SUPPORTING INFORMATION

Structure–Activity Relationship Studies for Enhancer of Zeste Homologue 2 (EZH2) and Enhancer of Zeste Homologue 1 (EZH1) Inhibitors

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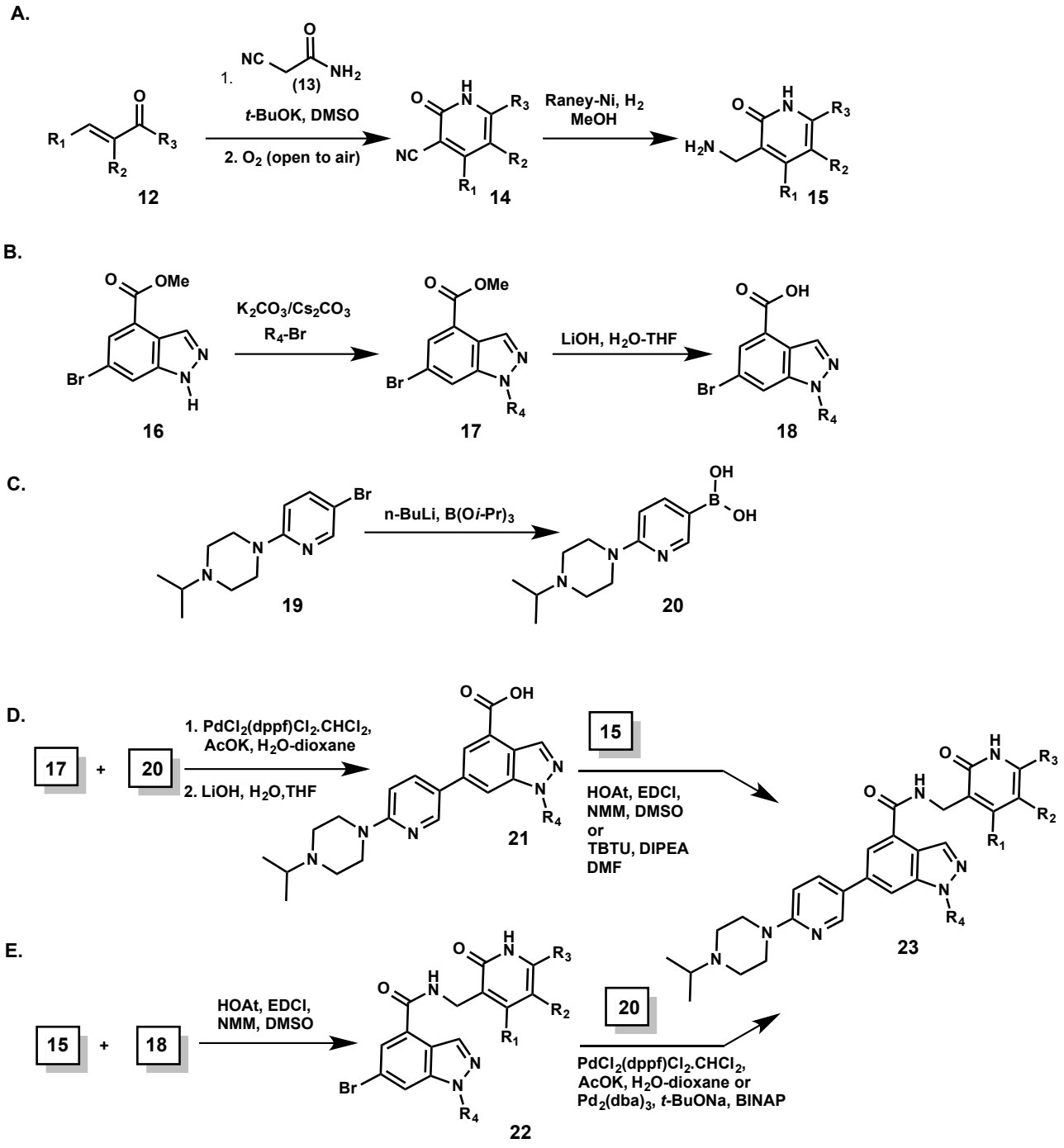
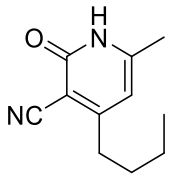
Chemistry General Procedures: HPLC spectra for all compounds were acquired using an Agilent 1200 Series system with DAD detector. Chromatography was performed on a 2.1×150 mm Zorbax 300SB-C18 5 μm column with water containing 0.1% formic acid as solvent A and acetonitrile containing 0.1% formic acid as solvent B at a flow rate of 0.4 mL/min. The gradient program was as follows: 1% B (0−1 min), 1−99% B (1−4 min), and 99% B (4−8 min). High-resolution mass spectra (HRMS) data were acquired in positive ion mode using an Agilent G1969A API-TOF with an electrospray ionization (ESI) source. Nuclear Magnetic Resonance (NMR) spectra were acquired on a Bruker DRX-600 spectrometer with 600 MHz for proton (^{1}H NMR) and 150 MHz for carbon (^{13}C NMR); chemical shifts are reported in (δ). Data are reported as follows: chemical shifts (δ), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet); coupling constant(s) (*J*) in Hz; integration. Unless otherwise noted, NMR data were collected at 25 °C. Flash column chromatography was performed using a TeledyneISCO Rf+ system. Preparative HPLC was performed on Agilent Prep 1200 series with UV detector set to 254 nm. Samples were injected onto a Phenomenex Luna 75 x 30 mm, 5 mm, C_{18} column at room temperature. The flow rate was 40 mL/min. A linear gradient was used with 10% (or 50%) of MeOH (A) in H_2O (with 0.1 % TFA) (B) to 100% of MeOH (A). All final compounds had > 95% purity by either UV absorbance at 254 nm during tandem liquid chromatography/mass spectrometry (LCMS) or by the HPLC methods described above.

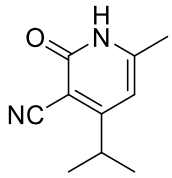
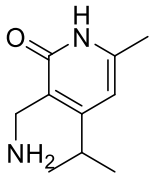
Scheme 1. General syntheses of key intermediates and derivatives of **5** for SAR studies.



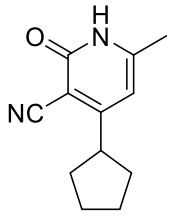
General Procedure C (Scheme 1A): Synthesis of 2-oxo-1,2-dihydropyridine-3-carbonitrile analogues and 3-(aminomethyl)pyridin-2(1H)-one analogues. Cyanoacetamide (**13**) (5.5 mmol, 1.1 eq) and potassium tert-butoxide (5.5 mmol, 1.1 eq) were dissolved in DMSO (10 mL) and stirred at room temperature under N_2 for 15 minutes before addition of (E)-pent-3-en-2-one analogues (**12**) (5.0 mmol, 1.0 eq)). The mixture was kept under N_2 for 3 hours before the addition of more potassium tert-butoxide (15.0 mmol, 3.0 eq), and then stirred overnight open to air at room temperature. The reaction was monitored via LC/MS, and after completion, diluted with H_2O, and aqueous HCl (10%) was added to precipitate the desired product (**14**). 2-oxo-1,2-dihydropyridine-3-carbonitrile analogues (2.0 mmol) was then dissolved in MeOH (15 mL) and ammonia in methanol (1.0 mL, 7.0 N) and was added a catalytic amount of Raney-Ni (20% wt). The contents were then purged and kept under H_2 overnight. The reaction was monitored via LC/MS. After completion, the contents were filtered, concentrated *in vacuo* to obtain the 3-(aminomethyl)pyridin-2(1H)-one analogues (**15**) and used for the next step without further characterization in most of the cases. The corresponding nitriles (**14**) for the preparation of compounds **24**, **25**, **33**, **34** and **39-43** were purchased and used directly as they are.



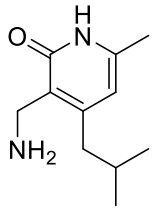
4-Butyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (Intermediate for the synthesis of compound **26**) Yield: 5.30 g (35%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.32 (s, 1H), 6.18 (s, 1H), 2.56 (t, 2H, J = 7.6 Hz), 2.21 (s, 3H), 1.56-1.51 (m, 2H), 1.33-1.27 (m, 2H), 0.88 (t, 3H, J = 7.3 Hz). HRMS (m/z) for $C_{11}H_{15}N_2O^+$ $[M + H]^+$: calculated 191.1179, found 191.1182.

4-Isopropyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (Intermediate for the synthesis of compound **27)** Yield: 676 mg (29%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H), 6.24 (s, 1H), 3.07-2.97 (m, 1H), 2.21 (s, 3H), 1.15 (d, 6H, J = 6.9 Hz). MS (m/z) $[M + H]^+$: 177.2. **3-(aminomethyl)-4-isopropyl-6-methylpyridin-2(1*H*)-one (**Intermediate for the synthesis of compound **27)** ^{1}H-NMR (400 MHz, DMSO-d_6) δ 7.88 (br s, 2H), 6.12 (s, 1H), 3.85 (s, 2H), 3.10-3.04 (m, 1H), 2.19 (s, 3H), 1.11 (d, 6H, J = 6.8 Hz). MS (m/z) $[M + H]^+$: 181.2.

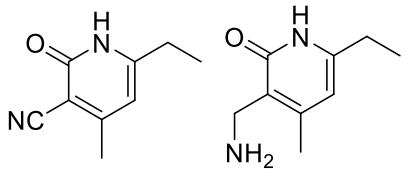


4-Cyclopentyl-6-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (Intermediate for the synthesis of compound **28**) Yield: 107 mg (67%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.33 (s, 1H), 6.26 (s, 1H), 3.10 (p, 1H, J = 8.2 Hz), 2.24 (s, 3H), 2.01-1.96 (m, 2H), 1.81-1.76 (m, 2H), 1.70-1.65 (m, 2H), 1.60-1.55 (m, 2H). HRMS (m/z) for $C_{12}H_{15}N_2O^+$ $[M + H]^+$: calculated 203.1179, found 203.1180.

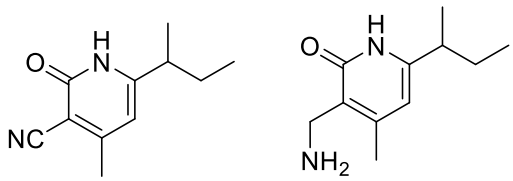


3-(Aminomethyl)-4-isobutyl-6-methylpyridin-2(1*H*)-one (Intermediate for the synthesis of compound **29**) Yield: 158 mg (10%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 11.90 (s, 1H), 7.90 (s, 2H), 5.98 (s, 1H), 3.82 (s, 2H), 2.37 (d, 2H, J = 7.3 Hz) 2.17 (s, 3H), 1.80-1.75 (m, 1H), 0.88

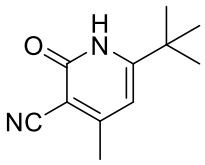
(d, 6H, J = 6.6 Hz). HRMS (m/z) for $C_{11}H_{19}N_2O^+$ $[M + H]^+$: calculated 195.1492, found 195.1497.



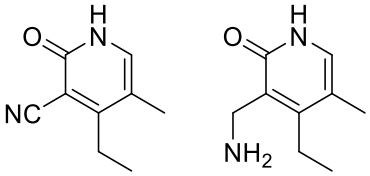
6-Ethyl-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (Intermediate for the synthesis of compound **30)** Yield: 525 mg (32%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.29 (s, 1H), 6.18 (s, 1H), 2.48 (q, 2H, J = 7.9Hz), 2.30 (s, 3H), 1.13 (t, 3H, J = 7.6Hz). HRMS (m/z) for $C_9H_{11}N_2O^+$ $[M + H]^+$: calculated 163.0866, found 163.0881. **3-(aminomethyl)-6-ethyl-4-methylpyridin-2(1*H*)-one** ^{1}H-NMR (600 MHz, Methanol-d_4) δ 6.17 (s, 1H), 4.02 (s, 2H), 2.55 (q, 2H, J = 7.9 Hz), 2.31 (s, 3H), 1.22 (t, 3H, J = 7.6 Hz). MS (m/z) $[M + H]^+$: 167.1.



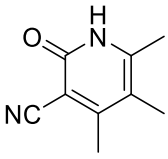
6-(*sec*-Butyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (Intermediate for the synthesis of compound **31**) Yield: 590 mg (38%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.26 (s, 1H), 6.23 (s, 1H), 2.59-2.53 (m, 1H), 2.33 (s, 3H), 1.64-1.57 (m, 1H), 1.56-1.49 (m, 1H), 1.17 (d, 3H, J = 7.0 Hz), 0.79 (t, 3H, J = 7.4 Hz). HRMS (m/z) for $C_{11}H_{15}N_2O^+$ $[M + H]^+$: calculated 191.1179, found 191.1183. **3-(aminomethyl)-6-(*sec*-butyl)-4-methylpyridin-2(1*H*)-one (**Intermediate for the synthesis of compound **31**) ^{1}H-NMR (600 MHz, Methanol-d_4) δ 6.20 (s, 1H), 4.05 (s, 2H), 2.62-2.56 (m, 1H), 2.34 (s, 3H), 1.73-1.66 (m, 1H), 1.66-1.59 (m, 1H), 1.27 (d, 3H, J = 7.0 Hz), 0.90 (t, 3H, J = 7.4 Hz). HRMS (m/z) for $C_{11}H_{19}N_2O^+$ $[M + H]^+$: calculated 195.1492, found 195.1494.



6-(*tert*-Butyl)-4-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (Intermediate for the synthesis of compound **32**) Yield: 400 mg (30%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 6.34 (s, 1H), 2.44 (s, 3H), 1.33 (s, 9H). HRMS (m/z) for $C_{11}H_{15}N_2O^+$ $[M + H]^+$: calculated 191.1179, found 191.1189.

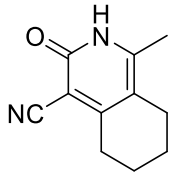


4-Ethyl-5-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (Intermediate for the synthesis of compound **35**) Yield: 271 mg (12%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.25 (s, 1H), 7.56 (s, 1H), 2.64 (q, 2H, J = 7.6 Hz), 2.05 (s, 3H), 1.14 (t, 3H, J = 7.6 Hz). HRMS (m/z) for $C_9H_{11}N_2O^+$ $[M + H]^+$: calculated 163.0866, found 163.0874. **3-(aminomethyl)-4-ethyl-5-methylpyridin-2(1*H*)-one** (Intermediate for the synthesis of compound **35**) ^{1}H-NMR (600 MHz, Methnanol-d_4) δ 7.30 (s, 1H), 4.08 (s, 2H), 2.70 (q, 2H, J = 6.9 Hz), 2.15 (s, 3H), 1.16 (t, 3H, J = 6.7 Hz). HRMS (m/z) for $C_9H_{15}N_2O^+$ $[M + H]^+$: calculated 167.1179, found 167.1189.

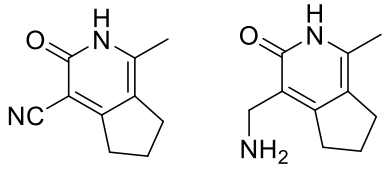


4,5,6-Trimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (Intermediate for the synthesis of compound **36**) Yield: 626 mg (38%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.21 (s, 1H), 2.30 (s,

3H), 2.23 (s, 3H), 1.91 (s, 3H). HRMS (m/z) for $C_9H_{11}N_2O^+$ $[M + H]^+$: calculated 163.0866, found 163.0867.



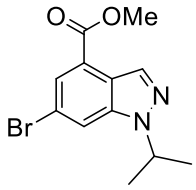
1-Methyl-3-oxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (Intermediate for the synthesis of compound **37**) Yield 861 mg (57%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.32 (s, 1H), 2.72-2.68 (m, 2H), 2.37-2.33 (m, 2H), 2.19 (s, 3H), 1.67-1.64 (m, 4H). HRMS (m/z) for $C_{11}H_{13}N_2O^+$ $[M + H]^+$: calculated 189.1022, found 189.1024.

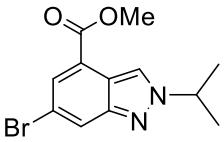


1-Methyl-3-oxo-3,5,6,7-tetrahydro-2*H*-cyclopenta[c]pyridine-4-carbonitrile (Intermediate for the synthesis of compound **38**) Yield 1.032 g (44%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 12.11 (s, 1H), 2.87 (t, 2H, J = 7.6 Hz), 2.62 (t, 2H, J = 7.3 Hz), 2.18 (s, 3H), 2.01-1.96 (m, 2H). HRMS (m/z) for $C_{10}H_{11}N_2O^+$ $[M + H]^+$: calculated 175.0866, found 175.0868. **4-(aminomethyl)-1-methyl-2,5,6,7-tetrahydro-3*H*-cyclopenta[c]pyridin-3-one** (Intermediate for the synthesis of compound **38**) ^{1}H-NMR (600 MHz, Methanol-d_4) δ 3.98 (s, 2H), 2.93 (t, 2H, J = 12 Hz), 2.77 (t, 2H, J = 9.0 Hz), 2.27 (s, 3H), 2.16-2.08 (m, 2H). MS (m/z) $[M + H]^+$: 179.2.

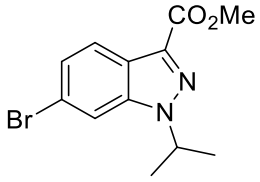
General Procedure D1 (Scheme 1B): Alkylation of methyl 6-bromo-1-alkyl-1H-indazole-4-carboxylate. To a stirred solution of methyl 6-bromo-1H-indazole-4-carboxylate (**16**) (2.0 mmol, 1.0 eq) in acetonitrile (50 mL), Cs_2CO_3 (3.0-4.0 mmol, 1.5-2.0 eq) was added followed by alkyl halide (2.4-4.0 mmol, 1.2-2.0 eq) and the reaction mixture stirred at 25-60 °C overnight. On completion, the reaction mixture was filtered, and the crude product was then purified by flash column chromatography (gradient from 100% hexane to 10% ethyl acetate) to yield methyl 6-bromo-1-alkyl-1H-indazole-4-carboxylate (**17**) and as well as its isomer (methyl 6-bromo-2-alkyl-2H-indazole-4-carboxylate). Then the desired isomer was dissolved in THF/H_2O, was added LiOH (2.0 eq), stirred for overnight, and concentrated. The crude product (**18**) was directly used for the next step.

General Procedure D2 (Scheme 1B): Alkylation of methyl 6-bromo-1-alkyl-1H-indazole-4-carboxylate. To a stirred solution of methyl 6-bromo-1H-indazole-4-carboxylate (**16**) (2.0 mmol, 1.0 eq) in DMF (50 mL), was added K_2CO_3 (6.0 mmol, 3.0 eq) followed by alkyl halide (2.4-4.0 mmol, 1.2-2.0 eq) and the reaction mixture stirred at 25-60 °C for overnight. On completion, the reaction mixture was filtered, and the crude product was purified by flash column chromatography (gradient from 100% hexane to 10% ethyl acetate) to yield the methyl 6-bromo-1-alkyl-1H-indazole-4-carboxylate (**17**) and its N-2 isomer (methyl 6-bromo-2-alkyl-2H-indazole-4-carboxylate). The desired alkylation product was then dissolved in THF/H_2O, was added LiOH (2.0 eq), stirred for overnight. After concentration, the crude product (**18**) was directly used for the next step.

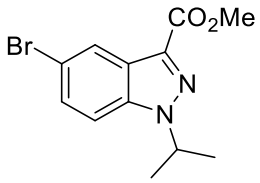




Methyl 6-bromo-1-isopropyl-1*H*-indazole-4-carboxylate (Intermediates for the synthesis of compounds **5** and **44**) was prepared according to the general procedure D1. Yield: 0.106 g (45%). ^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 8.00 (s, 1H), 7.83 (s, 1H), 4.83-4.78 (m, 1H), 4.02 (s, 3H), 1.60 (d, 6H, J = 6.7 Hz). MS (m/z) $[M + H]^{+}$: 297.2 and 299.2. Yield isomer: 0.096 g (41%). ^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 8.10 (s, 1H), 7.96 (d, 1H, J = 1.2 Hz), 4.85-4.78 (m, 1H), 3.98 (s, 3H), 1.67 (d, 6H, J = 6.7 Hz). MS (m/z) $[M + H]^{+}$: 297.2 and 299.2.

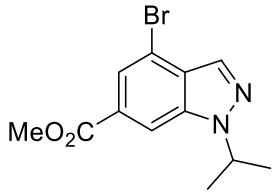


Methyl 6-bromo-1-isopropyl-1*H*-indazole-3-carboxylate (Intermediate for the synthesis of compound **45**) was prepared according to the general procedure D1. Yield: 0.100 g (43%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.99 (s, 1H), 7.89 (d, 1H, J = 9.0 Hz), 7.34 (d, 1H, J = 8.9 Hz), 5.96-5.90 (m, 1H), 4.03 (s, 3H), 1.62 (d, 6H, J = 6.6 Hz). MS (m/z) $[M + H]^{+}$: 297.2 and 299.2.

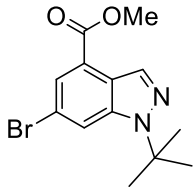


Methyl 5-bromo-1-isopropyl-1*H*-indazole-3-carboxylate (Intermediate for the synthesis of compound **46)** was prepared according to the general procedure D1. Yield: 0.100 g (43%). ^{1}H

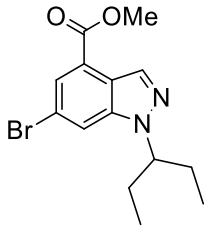
NMR (600 MHz, Chloroform-*d*) δ 8.19 (d, 1H, J = 1.7 Hz), 7.69 (d, 1H, J = 9.0 Hz), 7.41 (dd, 1H, J = 1.8 Hz, J = 9.1 Hz), 5.97-5.91 (m, 1H), 4.04 (s, 3H), 1.63 (d, 6H, J = 6.6 Hz). MS (m/z) $[M + H]^+$: 297.0 and 299.0.



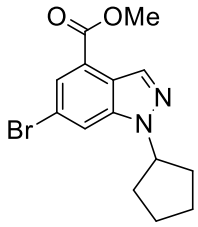
Methyl 4-bromo-1-isopropyl-1*H*-indazole-6-carboxylate (Intermediate for the synthesis of compound **47**) was prepared according to the general procedure D1. Yield: 0.100 g (43%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.17 (s, 1H), 8.06 (s, 1H), 7.96 (m, 1H), 4.94-4.87 (m, 1H), 3.98 (s, 3H), 1.61 (d, 6H, J = 6.7 Hz). MS (m/z) $[M + H]^+$: 297.0 and 299.0.



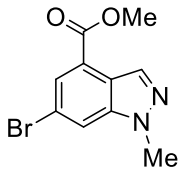
Methyl 6-bromo-1-(*tert*-butyl)-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **51**) was prepared according to the general procedure D1. Yield: 0.015 g (2.5%). ^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.44 (d, 1H, J = 0.6 Hz), 8.08 (d, 1H, J = 2.4 Hz), 7.99 (d, 1H, J = 1.5 Hz), 4.01 (s, 3H), 1.78 (s, 9H). MS (m/z) $[M + H]^+$: 310.9 and 312.9.



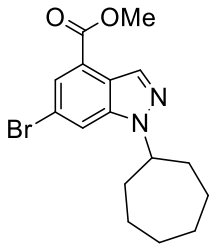
Methyl 6-bromo-1-(pentan-3-yl)-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **52**) was prepared according to the general procedure D1. Yield: 0.258 g (41%). ^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 8.00 (d, 1H, J = 1.2 Hz), 7.81 (s, 1H), 4.25-4.20 (m, 1H), 4.02 (s, 3H), 2.14-2.06 (m, 2H), 1.96-1.90 (m, 2H), 0.71 (t, 6H, J = 7.3 Hz). HRMS (m/z) for $C_{14}H_{18}BrN_2O_2^+$ $[M + H]^+$: calculated 325.0546 and 327.0526, found 325.0541 and 327.0521.



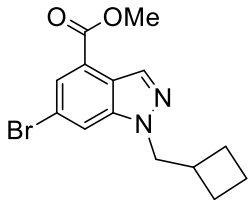
Methyl 6-bromo-1-cyclopentyl-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **53**) was prepared according to the general procedure D1. Yield: 0.250 g (40%). ^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.44 (s, 1H), 7.99 (s, 1H), 7.84 (s, 1H), 4.97-4.92 (m, 1H), 4.01 (s, 3H), 2.20-2.16 (m, 4H), 2.01-1.95 (m, 2H), 1.79-1.72 (m, 2H). MS (m/z) $[M + H]^+$: 323.2 and 325.2.



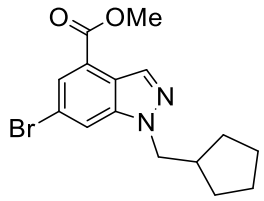
Methyl 6-bromo-1-methyl-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **55**) was prepared according to the general procedure D1. Yield: 0.290 g (55%). ^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.43 (s, 1H), 8.01 (s, 1H), 7.79 (s, 1H), 4.09 (s, 3H), 4.02 (s, 3H). MS (m/z) $[M + H]^+$: 269.0. HRMS (m/z) for $C_{10}H_{10}BrN_2O_2^+$ $[M + H]^+$: calculated 268.9920 and 270.9900, found 268.9926 and 270.9908.



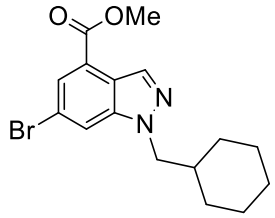
Methyl 6-bromo-1-cycloheptyl-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **56**) was prepared according to the general procedure D2. Yield: 0.100 g (14.5%). ^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.44 (s, 1H), 7.99 (d, 1H, J = 1.3 Hz), 7.82 (s, 1H), 4.60-4.55 (m, 1H), 2.23-2.17 (m, 2H), 2.10-2.06 (m, 2H), 1.92-1.87 (m, 2H), 1.74-1.66 (m, 4H), 1.63-1.57 (m, 2H), 1.56 (s, 3H). MS (m/z) $[M + H]^+$: 350.9 and 352.9.



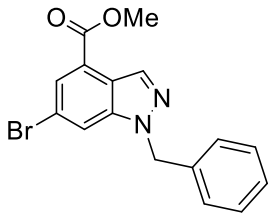
Methyl 6-bromo-1-(cyclobutylmethyl)-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **57**) was prepared according to the general procedure D1. Yield: 0.180 g (28%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.43 (s, 1H), 7.99 (s, 1H), 7.80 (s, 1H), 4.37 (dd, 2H, J = 1.5 Hz, J = 7.2 Hz), 4.02 (d, 3H, J = 1.7 Hz), 2.93-2.88 (m, 1H), 2.06-2.01 (m, 2H), 1.92-1.80 (m, 4H). MS (m/z) $[M + H]^+$: 323.2 and 325.2.



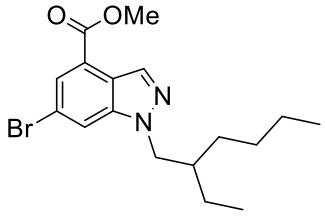
Methyl 6-bromo-1-(cyclopentylmethyl)-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **58**) was prepared according to the general procedure D2. Yield: 0.330 g (50%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.44 (s, 1H), 8.00 (d, 1H, J = 1.5 Hz), 7.80 (s, 1H), 4.29 (d, 2H, J = 7.6 Hz), 4.02 (s, 3H), 2.56-2.51 (m, 1H), 1.69-1.65 (m, 4H), 1.60-1.54 (m, 2H), 1.33-1.27 (m, 2H). MS (m/z) $[M + H]^+$: 337.0 and 339.0.



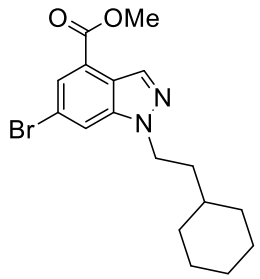
Methyl 6-bromo-1-(cyclohexylmethyl)-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **59**) was prepared according to the general procedure D1. Yield: 0.330 g (48%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 8.00 (s, 1H), 7.77 (s, 1H), 4.18 (d, 2H, J = 7.2 Hz), 4.02 (s, 3H), 2.02-1.97 (m, 1H), 1.72-1.66 (m, 4H), 1.25-1.15 (m, 4H), 1.05-0.99 (m, 2H). MS (m/z) $[M + H]^+$: 351.2 and 353.2.



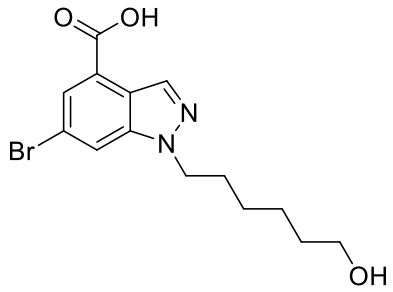
Methyl 1-benzyl-6-bromo-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **60**) was prepared according to the general procedure D1. Yield: 0.350 g (52%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 8.00 (d, 1H, J = 1.1 Hz), 7.71 (s, 1H), 7.33-7.28 (m, 3H), 7.17 (d, 2H, J = 7.1 Hz), 5.60 (s, 2H), 4.02 (s, 3H). MS (m/z) $[M + H]^+$: 345.0 and 346.0.



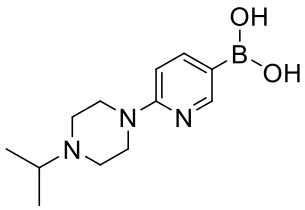
Methyl 6-bromo-1-(heptan-3-yl)-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **61**) was prepared according to the general procedure D1. Yield: 0.250 g (35%). ^{1}HNMR (600 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 8.00 (d, 1H, J = 1.3 Hz), 7.76 (s, 1H), 4.25 (d, 2H, J = 7.3 Hz), 4.02 (s, 3H), 2.06-2.01 (m, 1H), 1.35-1.24 (m, 8H), 0.90 (t, 3H, J = 7.5 Hz), 0.86 (t, 3H, J = 6.9 Hz). HRMS (m/z) for $C_{17}H_{24}BrN_2O_2^+$ $[M + H]^+$: calculated 367.1016 and 369.0995, found 367.1010 and 369.0991.



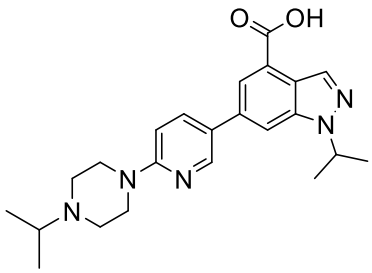
Methyl 6-bromo-1-(2-cyclohexylethyl)-1*H*-indazole-4-carboxylate (Intermediate for the synthesis of compound **62**) was prepared according to the general procedure D1. Yield: 0.198 g (27%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.44 (s, 1H), 8.00 (d, 1H, J = 1.3 Hz), 7.77 (s, 1H), 4.39 (t, 2H, J = 7.5 Hz), 4.02 (s, 3H), 1.82-1.64 (m, 7H), 1.29-1.13 (m, 4H), 1.01-0.95 (m, 2H). HRMS (m/z) for $C_{17}H_{22}BrN_2O_2^+$ $[M + H]^+$: calculated 365.0859 and 367.0839, found 365.0856 and 367.0837.



6-Bromo-1-(6-hydroxyhexyl)-1*H*-indazole-4-carboxylic acid (Intermediate for the synthesis of compound **63**) Yield: 420 mg (31%). ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.31 (d, 1H, J = 0.8 Hz), 8.29 (t, 1H, J = 1.6 Hz), 7.76 (d, 1H, J = 1.5 Hz), 4.39 (t, 2H, J = 7.0 Hz), 3.30 (t, 2H, J = 6.4 Hz), 1.81-1.69 (m, 2H), 1.12-1.40 (m, 8H). MS (m/z) $[M + H]^+$: 340.9 and 342.9.



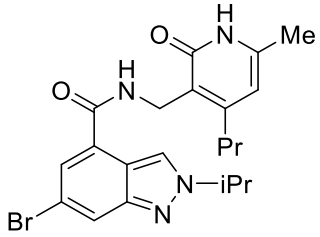
General Procedure E (Scheme 1C): Synthesis of 6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)boronic acid (20). To a solution of 1-(5-bromopyridin-2-yl)-4-isopropylpiperazine (**19**) (2.50 g, 8.80 mmol) in THF (100 mL) was added BuLi dropwise (2.5 M in hexanes, 4.22 mL, 10.56 mmol) under argon atmosphere at -78 ^{o}C. The resulting mixture was stirred for 30 min at -78^{o}C, and then triisopropyl borate (2.44 mL, 10.56 mmol) added dropwiase to the reaction mixture. The mixture was slowly warmed to -15 °C, and was quenched with saturated NH_4Cl. After removal of the solvent under reduced pressure, it was redisoveld in water and extracted with ether to remove impurity, the aqueous phase was collected and purified by reverse flash column chromatography (gradient from 100% water to 50% methanol) to yield the desired product (**20**) (1.80 g, 82%) as solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.41 (d, 1H, J = 1.7 Hz), 7.83 (s, 2H), 7.79 (dd, 1H, J = 2.0 Hz, J = 8.6 Hz), 6.69 (d, 1H, J = 8.6 Hz), 3.46-3.43 (m, 4H), 2.66-2.56 (m, 1H), 2.47-2.43 (m, 4H), 0.94 (d, 6H, J = 6.5 Hz). HRMS (m/z) for $C_{12}H_{21}BN_3O_2^+$ $[M + H]^+$: calculated 250.1721, found 250.1727.



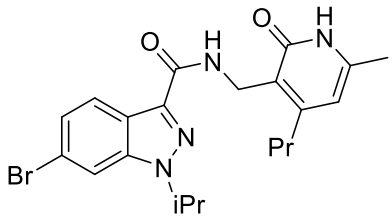
1-Isopropyl-6-(6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)-1H-indazole-4-carboxylic acid (21)

The solution of methyl 6-bromo-1-isopropyl-1H-indazole-4-carboxylate (0.225 g, 0.757 mmol), (6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)boronic acid (0.227 g, 0.908 mmol), AcOK (0.223 g, 2.271 mmol) and Pd(dppf)Cl_2·CH_2Cl_2 (33 mg) in 1,4-dioxane (50 mL)/water (10 mL), was heated to 80 °C overnight and cooled to room temperature. The crude mixture was then purified by flash column chromatography (gradient from 100% hexane to 100% ethyl acetate) to yield the coupling compound (300 mg, 90%). To a stirring solution of Methyl 1-isopropyl-6-(6-(4-isopropylpiperazin-1-yl)pyridin-3-yl)-1H-indazole-4-carboxylate (300 mg, 0.712 mmol, 1 eq.) in THF/H_2O (20 mL/5 mL) was added LiOH (anhydrous, 1.423 mmol. 34 mg, 2.0 eq.) and the resulting mixture was stirred overnight at room temperature. The disappearance of starting material was monitored by TLC, and adjusted PH = 6-7 by using aqueous HCl (1 N). The crude product was then purified by flash column chromatography (gradient from 100% dichloromethane to 15% methanol) to yield the title compound (**21**) (270 mg, 93%) as solid. ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.60 (d, 1H, J = 2.4 Hz), 8.45 (s, 1H), 8.12 (d, 1H, J = 1.3 Hz), 8.09 (dd, 1H, J = 2.5 Hz, J = 8.8 Hz), 8.07 (s, 1H), 7.10 (d, 1H, J = 8.9 Hz), 5.14-5.10 (m, 1H), 4.63 (br s, 4H), 3.65-3.59 (m, 5H), 1.59 (d, 6H, J = 6.6 Hz), 1.43 (d, 6H, J = 6.7 Hz). HRMS (m/z) for $C_{23}H_{30}N_5O_2^+$ $[M + H]^+$: calculated 408.2394, found 408.2408.

General Procedure F (Scheme 1E): (intermediates for the compounds **44-62**)**.** Crude 3-(Aminomethyl)pyridin-2(1H)-one analogues (**15**) (0.1 mmol), 6-bromo-1-alkyl-1H-indazole-4-carboxylic acid (**18**) (0.05-0.08 mmol), NMM (0.15 mmol), HOAt (11 mg, 0.10 mmol) and EDCI (0.10 mmol) were dissolved in DMSO (2 mL). The contents were stirred at room temperature overnight, monitored by LC/MS, quenched with water, the desired product (**22**) was separated out, filtered, get the compound (**22**) as solid.

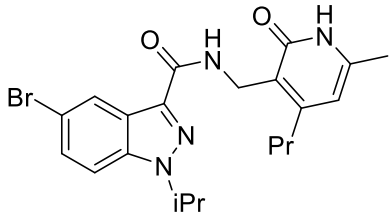


6-Bromo-2-isopropyl-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-2*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **44**) Yield: 100 mg (90%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.59 (s, 1H), 7.94 (s, 1H), 7.61 (s, 1H), 6.14 (s, 1H), 4.90-4.84 (m, 1H), 4.54 (s, 2H), 2.71 (t, 2H, J = 8.1 Hz), 2.26 (s, 3H), 1.64 (d, 6H, J = 6.7 Hz), 1.65-1.59 (m, 2H), 1.01 (t, 3H, J = 7.3 Hz). MS (m/z) $[M + H]^+$: 445.4 and 447.4.

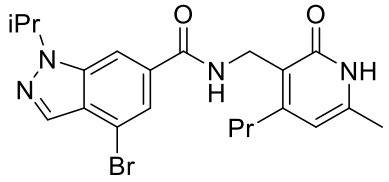


6-Bromo-1-isopropyl-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-3-carboxamide (Intermediate for the synthesis of compound **45**) Yield: 50 mg (33%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 7.85 (s, 1H), 7.70 (d, 1H, J = 8.9 Hz), 7.25 (dd, 1H, J=1.4Hz, J = 8.9 Hz), 6.14 (s, 1H), 5.52-5.48 (m, 1H), 4.56 (s, 2H), 2.73 (t, 2H, J = 7.5 Hz), 2.26

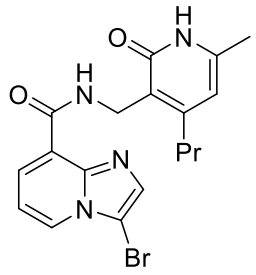
(s, 3H), 1.68-1.62 (m, 2H), 1.58 (d, 6H, J = 6.6 Hz), 1.02 (t, 3H, J = 7.4 Hz). MS (m/z) $[M + H]^+$: 445.4 and 447.4.



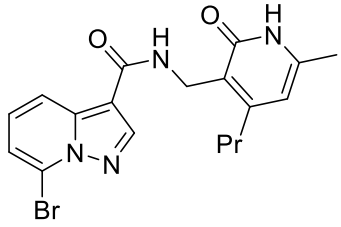
5-Bromo-1-isopropyl-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-3-carboxamide (Intermediate for the synthesis of compound **46**) Yield: 91 mg (60%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 7.95 (s, 1H), 7.60 (d, 1H, J = 9.0 Hz), 7.39 (d, 1H, J = 8.6 Hz), 6.15 (s, 1H), 5.52-5.47 (m, 1H), 4.56 (s, 2H), 2.74 (t, 2H, J = 7.5 Hz), 2.27 (s, 3H), 1.68-1.63 (m, 2H), 1.58 (d, 6H, J = 6.2 Hz), 1.03 (t, 3H, J = 6.8 Hz). MS (m/z) $[M + H]^+$: 445.1 and 447.1.



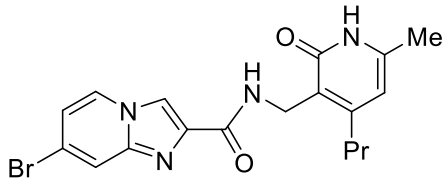
4-Bromo-1-isopropyl-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-6-carboxamide (Intermediate for the synthesis of compound **47**) Yield: 140 mg (93%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.10 (s, 1H), 8.04 (s, 1H), 7.76 (s, 1H), 6.15 (s, 1H), 5.03-4.98 (m, 1H), 4.54 (s, 2H), 2.70 (t, 2H, J = 7.5 Hz), 2.26 (s, 3H), 1.65-1.59 (m, 2H), 1.57 (d, 6H, J = 6.5 Hz), 1.00 (t, 3H, J = 7.3 Hz). MS (m/z) $[M + H]^+$: 445.1 and 447.1.



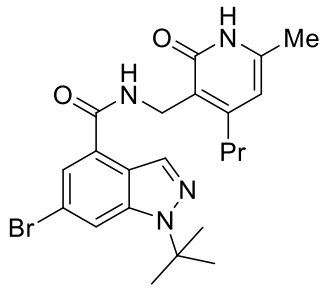
3-Bromo-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)imidazo[1,2-a]pyridine-8-carboxamide (Intermediate for the synthesis of compound **48**) Yield: 120 mg (90%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.50 (br s, 1H), 8.18 (d, 1H, J = 7.1 Hz), 7.67 (br s, 1H), 7.21 (t, 1H, J = 7.0 Hz), 6.11 (s, 1H), 4.63 (s, 2H), 2.67 (t, 2H, J = 7.8 Hz), 2.26 (s, 3H), 1.64-1.58 (m, 2H), 0.97 (t, 3H, J = 7.3 Hz). MS (m/z) $[M + H]^+$: 403.1 and 405.1.



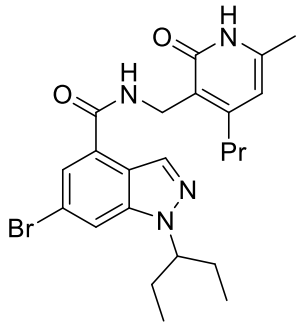
7-Bromo-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)pyrazolo[1,5-a]pyridine-3-carboxamide (Intermediate for the synthesis of compound **49**) Yield: 130 mg (97%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.51 (s, 1H), 8.30 (dd, 1H, J = 1.3Hz, J = 8.7 Hz), 7.40-7.35 (m, 2H), 6.14 (s, 1H), 4.52 (s, 2H), 2.68 (t, 2H, J = 7.8Hz), 2.26 (s, 3H), 1.64-1.58 (m, 2H), 0.98 (t, 3H, J = 7.4Hz). MS (m/z) $[M + H]^+$: 403.1 and 405.1.



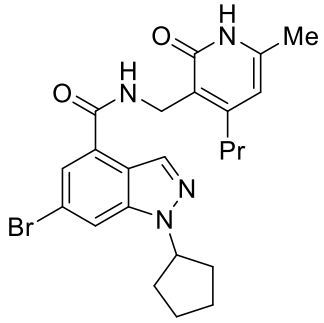
7-Bromo-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)imidazo[1,2-a]pyridine-2-carboxamide (Intermediate for the synthesis of compound **50**) Yield: 80 mg (48%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 11.58 (s, 1H), 8.53 (d, 1H, J = 7.1 Hz), 8.38 (s, 1H), 8.22 (br s, 1H), 7.96 (s, 1H), 7.17 (d, 1H, J = 7.2 Hz), 5.89 (s, 1H), 4.32 (d, 2H, J = 5.7 Hz), 2.51 (t, 2H, J = 7.8 Hz), 2.11 (s, 3H), 1.52-1.46 (m, 2H), 0.88 (t, 3H, J = 7.3 Hz). MS (m/z) $[M + H]^+$: 403.3 and 405.3.



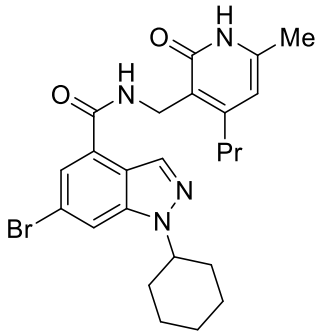
6-Bromo-1-(*tert*-butyl)-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **51**) Yield: 23 mg (97%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.27 (s, 1H), 8.17 (s, 1H), 7.61 (d, 1H, J = 1.3 Hz), 6.14 (s, 1H), 4.55 (s, 2H), 2.72 (t, 2H, J = 7.8 Hz), 2.26 (s, 3H), 1.75 (s, 9H), 1.66-1.60 (m, 2H), 1.01 (t, 3H, J = 7.3 Hz). MS (m/z) $[M + H]^+$: 459.1 and 461.1.



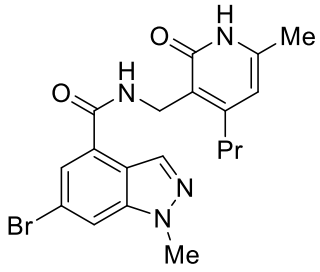
6-Bromo-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1-(pentan-3-yl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **52**) Yield: 135 mg (95%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.39 (s, 1H), 8.05 (s, 1H), 7.63 (d, 1H, J = 1.4 Hz), 6.14 (s, 1H), 4.56 (s, 2H), 4.46-4.42 (m, 1H), 2.72 (t, 2H, J = 8.1 Hz), 2.26 (s, 3H), 2.07-2.00 (m, 2H), 1.95-1.88 (m, 2H), 1.66-1.60 (m, 2H), 1.01 (t, 3H, J = 7.4 Hz), 0.67 (t, 6H, J = 7.4 Hz). MS (m/z) $[M + H]^+$: 473.1 and 475.1.



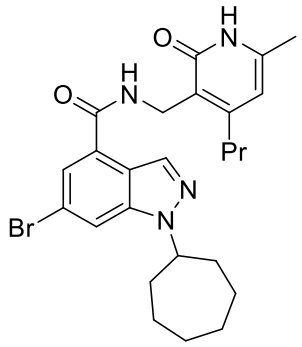
6-Bromo-1-cyclopentyl-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **53**) Yield: 160 mg (91%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.31 (s, 1H), 8.02 (s, 1H), 7.63 (s, 1H), 6.14 (s, 1H), 5.14-5.09 (m, 1H), 4.55 (s, 2H), 2.71 (t, 2H, J = 7.0 Hz), 2.26 (s, 3H), 2.21-2.15 (m, 2H), 2.10-2.05 (m, 2H), 1.98-1.93 (m, 2H), 1.80-1.74 (m, 2H), 1.66-1.50 (m, 2H), 1.01 (dt, 3H, J = 1.7 Hz, J = 7.3 Hz). MS (m/z) $[M + H]^+$: 471.1 and 473.1.



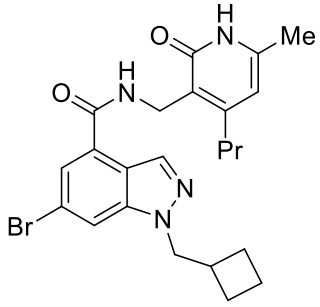
6-Bromo-1-cyclohexyl-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **54**). Yield: 65 mg (90%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.32 (s, 1H), 8.04 (s, 1H), 7.63 (d, 1H, J = 1.4 Hz), 6.14 (s, 1H), 4.58-4.53 (m, 3H), 2.72 (t, 2H, J = 7.8 Hz), 2.26 (s, 3H), 2.00-1.92 (m, 6H), 1.80-1.76 (m, 1H), 1.66-1.54 (m, 4H), 1.38-1.31 (m, 1H), 1.01 (t, 3H, J = 7.4 Hz). MS (m/z) $[M + H]^+$: 485.1 and 487.1.



6-Bromo-1-methyl-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **55**) Yield: 130 mg (93%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.31 (s, 1H), 7.99 (s, 1H), 7.65 (d, 1H, J = 1.4 Hz), 6.14 (s, 1H), 4.55 (s, 2H), 4.06 (s, 3H), 2.71 (t, 2H, J = 7.8 Hz), 2.26 (s, 3H), 1.66-1.59 (m, 2H), 1.01 (t, 3H, J = 7.4 Hz). MS (m/z) $[M + H]^+$: 417.0 and 419.0.

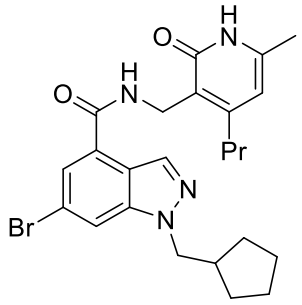


6-Bromo-1-cycloheptyl-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **56**) Yield: 87 mg (61%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 1H-NMR (600 MHz) δ 8.31 (s, 1H), 8.02 (s, 1H), 7.62 (s, 1H), 6.14 (s, 1H), 4.78-4.73 (m, 1H), 4.55 (s, 2H), 2.71 (t, 2H, J = 7.5 Hz), 2.26 (s, 3H), 2.16-2.11 (m, 2H), 2.05-2.02 (m, 2H), 1.89-1.84 (m, 2H), 1.75-1.60 (m, 8H), 1.01 (t, 3H, J = 7.1 Hz). HRMS (m/z) for $C_{25}H_{32}BrN_4O_2^+$ $[M + H]^+$: calculated 499.1703 and 501.1683, found 499.1711 and 501.1693.

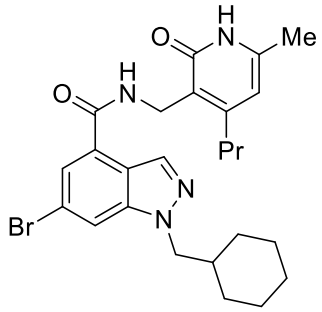


6-Bromo-1-(cyclobutylmethyl)-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **57**) Yield: 88 mg (60%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.31 (s, 1H), 8.04 (s, 1H), 7.64 (s, 1H), 6.20 (s, 1H), 4.56 (s, 2H), 4.42 (d, 2H, J = 7.2 Hz), 2.91-2.86 (m, 1H), 2.73 (t, 2H, J = 7.8 Hz), 2.28 (s,

3H), 2.00-1.96 (m, 2H), 1.93-1.82 (m, 4H), 1.65-1.61 (m, 2H), 1.01 (t, 3H, J = 7.3 Hz). HRMS (m/z) for $C_{23}H_{28}BrN_4O_2^+$ $[M + H]^+$: calculated 471.1390 and 473.1370, found 471.1397 and 473.1379.

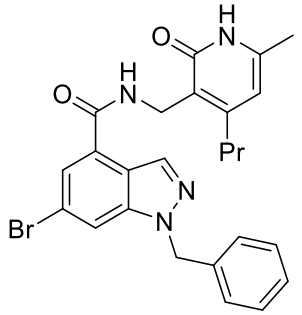


6-Bromo-1-(cyclopentylmethyl)-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **58**) Yield: 170 mg (90%). ^{1}H-NMR (600 MHz, DMSO-d_6) δ 11.53 (s, 1H), 8.61 (t, 1H, J = 4.6 Hz), 8.32 (s, 1H), 8.21 (s, 1H), 7.67 (s, 1H), 5.89 (s, 1H), 4.33 (d, 4H, J = 6.8 Hz), 2.43-2.38 (m, 2H), 2.11 (s, 3H), 1.62-1.57 (m, 2H), 1.54-1.45 (m, 5H), 1.25-1.20 (m, 2H), 0.86 (t, 3H, J = 7.3 Hz). HRMS (m/z) for $C_{24}H_{30}BrN_4O_2^+$ $[M + H]^+$: calculated 485.1547 and 487.1526, found 485.1552 and 487.1538.

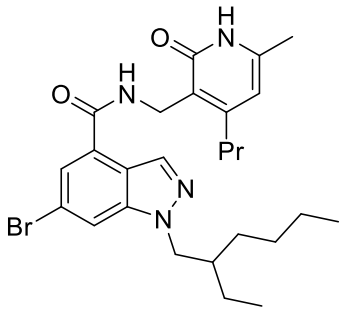


6-Bromo-1-(cyclohexylmethyl)-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **59**) Yield: 135 mg (86%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.33 (s, 1H), 8.00 (s, 1H), 7.64 (s, 1H), 6.14

(s, 1H), 4.55 (s, 2H), 4.24 (d, 2H, J = 7.2 Hz), 2.71 (t, 2H, J = 7.8 Hz), 2.26 (s, 3H), 1.97-1.92 (m, 1H), 1.72-1.69 (m, 2H), 1.66-1.59 (m, 3H), 1.52-1.50 (m, 2H), 1.25-1.18 (m, 3H), 1.07-1.03 (m, 2H), 1.01 (t, 3H, J = 6.9 Hz). MS (m/z) $[M + H]^+$: 499.2 and 501.2.

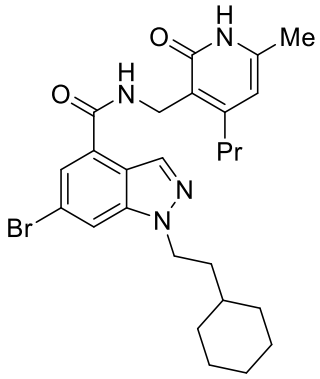


1-Benzyl-6-bromo-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **60**) Yield: 120 mg (84%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.38 (s, 1H), 7.94 (s, 1H), 7.64 (s, 1H), 7.31-7.25 (m, 3H), 7.18 (d, 2H, J = 7.1 Hz), 6.14 (s, 1H), 5.64 (s, 2H), 4.55 (s, 2H), 2.71 (t, 2H, J = 7.8 Hz), 2.26 (s, 3H), 1.66-1.61 (m, 2H), 1.01 (t, 3H, J = 7.3 Hz). MS (m/z) $[M + H]^+$: 494.2 and 496.2.

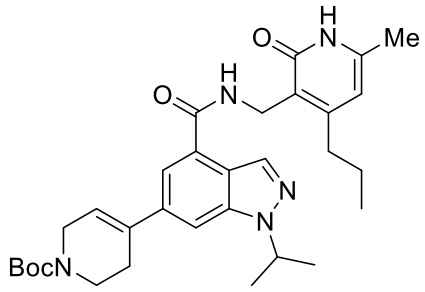


6-Bromo-1-(2-ethylhexyl)-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **61**) Yield: 130 mg (84%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.33 (s, 1H), 7.96 (s, 1H), 7.64 (s, 1H), 6.14 (s, 1H), 4.55 (s, 2H), 4.30 (d, 2H, J = 6.6 Hz), 2.73-2.69 (m, 2H), 2.26 (s, 3H), 2.01-1.99 (m, 1H), 1.64-

1.62 (m, 2H), 1.35-1.20 (m, 8H), 1.00 (t, 3H, J = 6.1 Hz), 0.89 (t, 3H, J = 6.9 Hz), 0.84 (t, 3H, J = 6.8 Hz). HRMS (m/z) for $C_{26}H_{36}BrN_4O_2^+$ $[M + H]^+$: calculated 515.2016 and 517.1996, found 515.2019 and 517.2002.

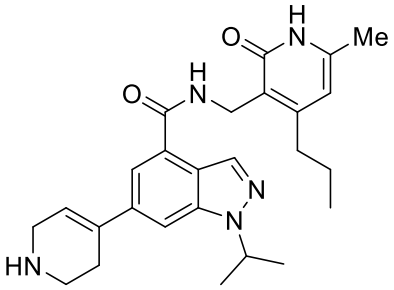


6-Bromo-1-(2-cyclohexylethyl)-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **62**) Yield: 120 mg (85%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.32 (s, 1H), 7.98 (s, 1H), 7.64 (s, 1H), 6.14 (s, 1H), 4.55 (s, 2H), 4.44 (t, 2H, J = 6.9 Hz), 2.71 (t, 2H, J = 7.5 Hz), 2.26 (s, 3H), 1.78-1.60 (m, 9H), 1.21-1.17 (m, 4H), 1.02-0.96 (m, 5H). MS (m/z) $[M + H]^+$: 513.1 and 515.1.



***tert*-Butyl 4-(1-isopropyl-4-(((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1H-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate** (Intermediate for the synthesis of compound **72**). 6-Bromo-1-isopropyl-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-1*H*-indazole-4-carboxamide (50 mg, 0.112 mmol), *tert*-

butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (42 mg, 0.135 mmol), KOAc (33 mg, 0.337 mmol), 1,4-dioxane (30 mL)/water (5 mL), Pd(dppf)Cl_2.CH_2Cl_2 (21 mg). Yield: 50 mg (82%). ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.50 (t, 1H, J = 5.2 Hz), 8.32 (s, 1H), 7.72 (s, 1H), 7.67 (s, 1H), 6.29 (br s, 1H), 6.14 (s, 1H), 5.06-5.01 (m, 1H), 4.58 (d, 2H, J = 5.1 Hz), 4.11-4.08 (m, 2H), 3.67 (br s, 2H), 2.72 (t, 2H, J = 7.8 Hz) 2.65 (br s, 2H) 2.26 (s, 3H) 1.66-1.60 (m, 2H), 1.54 (d, 6H, J = 6.6 Hz), 1.49 (s, 9H), 1.01 (t, 3H, J = 7.4 Hz). HRMS (m/z) for $C_{31}H_{42}N_5O_4^+$ $[M + H]^+$: calculated 548.3231, found 548.3241.



1-Isopropyl-*N*-((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)-6-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indazole-4-carboxamide (Intermediate for the synthesis of compound **72**). To a solution of *tert*-butyl 4-(1-isopropyl-4-(((6-methyl-2-oxo-4-propyl-1,2-dihydropyridin-3-yl)methyl)carbamoyl)-1*H*-indazol-6-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (25 mg) in dioxane (2 mL) was added dropwise hydrogen chloride (1.0 mL, 4 M in dioxane), stirred at room temperature for 2 hours, concentrated for the next step. ^{1}H-NMR (600 MHz, Methanol-d_4) δ 8.33 (s, 1H), 7.81 (s, 1H), 7.69 (d, 1H, J = 1.0 Hz), 6.36-6.35 (m, 1H), 6.19 (s, 1H), 5.07-5.03 (m, 1H), 4.58 (s, 2H), 3.90 (d, 2H, J = 2.8 Hz), 3.51 (t, 2H, J = 6.1 Hz), 2.94-2.91 (m, 2H), 2.75 (t, 2H, J = 7.8 Hz), 2.27 (s, 3H), 1.67-1.61 (m, 1H), 1.55 (d, 6H, J = 6.6 Hz), 1.02 (t, 3H, J = 7.3 Hz). HRMS (m/z) for $C_{26}H_{34}N_5O_2^+$ $[M + H]^+$: calculated 448.2707, found 448.2719

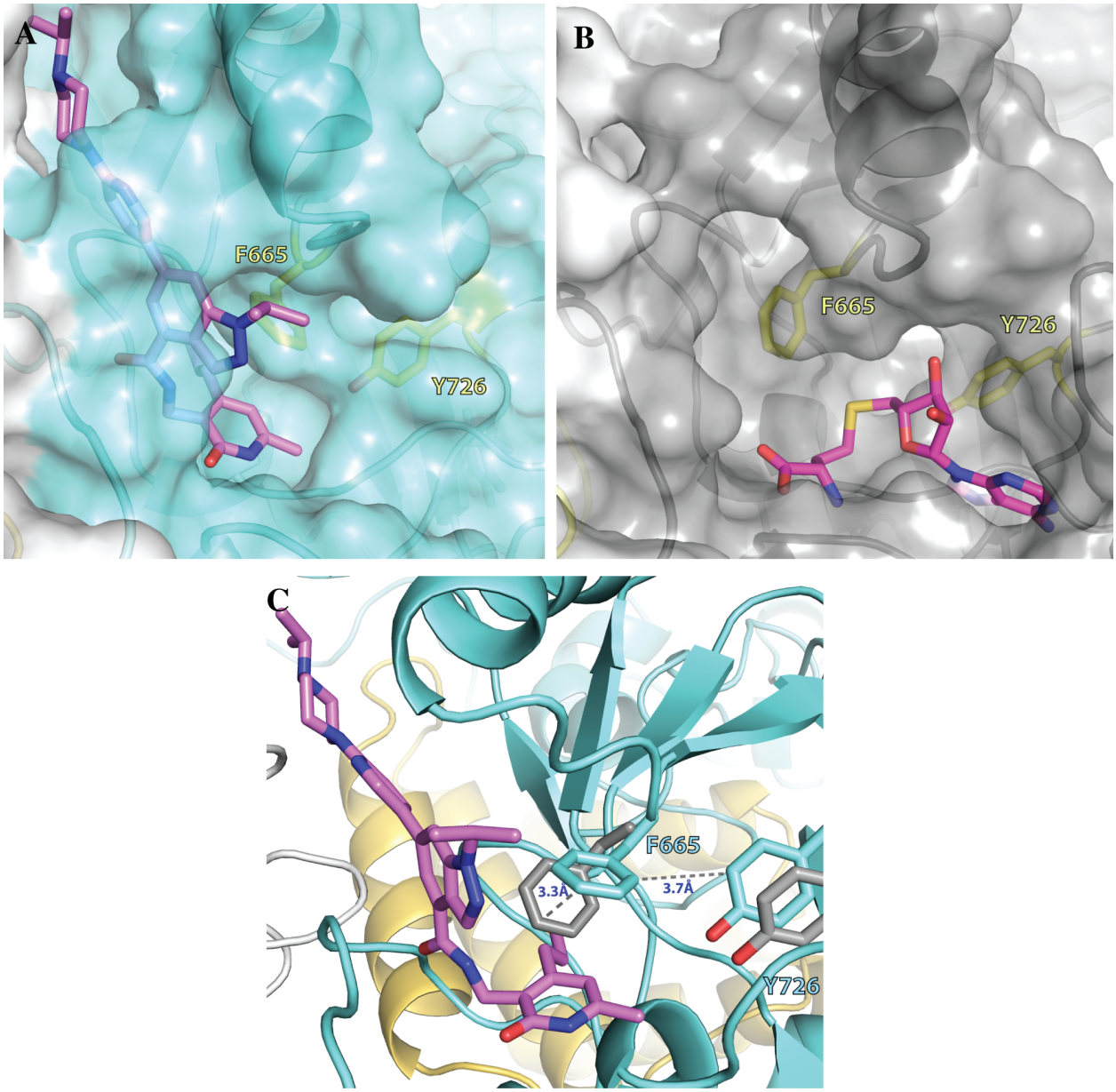


Figure S1. The side chain of F665 interacts with the pyridone moiety through pi-pi stacking and altering the cofactor binding site such as to obstruct the methionine moiety of the cofactor to be anchored at that location **(A)** The docking pose of Compound **5 (B)** SAH bound PRC2-EZH2 (PDB: 5HYN) **(C)** Superimposition of F655 and Y726 in SAH bound structure (grey) and inhibitor docked structure (aqua).