-1-(4-methoxyphenyl)ethylamino) pyrimidin-4-yl)oxazolidin-2-one	8.11 (d, J = 5.8 Hz, 1 H), 7.33 (d, J = 5.9 Hz, 1 H), 7.22 (d, J = 8.6 Hz, 2 H), 6.85 – 6.82 (m, 2 H), 4.98 (q, J = 6.9 Hz, 1 H), 4.67 – 4.63 (m, 1 H), 4.34 – 4.27 (m, 2 H), 3.75 (s, 3 H), 1.94 (br s, 1 H), 1.48 (d, J = 7.1 Hz, 3 H), 0.73 (br s, 3 H), 0.61 (br s, 3 H)	HRMS *m/z* 357.1922 $(M + H)^+$
5m: (*S*)-3-(2-((*S*)-1-(3,4-dimethoxyphenyl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.	8.13 (d, J = 5.8 Hz, 1 H), 7.32 (d, J = 5.7 Hz, 1 H), 6.94 (br d, J = 1.1 Hz, 1 H), 6.89 – 6.84 (m, 2 H), 4.99 (q, J = 7.1 Hz, 1 H), 4.67 – 4.63 (m, 1 H), 4.36 – 4.26 (m, 2 H), 3.79 (s, 6 H), 2.01 (br s, 1 H), 1.51(d, J = 7.1 Hz, 3 H), 0.71 (d, J = 7.1 Hz, 3 H), 0.63 (d, J = 7.0 Hz, 3 H)	HRMS *m/z* 387.2029 $(M + H)^+$.
5n: 4-((*S*)-1-(4-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)pyrimidin-2-ylamino)ethyl)benzonitrile	8.14 (d, J = 5.8 Hz, 1 H), 7.68 – 7.66 (m, 2 H), 7.52 (d, J = 8.1 Hz, 3 H), 7.36 (d, J = 5.9 Hz, 1 H), 5.08 (q, J = 7.1 Hz, 1 H), 4.61 (br s, 1 H), 4.34 – 4.26 (m, 2 H), 1.60 (br s, 1 H), 1.52 (d, J = 7.1 Hz, 3 H), 0.65 (br s, 3 H), 0.58 (br s, 3 H)	HRMS *m/z* 352.1775 $(M + H)^+$
5p: (*S*)-4-isopropyl-3-(2-((*S*)-	8.19 – 8.16 (m, 2 H), 7.88 (d, J = 8.1 Hz, 1 H),	HRMS *m/z*

1-(naphthalen-1-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	7.72 (d, J = 8.1 Hz, 1 H), 7.56 – 7.45 (m, 3 H), 7.40 – 7.32 (m, 2 H), 5.80 (q, J = 6.6 Hz, 1 H), 4.32 (br s, 1 H), 4.17 – 4.13 (m, 1 H), 4.05 (br s, 1 H), 1.64 (d, J = 7.1 Hz, 3 H), 1.15 (br s, 1 H), 0.23 (br s, 3 H), -0.31 (br s, 3 H)	377.1969 $(M + H)^+$
5q: (*S*)-4-isopropyl-3-(2-((*S*)-1-(naphthalen-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.15 (d, J = 5.7 Hz, 1 H), 7.81 – 7.73 (m, 4 H), 7.49 – 7.38 (m, 3 H), 7.33 (d, J = 5.8 Hz, 1 H), 5.18 (q, J = 7.1 Hz, 1 H), 4.57 (br s, 1 H), 4.30 – 4.25 (m, 1 H), 4.20 (br s, 1 H), 1.60 (d, J = 7.1 Hz, 3 H), 1.59 (br s, 1 H), 0.34 (br s, 6 H)	HRMS *m/z* 377.1979 $(M + H)^+$
5s (IDH662): (*S*)-4-isopropyl-3-(2-((*S*)-1-(4-phenoxyphenyl)ethylamino) pyrimidin-4-yl)oxazolidin-2-one	8.13 (d, J = 5.8 Hz, 1 H), 7.34 – 7.28 (m, 5 H), 7.09 – 7.05 (m, 1 H), 6.96 – 6.90 (m, 4 H), 5.06 (q, J = 7.1 Hz, 1 H), 4.71 – 4.67 (m, 1 H), 4.37 – 4.28 (m, 2 H), 2.08 (br s, 1 H), 1.52 (d, J = 7.1 Hz, 3 H), 0.76 (d, J = 7.1 Hz, 3 H), 0.67 (d, J = 7.1 Hz, 3 H)	HRMS *m/z* 419.2081 $(M + H)^+$

Table SI-3. Chemical name, NMR chemical shifts and LCMS signal for each compound synthesized by the same method as described for (S)-3-(2-((S)-1-(5-(4-fluoro-3-methylphenyl)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one (**5x**)

.

Example: Name	**^{1}H NMR (400 MHz, $CDCl_3$) δ ppm**	**LCMS**
5t: (S)-3-(2-((S)-1-(5-chloropyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one.	8.58 (s, 2H), 8.12 (d, J = 5.8 Hz, 1H), 7.40 (d, J = 5.8 Hz, 1H), 5.97 (br s, 1H), 5.17 (br s, 1H), 4.63 (dt, J = 8.0, 3.2 Hz, 1H), 4.29 – 4.15 (m, 2H), 2.10 (br s, 1H), 1.50 – 1.46 (m, 3H), 0.88 – 0.66 (m, 6H).	LC-MS m/z 363.1 (M + H)+; RT.: 1.39 min.
5v: (S)-3-(2-((S)-1-(5-(4-fluorophenoxy)pyrimidin-2-yl)ethylamino)pyrimidin-4-yl)-4-isopropyloxazolidin-2-one	8.42 (s, 2H), 8.21 (d, J = 5.8 Hz, 1H), 7.49 (d, J = 5.7 Hz, 1H), 7.18 – 6.99 (m, 4H), 6.18 (br s 1H), 5.28 (br s, 1H), 4.75 (dt, J = 8.2, 3.4 Hz, 1H), 4.39 – 4.25 (m, 2H), 2.34 (br s, 1H), 1.65 – 1.59 (m, 3H), 0.95 – 0.86 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H).	HRMS m/z 439.1876 (M + H)+.
5w: (4S)-4-isopropyl-3-(2-(1-(5-phenylpyrimidin-2-yl)ethylamino)pyrimidin-4-yl)oxazolidin-2-one	8.93 (d, J = 5.9 Hz, 4H), 8.26 – 8.17 (m, 2H), 7.64 – 7.44 (m, 12H), 6.41 (br s, 1H), 5.31 (br s, 1H), 4.79 – 4.65 (m, 2H), 4.41 – 4.24 (m, 4H), 2.65 (dddd, J = 27.4, 14.1, 7.1, 3.5 Hz, 1H), 2.20 (br s, 1H), 1.75-1.64 (m, 4H), 1.07 – 0.85 (m, 9H), 0.78 (s, 3H).	HRMS m/z 405.2024 and 405.2025 (M + H)+

(S)-3-(2-bromopyridin-4-yl)-4-isopropyloxazolidin-2-one

To a solution of 2-bromo-4-fluoropyridine (0.79 mL, 7.3 mmol) and (S)-4-isopropyloxazolidin-2-one (2.38 g, 18.2 mmol) in DMF (15 mL) was added potassium carbonate (3.0 g, 21.9 mmol). The mixture was heated by microwave apparatus to 110 °C for 3 hours, then diluted with ethyl acetate (100 mL) and washed with water (2 x 50 mL). The organic phase was dried over sodium

sulfate, filtered and concentrated under reduced pressure. DCM (30 mL) was added to the crude residue and the precipitate was collected by filtration. The resulting filtrate was then concentrated under reduced pressure, acetonitrile (20 mL) was added and the predipitate was filtered again through the same filter to obtain 494 mg as a white solid which was carried forward without further purification. MS m/z 285.3 (M+H)+.

[(S)-3-(6-fluoropyridin-2-yl)-4-isopropyloxazolidin-2-one

To a 20 mL microwave reactor vial containing 2-bromo-6-fluoropyridine (1.67 g, 9.49 mmol), (S)-4-isopropyloxazolidin-2-one (1.96 g, 15.18 mmol) and trans-N,N'-dimethyl-1,2-cyclohexanediamine (1.52 mL, 9.49 mmol) in 1,4-dioxane (10 mL), was added copper (I) iodide (1.81 g, 9.49 mmol) and potassium carbonate (3.95 g, 28.6 mmol). The vial was capped and heated by microwave apparatus to 130 °C for 1 hour. The reaction mixture was diluted with ethyl acetate (200mL) and vacuum filtered to remove a precipitate. The filtrate was washed with 3% aq ammonia (4 x 40 mL) followed by brine, then the organic portion was dried over sodium sulfate, filtered and concentrated with reduced pressure to a yellow oil. Silica-gel column chromatography (EtOAc / heptane, 0-10%) gave 991 mg as a white powder, which was carried forward without further purification. MS m/z 225.4 (M + H)+.

(S)-4-isopropyl-3-(2-(((S)-1-phenylethyl)amino)pyridin-4-yl)oxazolidin-2-one (**4b**)

To a 10 mL microwave reactor vial containing a nitrogen purged mixture of (S)-3-(2-bromopyridin-4-yl)-4-isopropyloxazolidin-2-one (485 mg, 1.70 mmol), (S)-1-phenylethan-1-amine (0.439 mL, 3.40 mmol) and dioxane (5 mL), added sodium t-butoxide (327 mg, 3.40 mmol) and bis(tri-t-butylphosphine)palladium(0) (87 mg, 0.17 mmol). The vial was capped and heated by microwave apparatus to 130 °C for 20 minutes. The mixture was then diluted with ethyl acetate (100 mL), sonicated and vacuum filtered to remove a precipitate. The filtrate was purified by silica gel column chromatography (EtOAc/Heptane 0 to 50%) to obtain (S)-4-isopropyl-3-(2-(((S)-1- phenylethyl)amino)pyridin-4-yl)oxazolidin-2-one as an off-white powder (117 mg, 20%).

1H NMR (400 MHz, DMSO-d6) δ 7.84 (d, J = 5.9 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.31 – 7.25 (m, 2H), 7.20 – 7.14 (m, 1H), 7.09 (d, J = 7.7 Hz, 1H), 6.79 (dd, J = 5.8, 1.6 Hz, 1H), 6.60 (s, 1H), 5.00 – 4.90 (m, 1H), 4.48 – 4.42 (m, 1H), 4.35 (t, J = 8.7 Hz, 1H), 4.29 (dd, J = 9.0, 3.4 Hz, 1H), 1.98 – 1.85 (m, 1H), 1.40 (d, J = 6.9 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H); HRMS *m/z* 326.1866 $(M + H)^+$.

(S)-4-isopropyl-3-(6-(((S)-1-phenylethyl)amino)pyridin-2-yl)oxazolidin-2-one (**4c**)

To a 5mL microwave reactor vial containing [(S)-3-(6-fluoropyridin-2-yl)-4-isopropyloxazolidin-2-one (310 mg, 1.38 mmol) in NMP (2 mL) was added ((S)-1-phenylethan-1-amine (0.356 mL, 2.76 mmol). The vial was capped and heated by microwave apparatus to 200 °C for 20 minutes. Further (S)-(-)-α-methylbenzylamine (0.710 mL, 5.52 mmol) was added and heating again to 200 °C for 20 minutes. The reaction mixture was diluted with EtOAc (20 mL), then washed with a saturated solution of sodium bicarbonate (2 x 10 mL) followed by water, then brine. Dried organic portion over sodium sulfate, filtered and concentrated under reduced pressure. Silica gel column chromatography (0-30% EtOAc in heptane) gave (S)-4-isopropyl-3-(6-(((S)-1-phenylethyl)amino)pyridin-2-yl)oxazolidin-2-one (55 mg, 12%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (t, *J* = 8.0 Hz, 1H), 7.32 – 7.23 (m, 4H), 7.20 – 7.13 (m, 2H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.29 (d, *J* = 8.1 Hz, 1H), 5.02 – 4.93 (m, 1H), 4.60 – 4.53 (m, 1H), 4.29 (t, *J* = 8.8 Hz, 1H), 4.19 (dd, *J* = 9.0, 3.3 Hz, 1H), 1.80 – 1.67 (m, 1H), 1.40 (d, *J* = 7.0 Hz, 3H), 0.61 (d, *J* = 7.0 Hz, 3H), 0.48 (d, *J* = 6.9 Hz, 3H); HRMS *m/z* 326.1874 $(M + H)^+$. [CAUTION : HF byproduct]

Biochemical IDH1$^{R132H+/+}$ 2-HG LCMS assay protocol

IDH enzyme assays were run in the following buffer: 50 mM HEPES, pH 7.3, 10 mM MgCl2, 50 mM KCl, 0.02% BSA, and 1mM DTT. Compounds were diluted in DMSO. IDH^{R132H} was added to a final concentration of 500 pM. Spin down for 1min. NADPH (5 µM final concentration) and αKG (200 µM final concentration) were added as a premixed solution to start the reaction. Reactions were incubated for 60mins then quenched using formic acid (4.4% final concentration). 20 µL of quenched sample was added to 100 uL of acetonitrile, and samples were centrifuged before injection onto the LC/MS/MS system. Quantitation of 2-HG was performed using Agilent 1260 LC systems coupled to an Applied Biosystems API 4000 mass spectrometer.

Biochemical mutant (R132H and R132C) and wild type IDH1 fluorescence assay protocol

Biochemical assays were run in the following reaction buffer: 50mM HEPES pH7.5, 50mM KCl, 1mM dithiothreitol (DTT), 10mM $MgCl_2$, and 0.02% bovine serum albumin (BSA). IDH1 WT assays used 30 µM isocitrate and 30 µM NADP. IDH1 mutant assays used 100µM α-ketoglutarate and 10 µM NADPH. Reactions were initiated through addition IDH1 protein, and monitored for the production (WT) or consumption (MUT) of NADPH through measuring the fluorescence of NADPH (excitation wavelength=355 nm, emission wavelength=520 nm). WT assay was run for 2h, R132H for 90mins, R132C for 45mins. No preincubation time prior to initiation of the reaction by addition of protein.

Cellular mutant IDH1^{R132H} assay

Parental and IDH1^{R132H} heterozygous mutant HCT116 cells (Horizon Discovery) were cultured in McCoy's 5A Modified medium with 10% fetal bovine serum. For assessing cellular 2-HG inhibition, cells were plated at 3,500 cells/well in 384-well plates (Corning) and incubated overnight at 37°C prior to compound addition. Compounds were added to wells in order to allow 10-point 3-fold dilutions in triplicate, starting at 10 µM. Cells were incubated with compounds for an additional 48 hours. To extract 2-HG, media was removed and 70 µL of 90% methanol was added to each well. Plates were then covered with foil seals and shaken for 30 seconds at high frequency, then incubated on dry ice for 15 minutes, spun at 2000 RPM for 15 minutes, and 30 µL of supernatant was used to measure 2-HG. 2-HG quantification was performed by LC-MS/MS analysis using an AB Sciex 4000 triple quadrupole mass spectrometer equipped with an Agilent 1200 series HPLC system, as previously described (Grassian, A.R.; Lin, F.; Barrett, R.; Liu, Y.; Jiang, W.; Korpal, M.; Astley, H.; Gitterman, D.; Henley, T.; Howes, R.; Levell, J.; Korn, J.M.; Pagliarini, R. Isocitrate dehydrogenase (IDH) mutations promote a reversible ZEB1/microRNA (miR)-200-dependent epithelial-mesenchymal transition (EMT). *J Biol Chem* **2012**, *287 (50)*, 42180-94.)

Proliferation assay of MCF10A-IDH1^{R132H} cells

IDH1$^{R132H/+}$ heterozygous mutant cells (Horizon Discovery) were cultured in DMEM/F12 media with hydrocortisone (0.5 mg/ml), cholera toxin (100 ng/ml), insulin (10 ug/ml), and 2% horse serum. Cells were plated for growth assays similarly to HCT116 cells as above, with the following exceptions. Compounds were incubated for 5 days, and cell proliferation was measured by the addition of Cell Titer Glo (Promega) according to manufacturer's instructions.

Cell Culture and Sample Preparation for DNA Methylation Studies

Parental, IDH1 wild type HCT116 human cell line, 2 isogenic mutant IDH1 cell lines (IDH1-R132C/+ 2A9 clone & IDH1-R132H/+ 2H1 clone) were grown in DMEM with 10% FCS and 1% Non-Essential Amino Acids and treated with DMSO (0.05%), IDH889 (3µM in DMSO) for 3, 7, 14 or 28 days. Cells were kept in culture with regular splitting and compound was replaced twice weekly. Genomic DNA was also obtained from Xenograft tumor samples from IDH889 pharmacology studies. Compound addition was as noted in the main text. Genomic DNA was extracted according to manufacturer's instructions (Qiagen AllPrep kit). Samples were analyzed according to manufacturer's instructions using the Illumina Infinium 450K BeadChip Array platform, which interrogates the methylation status of 485,000 potential methylation sites

across the genome. Infinium methylation data were pre-processed with the R/Bioconductor (Bioconductor.org) package 'minfi' to produce normalized beta (β) values, which range between 0 for unmethylated and 1 for fully methylated (0.5 being heterozygous methylation, assuming a diploid cell).

For cell-line samples, heatmaps were calculated with the R/Bioconductor packages 'fastcluster' and 'heatmap2' using Ward's clustering method.

For tumor tissue samples, hypermethylated and hypomethylated sites in xenograft tumors were heuristically selected by examining the minimum b-value difference at a site between replicates of a control and test sample. For example to select sites that were hypomethylated in IDH1^{R132H} mutant tumors in relation to wild type tumors the minimum b-value at a site of the wild type pair was subtracted from the maximum b-value of the mutant pair to get the methylation difference in the direction of hypomethylation. If the b-value difference was less than -0.3 then the site was declared hypomethylated. A similar comparison using the same cutoff was performed with for the hypermethylation and for the treated vs. vehicle comparison. Methylation sites that were not able to be categorized by this method where declared ambiguous. Due to the heuristic nature of this categorization, it is likely that the ambiguous site sets could contain, and seem to, sites that are significantly perturbed by IDH1^{R132H} mutation. Fisher's Exact test was used to confirm the methylation status of sites in the mutant are converted by **IDH889** to that similar to the WT.For example, a test for conversion from hypermethylated to hypomethylated was performed. This is represented in the first row (Hypermethylated vs. hypomethylated) of Table SI4. 'Common Sites' is the count of those sites that were declared hypermethylated in the mutant vs. WT context and hypomethylated in the vehicle vs. treatment comparison. 'Sites perturbed by mutation' are the sites that were classified as hypermethylated in the untreated mutant and 'Sites post treatment' are the sites that were classified as hypomethylated post treatment. The 'Total sites' is the number of sites that were assayed. The p-value was calculated by converting these numbers to a truth table and applying the fisher_exact function from the the SciPy Stats package (http://docs.scipy.org/doc/scipy/reference/stats.html).

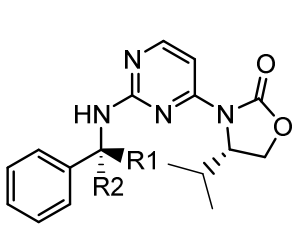
All methylation data is available in the Gene Expression Omnibus (GEO: http://www.ncbi.nlm.nih.gov) under accession number GSE85571.

Table SI-4. Statistical comparisons of the methylation state of sites perturbed by IDH1^{R132H} mutation vs. their status upon treatment with **IDH889**.

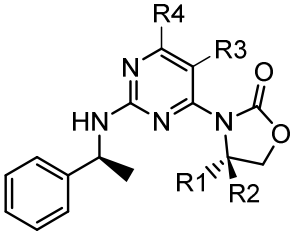
Sites perturbed by mutation vs. post	Common Sites	Sites perturbed by	Sites post treatment	Total sites	p.value	Odds Ratio

treatment		mutation				
Hypermethylated vs. hypomethylated	72	5152	172	485512	< 0.001	68.07
Hypermethylated vs. unchanged	0	5152	415	485512	1	0
Hypomethylated vs. hypermethylation	248	4226	415	485512	< 0.001	179.61
Hypomethylation vs. unchanged	1	4226	172	485512	0.778	0.67

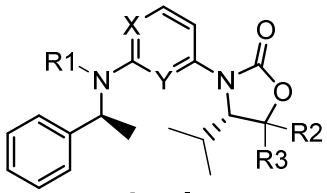
Table SI-5. IDH1^{R132H} biochemical activity of initial analogs of **IDH125** exploring tolerance for oxazolidinone, pyrimidine and α-methyl substitutions.



2a-d



3a-f



4a-d

Compound	R1	R2	R3	R4	X	Y	Biochemical LCMS IC_{50} / µM
2a	H	H	---	---	---	---	2.6
2b	Me	Me	---	---	---	---	1.7
2c	Et	H	---	---	---	---	2.3
2d	c-Pr		---	---	---	---	1.5
3a*	H	H	H	H	---	---	>50
3b	Me	Me	H	H	---	---	1.2
3c	Et	H	H	H	---	---	1.2
3d	Ph	H	H	H	---	---	0.5
3e	i-Pr	H	Me	H	---	---	0.65
3f	i-Pr	H	H	Me	---	---	0.41
4a	H	Me	Me	---	N	N	0.59
4b	H	H	H	---	N	CH	17.7
4c	H	H	H	---	CH	N	>50
4d	Me	H	H	---	N	N	>50

**-racemic at alpha-methyl benzylamine, not pure S-enantiomer as shown*

Small molecule crystallography for IDH125 and 1e

Crystallization, data collection and structure determination

Crystals of compounds **IDH125** and **1e** were obtained by dissolving in a minimum amount of solvents from which the solvent was allowed to slowly evaporate at room temperature: for compound **IDH125** acetone was used, for compound **1e** a solvent mixture of acetone, heptane and diisopropyl ether.

Diffraction data were collected at 100 K on a Bruker AXS MicroStar diffractometer using a SMART 6000 CCD detector on a three-circle platform goniometer with Cu(K_α) radiation (λ = 1.54178 Å) from a microfocus sealed tube generator equipped with Incoatec multilayer optics (QUAZAR focussing mirror system). 16 ω-scans at different ϕ-positions were performed to ensure appropriate data redundancy (5.6 in the monoclinic space group $P2_1$ for **IDH125** and 11.5 in the orthorhombic space group $P2_12_12_1$ for **1e**, Friedel pairs not merged, respectively).The use of Cu radiation enables the absolute structure determination of **IDH125** and **1e** based on the anomalous scatterers present (O and N). For the C3*S*, C15*S* the Flack *x* parameter refined to 0.00(16) for **IDH125** and for C5*S*, C17*R* (C35*S*, C47*R* in molecule 2) the Flack *x* parameter refined to 0.04(13) for **1e** (Flack HD (1983)).

Crystal data, data collection and structure refinement details are summarized in supplemental data tables 1-7, respectively. The crystal structures were solved by dual space-recycling methods and refined based on full-matrix least-squares on F^2 using the SHELXTL program suite (Sheldrick GM (2001)). The structure of **IDH125** consists of one independent molecule, the structure of **1e** consists of two independent molecules. In molecule 2, all numbers used for molecule 1 have been increased by 30. Data will be deposited at the Cambridge Crystallographic Data Centre CCDC.

Reference Citation (SHEXLTL and PLATON)

1. Sheldrick, G.M. **SHELXTL** Version 6.14, Bruker Analytical Instruments Inc. Madison, WI, USA, (2001).
2. Flack, H.D. On Enantiomorph-Polarity Estimation. *Acta Crystallogr.* **A39**, 876-881 (1983).
3. Spek, A.L. (2003) Single-crystal structure validation with the program PLATON. J. Appl. Cryst.; 36: 7-13.

Figure SI-2. ORTEP representation for the small-molecule structure of **IDH125**

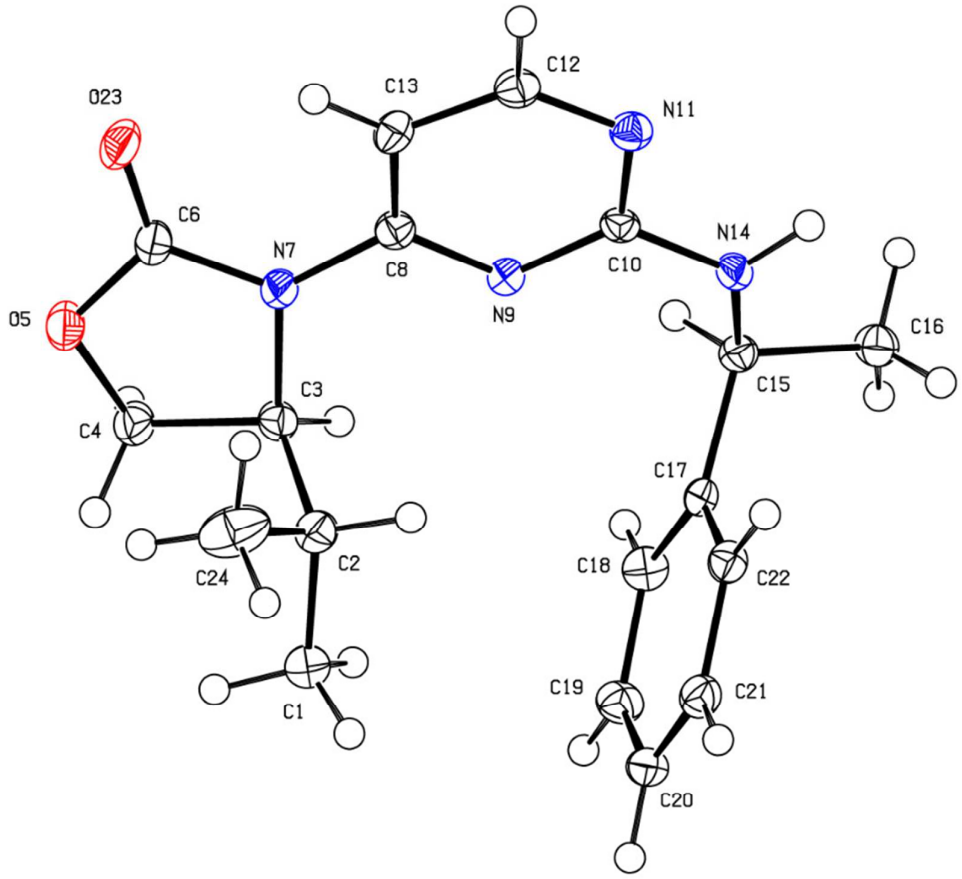


Table SI-6. Crystal data and structure refinement for **IDH125**.

Empirical formula	C18 H22 N4 O2	
Formula weight	326.40	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P21	
Unit cell dimensions	a = 5.942(2) Å	α= 90°
	b = 17.750(5) Å	β= 93.567(14)°
	c = 7.954(2) Å	γ = 90°
Volume	837.3(4) $Å^3$	
Z	2	
Density (calculated)	1.295 g/cm^3	
Absorption coefficient	0.701 mm^{-1}	
F(000)	348	
Crystal size	0.38 x 0.10 x 0.02 mm^3	
Theta range for data collection	4.98 to 68.25°	

Index ranges	-6<=h<=7, -21<=k<=21, -9<=l<=9
Reflections collected	16765
Independent reflections	3013 [R(int) = 0.0368]
Completeness to theta = 68.25°	98.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9861 and 0.7767
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3013 / 1 / 220
Goodness-of-fit on F^2	1.094
Final R indices [I>2sigma(I)]	R1 = 0.0283, wR2 = 0.0690
R indices (all data)	R1 = 0.0297, wR2 = 0.0697
Absolute structure parameter	0.00(16)
Largest diff. peak and hole	0.148 and -0.167 e.Å^{-3}

Table SI-7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3)
for IDH125. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8442(3)	8135(1)	-1394(2)	26(1)
C(2)	6862(2)	8178(1)	53(2)	21(1)
C(3)	8176(2)	8429(1)	1684(2)	18(1)
C(4)	9151(2)	9229(1)	1654(2)	22(1)
O(5)	7616(2)	9695(1)	2543(1)	22(1)
C(6)	6327(2)	9257(1)	3470(2)	19(1)
N(7)	6697(2)	8511(1)	3104(2)	18(1)
C(8)	5561(2)	7900(1)	3792(2)	16(1)
N(9)	6467(2)	7231(1)	3500(1)	16(1)
C(10)	5401(2)	6626(1)	4103(2)	15(1)
N(11)	3502(2)	6641(1)	4967(1)	18(1)
C(12)	2682(2)	7326(1)	5228(2)	19(1)
C(13)	3620(2)	7990(1)	4680(2)	19(1)
N(14)	6267(2)	5937(1)	3814(1)	16(1)
C(15)	8515(2)	5834(1)	3195(2)	17(1)
C(16)	9330(2)	5038(1)	3622(2)	21(1)
C(17)	8616(2)	5975(1)	1313(2)	16(1)

C(18)	10642(2)	6221(1)	709(2)	20(1)
C(19)	10885(2)	6297(1)	-1004(2)	22(1)
C(20)	9074(2)	6140(1)	-2146(2)	21(1)
C(21)	7037(2)	5908(1)	-1560(2)	20(1)
C(22)	6811(2)	5822(1)	167(2)	18(1)
O(23)	5069(2)	9517(1)	4460(1)	26(1)
C(24)	4841(3)	8679(1)	-427(2)	37(1)

Table SI-8. Bond lengths [Å] and angles [°] for IDH125.

C(1)-C(2)	1.532(2)
C(1)-H(1A)	0.9800
C(1)-H(1B)	0.9800
C(1)-H(1C)	0.9800
C(2)-C(24)	1.524(2)
C(2)-C(3)	1.538(2)
C(2)-H(2)	1.0000
C(3)-N(7)	1.4808(18)
C(3)-C(4)	1.5351(19)
C(3)-H(3)	1.0000
C(4)-O(5)	1.4479(17)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
O(5)-C(6)	1.3442(17)
C(6)-O(23)	1.2103(17)
C(6)-N(7)	1.3762(18)
N(7)-C(8)	1.4057(18)
C(8)-N(9)	1.3312(18)
C(8)-C(13)	1.399(2)
N(9)-C(10)	1.3495(17)
C(10)-N(14)	1.3523(18)
C(10)-N(11)	1.3572(18)
N(11)-C(12)	1.3297(18)
C(12)-C(13)	1.387(2)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
N(14)-C(15)	1.4636(18)
N(14)-H(14)	0.9272

C(15)-C(17)	1.5220(18)
C(15)-C(16)	1.5258(19)
C(15)-H(15)	1.0000
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-C(22)	1.3907(18)
C(17)-C(18)	1.394(2)
C(18)-C(19)	1.385(2)
C(18)-H(18)	0.9500
C(19)-C(20)	1.392(2)
C(19)-H(19)	0.9500
C(20)-C(21)	1.386(2)
C(20)-H(20)	0.9500
C(21)-C(22)	1.3970(19)
C(21)-H(21)	0.9500
C(22)-H(22)	0.9500
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800

C(2)-C(1)-H(1A)	109.5
C(2)-C(1)-H(1B)	109.5
H(1A)-C(1)-H(1B)	109.5
C(2)-C(1)-H(1C)	109.5
H(1A)-C(1)-H(1C)	109.5
H(1B)-C(1)-H(1C)	109.5
C(24)-C(2)-C(1)	110.55(13)
C(24)-C(2)-C(3)	113.12(12)
C(1)-C(2)-C(3)	110.22(12)
C(24)-C(2)-H(2)	107.6
C(1)-C(2)-H(2)	107.6
C(3)-C(2)-H(2)	107.6
N(7)-C(3)-C(4)	99.39(10)
N(7)-C(3)-C(2)	112.22(11)
C(4)-C(3)-C(2)	115.29(11)
N(7)-C(3)-H(3)	109.8
C(4)-C(3)-H(3)	109.8
C(2)-C(3)-H(3)	109.8

O(5)-C(4)-C(3)	105.76(11)
O(5)-C(4)-H(4A)	110.6
C(3)-C(4)-H(4A)	110.6
O(5)-C(4)-H(4B)	110.6
C(3)-C(4)-H(4B)	110.6
H(4A)-C(4)-H(4B)	108.7
C(6)-O(5)-C(4)	109.55(11)
O(23)-C(6)-O(5)	122.15(13)
O(23)-C(6)-N(7)	128.14(13)
O(5)-C(6)-N(7)	109.71(11)
C(6)-N(7)-C(8)	124.94(11)
C(6)-N(7)-C(3)	111.47(11)
C(8)-N(7)-C(3)	122.89(11)
N(9)-C(8)-C(13)	123.06(12)
N(9)-C(8)-N(7)	114.29(12)
C(13)-C(8)-N(7)	122.64(12)
C(8)-N(9)-C(10)	116.38(11)
N(9)-C(10)-N(14)	117.82(12)
N(9)-C(10)-N(11)	125.96(12)
N(14)-C(10)-N(11)	116.22(11)
C(12)-N(11)-C(10)	114.95(11)
N(11)-C(12)-C(13)	124.74(13)
N(11)-C(12)-H(12)	117.6
C(13)-C(12)-H(12)	117.6
C(12)-C(13)-C(8)	114.91(12)
C(12)-C(13)-H(13)	122.5
C(8)-C(13)-H(13)	122.5
C(10)-N(14)-C(15)	122.35(11)
C(10)-N(14)-H(14)	114.1
C(15)-N(14)-H(14)	120.3
N(14)-C(15)-C(17)	113.77(11)
N(14)-C(15)-C(16)	108.89(11)
C(17)-C(15)-C(16)	109.86(11)
N(14)-C(15)-H(15)	108.1
C(17)-C(15)-H(15)	108.1
C(16)-C(15)-H(15)	108.1
C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5

C(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(22)-C(17)-C(18)	118.84(12)
C(22)-C(17)-C(15)	122.46(12)
C(18)-C(17)-C(15)	118.58(12)
C(19)-C(18)-C(17)	120.97(13)
C(19)-C(18)-H(18)	119.5
C(17)-C(18)-H(18)	119.5
C(18)-C(19)-C(20)	119.90(14)
C(18)-C(19)-H(19)	120.1
C(20)-C(19)-H(19)	120.1
C(21)-C(20)-C(19)	119.73(13)
C(21)-C(20)-H(20)	120.1
C(19)-C(20)-H(20)	120.1
C(20)-C(21)-C(22)	120.12(13)
C(20)-C(21)-H(21)	119.9
C(22)-C(21)-H(21)	119.9
C(17)-C(22)-C(21)	120.42(13)
C(17)-C(22)-H(22)	119.8
C(21)-C(22)-H(22)	119.8
C(2)-C(24)-H(24A)	109.5
C(2)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(2)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table SI-9. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for IDH125. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	34(1)	22(1)	22(1)	-1(1)	8(1)	0(1)
C(2)	24(1)	20(1)	21(1)	-2(1)	3(1)	-2(1)
C(3)	18(1)	17(1)	19(1)	1(1)	4(1)	0(1)
C(4)	23(1)	18(1)	25(1)	-1(1)	7(1)	-2(1)

O(5)	24(1)	15(1)	28(1)	0(1)	7(1)	-1(1)
C(6)	21(1)	14(1)	21(1)	-1(1)	0(1)	0(1)
N(7)	21(1)	15(1)	18(1)	-1(1)	6(1)	-1(1)
C(8)	17(1)	18(1)	15(1)	-1(1)	-1(1)	-1(1)
N(9)	18(1)	15(1)	15(1)	-1(1)	2(1)	0(1)
C(10)	16(1)	17(1)	11(1)	0(1)	-1(1)	-1(1)
N(11)	17(1)	20(1)	17(1)	-1(1)	2(1)	-1(1)
C(12)	17(1)	23(1)	19(1)	-1(1)	4(1)	0(1)
C(13)	19(1)	17(1)	21(1)	-3(1)	2(1)	2(1)
N(14)	17(1)	15(1)	16(1)	1(1)	4(1)	0(1)
C(15)	17(1)	17(1)	16(1)	-1(1)	1(1)	-1(1)
C(16)	23(1)	21(1)	20(1)	2(1)	2(1)	6(1)
C(17)	20(1)	12(1)	16(1)	-1(1)	3(1)	3(1)
C(18)	17(1)	23(1)	20(1)	-1(1)	-1(1)	0(1)
C(19)	19(1)	25(1)	22(1)	2(1)	6(1)	0(1)
C(20)	27(1)	19(1)	16(1)	1(1)	3(1)	3(1)
C(21)	23(1)	18(1)	19(1)	-1(1)	-2(1)	1(1)
C(22)	17(1)	17(1)	20(1)	-1(1)	2(1)	0(1)
O(23)	31(1)	16(1)	33(1)	-6(1)	12(1)	0(1)
C(24)	30(1)	52(1)	29(1)	-10(1)	-5(1)	11(1)

Table SI-10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for IDH125.

	x	y	z	U(eq)
H(1A)	7676	7877	-2357	39
H(1B)	9806	7855	-1024	39
H(1C)	8855	8646	-1728	39
H(2)	6280	7658	243	26
H(3)	9406	8060	1988	21
H(4A)	10681	9242	2223	26
H(4B)	9241	9406	480	26
H(12)	1357	7361	5833	23
H(13)	2992	8471	4893	22

H(14)	5581	5548	4368	19
H(15)	9563	6197	3805	20
H(16A)	9312	4957	4840	31
H(16B)	10869	4973	3269	31
H(16C)	8331	4672	3032	31
H(18)	11874	6339	1482	24
H(19)	12285	6455	-1399	26
H(20)	9234	6191	-3321	25
H(21)	5791	5807	-2335	24
H(22)	5416	5658	561	21
H(24A)	5360	9194	-620	56
H(24B)	3811	8679	488	56
H(24C)	4054	8486	-1458	56

Table SI-11. Torsion angles [°] for IDH125.

C(24)-C(2)-C(3)-N(7)	53.15(17)
C(1)-C(2)-C(3)-N(7)	177.48(11)
C(24)-C(2)-C(3)-C(4)	-59.67(17)
C(1)-C(2)-C(3)-C(4)	64.66(16)
N(7)-C(3)-C(4)-O(5)	-19.57(13)
C(2)-C(3)-C(4)-O(5)	100.56(13)
C(3)-C(4)-O(5)-C(6)	17.70(14)
C(4)-O(5)-C(6)-O(23)	172.33(13)
C(4)-O(5)-C(6)-N(7)	-7.42(15)
O(23)-C(6)-N(7)-C(8)	3.1(2)
O(5)-C(6)-N(7)-C(8)	-177.20(12)
O(23)-C(6)-N(7)-C(3)	173.70(14)
O(5)-C(6)-N(7)-C(3)	-6.57(15)
C(4)-C(3)-N(7)-C(6)	16.26(14)
C(2)-C(3)-N(7)-C(6)	-106.09(13)
C(4)-C(3)-N(7)-C(8)	-172.88(12)
C(2)-C(3)-N(7)-C(8)	64.76(16)
C(6)-N(7)-C(8)-N(9)	-168.45(11)
C(3)-N(7)-C(8)-N(9)	21.95(18)
C(6)-N(7)-C(8)-C(13)	12.6(2)
C(3)-N(7)-C(8)-C(13)	-156.98(13)
C(13)-C(8)-N(9)-C(10)	0.40(18)

N(7)-C(8)-N(9)-C(10)	-178.52(11)
C(8)-N(9)-C(10)-N(14)	179.41(12)
C(8)-N(9)-C(10)-N(11)	0.24(18)
N(9)-C(10)-N(11)-C(12)	-0.57(18)
N(14)-C(10)-N(11)-C(12)	-179.75(12)
C(10)-N(11)-C(12)-C(13)	0.29(19)
N(11)-C(12)-C(13)-C(8)	0.3(2)
N(9)-C(8)-C(13)-C(12)	-0.63(19)
N(7)-C(8)-C(13)-C(12)	178.20(12)
N(9)-C(10)-N(14)-C(15)	12.76(18)
N(11)-C(10)-N(14)-C(15)	-167.99(11)
C(10)-N(14)-C(15)-C(17)	-78.20(15)
C(10)-N(14)-C(15)-C(16)	158.90(11)
N(14)-C(15)-C(17)-C(22)	-32.06(18)
C(16)-C(15)-C(17)-C(22)	90.30(15)
N(14)-C(15)-C(17)-C(18)	152.07(12)
C(16)-C(15)-C(17)-C(18)	-85.57(16)
C(22)-C(17)-C(18)-C(19)	-1.5(2)
C(15)-C(17)-C(18)-C(19)	174.50(13)
C(17)-C(18)-C(19)-C(20)	1.3(2)
C(18)-C(19)-C(20)-C(21)	0.0(2)
C(19)-C(20)-C(21)-C(22)	-0.9(2)
C(18)-C(17)-C(22)-C(21)	0.6(2)
C(15)-C(17)-C(22)-C(21)	-175.28(12)
C(20)-C(21)-C(22)-C(17)	0.6(2)

Symmetry transformations used to generate equivalent atoms:

Table SI-12. Hydrogen bonds for IDH125 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(14)-H(14)...O(23)#1	0.93	2.10	3.0009(16)	163.4

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1/2,-z+1

Figure SI-3. ORTEP representation for the small-molecule structure of **1e**

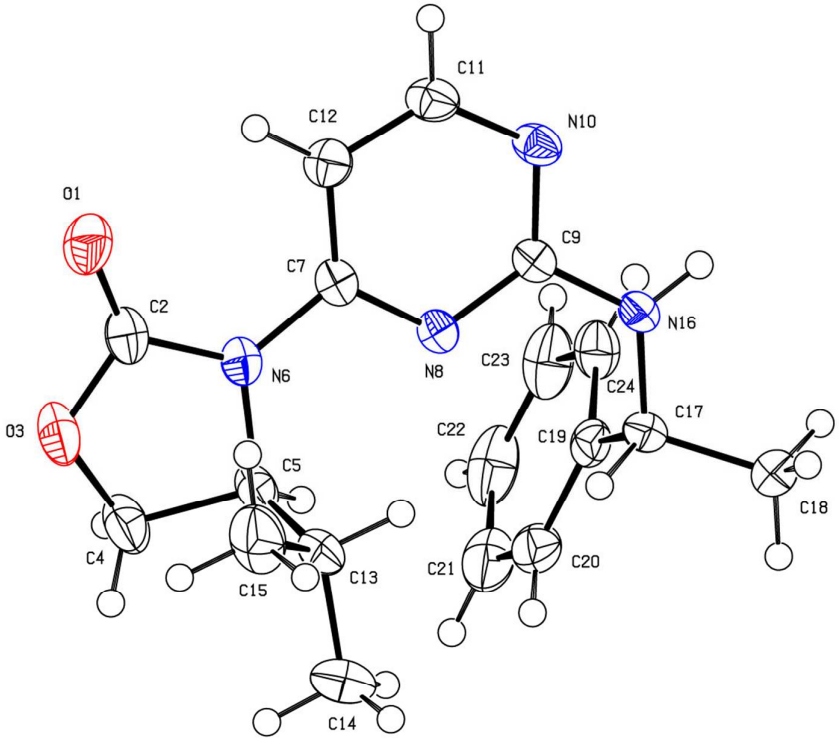


Table SI-13. Crystal data and structure refinement for 1e.

Empirical formula	C18 H22 N4 O2	
Formula weight	326.40	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 9.024(2) Å	α= 90°
	b = 12.896(3) Å	β= 90°
	c = 30.679(7) Å	γ = 90°
Volume	3570.2(14) Å^3	
Z	8	
Density (calculated)	1.214 g/cm^3	
Absorption coefficient	0.657 mm^{-1}	
F(000)	1392	
Crystal size	0.43 x 0.14 x 0.09 mm^3	
Theta range for data collection	2.88 to 68.30°	
Index ranges	-9<=h<=10, -15<=k<=15, -36<=l<=36	
Reflections collected	73775	
Independent reflections	6529 [R(int) = 0.0431]	

Completeness to theta = 68.30°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9432 and 0.7653
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6529 / 0 / 439
Goodness-of-fit on F^2	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0277, wR2 = 0.0678
R indices (all data)	R1 = 0.0291, wR2 = 0.0689
Absolute structure parameter	0.04(13)
Largest diff. peak and hole	0.167 and -0.198 e.$Å^{-3}$

Table SI-14. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for 1a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4235(1)	4934(1)	6290(1)	40(1)
C(2)	3170(2)	5485(1)	6257(1)	32(1)
O(3)	2908(1)	6288(1)	6532(1)	40(1)
C(4)	1656(2)	6884(1)	6376(1)	41(1)
C(5)	820(2)	6149(1)	6069(1)	31(1)
N(6)	2029(1)	5439(1)	5956(1)	26(1)
C(7)	1924(1)	4752(1)	5606(1)	23(1)
N(8)	696(1)	4873(1)	5369(1)	22(1)
C(9)	499(1)	4211(1)	5036(1)	22(1)
N(10)	1449(1)	3453(1)	4914(1)	28(1)
C(11)	2671(2)	3378(1)	5160(1)	31(1)
C(12)	2990(2)	4006(1)	5511(1)	29(1)
C(13)	-495(2)	5578(1)	6274(1)	37(1)
C(14)	-1760(2)	6335(2)	6353(1)	65(1)
C(15)	-70(2)	4974(2)	6684(1)	53(1)
N(16)	-786(1)	4291(1)	4808(1)	25(1)
C(17)	-1818(1)	5142(1)	4879(1)	26(1)
C(18)	-3283(2)	4885(1)	4655(1)	37(1)
C(19)	-1207(1)	6174(1)	4718(1)	27(1)
C(20)	-1608(2)	7092(1)	4924(1)	37(1)

C(21)	-1078(2)	8039(1)	4777(1)	49(1)
C(22)	-132(2)	8080(1)	4422(1)	51(1)
C(23)	257(2)	7172(1)	4211(1)	47(1)
C(24)	-277(2)	6226(1)	4356(1)	35(1)
O(31)	1493(1)	2604(1)	7577(1)	35(1)
C(32)	2784(2)	2814(1)	7631(1)	26(1)
O(33)	3333(1)	3071(1)	8024(1)	28(1)
C(34)	4928(1)	3153(1)	8002(1)	27(1)
C(35)	5290(1)	3264(1)	7516(1)	22(1)
N(36)	3916(1)	2844(1)	7327(1)	22(1)
C(37)	3808(1)	2524(1)	6892(1)	21(1)
N(38)	5083(1)	2544(1)	6674(1)	21(1)
C(39)	5028(1)	2246(1)	6253(1)	20(1)
N(40)	3827(1)	1864(1)	6044(1)	24(1)
C(41)	2582(1)	1861(1)	6280(1)	26(1)
C(42)	2478(1)	2200(1)	6704(1)	26(1)
C(43)	5615(2)	4377(1)	7369(1)	26(1)
C(44)	7079(2)	4736(1)	7568(1)	37(1)
C(45)	4361(2)	5130(1)	7477(1)	33(1)
N(46)	6272(1)	2355(1)	6012(1)	24(1)
C(47)	7725(1)	2503(1)	6211(1)	25(1)
C(48)	8801(2)	2885(1)	5863(1)	29(1)
C(49)	8283(1)	1513(1)	6421(1)	32(1)
C(50)	8334(2)	595(1)	6181(1)	45(1)
C(51)	8880(2)	-316(1)	6363(1)	68(1)
C(52)	9376(2)	-324(2)	6783(1)	73(1)
C(53)	9332(2)	573(2)	7028(1)	68(1)
C(54)	8782(2)	1495(2)	6847(1)	46(1)

Table SI-15. Bond lengths [Å] and angles [°] for 1a.

O(1)-C(2)	1.2000(18)
C(2)-O(3)	1.3558(17)
C(2)-N(6)	1.3835(17)
O(3)-C(4)	1.4476(19)
C(4)-C(5)	1.5326(19)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900

C(5)-N(6)	1.4656(17)
C(5)-C(13)	1.531(2)
C(5)-H(5)	1.0000
N(6)-C(7)	1.3953(16)
C(7)-N(8)	1.3343(16)
C(7)-C(12)	1.3917(18)
N(8)-C(9)	1.3444(15)
C(9)-N(10)	1.3522(16)
C(9)-N(16)	1.3569(17)
N(10)-C(11)	1.3392(18)
C(11)-C(12)	1.378(2)
C(11)-H(11)	0.9500
C(12)-H(12)	0.9500
C(13)-C(14)	1.522(2)
C(13)-C(15)	1.531(2)
C(13)-H(13)	1.0000
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-H(15A)	0.9800
C(15)-H(15B)	0.9800
C(15)-H(15C)	0.9800
N(16)-C(17)	1.4553(16)
N(16)-H(16)	0.8671
C(17)-C(19)	1.5224(18)
C(17)-C(18)	1.5257(19)
C(17)-H(17)	1.0000
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-C(20)	1.3890(19)
C(19)-C(24)	1.394(2)
C(20)-C(21)	1.388(2)
C(20)-H(20)	0.9500
C(21)-C(22)	1.384(3)
C(21)-H(21)	0.9500
C(22)-C(23)	1.383(3)
C(22)-H(22)	0.9500
C(23)-C(24)	1.385(2)

C(23)-H(23)	0.9500
C(24)-H(24)	0.9500
O(31)-C(32)	1.2071(17)
C(32)-O(33)	1.3447(16)
C(32)-N(36)	1.3846(16)
O(33)-C(34)	1.4447(17)
C(34)-C(35)	1.5344(17)
C(34)-H(34A)	0.9900
C(34)-H(34B)	0.9900
C(35)-N(36)	1.4725(16)
C(35)-C(43)	1.5319(18)
C(35)-H(35)	1.0000
N(36)-C(37)	1.4012(15)
C(37)-N(38)	1.3305(15)
C(37)-C(42)	1.3953(17)
N(38)-C(39)	1.3473(15)
C(39)-N(46)	1.3531(15)
C(39)-N(40)	1.3531(16)
N(40)-C(41)	1.3364(16)
C(41)-C(42)	1.3758(18)
C(41)-H(41)	0.9500
C(42)-H(42)	0.9500
C(43)-C(45)	1.5275(19)
C(43)-C(44)	1.5276(19)
C(43)-H(43)	1.0000
C(44)-H(44A)	0.9800
C(44)-H(44B)	0.9800
C(44)-H(44C)	0.9800
C(45)-H(45A)	0.9800
C(45)-H(45B)	0.9800
C(45)-H(45C)	0.9800
N(46)-C(47)	1.4600(16)
N(46)-H(46)	0.8875
C(47)-C(49)	1.516(2)
C(47)-C(48)	1.5241(17)
C(47)-H(47)	1.0000
C(48)-H(48A)	0.9800
C(48)-H(48B)	0.9800
C(48)-H(48C)	0.9800

C(49)-C(54)	1.384(2)
C(49)-C(50)	1.395(2)
C(50)-C(51)	1.391(2)
C(50)-H(50)	0.9500
C(51)-C(52)	1.365(3)
C(51)-H(51)	0.9500
C(52)-C(53)	1.379(3)
C(52)-H(52)	0.9500
C(53)-C(54)	1.403(3)
C(53)-H(53)	0.9500
C(54)-H(54)	0.9500

O(1)-C(2)-O(3)	122.59(12)
O(1)-C(2)-N(6)	128.92(13)
O(3)-C(2)-N(6)	108.49(12)
C(2)-O(3)-C(4)	109.64(10)
O(3)-C(4)-C(5)	104.97(11)
O(3)-C(4)-H(4A)	110.8
C(5)-C(4)-H(4A)	110.8
O(3)-C(4)-H(4B)	110.8
C(5)-C(4)-H(4B)	110.8
H(4A)-C(4)-H(4B)	108.8
N(6)-C(5)-C(13)	111.92(11)
N(6)-C(5)-C(4)	99.52(11)
C(13)-C(5)-C(4)	115.32(12)
N(6)-C(5)-H(5)	109.9
C(13)-C(5)-H(5)	109.9
C(4)-C(5)-H(5)	109.9
C(2)-N(6)-C(7)	126.21(11)
C(2)-N(6)-C(5)	111.67(10)
C(7)-N(6)-C(5)	121.89(10)
N(8)-C(7)-C(12)	122.70(11)
N(8)-C(7)-N(6)	113.69(11)
C(12)-C(7)-N(6)	123.61(11)
C(7)-N(8)-C(9)	116.76(10)
N(8)-C(9)-N(10)	125.82(11)
N(8)-C(9)-N(16)	117.13(11)
N(10)-C(9)-N(16)	117.02(11)
C(11)-N(10)-C(9)	114.76(11)

N(10)-C(11)-C(12)	124.71(12)
N(10)-C(11)-H(11)	117.6
C(12)-C(11)-H(11)	117.6
C(11)-C(12)-C(7)	115.21(12)
C(11)-C(12)-H(12)	122.4
C(7)-C(12)-H(12)	122.4
C(14)-C(13)-C(5)	109.81(14)
C(14)-C(13)-C(15)	112.54(14)
C(5)-C(13)-C(15)	112.84(13)
C(14)-C(13)-H(13)	107.1
C(5)-C(13)-H(13)	107.1
C(15)-C(13)-H(13)	107.1
C(13)-C(14)-H(14A)	109.5
C(13)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(13)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(13)-C(15)-H(15A)	109.5
C(13)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(13)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(9)-N(16)-C(17)	121.86(10)
C(9)-N(16)-H(16)	117.5
C(17)-N(16)-H(16)	118.5
N(16)-C(17)-C(19)	112.34(10)
N(16)-C(17)-C(18)	108.95(10)
C(19)-C(17)-C(18)	111.00(11)
N(16)-C(17)-H(17)	108.1
C(19)-C(17)-H(17)	108.1
C(18)-C(17)-H(17)	108.1
C(17)-C(18)-H(18A)	109.5
C(17)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(17)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5

C(20)-C(19)-C(24)	118.59(13)
C(20)-C(19)-C(17)	120.25(12)
C(24)-C(19)-C(17)	121.13(12)
C(21)-C(20)-C(19)	120.80(15)
C(21)-C(20)-H(20)	119.6
C(19)-C(20)-H(20)	119.6
C(22)-C(21)-C(20)	120.15(15)
C(22)-C(21)-H(21)	119.9
C(20)-C(21)-H(21)	119.9
C(23)-C(22)-C(21)	119.47(15)
C(23)-C(22)-H(22)	120.3
C(21)-C(22)-H(22)	120.3
C(22)-C(23)-C(24)	120.51(16)
C(22)-C(23)-H(23)	119.7
C(24)-C(23)-H(23)	119.7
C(23)-C(24)-C(19)	120.47(15)
C(23)-C(24)-H(24)	119.8
C(19)-C(24)-H(24)	119.8
O(31)-C(32)-O(33)	122.31(11)
O(31)-C(32)-N(36)	128.68(12)
O(33)-C(32)-N(36)	109.01(11)
C(32)-O(33)-C(34)	110.08(10)
O(33)-C(34)-C(35)	105.35(10)
O(33)-C(34)-H(34A)	110.7
C(35)-C(34)-H(34A)	110.7
O(33)-C(34)-H(34B)	110.7
C(35)-C(34)-H(34B)	110.7
H(34A)-C(34)-H(34B)	108.8
N(36)-C(35)-C(43)	112.99(10)
N(36)-C(35)-C(34)	99.71(10)
C(43)-C(35)-C(34)	114.49(10)
N(36)-C(35)-H(35)	109.8
C(43)-C(35)-H(35)	109.8
C(34)-C(35)-H(35)	109.8
C(32)-N(36)-C(37)	125.70(10)
C(32)-N(36)-C(35)	111.49(10)
C(37)-N(36)-C(35)	122.81(9)
N(38)-C(37)-C(42)	122.83(10)
N(38)-C(37)-N(36)	114.39(10)

C(42)-C(37)-N(36)	122.77(10)
C(37)-N(38)-C(39)	116.32(10)
N(38)-C(39)-N(46)	117.68(10)
N(38)-C(39)-N(40)	126.06(11)
N(46)-C(39)-N(40)	116.24(10)
C(41)-N(40)-C(39)	114.62(10)
N(40)-C(41)-C(42)	124.68(11)
N(40)-C(41)-H(41)	117.7
C(42)-C(41)-H(41)	117.7
C(41)-C(42)-C(37)	115.27(11)
C(41)-C(42)-H(42)	122.4
C(37)-C(42)-H(42)	122.4
C(45)-C(43)-C(44)	111.16(11)
C(45)-C(43)-C(35)	112.93(11)
C(44)-C(43)-C(35)	109.40(11)
C(45)-C(43)-H(43)	107.7
C(44)-C(43)-H(43)	107.7
C(35)-C(43)-H(43)	107.7
C(43)-C(44)-H(44A)	109.5
C(43)-C(44)-H(44B)	109.5
H(44A)-C(44)-H(44B)	109.5
C(43)-C(44)-H(44C)	109.5
H(44A)-C(44)-H(44C)	109.5
H(44B)-C(44)-H(44C)	109.5
C(43)-C(45)-H(45A)	109.5
C(43)-C(45)-H(45B)	109.5
H(45A)-C(45)-H(45B)	109.5
C(43)-C(45)-H(45C)	109.5
H(45A)-C(45)-H(45C)	109.5
H(45B)-C(45)-H(45C)	109.5
C(39)-N(46)-C(47)	121.96(9)
C(39)-N(46)-H(46)	116.4
C(47)-N(46)-H(46)	118.7
N(46)-C(47)-C(49)	111.43(10)
N(46)-C(47)-C(48)	108.71(10)
C(49)-C(47)-C(48)	110.99(11)
N(46)-C(47)-H(47)	108.5
C(49)-C(47)-H(47)	108.5
C(48)-C(47)-H(47)	108.5

C(47)-C(48)-H(48A)	109.5
C(47)-C(48)-H(48B)	109.5
H(48A)-C(48)-H(48B)	109.5
C(47)-C(48)-H(48C)	109.5
H(48A)-C(48)-H(48C)	109.5
H(48B)-C(48)-H(48C)	109.5
C(54)-C(49)-C(50)	118.32(15)
C(54)-C(49)-C(47)	121.56(15)
C(50)-C(49)-C(47)	120.11(12)
C(51)-C(50)-C(49)	121.07(17)
C(51)-C(50)-H(50)	119.5
C(49)-C(50)-H(50)	119.5
C(52)-C(51)-C(50)	120.2(2)
C(52)-C(51)-H(51)	119.9
C(50)-C(51)-H(51)	119.9
C(51)-C(52)-C(53)	119.84(18)
C(51)-C(52)-H(52)	120.1
C(53)-C(52)-H(52)	120.1
C(52)-C(53)-C(54)	120.44(17)
C(52)-C(53)-H(53)	119.8
C(54)-C(53)-H(53)	119.8
C(49)-C(54)-C(53)	120.16(19)
C(49)-C(54)-H(54)	119.9
C(53)-C(54)-H(54)	119.9

Symmetry transformations used to generate equivalent atoms:

Table SI-16. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 1a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	40(1)	45(1)	35(1)	5(1)	-13(1)	2(1)
C(2)	38(1)	30(1)	27(1)	3(1)	-6(1)	-7(1)
O(3)	50(1)	35(1)	35(1)	-6(1)	-16(1)	-5(1)
C(4)	54(1)	30(1)	41(1)	-10(1)	-14(1)	1(1)
C(5)	40(1)	25(1)	29(1)	-7(1)	-7(1)	3(1)

N(6)	29(1)	25(1)	24(1)	0(1)	-4(1)	-2(1)
C(7)	29(1)	21(1)	19(1)	4(1)	1(1)	-3(1)
N(8)	26(1)	22(1)	19(1)	1(1)	0(1)	-2(1)
C(9)	27(1)	21(1)	19(1)	3(1)	2(1)	-1(1)
N(10)	35(1)	27(1)	21(1)	-1(1)	-1(1)	8(1)
C(11)	37(1)	31(1)	25(1)	2(1)	-1(1)	12(1)
C(12)	32(1)	30(1)	26(1)	5(1)	-3(1)	4(1)
C(13)	35(1)	47(1)	29(1)	-16(1)	3(1)	0(1)
C(14)	50(1)	82(1)	64(1)	-37(1)	8(1)	16(1)
C(15)	55(1)	73(1)	30(1)	-4(1)	6(1)	-18(1)
N(16)	27(1)	26(1)	21(1)	-5(1)	-1(1)	2(1)
C(17)	26(1)	29(1)	24(1)	-4(1)	2(1)	3(1)
C(18)	26(1)	41(1)	44(1)	-11(1)	-2(1)	1(1)
C(19)	25(1)	30(1)	27(1)	1(1)	-8(1)	2(1)
C(20)	32(1)	33(1)	47(1)	-5(1)	-7(1)	6(1)
C(21)	46(1)	29(1)	72(1)	-1(1)	-22(1)	5(1)
C(22)	52(1)	39(1)	62(1)	22(1)	-27(1)	-11(1)
C(23)	49(1)	55(1)	36(1)	16(1)	-12(1)	-17(1)
C(24)	38(1)	41(1)	26(1)	3(1)	-7(1)	-5(1)
O(31)	29(1)	41(1)	34(1)	-9(1)	10(1)	-9(1)
C(32)	31(1)	21(1)	25(1)	-2(1)	5(1)	-2(1)
O(33)	33(1)	31(1)	21(1)	0(1)	5(1)	-3(1)
C(34)	30(1)	30(1)	22(1)	1(1)	0(1)	2(1)
C(35)	22(1)	25(1)	20(1)	-2(1)	-2(1)	1(1)
N(36)	22(1)	23(1)	20(1)	-1(1)	2(1)	-2(1)
C(37)	24(1)	17(1)	21(1)	0(1)	1(1)	1(1)
N(38)	22(1)	21(1)	20(1)	0(1)	1(1)	0(1)
C(39)	22(1)	18(1)	21(1)	0(1)	-1(1)	1(1)
N(40)	22(1)	26(1)	22(1)	-2(1)	-1(1)	0(1)
C(41)	20(1)	28(1)	28(1)	-3(1)	-2(1)	-1(1)
C(42)	21(1)	29(1)	27(1)	-2(1)	3(1)	-1(1)
C(43)	29(1)	28(1)	20(1)	-1(1)	0(1)	-6(1)
C(44)	34(1)	43(1)	32(1)	-8(1)	2(1)	-13(1)
C(45)	40(1)	23(1)	37(1)	1(1)	0(1)	-1(1)
N(46)	22(1)	33(1)	18(1)	-4(1)	0(1)	-4(1)
C(47)	23(1)	31(1)	22(1)	-4(1)	0(1)	-6(1)
C(48)	26(1)	30(1)	31(1)	3(1)	2(1)	-5(1)
C(49)	19(1)	47(1)	30(1)	13(1)	-3(1)	-12(1)
C(50)	41(1)	33(1)	60(1)	12(1)	-20(1)	-9(1)

C(51)	51(1)	40(1)	114(2)	30(1)	-31(1)	-12(1)
C(52)	38(1)	74(1)	107(2)	60(1)	-17(1)	-16(1)
C(53)	24(1)	131(2)	49(1)	53(1)	-5(1)	-6(1)
C(54)	21(1)	88(1)	30(1)	16(1)	-1(1)	-9(1)

Table SI-17. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for 1a.

	x	y	z	U(eq)
H(4A)	1994	7509	6217	50
H(4B)	1015	7101	6621	50
H(5)	488	6534	5804	38
H(11)	3368	2854	5086	37
H(12)	3874	3934	5676	35
H(13)	-850	5061	6054	45
H(14A)	-1459	6848	6571	98
H(14B)	-2630	5955	6459	98
H(14C)	-2008	6689	6080	98
H(15A)	729	4486	6615	79
H(15B)	-934	4589	6791	79
H(15C)	267	5458	6910	79
H(16)	-867	3929	4571	30
H(17)	-2004	5201	5199	31
H(18A)	-3131	4845	4340	55
H(18B)	-4010	5429	4721	55
H(18C)	-3651	4217	4763	55
H(20)	-2253	7070	5169	45
H(21)	-1364	8661	4920	58
H(22)	246	8727	4324	61
H(23)	895	7198	3965	56
H(24)	-6	5608	4208	42
H(34A)	5402	2525	8125	33
H(34B)	5278	3766	8167	33
H(35)	6144	2805	7439	27

H(41)	1706	1607	6145	31
H(42)	1565	2212	6858	31
H(43)	5739	4369	7045	31
H(44A)	7355	5409	7444	55
H(44B)	7855	4227	7504	55
H(44C)	6966	4804	7884	55
H(45A)	3444	4893	7337	50
H(45B)	4614	5822	7369	50
H(45C)	4220	5156	7793	50
H(46)	6227	2128	5739	29
H(47)	7638	3048	6441	31
H(48A)	8976	2331	5651	44
H(48B)	9741	3080	6000	44
H(48C)	8377	3489	5715	44
H(50)	7989	591	5888	54
H(51)	8908	-933	6194	82
H(52)	9751	-946	6907	88
H(53)	9677	566	7320	81
H(54)	8752	2109	7018	55

Table SI-18. Torsion angles [°] for 1a.

O(1)-C(2)-O(3)-C(4)	172.67(14)
N(6)-C(2)-O(3)-C(4)	-7.87(15)
C(2)-O(3)-C(4)-C(5)	20.20(16)
O(3)-C(4)-C(5)-N(6)	-23.04(14)
O(3)-C(4)-C(5)-C(13)	96.83(15)
O(1)-C(2)-N(6)-C(7)	-3.8(2)
O(3)-C(2)-N(6)-C(7)	176.78(11)
O(1)-C(2)-N(6)-C(5)	170.77(14)
O(3)-C(2)-N(6)-C(5)	-8.65(15)
C(13)-C(5)-N(6)-C(2)	-102.55(12)
C(4)-C(5)-N(6)-C(2)	19.78(14)
C(13)-C(5)-N(6)-C(7)	72.29(15)
C(4)-C(5)-N(6)-C(7)	-165.37(11)
C(2)-N(6)-C(7)-N(8)	179.54(11)
C(5)-N(6)-C(7)-N(8)	5.48(16)
C(2)-N(6)-C(7)-C(12)	-0.21(19)

C(5)-N(6)-C(7)-C(12)	-174.27(12)
C(12)-C(7)-N(8)-C(9)	2.06(16)
N(6)-C(7)-N(8)-C(9)	-177.69(10)
C(7)-N(8)-C(9)-N(10)	-1.62(17)
C(7)-N(8)-C(9)-N(16)	176.41(10)
N(8)-C(9)-N(10)-C(11)	0.70(18)
N(16)-C(9)-N(10)-C(11)	-177.32(11)
C(9)-N(10)-C(11)-C(12)	-0.21(19)
N(10)-C(11)-C(12)-C(7)	0.6(2)
N(8)-C(7)-C(12)-C(11)	-1.62(18)
N(6)-C(7)-C(12)-C(11)	178.11(12)
N(6)-C(5)-C(13)-C(14)	-175.70(12)
C(4)-C(5)-C(13)-C(14)	71.50(16)
N(6)-C(5)-C(13)-C(15)	57.87(15)
C(4)-C(5)-C(13)-C(15)	-54.93(17)
N(8)-C(9)-N(16)-C(17)	8.46(16)
N(10)-C(9)-N(16)-C(17)	-173.33(11)
C(9)-N(16)-C(17)-C(19)	69.35(14)
C(9)-N(16)-C(17)-C(18)	-167.24(11)
N(16)-C(17)-C(19)-C(20)	-148.97(12)
C(18)-C(17)-C(19)-C(20)	88.77(15)
N(16)-C(17)-C(19)-C(24)	32.99(17)
C(18)-C(17)-C(19)-C(24)	-89.27(15)
C(24)-C(19)-C(20)-C(21)	-0.9(2)
C(17)-C(19)-C(20)-C(21)	-178.99(13)
C(19)-C(20)-C(21)-C(22)	-0.3(2)
C(20)-C(21)-C(22)-C(23)	1.2(2)
C(21)-C(22)-C(23)-C(24)	-0.8(2)
C(22)-C(23)-C(24)-C(19)	-0.3(2)
C(20)-C(19)-C(24)-C(23)	1.2(2)
C(17)-C(19)-C(24)-C(23)	179.28(13)
O(31)-C(32)-O(33)-C(34)	172.76(12)
N(36)-C(32)-O(33)-C(34)	-7.42(13)
C(32)-O(33)-C(34)-C(35)	18.05(13)
O(33)-C(34)-C(35)-N(36)	-20.14(12)
O(33)-C(34)-C(35)-C(43)	100.74(12)
O(31)-C(32)-N(36)-C(37)	-7.0(2)
O(33)-C(32)-N(36)-C(37)	173.17(10)
O(31)-C(32)-N(36)-C(35)	172.77(13)

O(33)-C(32)-N(36)-C(35)	-7.03(14)
C(43)-C(35)-N(36)-C(32)	-105.03(12)
C(34)-C(35)-N(36)-C(32)	16.93(13)
C(43)-C(35)-N(36)-C(37)	74.77(14)
C(34)-C(35)-N(36)-C(37)	-163.26(10)
C(32)-N(36)-C(37)-N(38)	-174.51(11)
C(35)-N(36)-C(37)-N(38)	5.72(16)
C(32)-N(36)-C(37)-C(42)	4.83(18)
C(35)-N(36)-C(37)-C(42)	-174.95(11)
C(42)-C(37)-N(38)-C(39)	0.91(16)
N(36)-C(37)-N(38)-C(39)	-179.76(10)
C(37)-N(38)-C(39)-N(46)	173.66(10)
C(37)-N(38)-C(39)-N(40)	-4.84(17)
N(38)-C(39)-N(40)-C(41)	4.73(17)
N(46)-C(39)-N(40)-C(41)	-173.79(10)
C(39)-N(40)-C(41)-C(42)	-0.73(18)
N(40)-C(41)-C(42)-C(37)	-2.57(19)
N(38)-C(37)-C(42)-C(41)	2.47(17)
N(36)-C(37)-C(42)-C(41)	-176.81(11)
N(36)-C(35)-C(43)-C(45)	57.40(13)
C(34)-C(35)-C(43)-C(45)	-55.83(15)
N(36)-C(35)-C(43)-C(44)	-178.23(10)
C(34)-C(35)-C(43)-C(44)	68.54(14)
N(38)-C(39)-N(46)-C(47)	17.07(17)
N(40)-C(39)-N(46)-C(47)	-164.28(11)
C(39)-N(46)-C(47)-C(49)	72.44(15)
C(39)-N(46)-C(47)-C(48)	-164.93(11)
N(46)-C(47)-C(49)-C(54)	-128.67(13)
C(48)-C(47)-C(49)-C(54)	110.01(14)
N(46)-C(47)-C(49)-C(50)	52.84(16)
C(48)-C(47)-C(49)-C(50)	-68.48(16)
C(54)-C(49)-C(50)-C(51)	-0.4(2)
C(47)-C(49)-C(50)-C(51)	178.13(15)
C(49)-C(50)-C(51)-C(52)	0.1(3)
C(50)-C(51)-C(52)-C(53)	0.1(3)
C(51)-C(52)-C(53)-C(54)	-0.1(3)
C(50)-C(49)-C(54)-C(53)	0.4(2)
C(47)-C(49)-C(54)-C(53)	-178.07(13)
C(52)-C(53)-C(54)-C(49)	-0.2(2)

Symmetry transformations used to generate equivalent atoms:

Table SI-19. Hydrogen bonds for 1a [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(16)-H(16)...N(40)#1	0.87	2.16	3.0282(15)	175.0
N(46)-H(46)...N(10)#2	0.89	2.15	3.0285(16)	171.9

Symmetry transformations used to generate equivalent atoms:

#1 x-1/2,-y+1/2,-z+1 #2 x+1/2,-y+1/2,-z+1

Figure SI-4. DiscoveRX Profiling for IDH125

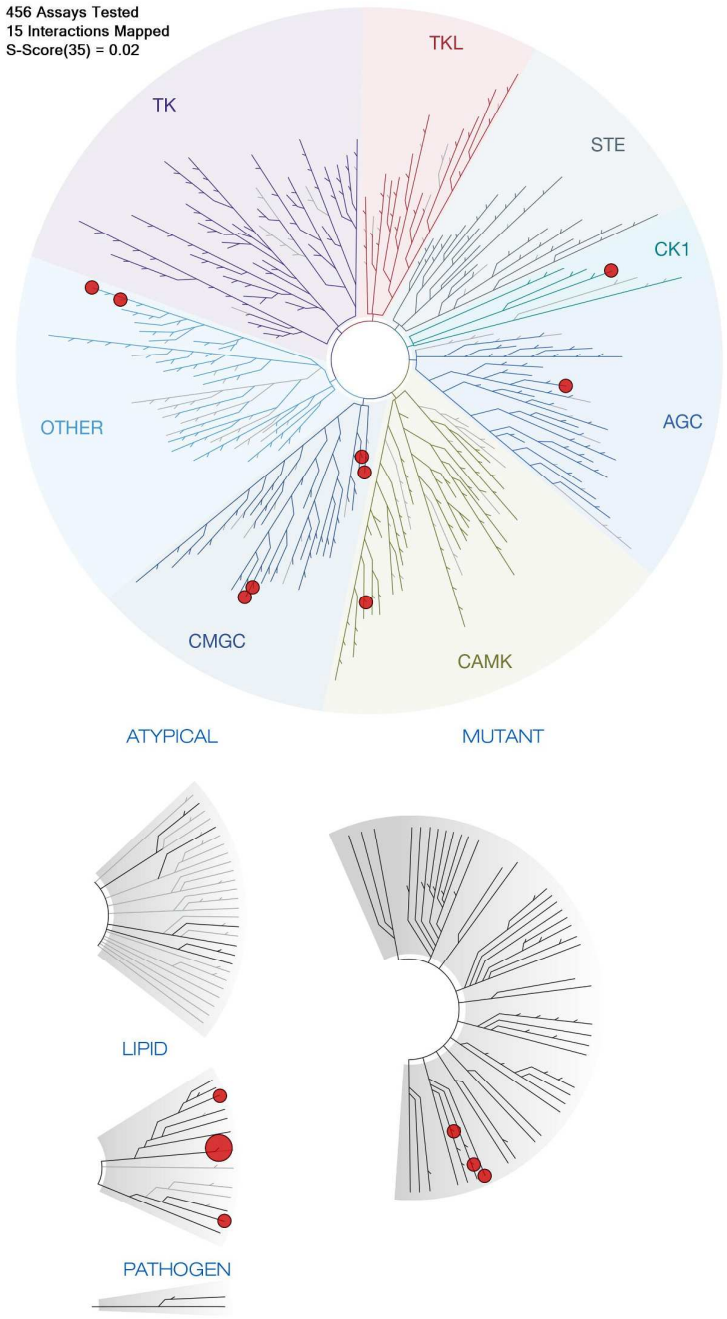


Table SI-20: %control values for IDH125 at 10µM vs DiscoverX kinase panel

KINOMEscan Gene Symbol	Entrez Gene Symbol	Percent Control (IDH125 10 µM)
AAK1	AAK1	80
ABL1(E255K)-phosphorylated	ABL1	75
ABL1(F317I)-nonphosphorylated	ABL1	100
ABL1(F317I)-phosphorylated	ABL1	78
ABL1(F317L)-nonphosphorylated	ABL1	100

ABL1(F317L)-phosphorylated	ABL1	64
ABL1(H396P)-nonphosphorylated	ABL1	100
ABL1(H396P)-phosphorylated	ABL1	62
ABL1(M351T)-phosphorylated	ABL1	76
ABL1(Q252H)-nonphosphorylated	ABL1	100
ABL1(Q252H)-phosphorylated	ABL1	79
ABL1(T315I)-nonphosphorylated	ABL1	98
ABL1(T315I)-phosphorylated	ABL1	82
ABL1(Y253F)-phosphorylated	ABL1	81
ABL1-nonphosphorylated	ABL1	100
ABL1-phosphorylated	ABL1	52
ABL2	ABL2	97
ACVR1	ACVR1	100
ACVR1B	ACVR1B	100
ACVR2A	ACVR2A	100
ACVR2B	ACVR2B	100
ACVRL1	ACVRL1	68
ADCK3	CABC1	94
ADCK4	ADCK4	100
AKT1	AKT1	89
AKT2	AKT2	94
AKT3	AKT3	100
ALK	ALK	100
ALK(C1156Y)	ALK	83
ALK(L1196M)	ALK	74
AMPK-alpha1	PRKAA1	49
AMPK-alpha2	PRKAA2	100
ANKK1	ANKK1	90
ARK5	NUAK1	28
ASK1	MAP3K5	100
ASK2	MAP3K6	78
AURKA	AURKA	100
AURKB	AURKB	62
AURKC	AURKC	100
AXL	AXL	94
BIKE	BMP2K	100
BLK	BLK	100

BMPR1A	BMPR1A	100
BMPR1B	BMPR1B	88
BMPR2	BMPR2	59
BMX	BMX	92
BRAF	BRAF	77
BRAF(V600E)	BRAF	87
BRK	PTK6	81
BRSK1	BRSK1	70
BRSK2	BRSK2	51
BTK	BTK	100
BUB1	BUB1	89
CAMK1	CAMK1	81
CAMK1D	CAMK1D	76
CAMK1G	CAMK1G	92
CAMK2A	CAMK2A	72
CAMK2B	CAMK2B	92
CAMK2D	CAMK2D	90
CAMK2G	CAMK2G	89
CAMK4	CAMK4	80
CAMKK1	CAMKK1	95
CAMKK2	CAMKK2	86
CASK	CASK	67
CDC2L1	CDK11B	80
CDC2L2	CDC2L2	66
CDC2L5	CDK13	90
CDK11	CDK19	100
CDK2	CDK2	90
CDK3	CDK3	93
CDK4-cyclinD1	CDK4	79
CDK4-cyclinD3	CDK4	43
CDK5	CDK5	100
CDK7	CDK7	67
CDK8	CDK8	100
CDK9	CDK9	75
CDKL1	CDKL1	84
CDKL2	CDKL2	78
CDKL3	CDKL3	100

CDKL5	CDKL5	79
CHEK1	CHEK1	100
CHEK2	CHEK2	100
CIT	CIT	93
CLK1	CLK1	100
CLK2	CLK2	100
CLK3	CLK3	100
CLK4	CLK4	100
CSF1R	CSF1R	100
CSF1R-autoinhibited	CSF1R	74
CSK	CSK	96
CSNK1A1	CSNK1A1	66
CSNK1A1L	CSNK1A1L	75
CSNK1D	CSNK1D	42
CSNK1E	CSNK1E	12
CSNK1G1	CSNK1G1	76
CSNK1G2	CSNK1G2	94
CSNK1G3	CSNK1G3	95
CSNK2A1	CSNK2A1	42
CSNK2A2	CSNK2A2	100
CTK	MATK	95
DAPK1	DAPK1	100
DAPK2	DAPK2	94
DAPK3	DAPK3	100
DCAMKL1	DCLK1	60
DCAMKL2	DCLK2	92
DCAMKL3	DCLK3	100
DDR1	DDR1	91
DDR2	DDR2	66
DLK	MAP3K12	88
DMPK	DMPK	100
DMPK2	CDC42BPG	62
DRAK1	STK17A	94
DRAK2	STK17B	100
DYRK1A	DYRK1A	94
DYRK1B	DYRK1B	100
DYRK2	DYRK2	100

EGFR	EGFR	100
EGFR(E746-A750del)	EGFR	92
EGFR(G719C)	EGFR	100
EGFR(G719S)	EGFR	99
EGFR(L747-E749del, A750P)	EGFR	100
EGFR(L747-S752del, P753S)	EGFR	97
EGFR(L747-T751del,Sins)	EGFR	87
EGFR(L858R)	EGFR	100
EGFR(L858R,T790M)	EGFR	76
EGFR(L861Q)	EGFR	100
EGFR(S752-I759del)	EGFR	100
EGFR(T790M)	EGFR	98
EIF2AK1	EIF2AK1	79
EPHA1	EPHA1	93
EPHA2	EPHA2	96
EPHA3	EPHA3	86
EPHA4	EPHA4	94
EPHA5	EPHA5	100
EPHA6	EPHA6	100
EPHA7	EPHA7	89
EPHA8	EPHA8	100
EPHB1	EPHB1	88
EPHB2	EPHB2	78
EPHB3	EPHB3	100
EPHB4	EPHB4	92
EPHB6	EPHB6	100
ERBB2	ERBB2	100
ERBB3	ERBB3	86
ERBB4	ERBB4	100
ERK1	MAPK3	100
ERK2	MAPK1	98
ERK3	MAPK6	42
ERK4	MAPK4	77
ERK5	MAPK7	72
ERK8	MAPK15	93
ERN1	ERN1	100
FAK	PTK2	83

FER	FER	100
FES	FES	100
FGFR1	FGFR1	100
FGFR2	FGFR2	100
FGFR3	FGFR3	97
FGFR3(G697C)	FGFR3	100
FGFR4	FGFR4	77
FGR	FGR	100
FLT1	FLT1	58
FLT3	FLT3	100
FLT3(D835H)	FLT3	100
FLT3(D835Y)	FLT3	68
FLT3(ITD)	FLT3	100
FLT3(K663Q)	FLT3	84
FLT3(N841I)	FLT3	100
FLT3(R834Q)	FLT3	96
FLT3-autoinhibited	FLT3	72
FLT4	FLT4	95
FRK	FRK	85
FYN	FYN	93
GAK	GAK	87
GCN2(Kin.Dom.2,S808G)	EIF2AK4	49
GRK1	GRK1	56
GRK4	GRK4	100
GRK7	GRK7	17
GSK3A	GSK3A	29
GSK3B	GSK3B	70
HASPIN	GSG2	85
HCK	HCK	100
HIPK1	HIPK1	97
HIPK2	HIPK2	48
HIPK3	HIPK3	73
HIPK4	HIPK4	100
HPK1	MAP4K1	68
HUNK	HUNK	48
ICK	ICK	29
IGF1R	IGF1R	100

IKK-alpha	CHUK	93
IKK-beta	IKBKB	71
IKK-epsilon	IKBKE	83
INSR	INSR	85
INSRR	INSRR	99
IRAK1	IRAK1	76
IRAK3	IRAK3	100
IRAK4	IRAK4	76
ITK	ITK	91
JAK1(JH1domain-catalytic)	JAK1	36
JAK1(JH2domain-pseudokinase)	JAK1	97
JAK2(JH1domain-catalytic)	JAK2	46
JAK3(JH1domain-catalytic)	JAK3	73
JNK1	MAPK8	20
JNK2	MAPK9	44
JNK3	MAPK10	26
KIT	KIT	67
KIT(A829P)	KIT	94
KIT(D816H)	KIT	100
KIT(D816V)	KIT	93
KIT(L576P)	KIT	83
KIT(V559D)	KIT	83
KIT(V559D,T670I)	KIT	100
KIT(V559D,V654A)	KIT	100
KIT-autoinhibited	KIT	69
LATS1	LATS1	88
LATS2	LATS2	100
LCK	LCK	68
LIMK1	LIMK1	74
LIMK2	LIMK2	39
LKB1	STK11	100
LOK	STK10	100
LRRK2	LRRK2	98
LRRK2(G2019S)	LRRK2	82
LTK	LTK	100
LYN	LYN	66
LZK	MAP3K13	100

MAK	MAK	69
MAP3K1	MAP3K1	70
MAP3K15	MAP3K15	68
MAP3K2	MAP3K2	92
MAP3K3	MAP3K3	81
MAP3K4	MAP3K4	88
MAP4K2	MAP4K2	70
MAP4K3	MAP4K3	100
MAP4K4	MAP4K4	94
MAP4K5	MAP4K5	100
MAPKAPK2	MAPKAPK2	100
MAPKAPK5	MAPKAPK5	100
MARK1	MARK1	83
MARK2	MARK2	100
MARK3	MARK3	93
MARK4	MARK4	91
MAST1	MAST1	89
MEK1	MAP2K1	100
MEK2	MAP2K2	100
MEK3	MAP2K3	50
MEK4	MAP2K4	100
MEK5	MAP2K5	55
MEK6	MAP2K6	83
MELK	MELK	46
MERTK	MERTK	70
MET	MET	40
MET(M1250T)	MET	43
MET(Y1235D)	MET	100
MINK	MINK1	47
MKK7	MAP2K7	100
MKNK1	MKNK1	85
MKNK2	MKNK2	72
MLCK	MYLK3	98
MLK1	MAP3K9	100
MLK2	MAP3K10	90
MLK3	MAP3K11	98
MRCKA	CDC42BPA	100

MRCKB	CDC42BPB	100
MST1	STK4	100
MST1R	MST1R	100
MST2	STK3	80
MST3	STK24	100
MST4	MST4	50
MTOR	MTOR	99
MUSK	MUSK	86
MYLK	MYLK	66
MYLK2	MYLK2	100
MYLK4	MYLK4	100
MYO3A	MYO3A	58
MYO3B	MYO3B	66
NDR1	STK38	83
NDR2	STK38L	100
NEK1	NEK1	100
NEK10	NEK10	82
NEK11	NEK11	100
NEK2	NEK2	91
NEK3	NEK3	41
NEK4	NEK4	100
NEK5	NEK5	49
NEK6	NEK6	100
NEK7	NEK7	100
NEK9	NEK9	100
NIK	MAP3K14	84
NIM1	MGC42105	40
NLK	NLK	95
OSR1	OXSR1	46
p38-alpha	MAPK14	100
p38-beta	MAPK11	95
p38-delta	MAPK13	100
p38-gamma	MAPK12	100
PAK1	PAK1	67
PAK2	PAK2	70
PAK3	PAK3	100
PAK4	PAK4	86

PAK6	PAK6	87
PAK7	PAK7	89
PCTK1	CDK16	74
PCTK2	CDK17	96
PCTK3	CDK18	81
PDGFRA	PDGFRA	64
PDGFRB	PDGFRB	72
PDPK1	PDPK1	71
PFCDPK1(P.falciparum)	CDPK1	100
PFPK5(P.falciparum)	MAL13P1.279	79
PFTAIRE2	CDK15	100
PFTK1	CDK14	96
PHKG1	PHKG1	85
PHKG2	PHKG2	100
PIK3C2B	PIK3C2B	100
PIK3C2G	PIK3C2G	96
PIK3CA	PIK3CA	100
PIK3CA(C420R)	PIK3CA	34
PIK3CA(E542K)	PIK3CA	100
PIK3CA(E545A)	PIK3CA	25
PIK3CA(E545K)	PIK3CA	94
PIK3CA(H1047L)	PIK3CA	44
PIK3CA(H1047Y)	PIK3CA	51
PIK3CA(I800L)	PIK3CA	60
PIK3CA(M1043I)	PIK3CA	35
PIK3CA(Q546K)	PIK3CA	100
PIK3CB	PIK3CB	100
PIK3CD	PIK3CD	42
PIK3CG	PIK3CG	33
PIK4CB	PI4KB	2.6
PIM1	PIM1	79
PIM2	PIM2	100
PIM3	PIM3	89
PIP5K1A	PIP5K1A	81
PIP5K1C	PIP5K1C	100
PIP5K2B	PIP4K2B	100
PIP5K2C	PIP4K2C	21

PKAC-alpha	PRKACA	80
PKAC-beta	PRKACB	58
PKMYT1	PKMYT1	100
PKN1	PKN1	100
PKN2	PKN2	100
PKNB(M.tuberculosis)	pknB	100
PLK1	PLK1	23
PLK2	PLK2	18
PLK3	PLK3	38
PLK4	PLK4	100
PRKCD	PRKCD	100
PRKCE	PRKCE	70
PRKCH	PRKCH	100
PRKCI	PRKCI	65
PRKCQ	PRKCQ	100
PRKD1	PRKD1	49
PRKD2	PRKD2	47
PRKD3	PRKD3	88
PRKG1	PRKG1	100
PRKG2	PRKG2	89
PRKR	EIF2AK2	100
PRKX	PRKX	100
PRP4	PRPF4B	91
PYK2	PTK2B	92
QSK	KIAA0999	77
RAF1	RAF1	86
RET	RET	100
RET(M918T)	RET	100
RET(V804L)	RET	100
RET(V804M)	RET	100
RIOK1	RIOK1	85
RIOK2	RIOK2	62
RIOK3	RIOK3	100
RIPK1	RIPK1	50
RIPK2	RIPK2	83
RIPK4	RIPK4	37
RIPK5	DSTYK	62

ROCK1	ROCK1	59
ROCK2	ROCK2	61
ROS1	ROS1	100
RPS6KA4(Kin.Dom.1-N-terminal)	RPS6KA4	100
RPS6KA4(Kin.Dom.2-C-terminal)	RPS6KA4	100
RPS6KA5(Kin.Dom.1-N-terminal)	RPS6KA5	100
RPS6KA5(Kin.Dom.2-C-terminal)	RPS6KA5	77
RSK1(Kin.Dom.1-N-terminal)	RPS6KA1	100
RSK1(Kin.Dom.2-C-terminal)	RPS6KA1	100
RSK2(Kin.Dom.1-N-terminal)	RPS6KA3	73
RSK2(Kin.Dom.2-C-terminal)	RPS6KA3	84
RSK3(Kin.Dom.1-N-terminal)	RPS6KA2	100
RSK3(Kin.Dom.2-C-terminal)	RPS6KA2	100
RSK4(Kin.Dom.1-N-terminal)	RPS6KA6	86
RSK4(Kin.Dom.2-C-terminal)	RPS6KA6	100
S6K1	RPS6KB1	100
SBK1	SBK1	43
SGK	SGK1	100
SgK110	SgK110	100
SGK2	SGK2	92
SGK3	SGK3	100
SIK	SIK1	100
SIK2	SIK2	100
SLK	SLK	100
SNARK	NUAK2	94
SNRK	SNRK	79
SRC	SRC	86
SRMS	SRMS	100
SRPK1	SRPK1	100
SRPK2	SRPK2	65
SRPK3	SRPK3	100
STK16	STK16	81
STK33	STK33	86
STK35	STK35	100
STK36	STK36	85
STK39	STK39	98
SYK	SYK	100

TAK1	MAP3K7	69
TAOK1	TAOK1	45
TAOK2	TAOK2	40
TAOK3	TAOK3	51
TBK1	TBK1	100
TEC	TEC	88
TESK1	TESK1	86
TGFBR1	TGFBR1	90
TGFBR2	TGFBR2	85
TIE1	TIE1	100
TIE2	TEK	100
TLK1	TLK1	100
TLK2	TLK2	100
TNIK	TNIK	88
TNK1	TNK1	100
TNK2	TNK2	100
TNNI3K	TNNI3K	94
TRKA	NTRK1	76
TRKB	NTRK2	94
TRKC	NTRK3	97
TRPM6	TRPM6	100
TSSK1B	TSSK1B	74
TTK	TTK	100
TXK	TXK	94
TYK2(JH1domain-catalytic)	TYK2	96
TYK2(JH2domain-pseudokinase)	TYK2	100
TYRO3	TYRO3	94
ULK1	ULK1	46
ULK2	ULK2	58
ULK3	ULK3	60
VEGFR2	KDR	68
VRK2	VRK2	46
WEE1	WEE1	100
WEE2	WEE2	100
WNK1	WNK1	100
WNK3	WNK3	84
YANK1	STK32A	64

YANK2	STK32B	69
YANK3	STK32C	87
YES	YES1	100
YSK1	STK25	96
YSK4	YSK4	100
ZAK	ZAK	87
ZAP70	ZAP70	92

Crystallography for IDH889 with IDH1$^{R132H+/+}$ [PDB ID: 5TQH]

Protein expression and purification

The R132H mutant IDH1 was expressed in *E. coli* cells using a construct expressing human IDH1 bearing the R132H mutation with N-terminal 6xHis tag and PreScission protease cleavage site. *E. coli* strain Rosetta™2(DE3) (Novagen) transformed with the IDH1^{R132H} expression construct was grown at 37°C in shaker flasks to an OD_{600} of 0.8 in Terrific Broth (Teknova) with 50µg/ml of Kanamycin and 34µg/mL of chloramphenicol, then cooled down to below 18°C. IDH1^{R132H} protein expression was induced by addition of Isopropyl-*β*-D-thiogalactopyranoside (IPTG) to 0.2 mM for 18 hours at 18°C. The harvested cells were resuspended in lysis buffer (50mM Tris pH=7.4, 500mM NaCl, 20mM Imidazole, 0.5mM DTT) containing DNAse I and protease inhibitors (complete EDTA-free protease inhibitor tablets (1 tablet per 50mL of buffer) and 200uM PMSF), and lysed on ice using a microfluidizer (M-110L, Microfluidics). After lysis, Trition X-100 was added to 0.1% and stirred at 4°C for 30 minutes. The cleared lysate containing His-tagged IDH1^{R132H} fusion protein was then loaded onto 2x 5mL HisTrap FF crude columns (GE Healthcare), and the His-tagged protein eluted with Ni Elution Buffer (50mM Tris pH=7.4, 150mM NaCl, 200mM Imidazole, 0.5mM DTT). Peak eluted fractions were concentrated to 30mL, EDTA was added to 1mM and GST-PreScission protease (*in house*) was added to 3U/100µg of protein. The sample was dialyzed against 2L Dialysis Buffer I (20mM Tris pH=7.4, 150mM NaCl, 0.5mM DTT, 50mM Imidazole) for 6 hours at 4°C, then dialyzed against 2L of Dialysis Buffer II (20mM Tris pH=7.4, 150mM NaCl, 0.5mM DTT) at 4°C for at least 6 more hours. GST-PreScission cleaved sample was rocked with Glutathione Agarose Beads, spun down and then the supernatant was loaded through a 5mL HisTrap HP column (GE Healthcare) and the flow through was collected. The collected flow through was then diluted with 20mM Tris pH 7.4 and 0.5mM DTT until the conductivity dropped to less than 5 mS/cm and loaded onto a HiTrap Q column (GE Healthcare). The tag-free IDH1^{R132H} protein was then collected from the flow through of HiTrapQ column (GE Healthcare) and further purified by size exclusion chromatography (HiLoad 26/60 Superdex 200,

GE Healthcare). The purified IDH1^{R132H} was concentration to 5 mg/ml in buffer (20 mM Tris pH7.5, 150mM NaCl), and frozen in liquid N2 for storage at -80°C.

Crystallization, data collection and structure determination

To obtained crystals of IDH1^{R132H}:compound complex, IDH1^{R132H} was diluted to 1mg/mL in storage buffer then incubated with compound at 2-5x molar excess of protein concentration. The mixture was concentrated 10 fold prior to crystallization. The complexes were crystallized using sitting drop vapor diffusion method at 20 °C by mixing equal volumes (2 µL + 2 µL) of protein:compound mixture and crystallization solution (0.1 M Bis-Tris pH5.5-6.5 and 1.45-1.7 M Trisodium citrate dehydrate). In all cases, the crystals were directly looped from their mother liquor and flash frozen in liquid nitrogen for diffraction experiment.

Crystals of all three IDH1^{R132H}: compound complexes were determined to have the orthorhombic space group $P2_12_12_1$ with two complexes in the asymmetric unit. Each complex comprises a dimer of IDH1^{R132H}, with each protein in complex with one NADPH molecule (co-purified with protein) and one compound molecule. A citrate molecule is also modeled at the substrate binding site for each protein, as a result of presence of high concentration of trisodium citrate dihydrate in the crystallization solution.

All diffraction data were collected at the X-ray Operations and Research beamline 17-ID at the Advanced Photon Source, Argonne National Laboratory, with the crystal kept at 100K and wavelength of X-ray beam at 1.0 Å. The diffraction data from all crystals were integrated and scaled using autoPROC (6). The structures were solved by molecular replacement with Phaser (1) using another IDH1^{R132H} structure[6] as a starting model. Model building and refinement was performed using COOT (5) and PHENIX (2). Statistics for the collected data and refined model are summarized in Table SI-21. PDB coordinates and accompanying structure factors will be deposed to protein data bank.

Reference Citation (PHENIX and COOT)

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Richardson JS, Terwilliger TC, and Zwart PH. **PHENIX**: a comprehensive Python-based system for macromolecular structure solution. Acta Cryst. D66, 213-221 (2010).

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9. Vonrhein, C., Flensburg, C., Keller, P., Sharff, A., Smart, O., Paciorek, W., Womack, T. & Bricogne, G. (2011).Data processing and analysis with the **autoPROC** toolbox. Acta Cryst. D67, 293-302.

[full dataset will be deposited to the PDB upon publication].

Table SI-21: IDH1-R132H:NADPH:IDH889

	IDH1-R132H:NADPH: IDH889 *
Data collection	
Space group	P212121
Cell dimensions	
a, *b*, *c* (Å)	81.73, 155.75, 163.05
(°)	90, 90, 90
Resolution (Å)	163.05 – 2.20 (2.32 – 2.20)
R_{sym} or R_{merge}	0.051 (0.495)
I / ΔI	20.7 (3.5)
Completeness (%)	99.9 (100.0)
Redundancy	6.6 (6.9)
Refinement	
Resolution (Å)	72.23 – 2.20 (2.28 – 2.20)
No. reflections used in refinement	106023 (10485)
No. reflections used for R_{free}	5294 (539)
R_{work} / R_{free}	0.196 (0.236) / 0.250 (0.305)
No. atoms	
Protein	12869
Ligand/ion	372
Water	646
B-factors	
Protein	52.3
Ligand/ion	52.6
Water	48.3
RMS deviations	

Bond lengths (Å)	0.005
Bond angles (°)	0.88

* Values in parentheses are for highest-resolution shell.

Determination of plasma protein and brain homogenate binding

In vitro plasma and brain protein binding of IDH662 and IDH889 were assessed in triplicate using an equilibrium dialysis method (Rapid Equilibrium Dialysis (RED) System; Thermo Fisher Scientific, Inc., Waltham MA). For plasma protein binding, compound was added to mouse or human plasma at a final concentration of 1 μM (in 1% DMSO). For brain protein binding, brain tissue was homogenized in 4 volumes (w/v) of phosphate-buffered saline (PBS) (dilution factor D = 5). Compound was then added to brain homogenate at a final concentration of 1 μM (in 1% DMSO). The plasma or brain homogenate were incubated at 37°C under 5% CO_2 for 4 h in the rapid equilibrium dialysis (RED) Device. Parent compound concentrations in the plasma or brain homogenate and phosphate-buffered saline (PBS) compartments were measured at time 0 and 4 h by LC/MS/MS.

A fraction unbound (fu) of compound in plasma was calculated as:

$fu = [PBS]_{4\,h}/[Plasma]_{4\,h}$

A fraction unbound (fu_{brain}) of compound in brain tissue (undiluted) was calculated as:

$fu_{brain} = (1/D) / (((1/fu)-1)+1/D)$

reference for the RED assay for PPB:

J Pharm Sci. 2008 Oct;97(10):4586-95. doi: 10.1002/jps.21317.

Pharmacokinetics in Mice

Naive mouse PK study

Mouse pharmacokinetics (PK) studies were performed with male C57BL/6 mice weighing 25-30g that are approximately 6-8 weeks old, obtained from Harlan Research Laboratories (South Easton, MA; now Envigo). For this study, PK in mice was assessed at doses of 10 and 100 mg/kg with n=3 mice per dose level. The oral dose for compound **IDH662** was prepared at 1 and 10 mg/mL in a solution containing 3% 0.2N HCl, 20% PEG400, 50% of (20% Crem El) in Water for Injection. Each animal received 10 mL of the dosing solution per kg of body weight by oral gavage of the 1 and 10 mg/mL solution for the 10 and 100 mg/kg dose groups, respectively. For PK determination, approximately 50 μl of whole blood was collected from the tail of each animal using microvette EDTA tube at 0.25, 0.5, 1, 2, 4, and 7 h post-dose and transferred to a EDTA tube. The blood was centrifuged at 3000 rpm and plasma was transferred to PCR-96-AB-C WELL plate, capped with PCR strip cap and stored frozen (-20 °C) for parent compound analysis.

Bioanalysis for determination of plasma drug levels from PK and PK/PD studies

For determination of **IDH662** and **IDH889** plasma concentrations, blood was collected via tail nick (non-terminal) or cardiac puncture (terminal), collected into EDTA-lined microtainers (BD Microtainer®, Cat No. 365973), centrifuged at 13,200 rpm for 5 minutes and the plasma supernatant placed in a 1 mL 96 well collection plate and stored at -20°C until analysis. Plasma concentrations were determined by LC-MS/MS. Acetonitrile protein precipitation was employed to extract plasma samples, which were processed using a Freedom EVO® 150 and a Freedom EVO® from TECAN. Test samples were diluted with blank mouse plasma 2 to 10 fold and 25 µL of each undiluted or diluted test sample were transferred to a 96-well plate. A 150 µL volume of acetonitrile with 100 ng/mL glyburide (internal standard) was added to each well containing test sample, or calibration standard, vortexed, then centrifuged at 4,000 rpm for 10 minutes. 125 µL of each supernatant were transferred to a clean 1 mL 96-well plate, followed by the addition of 50 µL of water. For each sample, a 10 µL aliquot was injected into the LC-MS/MS system. Chromatographic separation was achieved with an ACE C18 column (3 µm, 2.1 × 30 mm) from MAC-MOD Analytical, Inc. (Chadds Ford, PA), using 0.1% formic acid in water (A) and 0.1% formic acid in acetonitrile (B) as solvents in a multistep gradient. Data were acquired and processed using Sciex Analyst 1.4.2 software. All pharmacokinetic (PK) parameters were derived from concentration-time data by noncompartmental analyses (Thermo Watson 7, Thermo Fisher Scientific, Inc., Philadelphia, PA). The peak concentrations (C_{max}) and times they occurred (T_{max}) were recorded. The area under the concentration-time curve (AUC_{last}) was calculated using the linear trapezoidal rule. The area under the concentration-time curve from time 0 to infinity (AUC_{inf}) was calculated using the following equation, $AUC_{\inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$ Where the terminal elimination rate constant (λ_z) for the unchanged compound was the slope of the log linear line from at least the last three data points. Results are expressed as mean ± SD when are applicable. No further statistical analysis was performed.

HCT116$^{IDH1\ R132H/+}$ xenograft model

Cell culture

HCT116 cells expressing the R132H mutant form of IDH1 (HCT116$^{IDH1\ R132H/+}$ Clone 2H1, HCHZ2H1) were purchased from Horizon (Cat#: HD 115-002, clone 2H1), expanded for 5 passages, then stored in liquid Nitrogen. Cells were tested free of Mycoplasma and viral contamination (MAP Impact panel VIII testing, Radil). Cells used for subcutaneous implantation were cultured in

McCoy's 5A medium (Corning, Cat #: 10-050-CV) supplemented with 10% FBS (High Clone cat#sh30071) and split 1:3 twice weekly. Cells were cultured for 7-10 passages prior to implantation.

Generation of HCHZ2H1 xenografts

All studies were performed in accordance with Novartis Institutes for Biomedical Research (NIBR) Animal Care and Use Committee. Outbred athymic (*nu/nu*) female mice ("HSD: Athymic Nude-nu") weighing 19-32 grams (Envigo, Indianapolis) were allowed to acclimate in the NIBR animal facility with access to food and water *ad libitum* for minimum of 3 days prior to manipulation. All studies were performed in accordance with Novartis Institutes for Biomedical Research Animal Care and Use Committee. HCHZ2H1 cells were harvested at 80-90% confluency, washed once with Hank's Balanced Salt Solutions (HBSS, Cat No. 14175, Invitrogen Corporation, Gibco, Grand Island, NY), and suspended in 100% HBSS at 5×10^7 cells/mL for implantation. For tumor cell implantation, mice were anesthetized with continuous flow of 2-4% isoflurane/oxygen mixture using the Integrated Multi Patient Anesthesia Center (IMPAC6) and induction chamber (Vetequip, Inc., Pleasanton, CA). Female nude mice were injected subcutaneously (dorsal right supra-axillary region) with 5×10^6 HCHZ2H1 tumor cells suspended in 100% HBSS in a total volume of 100 µL. Mice were monitored for tumor growth, and once palpable, tumors were measured by caliper. 14-22 days post implant mice with tumors ranging from 100-300 mm^3 were selected for enrollment on study and randomized to experimental groups.

PK/PD experiment

Table SI-22. Plasma concentration, normalized tumor 2-HG concentration and percent tumor 2-HG inhibition by **IDH889** following a single oral dose at 200 mg/kg dose in HCHZ2H1 xenograft model.

Time post dose (h)	Total IDH889 (nM) (Mean ± SD)	Calculated free IDH889 (nM) (Mean ± SD)	Normalized 2-HG (ng/mg sample weight) (Mean ± SEM)	% 2-HG Inhibition (Mean ± SEM)
0	(Untreated)	-	595 ± 48	100 ± 8
2	19529 ± 4369	391 ± 87	465 ± 124	78 ± 21
4	10354 ± 4142	207 ± 4	311 ± 57	53 ± 10
8	9577 ± 1717	192 ± 4	161 ± 24	27 ± 4
12	7863 ± 976	157 ± 3	156 ± 45	27 ± 8
16	390 ± 58	7.8 ± 0.2	192 ± 46	32 ± 8
20	46 ± 2	ND	425 ± 15	71 ± 2

24	ND	ND	548 ± 89	92 ± 15
36	ND	ND	773 ±149	130 ± 25

Table SI-22 notes: The LLOQ for IDH889 was 10 nM; ND (not determined); fu (fraction unbound) in mouse plasma: 0.02

Table SI-23. Normalized tumor 2-HG concentration and percent tumor 2-HG inhibition by **IDH889** following a four consecutive oral doses at 25 mg/kg (12:12) dose in HCHZ2H1 xenograft model.

Time post first dose (h)	Normalized 2-HG (ng/mg protein) (Mean ± SEM)	% 2-HG Inhibition (Mean ± SEM)
24	93 ± 29	28 ± 8
36	35 ± 9	10 ± 3
46	31 ± 20	9 ± 6
48	31 ± 11	9 ± 3
54	46 ± 35	14 ±10
72	69 ± 17	21 ±5

Female nude mice bearing HCHZ2H1 tumors were administered either a single dose of 200 mg/kg or four consecutive doses (every 12 hours) of 25 mg/kg of IDH889 in 25% PEG300; 10% Cremophor EL; 10% Solutol; 3% 0.2N HCl, and 52% WFI, pH=3.5, by oral gavage. Mice that were treated with a single, 200 mg/kg dose of IDH889 were euthaized by carbon dioxide inhalation at 0 (untreated), 2, 4, 8, 12, 16, 20, 24, and 36 hours following treatment (n=3/time-point). Blood was collected by cardiac puncture into EDTA-lined microtainers (BD Microtainer Tubes, Cat No 365974, BD Diatnostics, Franklin Lakes, NJ), placed on wet ice and centrifuged at 13,200 rpm at 4° C within 30 minutes of collection. Plasma supernatant was collected into a 96 well plate and stored at -80° C until PK analysis. Tumors were collected into 15 ml geno/grinder tube (Pre-Cleaned 5 mL Polycarbonate Vial Set, SPEX SamplePrep LLC, 15 Liberty Street, Metuchen, NJ, USA, Catalog# 2240-PC) , snap-frozen in liquid nitrogen and stored at -80° C until 2-HG analysis. For the 25 mg/kg multi-dose study, five (n=5) mice were treated with 25 mg/kg IDH889 in 25% PEG300; 10% Cremophor EL; 10% Solutol; 3% 0.2N HCl, and 52% WFI, pH=3.5, by oral gavage every 12 hours**.** Just prior to first treatment and 24 (just prior to 3rd dose), 36 (just prior to 4th , final, dose), 46, 48, 54 and 72 hours following first dose animals were anesthetized with

continuous flow of 2-4% isoflurane/oxygen mixture using the Integrated Multi Patient Anesthesia Center (IMPAC6) and induction chamber (Vetequip, Inc., Pleasanton, CA). After disinfecting the tumor area with 70% ethanol, fine needle aspirate biopsies (FNA) were collected by inserting a 22 G needle attached to a 20ml syringe into the tumor mass and gently drawing back on syringe. FNA biopsies were flushed from needle with 270 µl of 80% methanol and were snap-frozen in liquid nitrogen and stored at -80° C until 2-HG analysis.

Tumors 2-HG levels were normalized to amount of pulverized tumor used for extraction; FNA levels were normalized to total protein as determined by bicinchoninic acid detection (Pierce BCA Protein Assay Kit, Cat No 23227, Thermo Fisher Scientific, Waltham, MA). Percent 2-HG inhibition was calculated relative to untreated or pre-treated controls.

Determination of tumor 2-HG level

Tumor fragments of approximately 50 mg were placed into 15 ml geno/grinder tube (Pre-Cleaned 5 mL Polycarbonate Vial Set, SPEX SamplePrep LLC, 15 Liberty Street, Metuchen, NJ, USA, Catalog# 2240-PC), snap frozen in liquid nitrogen, then transferred to -80°C until extraction. For extraction, geno/grinder tubes with tumor were placed on dry ice. The geno/grinder adaptor and cover was chilled on dry ice, then adaptor was loaded with sample tubes, placed in the geno/grinder (SPEX SamplePrep LLC, Catalog# 2010-geno/grinder) and homogenized for 30 seconds. Samples were then removed from the adaptor and set on dry ice. 2-10 mg of pulverized tumor sample was weighed out and transferred to a fresh 2 ml screw-top tube on dry ice. Two-hundred microliters (200 µl) of 80% cold methanol for every mg of tumor powder was added, then tubes vortexed until sample fully resuspended. Samples were sonicated for 10 minutes in an ice-water bath, then incubated on dry ice for a minimum of 30 minutes. Samples were then centrifuged for 10 minutes at 13,200 rpm at 4ºC. Supernatants were diluted 1:25 in 80% methanol and were transferred to a 96 well plate, sealed using LC-MS/MS plate sealer and stored at -80C until LC-MS/MS analysis**.**

FNA biopsies were vortexed, incubated on dry ice for 30 minutes and centrifuged at 13,200 rpm at 4 C for 10 minutes. Supernatants were diluted 1:25 in 80% methanol and were transferred to a 96 well plate, sealed using LC-MS/MS plate sealer and stored at -80C until LC-MS/MS analysis. Pelleted material was reserved for total protein concentration determination.

The growth of the HCT116$^{IDH1\ R132H/+}$ cell lines used in our in vitro and in vivo studies are not dependent upon mutant IDH1, and therefore the in vitro and in vivo growth is not impacted by selective mutant IDH1 inhibitors.

Table SI-24. $IDH1^{R132C}$ and $IDH1^{WT}$ biochemical activity

Compound	$IDH1^{R132C}$ IC_{50} / μM	$IDH1^{WT}$ IC_{50} / μM
1f / IDH125	0.150	>50
2a	11.3	>25
2b	4.6	>25
2c	8.5	>25
2d	ND	>25
3b	2.4	>25
3c	1.5	>25
5a	0.618	>25
5f	0.184	13
5g	0.083	2.9
5h	0.353	>25
5n	1.567	>25
5r	0.324	24.6
5s / IDH662	0.041	1.03
5v	0.056	3.65
5w	ND	12.3
5x / IDH889	0.072	1.375