Electronic supplementary information (ESI)

Identification of multidentate tyrosyl-DNA phosphodiesterase 1 (TDP1) inhibitors that simultaneously access the DNA, protein and catalytic-binding sites by oxime diversification

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I. SYNTHETIC PROCEDURES

1. General Synthetic Procedures

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian 400 MHz spectrometer or a Varian 500 MHz spectrometer and are reported in ppm relative to TMS and referenced to the solvent in which the spectra were collected. Solvent was removed by rotary evaporation under reduced pressure, and anhydrous solvents were obtained commercially and used without further drying. Room temperature (rt) is around 22 °C. Purification by silica gel chromatography was performed using Teledyne Rf200i CombiFlash with EtOAc−hexanes or MeOH-DCM solvent systems. Preparative high pressure liquid chromatography (HPLC) was conducted using a Waters Prep 2535 system having photodiode array detection and Phenomenex C18 columns (catalogue no. 00G4436-P0-AX, 250 mm × 21.2 mm 10 μm particle size, 110 Å pore) at a flow rate of 20 mL/min. Binary solvent systems consisting of A = 0.1% aqueous TFA and B = 0.1% TFA in acetonitrile were employed with gradients as indicated. Products were obtained as amorphous solids following lyophilization. Electrospray ionization-mass spectrometric (ESI-MS) were acquired with an Agilent LC/MSD system equipped with a multimode ion source. Dual ionization mass spectrometric (DUIS-MS) were acquired with a Shimadzu LCMS system equipped with dual ionization source, electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI). High resolution mass spectrometric (HRMS) were acquired by LC/MS-ESI using LTQ-Orbitrap-XL at 30K resolution.

1.1 General procedure A. Mitsunobu reaction to prepare phthalimide protected compounds (11 and 19).[1] Diisopropyl (*E*)-diazene-1,2-dicarboxylate (DIAD, 7 mmol) was added dropwise to the mixture of alcohols (**10** or **18**, 6 mmol), 2-hydroxyisoindoline-1,3-dione (6.5 mmol) and PPh_3 (7 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred (rt, 18

h) and concentrated. The residue was stirred with MeOH (5 mL) (rt, 1 h). The suspension was filtered and washed by MeOH (10 mL). The solid was collected to afford the phthalimide protected products (**11** or **19**) separately.

1.2 General procedure B. Groebke-Blackburn-Bienayme (GBBR) multicomponent reactions to prepare imidazopyridines (14, 18, 24a-e, 29a,b and 32a-c).[2-6] Pyridine-2-amines (6 mmol), aldehydes (6 mmol), and acetic acid (12 mmol) were mixed in MeOH (5 mL) and THF (5 mL) (rt, 20 min). Isonitrile (6 mmol) was added. The reaction solution was stirred (80 °C, 4 h / rt, 24 h). The final suspension was filtered and washed by hexanes and water. The solid product was collected to provide final imidazo[*1*,*2*-*a*]pyridines (**14, 18, 24a-e, 29a,b** and **32a-c**) separately.

1.3 General procedure C. Deprotection of phthalimide to prepare aminoxyl compounds (15 and 20). Phthalimide protected compounds (**14** or **19**, 1 mmol) was dissolved in DCM (100 mL). Hydrazine hydrate (5 mmol) was added. The suspension was stirred (rt, 5 h). The suspension was filtered and washed by DCM. The filtrate was concentrated. The residue was collected to afford aminoxyl-labelled compounds (**15** or **20**) separately.

1.4 General procedure D. Deprotection of methyl ester to prepare imidazopyridines (5, 6, 25a-e, and 9a-c). Methyl esters (**15**, **20**, **24a-e,** and **32a-c**, 1 mmol) was suspended in MeOH (4 mL) in a microwave tube. NaOH (4 mL, aq. 2M) was added. The suspension in the sealed tube was microwave-heated (100 °C, 4 h). The reaction mixture was cooled to rt and acidified by HCl (aq. 2N). The formed suspension was filtered and washed by water and hexanes. The solid was collected to afford the carboxylic acids (**5**, **6**, **25a-e,** and **9a-c**) separately after HPLC purification.

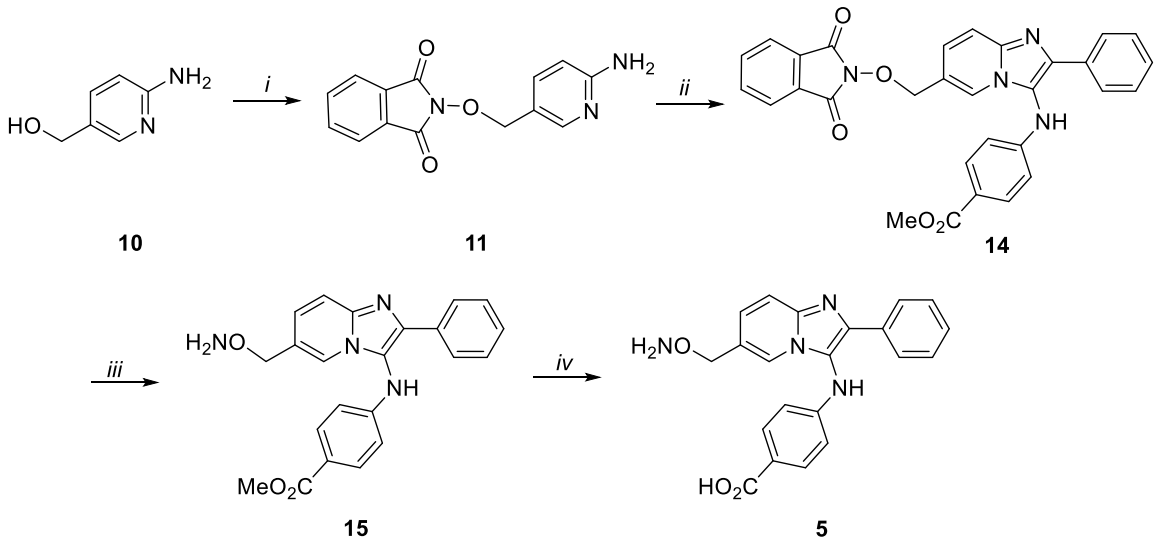
1.5 General procedure E. Reaction of aminoxyls and aldehydes to prepare (*Z*)- and (*E*)-isomers of oximes (5-D1, 5-P3, 6-D1, 6-E6, 6-B7, 6-P3, 6-M10). Aminoxyls (**5** or **6**, 0.2 mmol) and lead aldehydes (**B7**, **D1**, **E6**, **P3** or **M10**, 0.2 mmol) was mixed in DMSO (1 mL). Acetic acid (1 mmol) was added. The reaction mixture was stirred (rt, 18 h). The formed suspension was filtered and washed by MeOH. The white solid was collected to afforded oximes (**5-Y** or **6-Y**), which were purified by HPLC to afforded (*Z*)- and (*E*)-isomers of oximes (**5-D1**, **5-P3**, **6-D1**, **6-E6**, **6-B7**, **6-P3**, **6-M10**) separately.

1.6 General procedure F. Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) to prepare triazole compounds (7a-e).[7] Alkynes (**25a-e**, 0.1 mmol, 1 mg in10 µL DMSO), azide (**23**, 0.1 mmol, 1 mg in 10 µL DMSO) and tris((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amine (TBTA, 0.04 mmol, 1 mg in 10 µL DMSO) were mixed in a vial with a stirrer bar. Sodium ascorbate (0.1 mmol, 1 mg in 10 µL H_2O) and $CuSO_4$-$5H_2O$ (0.02 mmol, 1 mg in 10 µL water) were added. The reaction was diluted in DMSO (2 mL). The formed bright yellow solution was stirred at rt overnight under Argon. A yellow suspension was formed. The reaction mixture was dissolved in DMSO and purified by HPLC to afford triazole compounds (**7a-e**) separately.

1.7 General procedure G. Deprotection of tert-butyl protection to prepare acids (8a,b) using TFA. tert-Butyl ester (**29a**,**b**, 0.06 mmol) was mixed with the cocktail of TFA/H_2O/TIS (90/5/5, 0.5 mL). The reaction mixture was stirred (rt, 1.5 h). The final mixture was diluted by MeOH (5 mL) and filtered by a PTFE filter (PHENEX, 0.20 µm pore). The clear solution was purified by preparative HPLC as the describe in general experiments. After lyophilized the correct HPLC fraction, the acids (**8a**,**b**) were afforded.

1.8 General procedure H. Preparation of aldehydes (27a-c).[8] The mixture of 4-(2-hydroxyethyl)benzaldehyde (**26**, 2 mmol), bromide (**22, 30a,b**, 2 mmol) and Hunig's base DIEA (2.5 mmol) was heated (150 °C, 1 h). The brown reaction suspension was cooled down to rt and purified by silica gel chromograph using CombiFalsh. Aldehydes (**27a-c**) were afforded as white solids.

2. Preparation of aminooxyl-labelled imidazopyridine (5)



Scheme S1. Synthesis of aminooxyl-labelled imidazopyridine **5**. *Reagents and conditions:* (i) *N*-hydroxyphthalimide, Ph_3P, DIAD, THF; (ii) PhCHO (**12a**), $CNPhCO_2Me$ (**13**), HOAc, MeOH, 80 °C; (iii) NH_2NH_2-H_2O, DCM; (iv) NaOH (aq. 2N), MeOH.

2.1 Preparation of 2-((6-aminopyridin-3-yl)methoxy)isoindoline-1,3-dione (11).

Treatment of commercially available (6-aminopyridin-3-yl)methanol **10** as outlined in general procedure A provided 2-((6-aminopyridin-3-yl)methoxy)isoindoline-1,3-dione (**11**) as a red solid (54 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.91 (m, 1H), 7.85 (s, 4H), 7.49 (dd, J = 8.5, 2.4 Hz, 1H), 6.43 (dd, J = 8.5, 0.8 Hz, 1H), 6.14 (s, 2H), 4.97 (s, 2H). ^{13}C NMR (101 MHz,

DMSO-d_6) δ 163.68, 160.83 (2C), 150.32 (2C), 139.57, 135.25 (2C), 128.95, 123.69 (2C), 117.68, 108.00, 77.57. DUIS-MS: m/z: 519.2 (MH^+).

2.2 Preparation of methyl 4-((6-(((1,3-dioxoisoindolin-2-yl)oxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (14). Treatment of 2-((6-aminopyridin-3-yl)methoxy)isoindoline-1,3-dione (**11**), benzaldehyde (**12a**) and methyl 4-isocyanobenzoate (**13**)[6] as outlined in general procedure B (80 °C, 4 h) provided methyl 4-((6-(((1,3-dioxoisoindolin-2-yl)oxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**14**) as a red solid (38 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.24 (s, 1H), 7.98 (d, J = 7.7 Hz, 2H), 7.83 (d, J = 2.5 Hz, 4H), 7.71 (d, J = 9.2 Hz, 1H), 7.67 (d, J = 8.5 Hz, 2H), 7.54 (dd, J = 9.2, 1.7 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 6.51 (s, 2H), 5.22 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.47, 163.59 (2C), 150.57, 142.25, 138.52, 135.24 (2C), 133.67, 131.83 (2C), 129.04 (2C), 128.88 (2C), 128.27, 128.09, 126.90 (2C), 124.51, 123.72 (2C), 120.39, 119.87, 118.52, 117.55, 112.90 (2C), 77.02, 51.97. ESI-MS m/z: 519.10 (MH^+).

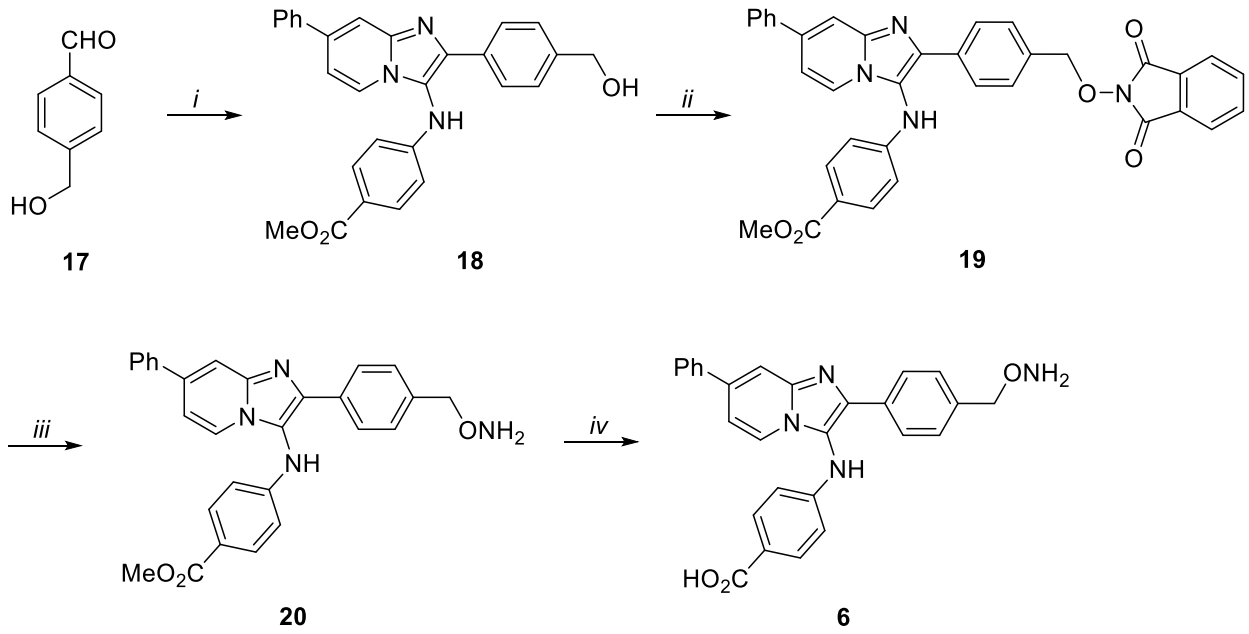
2.3 Preparation of methyl 4-((6-((aminooxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (15).

Treatment of methyl 4-((6-(((1,3-dioxoisoindolin-2-yl)oxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**14**) as outlined in general procedure C (rt, 5 h) provided methyl 4-((6-((aminooxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**15**) as a yellow solid (95 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.00 (d, J = 7.7 Hz, 2H), 7.94 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 9.2 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 7.31 (dd, J = 12.0, 8.4 Hz, 2H), 6.60 (s, 2H), 6.06 (s, 2H), 4.57 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (101 MHz,

DMSO-d_6) δ 166.53, 150.66, 142.18, 138.31, 133.88, 131.94 (2C), 129.00 (2C), 128.14, 127.21, 126.85 (2C), 123.50, 122.07, 119.97, 118.15, 117.38, 113.06 (2C), 74.37, 51.98. ESI-MS m/z: 389.10 (MH^+).

2.4 Preparation of 4-((6-((aminooxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (5). Treatment of methyl 4-((6-((aminooxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**15**) as outlined in general procedure D (μw, 100°C, 4 h) and purification by preparative HPLC (linear gradient of 5% B to 25% B over 20 min with a flow rate 20 mL/min, retention time = 16.1 min.) provided 4-((6-((aminooxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**5**) as a white solid (66 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.17 (s, 1H), 7.89 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.77 (d, *J* = 9.3 Hz, 1H), 7.69 (d, *J* = 9.1 Hz, 2H), 7.52 – 7.48 (m, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.32 – 7.28 (m, 1H), 6.58 (d, *J* = 8.1 Hz, 2H), 4.94 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.59, 149.82, 141.08, 136.12, 132.03 (2C), 131.52, 129.31 (2C), 129.10, 127.08 (2C), 124.55, 121.60, 119.21, 118.04, 116.60, 115.69, 113.18 (2C), 73.44. ESI-MS: m/z: 375.10 (MH^+). HRMS cacld. for $C_{21}H_{19}N_4O_3$(MH^+): 375.1452; found: 375.1437.

3. Preparation of aminooxyl-labelled imidazopyridine (6)



Scheme S2. Synthesis of aminooxyl-labelled imidazopyridine **6**. *Reagents and conditions:* (i) 4-phenylpyridin-2-amine (**16a**), $CNPhCO_2Me$ (**13**), HOAc, MeOH, rt; (ii) *N*-hydroxyphthalimide, Ph_3P, DIAD, THF; (iii) NH_2NH_2-H_2O, DCM; (iv) NaOH (aq. 2N), MeOH, 80 °C (µw), 3 h

3.1 Preparation of methyl 4-((2-(4-(hydroxymethyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (18). Treatment of commercially available 4-phenylpyridin-2-amine (**16a**), 4-(hydroxymethyl)benzaldehyde (**17**) and methyl 4-isocyanobenzoate (**13**) as outlined in general procedure B (rt, 18 h) provided methyl 4-((2-(4-(hydroxymethyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**18**) as a white solid (63 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.03 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.97 (d, *J* = 0.9 Hz, 1H), 7.85 (d, *J* = 7.1 Hz, 2H), 7.79 (d, *J* = 9.1 Hz, 2H), 7.53 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.34 (t, *J* = 8.6 Hz, 3H), 6.62 (brs, 2H), 5.18 (t, *J* = 5.7 Hz, 1H), 4.50 (d, *J* = 5.6 Hz, 2H), 3.76 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.52, 150.63, 142.87, 142.63, 138.94, 138.31, 137.32, 132.25, 131.94 (2C), 129.61 (2C), 128.80, 127.09 (4C),

126.65 (2C), 123.57, 119.95, 117.75, 113.96, 113.09 (2C), 112.26, 63.14, 51.99. ESI-MS m/z: 450.2 (MH^+).

3.2 Preparation of methyl 4-((2-(4-(((1,3-dioxoisoindolin-2-yl)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (19). Treatment of methyl 4-((2-(4-(hydroxymethyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**18**) as outlined in general procedure A provided title compound (**19**) as a yellow solid (79 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 8.04 (d, *J* = 7.1 Hz, 1H), 7.99 (s, 1H), 7.86 (s, 5H), 7.85 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.35 (dd, *J* = 7.1, 1.8 Hz, 1H), 6.63 (s, 2H), 5.17 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.51, 163.58 (2C), 150.45, 142.98, 138.28, 138.24, 137.55, 135.27 (2C), 134.52, 134.06, 131.96 (2C), 130.41 (2C), 129.62 (2C), 129.00 (2C), 128.85, 127.11 (2C), 126.80 (2C), 123.73 (2C), 123.68, 120.07, 118.33, 114.07, 113.15 (2C), 112.44, 79.45, 52.00. ESI-MS m/z: 595.2 (MH^+), 617.1 (MNa^+).

3.3 Preparation of methyl 4-((2-(4-((aminooxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (20). Treatment of methyl 4-((2-(4-(((1,3-dioxoisoindolin-2-yl)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**19**) as outlined in general procedure C provided methyl 4-((2-(4-((aminooxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**20**) as a yellow solid (99 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.07 (d, *J* = 8.1 Hz, 3H), 8.03 (s, 1H), 7.89 (d, *J* = 7.1 Hz, 2H), 7.84 (d, *J* = 8.9 Hz, 2H), 7.56 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.37 (dd, *J* = 7.1, 1.8 Hz, 1H), 6.68 (brs, 2H), 6.11 (brs, 2H), 4.62 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.53, 150.61, 142.93, 138.79, 138.41, 138.29, 137.40, 133.01, 131.96 (2C),

129.60 (2C), 128.80, 128.63 (2C), 127.09 (2C), 126.71 (2C), 123.59, 120.01, 117.91, 114.02, 113.11 (2C), 112.31, 77.06, 51.99. DUIS-MS: m/z: 465.2 (MH^+).

3.4 Preparation of 4-((2-(4-((aminooxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (6). Treatment of methyl 4-((2-(4-((aminooxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**20**) as outlined in general procedure D and purification by preparative HPLC (linear gradient of 10% B to 30% B over 20 min with a flow rate 20 mL/min; retention time = 18.0 min) provided 4-((2-(4-((aminooxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**6**) as a light yellow solid (83 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.12 (d, J = 7.1 Hz, 1H), 7.99 (d, J = 6.5 Hz, 2H), 7.98 (s, 1H), 7.80 (d, J = 7.2 Hz, 2H), 7.70 (d, J = 9.1 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.45 – 7.39 (m, 4H), 6.60 (d, J = 7.5 Hz, 2H), 4.89 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.58, 149.73, 141.85, 137.65, 134.43, 132.03 (2C), 130.01 (2C), 129.75 (2C), 129.41, 127.34 (2C), 127.19 (2C), 124.37, 121.60, 120.41, 118.98, 118.06, 115.70, 113.74, 113.23 (2C), 112.59, 76.04. ESI-MS m/z: 451.10 (MH^+). HRMS cacld. for $C_{27}H_{23}N_4O_3$ (MH^+), 451.1765; found: 451.1753.

4. Preparation of oximes (5-Y and 6-Y)

4.1 Preparation of (*Z*)-4-((6-((((4-(5-cyanopyridin-2-yl)benzylidene)amino)oxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(*Z*)-5-D1] and (*E*)-4-((6-((((4-(5-cyanopyridin-2-yl)benzylidene)amino)oxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(*E*)-5-D1]. Treatment of 4-((6-((aminooxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**5**) and commercially available 6-(4-formylphenyl)nicotinonitrile as outlined in general procedure E

afforded 4-((6-((((4-(5-cyanopyridin-2-yl)benzylidene)amino)oxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**5-D1,** white solid, 33 % yield) as a mixture of (*Z*) and (*E*) isomers with a ratio 5:95 based on LC. Purification by preparative HPLC (linear gradient of 30% B to 40% B over 20 min with a flow rate 20 mL/min) provided the title isomers separately.

(*Z*)-isomer ((*Z*)-**5-D1**) at retention time = 12.7 min as a white solid. ESI-MS m/z: 565.2 (MH^+). HRMS cacld. for $C_{34}H_{25}N_6O_3$ (MH^+): 565.1983; found: 565.1966.

(*E*)-isomer ((*E*)-**5-D1**) at retention time = 15.5 min as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.25 (s, 1H), 9.04 (d, *J* = 2.1 Hz, 1H), 8.81 (s, 1H), 8.34 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.29 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 2H), 8.09 (s, 1H), 7.93 (d, *J* = 7.0 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 3H), 7.39 (dd, *J* = 9.3, 1.6 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.52 (s, 2H), 5.16 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.52, 156.54, 150.94, 148.14, 147.35, 139.82, 139.40, 136.46, 136.09, 131.95, 131.44, 129.95 (2C), 126.92 (2C), 126.17, 125.96 (2C), 125.78 (2C), 125.41, 124.75 (2C), 120.88 (2C), 119.06, 118.70, 116.42, 115.60, 115.32, 110.77 (2C), 105.99, 71.16. ESI-MS m/z: 565.2 (MH^+). HRMS cacld. for $C_{34}H_{25}N_6O_3$ (MH^+): 565.1983; found: 565.1980.

4.2 Preparation of (*Z*)-4-((6-((((4-((6-methylpyrazin-2-yl)oxy)benzylidene)amino)oxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(*Z*)-5-P3] and (*E*)-4-((6-((((4-((6-methylpyrazin-2-yl)oxy)benzylidene)amino)oxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(*E*)-5-P3]. Treatment of 4-((6-((aminooxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**5**) and commercially available 4-((6-methylpyrazin-2-yl)oxy)benzaldehyde as outlined in general procedure E afforded 4-((6-((((4-((6-methylpyrazin-

2-yl)oxy)benzylidene)amino)oxy)methyl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**5-P3**, white solid, 40 % yield) as a mixture of (*Z*)- and (*E*)-isomers with a ratio 5:95 based on LC. Purification by preparative HPLC (linear gradient of 30% B to 40% B over 20 min with a flow rate 20 mL/min) provided the title isomers separately.

(*Z*)-isomer ((*Z*)-**5-P3**) at retention time = 10.6 min as a white solid. ESI-MS m/z: 571.2 (MH^+). HRMS cacld. for $C_{33}H_{27}N_6O_4$ (MH^+): 571.2088; found: 571.2090.

(*E*)-isomer ((*E*)-**5-P3**) at retention time = 11.7 min as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.28 (s, 1H), 8.25 (d, *J* = 10.2 Hz, 3H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.80 (d, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 3H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 7.9 Hz, 2H), 5.19 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.57, 158.75, 155.13, 151.54, 149.67, 149.58, 140.10, 139.24, 132.69, 131.99 (2C), 129.43(3C), 128.96 (2C), 128.77, 127.13 (2C), 125.64, 123.59, 121.75 (3C), 119.32, 118.03, 115.68, 115.50 (2C), 113.29 (2C), 72.55, 21.05. ESI-MS m/z: 571.2 (MH^+). HRMS cacld. for $C_{33}H_{27}N_6O_4$ (MH^+): 571.2088; found: 571.2089.

4.3 Preparation of (Z)-4-((2-(4-((((4-(5-cyanopyridin-2-yl)benzylidene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(Z)-6-D1] and (E)-4-((2-(4-((((4-(5-Cyanopyridin-2-yl)benzylidene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(E)-6-D1]. Treatment of 4-((2-(4-((aminooxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**6**) and commercially available 6-(4-formylphenyl)nicotinonitrile as outlined in general procedure E afforded 4-((2-(4-((((4-(5-cyanopyridin-2-yl)benzylidene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-

yl)amino)benzoic acid (**6-D1**, white solid, 58 % yield) as a mixture of (*Z*) and (*E*) isomers with a ratio 4:96 based on LC. Purification by preparative HPLC (linear gradient of 30% B to 50% B over 20 min with a flow rate 20 mL/min) provided the title isomers separately.

(*Z*)-isomer (*(Z)*-**6-D1**) at retention time = 17.7 min as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.13 (dd, *J* = 2.2, 0.9 Hz, 1H), 9.00 (brs, 1H), 8.44 (dd, *J* = 8.3, 2.2 Hz, 1H), 8.30 – 8.24 (m, 3H), 8.10 (d, *J* = 8.6 Hz, 2H), 8.04 (s, 2H), 8.02 (d, *J* = 8.0 Hz, 3H), 7.88 (d, *J* = 7.4 Hz, 2H), 7.78 (d, *J* = 9.1 Hz, 2H), 7.66 (s, 1H), 7.52 (ddt, *J* = 21.6, 14.6, 7.4 Hz, 6H), 6.68 (brs, 2H), 5.29 (s, 2H). ESI-MS m/z: 641.2 (MH^+) HRMS cacld. for $C_{40}H_{29}N_6O_3$ (MH^+): 641.2296; found: 641.2287.

(*E*)-isomer (*(E)*-**6-D1**) at retention time = 19.2 min as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.37 (brs, 1H), 9.12 (dd, *J* = 2.2, 0.9 Hz, 1H), 9.00 (s, 1H), 8.42 (d, *J* = 8.2 Hz, 1H), 8.41 (s, 1H), 8.25 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 2H), 8.18 (brs, 1H), 8.04 (s, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.88 (d, *J* = 7.1 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 4H), 7.59 – 7.46 (m, 6H), 6.69 (s, 2H), 5.24 (S, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.82, 158.70, 153.06, 149.24, 142.85, 141.54, 138.50, 138.30, 137.39, 134.28, 133.56, 131.94, 129.60 (3C), 129.01 (2C), 128.79, 128.13 (3C), 127.94 (3C), 127.09 (3C), 126.86 (2C), 123.65, 120.85 (2C), 118.49, 117.72, 114.01, 112.79 (2C), 112.28, 108.12, 75.91. ESI-MS m/z: 641.2 (MH^+). HRMS cacld. for $C_{40}H_{29}N_6O_3$ (MH^+): 641.2296; found: 641.2289.

4.4 Preparation of (Z)-4-((7-phenyl-2-(4-((((4-(pyrazin-2-yl)benzylidene)amino)oxy)methyl)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(Z)-6-E6] and (*E*)-4-((7-phenyl-2-(4-((((4-(pyrazin-2-yl)benzylidene)amino)oxy)methyl)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid

[(*E*)-6-E6]. Treatment of 4-((2-(4-((aminooxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**6**) and commercially available 4-(pyrazin-2-yl)benzaldehyde as outlined in general procedure E afforded 4-((7-phenyl-2-(4-((((4-(pyrazin-2-yl)benzylidene)amino)oxy)methyl)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**6-E6**, white solid, 34 % yield) as a mixture of (*Z*) and (*E*) isomers with a ratio 4:96 based on LC. Purification by preparative HPLC (linear gradient of 30% B to 45% B over 20 min with a flow rate 20 mL/min) provided the title isomers separately.

(*Z*)-isomer (*(Z)*-**6-E6**) at retention time = 14.3 min as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.34 (brs, 1H), 9.32 (d, *J* = 1.5 Hz, 1H), 8.93 (s, 1H), 8.76 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.66 (d, *J* = 2.5 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 2H), 8.11 (d, *J* = 8.6 Hz, 2H), 8.05 (d, *J* = 8.3 Hz, 3H), 8.00 (s, 1H), 7.86 (d, *J* = 7.1 Hz, 2H), 7.77 (d, *J* = 9.0 Hz, 2H), 7.65 (s, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 6.63 (brs, 1H), 6.55 (brs, 1H), 5.27 (s, 2H). ESI-MS m/z: 617.2 (MH^+). HRMS cacld. for $C_{38}H_{29}N_6O_3$ (MH^+): 617.2296; found: 617.2295.

(*E*)-isomer (*(E)*-**6-E6**) at retention time = 15.4 min. as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.38 (brs, 1H), 9.30 (d, *J* = 1.6 Hz, 1H), 9.02 (s, 1H), 8.74 (dd, *J* = 2.5, 1.5 Hz, 1H), 8.65 (d, *J* = 2.5 Hz, 1H), 8.41 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 3H), 8.05 (d, *J* = 1.8 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 2H), 7.89 (d, *J* = 7.5 Hz, 2H), 7.78 (dd, *J* = 8.8, 2.5 Hz, 4H), 7.60 – 7.46 (m, 6H), 6.70 (brs, 2H), 5.24 (s, 2H). ESI-MS m/z: 617.2 (MH^+). HRMS cacld. for $C_{38}H_{29}N_6O_3$ (MH^+): 617.2296; found: 617.2301.

4.5 Preparation of (*Z*)-4-((2-(4-((((4-(2-oxopyrrolidin-1-yl)benzylidene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(Z)-6-B7] and

(*E*)-4-((2-(4-((((4-(2-oxopyrrolidin-1-yl)benzylidene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(*E*)-6-B7]. Treatment of 4-((2-(4-((aminooxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**6**) and commercially available 4-(2-oxopyrrolidin-1-yl)benzaldehyde as outlined in general procedure E afforded 4-((2-(4-((((4-(2-oxopyrrolidin-1-yl)benzylidene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**6-B7**, white solid, 28 % yield) as a mixture of (*Z*) and (*E*) isomers with a ratio 5:95 based on LC. Purification by preparative HPLC (linear gradient of 30% B to 40% B over 20 min with a flow rate 20 mL/min) provided the title isomers separately.

(*Z*)-isomer (*(Z)*-**6-B7**) at retention time = 14.2 min as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.36 (brs, 1H), 8.97 (s, 1H), 8.13 (s, 1H), 8.02 (d, *J* = 8.3 Hz, 3H), 7.96 (d, *J* = 8.9 Hz, 2H), 7.87 (d, *J* = 7.7 Hz, 2H), 7.77 (dd, *J* = 8.8, 6.4 Hz, 3H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.9 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.50 – 7.44 (m, 5H), 6.66 (s, 2H), 5.22 (brs, 2H), 3.87 – 3.84 (m, 2H), 2.56 – 2.52 (m, 2H), 2.12 – 2.01 (m, 2H). ESI-MS m/z: 622.2 (MH^+). HRMS cacld. for $C_{38}H_{32}N_5O_4$ (MH^+): 622.2449; found: 622.2444.

(*E*)-isomer (*(E)*-**6-B7**) at retention time = 15.3 min as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.28 (s, 1H), 8.25 (d, *J* = 7.1 Hz, 1H), 8.08 (s, 1H), 7.98 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 7.2 Hz, 2H), 7.78 (d, *J* = 9.1 Hz, 2H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.58 (dd, *J* = 14.1, 8.4 Hz, 5H), 7.52 (dd, *J* = 13.9, 7.9 Hz, 3H), 6.72 (d, *J* = 7.9 Hz, 2H), 5.19 (s, 2H), 3.84 (t, *J* =

7.0 Hz, 2H), 2.52 - 2.50 (m, 2H), 2.11 – 2.02 (m, 2H). ESI-MS m/z: 622.2 (MH^+). HRMS cacld. for $C_{38}H_{32}N_5O_4$ (MH^+): 622.2449; found: 622.2443.

4.6 Preparation of (Z)-4-((2-(4-((((4-((6-methylpyrazin-2-yl)oxy)benzylidene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(Z)-6-P3] and (E)-4-((2-(4-((((4-((6-methylpyrazin-2-yl)oxy)benzylidene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(E)-6-P3]. Treatment of 4-((2-(4-((aminooxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**6**) and commercially available 4-((6-methylpyrazin-2-yl)oxy)benzaldehyde as outlined in general procedure E afforded 4-((2-(4-((((4-((6-methylpyrazin-2-yl)oxy)benzylidene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**6-P3**, white solid, 34 % yield) as a mixture of (*Z*) and (*E*) isomers with a ratio 5:95 based on LC. Purification by preparative HPLC (linear gradient of 30% B to 50% B over 20 min with a flow rate 20 mL/min) provided the title isomers separately.

(*Z*)-isomer (*(Z)*-**6-P3**) at retention time = 15.5 min as a white solid. ESI-MS m/z: 647.2 (MH^+). HRMS cacld. for $C_{39}H_{31}N_6O_4$ (MH^+): 647.2401; found: 647.2396.

(*E*)-isomer (*(E)*-**6-P3**) at retention time = 16.3 min as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.28 (s, 1H), 8.27 – 8.22 (m, 2H), 8.19 (d, *J* = 7.1 Hz, 1H), 8.01 (s, 1H), 7.91 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 7.1 Hz, 2H), 7.71 (d, *J* = 9.0 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.54 – 7.42 (m, 6H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.66 (d, *J* = 8.3 Hz, 2H), 5.13 (s, 2H), 2.27 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.57, 158.78, 155.05, 151.57, 149.53, 149.22, 141.55, 140.96, 139.23 (2C), 137.26, 134.35, 132.69(2C), 132.02(2C), 129.81(2C), 129.75, 129.16(2C), 129.00, 128.95(2C), 127.49(2C), 127.16(2C), 124.78, 121.83, 121.77(2C), 119.08, 114.59,

113.39, 113.35, 111.49, 75.39, 21.05. ESI-MS m/z: 647.2 (MH^+). HRMS cacld. for $C_{39}H_{31}N_6O_4$ (MH^+): 647.2401; found: 647.2396.

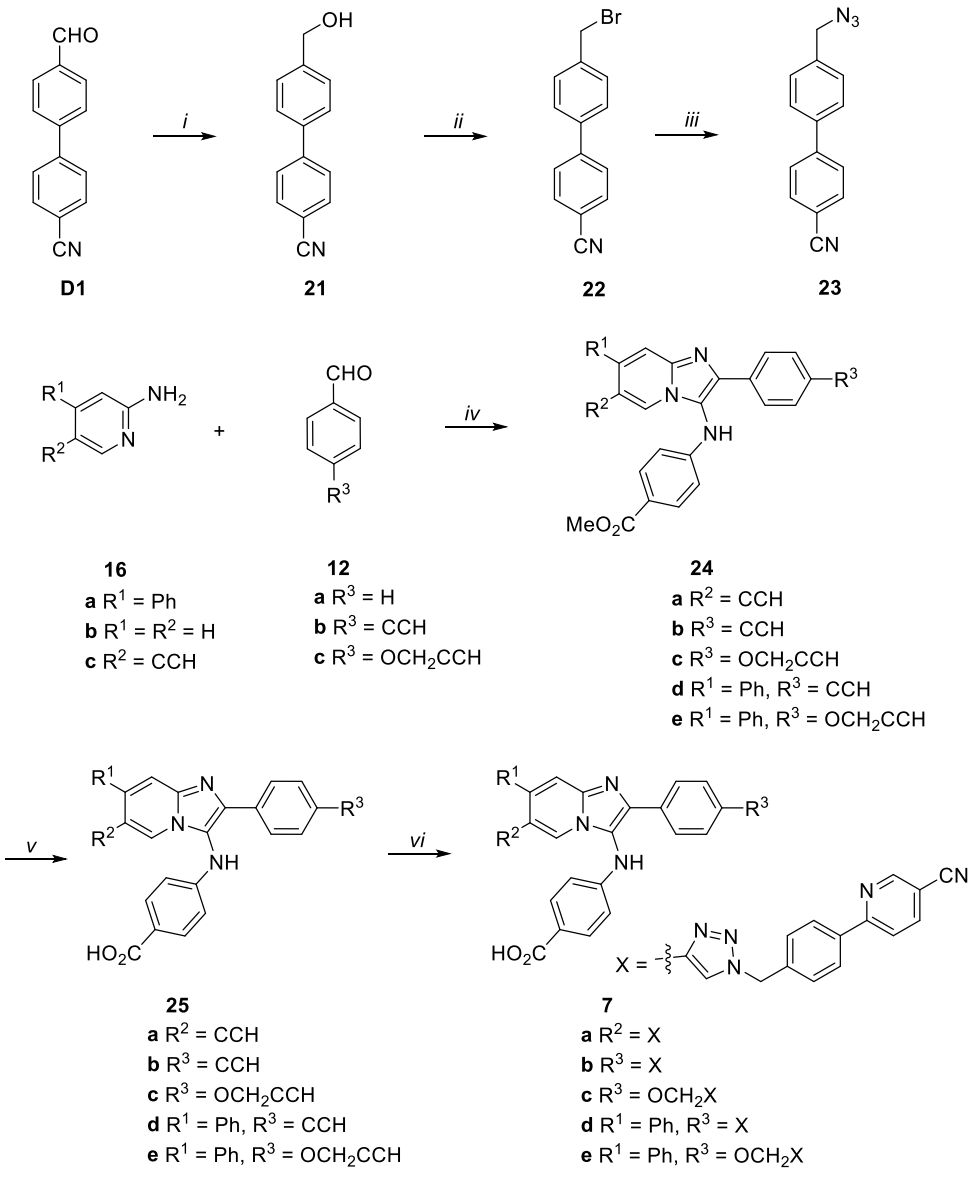
4.7 Preparation of (*Z*)-4-((2-(4-((((([1,1'-biphenyl]-4-ylmethylene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(*Z*)-6-M10] and (*E*)-4-((2-(4-((((([1,1'-biphenyl]-4-ylmethylene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid [(*E*)-6-M10]. Treatment of 4-((2-(4-((aminooxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**6**) and commercially available [1,1'-biphenyl]-4-carbaldehyde as outlined in general procedure E afforded 4-((2-(4-((((([1,1'-biphenyl]-4-ylmethylene)amino)oxy)methyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**6-M10**, white solid, 20 % yield) as a mixture of (*Z*) and (*E*) isomers with a ratio 4:96 based on LC. Purification by preparative HPLC (linear gradient of 40% B to 60% B over 20 min with a flow rate 20 mL/min) provided the title isomers separately.

(*Z*)-isomer (*(Z)*-**6-M10**) at retention time = 12.7 min as a white solid. ESI-MS m/z: 615.2 (MH^+). HRMS cacld. for $C_{40}H_{31}N_4O_3$ (MH^+): 615.2391; found: 615.2390.

(*E*)-isomer (*(E)*-**6-M10**) at retention time = 13.7 min as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.30 (s, 1H), 8.13 (d, *J* = 7.1 Hz, 1H), 7.98 (s, 1H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.81 (d, *J* = 7.1 Hz, 2H), 7.70 (d, *J* = 9.0 Hz, 2H), 7.68 – 7.60 (m, 6H), 7.52 – 7.44 (m, 5H), 7.44 – 7.39 (m, 3H), 7.32 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 7.3 Hz, 2H), 5.14 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.58, 149.72, 149.56, 142.02, 141.51, 139.74, 138.68, 137.55, 132.04 (2C), 131.35, 129.75(2C), 129.49 (4C), 129.15(2C), 128.38, 127.98(2C), 127.53(2C),

127.38(2C), 127.14(4C), 127.08, 124.46, 121.64, 118.85, 113.95, 113.27 (2C), 112.22, 75.53. ESI-MS m/z: 615.2 (MH^+). HRMS cacld. for $C_{40}H_{31}N_4O_3$ (MH^+): 615.2391; found: 615.2387.

5. Preparation of triazole-containing imidazopyridines (7a-e)



Scheme S3. Synthesis of triazole-containing imidazopyridines **7a-e**. *Reagents and conditions:* (i) $NaBH_4$, MeOH, 0 °C; (ii) CBr_4, Ph_3P, CH_3CN, rt; (iii) NaN_3, CH_3COCH_3, 55 °C; (iv)

CNPhCO$_2$Me (**13**), HOAc, MeOH; (v) NaOH, MeOH; (vi) Azide (**23**), TBTA, $CuSO_4$-5H_2O, sodium L-ascorbate, DMSO, H_2O, rt.

5.1 Preparation of 6-(4-(hydroxymethyl)phenyl)nicotinonitrile (21). To a solution of commercially available 6-(4-formylphenyl)nicotinonitrile (**D1**, 1.02 g, 4.66 mmol) in MeOH (50 mL) and THF (50 mL). Sodium borohydride (176 mg, 4.66 mmol) was added portionwise at 0 °C. After 30 min, the reaction mixture was concentrated. The residue was purified by silica gel column chromograph. The fraction was collected and afforded 6-(4-(hydroxymethyl)phenyl)nicotinonitrile (**21**, 898 mg) as a white solid (92 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 8.04 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.88 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.29 (s, 1H), 4.82 (s, 2H). ^{13}C NMR (126 MHz, CDCl3) δ 160.15, 152.45, 143.57, 139.94, 136.57, 127.61 (2C), 127.41 (2C), 119.95, 116.99, 107.87, 64.80. DUIS-MS m/z: 211.0 (MH^+).

5.2 Preparation of 6-(4-(bromomethyl)phenyl)nicotinonitrile (22). To a suspension of 6-(4-(hydroxymethyl)phenyl)nicotinonitrile (**21**, 346 mg, 1.65 mmol) in acetonitrile (10 mL) was added triphenylphosphane (648 mg, 2.47 mmol). The resulting white suspension was cooled to 0° C and perbromomethane (819 mg, 2.47 mmol) was added. The formed light brown solution was stirred (rt, 30 min). The reaction mixture was concentrated and purified by silica gel column chromograph to provide 6-(4-(bromomethyl)phenyl)nicotinonitrile (**22**, 438 mg) as a white solid (97 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 1.3 Hz, 1H), 8.06 - 8.02 (m, 3H), 7.87 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 4.57 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.67, 152.50, 140.34, 139.98, 137.33, 129.77(2C), 127.83(2C), 119.99, 116.91, 108.13, 32.59. DUIS-MS m/z: 272.9, 274.9 (MH^+).

5.3 Preparation of 6-(4-(azidomethyl)phenyl)nicotinonitrile (23). A solution of 6-(4-(bromomethyl)phenyl)nicotinonitrile (**22,** 286 mg, 1.05 mmol) and sodium azide (272 mg, 4.19 mmol) in acetone (5 mL) and water (1 mL) was heated (55 °C, 18 h). The mixture was purified by silica gel column chromograph and 6-(4-(azidomethyl)phenyl)nicotinonitrile (**23**, 217 mg) was afforded as a white solid (88 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 2.1 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 2H), 8.04 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 4.46 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.81, 152.50, 139.98, 138.01, 137.30, 128.79 (2C), 127.87 (2C), 120.00, 116.91, 108.11, 54.34. ESI-MS m/z: 236.1 (MH^+).

5.4 Preparation of methyl 4-((6-ethynyl-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (24a). Treatment of 5-ethynylpyridin-2-amine (**16c**), benzaldehyde (**12a**) and methyl 4-isocyanobenzoate (**13**) as outlined in general procedure B (rt, 24 h) provided methyl 4-((6-ethynyl-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**24a**) as a pale brown solid (43 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 11.5 Hz, 2H), 7.91 (dd, *J* = 6.0, 2.8 Hz, 3H), 7.58 (d, *J* = 9.3 Hz, 1H), 7.39 – 7.27 (m, 4H), 6.60 (d, *J* = 8.4 Hz, 2H), 5.99 (s, 1H), 3.86 (s, 3H), 3.09 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.82, 148.61, 141.94, 140.83, 132.58, 132.10 (2C), 128.76 (2C), 128.44, 128.32, 127.05 (2C), 126.16, 122.08, 117.61, 116.94, 112.85 (2C), 108.25, 79.83, 79.13, 51.84. ESI-MS m/z: 368.1 (MH^+).

5.5 Preparation of methyl 4-((2-(4-ethynylphenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoate (24b). Treatment of pyridin-2-amine (**16b**), 4-ethynylbenzaldehyde (**12b**) and methyl 4-isocyanobenzoate (**13**) as outlined in general procedure B (rt, 24 h) provided methyl 4-((2-(4-ethynylphenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoate (**24b**) as a white solid (35 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.5, 3.3 Hz, 4H), 7.80 (d, *J* = 6.8 Hz, 1H), 7.65 (d, *J* = 9.1 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.82 (t, *J* = 6.7

Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 2H), 6.04 (s, 1H), 3.86 (s, 3H), 3.11 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.84, 148.69, 142.95, 138.64, 133.32, 132.33 (2C), 132.00 (2C), 126.62 (2C), 125.70, 122.54, 121.72, 121.51, 117.71, 117.13, 112.74 (2C), 112.70, 83.53, 78.06, 51.81. ESI-MS m/z: 368.1 (MH^+).

5.6 Preparation of methyl 4-((2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoate (24c). Treatment of pyridin-2-amine (**16b**), 4-(prop-2-yn-1-yloxy)benzaldehyde (**12c**) and methyl 4-isocyanobenzoate (**13**) as outlined in general procedure B (rt, 24 h) provided methyl 4-((2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoate (**24c**) as a green solid (57 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (t, *J* = 8.6 Hz, 4H), 7.78 (d, *J* = 5.7 Hz, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.28 – 7.22 (m, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.80 (t, *J* = 6.7 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 2H), 6.15 (s, 1H), 4.70 (d, *J* = 2.3 Hz, 2H), 3.88 (s, 3H), 2.54 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.88, 157.48, 148.93, 142.79, 139.34, 132.01 (2C), 128.29 (2C), 126.37, 125.41, 122.47, 121.68, 117.50, 115.95, 115.02 (2C), 112.77 (2C), 112.50, 78.40, 75.69, 55.77, 51.82. ESI-MS m/z: 398.2 (MH^+).

5.7 Preparation of methyl 4-((2-(4-ethynylphenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (24d).

Treatment of 4-phenylpyridin-2-amine (**16a**), 4-ethynylbenzaldehyde (**12b**) and methyl 4-isocyanobenzoate (**13**) as outlined in general procedure B (rt, 24 h) provided methyl 4-((2-(4-ethynylphenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**24d**) as a pale yellow solid (37 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.8, 1.6 Hz, 4H), 7.84 (d, *J* = 0.8 Hz, 1H), 7.81 (dd, *J* = 7.2, 0.9 Hz, 1H), 7.66 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.48

(d, *J* = 8.4 Hz, 2H), 7.46 – 7.41 (m, 1H), 7.10 (dd, *J* = 7.1, 1.8 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 2H), 6.18 (s, 1H), 3.88 (s, 3H), 3.13 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.81, 148.62, 143.41, 139.32, 138.85, 138.34, 133.29, 132.42 (2C), 132.07 (2C), 129.17 (2C), 128.52, 126.80 (2C), 126.67 (2C), 122.47, 121.93, 121. 65, 116.93, 114.42, 112.84 (2C), 112.73, 83.56, 78.13, 51.85. ESI-MS m/z: 444.1 (MH^+).

5.8 Preparation of methyl 4-((7-phenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoate (24e). Treatment of 4-phenylpyridin-2-amine (**16a**), 4-(prop-2-yn-1-yloxy)benzaldehyde (**12c**) and methyl 4-isocyanobenzoate (**13**) as outlined in general procedure B (rt, 24 h) provided methyl 4-((7-phenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoate (**24e**) as a white solid (49 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.89 (m, 4H), 7.80 (d, *J* = 10.8 Hz, 2H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.2 Hz, 2H), 6.18 (s, 1H), 4.69 (d, *J* = 2.4 Hz, 2H), 3.88 (s, 3H), 2.53 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.87, 157.51, 148.94, 143.21, 140.01, 138.43, 132.03 (2C), 129.15 (2C), 128.41, 128.25 (2C), 126.76 (2C), 126.43, 122.39 (2C), 121.69, 115.80, 115.03 (2C), 114.15, 112.80 (2C), 112.35, 78.39, 75.72, 55.75, 51.82. ESI-MS m/z: 474.1 (MH^+).

5.9 Preparation of 4-((6-ethynyl-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (25a). Treatment of methyl 4-((6-ethynyl-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**24a**) as outlined in general procedure D (rt, 24 h) provided 4-((6-ethynyl-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**25a**) as a brown solid (48 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.83 (s, 1H), 8.16 (s, 1H), 8.01 (d, *J* = 7.7 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 9.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 9.2 Hz,

1H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.58 (s, 2H), 4.31 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.60, 149.88, 141.31, 138.88, 133.32, 132.02 (2C), 129.08 (2C), 128.49, 128.22, 126.96 (2C), 126.79, 121.34, 118.74, 117.92, 113.07 (2C), 107.79, 82.81, 80.47. ESI-MS m/z: 354.10 (MH^+).

5.10 Preparation of 4-((2-(4-ethynylphenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (25b). Treatment of methyl 4-((2-(4-ethynylphenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoate (**24b**) as outlined in general procedure D (60 °C, 18 h) and purification by preparative HPLC (linear gradient of 10% B to 50% B over 20 min with a flow rate 20 mL/min; retention time = 13.5 min) provided 4-((2-(4-ethynylphenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**25b**) as a white solid (67 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.43 (brs, 1H), 9.07 (s, 1H), 8.21 (d, *J* = 6.8 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.77 (d, *J* = 9.1 Hz, 2H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.23 (t, *J* = 6.8 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 2H), 4.33 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.55, 149.32, 140.69, 133.09, 132.75 (2C), 132.00 (2C), 130.77, 130.28, 127.19 (2C), 124.66, 122.52, 121.87, 119.59, 115.58 (2C), 113.35 (2C), 83.58, 82.81. ESI-MS m/z: 354.1 (MH^+).

5.11 Preparation of 4-((2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (25c). Treatment of methyl 4-((2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoate (**24c**) as outlined in general procedure D (65 °C, 18 h) and purification by preparative HPLC (linear gradient of 10% B to 50% B over 20 min with a flow rate 20 mL/min; retention time = 13.9 min) provided 4-((2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**25c**) as a white solid (70 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.45 (brs, 1H), 9.06 (s, 1H), 8.30 (d, *J* = 6.6 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.87 (d, *J* = 8.9 Hz, 2H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 9.1 Hz, 2H), 7.34

(t, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 2H), 4.86 (d, *J* = 2.4 Hz, 2H), 3.60 (t, *J* = 2.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d6) δ 165.42, 147.22, 137.32, 129.86 (2C), 126.57 (2C), 122.84, 119.88, 118.41, 116.40, 116.05, 114.34, 113.85 (2C), 113.69, 112.17, 111.33, 111.30 (2C), 77.25, 76.90, 53.88. ESI-MS m/z: 384.1 (MH^+).

5.12 Preparation of 4-((2-(4-ethynylphenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (25d). Treatment of methyl 4-((2-(4-ethynylphenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**24d**) as outlined in general procedure D (65 °C, 18 h) and purification by preparative HPLC (linear gradient of 20% B to 60% B over 20 min with a flow rate 20 mL/min; retention time = 12.9 min) provided 4-((2-(4-ethynylphenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**25d**) as a brown solid (95 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.09 (s, 1H), 8.23 (d, *J* = 7.1 Hz, 1H), 8.09 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 7.1 Hz, 2H), 7.78 (d, *J* = 9.1 Hz, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 3H), 7.53 – 7.48 (m, 1H), 6.72 (d, *J* = 8.3 Hz, 2H), 4.32 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.56, 149.39, 141.33, 137.31, 132.73 (2C), 132.38, 132.03 (2C), 131.32, 129.95, 129.79 (2C), 129.69, 127.47 (2C), 127.17 (2C), 124.72, 122.44, 121.85, 119.45, 114.43, 113.39 (2C), 111.85, 83.63, 82.77. ESI-MS m/z: 430.1 (MH^+).

5.13 Preparation of 4-((7-phenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (25e). Treatment of methyl 4-((7-phenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoate (**24e**) as outlined in general procedure D (rt, 24 h) and purification by preparative HPLC (linear gradient of 20% B to 50% B over 20 min with a flow rate 20 mL/min; retention time = 14.8 min) provided 4-((7-phenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**25e**) as a pale yellow solid (57 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.36 (brs, 1H), 8.86 (s, 1H), 8.00 (t, *J* = 8.4 Hz,

3H), 7.96 (s, 1H), 7.84 (d, *J* = 7.0 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.45 – 7.40 (m, 1H), 7.31 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 2H), 6.60 (s, 2H), 4.82 (d, *J* = 2.4 Hz, 2H), 3.57 (t, *J* = 2.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.65, 157.35, 150.31, 142.81, 138.79, 138.33, 137.17, 132.10 (2C), 129.58 (2C), 128.73, 128.12 (2C), 127.10, 127.05 (2C), 123.49, 121.16, 117.25, 115.41 (2C), 113.83, 112.89 (2C), 112.11, 79.68, 78.77, 55.84. ESI-MS m/z: 460.2 (MH^+). HRMS cacld. for $C_{29}H_{22}N_3O_3$ (MH^+), 460.1656; found, 460.1641.

5.14 Preparation of 4-((6-(1-(4-(5-cyanopyridin-2-yl)benzyl)-1H-1,2,3-triazol-4-yl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (7a). Treatment of 4-((6-ethynyl-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**25a**) and 6-(4-(azidomethyl)phenyl)nicotinonitrile (**23**) as outlined in general procedure F and purification by preparative HPLC (linear gradient of 20% B to 50% B over 20 min with a flow rate 20 mL/min, retention time = 15.1 min) provided 4-((6-(1-(4-(5-cyanopyridin-2-yl)benzyl)-1H-1,2,3-triazol-4-yl)-2-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**7a**) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (brs, 1H), 9.10 (d, *J* = 2.1 Hz, 1H), 8.85 (s, 1H), 8.80 (s, 1H), 8.47 (s, 1H), 8.40 (dd, *J* = 8.3, 2.2 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 3H), 8.02 (d, *J* = 7.7 Hz, 2H), 7.84 – 7.70 (m, 4H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.61 (s, 2H), 5.75 (s, 2H). ESI-MS m/z: 589.20 (MH^+). HRMS cacld. for $C_{35}H_{24}N_8O_2$ (MH^+), 589.2095; found, 589.2117.

5.15 Preparation of 4-((2-(4-(1-(4-(5-cyanopyridin-2-yl)benzyl)-1H-1,2,3-triazol-4-yl)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (7b). Treatment of 4-((2-(4-ethynylphenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**25b**) and 6-(4-(azidomethyl)phenyl)nicotinonitrile (**23**) as outlined in general procedure F and purification by

preparative HPLC (linear gradient of 20% B to 50% B over 20 min with a flow rate 20 mL/min, retention time = 14.5 min) provided 4-((2-(4-(1-(4-(5-cyanopyridin-2-yl)benzyl)-1H-1,2,3-triazol-4-yl)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**7b**) as a white solid (33 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H), 9.11 – 9.08 (m, 1H), 8.90 (s, 1H), 8.69 (s, 1H), 8.40 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 3H), 8.08 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 6.9 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 9.1 Hz, 2H), 7.70 (d, *J* = 9.1 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.39 (m, 1H), 7.01 (brs, 1H), 6.60 (d, *J* = 8.3 Hz, 2H), 5.75 (s, 2H). ESI-MS m/z: 589.2 (MH^+). HRMS cacld. for $C_{35}H_{25}N_8O_2$ (MH^+), 589.2095; found, 589.2106.

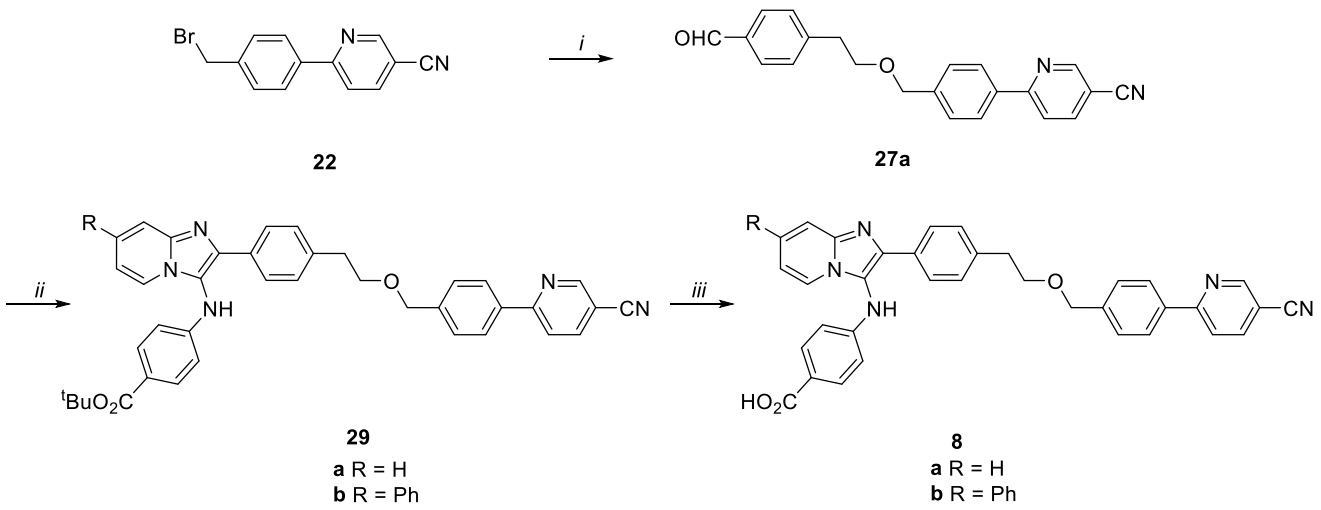
5.16 Preparation of 4-((2-(4-((1-(4-(5-cyanopyridin-2-yl)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (7c). Treatment of 4-((2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**25c**) and 6-(4-(azidomethyl)phenyl)nicotinonitrile (**23**) as outlined in general procedure F and purification by preparative HPLC (linear gradient of 20% B to 50% B over 20 min with a flow rate 20 mL/min, retention time = 14.2 min) provided 4-((2-(4-((1-(4-(5-cyanopyridin-2-yl)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**7c**) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 9.10 – 9.05 (m, 1H), 8.80 (s, 1H), 8.38 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.34 (s, 1H), 8.21 – 8.14 (m, 3H), 7.97 (d, *J* = 6.8 Hz, 1H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 9.0 Hz, 2H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.36 (s, 1H), 7.08 (d, *J* = 8.9 Hz, 2H), 6.96 (brs, 1H), 6.54 (brs, 2H), 5.71 (s, 2H), 5.17 (s, 2H). ESI-MS m/z: 619.20 (MH^+). HRMS cacld. for $C_{36}H_{27}N_8O_3$ (MH^+), 619.2201; found, 619.2232.

5.17 Preparation of 4-((2-(4-(1-(4-(5-cyanopyridin-2-yl)benzyl)-1H-1,2,3-triazol-4-yl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (7d). Treatment of 4-((2-(4-ethynylphenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**25d**) and 6-(4-

(azidomethyl)phenyl)nicotinonitrile (**23**) as outlined in general procedure F and purification by preparative HPLC (linear gradient of 30% B to 50% B over 20 min with a flow rate 20 mL/min, retention time = 13.9 min) provided 4-((2-(4-(1-(4-(5-cyanopyridin-2-yl)benzyl)-1H-1,2,3-triazol-4-yl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**7d**) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (brs, 1H), 9.10 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.98 (s, 1H), 8.70 (s, 1H), 8.41 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 3H), 8.14 (d, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 2H), 8.02 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 7.2 Hz, 2H), 7.78 (d, *J* = 9.1 Hz, 2H), 7.58 – 7.42 (m, 6H), 6.67 (d, *J* = 8.2 Hz, 2H), 5.76 (s, 2H). ESI-MS m/z: 665.2 (MH^+). HRMS cacld. for $C_{41}H_{29}N_8O_2$ (MH^+), 665.2408; found, 665.2420.

5.18 Preparation of 4-((2-(4-((1-(4-(5-cyanopyridin-2-yl)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (7e). Treatment of 4-((7-phenyl-2-(4-(prop-2-yn-1-yloxy)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**25e**) and 6-(4-(azidomethyl)phenyl)nicotinonitrile (**23**) as outlined in general procedure F and purification by preparative HPLC (linear gradient of 30% B to 50% B over 20 min with a flow rate 20 mL/min, retention time = 13.9 min) provided 4-((2-(4-((1-(4-(5-cyanopyridin-2-yl)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (**7e**) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.31 (brs, 1H), 9.01 (d, *J* = 2.1 Hz, 1H), 8.91 (s, 1H), 8.32 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.28 (s, 1H), 8.14 – 8.09 (m, 4H), 7.96 (s, 1H), 7.83 (dd, *J* = 14.8, 7.9 Hz, 4H), 7.70 (d, *J* = 9.1 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 3H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.62 (s, 2H), 5.64 (s, 2H), 5.13 (s, 2H). ESI-MS m/z: 695.2 (MH^+). HRMS cacld. for $C_{42}H_{31}N_8O_3$ (MH^+), 695.2514; found, 695.2520.

6. Preparation of ether-linked imidazopyridines (8a, b)



Scheme S4. Synthesis of ether-linked imidazopyridines **8a,b**. *Reagents and conditions:* (i) $HOCH_2CH_2PhCHO$ (**26**), DIPEA, 150 °C; (ii) 2-aminopyridine (**16b**) or 4-phenylpyridin-2-amine (**16a**), $CNPhCO_2{}^tBu$ (**28**), AcOH, MeOH; (iii) TFA, DCM.

6.1 Preparation of 6-(4-((4-formylphenethoxy)methyl)phenyl)nicotinonitrile (27a). Treatment of commercially available 4-(2-hydroxyethyl)benzaldehyde (**26**) and 6-(4-(bromomethyl)phenyl)nicotinonitrile (**22**) as outlined in general procedure H provided the title compound (**27a**) as a white solid (60 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.91 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.02 – 7.96 (m, 3H), 7.84 – 7.79 (m, 3H), 7.41 (dd, *J* = 8.2, 1.7 Hz, 4H), 4.59 (s, 2H), 3.77 (t, *J* = 6.6 Hz, 2H), 3.03 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.01, 160.12, 152.45, 146.57, 141.03, 139.90, 136.64, 134.85, 129.88 (2C), 129.68 (2C), 128.00 (2C), 127.45 (2C), 119.90, 117.03, 107.83, 72.46, 70.58, 36.57. ESI-MS m/z: 343.10 (MH^+).

6.2 Preparation of *tert*-butyl 4-isocyanobenzoate (28) [6]. The mixture of formic acid (3.2 mL, 85 mmol) and acetic anhydride (7.34 ml, 78 mmol) was heated (55 °C, 2 h) and cooled to rt. The mixture was added dropwise to a solution of commercially available *tert*-butyl 4-

aminobenzoate (5 g, 26 mmol) in THF (50 mL) at 0 °C. The mixture was stirred (rt, 2 h). The solution was concentrated, and the residue oil was purified by silica gel chromatography. A mixture of *tert*-butyl 4-formamidobenzoate and (*E*)-*N*-(4-(*tert*-butoxycarbonyl)phenyl)formimidic acid (5.8 g) was afforded as a white solid, which was used in the next reaction directly. [^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 11.2 Hz, 1H), 8.61 (d, *J* = 11.1 Hz, 1H), 8.43 (d, *J* = 1.8 Hz, 1H), 7.97 (dd, *J* = 9.6, 8.7 Hz, 4H), 7.84 (s, 1H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 1.60 (s, 9H), 1.59 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.28, 165.03, 162.13, 159.15, 140.65, 140.49, 131.36 (2C), 130.70 (2C), 128.58, 128.06, 119.00 (2C), 117.15 (2C), 81.32, 81.11, 28.22 (6C). ESI-MS m/z: 166.10 (MH^+-^{t}Bu), 222.10 (MH^+).] *tert*-Butyl 4-formamidobenzoate (5.69 g, 26 mmol) and triethylamine (10.7 mL, 77 mmol) were dissolved in THF (50 mL). Phosphoryl trichloride ($POCl_3$, 2.9 mL, 31 mmol) was added dropwise at 0 °C. The formed yellow suspension was stirred (0 °C, 1 h) and quenched by Na_2CO_3 (sat. aq.) at 0 °C. The reaction mixture was extracted by DCM, washed by brine and dried by Na_2SO_4. The solution was filtered and concentrated. The residue was purified by silica gel column chromograph. Compound tert-butyl 4-isocyanobenzoate (**28**, 4.39 g) was afforded as a light green solid (84 % yield for two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.74, 164.06, 132.82, 130.66 (2C), 129.54, 126.25 (2C), 82.01, 28.11(3C). ESI-MS m/z: 204.10 (MH^+).

6.3 Preparation of *tert*-butyl 4-((2-(4-(2-((4-(5-((λ^2-azaneylidene)-λ^3-methyl)pyridin-2-yl)phenyl)methoxy)ethyl)phenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)benzoate (29a).

Treatment of pyridin-2-amine (**16b**), and 6-(4-((4-formylphenethoxy)methyl)phenyl)nicotinonitrile (**27a**), acetic acid and tert-butyl 4-isocyanobenzoate (**28**) as outlined in general procedure B (75 °C, 16 h) provided the title

compound (**29a**) as a white solid (21 % yield). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.01 (d, *J* = 2.2 Hz, 1H), 8.73 (s, 1H), 8.31 (dd, *J* = 8.4, 2.3 Hz, 1H), 8.11 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 2H), 7.88 – 7.83 (m, 3H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 9.0 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.86 (td, *J* = 6.8, 1.2 Hz, 1H), 6.47 (s, 2H), 4.49 (s, 2H), 3.62 (t, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 6.8 Hz, 2H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 165.36, 159.35, 153.00, 150.25, 142.41, 141.74, 141.39, 139.08, 138.16, 136.38, 131.80, 131.74 (2C), 129.53 (2C), 128.26 (2C), 127.63 (2C), 126.80 (2C), 125.72, 123.42, 121.74, 120.54, 117.85, 117.78, 117.63, 112.90 (3C), 107.75, 79.99, 71.70, 71.05, 35.76, 28.36 (3C). ESI-MS m/z: 622.20 (MH^+).

6.4 Preparation of 4-((2-(4-(2-((4-(5-((λ^2-azaneylidene)-λ^3-methyl)pyridin-2-yl)phenyl)methoxy)ethyl)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (8a).

Treatment of *tert*-butyl 4-((2-(4-(2-((4-(5-((λ^2-azaneylidene)-λ^3-methyl)pyridin-2-yl)phenyl)methoxy)ethyl)phenyl)imidazo[1,2-*a*]pyridin-3-yl)amino)benzoate (**29a**) as outlined in general procedure G (rt, 1.5 h) and purification by preparative HPLC (with eluent solvent B from 25 % to 50% within 20 min, flow rate: 20 mL/min, retention time = 14.5 min.) provided the title compound (**8a**) as a white solid (39 % yield). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 12.40 (brs, 1H), 9.09 (dd, *J* = 2.2, 0.9 Hz, 1H), 9.05 (s, 1H), 8.39 (dd, *J* = 8.4, 2.2 Hz, 1H), 8.27 (d, *J* = 6.9 Hz, 1H), 8.19 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 9.0 Hz, 3H), 7.46 – 7.39 (m, 4H), 7.30 (s, 1H), 6.72 (d, *J* = 8.3 Hz, 2H), 4.57 (s, 2H), 3.71 (t, *J* = 6.7 Hz, 2H), 2.93 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d$_6$) δ 167.54, 159.32, 153.00, 149.43, 141.68, 141.41, 136.41, 131.98 (2C), 130.05 (2C), 128.27 (4C), 127.63 (4C), 127.10 (2C), 124.85, 121.91, 120.54 (2C), 119.01, 118.19, 117.78, 115.83,

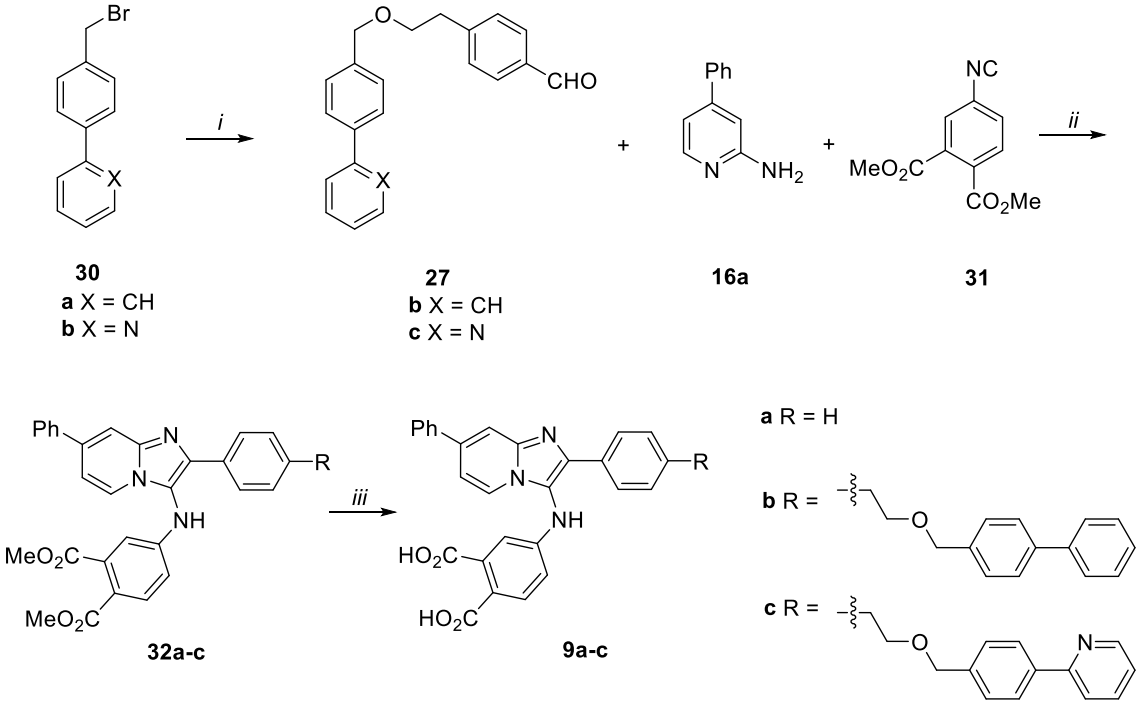
113.38 (2C), 107.77, 71.71, 70.80, 35.73. DUIS-MS m/z: 566.3 (MH^+); 564.2 $(M-H)^-$. ESI-MS m/z: 566.10 (MH^+).

6.5 Preparation of *tert*-butyl 4-((2-(4-(2-((4-(5-((λ^3-azaneylidene)-λ^3-methyl)pyridin-2-yl)phenyl)methoxy)ethyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (29b). Treatment of commercially available 4-phenylpyridin-2-amine (**16a**), and 6-(4-((4-formylphenethoxy)methyl)phenyl)nicotinonitrile (**27a**) and tert-butyl 4-isocyanobenzoate (**28**) as outlined in general procedure B (75 °C, 16 h) provided the title compound (**29b**) as a white solid (13 % yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (dd, *J* = 2.2, 0.8 Hz, 1H), 8.85 (s, 1H), 8.38 (dd, *J* = 8.3, 2.2 Hz, 1H), 8.18 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 2H), 8.00 (s, 1H), 7.95 (d, *J* = 8.3 Hz, 3H), 7.84 (d, *J* = 7.1 Hz, 2H), 7.72 (d, *J* = 9.1 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 3H), 7.31 (dd, *J* = 7.5, 5.2 Hz, 3H), 6.59 (d, *J* = 7.8 Hz, 2H), 4.57 (s, 2H), 3.70 (t, *J* = 6.8 Hz, 2H), 2.90 (t, *J* = 6.8 Hz, 2H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.37, 159.34, 152.99, 150.23, 142.84, 141.74, 141.38, 139.17, 138.94, 138.32, 137.25, 136.38, 131.77 (2C), 129.60 (2C), 129.56 (2C), 128.78 (2C), 128.26, 127.63 (2C), 127.07 (2C), 126.79 (2C), 123.52, 121.81, 120.53 (2C), 117.81, 117.77, 113.96, 112.91 (2C), 112.20, 107.75, 80.00, 71.71, 71.05, 35.77, 28.36 (3C). ESI-MS m/z: 698.30 (MH^+).

6.6 Preparation of 4-((2-(4-(2-((4-(5-((λ^2-azaneylidene)-λ^3-methyl)pyridin-2-yl)phenyl)methoxy)ethyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoic acid (8b). Treatment of *tert*-butyl 4-((2-(4-(2-((4-(5-((λ^2-azaneylidene)-λ^3-methyl)pyridin-2-yl)phenyl)methoxy)ethyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)benzoate (**29b**) as outlined in general procedure G (rt, 1.5 h) and purification by preparative HPLC (with eluent solvent B from 30 % to 50% within 20 min, flow rate: 20 mL/min, retention time = 16.8 min.) provided the title compound (**8b**) as a white solid (49 % yield). ^{1}H NMR (500 MHz, DMSO-d_6)

δ 12.39 (brs, 1H), 9.08 (dd, *J* = 2.3, 0.9 Hz, 1H), 9.05 (s, 1H), 8.38 (dd, *J* = 8.3, 2.2 Hz, 1H), 8.27 (d, *J* = 7.2 Hz, 1H), 8.18 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 2H), 8.07 (s, 1H), 7.89 (td, *J* = 6.2, 3.2 Hz, 4H), 7.77 (d, *J* = 9.0 Hz, 2H), 7.62 – 7.55 (m, 3H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 2H), 4.56 (s, 2H), 3.71 (t, *J* = 6.7 Hz, 2H), 2.92 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.57, 159.33, 153.00, 149.59, 141.70, 141.41, 140.86, 137.24, 136.41, 132.01 (2C), 129.98 (2C), 129.82 (2C), 128.27 (4C), 127.63 (4C), 127.51 (2C), 127.07 (2C), 124.79, 121.81, 120.54 (2C), 118.76, 118.19, 117.78, 115.83, 114.71, 113.37 (2C), 111.29, 107.77, 71.71, 70.85, 35.75. ESI-MS m/z: 642.20 (MH^+).

7. Preparation of phthalic acid-containing imidazopyridines (9a-c)



Scheme S5. Synthesis of phthalic acid-containing imidazopyridines **9a-c**. *Reagents and conditions:* (i) $HOCH_2CH_2PhCHO$ (**26**), DIPEA, 150 °C; (ii) 4-phenylpyridien-2-amine (**16a**), dimethyl 4-isocyanophthalate (**31**), AcOH, MeOH (**32a** from benzaldehyde **12a**; **32b,c** from aldehydes **27b,c**); (iii) NaOH, MeOH.

7.1 Preparation of dimethyl 4-((2,7-diphenylimidazo[1,2-a]pyridin-3-yl)amino)phthalate (32a). Treatment of commercially available 4-phenylpyridin-2-amine (**16a**), benzaldehyde (**12a**) with dimethyl 4-isocyanophthalate (**31**) as outlined in general procedure B (rt, 16 h) provided the title compound (**32a**) as a purple oil (55 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.87 (m, 2H), 7.75 (s, 1H), 7.69 (t, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 7.0 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.41 – 7.36 (m, 1H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.00 (dd, *J* = 7.1, 1.7 Hz, 1H), 6.79 (s, 1H), 6.67 (s, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.36, 166.53, 148.30, 143.33, 140.15, 138.73, 138.23, 136.60, 132.60, 132.29, 129.13 (2C), 128.71 (2C), 128.47, 128.25, 126.89 (2C), 126.75 (2C), 122.35, 120.23, 116.01, 114.10, 113.76, 112.76, 112.61, 52.79, 52.26. ESI-MS m/z: 478.20 (MH^+).

7.2 Preparation of 4-((2,7-diphenylimidazo[1,2-a]pyridin-3-yl)amino)phthalic acid (9a). Treatment of dimethyl 4-((2,7-diphenylimidazo[1,2-a]pyridin-3-yl)amino)phthalate (**32a**) as outlined in general procedure D and purification by preparative HPLC (with eluent solvent B from 10 % to 50% within 20 min, flow rate: 20 mL/min, retention time = 17.8 min.) provided the title compound (**9a**) as a pale yellow solid (20 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.23 (d, *J* = 7.1 Hz, 1H), 8.03 (s, 1H), 7.90 (d, *J* = 7.1 Hz, 2H), 7.83 (d, *J* = 7.1 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.55 – 7.52 (m, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.46 - 7.42 (m, 3H), 7.38 – 7.34 (m, 1H), 6.77 (brs, 1H), 6.63 (brs, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.18,

167.65, 148.47, 141.45, 141.07, 138.10, 137.25, 134.67, 132.11, 130.20, 129.82 (2C), 129.76, 129.60, 129.51 (2C), 127.50 (2C), 127.15 (2C), 124.80, 120.88, 118.59, 114.61, 113.88, 112.63, 111.55. ESI-MS m/z: 450.10 (MH^+). HRMS cacld. for $C_{27}H_{20}N_3O_4$ (MH^+), 450.1448; found, 450.1445.

7.3 Preparation of 4-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)benzaldehyde (27b). Treatment of commercially available 4-(2-hydroxyethyl)benzaldehyde (**26**) and 4-(bromomethyl)-1,1'-biphenyl (**30a**) as outlined in general procedure H provided the title compound (**27b**) as a white solid (95 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.60 – 7.54 (m, 4H), 7.47 – 7.40 (m, 4H), 7.37 – 7.32 (m, 3H), 4.56 (s, 2H), 3.76 (t, *J* = 6.7 Hz, 2H), 3.02 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.03, 146.66, 140.86, 140.66, 137.17, 134.83, 129.89 (2C), 129.67 (2C), 128.79 (2C), 128.06 (2C), 127.32, 127.19 (2C), 127.10 (2C), 72.81, 70.38, 36.61.

7.4 Preparation of 4-((2-(4-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)phthalic acid (9b). Treatment of 4-phenylpyridin-2-amine (**16a**), 4-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)benzaldehyde (**27b**) with dimethyl 4-isocyanophthalate (**31**)[6] as outlined in general procedure B (75 °C, 72 h) and treatment of the formed crude dimethyl 4-((2-(4-(2-([1,1'-biphenyl]-4-ylmethoxy)ethyl)phenyl)-7-phenylimidazo[1,2-a]pyridin-3-yl)amino)phthalate (**32b**) [DUIS-MS m/z: 688.2 (MH^+)] as outlined in general procedure D and purification by preparative HPLC (with eluent solvent B from 20 % to 70% within 20 min, flow rate: 20 mL/min, retention time = 15.7 min.) provided the title compound (**9b**) as a pale colorless solid (12 % yield for two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.37 (d, *J* = 7.1 Hz, 1H), 8.13 (s, 1H), 7.93 (t, *J* = 8.2 Hz, 4H), 7.70 – 7.64 (m, 6H), 7.62 (dd, *J* = 8.2, 6.7 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.52 – 7.44 (m, 4H), 7.43 –

7.37 (m, 3H), 6.90 (s, 1H), 6.76 (s, 1H), 4.57 (s, 2H), 3.75 (t, *J* = 6.8 Hz, 2H), 2.96 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.17, 167.64, 148.39, 141.31, 140.52, 140.36, 139.72, 138.16, 138.13, 137.02, 132.08 , 130.10 (2C), 129.97, 129.87 (2C), 129.41 (3C), 128.53 (3C), 127.87, 127.59 (2C), 127.08 (4C), 127.02 (3C), 125.03, 120.97, 118.49, 115.11, 113.97, 112.67, 110.85, 71.94, 70.66, 35.78. ESI-MS m/z: 660.2 (MH^+). HRMS cacld. for $C_{42}H_{34}N_3O_5$ (MH^+), 660.2493; found, 660.2494.

7.5 Preparation of 4-(2-((4-(pyridin-2-yl)benzyl)oxy)ethyl)benzaldehyde (27b).

Treatment of commercially available 4-(2-hydroxyethyl)benzaldehyde (**26**) and -(4-(bromomethyl)phenyl)pyridine (**30b**) as outlined in general procedure H provided the title compound (**27c**) as a white solid (29 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.70 – 8.67 (m, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.76 – 7.69 (m, 2H), 7.42 – 7.35 (m, 4H), 7.21 (ddt, *J* = 6.5, 4.9, 1.7 Hz, 1H), 4.57 (s, 2H), 3.74 (t, *J* = 6.7 Hz, 2H), 3.01 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.03, 157.13, 149.71, 146.64, 139.00, 138.82, 136.77, 134.82, 129.88 (2C), 129.67 (2C), 127.93 (2C), 126.96 (2C), 122.15, 120.48, 72.70, 70.32, 36.59. ESI-MS m/z: 318.20 (MH^+), 340.10 (MNa^+).

7.6 Preparation of 4-((7-phenyl-2-(4-(2-((4-(pyridin-2-yl)benzyl)oxy)ethyl)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)phthalic acid (9c). Treatment of 4-phenylpyridin-2-amine (**16a**), 4-(2-((4-(pyridin-2-yl)benzyl)oxy)ethyl)benzaldehyde (**27c**) with dimethyl 4-isocyanophthalate (**31**) [6] as outlined in general procedure B (75 °C, 72 h) and treatment of the formed crude dimethyl 4-((7-phenyl-2-(4-(2-((4-(pyridin-2-yl)benzyl)oxy)ethyl)phenyl)imidazo[1,2-a]pyridin-3-yl)amino)phthalate (**32c**) [DUIS-MS m/z: 689.2 (MH^+)] as outlined in general procedure D and purification by preparative HPLC (with eluent solvent B from 10 % to 40% within 20 min, flow rate: 20 mL/min, retention time = 17.3

min.) provided the title compound (**9c**) as a white solid (9 % yield for two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H), 8.71 (d, *J* = 4.7 Hz, 1H), 8.41 (d, *J* = 7.1 Hz, 1H), 8.16 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.98 – 7.93 (m, 3H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.73 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 2H), 7.57 (t, *J* = 7.3 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.42 (ddd, *J* = 7.3, 4.8, 1.2 Hz, 1H), 6.93 (s, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 4.59 (s, 2H), 3.76 (t, *J* = 6.7 Hz, 2H), 2.98 (t, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.07, 167.64, 156.02, 149.57, 148.25, 142.87, 141.51, 140.26, 140.11, 138.21, 138.07, 137.81, 136.91, 133.22, 132.03, 130.13 (2C), 130.08, 129.88 (2C), 128.21 (2C), 127.62 (2C), 127.16 (2C), 126.99 (2C), 126.64, 125.16, 123.16, 121.21, 120.92, 118.67, 115.43, 114.06, 112.83, 110.53, 71.91, 70.72, 35.78. ESI-MS m/z: 661.2 (MH^+). LCRT = 14.926 min. HRMS cacld. for $C_{41}H_{33}N_4O_5$ (MH^+), 661.2445; found, 661.2445. HRMS cacld. for $C_{41}H_{34}N_4O_5$ (MH_2^{2+}), 331.1259; found, 331.1256.

II. BIOLOGICAL EVALUATION

1. TDP1 inhibition assay

The inhibition of TDP1 was conducted according to gel-based methods as previously described.[9,10] Briefly, 1 nM of the DNA substrate (N14Y, 5´Cy5-GATCTAAAAGACTT-pY-3´) was incubated with 40 pM recombinant TDP1 in the absence or presence of inhibitors for 15 min at room temperature in TDP1 reaction buffer (50 mM Tris-HCl, pH 7.5, 80 mM KCl, 2 mM EDTA, 1 mM DTT, 40 μg/mL BSA and 0.01% Tween 20). The inhibition of TDP2 was also conducted by using similar conditions. Briefly, 1 nM of DNA substrate (YN18, 5'-pY-TCCGTTGAAGCCTGCTTT-Cy5-3') was incubated with 40 pM recombinant TDP2 in the absence or presence of inhibitors for 15 min at RT in TDP2

reaction buffer (50 mM Tris-HCl, pH 7.5, 80 mM KCl, 5 mM $MgCl_2$, 0.1 mM EDTA, 1 mM DTT, 40 μg/mL BSA, and 0.01% Tween 20). The reactions of both TDP1 and TDP2 were stopped by adding an equal volume of gel loading buffer (99.5% (v/v) formamide, 5 mM EDTA). The samples were then subjected to a 20% denaturing PAGE gel followed by gel scanning using a Typhoon FLA 9500 scanner (GE Healthcare). The IC_{50} values of the TDP1 inhibitors were calculated by comparing the percentage of the cleavage product (N14P, 5´Cy5-GATCTAAAAGACTT-p-3´) produced to that in the DMSO control. The IC_{50} values of the TDP2 inhibitors were calculated by comparing the percentage of the cleavage product (PN18, 5'-p-TCCGTTGAAGCCTGCTTT-Cy5-3') produced to that in the DMSO control.

2. Survival curve and cytotoxicity

HCT116 cells were seeded in a 384-well black-clear plate until 30% confluency and then incubated with a two-fold serial dilution of TDP1 inhibitors for 72 h at 37 ^{o}C (0.39 μM to 200 μM for **7d**; 0.048 to 25 μM for (*E*)-**6-D1** and **8b**). The cell numbers were counted from the brightfield images taken by Biotek Cytation 5. The cell cytotoxicity was calculated based on 50% cell survival using DMSO as a control.

3. Synergistic effect of TDP1 inhibitors with camptothecin (CPT) in human colon cancer cell line HCT116.

The synergistic effects of the TDP1 inhibitors with CPT were tested in human colon cancer cell line HCT116 based on cell viability (Fig. S6). Cells were first seeded in a 384-well black-clear plate until 30% confluency and then incubated with a serial dilution of CPT at the range of 0-100 nM (0, 12.5, 25, 50, 100 nM) in the present or the absence of desired concentrations of TDP1 inhibitors for 72 h at 37 ^{o}C. DMSO was used as control. Viable cell numbers were counted from the brightfield images taken by Biotek Cytation 5.

III. X-RAY CRYSTALLOGRAPHY

1. Protein expression, purification, and crystallization

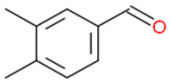
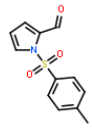
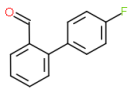
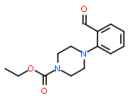
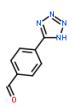
The catalytic domain of TDP1 (residues S148-S608) was expressed and purified as previously reported.[6, 9] Crystals of TDP1 were grown by the hanging drop vapor diffusion method by mixing 2 μL of TDP1 (20 mg/mL in 25 mM Tris-HCl pH 7.2, 150 mM NaCl, 2 mM tris(2-carboxyethyl)phosphine) with 2 μL of well solution composed of 0.1 M MOPS/HEPES pH 7.5, 10% (w/v) PEG 8000, 20% (v/v) ethylene glycol, 0.03 M sodium fluoride, 0.03 M sodium bromide and 0.03 M sodium iodide and sealed over 500 μL of well solution in a Nextal 15-well crystallization plate (Qiagen). Crystals od TDP1 were transferred to a 4 μL drop consisting of mother liquor supplemented with 16 mM **9a** or 14.4 mM **9c** (dissolved in DMSO, 10% (v/v) final DMSO concentration in drop), sealed over well solution, and soaked for 48 hours. Crystals for data collection were harvested with a LithoLoop (Mitegen) and flash-cooled by plunging into liquid N_2 without any additional cryoprotectant.

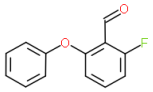
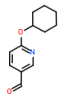
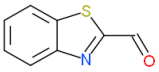
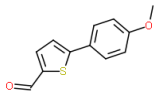
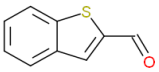
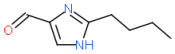
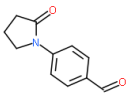
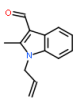
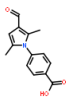
2. Data collection, structure determination, and refinement

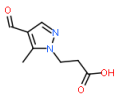
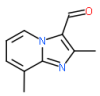
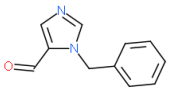
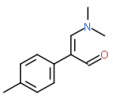
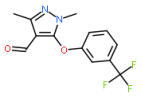
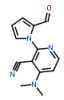
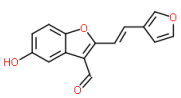
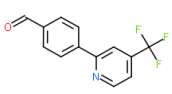
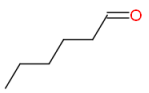
X-ray diffraction data sets were collected remotely at the Advanced Photon Source, SER-CAT beamline 22-BM, Argonne National Laboratory. Data were collected using a wavelength of 1.0000 Å, a crystal to detector distance of 200 mm, exposure time of 2 seconds, and an oscillation range of 1.0° with an Rayonix MAR300 HS detector. Diffraction images were processed using HKL3000.[11] The structures were determined by molecular replacement using the previously reported structure of TDP1 (PDB code: 6DHU, chain A)[9] as a search model after removing all solvent and ligand molecules and searching for two molecules in the asymmetric unit with the program PHASER[12] in the PHENIX suite of programs.[13] Electron density maps

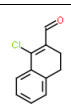
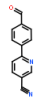
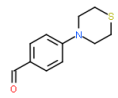
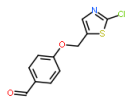
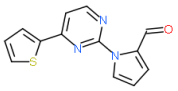
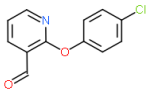
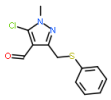
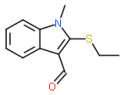
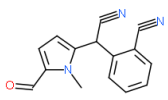
were examined for different electron density features (contoured at 3.0s) to identify bound inhibitors. The coordinate files for the inhibitors were prepared using the Molinspiration server (www.molinspiration.com) and .cif files for use during refinement were generated using eLBOW[14] in PHENIX. Iterative rounds of manual rebuilding of the structures were performed with COOT[15] followed by refinement with phenix.refine.[16] Water molecules were identified with COOT, manually inspected, and refined with phenix.refine. Model quality and structure validation were performed using MolProbity.[15]

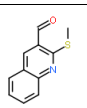
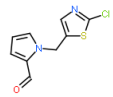
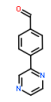
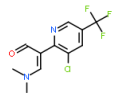
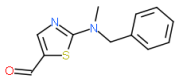
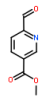
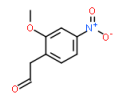
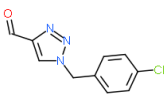
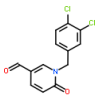
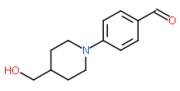
Table S1 Library of aldehydes using in our oxime library preparation with their structures and the SMILES strings.

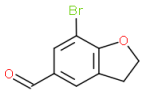
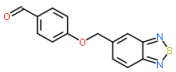
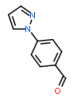
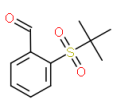
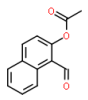
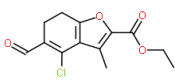
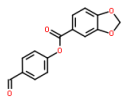
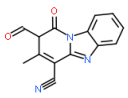
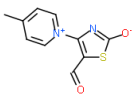
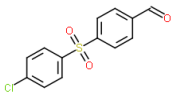
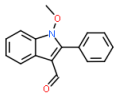
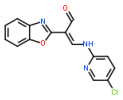
Aldehydes	**IUPAC Names**	**Structures**	**SMILES**
A1	3,4-dimethyl-benzaldehyde		Cc1ccc(C=O)cc1C
A2	1-tosyl-1H-pyrrole-2-carbaldehyde		Cc1ccc(cc1)S(n1cccc1C=O)(=O)=O
A3	2-(4-fluoro-phenyl)-benzaldehyde		C(c1ccccc1c1ccc(cc1)F)=O
A4	methyl 5-chloro-4-formyl-1-methyl-1H-pyrazole-3-carboxylate		Cn1c(c(C=O)c(C(=O)OC)n1)[Cl]
A5	ethyl 4-(2-formyl-phenyl)-piperazine-1-carboxylate		CCOC(N1CCN(CC1)c1ccccc1C=O)=O
A6	4-(1H-1,2,3,4-tetraazol-5-yl)-benzaldehyde		C(c1ccc(cc1)c1nnn[nH]1)=O
A7	4-(2-chloro-phenyl)-tetrahydro-2H-pyran-4-carbaldehyde		C1COCCC1(C=O)c1ccccc1[Cl]

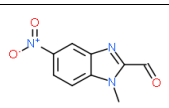
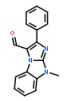
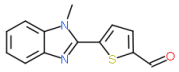
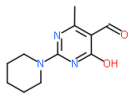
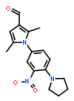
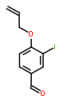
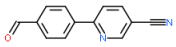
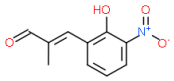
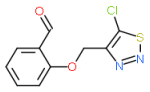
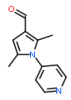
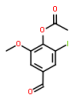
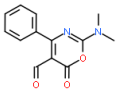
A8	2-fluoro-6-phenoxy-benzaldehyde		C(c1c(cccc1F)Oc1ccccc1)=O
A9	phenyl-methyl 2-formyl-piperidine-1-carboxylate		C1CCN(C(C1)C=O)C(=O)OCc1ccccc1
A10	6-cyclohexyloxy-pyridine-3-carbaldehyde		C1CCC(CC1)Oc1ccc(C=O)cn1
A11	7-thia-9-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraene-8-carbaldehyde		C(c1nc2ccccc2s1)=O
A12	5-(4-methoxy-phenyl)-thiophene-2-carbaldehyde		COc1ccc(cc1)c1ccc(C=O)s1
B1	7-thia-bicyclo[4.3.0]nona-1,3,5,8-tetraene-8-carbaldehyde		C(c1cc2ccccc2s1)=O
B2	4-(1H-imidazol-1-yl)-benzaldehyde		C(c1ccc(cc1)n1ccnc1)=O
B3	2-butyl-1H-imidazole-4-carbaldehyde		CCCCc1nc(C=O)c[nH]1
B4	4-bromo-2H-pyrazole-3-carbaldehyde		C(c1c(cn[nH]1)[Br])=O
B5	methyl 2-formyl-benzoate		COC(c1ccccc1C=O)=O
B6	2-amino-3,6-dimethoxy-benzaldehyde		COc1ccc(c(c1C=O)N)OC
B7	4-(2-oxo-pyrrolidin-1-yl)-benzaldehyde		C1CC(N(C1)c1ccc(C=O)cc1)=O
B8	7-allyl-8-methyl-7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carbaldehyde		Cc1c(C=O)c2ccccc2n1CC=C
B9	4-(3-formyl-2,5-dimethyl-1H-pyrrol-1-yl)-benzoic acid		Cc1cc(C=O)c(C)n1c1ccc(cc1)C(O)=O

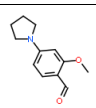
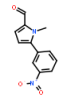
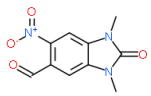
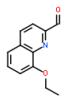
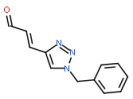
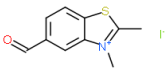
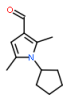
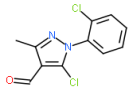
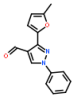
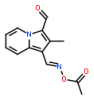
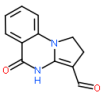
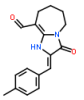
B10	7-allyl-7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carbaldehyde		C=CCn1cc(C=O)c2ccccc12
B11	2-(9-formyl-7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraen-7-yl)-ethanenitrile		C(C#N)n1cc(C=O)c2ccccc12
B12	3-(4-formyl-5-methyl-1H-pyrazol-1-yl)-propanoic acid		Cc1c(C=O)cnn1CCC(O)=O
C1	5,8-dimethyl-1,7-diaza-bicyclo[4.3.0]nona-2,4,6,8-tetraene-9-carbaldehyde		Cc1cccn2c(C=O)c(C)nc12
C2	3-benzyl-3H-imidazole-4-carbaldehyde		C(c1ccccc1)n1cncc1C=O
C3	3-(pyrimidin-2-yloxy)-benzaldehyde		C(c1cccc(c1)Oc1ncccn1)=O
C4	3-dimethylamino-2-p-tolyl-prop-2-enal		Cc1ccc(cc1)C(=CN(C)C)C=O
C5	1,3-dimethyl-5-(3-(trifluoro-methyl)-phenoxy)-1H-pyrazole-4-carbaldehyde		Cc1c(C=O)c(n(C)n1)Oc1cccc(c1)C(F)(F)F
C6	4-dimethylamino-2-(2-formyl-1H-pyrrol-1-yl)-pyridine-3-carbonitrile		CN(C)c1ccnc(c1C#N)n1cccc1C=O
C7	5-chloro-2-phenyl-1H-imidazole-4-carbaldehyde		C(c1c([nH]c(c2ccccc2)n1)[Cl])=O
C8	8-(2-(furan-3-yl)-vinyl)-3-hydroxy-7-oxa-bicyclo[4.3.0]nona-1,3,5,8-		C(=Cc1c(C=O)c2cc(ccc2o1)O)c1ccoc1
C9	4-(4-(trifluoro-methyl)-pyridin-2-yl)-benzaldehyde		C(c1ccc(cc1)c1cc(ccn1)C(F)(F)F)=O
C10	hexanal		CCCCCC=O
C11	2-methyl-2-phenylsulfanyl-propanal		CC(C)(C=O)Sc1ccccc1

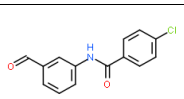
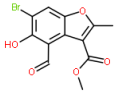
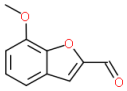
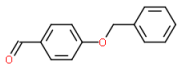
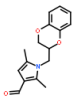
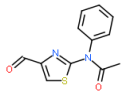
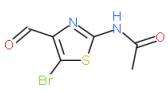
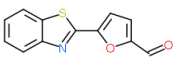
C12	7-chloro-bicyclo[4.4.0]deca-1,3,5,7-tetraene-8-carbaldehyde		C1Cc2ccccc2C(=C1C=O)[Cl]
D1	6-(4-formyl-phenyl)-pyridine-3-carbonitrile		C(c1ccc(cc1)c1ccc(C#N)cn1)=O
D2	4-(thiomorpholin-4-yl)-benzaldehyde		C1CSCCN1c1ccc(C=O)cc1
D3	4-((2-chloro-thiazol-5-yl)-methoxy)-benzaldehyde		C(c1cnc(s1)[Cl])Oc1ccc(C=O)cc1
D4	3-chloro-8-methyl-2-aza-bicyclo[4.4.0]deca-2,4,7,9-tetraene-4-carbaldehyde		CC1C=CC2C(C=1)C=C(C=O)C(=N2)[Cl]
D5	7-(3-fluoro-phenyl)-4-thia-1,6-diaza-bicyclo[3.3.0]octa-2,5,7-triene-8-carbaldehyde		C(c1c(c2cccc(c2)F)nc2n1ccs2)=O
D6	1-(4-(thiophen-2-yl)-pyrimidin-2-yl)-1H-pyrrole-2-carbaldehyde		C(c1cccn1c1nccc(c2cccs2)n1)=O
D7	2-(4-chloro-phenoxy)-pyridine-3-carbaldehyde		C(c1cccnc1Oc1ccc(cc1)[Cl])=O
D8	5-chloro-1-methyl-3-(phenylsulfanyl-methyl)-1H-pyrazole-4-carbaldehyde		Cn1c(c(C=O)c(CSc2ccccc2)n1)[Cl]
D9	8-ethylsulfanyl-7-methyl-7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carbaldehyde		CCSc1c(C=O)c2ccccc2n1C
D10	10-formyl-7,9-dioxo-8-oxa-2-aza-bicyclo[4.4.0]deca-1(6),2,4-triene		C(C1C(=O)OC(c2cccnc12)=O)=O
D11	1-phenyl-1H-1,2,3-triazole-4-carbaldehyde		C(c1cn(c2ccccc2)nn1)=O
D12 [ii]	N/A	N/A	N/A
E1	2-(2-cyano-phenyl)-2-(5-formyl-1-methyl-1H-pyrrol-2-yl)-ethanenitrile		Cn1c(C=O)ccc1C(C#N)c1ccccc1C#N

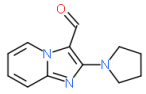
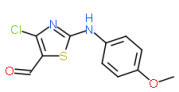
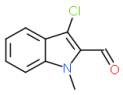
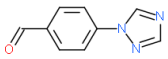
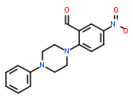
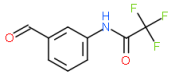
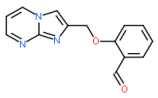
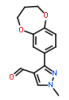
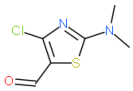
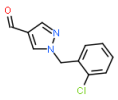
E2	3-methylsulfanyl-2-aza-bicyclo[4.4.0]deca-1,3,5,7,9-pentaene-4-carbaldehyde		CSc1c(C=O)cc2ccccc2n1
E3 [ii]	N/A	N/A	N/A
E4 [ii]	N/A	N/A	N/A
E5	1-((2-chloro-thiazol-5-yl)-methyl)-1H-pyrrole-2-carbaldehyde		C(c1cnc(s1)[Cl])n1cccc1C=O
E6	4-(pyrazin-2-yl)-benzaldehyde		C(c1ccc(cc1)c1cnccn1)=O
E7	2-(3-chloro-5-(trifluoro-methyl)-pyridin-2-yl)-3-dimethylamino-prop-2-enal		CN(C)C=C(C=O)c1c(cc(cn1)C(F)(F)F)[Cl]
E8	5-methoxy-1,3-dimethyl-1H-pyrazole-4-carbaldehyde		Cc1c(C=O)c(n(C)n1)OC
E9	2-(methyl-(phenyl-methyl)-amino)-thiazole-5-carbaldehyde		CN(Cc1ccccc1)c1ncc(C=O)s1
E10	methyl 6-formyl-pyridine-3-carboxylate		COC(c1ccc(C=O)nc1)=O
E11	2-(2-methoxy-4-nitro-phenyl)-acetaldehyde		COc1cc(ccc1CC=O)[N+]([O-])=O
E12	1-(4-chloro-benzyl)-1H-1,2,3-triazole-4-carbaldehyde		C(c1ccc(cc1)[Cl])n1cc(C=O)nn1
F1	5-chloro-6-hydroxy-pyridine-3-carbaldehyde		C(c1cc(c(nc1)O)[Cl])=O
F2	1-(3,4-dichloro-benzyl)-6-oxo-1,6-dihydro-pyridine-3-carbaldehyde		C(c1ccc(c(c1)[Cl])[Cl])N1C=C(C=CC1=O)C=O
F3	4-(4-(hydroxy-methyl)-piperidin-1-yl)-benzaldehyde		C1CN(CCC1CO)c1ccc(C=O)cc1

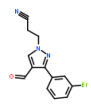
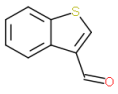
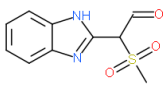
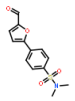
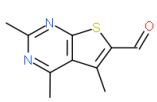
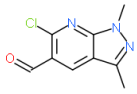
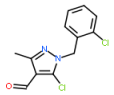
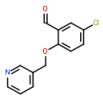
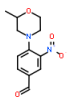
F4	5-bromo-7-oxa-bicyclo[4.3.0]nona-1(6),2,4-triene-3-carbaldehyde		C1COc2c1cc(C=O)cc2[Br]
F5	4-((8-thia-7,9-diaza-bicyclo[4.3.0]nona-1(9),2,4,6-tetraen-3-yl)-methoxy)-		C(c1ccc2c(c1)nsn2)Oc1ccc(C=O)cc1
F6	4-(1H-pyrazol-1-yl)-benzaldehyde		C(c1ccc(cc1)n1cccn1)=O
F7	2-(1,1-dimethyl-ethylsulfonyl)-benzaldehyde		CC(C)(C)S(c1ccccc1C=O)(=O)=O
F8	2-formyl-bicyclo[4.4.0]deca-1,3,5,7,9-pentaen-3-yl ethanoate		CC(=O)Oc1ccc2ccccc2c1C=O
F9	10-formyl-bicyclo[4.4.0]deca-1(6),2,4,7,9-pentaene-2-carboxylic acid		C(c1cccc2cccc(C(O)=O)c12)=O
F10	ethyl 4-chloro-5-formyl-3-methyl-6,7-dihydrobenzofuran-2-carboxylate		CCOC(c1c(C)c2C(=C(CCc2o1)C=O)[Cl])=O
F11	5-formyl-2-hydroxy-4-phenylamino-pyridine-3-carbonitrile		C(c1cnc(c(C#N)c1Nc1ccccc1)O)=O
F12	4-formylphenyl benzo[d][1,3]dioxole-5-carboxylate		C1Oc2ccc(cc2O1)C(=O)Oc1ccc(C=O)cc1
G1	2-formyl-3-methyl-1-oxo-1,2-dihydrobenzo[4,5]imidazo[1,2-a]pyridine-4-carbonitrile		CC1C(C=O)C(n2c3ccccc3nc2C=1C#N)=O
G2	5-formyl-4-(4-methylpyridin-1-ium-1-yl)thiazol-2-olate		Cc1cc[n+](cc1)c1c(C=O)sc(n1)[O-]
G3	4-(4-chloro-phenylsulfonyl)-benzaldehyde		C(c1ccc(cc1)S(c1ccc(cc1)[Cl])(=O)=O)=O
G4	7-methoxy-8-phenyl-7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carbaldehyde		COn1c(c2ccccc2)c(C=O)c2ccccc12
G5	3-(5-chloro-pyridin-2-ylamino)-2-(7-oxa-9-aza-bicyclo[4.3.0]nona-1,3,5,8-		C(=C(C=O)c1nc2ccccc2o1)Nc1ccc(cn1)[Cl]

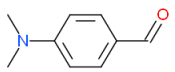
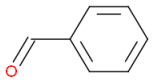
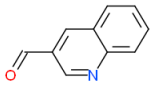
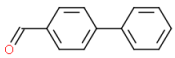
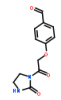
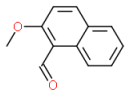
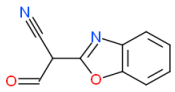
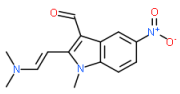
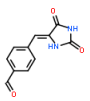
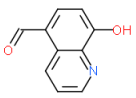
G6	9-methyl-4-nitro-7,9-diaza-bicyclo[4.3.0]nona-1,3,5,7-tetraene-8-carbaldehyde		Cn1c2ccc(cc2nc1C=O)[N+]([O-])=O
G7	9-methyl-2-phenyl-9H-benzo[d]imidazo[1,2-a]imidazole-3-carbaldehyde		Cn1c2ccccc2n2c(C=O)c(c3ccccc3)nc12
G8	5-(9-methyl-7,9-diaza-bicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl)-thiophene-2-		Cn1c2ccccc2nc1c1ccc(C=O)s1
G9	4-hydroxy-6-methyl-2-(piperidin-1-yl)-pyrimidine-5-carbaldehyde		Cc1c(C=O)c(nc(n1)N1CCCCC1)O
G10	2,5-dimethyl-1-(3-nitro-4-(pyrrolidin-1-yl)-phenyl)-1H-pyrrole-3-carbaldehyde		Cc1cc(C=O)c(C)n1c1ccc(c(c1)[N+]([O-])=O)N1CCCC1
G11	4-allyloxy-3-iodo-benzaldehyde		C=CCOc1ccc(C=O)cc1I
G12	1-(2-methoxy-4-nitro-phenyl)-2,5-dimethyl-1H-pyrrole-3-carbaldehyde		Cc1cc(C=O)c(C)n1c1ccc(cc1OC)[N+]([O-])=O
H1 (D1) [i]	6-(4-formyl-phenyl)-pyridine-3-carbonitrile		C(c1ccc(cc1)c1ccc(C#N)cn1)=O
H2	3-(2-hydroxy-3-nitro-phenyl)-2-methyl-prop-2-enal		CC(=Cc1cccc(c1O)[N+]([O-])=O)C=O
H3 (D12) [i]	2-((5-chloro-1,2,3-thiadiazol-4-yl)-methoxy)-benzaldehyde		C(c1c(snn1)[Cl])Oc1ccccc1C=O
H4	2-(9-formyl-8-methyl-7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraen-7-yl)-acetic acid		Cc1c(C=O)c2ccccc2n1CC(O)=O
H5	2,5-dimethyl-1-(pyridin-4-yl)-1H-pyrrole-3-carbaldehyde		Cc1cc(C=O)c(C)n1c1ccncc1
H6	4-formyl-2-iodo-6-methoxy-phenyl ethanoate		CC(=O)Oc1c(cc(C=O)cc1I)OC
H7	2-dimethylamino-5-formyl-6-oxo-4-phenyl-6H-1,3-oxazine		CN(C)C1=NC(=C(C=O)C(=O)O1)c1ccccc1

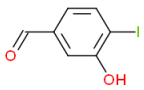
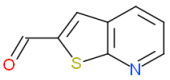
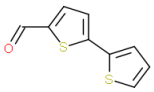
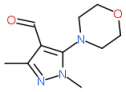
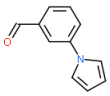
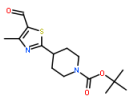
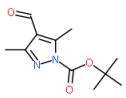
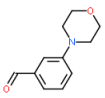
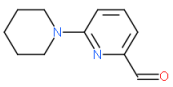
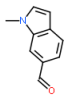
H8	2-methoxy-4-(pyrrolidin-1-yl)-benzaldehyde		COc1cc(ccc1C=O)N1CCCC1
H9	5-dimethylamino-7-methoxy-bicyclo[4.4.0]deca-1(6),2,4,7,9-pentaene-2-carbaldehyde		CN(C)c1ccc(C=O)c2cccc(c12)OC
H10	1-methyl-5-(3-nitro-phenyl)-1H-pyrrole-2-carbaldehyde		Cn1c(C=O)ccc1c1cccc(c1)[N+]([O-])=O
H11	7,9-dimethyl-4-nitro-8-oxo-7,9-diaza-bicyclo[4.3.0]nona-1,3,5-triene-3-carbaldehyde		CN1C(N(C)c2cc(c(C=O)cc12)[N+]([O-])=O)=O
H12	10-ethoxy-2-aza-bicyclo[4.4.0]deca-1(6),2,4,7,9-pentaene-3-carbaldehyde		CCOc1cccc2ccc(C=O)nc12
I1	7-methyl-4-thia-1,6-diaza-bicyclo[3.3.0]octa-2,5,7-triene-8-carbaldehyde		Cc1c(C=O)n2ccsc2n1
I2	3-(1-benzyl-1H-1,2,3-triazol-4-yl)-acrylaldehyde		C(c1ccccc1)n1cc(C=CC=O)nn1
I3	5-formyl-2,3-dimethylbenzo[d]thiazol-3-ium iodide		Cc1[n+](C)c2cc(C=O)ccc2s1.[I-]
I4	1-cyclopentyl-2,5-dimethyl-1H-pyrrole-3-carbaldehyde		Cc1cc(C=O)c(C)n1C1CCCC1
I5	5-chloro-1-(2-chloro-phenyl)-3-methyl-1H-pyrazole-4-carbaldehyde		Cc1c(C=O)c(n(c2ccccc2[Cl])n1)[Cl]
I6	3-(5-methyl-furan-2-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde		Cc1ccc(c2c(C=O)cn(c3ccccc3)n2)o1
I7	1-((acetoxyimino)methyl)-2-methylindolizine-3-carbaldehyde		CC(=O)ON=Cc1c(C)c(C=O)n2ccccc12
I8	5-oxo-1,2,4,5-tetrahydropyrrolo[1,2-a]quinazoline-3-carbaldehyde		C1CN2C(=C1C=O)NC(c1ccccc12)=O
I9	9-(4-methyl-benzyl)-10-oxo-1,8-diaza-bicyclo[5.3.0]dec-6-ene-6-carbaldehyde		Cc1ccc(C=C2C(N3CCCCC(C=O)=C3N2)=O)cc1

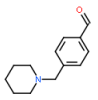
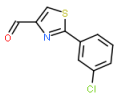
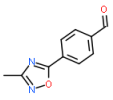
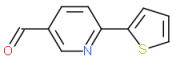
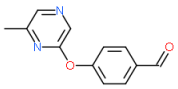
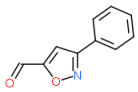
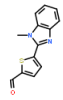
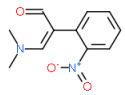
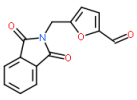
I10	3-((4-chloro-phenyl)-formylamino)-benzaldehyde		C(c1cccc(c1)NC(c1ccc(cc1)[Cl])=O)=O
I11	3-(7-formyl-8-methyl-1-aza-bicyclo[4.3.0]nona-2,4,6,8-tetraen-9-yl)-propanenitrile		Cc1c(C=O)c2ccccn2c1CCC#N
I12	2-(5-formyl-2-methoxy-phenoxy)-ethanenitrile		COc1ccc(C=O)cc1OCC#N
J1	bicyclo[2.2.1]hept-2-ene-5-carbaldehyde		Cc1c(C(=O)OC)c2c(C=O)c(c(cc2o1)[Br])O
J2	9*H*-fluorene-2-carbaldehyde		C1c2ccccc2c2ccc(C=O)cc12
J3	4-methyl-3-nitro-benzaldehyde		Cc1ccc(C=O)cc1[N+]([O-])=O
J4	5-methoxy-7-oxa-bicyclo[4.3.0]nona-1,3,5,8-tetraene-8-carbaldehyde		COc1cccc2cc(C=O)oc12
J5	3-(9-formyl-7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraen-7-yl)-propanenitrile		C(Cn1cc(C=O)c2ccccc12)C#N
J6	4-(phenyl-methoxy)-benzaldehyde		C(c1ccccc1)Oc1ccc(C=O)cc1
J7	3-amino-8-fluoro-5-oxo-2-oxa-bicyclo[4.4.0]deca-1(10),3,6,8-tetraene-4-carbaldehyde		C(C1=C(N)Oc2ccc(cc2C1=O)F)=O
J8	1-((2,5-dioxa-bicyclo[4.4.0]deca-1(10),6,8-trien-3-yl)-methyl)-2,5-		Cc1cc(C=O)c(C)n1CC1COc2ccccc2O1
J9	2-(acetyl-phenyl-amino)-thiazole-4-carbaldehyde		CC(N(c1ccccc1)c1nc(C=O)cs1)=O
J10	2-acetylamino-5-bromo-thiazole-4-carbaldehyde		CC(Nc1nc(C=O)c(s1)[Br])=O
J11	5-(7-thia-9-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraen-8-yl)-furan-2-		C(c1ccc(c2nc3ccccc3s2)o1)=O

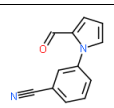
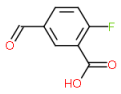
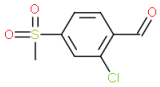
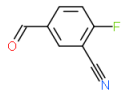
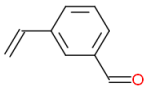
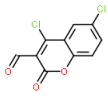
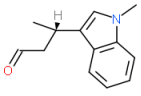
J12	8-(pyrrolidin-1-yl)-1,7-diaza-bicyclo[4.3.0]nona-2,4,6,8-tetraene-9-carbaldehyde		C1CCN(C1)c1c(C=O)n2ccccc2n1
K1	5-(piperidin-1-yl)-furan-2-carbaldehyde		C1CCN(CC1)c1ccc(C=O)o1
K2	2,5-dimethyl-1-(5-methyl-isoxazol-3-yl)-1H-pyrrole-3-carbaldehyde		Cc1cc(C=O)c(C)n1c1cc(C)on1
K3	4-chloro-2-(4-methoxy-phenylamino)-thiazole-5-carbaldehyde		COc1ccc(cc1)Nc1nc(c(C=O)s1)[Cl]
K4	9-chloro-7-methyl-7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraene-8-carbaldehyde		Cn1c(C=O)c(c2ccccc12)[Cl]
K5	8-nitro-2,4-dioxa-bicyclo[4.4.0]deca-1(10),6,8-triene-10-carbaldehyde		C1c2cc(cc(C=O)c2OCO1)[N+]([O-])=O
K6	4-(1H-1,2,4-triazol-1-yl)-benzaldehyde		C(c1ccc(cc1)n1cncn1)=O
K7	5-nitro-2-(4-phenyl-piperazin-1-yl)-benzaldehyde		C1CN(CCN1c1ccccc1)c1ccc(cc1C=O)[N+]([O-])=O
K8	3-(2,2,2-trifluoro-acetylamino)-benzaldehyde		C(c1cccc(c1)NC(C(F)(F)F)=O)=O
K9	2-((1,5,7-triaza-bicyclo[4.3.0]nona-2,4,6,8-tetraen-8-yl)-methoxy)-		C(c1cn2cccnc2n1)Oc1ccccc1C=O
K10	3-(2,6-dioxa-bicyclo[5.4.0]undeca-1(11),7,9-trien-9-yl)-1-methyl-1H-		Cn1cc(C=O)c(c2ccc3c(c2)OCCCO3)n1
K11	8-fluoro-2,4-dioxa-bicyclo[4.4.0]deca-1(10),6,8-triene-10-carbaldehyde		C1c2cc(cc(C=O)c2OCO1)F
K12	4-chloro-2-dimethylamino-thiazole-5-carbaldehyde		CN(C)c1nc(c(C=O)s1)[Cl]
L1	1-(2-chloro-benzyl)-1H-pyrazole-4-carbaldehyde		C(c1ccccc1[Cl])n1cc(C=O)cn1

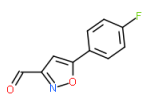
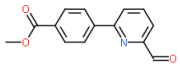
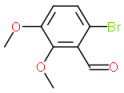
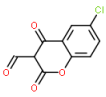
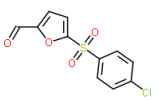
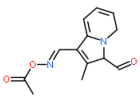
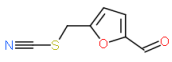
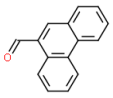
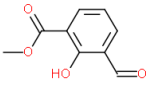
L2	3-(3-(3-bromo-phenyl)-4-formyl-1H-pyrazol-1-yl)-propanenitrile		C(Cn1cc(C=O)c(c2cccc(c2)[Br])n1)C#N
L3	7-thia-bicyclo[4.3.0]nona-1,3,5,8-tetraene-9-carbaldehyde		C(c1csc2ccccc12)=O
L4	9-nitro-2,5-dioxa-bicyclo[4.4.0]deca-1(10),6,8-triene-8-carbaldehyde		C1COc2cc(c(C=O)cc2O1)[N+]([O-])=O
L5	2-(7,9-diaza-bicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl)-2-methylsulfonyl-acetaldehyde		CS(C(C=O)c1nc2ccccc2[nH]1)(=O)=O
L6	4-(5-formylfuran-2-yl)-N,N-dimethylbenzenesulfonamide		CN(C)S(c1ccc(cc1)c1ccc(C=O)o1)(=O)=O
L7	3-fluoro-4-(1H-1,2,4-triazol-1-yl)-benzaldehyde		C(c1ccc(c(c1)F)n1cncn1)=O
L8	3,5,7-trimethyl-9-thia-2,4-diaza-bicyclo[4.3.0]nona-1(6),2,4,7-tetraene-8-carbaldehyde		Cc1c2c(C)nc(C)nc2sc1C=O
L9	8-methyl-2-(trifluoro-methyl)-1,5,9-triaza-bicyclo[4.3.0]nona-2,4,6,8-tetraene-7-		Cc1c(C=O)c2nccc(C(F)(F)F)n2n1
L10	3-chloro-7,9-dimethyl-2,8,9-triaza-bicyclo[4.3.0]nona-1,3,5,7-tetraene-4-		Cc1c2cc(C=O)c(nc2n(C)n1)[Cl]
L11	4-methoxy-7-methyl-2-oxo-1,5-diaza-bicyclo[4.4.0]deca-3,5,7,9-tetraene-3-		CC1=CC=CN2C1=NC(=C(C=O)C2=O)OC
L12	5-chloro-1-(2-chloro-benzyl)-3-methyl-1H-pyrazole-4-carbaldehyde		Cc1c(C=O)c(n(Cc2ccccc2[Cl])n1)[Cl]
M1	5-chloro-2-((pyridin-3-yl)-methoxy)-benzaldehyde		C(c1cccnc1)Oc1ccc(cc1C=O)[Cl]
M2	4-(2-methyl-morpholin-4-yl)-3-nitro-benzaldehyde		CC1CN(CCO1)c1ccc(C=O)cc1[N+]([O-])=O
M3 [ii]	N/A	N/A	N/A

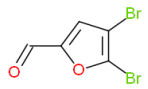
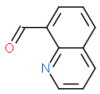
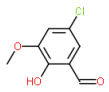
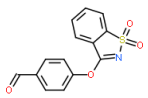
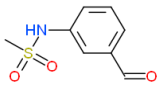
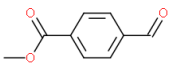
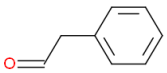
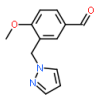
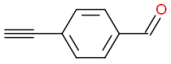
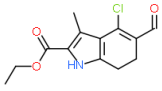
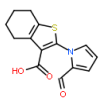
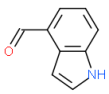
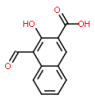
M4 [ii]	N/A	N/A	N/A
M5	4-dimethylamino-benzaldehyde		CN(C)c1ccc(C=O)cc1
M6	benzaldehyde		C(c1ccccc1)=O
M7	7,9-dioxa-bicyclo[4.3.0]nona-1(6),2,4-triene-2-carbaldehyde		C1Oc2cccc(C=O)c2O1
M8	2-aza-bicyclo[4.4.0]deca-1(10),2,4,6,8-pentaene-4-carbaldehyde		C(c1cc2ccccc2nc1)=O
M9	4,10-dimethoxy-bicyclo[4.4.0]deca-1,3,5,7,9-pentaene-7-carbaldehyde		COc1ccc2c(ccc(C=O)c2c1)OC
M10	4-phenyl-benzaldehyde		C(c1ccc(cc1)c1ccccc1)=O
M11	4-(2-oxo-2-(2-oxo-imidazolidin-1-yl)-ethoxy)-benzaldehyde		C1CN(C(COc2ccc(C=O)cc2)=O)C(N1)=O
M12	8-methoxy-bicyclo[4.4.0]deca-1,3,5,7,9-pentaene-7-carbaldehyde		COc1ccc2ccccc2c1C=O
N1	8-hydroxy-3-nitro-bicyclo[4.4.0]deca-1,3,5,7,9-pentaene-7-carbaldehyde		C(c1c(ccc2cc(ccc12)[N+]([O-])=O)O)=O
N2	2-(7-oxa-9-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraen-8-yl)-3-oxo-		C(C(C#N)c1nc2ccccc2o1)=O
N3	8-(2-dimethylamino-vinyl)-7-methyl-3-nitro-7-aza-bicyclo[4.3.0]nona-1,3,5,8-		CN(C)C=Cc1c(C=O)c2cc(ccc2n1C)[N+]([O-])=O
N4	4-((2,5-dioxo-imidazolidin-4-ylidene)-methyl)-benzaldehyde		C(=C1C(NC(N1)=O)=O)c1ccc(C=O)cc1
N5	10-hydroxy-2-aza-bicyclo[4.4.0]deca-1(10),2,4,6,8-pentaene-7-carbaldehyde		C(c1ccc(c2c1cccn2)O)=O

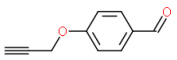
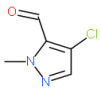
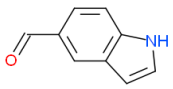
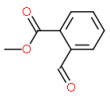
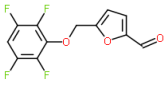
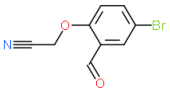
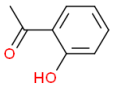
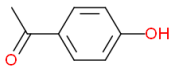
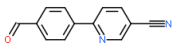
N6	4-fluoro-3-methoxy-benzaldehyde		COc1cc(C=O)ccc1F
N7	2-fluoro-5-(trifluoro-methyl)-benzaldehyde		C(c1cc(ccc1F)C(F)(F)F)=O
N8	3-hydroxy-4-iodo-benzaldehyde		C(c1ccc(c(c1)O)I)=O
N9	9-thia-2-aza-bicyclo[4.3.0]nona-1(6),2,4,7-tetraene-8-carbaldehyde		C(c1cc2cccnc2s1)=O
N10	2,4-dimethyl-thiazole-5-carbaldehyde		Cc1c(C=O)sc(C)n1
N11	5-(thiophen-2-yl)-thiophene-2-carbaldehyde		C(c1ccc(c2cccs2)s1)=O
N12	1,3-dimethyl-5-(morpholin-4-yl)-1H-pyrazole-4-carbaldehyde		Cc1c(C=O)c(N2CCOCC2)n(C)n1
O1	3-(1H-pyrrol-1-yl)-benzaldehyde		C(c1cccc(c1)n1cccc1)=O
O2	3-(1H-pyrrol-1-yl)-thiophene-2-carbaldehyde		C(c1c(ccs1)n1cccc1)=O
O3	1,1-dimethyl-ethyl 4-(5-formyl-4-methyl-thiazol-2-yl)-piperidine-1-carboxylate		Cc1c(C=O)sc(C2CCN(CC2)C(=O)OC(C)(C)C)n1
O4	1,1-dimethyl-ethyl 4-formyl-3,5-dimethyl-1H-pyrazole-1-carboxylate		Cc1c(C=O)c(C)n(C(=O)OC(C)(C)C)n1
O5	3-(morpholin-4-yl)-benzaldehyde		C1COCCN1c1cccc(C=O)c1
O6	6-(piperidin-1-yl)-pyridine-2-carbaldehyde		C1CCN(CC1)c1cccc(C=O)n1
O7	7-methyl-7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraene-4-carbaldehyde		Cn1ccc2ccc(C=O)cc12

O8	4-((piperidin-1-yl)-methyl)-benzaldehyde		C1CCN(CC1)Cc1ccc(C=O)cc1
O9	1-methyl-5-phenyl-1H-pyrazole-3-carbaldehyde		Cn1c(cc(C=O)n1)c1ccccc1
O10	2-(3-chloro-phenyl)-thiazole-4-carbaldehyde		C(c1csc(c2cccc(c2)[Cl])n1)=O
O11	4-(3-methyl-1,2,4-oxadiazol-5-yl)-benzaldehyde		Cc1nc(c2ccc(C=O)cc2)on1
O12	6-(thiophen-2-yl)-pyridine-3-carbaldehyde		C(c1ccc(c2cccs2)nc1)=O
P1	1-(6-methyl-pyrazin-2-yl)-piperidine-4-carbaldehyde		Cc1cncc(n1)N1CCC(CC1)C=O
P2	5-methyl-2-oxa-5,7-diaza-bicyclo[4.4.0]deca-1(10),6,8-triene-9-carbaldehyde		CN1CCOc2cc(C=O)cnc12
P3	4-(6-methyl-pyrazin-2-yloxy)-benzaldehyde		Cc1cncc(n1)Oc1ccc(C=O)cc1
P4	3-phenyl-isoxazole-5-carbaldehyde		C(c1cc(c2ccccc2)no1)=O
P5 (G8) [i]	5-(9-methyl-7,9-diaza-bicyclo[4.3.0]nona-1,3,5,7-tetraen-8-yl)-thiophene-2-		Cn1c2ccccc2nc1c1ccc(C=O)s1
P6	3-dimethylamino-2-(2-nitro-phenyl)-acrylaldehyde		CN(C)C=C(C=O)c1ccccc1[N+]([O-])=O
P7	4,6-dimethyl-2,8-dithia-bicyclo[3.3.0]octa-1(5),3,6-triene-3-carbaldehyde		Cc1csc2c1c(C)c(C=O)s2
P8	3-phenoxy-thiophene-2-carbaldehyde		C(c1c(ccs1)Oc1ccccc1)=O
P9	5-((7,9-dioxo-8-aza-bicyclo[4.3.0]nona-1,3,5-trien-8-yl)-methyl)-furan-2-		C(c1ccc(C=O)o1)N1C(c2ccccc2C1=O)=O

P10	3-(2-formyl-1H-pyrrol-1-yl)-benzonitrile		C(c1cccn1c1cccc(C#N)c1)=O
P11	2-fluoro-5-formyl-benzoic acid		C(c1ccc(c(c1)C(O)=O)F)=O
P12	6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidine-5-carbaldehyde		CN1C(=C(C=O)C(N(C)C1=O)=O)N
Q1	3-chloro-thiophene-2-carbaldehyde		C(c1c(ccs1)[Cl])=O
Q2	6-formyl-2-methylsulfanyl-pyridine-3-carbonitrile		CSc1c(C#N)ccc(C=O)n1
Q3	2-chloro-4-methylsulfonyl-benzaldehyde		CS(c1ccc(C=O)c(c1)[Cl])(=O)=O
Q4 (G6) [i]	9-methyl-4-nitro-7,9-diaza-bicyclo[4.3.0]nona-1,3,5,7-tetraene-8-carbaldehyde		C1c2ccccc2c2ccc(C=O)cc12
Q5	2,5-dihydroxy-benzaldehyde		C(c1cc(ccc1O)O)=O
Q6	2-fluoro-5-formyl-benzonitrile		C(c1ccc(c(C#N)c1)F)=O
Q7	3-vinyl-benzaldehyde		C=Cc1cccc(C=O)c1
Q8	2-fluoro-6-methoxy-benzaldehyde		COc1cccc(c1C=O)F
Q9	5,8-dichloro-4-formyl-3-oxo-2-oxa-bicyclo[4.4.0]deca-1(10),4,6,8-tetraene		C(C1=C(c2cc(ccc2OC1=O)[Cl])[Cl])=O
Q10	3,5-dichloro-pyridine-4-carbaldehyde		C(c1c(cncc1[Cl])[Cl])=O
Q11	3-(7-methyl-7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraen-9-yl)-butanal		[H][C@](C)(CC=O)c1cn(C)c2ccccc12

Q12	5-(4-fluoro-phenyl)-isoxazole-3-carbaldehyde		C(c1cc(c2ccc(cc2)F)on1)=O
R1	methyl 4-(6-formyl-pyridin-2-yl)-benzoate		COC(c1ccc(cc1)c1cccc(C=O)n1)=O
R2	2-methoxy-4-nitro-benzaldehyde		COc1cc(ccc1C=O)[N+]([O-])=O
R3	4-bromo-2-methoxy-benzaldehyde		COc1cc(ccc1C=O)[Br]
R4	4,5-dimethyl-thiophene-2-carbaldehyde		Cc1cc(C=O)sc1C
R5	6-bromo-2,3-dimethoxy-benzaldehyde		COc1ccc(c(C=O)c1OC)[Br]
R6	2-hydroxy-5-methoxy-3-((morpholin-4-yl)-methyl)-benzaldehyde		COc1cc(CN2CCOCC2)c(c(C=O)c1)O
R7	8-chloro-4-formyl-3,5-dioxo-2-oxa-bicyclo[4.4.0]deca-1(10),6,8-triene		C(C1C(c2cc(ccc2OC1=O)[Cl])=O)=O
R8	2-chloro-6-phenyl-pyridine-4-carbaldehyde		C(c1cc(c2ccccc2)nc(c1)[Cl])=O
R9	5-(4-chloro-phenylsulfonyl)-furan-2-carbaldehyde		C(c1ccc(o1)S(c1ccc(cc1)[Cl])(=O)=O)=O
R10 (I7) [i]	1-((acetoxyimino)methyl)-2-methylindolizine-3-carbaldehyde		CC(=O)ON=Cc1c(C)c(C=O)n2ccccc12
R11	5-(thiocyanato-methyl)-furan-2-carbaldehyde		C(c1ccc(C=O)o1)SC#N
R12	Phenanthrene-9-carboxaldehyde		C(c1cc2ccccc2c2ccccc12)=O
S1	methyl 3-formyl-2-hydroxy-benzoate		COC(c1cccc(C=O)c1O)=O

S2	4,5-dibromo-furan-2-carbaldehyde		C(c1cc(c(o1)[Br])[Br])=O
S3	3-iodo-4,5-dimethoxy-benzaldehyde		COc1cc(C=O)cc(c1OC)I
S4	2-aza-bicyclo[4.4.0]deca-1(6),2,4,7,9-pentaene-10-carbaldehyde		C(c1cccc2cccnc12)=O
S5	5-chloro-2-hydroxy-3-methoxy-benzaldehyde		COc1cc(cc(C=O)c1O)[Cl]
S6	4-((1,1-dioxidobenzo[d]isothiazol-3-yl)oxy)benzaldehyde		C(c1ccc(cc1)OC1c2ccccc2S(N=1)(=O)=O)=O
S7	N-(3-formylphenyl)methanesulfonamide		CS(Nc1cccc(C=O)c1)(=O)=O
S8	methyl 4-formyl-benzoate		COC(c1ccc(C=O)cc1)=O
S9	2-phenyl-acetaldehyde		C(C=O)c1ccccc1
S10	4-methoxy-3-((1H-pyrazol-1-yl)-methyl)-benzaldehyde		COc1ccc(C=O)cc1Cn1cccn1
S11	4-ethynyl-benzaldehyde		C#Cc1ccc(C=O)cc1
S12	-ethyl 2-chloro-3-formyl-9-methyl-7-aza-bicyclo[4.3.0]nona-1(6),2,8-		CCOC(c1c(C)c2C(=C(CCc2[nH]1)C=O)[Cl])=O
T1	8-(2-formyl-1H-pyrrol-1-yl)-7-thia-bicyclo[4.3.0]nona-1(6),8-diene-9-carboxylic acid		C1CCc2c(C1)c(C(O)=O)c(n1cccc1C=O)s2
T2	7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraene-2-carbaldehyde		C(c1cccc2c1cc[nH]2)=O
T3	5-formyl-4-hydroxy-bicyclo[4.4.0]deca-1,3,5,7,9-pentaene-3-carboxylic acid		C(c1c(c(cc2ccccc12)C(O)=O)O)=O

T4	4-(prop-2-ynoxy)-benzaldehyde		C#CCOc1ccc(C=O)cc1
T5	4-chloro-2-methyl-2H-pyrazole-3-carbaldehyde		Cn1c(C=O)c(cn1)[Cl]
T6	7-aza-bicyclo[4.3.0]nona-1,3,5,8-tetraene-3-carbaldehyde		C(c1ccc2c(cc[nH]2)c1)=O
T7	methyl 2-formyl-benzoate		COC(c1ccccc1C=O)=O
T8	5-((2,3,5,6-tetrafluoro-phenoxy)-methyl)-furan-2-carbaldehyde		C(c1ccc(C=O)o1)Oc1c(c(cc(c1F)F)F)F
T9	2-(4-bromo-2-formyl-phenoxy)-ethanenitrile		C(C#N)Oc1ccc(cc1C=O)[Br]
T10	1-(2-hydroxy-phenyl)-ethanone		CC(c1ccccc1O)=O
T11	1-(4-hydroxy-phenyl)-ethanone		CC(c1ccc(cc1)O)=O
T12 (H1, D1)[i]	6-(4-formyl-phenyl)-pyridine-3-carbonitrile		C(c1ccc(cc1)c1ccc(C#N)cn1)=O

[i]Repeat aldehydes. [ii]Blank spaces.

Table S2. Inhibition values of oximes **5-Y** determined in gel-based TDP1 binding assays.[i] 16 Oximes (red) show >90% TDP1 inhibition at 100 μM, Hit/Library = 16/230 = 7%.

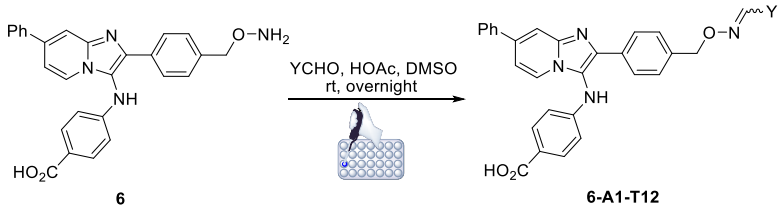
5 **5-A1-T12**

	1	2	3	4	5	6	7	8	9	10	11	12
A	**5-A1**	**5-A2**	**5-A3**	**5-A4**	**5-A5**	**5-A6**	**5-A7**	**5-A8**	**5-A9**	**5-A10**	**5-A11**	**5-A12**
%	22.7	27.4	48.3	54.6	49.0	2.5	14.0	54.6	6.5	35.4	10.6	42.6
B	**5-B1**	**5-B2**	**5-B3**	**5-B4**	**5-B5**	**5-B6**	**5-B7**	**5-B8**	**5-B9**	**5-B10**	**5-B11**	**5-B12**
%	25.1	12.9	14.6	-2.0	63.2	19.4	45.5	36.9	73.5	22.2	77.8	7.9
C	**5-C1**	**5-C2**	**5-C3**	**5-C4**	**5-C5**	**5-C6**	**5-C7**	**5-C8**	**5-C9**	**5-C10**	**5-C11**	**5-C12**
%	1.3	3.1	12.9	48.6	-1.5	-0.5	51.5	47.9	32.2	-16.8	11.2	47.5
D	**5-D1**	**5-D2**	**5-D3**	**5-D4**	**5-D5**	**5-D6**	**5-D7**	**5-D8**	**5-D9**	**5-D10**	**5-D11**	**5**
%	93.9	52.1	77.8	79.7	71.9	49.7	-6.3	-2.3	58.8	-25.1	13.8	-5.3
E	**5-E1**	**5-E2**	**Blank**[iii]	**5**[ii]	**5-E5**	**5-E6**	**5-E7**	**5-E8**	**5-E9**	**5-E10**	**5-E11**	**5-E12**
%	23.9	14.5	0.0	3.1	13.9	45.6	21.0	-10.6	11.4	21.8	-2.6	15.6
F	**5-F1**	**5-F2**	**5-F3**	**5-F4**	**5-F5**	**5-F6**	**5-F7**	**5-F8**	**5-F9**	**5-F10**	**5-F11**	**5-F12**
%	1.4	41.6	10.1	45.6	98.2	34.0	5.5	45.4	-8.2	61.5	-3.6	25.1
G	**5-G1**	**5-G2**	**5-G3**	**5-G4**	**5-G5**	**5-G6**	**5-G7**	**5-G8**	**5-G9**	**5-G10**	**5-G11**	**5-G12**
%	20.0	-10.6	65.4	34.0	57.6	93.1	106.5	90.5	34.2	0.7	4.4	24.1
H	**5-H1/D1**	**5-H2**	**5-H3**	**5-H4**	**5-H5**	**5-H6**	**5-H7**	**5-H8**	**5-H9**	**5-H10**	**5-H11**	**5-H12**
%	81.0	76.7	33.9	-4.6	16.0	3.5	1.3	35.6	4.5	35.2	26.7	-20.6
I	**5-I1**	**5-I2**	**5-I3**	**5-I4**	**5-I5**	**5-I6**	**5-I7**	**5-I8**	**5-I9**	**5-I10**	**5-I11**	**5-I12**
%	15.2	5.2	44.5	16.8	46.4	58.9	98.3	29.7	16.4	0.2	-16.5	-2.5
J	**5-J1**	**5-J2**	**5-J3**	**5-J4**	**5-J5**	**5-J6**	**5-J7**	**5-J8**	**5-J9**	**5-J10**	**5-J11**	**5-J12**
%	3.2	82.5	25.8	-3.6	12.0	40.3	2.6	37.9	-17.8	30.8	24.0	-2.8
K	**5-K1**	**5-K2**	**5-K3**	**5-K4**	**5-K5**	**5-K6**	**5-K7**	**5-K8**	**5-K9**	**5-K10**	**5-K11**	**5-K12**
%	0.5	10.8	35.1	32.3	-1.5	20.9	2.0	39.9	9.7	9.7	-6.7	6.6
L	**5-L1**	**5-L2**	**5-L3**	**5-L4**	**5-L5**	**5-L6**	**5-L7**	**5-L8**	**5-L9**	**5-L10**	**5-L11**	**5-L12**
%	14.6	4.7	0.4	-1.1	5.5	47.7	-6.2	0.3	-28.5	22.5	-19.0	-17.1
M	**5-M1**	**5-M2**	**5**[iii]	**Blank**[ii]	**5-M5**	**5-M6**	**5-M7**	**5-M8**	**5-M9**	**5-M10**	**5-M11**	**5-M12**
%	11.9	-6.5	4.2	0.0	62.9	0.1	20.1	-0.1	-4.5	-2.8	112.9	-23.6
N	**5-N1**	**5-N2**	**5-N3**	**5-N4**	**5-N5**	**5-N6**	**5-N7**	**5-N8**	**5-N9**	**5-N10**	**5-N11**	**5-N12**
%	84.6	-13.1	98.5	102.7	25.6	-13.6	-3.2	87.6	29.5	-10.9	24.4	-10.1

O	5-O1	5-O2	5-O3	5-O4	5-O5	5-O6	5-O7	5-O8	5-O9	5-O10	5-O11	5-O12
%	-4.2	-6.2	1.6	-3.6	72.1	2.9	20.6	8.7	6.7	6.5	113.0	-9.4
P	**5-P1**	**5-P2**	**5-P3**	**5-P4**	**5-P5/G8**	**5-P6**	**5-P7**	**5-P8**	**5-P9**	**5-P10**	**5-P11**	**5-P12**
%	95.4	3.0	110.6	113.2	36.5	-0.4	12.2	93.3	35.1	-3.2	27.0	-4.9
Q	**5-Q1**	**5-Q2**	**5-Q3**	**5-Q4/G6**	**5-Q5**	**5-Q6**	**5-Q7**	**5-Q8**	**5-Q9**	**5-Q10**	**5-Q11**	**5-Q12**
%	49.1	64.8	49.0	85.3	61.2	27.7	8.2	13.0	12.7	57.8	53.0	-5.3
R	**5-R1**	**5-R2**	**5-R3**	**5-R4**	**5-R5**	**5-R6**	**5-R7**	**5-R8**	**5-R9**	**5-R10/I7**	**5-R11**	**5-R12**
%	42.2	64.4	35.5	17.2	45.5	9.9	18.4	29.9	32.3	101.3	91.2	38.4
S	**5-S1**	**5-S2**	**5-S3**	**5-S4**	**5-S5**	**5-S6**	**5-S7**	**5-S8**	**5-S9**	**5-S10**	**5-S11**	**5-S12**
%	70.5	37.0	33.7	94.9	76.5	14.5	7.1	28.7	22.9	15.8	51.3	115.8
T	**5-T1**	**5-T2**	**5-T3**	**5-T4**	**5-T5**	**5-T6**	**5-T7**	**5-T8**	**5-T9**	**5-T10**	**5-T11**	**5-T12/D1/H1**
%	73.6	39.7	50.5	30.1	17.2	37.6	30.2	20.7	34.3	3.2	29.1	118.2

Notes: [i]See Figure S1. The oximes were evaluated by gel-based TDP1 fluorescence assay in a concentration of 100 μM in DMSO. The fluorescence of DMSO blank vial was set as 0 and the fluorescence for the reference without TDP1 was set as 100%. Oximes **5-M1-T12** (30 uL, 10 mM in DMSO). Preparation: A mixture of aminooxy-containing **5** (10 μL, 30 mM in DMSO), aldehydes **M1-T12** (10 μL, 30 mM in DMSO) and acetic acid (10 μL, 150 mM in DMSO) were agitated at room temperature overnight. Oximes **5-M1-T12** (30 uL, 10 mM in DMSO) were afforded. [ii]Aminooxy-containing **5** (10 mM) and HOAc (50 mM).[iii]Blank: HOAc (50 mM in DMSO).

Table S3. Inhibition values of oximes **6-Y** determined in gel-based TDP1 binding assays.[i] 42 Oximes (red) show >90% TDP1 inhibition at 100 μM, Hit/Library = 42/230 = 18%.



6 **6-A1-T12**

	1	2	3	4	5	6	7	8	9	10	11	12
A	**6-A1**	**6-A2**	**6-A3**	**BLANK**[ii]	**6-A5**	**6-A6**	**6-A7**	**6-A8**	**6-A9**	**6-A10**	**6-A11**	**6-A12**
%	37.9	24.0	26.4	0.0	11.7	96.6	30.1	73.0	17.9	63.4	87.1	26.5
B	**6-B1**	**6-B2**	**6-B3**	**6-B4**	**6-B5**	**6-B6**	**6-B7**	**6-B8**	**6-B9**	**6-B10**	**6-B11**	**6-B12**
%	35.5	77.5	57.1	81.1	81.3	26.0	90.7	17.9	98.2	24.3	90.8	64.5
C	**6-C1**	**6-C2**	**6-C3**	**6-C4**	**6-C5**	**6-C6**	**6-C7**	**6-C8**	**6-C9**	**6-C10**	**6-C11**	**6-C12**
%	83.2	54.7	67.4	54.2	37.3	57.4	25.6	51.1	53.1	26.0	68.4	34.7
D	**6-D1**	**6-D2**	**6-D3**	**6-D4**	**6-D5**	**6-D6**	**6-D7**	**6-D8**	**6-D9**	**6-D10**	**6-D11**	**6**[iii]
%	98.7	43.7	37.6	79.6	30.9	75.6	17.7	61.6	17.3	97.7	82.7	34.5
E	**6-E1**	**6-E2**	**Blank**[iii]	**6**[ii]	**6-E5**	**6-E6**	**6-E7**	**6-E8**	**6-E9**	**6-E10**	**6-E11**	**6-E12**
%	46.1	50.6	0.0	44.8	39.1	102.1	87.4	60.3	35.5	86.0	37.7	45.7
F	**6-F1**	**6-F2**	**6-F3**	**6-F4**	**6-F5**	**6-F6**	**6-F7**	**6-F8**	**6-F9**	**6-F10**	**6-F11**	**6-F12**
%	99.7	74.5	98.7	66.7	75.7	89.7	71.4	71.6	92.8	92.3	98.6	72.7
G	**6-G1**	**6-G2**	**6-G3**	**6-G4**	**6-G5**	**6-G6**	**6-G7**	**6-G8**	**6-G9**	**6-G10**	**6-G11**	**6-G12**
%	79.6	68.1	76.3	45.3	69.5	96.3	77.0	96.9	84.3	75.8	45.6	42.1
H	**6-H1/D1**	**6-H2**	**6-H3**	**6-H4**	**6-H5**	**6-H6**	**6-H7**	**6-H8**	**6-H9**	**6-H10**	**6-H11**	**6-H12**
%	101.8	76.4	58.4	79.3	83.7	68.5	100.4	87.2	59.7	87.1	100.6	89.0
I	**6-I1**	**6-I2**	**6-I3**	**6-I4**	**6-I5**	**6-I6**	**6-I7**	**6-I8**	**6-I9**	**6-I10**	**6-I11**	**6-I12**
%	93.0	59.1	100.8	42.7	45.9	78.3	99.0	99.9	83.9	63.5	69.4	33.2
J	**6-J1**	**6-J2**	**6-J3**	**6-J4**	**6-J5**	**6-J6**	**6-J7**	**6-J8**	**6-J9**	**6-J10**	**6-J11**	**6-J12**
%	66.9	53.0	75.3	64.5	49.7	60.7	61.9	-17.5	99.9	83.6	33.2	85.4
K	**6-K1**	**6-K2**	**6-K3**	**6-K4**	**6-K5**	**6-K6**	**6-K7**	**6-K8**	**6-K9**	**6-K10**	**6-K11**	**6-K12**
%	92.6	58.4	84.9	41.4	69.0	75.3	84.0	53.8	99.2	81.2	23.9	65.6
L	**6-L1**	**6-L2**	**6-L3**	**6-L4**	**6-L5**	**6-L6**	**6-L7**	**6-L8**	**6-L9**	**6-L10**	**6-L11**	**6-L12**
%	45.1	47.4	72.0	52.3	73.3	85.8	82.4	95.7	62.6	87.6	96.1	54.5
M	**6-M1**	**6-M2**	**6**[ii]	**Blank**[iii]	**6-M5**	**6-M6**	**6-M7**	**6-M8**	**6-M9**	**6-M10**	**6-M11**	**6-M12**
%	15.1	12.2	23.5	0.0	40.9	22.4	44.8	76.5	18.4	36.2	100.1	0.1
N	**6-N1**	**6-N2**	**6-N3**	**6-N4**	**6-N5**	**6-N6**	**6-N7**	**6-N8**	**6-N9**	**6-N10**	**6-N11**	**6-N12**
%	29.9	96.0	97.0	95.6	80.4	23.7	30.5	93.4	85.6	39.0	71.3	84.8

O	6-O1	6-O2	6-O3	6-O4	6-O5	6-O6	6-O7	6-O8	6-O9	6-O10	6-O11	6-O12
%	21.8	13.9	26.3	10.4	47.9	31.2	54.7	82.5	28.2	42.8	98.5	6.9
P	**6-P1**	**6-P2**	**6-P3**	**6-P4**	**6-P5/G8**	**6-P6**	**6-P7**	**6-P8**	**6-P9**	**6-P10**	**6-P11**	**6-P12**
%	41.2	94.2	99.5	94.5	85.4	27.0	31.0	95.3	87.6	39.8	71.4	84.0
Q	**6-Q1**	**6-Q2**	**6-Q3**	**6-Q4/G6**	**6-Q5**	**6-Q6**	**6-Q7**	**6-Q8**	**6-Q9**	**6-Q10**	**6-Q11**	**6-Q12**
%	38.8	35.7	55.8	79.9	87.0	39.4	49.6	67.4	99.4	59.5	71.7	91.8
R	**6-R1**	**6-R2**	**6-R3**	**6-R4**	**6-R5**	**6-R6**	**6-R7**	**6-R8**	**6-R9**	**6-R10/I7**	**6-R11**	**6-R12**
%	52.0	41.5	40.7	61.8	71.4	32.7	101.6	50.6	70.5	96.6	100.7	18.8
S	**6-S1**	**6-S2**	**6-S3**	**6-S4**	**6-S5**	**6-S6**	**6-S7**	**6-S8**	**6-S9**	**6-S10**	**6-S11**	**6-S12**
%	28.9	91.9	39.0	32.5	37.6	80.8	45.8	59.3	38.6	67.1	91.7	52.7
T	**6-T1**	**6-T2**	**6-T3**	**6-T4**	**6-T5**	**6-T6**	**6-T7**	**6-T8**	**6-T9**	**6-T10**	**6-T11**	**6-T12/D1/H1**
%	101.9	17.2	101.9	47.3	31.4	42.5	30.4	36.9	62.3	59.4	63.0	101.1

Notes: [i]See Figure S1. The oximes were evaluated by gel-based TDP1 fluorescence assay in a concentration of 100 μM in DMSO. The fluorescence of DMSO blank vial was set as 0 and the fluorescence for the reference without TDP1 was set as 100%. Oximes **6-M1-T12** (30 uL, 10 mM in DMSO) were prepared based on the following method. A mixture of aminooxy-containing **6** (10 μL, 30 mM in DMSO), aldehydes **M1**-**T12** (10 μL, 30 mM in DMSO) and acetic acid (10 μL, 150 mM in DMSO) was agitated at room temperature overnight. The formed oximes **6-M1-T12** (30 uL, 10 mM in DMSO) were diluted to 100 μM in DMSO and evaluated by gel-based TDP1 assay. [ii]Aminooxy-containing **6** (10 mM) and HOAc (50 mM). [iii] Blank: HOAc (50 mM in DMSO).

Table S4. X-ray Data Collection and Refinement Statistics.

	TDP1-XZ761 (9a)	**TDP1-XZ760 (9c) complex**
Data collection Statistics		
Diffraction source	SER-CAT, 22-BM	SER-CAT, 22-BM
Wavelength (Å)	1.0000	1.0000
Temperature (K)	100	100
Detector	Rayonix MX300-HS	Rayonix MX300-HS
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell parameters		
a=, b=, c= (Å)	49.80, 105.01, 192.90	49.73, 104.76, 193.21
$\alpha = \beta = \gamma$ = (°)	90	90
Resolution range (Å)	50-1.65 (1.68-1.65)	50-1.81(1.84-1.81)*
Total reflections	888797	593632
Unique reflections	122399 (6022)	89034 (4242)
Completeness (%)	100 (99.9)	95.9 (91.4)
Multiplicity	7.3 (5.7)	6.7 (6.6)
Mean $I/\sigma(I)$	20.2 (2.1)	21.9 (2.1)
R_{merge}	0.110 (0.724)	0.075 (0.692)
$R_{p.i.m.}$	0.044 (0.319)	0.031 (0.280)
$CC_{1/2}$	0.994 (0.853)	0.997 (0.861)
Refinement Statistics		
Resolution range (Å)	46.12-1.65 (1.67-1.65)	40.64-1.81(1.83-1.81)
Number of reflections	122293	88944
Number of reflections used in R_{free}	6086	4399
Final R_{work}	0.167 (0.241)	0.156 (0.229)
Final R_{free}	0.194 (0.266)	0.191 (0.263)
Number of non-H atoms		
Protein, chain A	3652	3612
Protein, chain B	3622	3629
XZ760		50 (chain A), 35 (chain B)
XZ761	34 (chain A), 34 (chain B)	
Ethylene glycol	28	20
DMSO		4
MOPS	26	13
Water	793	699
Average *B* factors (Å^2)		
Protein chain A	19.3	25.6
Protein chain B	25.5	32.4
XZ760 (**9c**)		38.0 (chain A),46.3 (chain B)
XZ761 (**9a**)	25.7 (chain A), 31.3 (chain B)	
MOPS	24.3	30.7
Ethylene glycol	26.5	30.7
DMSO		55.0
Water	35.2	40.3
Estimated coordinate error (Å)	0.17	0.16
R.m.s. deviations from ideal		
Bond lengths (Å)	0.006	0.006

Bond angles (°)	0.86	0.83
Ramachandran plot		
Favored (%)	98.0	97.7
Allowed (%)	1.9	2.3
Outliers (%)	0.1	0
MolProbity Analysis		
Clashscore, all atoms	3.0 (98^{th} percentile)	2.61 (99^{th} percentile)
Protein geometry score	1.09 (99^{th} percentile)	1.07 (100^{th} percentile)
PDB deposition code	8CVQ	8CW2
*Values in parenthesis are for the highest resolution shell of data		

Table S5. TDP1 selectivity of lead compounds over TDP2 using gel-based assays *in vitro*.

Compound	**TDP1 IC_{50} (µM)**[i]	**TDP2 IC_{50} (µM)**[ii]	**TDP1 Selectivity**[iii]
(*E*)-6-D1	0.38 ± 0.06	28.1 ± 8.9	74
7d	3.1 ± 0.2	25.9 ± 0.4	8
8b	2.75 ± 0.25	>100	>36

Note: [i]The half maximal inhibitory concentration (IC_{50}) based on gel based TDP1 fluorescence assay. [ii]The half maximal inhibitory concentration (IC_{50}) based on gel based TDP2 fluorescence assay. [iii]TDP1 selectivity based on the ratio of IC_{50} values of TDP1/TDP2.

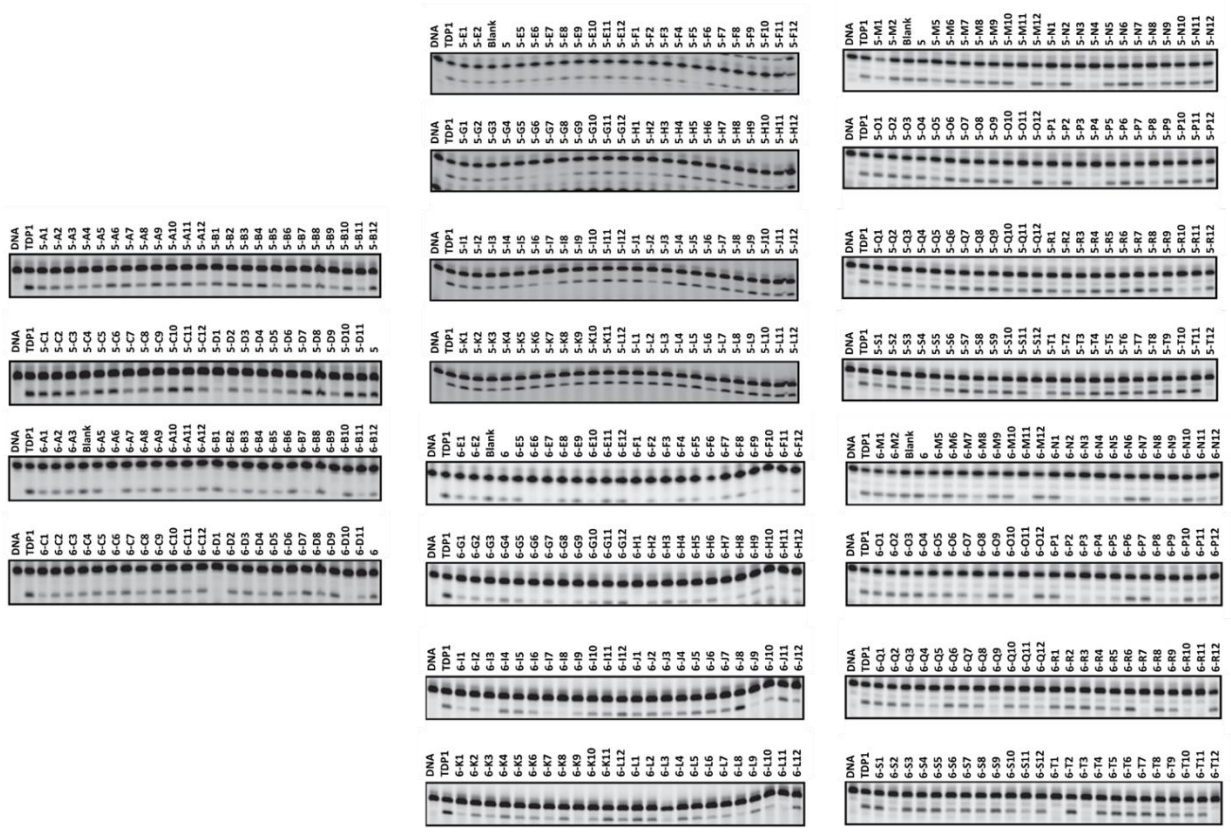


Fig. S1 Primary screen of oximes **5-Y** and **6-Y** in gel-based TDP1 binding assays (TDP1 40 pM, DNA Cy5N14Y 1 nM, Drug 100 μM).

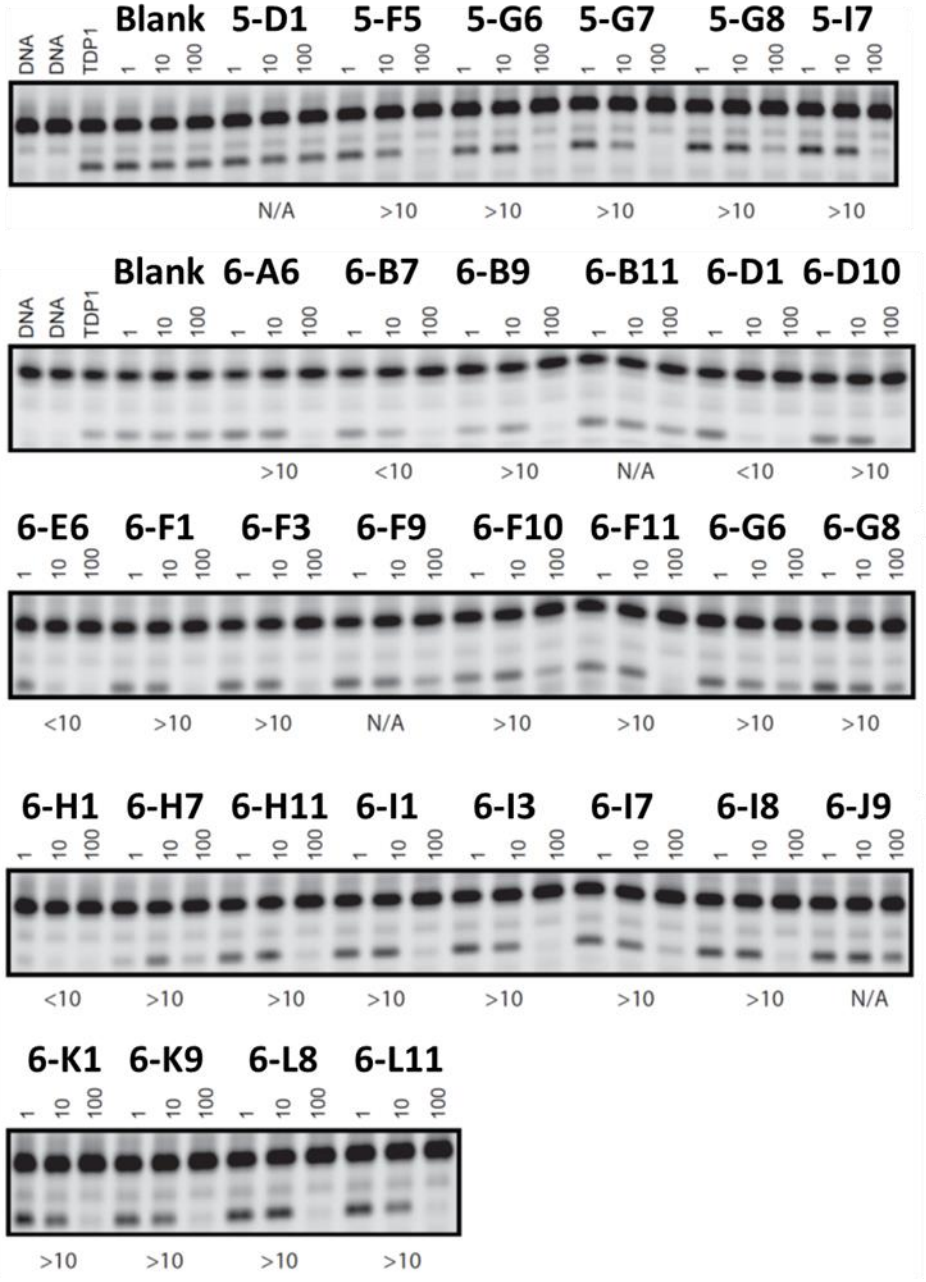


Fig. S2 Secondary screen of oximes **5-Y** and **6-Y** in gel-based TDP1 binding assays (TDP1: 40 pM, DNA Cy5N14Y: 1 nM, Drug: 1, 10, 100 μM). Oximes from aldehydes B7, D1 (H1), E6, M10, P3 show less than 10 μM TDP1 inhibition.

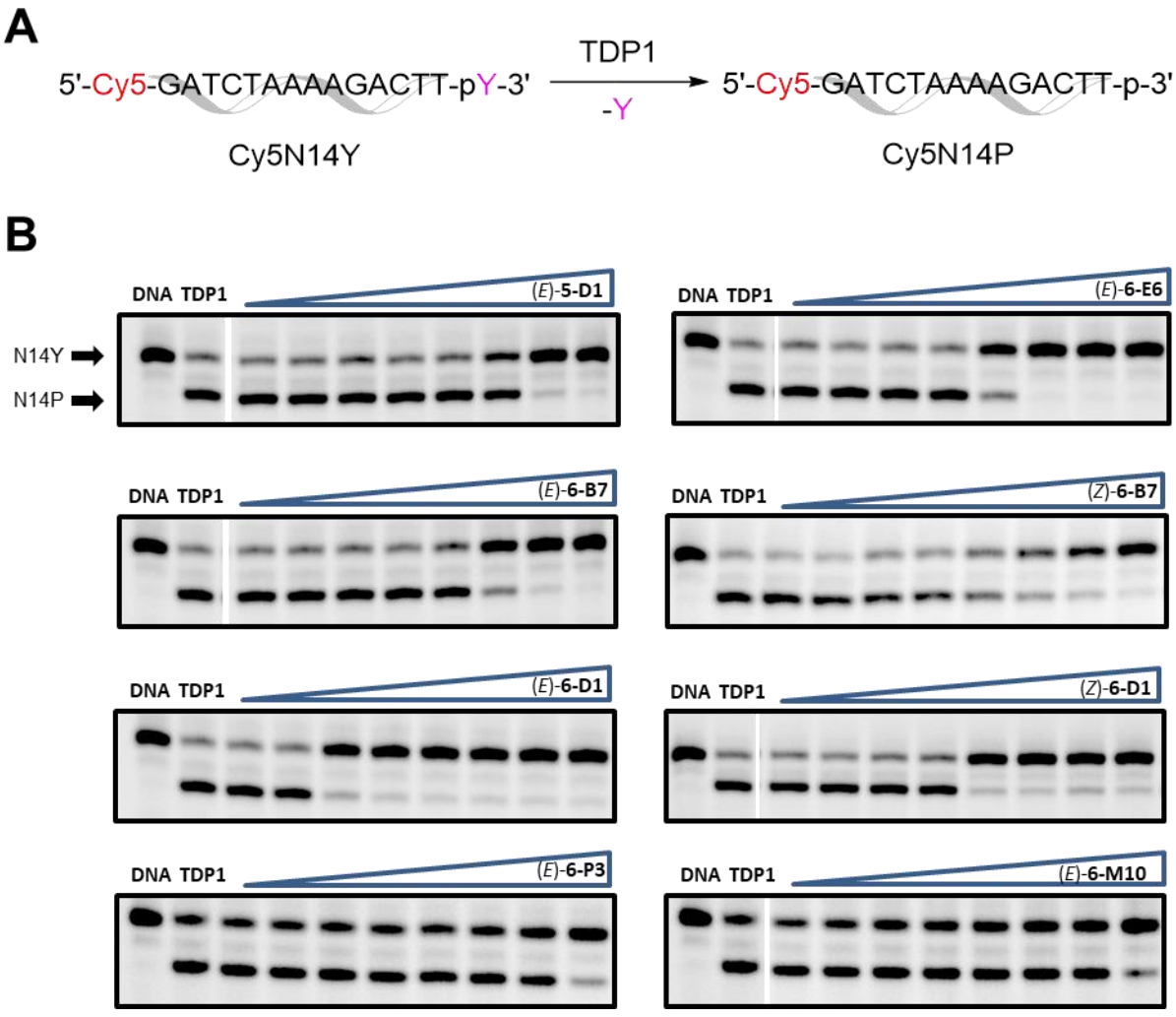


Fig. S3 TDP1 catalytic reaction and representative gel images. (A) Scheme of the TDP1 catalytic reaction applied in the gel assay. (B) Representative gels showing the inhibition of full-length TDP1-catalyzed hydrolysis by the oxime leads. In each gel: lane 1, Cy5N14Y only; lane 2, Cy5N14Y and TDP1; lanes 3-10, 3-fold serial dilutions of the oxime leads from 0.05 μM to 111 μM.

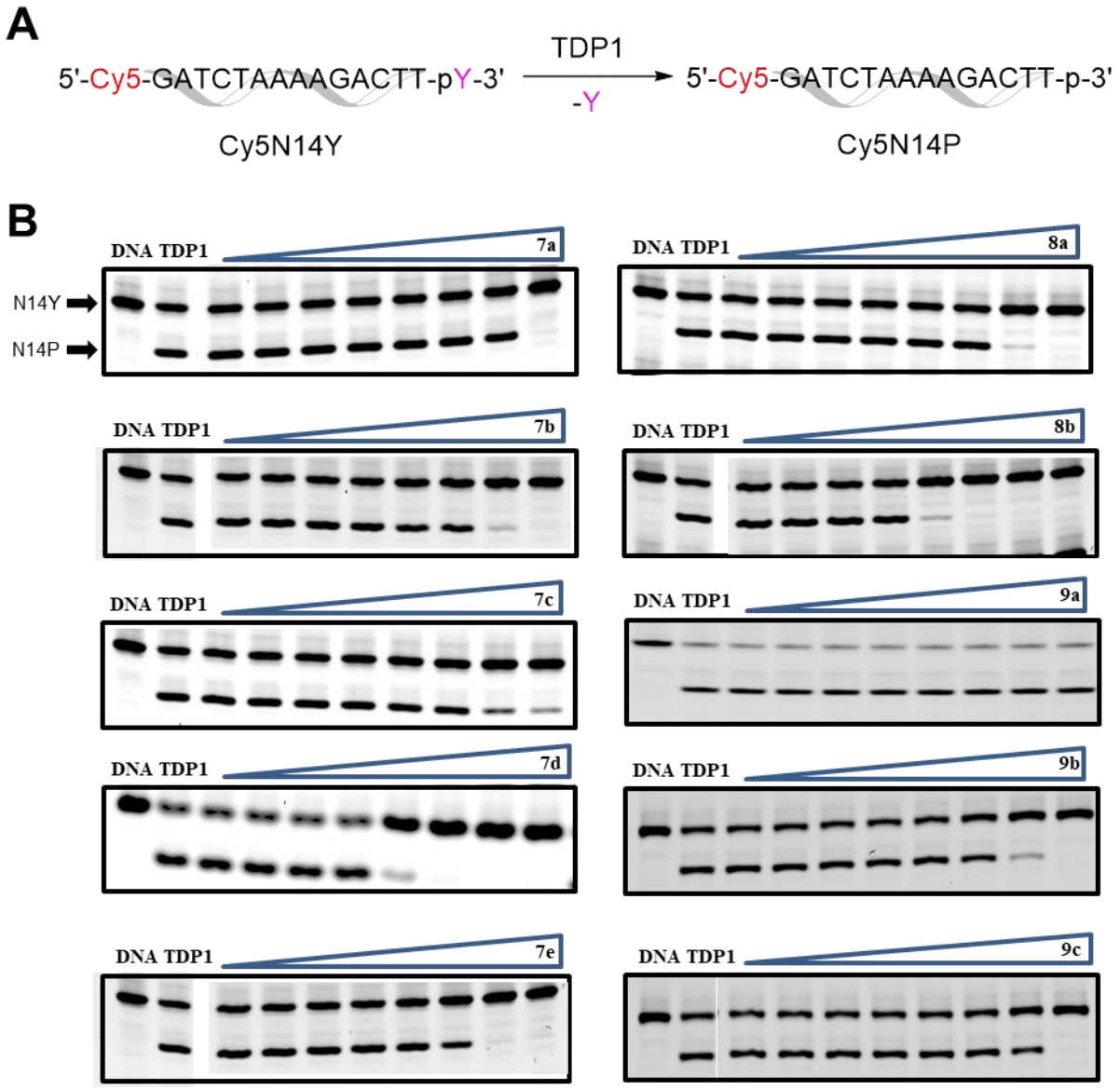


Fig. S4 TDP1 catalytic reaction and representative gel images. (A) Scheme of the TDP1 catalytic reaction applied in the gel assay. (B) Representative gels showing the inhibition of full-length TDP1-catalyzed hydrolysis by isosteres **7a-e**, **8a,b** and **9a-c**. In each gel: lane 1, Cy5N14Y only; lane 2, Cy5N14Y and TDP1; lanes 3-10, 3-fold serial dilutions of drugs from 0.05 μM to 111 μM.

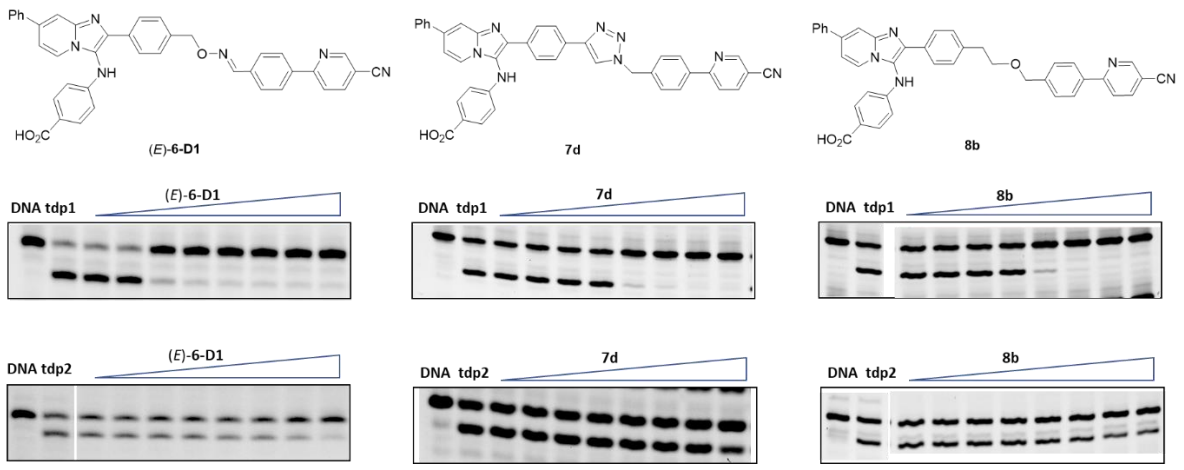


Fig. S5. TDP1 and TDP2 catalytic reaction and representative gel images showing the inhibition of oxime (*E*)-**6-D1**, triazole **7d** and ether **8b**. In each gel: lane 1, Cy5N14Y only; lane 2, Cy5N14Y and TDP1; lanes 3-10, 3-fold serial dilutions of drugs from 0.05 μM to 111 μM.

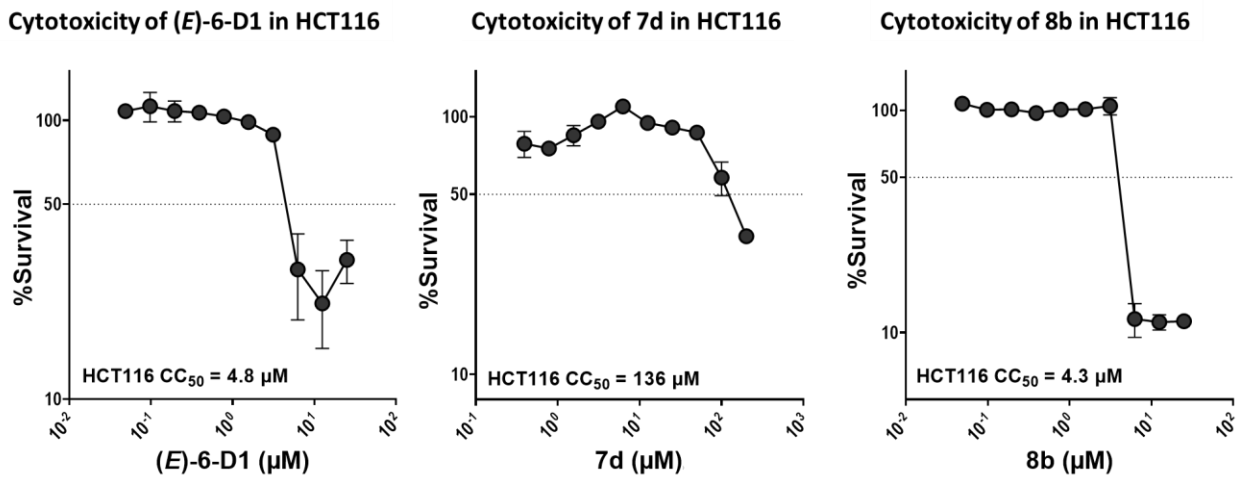


Fig. S6. Cytotoxicity of selective TDP1 inhibitors oxime (*E*)-**6-D1**, triazole **7d** and ether **8b** in human colon cancer cell line HCT116 based on cell viability.

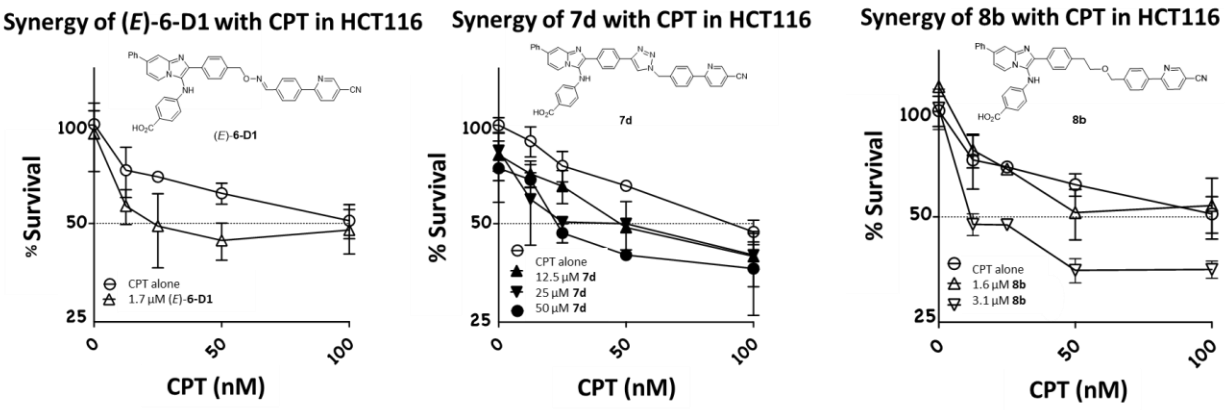


Fig. S7. Synergistic effect of selective TDP1 inhibitors with camptothecin (CPT) in human colon cancer cell line HCT116 based on cell viability.

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