SUPPORTING INFORMATION

Structure-guided Optimization of Replication Protein A (RPA)-DNA Interaction Inhibitors.

Navnath S. Gavande,*,†,‡ Pamela VanderVere-Carozza,† Katherine S. Pawelczak,§ Tyler L. Vernon,† Matthew Jordan,† and John J. Turchi*,†,§,⊥

†Department of Medicine, Indiana University School of Medicine (IUSM), Indianapolis, IN 46202 USA; ‡Department of Pharmaceutical Sciences, Wayne State University College of Pharmacy and Health Sciences, Detroit, MI 48201, USA; §NERx Biosciences, 212 W 10th St. Suite A480, Indianapolis, IN 46202, USA; ⊥Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN 46202, USA

*Corresponding authors at:

1. John J. Turchi: Departments of Medicine and Department of Biochemistry & Molecular Biology, Indiana University School of Medicine, Indianapolis, IN 46202, USA. *E-mail:* jturchi@iu.edu. Tel.: +1-(317)-278-1996; fax, +1-(317)-274-0396.
2. Navnath S. Gavande: Department of Pharmaceutical Sciences, Wayne State University College of Pharmacy and Health Sciences, Detroit, MI 48201, USA. *E-mail:* ngavande@wayne.edu. Tel.: +1-(313)-577-1523; fax, +1-(313)-577-2033.

*Schematic Representation of the RPA Heterotrimeric Subunits:

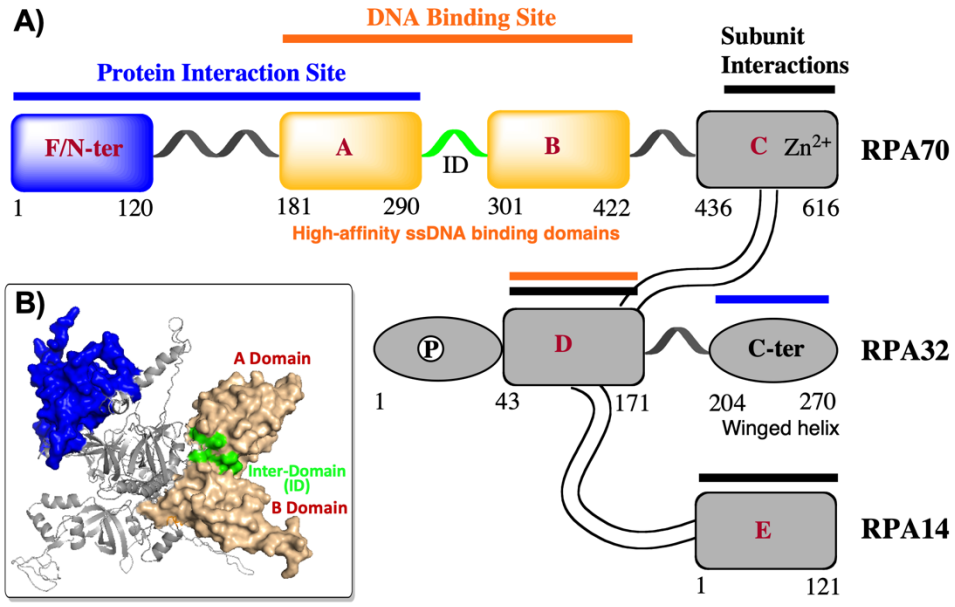
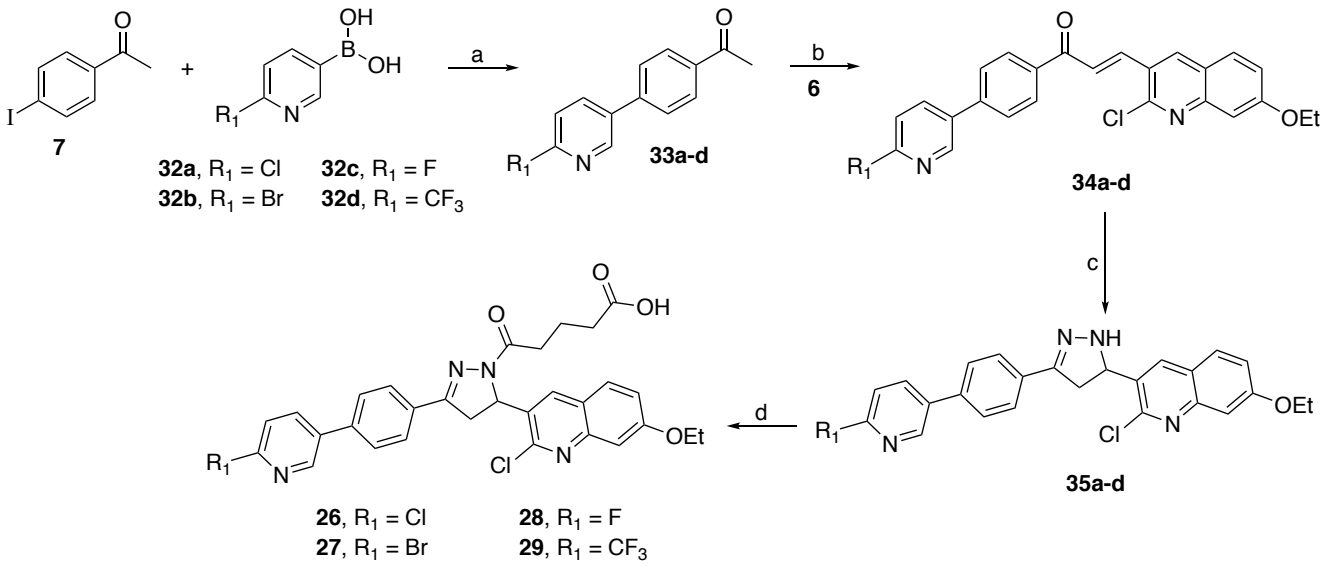


Figure S1. **A**) Schematic representation of the RPA heterotrimeric subunits (70, 32, and 14 kDa) and OB-fold domains (A-F).[1-3] The DNA interaction sites are indicated by the orange bars, subunit interaction sites by the black bars and domains associated with other proteins binding by the blue bars. **B**) The composite RPA heterotrimer structure is colored according to the schematic diagram A.

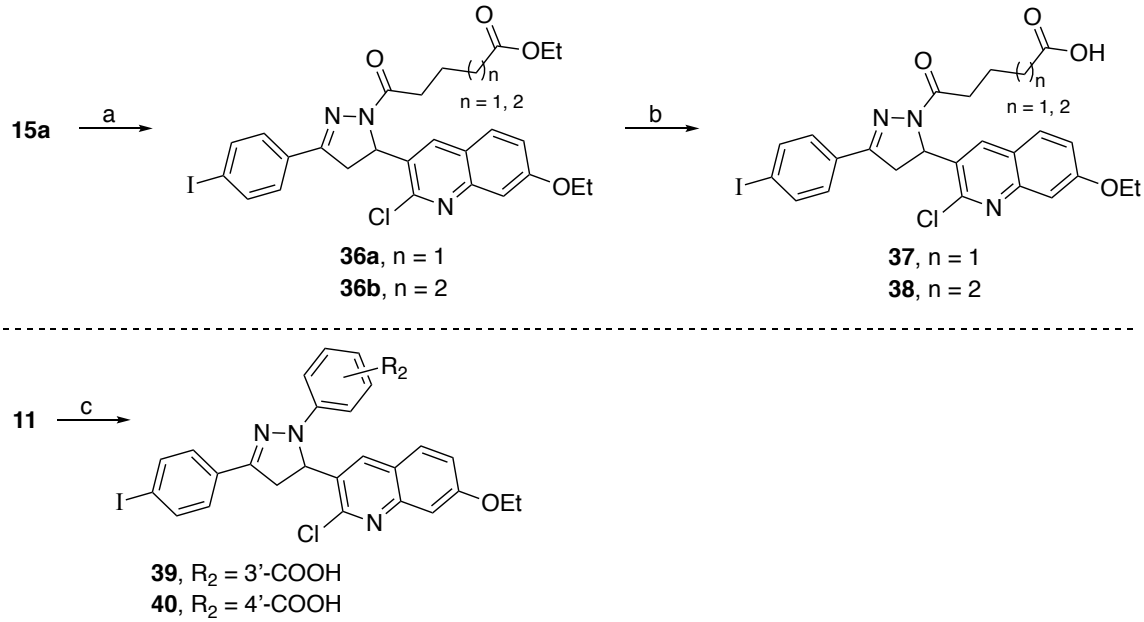
2) Synthetic Schemes and Biological Activity Tables:

Supplemental Scheme S1. Synthesis of Analogs 26-29[a]



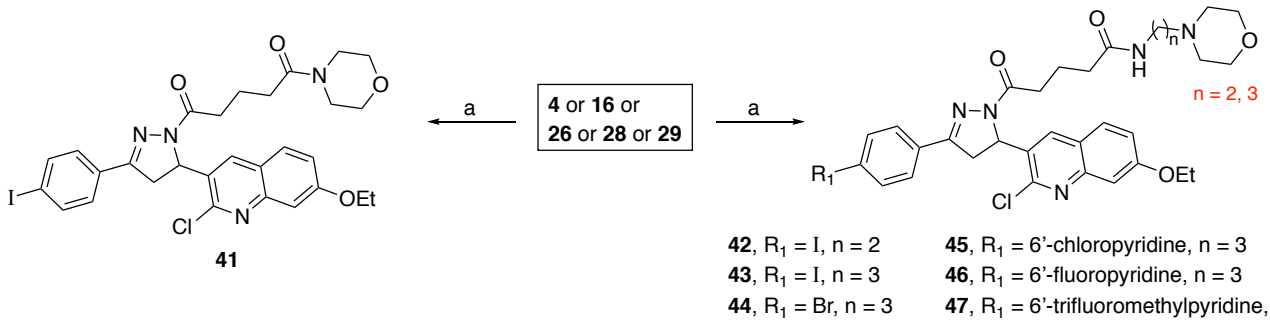
[a]Reagents and conditions: (a) $Pd(PPh_3)_4$, K_2CO_3, toluene:H_2O (3:1), 90°C for 18 h, 84-90%; (b) 10% NaOH, EtOH, 45°C for 2-3 hr, 48-68%; (c) hydrazine hydrate, EtOH, reflux for 2-3 h, 73-80%; (d) glutaric anhydride, $CHCl_3$, reflux for 2 h, 65-73% (after recrystallization).

Supplemental Scheme S2. Synthesis of Analogs 37-40[a]



[a]Reagents and conditions: (a) acyl chloride, DIPEA, DCM, rt for 12 h, 84-86%; (b) 10N NaOH, THF:MeOH (1:2), rt for 8 h, 90-92%; (c) 3'- or 4'-hydrazinobenzoic acid, AcOH:nBuOH (1:2), 120°C for 20 h, 58-62%

Supplemental Scheme S3. Synthesis of Analogs 41-47[a]

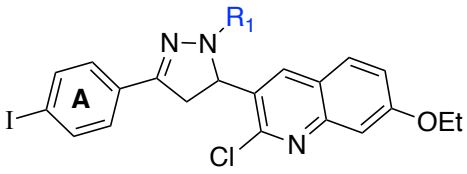


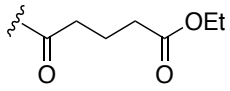
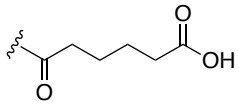
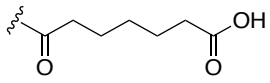
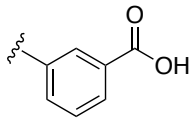
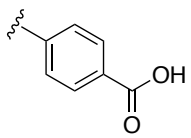
41

42, R_1 = I, n = 2
43, R_1 = I, n = 3
44, R_1 = Br, n = 3
45, R_1 = 6'-chloropyridine, n = 3
46, R_1 = 6'-fluoropyridine, n = 3
47, R_1 = 6'-trifluoromethylpyridine, n = 3

[a]Reagents and conditions: (a) morpholine/morpholinoalkylamine, EDCI, HOBt, DIPEA, DMF, rt for 18 h, 74-81%.

Supplemental Table S1. SAR of Carboxylic acid Modifications with RPA IC_{50} Values of Analogs 30 and 37-40[a]



Compound	R_1	RPA IC_{50} (μM)[b,c]
30		>25
37		6.8 ± 0.23
38		9.9 ± 1.23
39		>25
40		>25

[a]Determined using EMSA, binding of full length human RPA to DNA was assessed. [b]Compounds that displayed greater than 80% inhibition at 25 μM were analyzed in titration experiments. [c]IC_{50} values are a mean of minimum of triplicate independent experiments and data are presented as the mean ± SD.

Supplemental Table S2. Inhibition of RPA DBD A/B Domain by Analogs 23-27[a]

Compoud	$RPA_{A/B}$ IC_{50} (μM)[b]
23	3.3 ± 0.07
24	4.0 ± 0.28
25	16.4 ± 2.09
26	11.7 ± 0.30
27	3.3 ± 0.016

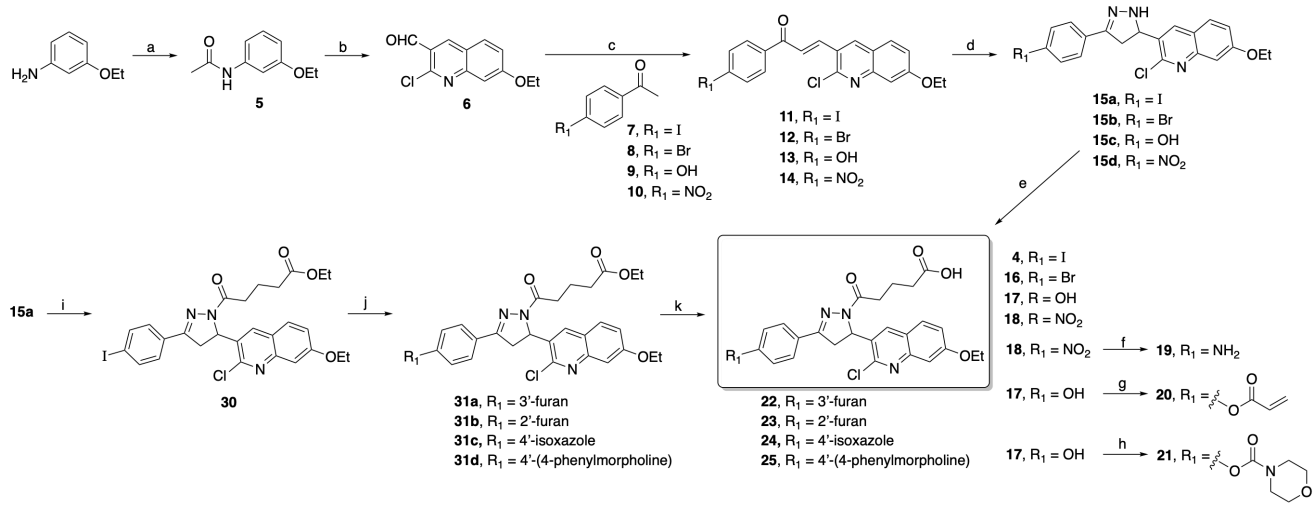
[a]Determined using EMSA, binding of RPA DBD-A/B constructs to DNA was assessed. [b]IC_{50} values are a mean of minimum of triplicate independent experiments and data are presented as the mean ± SD.

3) Synthetic Experimental Details:

General. All chemicals used for synthesis were purchased from Aldrich, Acros, Fisher Scientific and Combi-Blocks Chemical Co. (USA) and used without further purification. Anhydrous solvents were obtained from Fisher Scientific or Aldrich and used directly. All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen atmosphere. ^{1}H NMR spectra were recorded at 300 or 400 or 500 MHz using Bruker AV NMR spectrometer. ^{13}C NMR spectra were recorded at 75 or 100 or 125 MHz using Bruker AV NMR spectrometer. The chemical shifts were reported as δ ppm relative to TMS, using the residual solvent peak as the reference unless otherwise noted. All coupling constants (*J*) are given in hertz. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet or quintet, brs = broad singlet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets), number of protons and coupling constants. Thin layer chromatography was performed using Merck silica gel 60 F-254 thin layer plates, which were developed using one of the following techniques: UV fluorescence (254 nm), alkaline potassium permanganate solution (0.5% w/v) or ninhydrin (0.2% w/v) and iodine vapors. Automated flash column chromatography was carried out on prepacked silica cartridges using the indicated solvent system on Biotage Isolera chromatography system. Purities of all new compounds were determined by analytical HPLC coupled to electrospray ionization mass spectrometry (LC/ESI-MS) using the area percentage method on the UV trace recorded at a wavelength of 214 nm, and compounds were found to have ≥95% purity unless otherwise specified. LC–MS analyses and purity data of compounds were obtained using an Agilent 6545 Q-ToF LC/MS instrument connected to an Agilent 1200 HPLC system, and both instruments were connected to an Agilent photodiode array (PDA) UV detector. A C-18 reversed phase column (Agilent Zorbax EclipsePlus C18 RRHD, 1.8 μM particle size, 2.1 mm x 50 mm) was used as stationary phase, and water and acetonitrile (both containing 0.1% formic acid) were used as mobile phase at room temperature. The HPLC gradient method utilized was 5-90% acetonitrile in water (both containing 0.1% formic acid) over 10 min with a 0.6 mL/min flow rate. UV absorbance at the fixed wavelength of 254 nm and positive and negative ESI-MS data were recorded. The retention time and corresponding ESI-MS data were used to identify molecules. HRMS data were obtained using Waters/Macromass LCT electrospray ionization (ESI) on a time-of-flight (TOF) mass spectrometer at the Mass Spectrometry Facility at Indiana University Chemistry Department (http://msf.chem.indiana.edu).

All final compounds were purified by recrystallization or automated flash column chromatography, and the analytical and spectroscopic data confirmed their purity and structures, as detailed in the experimental section.

Synthesis of Target Compounds 4 and 16-25.



N-(3-Ethoxyphenyl)acetamide (5). To a stirred solution of 3-ethoxyaniline (1 gm, 1 equiv.) in dry DCM (25 mL) were added DIPEA (1.89 mL, 1.5 equiv.), DMAP (89 mg, 0.1 equiv.) and acetic anhydride (0.69 mL, 1 equiv.) under an argon atmosphere. The reaction mixture was stirred for 2 h at room temperature. The solution was then diluted with more DCM (30 mL), the combined organic extracts were washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain *N*-(3-ethoxyphenyl)acetamide **5** (1.15 gm, 88% yield, require no further purification) as an off-white solid. TLC: 50% EtOAc in hexanes, R_f = 0.35; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 9.88 (s, 1H, *NH*), 7.27 (s, 1H), 7.16 (t, 1H, *J* = 8.07 and 16.14 Hz), 7.07 (d, 1H, *J* = 7.08 Hz), 6.59 (d, 1H, *J* = 8.1 Hz), 3.99-3.92 (q, 2H, *OCH*$_2$), 2.02 (s, 3H, *COCH*$_3$), 1.31 (t, 3H, *J* = 6.93 and 13.92 Hz, *CH*$_3$); ^{13}C NMR (100 MHz, DMSO): δ 168.75, 159.21, 140.95, 129.85, 111.64, 109.32, 105.81, 63.31, 24.53, 15.11. MS (ESI) *m*/*z* = 180.1 $[M + H]^+$.

2-Chloro-7-ethoxyquinoline-3-carbaldehyde (6). In a three-necked round flask equipped with condenser, $POCl_3$ (4 mL, 7 equiv.) was added drop wise at 0°C to dry DMF (1.20 mL, 2.5 equiv.) under an argon atmosphere with vigorous stirring for 25 min. Then, *N*-(3-ethoxyphenyl)acetamide **5** (1.10 gm, 1 equiv.) was added portion wise at 0°C. The reaction mixture was warmed up to room temperature and allowed to stir at that temperature for 10 min until clear solution was obtained. After that the reaction mixture was heated at 110°C for 3 h, and then cooled down to room temperature, poured onto stirring ice water (80 mL) and stirred yellow mixture for 15-20 min. The obtained solid was filtered off, washed with water 4-5 times (10 mL) to neutralize the reaction mixture, air dried and crystallized using 70% EtOAc in hexanes to afford 2-chloro-7-ethoxyquinoline-3-carbaldehyde **6** (1.07 gm, 74% yield, require no further purification) as a yellow solid. TLC: 20% EtOAc in hexanes, R_f = 0.51; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 10.32 (s, 1H, *CHO*), 8.87 (s, 1H), 8.18 (d, 1H, *J* = 8.97 Hz), 7.42 (s, 1H), 7.39 (d, 1H, *J* = 8.94 Hz), 4.28-4.21 (q, 2H, *OCH*$_2$), 1.41 (t, 3H, *J* = 6.96 and 13.95 Hz, *CH*$_3$); ^{13}C NMR (75 MHz, DMSO): δ 189.64, 163.54, 151.53, 150.25, 141.03, 132.02, 124.52, 121.86, 121.63, 107.62, 64.69, 14.81. MS (ESI) *m*/*z* = 236.1 $[M + H]^+$.

Synthesis of 11-14: ***(E)-3-(2-Chloro-7-ethoxyquinolin-3-yl)-1-(4-iodophenyl)prop-2-en-1-one (11).*** To a stirred solution of 4-iodoacetophenone **7** (0.36 gm, 1.0 equiv.) and 2-chloro-7-ethoxyquinoline-3-carbaldehyde **6** (0.35 gm, 1.0 equiv.) in 15 mL EtOH was added NaOH (0.83 mL, 2.5 M in water, 2.0 equiv.) drop wise at room temperature. The reaction mixture was stirred for 45 min at 45°C, then cooled down to room temperature and reaction mixture was quenched with HCl (3 M) to pH 2-3. The obtained solid was filtered off, washed with water 2-3 times (5 mL) and crystallized using EtOH to afford (*E*)-3-(2-chloro-7-ethoxyquinolin-3-yl)-1-(4-iodophenyl)prop-2-en-1-one **11** (0.51 gm, 74% yield) as a yellow solid and product was used for the next reaction without further purification. TLC: 30% EtOAc in hexanes, R_f = 0.48; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 9.17 (s, 1H), 8.06 (d, 2H, *J* = 2.1 Hz), 8.02-7.93 (m, 5H), 7.36 (s, 2H), 4.25-4.18 (q, 2H, *OCH*$_2$), 1.41 (t, 3H, *J* = 6.9 and 13.89 Hz, *CH*$_3$); ^{13}C NMR (100 MHz, DMSO): δ 188.53, 162.18, 150.61, 149.95, 138.85, 138.31, 137.75, 137.00, 130.78, 130.37, 124.92, 124.58, 122.48, 121.45, 107.59, 102.80, 64.47, 14.87. MS (ESI) *m*/*z* = 464.1 [M + H]$^+$.

(E)-1-(4-Bromophenyl)-3-(2-chloro-7-ethoxyquinolin-3-yl)prop-2-en-1-one (12). **12** was prepared by an above described procedure using **6** (0.35 gm, 1 equiv.) and **8** (0.29 gm, 1 equiv.) as starting materials. Brown solid, (433 mg, 70% yield). ^{1}H NMR (300 MHz, DMSO): δ 9.21 (s, 1H), 8.15 (d, 2H, *J* = 15.18 Hz), 8.11 (d, 2H, *J* = 15.00 Hz), 7.99 (d, 1H, *J* = 8.97 Hz), 7.85 (d, 2H, *J* = 9.09 Hz), 7.40-7.36 (m, 2H), 4.27-4.21 (q, 2H, *OCH*$_2$), 1.42 (t, 3H, *J* = 6.2 and 13.82 Hz, *CH*$_3$). MS (ESI) *m*/*z* = 417.1 [M + H]$^+$.

(E)-3-(2-Chloro-7-ethoxyquinolin-3-yl)-1-(4-hydroxyphenyl)prop-2-en-1-one (13). **13** was prepared by an above described procedure using **6** (0.35 gm, 1 equiv.) and **9** (0.20 gm, 1 equiv.) as starting materials. Yellow solid, (278 mg, 53% yield). ^{1}H NMR (300 MHz, DMSO): δ 10.54 (s, 1H, *OH*), 9.13 (s, 1H), 8.12-7.90 (m, 5H), 7.34-7.29 (m, 2H), 6.94 (d, 2H, *J* = 8.76 Hz), 4.24-4.17 (q, 2H, *OCH*$_2$), 1.40 (t, 3H, *J* = 6.93 and 13.95 Hz, *CH*$_3$); ^{13}C NMR (125 MHz, DMSO): δ 186.46, 162.51, 161.45, 150.04, 149.24, 136.92, 136.71, 131.30, 129.75, 128.77, 125.02, 124.40, 122.04, 120.83, 115.47, 107.00, 63.90, 14.36. MS (ESI) *m*/*z* = 355.1 [M + H]$^+$.

(E)-3-(2-Chloro-7-ethoxyquinolin-3-yl)-1-(4-nitrophenyl)prop-2-en-1-one (14). **14** was prepared by an above described procedure using **6** (0.35 gm, 1 equiv.) and **10** (0.25 gm, 1 equiv.) as starting materials. Red solid, (346 mg, 61% yield). ^{1}H NMR (300 MHz, DMSO): δ 9.16 (s, 1H), 8.16-8.11 (m, 3H), 8.04 (d, 1H, *J* = 14.5 Hz), 7.84 (d, 1H, *J* = 8.96 Hz), 7.51 (dd, 1H, *J* = 2.74 and 8.91 Hz), 7.47-7.42 (m, 3H), 4.26-4.19 (q, 2H, *OCH*$_2$), 1.41 (t, 3H, *J* = 6.91 and 13.90 Hz, *CH*$_3$). MS (ESI) *m*/*z* = 384.1 [M + H]$^+$.

Synthesis of 15a-d: ***2-Chloro-7-ethoxy-3-(3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-5-yl)quinoline (15a).*** To a stirred suspension of 3-(2-chloro-7-ethoxyquinolin-3-yl)-1-(4-iodophenyl) prop-2-en-1-one **11** (500 mg, 1 equiv.) in ethanol (15 mL) was added hydrazine monohydrate (0.52 mL, 10 equiv.) dropwise. The reaction mixture was refluxed for 2 h, after which it was allowed to cool to room temperature. The obtained solid was filtered and washed with EtOH (2 times). Further purification by

trituration with EtOH furnished the 2-chloro-7-ethoxy-3-(3-(4-iodophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)quinoline **15a** (427 mg, 83% yield) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO): 8.41 (s, 1H), 7.98 (d, 1H, *J* = 9.03 Hz), 7.74 (d, 2H, *J* = 8.52 Hz), 7.44 (d, 2H, *J* = 8.49 Hz), 7.33 (s, 1H), 7.28 (dd, 1H, *J* = 2.46 and 8.94 Hz), 5.21 (t, 1H, *J* = 10.32 and 20.73 Hz), 4.21-4.14 (q, 2H, OCH_2), 3.70-3.61 (dd, 1H), 2.92-2.83 (dd, 1H), 1.41 (t, 3H, *J* = 6.93 and 13.89 Hz, CH_3). ^{13}C NMR (100 MHz, DMSO): *δ* 160.76, 149.83, 148.60, 148.11, 137.75, 136.48, 132.98, 132.17, 129.70, 127.99, 122.57, 120.63, 107.19, 94.75, 64.14, 60.74, 14.91. MS (ESI) *m*/*z* = 479.1 $[M + H]^+$.

3-(3-(4-Bromophenyl)-4,5-dihydro-1H-pyrazol-5-yl)-2-chloro-7-ethoxyquinoline (15b). **15b** was prepared by an above described procedure using **12** (350 mg, 1 equiv.) as a starting material. Light brown solid, (278 mg, 77% yield). ^{1}H NMR (500 MHz, DMSO): *δ* 8.42 (s, 1H), 7.98 (d, 1H, *J* = 8.64 Hz), 7.85 (d, 1H, *J* = 3.3 Hz), 7.61-7.56 (m, 4H), 7.35 (d, 1H, *J* = 2.34 Hz), 7.29-7.25 (dd, 1H, *J* = 2.36 and 8.9 Hz), 5.22 (t, 1H, *J* = 10.32 and 19.87 Hz), 4.21-4.16 (q, 2H, OCH_2), 3.71-3.63 (dd, 1H), 2.93-2.88 (dd, 1H), 1.42 (t, 3H, *J* = 6.9 and 13.87 Hz, CH_3). MS (ESI) *m*/*z* = 430.1 $[M + H]^+$.

4-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenol (15c). **15c** was prepared by an above described procedure using **13** (250 mg, 1 equiv.) as a starting material. Yellow solid, (182 mg, 70% yield). ^{1}H NMR (500 MHz, DMSO): *δ* 9.66 (s, 1H), 8.44 (s, 1H), 7.97 (d, 1H, *J* = 9 Hz), 7.49-7-42 (m, 2H), 7.34 (s, 1H), 7.27 (dd, 1H, *J* = 2.5 and 8.95 Hz), 6.77 (d, 2H, *J* = 8.7 Hz), 5.12 (t, 1H, *J* = 10.35 and 20.7 Hz), 4.21-4.17 (q, 2H, OCH_2), 3.65-3.59 (dd, 1H), 2.85-2.79 (dd, 1H), 1.42 (t, 3H, *J* = 6.95 and 13.95 Hz, CH_3). MS (ESI) *m*/*z* = 369.1 $[M + H]^+$.

2-Chloro-7-ethoxy-3-(3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-5-yl)quinoline (15d). **15d** was prepared by an above described procedure using **14** (300 mg, 1 equiv.) as a starting material. Brown solid, (227 mg, 73% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 8.38-8.36 (m, 2H), 8.23 (d, 2H, *J* = 8.88 Hz), 7.98 (d, 1H, *J* = 9 Hz), 7.86 (d, 2H, *J* = 8.85 Hz), 7.34 (s, 1H), 7.28 (dd, 1H, *J* = 2.34 and 8.88 Hz), 5.33 (t, 1H, *J* = 11.52 and 21.03 Hz), 4.21-4.14 (q, 2H, OCH_2), 3.78-3.69 (dd, 1H), 3.04-2.95 (dd, 1H), 1.41 (t, 3H, *J* = 6.9 and 13.83 Hz, CH_3); ^{13}C NMR (125 MHz, DMSO): *δ* 160.32, 149.98, 148.16, 146.31, 145.90, 139.40, 135.97, 131.33, 129.21, 126.07, 123.84, 122.04, 120.18, 106.69, 63.65, 60.65, 14.40. MS (ESI) *m*/*z* = 398.1 $[M + H]^+$.

Synthesis of compound 4, 16-18: *5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (4/TDRL-551).* To a stirred suspension of 2-chloro-7-ethoxy-3-(3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-5-yl)quinoline **15a** (410 mg, 1.0 equiv.) in $CHCl_3$ (15 mL) was added glutaric anhydride (107 mg, 1.1 equiv.) under an argon atmosphere through the condenser in one portion. The resulting solution was refluxed for 2 h with stirring, after which it was allowed to cool to room temperature. The obtained solid was filtered and washed with EtOAc and further purification by trituration and crystallization with EtOAc yielded 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-5-oxopentanoic acid **4** (360 mg, 71% yield) as an off-white solid. TLC: 75% EtOAc in hexanes, R_f = 0.51; visualized with UV. ^{1}H NMR (300 MHz, DMSO): *δ* 12.10 (brs, 1H, *COOH*), 7.98 (s, 1H), 7.93 (d, 1H, *J* = 9.06 Hz), 7.85 (d, 2H, *J* = 8.52 Hz), 7.58 (d, 2H, *J* = 8.49

Hz), 7.34 (d, 1H, *J* = 2.4 Hz), 7.27 (dd, 1H, *J* = 2.49 and 8.97 Hz), 5-84-5.79 (dt, 1H, *J* = 3.39 and 11.91 Hz), 4.21-4.14 (q, 2H, OCH_2), 3.97 (dd, 1H, *J* = 12.15 and 18.12 Hz), 3.28 (dd, 1H, *J* = 5.01 and 12.75 Hz), 2.96-2.71 (m, 2H, CH_2), 2.32 (t, 2H, *J* = 7.35 and 14.58 Hz, CH_2), 1.86-1.76 (p, 2H, CH_2), 1.41 (t, 3H, *J* = 6.93 and 13.89 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): *δ* 174.71, 170.38, 160.83, 154.27, 148.63, 138.05, 130.91, 130.44, 129.62, 129.02, 122.53, 120.71, 107.09, 97.88, 64.15, 57.88, 33.40, 33.03, 20.24, 14.87. MS (ESI) *m*/*z* = 614.1 $[M + Na]^+$; HRMS (ESI): calcd for $C_{25}H_{24}N_3O_4ICl$ $[M + H]^+$ *m*/*z* = 592.0500, found 592.0503. HPLC purity: 98.36% (R_t = 6.29 min).

5-(3-(4-Bromophenyl)-5-(2-chloro-7-ethoxyquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (16). Compound **16** was prepared by an above described procedure using **15b** (150 mg, 1 equiv.) as a starting material. Yellow solid, (132 mg, 70% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 12.10 (brs, 1H, *COOH*), 7.98 (s, 1H), 7.93 (d, 1H, *J* = 9.06 Hz), 7.76-7.65 (m, 4H), 7.34 (d, 1H, *J* = 2.37 Hz), 7.27-7.23 (dd, 1H, *J* = 2.46 and 8.97 Hz), 5-85-5.79 (dt, 1H, *J* = 5.22 and 11.97 Hz), 4.21-4.14 (q, 2H, OCH_2), 4.02 (dd, 1H, *J* = 12.09 and 18.09 Hz), 3.30 (dd, 1H, *J* = 12.84 and 18.06 Hz), 2.96-2.72 (m, 2H, CH_2), 2.32 (t, 2H, *J* = 7.29 and 14.52 Hz, CH_2), 1.89-1.77 (p, 2H, CH_2), 1.41 (t, 3H, *J* = 6.93 and 13.89 Hz, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 174.71, 170.41, 160.83, 154.08, 148.64, 135.38, 132.24, 130.66, 130.44, 129.64, 129.16, 124.25, 122.54, 120.72, 107.10, 64.15, 57.92, 33.40, 33.03, 20.24, 14.87. MS (ESI) *m*/*z* = 542.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{25}H_{22}N_3O_4BrCl$ $[M - H]^-$ *m*/*z* = 542.0482, found 542.0479. HPLC purity: 98.03%.

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (17). Compound **17** was prepared by an above described procedure using **15c** (170 mg, 1 equiv.) as a starting material. Yellow solid, (142 mg, 64% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 12.10 (brs, 1H, *COOH*), 10.0 (brs, 1H, *OH*), 7.93 (s, 1H), 7.90 (d, 1H, *J* = 9.02 Hz), 7.63 (d, 2H, *J* = 8.7 Hz), 7.33 (d, 1H, *J* = 2.37 Hz), 7.26 (dd, 1H, *J* = 2.46 and 8.94 Hz), 6.83 (d, 2H, *J* = 8.76 Hz), 5-80-5.74 (dt, 1H, *J* = 4.89 and 11.73 Hz), 4.20-4.14 (q, 2H, OCH_2), 3.96 (dd, 1H, *J* = 11.94 and 17.91 Hz), 3.24 (dd, 1H, *J* = 5.07 and 17.94 Hz), 2.92-2.76 (m, 2H, CH_2), 2.32 (t, 2H, *J* = 7.35 and 14.58 Hz, CH_2), 1.85-1.80 (p, 2H, CH_2), 1.41 (t, 3H, *J* = 6.93 and 13.89 Hz, CH_3). MS (ESI) *m*/*z* = 480.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{25}H_{23}N_3O_5Cl$ $[M - H]^-$ *m*/*z* = 480.1326, found 480.1321. HPLC purity: 97.24%.

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (18): Compound **18** was prepared by an above described procedure using **15d** (210 mg, 1 equiv.) as a starting material. Red solid, (157 mg, 58% yield). ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 12.14 (brs, 1H, *COOH*), 8.37 (d, 2H, *J* = 6.5 Hz), 7.91 (d, 2H, *J* = 7 Hz), 7.72 (s, 1H), 7.65 (d, 1H, *J* = 9 Hz), 7.31 (s, 1H), 7.19 (dd, 1H, *J* = 2.5 and 11.5 Hz), 5-96-5.92 (dt, 1H, *J* = 5 and 12 Hz), 4.09-4.05 (q, 2H, OCH_2), 3.92 (dd, 1H, *J* = 12 and 17.5 Hz), 3.20 (dd, 1H, *J* = 5 and 18 Hz), 2.93-2.87 (m, 2H, CH_2), 2.39 (t, 2H, *J* = 7.5 and 14.6 Hz, CH_2), 1.90-1.87 (p, 2H, CH_2), 1.40 (t, 3H, *J* = 6.95 and 13.84 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 173.44, 172.24, 161.06, 151.98, 149.09, 148.36, 137.01, 128.80 128.59, 127.36, 124.06, 122.16, 120.99, 106.92, 63.92, 60.31, 33.56, 33.20, 20.37, 14.46. MS (ESI) *m*/*z* = 510.1

[M - H]$^-$; HRMS (ESI): calcd for $C_{25}H_{25}N_4O_6Cl$ [M + 2H]$^+$ *m*/*z* = 512.1463, found 512.1389. HPLC purity: 95.07%.

5-(3-(4-Aminophenyl)-5-(2-chloro-7-ethoxyquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (19). To a solution of **18** (120 mg, 1 equiv.) in the mixture of THF:EtOH (1:1, 8 mL) were added 89 mg $SnCl_2$ (2 equiv.) and the resulting suspension was gently refluxed for 2 hr. After cooling, the reaction mixture was diluted with ice, made slightly alkaline with 5% $NaHCO_3$, precipitate was filtered and washed with DCM and water. The filtrate was concentrated under reduced pressure and then residue was acidified with 20% citric acid. The precipitate was extracted with dichloromethane (3 x 30 mL); the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to obtain crude product. The crude product was crystallized in 2% ethanol in EtOAc mixture and triturated with 70% EtOAc in hexanes to afford 5-(3-(4-aminophenyl)-5-(2-chloro-7-ethoxyquinolin-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-5-oxopentanoic acid **19** (54 mg, 48% yield) as a red solid. ^{1}H NMR (300 MHz, DMSO): *δ* 12.11 (brs, 1H, *COOH*), 7.89 (s, 1H), 7.87 (d, 1H, *J* = 9 Hz), 7.61 (d, 2H, *J* = 8.5 Hz), 7.31 (d, 1H, *J* = 2.41 Hz), 7.28 (dd, 1H, *J* = 2.45 and 8.91 Hz), 6.83 (d, 2H, *J* = 8.76 Hz), 5-79-5.73 (dt, 1H, *J* = 4.87 and 11.73 Hz), 4.21-4.13 (q, 2H, *OCH*$_2$), 3.93 (dd, 1H), 3.27 (dd, 1H, *J* = 5 and 17.96 Hz), 2.90-2.79 (m, 2H, *CH*$_2$), 2.35 (t, 2H, *J* = 7.3 and 14.5 Hz, *CH*$_2$), 1.82-1.76 (p, 2H, *CH*$_2$), 1.40 (t, 3H, *J* = 6.91 and 13.85 Hz, *CH*$_3$). MS (ESI) *m*/*z* = 479.1 [M - H]$^-$; HRMS (ESI): calcd for $C_{25}H_{24}N_4O_4Cl$ [M - H]$^-$ *m*/*z* = 479.1486, found 479.1483. HPLC purity: 95.63% (R_t = 4.39 min).

5-(3-(4-(Acryloyloxy)phenyl)-5-(2-chloro-7-ethoxyquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (20). To a stirred suspension of **17** (60 mg, 1 equiv.) in THF (5 mL) was added 2N NaOH (0.5 mL). The reaction mixture was stirred at 0°C for 15 min then acryloyl chloride (13 mg, 1.1 equiv.) was added in one portion. The reaction mixture was stirred for further 2 h at room temperature. Solvent was removed *in vacuo* and residue was acidified to pH 2-3 using 20% citric acid solution. The product was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by Biotage automated flash column chromatography using 1-5% MeOH in DCM as the eluent to furnish 5-(3-(4-(acryloyloxy)phenyl)-5-(2-chloro-7-ethoxyquinolin-3-yl)-4,5-dihydro-1*H*-pyrazol-1-yl)-5-oxopentanoic acid **20** (22 mg, 34% yield) as a white solid. TLC: 5% MeOH in DCM, R_f = 0.44; visualized with UV. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.78 (d, 2H, *J* = 7.35 Hz), 7.70 (s, 1H), 7.64 (d, 1H, *J* = 8.76 Hz), 7.29 (d, 2H, *J* = 8.7 Hz), 7.20 (d, 2H, *J* = 8.07 Hz), 6.64 (d, 1H, *J* = 16.83 Hz), 6.35 (t, 1H, *J* = 10.29 and 27.21 Hz), 6.05-5.96 (m, 2H), 4.20-4.12 (q, 2H, *OCH*$_2$), 3.96 (dd, 1H, *J* = 11.82 and 16.89 Hz), 3.17-2.94 (m, 3H), 2.65-2.52 (m, 2H, *CH*$_2$), 2.15-2.07 (p, 2H, *CH*$_2$), 1.46 (t, 3H, *J* = 6.95 and 13.80 Hz, *CH*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 177.80, 170.82, 170.48, 169.10, 164.15, 160.93, 153.75, 152.31, 148.97, 148.52, 134.31, 133.23, 129.23, 128.64, 127.97, 127.56, 122.23, 122.07, 120.86, 106.83, 63.86, 57.79, 41.43, 33.07, 19.89, 14.58. MS (ESI) *m*/*z* = 535.1 [M - H]$^-$; HRMS (ESI): calcd for $C_{28}H_{26}N_3O_6ClNa$ [M + Na]$^+$ *m*/*z* = 558.1408, found 558.1407. HPLC purity: 99.21% (R_t = 4.74 min).

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-((morpholine-4-carbonyl)oxy)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (21). To a stirred suspension of **17** (60 mg, 1 equiv.) in dry THF (5 mL) were added trimethylamine/TEA (34 uL, 2 equiv.) and DMAP (3 mg, 0.2 equiv.) under an argon atmosphere and reaction mixture was stirred for 15 min at 0°C then 4-morpholinecarbonyl chloride (20 mg, 1.1 equiv.) was added. The reaction mixture was stirred for further 12 h at room temperature. Solvent was removed *in vacuo* and residue was acidified to pH 2-3 using 20% citric acid solution. The product was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained solid was washed with EtOAc and further purification by trituration and crystallization with EtOAc yielded 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-((morpholine-4-carbonyl)oxy)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-5-oxopentanoic acid **21** (46 mg, 63% yield) as a white solid. TLC: 5% MeOH in EtOAc, R_f = 0.41; visualized with UV. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.94 (d, 1H, J = 9.09 Hz), 7.82 (d, 2H, J = 8.79 Hz), 7.34 (d, 1H, J = 2.4 Hz), 7.27 (d, 1H, J = 8.94 Hz), 7.26 (d, 2H, J = 8.79 Hz), 5-85-5.80 (dt, 1H, J = 5.79 and 11.91 Hz), 4.21-4.15 (q, 2H, OCH_2), 3.97 (dd, 1H, J = 12.11 and 18.10 Hz), 3.53-3.46 (m, 4H), 3.44-3.37 (m, 4H), 3.27 (dd, 1H, J = 5.1 and 17.94 Hz), 2.96-2.79 (m, 2H, CH_2), 2.37 (m, 2H, CH_2), 1.87-1.78 (p, 2H, CH_2), 1.40 (t, 3H, J = 6.12 and 13.89 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.99, 170.51, 160.82, 154.25, 153.09, 148.67, 130.60, 129.64, 128.51, 122.72, 122.56, 120.69, 107.09, 66.53, 66.20, 64.15, 57.81, 45.77, 43.12, 33.26, 32.02, 20.40, 14.87. MS (ESI) m/z = 594.1 [M - H]$^-$; HRMS (ESI): calcd for $C_{30}H_{32}N_4O_7Cl$ [M + H]$^+$ m/z = 595.1960, found 595.1958. HPLC purity: 96.71% (R_t = 4.92 min).

Synthesis of Target Compounds 22-25:

Step 1. ***Synthesis of ethyl 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoate (30).*** To a stirred suspension of **15a** (600 mg, 1 equiv.) in dry DCM (25 mL) was added DIPEA (0.54 mL, 2.5 equiv.). The reaction mixture was stirred for 15 min at room temperature and then ethyl glutaryl chloride (0.30 mL, 1.5 equiv.) was added dropwise. The reaction mixture was stirred for further 12 h at room temperature. The reaction mixture was diluted with water and product was extracted with DCM (3 x 15 mL). The combined organic extracts were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by Biotage automated flash column chromatography using 5-40% EtOAc in hexanes as the eluent to furnish ethyl 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-5-oxopentanoate **30** (607 mg, 78% yield) as a white solid. TLC: 40% EtOAc in hexanes, R_f = 0.51; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 7.98 (s, 1H), 7.93 (d, 1H, J = 9.03 Hz), 7.85 (d, 2H, J = 8.52 Hz), 7.57 (d, 2H, J = 8.52 Hz), 7.34 (d, 1H, J = 2.43 Hz), 7.27 (dd, 1H, J = 2.49 and 8.97 Hz), 5-84-5.79 (dt, 1H, J = 3.54 and 12 Hz), 4.21-4.14 (q, 2H, OCH_2), 4.08-4.01 (q, 2H, OCH_2), 3.96 (dd, 1H, J = 12.10 and 17.97 Hz), 3.30 (dd, 1H, J = 5.61 and 18.27 Hz), 2.96-2.76 (m, 2H, CH_2), 2.36 (t, 2H, J = 7.41 and 14.76 Hz, CH_2), 1.89-1.79 (p, 2H, CH_2), 1.41 (t, 3H, J = 6.93 and 13.92 Hz, CH_3), 1.17 (t, 3H, J = 7.08 and 10.83 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): δ 173.12, 170.28,

160.84, 154.34, 148.63, 138.07, 130.89, 130.43, 129.62, 129.02, 122.53, 120.73, 107.09, 97.92, 64.16, 60.25, 57.92, 33.26, 32.87, 20.25, 14.87, 14.58. MS (ESI) *m*/*z* = 621.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{27}H_{28}N_3O_4ICl$ $[M + H]^+$ *m*/*z* = 620.0813, found 620.0814. HPLC purity: 99.08%.

Step 2. Synthesis of 31a-d:

Synthesis of ethyl 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-(furan-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoate (31a). To a stirred suspension of **30** (100 mg, 1 equiv.) and 3-furan boronic acid (24 mg, 1.3 equiv.) in dimethoxyethane/DME (8 mL) was added CsF (98 mg, 4 equiv.). The reaction mixture was degassed with argon for 5 minute and then $Pd(PPh_3)_4$ (19 mg, 0.1 equiv.) was added. The reaction mixture was stirred for 18 h at 90°C. The reaction mixture was cooled to room temperature, precipitated reaction mixture was extracted with dichloromethane (3 x 20 mL); the combined organic fractions were washed with saturated $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by Biotage automated flash column chromatography using 5-40% EtOAc in hexanes as the eluent to furnish ethyl 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-(furan-3-yl)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-5-oxopentanoate **31a** (58 mg, 64% yield) as a yellow solid. TLC: 40% EtOAc in hexanes, R_f = 0.47; visualized with UV. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.80 (d, 2H, *J* = 11.97 Hz), 7.74 (d, 2H, *J* = 2.07 Hz), 7.66 (d, 1H, *J* = 9 Hz), 7-54-7.49 (m, 3H), 7.30 (d, 1H, *J* = 2.28 Hz), 7.18 (dd, 1H, *J* = 2.43 and 8.97 Hz), 6.73 (s, 1H), 6.00-5.95 (dt, 1H, *J* = 4.86 and 11.79 Hz), 4.20-4.09 (m, 4H, *2OCH*$_2$), 3.98 (dd, 1H, *J* = 11.82 and 17.97 Hz), 3.21 (dd, 1H, *J* = 4.95 and 17.76 Hz), 3.10-2.89 (m, 2H, *CH*$_2$), 2.48 (t, 2H, *J* = 7.26 and 14.61 Hz, *CH*$_2$), 2.16-2.07 (p, 2H, *CH*$_2$), 1.47 (t, 3H, *J* = 6.96 and 13.92 Hz, *CH*$_3$), 1.22 (t, 3H, *J* = 7.10 and 10.85 Hz, *CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 173.33, 170.75, 160.86, 153.99, 148.96, 148.61, 144.04, 139.19, 134.68, 129.48, 129.43, 128.62, 127.19, 125.98, 125.69, 122.26, 120.78, 108.56, 106.84, 63.84, 60.40, 57.65, 41.32, 33.69, 33.16, 20.22, 14.58, 14.29. MS (ESI) *m*/*z* = 561.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{31}H_{31}N_3O_5Cl$ $[M + H]^+$ *m*/*z* = 560.1952, found 560.1934.

Compounds **31b-d** were synthesized using an appropriate boronic acid/ester by an above Suzuki coupling synthetic procedure described for the preparation of compound **31a**. Each compound was purified by Biotage automated flash column chromatography using 5-50% EtOAc in hexanes (**31b**) or 0-7% MeOH in DCM (**31c-d**) as the eluent to afford desired compound.

Ethyl 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-(furan-2-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoate (31b). Yellow solid (57 mg, 63% yield). TLC: 50% EtOAc in hexanes, R_f = 0.52; visualized with UV. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.85 (d, 1H, *J* = 8.43 Hz), 7.78-7.62 (m, 5H), 7.54-7.36 (m, 3H), 7.30 (t, 1H, *J* = 2.49 and 5.07 Hz), 7.19 (dd, 1H, *J* = 2.22 and 8.97 Hz), 6-03-5.94 (m, 1H), 4.20-4.10 (m, 4H, *2OCH*$_2$), 4.01-3.83 (m, 1H), 3.24-2.86 (m, 3H), 2.51-2.42 (m, 2H, *CH*$_2$), 2.17-2.05 (p, 2H, *CH*$_2$), 1.49 (t, 3H, *J* = 6.93 and 13.92 Hz, *CH*$_3$), 1.27 (t, 3H, *J* = 7.17 and 10.95 Hz, *CH*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 173.32, 173.22, 170.82, 160.91, 153.78, 148.99, 148.49, 141.98, 135.31, 130.64, 129.16, 128.33, 127.91, 127.33, 122.25, 120.83, 106.85, 63.86, 60.41, 57.79, 41.34,

33.69, 33.19, 20.21, 14.59, 14.30. MS (ESI) *m*/*z* = 561.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{31}H_{32}N_3O_5Cl$ $[M + 2H]^+$ *m*/*z* = 561.2030, found 561.2039.

Ethyl 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-(isoxazol-4-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoate (31c). Light brown solid (59 mg, 65% yield). TLC: 5% MeOH in DCM, R_f = 0.43; visualized with UV. MS (ESI) *m*/*z* = 562.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{30}H_{30}N_4O_5Cl$ $[M + H]^+$ *m*/*z* = 561.1905, found 561.1908.

Ethyl 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4'-morpholino-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoate (31d). Yellow solid (73 mg, 69% yield). TLC: 5% MeOH in DCM, R_f = 0.41; visualized with UV. MS (ESI) *m*/*z* = 578.1 $[M + Na]^+$; HRMS (ESI): calcd for $C_{37}H_{40}N_4O_5Cl$ $[M + H]^+$ *m*/*z* = 655.2687, found 655.2683.

Step 3. Synthesis of target compounds 22-25:

Synthesis of 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-(furan-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (22). To a stirred solution of compound **31a** (50 mg) in THF:MeOH (1:2, v/v, 6 mL) was added 10N NaOH (0.4 mL) solution. The reaction mixture was stirred at room temperature for 6-8 h. Solvent was removed *in vacuo* and residue was acidified to pH 2-3 using 1N HCl solution. The product was extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The product was triturated with 70% EtOAc in hexanes and crystallized in 2% EtOH in EtOAc to afford 5-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-(furan-3-yl)phenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-5-oxopentanoic acid **22** (41 mg, 87% yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO): *δ* 12.11 (brs, 1H, *COOH*), 8.30 (s, 1H), 7.98 (s, 1H), 7.94 (d, 1H, *J* = 9.06 Hz), 7.82-7.69 (m, 5H), 7.34 (s, 1H), 7.27 (dd, 1H, *J* = 2.31 and 8.97 Hz), 7.03 (s, 1H), 5.85-5.80 (dt, 1H, *J* = 4.98 and 11.79 Hz), 4.21-4.14 (m, 2H, *2OCH$_2$*), 4.01 (dd, 1H, *J* = 12.09 and 18.27 Hz), 3.30 (dd, 1H, *J* = 4.92 and 17.72 Hz), 2.98-2.78 (m, 2H, *CH$_2$*), 2.32 (t, 2H, *J* = 7.23 and 14.47 Hz, *CH$_2$*), 1.89-1.80 (p, 2H, *CH$_2$*), 1.49 (t, 3H, *J* = 6.84 and 13.77 Hz, *CH$_3$*); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 174.74, 170.28, 160.81, 154.65, 148.63, 145.05, 140.70, 134.37, 130.61, 129.80, 129.64, 127.76, 126.12, 125.66, 122.55, 120.72, 109.02, 107.09, 64.15, 57.71, 33.43, 33.04, 20.29, 14.88. MS (ESI) *m*/*z* = 532.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{29}H_{27}N_3O_5Cl$ $[M + H]^+$ *m*/*z* = 532.1639, found 532.1638. HPLC purity: 98.56% (R_t = 5.98 min).

Compounds **23-25** were synthesized using an above ester hydrolysis synthetic procedure described for the preparation of compound **22**. Each compound was purified by trituration with 70% EtOAc in hexanes and crystallized in 2% EtOH in EtOAc to afford desired compound.

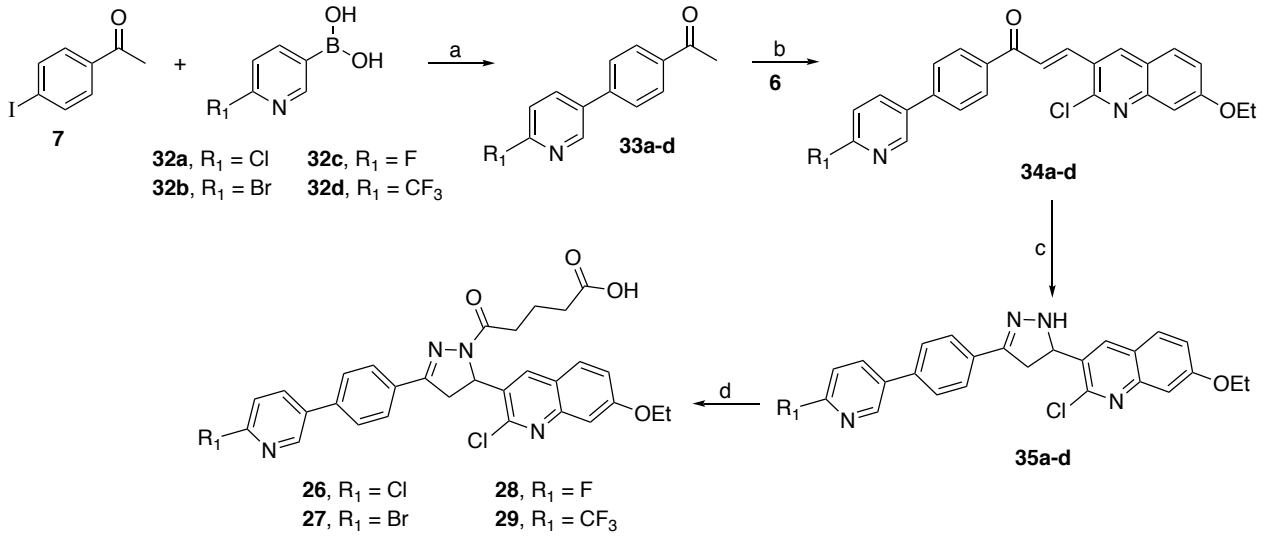
5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-(furan-2-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (23). Yellow solid (35 mg, 75% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 12.12 (brs, 1H, *COOH*), 8.25 (s, 1H), 7.94 (s, 1H), 7.92-7.80 (m, 5H), 7.62-7.59 (m, 2H), 7.34 (s, 1H), 7.27 (dd, 1H, *J* = 2.35 and 8.94 Hz), 5.85-5.80 (dt, 1H, *J* = 4.95 and 11.76 Hz), 4.21-4.14 (m, 2H, *2OCH$_2$*),

4.02 (dd, 1H, *J* = 12.13 and 18.23 Hz), 2.99-2.79 (m, 2H, CH_2), 2.31 (t, 2H, *J* = 7.26 and 14.43 Hz, CH_2), 1.88-1.82 (p, 2H, CH_2), 1.39 (t, 3H, *J* = 6.87 and 13.74 Hz, CH_3). MS (ESI) *m*/*z* = 531.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{29}H_{26}N_3O_5Cl$ $[M]^+$ *m*/*z* = 531.1561, found 531.1564. HPLC purity: 98.04% (R_t = 5.82 min).

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-(isoxazol-4-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (24). Light brown solid (37 mg, 79% yield). ^{1}H NMR (300 MHz, DMSO): δ 12.11 (brs, 1H, *COOH*), 8.17 (s, 1H), 7.97 (s, 1H), 7.77 (m, 3H), 7.57 (d, 1H, *J* = 8.4 Hz), 7.51 (d, 1H, *J* = 8.49 Hz), 7.41 (s, 1H), 6.81-6.74 (m, 2H), 5.52-5.47 (dt, 1H, *J* = 4.53 and 11.31 Hz), 4.10-3.99 (m, 2H, $2OCH_2$), 3.78 (dd, 1H, *J* = 12.24 and 18.18 Hz), 3.13 (dd, 1H, *J* = 4.74 and 17.91 Hz), 2.93-2.72 (m, 2H, CH_2), 2.31 (t, 2H, *J* = 7.14 and 14.28 Hz, CH_2), 1.89-1.80 (p, 2H, CH_2), 1.34 (t, 3H, *J* = 6.87 and 13.83 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.76, 170.08, 161.45, 160.49, 154.97, 140.22, 134.10, 132.01, 129.76, 128.82, 127.36, 126.92, 116.99, 113.37, 111.53, 98.61, 89.91, 63.82, 33.46, 33.09, 20.38, 14.97. MS (ESI) *m*/*z* = 532.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{28}H_{24}N_4O_5Cl$ $[M - H]^-$ *m*/*z* = 531.1435, found 531.1440. HPLC purity: 96.27% (R_t = 5.49 min).

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4'-morpholino-[1,1'-biphenyl]-4-yl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (25). Yellow solid (40 mg, 84% yield). ^{1}H NMR (300 MHz, DMSO): δ 12.11 (brs, 1H, *COOH*), 8.21 (s, 1H), 7.94 (d, 1H, *J* = 9.57 Hz), 7.79-7.60 (m, 4H), 7.46 (d, 1H, *J* = 11.76 Hz), 7.06-7.01 (m, 3H), 6.78-6.75 (m, 2H), 5.85-5.80 (dt, 1H, *J* = 4.49 and 11.63 Hz), 4.20-4.15 (m, 2H, $2OCH_2$), 4.05 (dd, 1H, *J* = 12.44 and 18.29 Hz), 3.74 (brs, 4H), 3.16 (brs, 5H), 2.88-2.72 (m, 2H, CH_2), 2.31 (t, 2H, *J* = 7.11 and 14.34 Hz, CH_2), 1.90-1.80 (p, 2H, CH_2), 1.36 (t, 3H, *J* = 6.45 and 13.98 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.77, 170.11, 160.82, 160.49, 151.32, 142.10, 133.34, 133.98, 129.82, 127.68, 126.27, 115.64, 112.34, 111.67, 66.47, 48.44, 20.29, 14.88. MS (ESI) *m*/*z* = 626.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{35}H_{34}N_4O_5Cl$ $[M - H]^-$ *m*/*z* = 625.2218, found 625.2215. HPLC purity: 97.63% (R_t = 6.18 min).

Synthesis of Target Compounds 26-29:



Step 1. Synthesis of Intermediates 33a-d:

Synthesis of 1-(4-(6-chloropyridin-3-yl)phenyl)ethan-1-one (33a). A solution of K_2CO_3 (421 mg, 3 equiv.) in water (4 mL) was added to a mixture of 4-iodoacetophenone **7** (250 mg, 1.2 equiv.) and 6-chloro-3-pyridinylboronic acid **32a** (192 mg, 1.2 equiv.) in toluene (12 mL). The mixture was degassed with argon for 5 minute and then $Pd(PPh_3)_4$ (117 mg, 0.1 equiv.) was added. The reaction mixture was stirred at 90°C for 18 h. The reaction mixture was cooled to room temperature and solvent was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 15 mL); the combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by Biotage automated flash column chromatography using 0 to 50% EtOAc in hexanes as the eluent to furnish 1-(4-(6-chloropyridin-3-yl)phenyl)ethan-1-one **33a** as a white solid (197 mg, 84% yield). TLC: 30% EtOAc in hexanes, R_f = 0.47; visualized with UV. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.66 (d, 1H, J = 2.61 Hz), 8.09 (d, 2H, J = 8.64 Hz), 7.91 (dd, 1H, J = 2.61 and 8.28 Hz), 7.68 (d, 2H, J = 8.64 Hz), 7.47 (d, 1H, J = 8.28 Hz), 2.67 (s, 2H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.47, 151.31, 148.08, 140.97, 137.25, 136.78, 134.43, 129.24, 127.22, 124.45, 26.74. MS (ESI) m/z = 232.1 $[M + H]^+$.

Intermediates **33b-d** were synthesized using an appropriate boronic acid/ester (**32b-d**) by above Suzuki coupling synthetic procedure described for the preparation of intermediate **33a**. Each compound was purified by Biotage automated flash column chromatography using 0 to 50% EtOAc in hexanes as the eluent to afford desired compound.

1-(4-(6-Bromopyridin-3-yl)phenyl)ethan-1-one (33b). Off-white solid (241 mg, 86% yield). TLC: 30% EtOAc in hexanes, R_f = 0.48; visualized with UV. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, 1H), 8.10 (m, 2H), 7.93 (dd, 1H, J = 2.64 and 8.32 Hz), 7.69 (d, 2H, J = 8.58 Hz), 7.47 (d, 1H, J = 8.32 Hz), 2.67 (s, 2H, CH_3). MS (ESI) m/z = 276.1 $[M + H]^+$.

1-(4-(6-Fluoropyridin-3-yl)phenyl)ethan-1-one (33c). White solid (196 mg, 90% yield). TLC: 30% EtOAc in hexanes, R_f = 0.50; visualized with UV. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.10-8.01 (m, 3H), 7.67 (d, 2H, J = 8.52 Hz), 7.09 (dd, 1H, J = 3.03 and 8.49 Hz), 2.67 (s, 2H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.50, 146.23, 146.03, 141.36, 139.90, 139.79, 136.58, 129.21, 127.20, 110.03, 109.53, 26.73. MS (ESI) m/z = 216.1 $[M + H]^+$.

1-(4-(6-(Trifluoromethyl)pyridin-3-yl)phenyl)ethan-1-one (33d). White solid (229 mg, 85% yield). TLC: 30% EtOAc in hexanes, R_f = 0.50; visualized with UV. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.14-8.08 (m, 3H), 7.83 (d, 1H, J = 8.16 Hz), 7.74 (d, 2H, J = 8.64 Hz), 2.68 (s, 2H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.40, 148.53, 140.75, 137.21, 135.80, 129.32, 127.61, 120.58, 26.77. MS (ESI) m/z = 266.1 $[M + H]^+$.

Step 2. Synthesis of Intermediates 34a-d: Intermediates **34a-d** were synthesized using aldehyde **6** and corresponding acetophenone (**33a-d)** by above Claisen-Schmidt condensation

synthetic procedure described for the preparation and purification of compound **11**.

(E)-3-(2-Chloro-7-ethoxyquinolin-3-yl)-1-(4-(6-chloropyridin-3-yl)phenyl)prop-2-en-1-one (34a). Yellow solid (204 mg, 57% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 9.27 (s, 1H), 8.88 (d, 1H, *J* = 2.04 Hz), 8.33 (m, 2H), 8.19 (s, 1H), 8.11 (s, 1H), 8.07-7.97 (m, 4H), 7.69 (d, 1H, *J* = 8.91 Hz), 7.38-7.35 (m, 2H), 4.26-4.20 (q, 2H, OCH_2), 1.41 (t, 3H, *J* = 6.90 and 13.92 Hz, CH_3). MS (ESI) *m*/*z* = 450.1 $[M + H]^+$.

(E)-1-(4-(6-Bromopyridin-3-yl)phenyl)-3-(2-chloro-7-ethoxyquinolin-3-yl)prop-2-en-1-one (34b). Brown solid (193 mg, 48% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 9.21 (s, 1H), 8.90 (d, 1H, *J* = 1.96 Hz), 8.29 (m, 2H), 8.16 (d, 2H), 8.10 (d, 2H), 7.97 (d, 1H), 7.86 (d, 2H, *J* = 8.95 Hz), 7.40-7.36 (m, 2H), 4.26-4.21 (q, 2H, OCH_2), 1.41 (t, 3H, *J* = 6.88 and 13.92 Hz, CH_3). MS (ESI) *m*/*z* = 495.1 $[M + H]^+$.

(E)-3-(2-Chloro-7-ethoxyquinolin-3-yl)-1-(4-(6-fluoropyridin-3-yl)phenyl)prop-2-en-1-one (34c). Orange solid (253 mg, 68% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 9.23 (s, 1H), 8.70 (d, 1H, *J* = 2.49 Hz), 8.46-8.39 (m, 1H), 8.32 (d, 2H, *J* = 8.49 Hz), 8.21-8.04 (m, 2H), 7.99-7.93 (m, 3H), 7.37-7.32 (m, 3H), 4.25-4.18 (q, 2H, OCH_2), 1.40 (t, 3H, *J* = 6.93 and 13.89 Hz, CH_3). ^{13}C NMR (75 MHz, DMSO): *δ* 188.46, 162.15, 150.63, 149.92, 146.60, 146.40, 141.35, 141.24, 138.62, 137.80, 137.06, 133.48, 130.41, 129.96, 127.76, 125.17, 124.60, 122.50, 121.43, 110.60, 107.51, 64.46, 14.86. MS (ESI) *m*/*z* = 434.1 $[M + H]^+$.

(E)-3-(2-Chloro-7-ethoxyquinolin-3-yl)-1-(4-(6-(trifluoromethyl)pyridin-3-yl)phenyl)prop-2-en-1-one (34d). Yellow solid (229 mg, 60% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 8.22 (s, 1H), 8.06 (s, 1H), 7.81-7.64 (m, 4H), 7.48 (d, 1H, *J* = 8.19 Hz), 7.40 (d, 1H, *J* = 8.22 Hz), 7.29 (s, 2H), 7.15-7.03 (m, 3H), 4.22-4.15 (q, 2H, OCH_2), 1.38 (t, 3H, *J* = 6.72 and 13.44 Hz, CH_3). MS (ESI) *m*/*z* = 484.1 $[M + H]^+$.

Step 3. Synthesis of Intermediates 35a-d: Intermediates **35a-d** were synthesized using synthetic procedure described above for the preparation and purification of compound **15a**.

2-Chloro-3-(3-(4-(6-chloropyridin-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)-7-ethoxyquinoline (35a). Light yellow solid (150 mg, 77% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 8.78 (d, 1H, *J* = 2.64 Hz), 8.44 (s, 1H), 8.21-8.17 (dd, 1H, *J* = 2.67 and 8.4 Hz), 7.99 (d, 1H, *J* = 9.03 Hz), 7.77 (s, 4H), 7.62 (d, 1H, *J* = 8.37 Hz), 7.34 (d, 1H, *J* = 2.43 Hz), 7.28-7.24 (dd, 1H, *J* = 2.49 and 8.94 Hz), 5.24 (t, 1H, *J* = 10.44 and 20.85 Hz), 4.22-4.15 (q, 2H, OCH_2), 3.77-3.68 (dd, 1H, *J* = 11.16 and 16.65 Hz), 2.99-2.90 (dd, 1H, *J* = 10.02 and 16.65 Hz), 1.40 (t, 3H, *J* = 6.96 and 13.92 Hz, CH_3). MS (ESI) *m*/*z* = 464.1 $[M + H]^+$.

3-(3-(4-(6-Bromopyridin-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)-2-chloro-7-ethoxyquinoline (35b). Brown solid (139 mg, 73% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 8.77 (d, 1H, *J* = 2.25 Hz), 8.42 (s, 1H), 8.13 (d, 1H, *J* = 8.34 Hz), 8.01 (s, 1H), 7.94-7.85 (m, 4H), 7.77 (d, 1H, *J* = 8.43 Hz), 7.34 (s, 1H), 7.27-7.24 (dd, 1H, *J* = 2.19 and 9.0 Hz), 5.26 (t, 1H, *J* = 10.42 and 20.80 Hz), 4.21-4.14 (q, 2H, OCH_2), 3.75-3.70 (dd, 1H, *J* = 11.12 and 16.48 Hz), 2.95-2.89 (dd, 1H, *J* = 10 and 16.60

Hz), 1.42 (t, 3H, *J* = 6.9 and 13.77 Hz, *CH₃*). MS (ESI) *m*/*z* = 509.1 $[M + H]^+$.

2-Chloro-7-ethoxy-3-(3-(4-(6-fluoropyridin-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)quinoline (35c). Yellow solid (198 mg, 80% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 8.59 (d, 1H, *J* = 2.49 Hz), 8.44 (s, 1H), 8.35-8.29 (m, 1H), 7.99 (d, 1H, *J* = 9.0 Hz), 7.75 (s, 4H), 7.34 (d, 1H, *J* = 2.4 Hz), 7.30-7.24 (m, 2H), 5.24 (t, 1H, *J* = 10.38 and 20.91 Hz), 4.22-4.15 (q, 2H, *OCH₂*), 3.77-3.68 (dd, 1H, *J* = 11.16 and 16.65 Hz), 2.95-2.89 (dd, 1H, *J* = 9.99 and 16.65 Hz), 1.42 (t, 3H, *J* = 6.96 and 13.92 Hz, *CH₃*). MS (ESI) *m*/*z* = 448.1 $[M + H]^+$.

2-Chloro-7-ethoxy-3-(3-(4-(6-(trifluoromethyl)pyridin-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-5-yl)quinoline (35d). Light yellow solid (170 mg, 77% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 9.13 (s, 1H), 8.44 (s, 1H), 8.41-8.38 (d, 1H, *J* = 8.16 Hz), 7.99-7.78 (m, 6H), 7.35 (d, 1H, *J* = 2.19 Hz), 7.28-7.25 (dd, 1H, *J* = 2.43 and 8.97 Hz), 5.26 (t, 1H, *J* = 10.42 and 20.94 Hz), 4.22-4.15 (q, 2H, *OCH₂*), 3.78-3.69 (dd, 1H, *J* = 11.22 and 16.53 Hz), 2.97-2.92 (dd, 1H, *J* = 6.81 and 16.53 Hz), 1.42 (t, 3H, *J* = 6.90 and 13.89 Hz, *CH₃*). MS (ESI) *m*/*z* = 498.1 $[M + H]^+$.

Step 4. Synthesis of target compounds 26-29: Target compounds **26-29** were synthesized using synthetic procedure described above for the preparation and purification of compound **4**.

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-(6-chloropyridin-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (26). White solid (113 mg, 70% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 12.10 (brs, 1H, *COOH*), 8.81 (d, 1H, *J* = 2.58 Hz), 8.24-8.20 (dd, 1H, *J* = 2.64 and 8.4 Hz), 8.0 (s, 1H), 7.94-7.84 (m, 5H), 7.65 (d, 1H, *J* = 8.34 Hz), 7.35 (d, 1H, *J* = 2.31 Hz), 7.27-7.23 (dd, 1H, *J* = 2.46 and 8.97 Hz), 5.88-5.82 (dt, 1H, *J* = 5.16 and 11.85 Hz), 4.22-4.15 (q, 2H, *OCH₂*), 4.08-3.97 (dd, 1H, *J* = 12.42 and 18.27 Hz), 3.39-3.31 (dd, 1H, *J* = 5.4 and 17.91 Hz), 2.99-2.78 (m, 2H, *CH₂*), 2.32 (t, 2H, *J* = 7.32 and 14.52 Hz, *CH₂*), 1.89-1.79 (p, 2H, *CH₂*), 1.41 (t, 3H, *J* = 6.93 and 13.89 Hz, *CH₃*); ^{13}C NMR (75 MHz, DMSO): *δ* 174.72, 170.42, 160.84, 154.40, 150.17, 148.64, 148.31, 138.23, 137.71, 134.50, 131.48, 130.54, 129.64, 127.99, 127.64, 124.93, 122.55, 120.73, 107.11, 64.16, 57.89, 33.43, 33.07, 20.29, 14.88. MS (ESI) *m*/*z* = 576.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{30}H_{27}N_4O_4Cl_2$ $[M + H]^+$ *m*/*z* = 577.1409, found 577.1412. HPLC purity: 98.23% (R_t = 5.98 min).

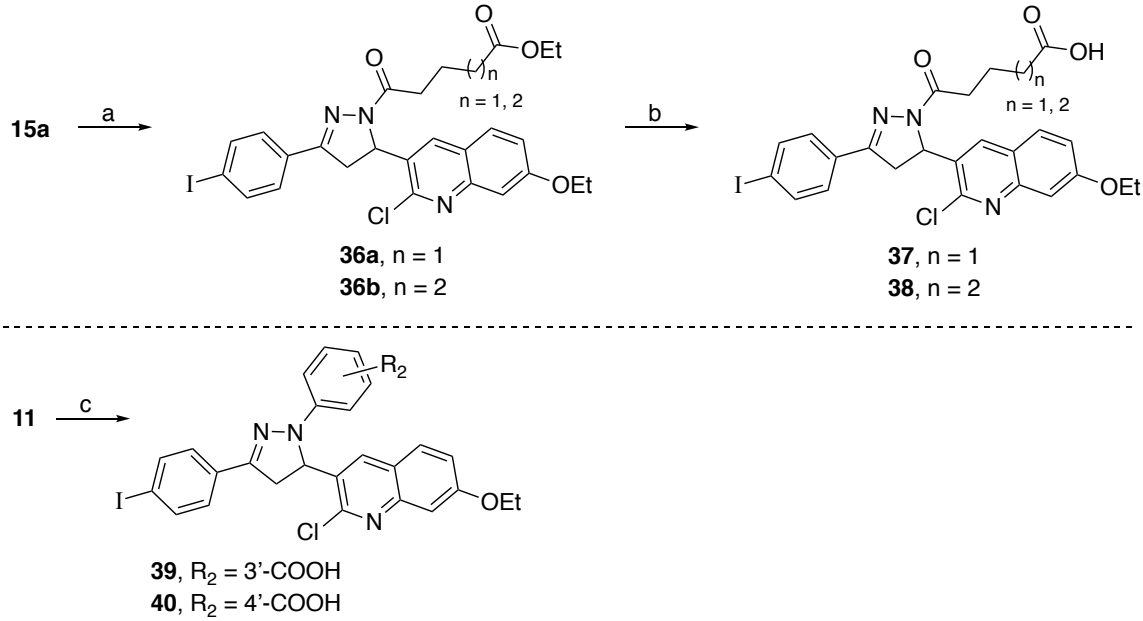
5-(3-(4-(6-Bromopyridin-3-yl)phenyl)-5-(2-chloro-7-ethoxyquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (27). Off-white solid (95 mg, 65% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 12.10 (brs, 1H, *COOH*), 8.77 (d, 1H, *J* = 2.28 Hz), 8.11 (dd, 1H, *J* = 2.52 and 8.34 Hz), 8.0 (s, 1H), 7.94-7.82 (m, 5H), 7.77 (d, 1H, *J* = 8.38 Hz), 7.33 (s, 1H), 7.27-7.23 (dd, 1H, *J* = 2.13 and 8.91 Hz), 5.87-5.82 (dt, 1H, *J* = 5.25 and 11.82 Hz), 4.21-4.14 (q, 2H, *OCH₂*), 4.07-3.97 (dd, 1H, *J* = 12.12 and 17.91 Hz), 3.38-3.30 (dd, 1H), 2.98-2.79 (m, 2H, *CH₂*), 2.33 (t, 2H, *J* = 7.29 and 14.49 Hz, *CH₂*), 1.89-1.80 (p, 2H, *CH₂*), 1.40 (t, 3H, *J* = 6.84 and 13.74 Hz, *CH₃*); ^{13}C NMR (75 MHz, DMSO): *δ* 174.32, 170.41, 160.84, 154.39, 148.84, 148.64, 141.26, 137.95, 137.73, 134.77, 131.50, 130.53, 129.63, 129.31, 129.15, 128.66, 127.99, 127.60, 122.55, 120.72, 107.10, 64.16, 57.90, 33.43, 33.08, 20.29,

14.88. MS (ESI) *m*/*z* = 619.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{30}H_{25}N_4O_4BrCl$ $[M - H]^-$ *m*/*z* = 619.0748, found 619.0744. HPLC purity: 96.08% (R_t = 5.77 min).

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-(6-fluoropyridin-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (28). White solid (164 mg, 73% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 12.10 (brs, 1H, *COOH*), 8.62 (d, 1H, *J* = 2.43 Hz), 8.38-8.31 (m, 1H), 8.0 (s, 1H), 7.94-7.82 (m, 5H), 7.34-7.23 (m, 3H), 5.87-5.82 (dt, 1H, *J* = 5.25 and 11.88 Hz), 4.21-4.14 (q, 2H, *OCH*$_2$), 4.07-3.97 (dd, 1H, *J* = 12.33 and 18.21 Hz), 3.38-3.30 (dd, 1H, *J* = 5.37 and 17.82 Hz), 2.96-2.81 (m, 2H, *CH*$_2$), 2.31 (t, 2H, *J* = 7.41 and 14.61 Hz, *CH*$_2$), 1.90-1.78 (p, 2H, *CH*$_2$), 1.41 (t, 3H, *J* = 6.93 and 13.86 Hz, *CH*$_3$); ^{13}C NMR (75 MHz, DMSO): *δ* 174.72, 170.39, 161.69, 160.84, 154.44, 148.65, 146.12, 145.92, 140.91, 140.80, 137.95, 133.74, 131.16, 130.55, 129.64, 127.96, 127.57, 122.56, 120.73, 110.51, 110.01, 107.10, 64.16, 57.88, 33.43, 33.08, 20.30, 14.88. MS (ESI) *m*/*z* = 559.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{30}H_{27}N_4O_4FCl$ $[M + H]^+$ *m*/*z* = 561.1705, found 561.1746. HPLC purity: 96.08% (R_t = 5.68 min).

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-(6-(trifluoromethyl)pyridin-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-oxopentanoic acid (29). White solid (130 mg, 71% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 12.10 (brs, 1H, *COOH*), 9.15 (s, 1H), 8.44 (d, 1H, *J* = 8.16 Hz), 8.02-7.92 (m, 7H), 7.34 (s, 1H), 7.27-7.23 (dd, 1H, *J* = 2.19 and 8.94 Hz), 5.89-5.83 (dt, 1H, *J* = 5.19 and 12 Hz), 4.22-4.15 (q, 2H, *OCH*$_2$), 4.09-3.99 (dd, 1H, *J* = 12.72 and 18.36 Hz), 3.40-3.33 (dd, 1H, *J* = 5.37 and 17.80 Hz), 2.97-2.80 (m, 2H, *CH*$_2$), 2.34 (t, 2H, *J* = 7.2 and 14.31 Hz, *CH*$_2$), 1.92-1.80 (p, 2H, *CH*$_2$), 1.41 (t, 3H, *J* = 6.84 and 13.71 Hz, *CH*$_3$); ^{13}C NMR (75 MHz, DMSO): *δ* 174.72, 170.46, 160.85, 154.34, 148.74, 148.65, 138.38, 137.56, 136.60, 132.04, 129.65, 128.14, 128.05, 122.56, 121.42, 120.74, 107.11, 64.16, 57.94, 33.43, 33.09, 20.30, 14.88. MS (ESI) *m*/*z* = 611.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{31}H_{27}N_4O_4F_3Cl$ $[M + H]^+$ *m*/*z* = 611.1673, found 611.1678. HPLC purity: 97.46% (R_t = 6.25 min).

Synthesis of Target Compounds 37-40:



Intermediates **36a-b** were synthesized from compound **15a** and using corresponding acyl chloride by an above synthetic procedure described for the preparation of compound **30**. Each compound was purified by Biotage automated flash column chromatography using 0-50% EtOAc in hexanes as the eluent to afford desired compound.

Ethyl 6-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-6-oxohexanoate (36a). White solid (55 mg, 84% yield). TLC: 40% EtOAc in hexanes, R_f = 0.49; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 7.74-7.69 (t, 3H, *J* = 8.37 and 17.64 Hz), 7.64 (d, 1H, *J* = 8.97 Hz), 7.46 (d, 2H, *J* = 8.37 Hz), 7.27 (d, 1H, *J* = 2.22 Hz), 7.16-7.12 (dd, 1H, *J* = 2.22 and 8.91 Hz), 5.97-5.91 (dt, 1H, *J* = 4.92 and 11.79 Hz), 4.15-4.08 (q, 4H, 2OCH_2), 3.92-3.82 (dd, 1H, *J* = 11.97 and 17.7 Hz), 3.15-3.07 (dd, 1H, *J* = 4.98 and 17.82 Hz), 3.00-2.81 (m, 2H, CH_2), 2.37 (t, 2H, *J* = 6.57 and 13.02 Hz, CH_2), 1.82-1.75 (m, 4H, 2CH_2), 1.48 (t, 3H, *J* = 6.93 and 13.86 Hz, CH_3), 1.26 (t, 3H, *J* = 7.14 and 14.25 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): δ 173.50, 171.26, 160.88, 153.36, 148.95, 148.51, 137.94, 130.51, 129.26, 128.61, 128.10, 122.19, 120.80, 106.83, 96.95, 63.85, 60.31, 57.82, 41.08, 34.10, 33.77, 24.66, 24.35, 14.59, 14.28. MS (ESI) *m*/*z* = 634.1 $[M + H]^+$.

Ethyl 7-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-7-oxoheptanoate (36b). White solid (58 mg, 86% yield). TLC: 40% EtOAc in hexanes, R_f = 0.48; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 7.76 (d, 2H, *J* = 7.92 Hz), 7.68-7.60 (m, 2H) 7.47 (d, 2H, *J* = 7.98 Hz), 7.28 (d, 1H, *J* = 2.2 Hz), 7.18-7.15 (dd, 1H, *J* = 2.26 and 8.94 Hz), 5.98-5.93 (dt, 1H, *J* = 4.11 and 11.28 Hz), 4.15-4.09 (q, 4H, 2OCH_2), 3.93-3.83 (dd, 1H, *J* = 12.15 and 17.64 Hz), 3.15-3.08 (dd, 1H, *J* = 4.38 and 17.85 Hz), 3.00-2.81 (m, 2H, CH_2), 2.35 (t, 2H, *J* = 7.17 and 14.4 Hz, CH_2), 1.83-1.69 (m, 4H, 2CH_2), 1.51-1.44 (m, 5H, CH_2 and CH_3), 1.27 (t, 3H, *J* = 6.93 and 13.89 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): δ 173.73, 171.57, 160.89, 153.27, 148.96, 148.54, 137.96, 130.54, 129.30, 128.57, 128.10, 122.18, 120.83, 106.86, 96.92, 63.86, 60.25, 57.80, 41.06, 34.19, 33.93, 28.87, 24.71, 24.51, 14.59, 14.28. MS (ESI) *m*/*z* = 648.1 $[M + H]^+$.

Compounds **37-38** were synthesized using an above ester hydrolysis synthetic procedure described for the preparation of compound **22**. Each compound was purified by trituration with 70% EtOAc in hexanes and crystallized in 2% EtOH in EtOAc to afford desired final compound.

6-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-6-oxohexanoic acid (37). White solid (35 mg, 92% yield). TLC: 75% EtOAc in hexanes, R_f = 0.48; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 12.05 (brs, 1H, *COOH*), 7.96 (s, 1H), 7.93 (d, 1H, *J* = 9.0 Hz), 7.84 (d, 2H, *J* = 8.28 Hz), 7.58 (d, 2H, *J* = 8.25 Hz), 7.33 (d, 1H, *J* = 1.59 Hz), 7.25-7.22 (dd, 1H, *J* = 2.13 and 8.88 Hz), 5.84-5.78 (dt, 1H, *J* = 5.01 and 11.91 Hz), 4.20-4.14 (q, 2H, OCH_2), 4.01-3.90 (dd, 1H, *J* = 12.18 and 18.12 Hz), 3.31-3.23 (dd, 1H, *J* = 5.43 and 18.24 Hz), 2.91-2.70 (m, 2H, CH_2), 2.27 (t, 2H, *J* = 6.87 and 12.78 Hz, CH_2), 1.62-1.58 (m, 4H, 2CH_2), 1.40 (t, 3H, *J* = 6.81 and 13.68 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): δ 174.90, 170.65, 160.82, 154.20, 148.62, 138.05, 130.92,

130.48, 129.65, 129.04, 122.52, 120.70, 107.07, 97.88, 64.15, 57.82, 33.90, 33.58, 24.62, 24.37, 14.88. MS (ESI) *m*/*z* = 604.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{26}H_{26}N_3O_4ICl$ $[M + H]^+$ *m*/*z* = 606.0657, found 606.0662. HPLC purity: 98.91% (R_t = 6.46 min).

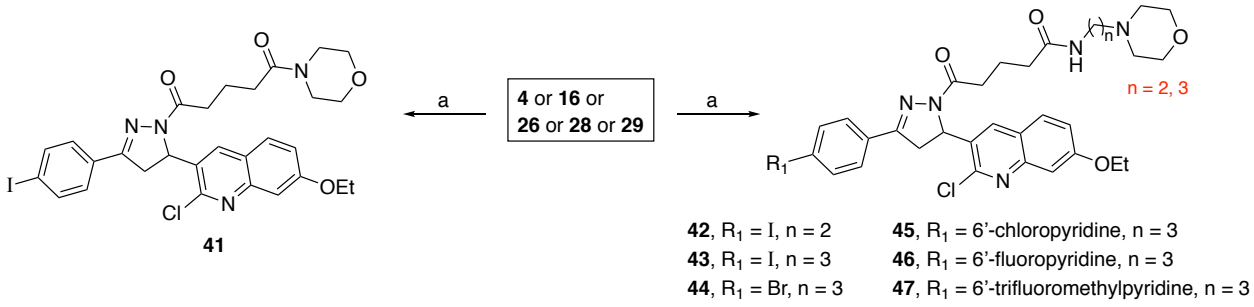
7-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-7-oxoheptanoic acid (38). White solid (34 mg, 90% yield). TLC: 75% EtOAc in hexanes, R_f = 0.47; visualized with UV. ^{1}H NMR (300 MHz, DMSO): *δ* 12.02 (brs, 1H, *COOH*), 7.96 (s, 1H), 7.93 (d, 1H, *J* = 9.06 Hz), 7.84 (d, 2H, *J* = 8.46 Hz), 7.58 (d, 2H, *J* = 8.43 Hz), 7.33 (d, 1H, *J* = 2.19 Hz), 7.26-7.22 (dd, 1H, *J* = 2.4 and 8.97 Hz), 5.83-5.78 (dt, 1H, *J* = 5.07 and 11.79 Hz), 4.21-4.14 (q, 2H, OCH_2), 4.01-3.91 (dd, 1H, *J* = 12.27 and 18.27 Hz), 3.31-3.23 (dd, 1H, *J* = 5.55 and 18.36 Hz), 2.90-2.70 (m, 2H, CH_2), 2.22 (t, 2H, *J* = 7.2 and 14.49 Hz, CH_2), 1.65-1.48 (m, 4H, $2CH_2$), 1.41-1.33 (m, 5H, CH_2 and CH_3); ^{13}C NMR (75 MHz, DMSO): *δ* 174.95, 170.76, 160.82, 154.16, 148.62, 138.05, 130.94, 130.51, 129.65, 129.02, 122.52, 120.71, 107.07, 97.86, 64.15, 55.39, 34.00, 33.66, 31.17, 28.68, 24.72, 24.51, 14.88. MS (ESI) *m*/*z* = 618.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{27}H_{28}N_3O_4ICl$ $[M + H]^+$ *m*/*z* = 620.0813, found 620.0809. HPLC purity: 97.34% (R_t = 6.70 min).

3-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzoic acid (39). To a stirred suspension of 3-(2-chloro-7-ethoxyquinolin-3-yl)-1-(4-iodophenyl) prop-2-en-1-one **11** (100 mg, 1 equiv.) and 3'-hydrazino benzoic acid (65 mg, 1 equiv.) in n-butanol (8 mL) was added acetic acid (4 mL). The reaction mixture was heated at 120 °C for 20 h. The reaction mixture was concentrated under reduced pressure. The crude solid was washed with EtOH (3 x 1.5 mL) and crystalized in 2% EtOH in EtOAc to afford compound **39** (79 mg, 62%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO): *δ* 12.86 (brs, 1H, *COOH*), 7.80 (d, 2H, *J* = 7.35 Hz), 7.64 (s, 1H), 7.55-7.45 (m, 4H), 7.36-7.29 (m, 2H), 7.18-7.12 (m, 1H), 6.79 (s, 1H), 6.71 (dd, 1H, *J* = 8.19 Hz), 5.54-5.48 (dt, 1H, *J* = 5.12 and 11.82 Hz), 4.04-3.99 (q, 2H, OCH_2), 3.95-3.85 (dd, 1H, *J* = 12.78 and 18.64 Hz), 3.17-3.09 (dd, 1H, *J* = 4.89 and 18.06 Hz), 1.34 (t, 3H, *J* = 6.3 and 12.51 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): *δ* 170.91, 167.92, 161.67, 150.24, 148.66, 144.35, 140.31, 134.95, 132.07, 129.95, 129.79, 128.63, 120.04, 113.84, 112.57, 111.62, 98.70, 95.70, 63.85, 58.69, 14.39. MS (ESI) *m*/*z* = 596.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{27}H_{20}N_3O_3ICl$ $[M - H]^-$ *m*/*z* = 596.0238, found 596.0243. HPLC purity: 96.12% (R_t = 6.82 min).

4-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzoic acid (40). Compound **40** was prepared and purified by an above described procedure using **11** (100 mg, 1 equiv.) and 4'-hydrazino benzoic acid (65 mg, 1 equiv.) as starting materials. Yellow solid, (74 mg, 58% yield). ^{1}H NMR (300 MHz, DMSO): *δ* 12.32 (brs, 1H, *COOH*), 7.80-7.76 (m, 4H), 7.57 (d, 2H, *J* = 8.25 Hz), 7.48 (d, 1H, *J* = 8.76 Hz), 7.40 (s, 1H), 7.05 (d, 2H, *J* = 8.58 Hz), 6.79 (s, 1H), 6.71 (dd, 1H, *J* = 1.62 and 8.64 Hz), 5.60-5.54 (dt, 1H, *J* = 5.01 and 12.03 Hz), 4.05-3.97 (q, 2H, OCH_2), 3.96-3.85 (dd, 1H, *J* = 12.72 and 17.61 Hz), 3.21-3.14 (dd, 1H, *J* = 5.16 and 17.79 Hz), 1.34 (t, 3H, *J* = 6.69 and 13.83 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): *δ* 170.89, 167.67, 161.61, 150.25, 148.66, 144.35,

140.31, 137.92, 134.89, 131.84, 129.97, 128.42, 128.28, 120.60, 117.11, 113.32, 112.55, 111.62, 98.68, 96.18, 63.95, 58.35, 14.92. MS (ESI) *m*/*z* = 596.1 $[M - H]^-$; HRMS (ESI): calcd for $C_{27}H_{20}N_3O_3ICl$ $[M - H]^-$ *m*/*z* = 596.0238, found 596.0236. HPLC purity: 96.55% (R_t = 6.84 min).

Synthesis of Target Compounds 41-47:



1-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-5-morpholinopentane-1,5-dione (41). To a solution of compound **4** (50 mg, 1 equiv.) in dry DMF (4 mL) was added EDCI.HCl (24 mg, 1.5 equiv.), HOBt (17 mg 1.5 equiv.), DIPEA (22 µL, 1.5 equiv.) and the mixture was stirred for 30 min at room temperature under an argon atmosphere. Morpholine (9 µL, 1.1 equiv.) and DIPEA (22 µL, 1.5 equiv.) were added to the reaction mixture. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was poured into water and extracted with DCM (3 x 10 mL). The combined organic extracts was washed with saturated $NaHCO_3$ (2 x 10 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by Biotage automated flash column chromatography using 1-2% MeOH in DCM as the eluent to furnish 1-(5-(2-chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-5-morpholinopentane-1,5-dione **41** (44 mg, 78% yield) as a white solid. TLC: 1% MeOH in DCM, R_f = 0.38; visualized with UV. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (t, 3H, *J* = 8.37 and 17.58 Hz), 7.65 (d, 1H, *J* = 8.97 Hz), 7.47 (d, 2H, *J* = 8.37 Hz), 7.29 (d, 1H, *J* = 1.74 Hz), 7.18-7.15 (dd, 1H, *J* = 2.25 and 8.91 Hz), 5.98-5.92 (dt, 1H, *J* = 4.8 and 11.76 Hz), 4.18-4.08 (q, 2H, OCH_2), 3.93-3.83 (dd, 1H, *J* = 11.97 and 17.82 Hz), 3.61 (brs, 4H), 3.15-2.89 (m, 3H, *CH* and CH_2), 2.52-2.38 (m, 2H, CH_2), 2.27 (brs, 4H), 2.13-2.04 ((p, 2H, CH_2), 1.48 (t, 3H, *J* = 6.9 and 13.86 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.26, 171.07, 160.95, 153.46, 149.00, 148.51, 137.97, 130.44, 128.59, 128.14, 122.19, 120.89, 106.85, 97.02, 66.60, 63.89, 57.84, 53.61, 36.18, 33.36, 32.54, 21.08, 14.58. MS (ESI) *m*/*z* = 661.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{29}H_{31}N_4O_4ICl$ $[M + H]^+$ *m*/*z* = 661.1079, found 661.1076. HPLC purity: 95.37% (R_t = 4.09 min).

Compounds **42-47** were synthesized by an above synthetic procedure described for the preparation of amide **41** using appropriate starting materials. Each compound was triturated with the mixture of 1-2% MeOH in EtOAc (2-3 times) to afford desired compound.

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(2-morpholinoethyl)-5-oxopentanamide (42). White solid (44 mg, 74% yield). TLC: 10% MeOH in DCM, R_f = 0.42; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 7.98 (s, 1H), 7.94 (d, 1H, J = 9.03 Hz), 7.85 (d, 2H, J = 8.43 Hz), 7.77 (t, 1H, J = 5.49 and 11.13 Hz), 7.57 (d, 2H, J = 8.4 Hz), 7.34 (d, 1H, J = 2.31 Hz), 7.26-7.22 (dd, 1H, J = 2.4 and 8.97 Hz), 5-84-5.78 (dt, 1H, J = 5.13 and 11.88 Hz), 4.21-4.14 (q, 2H, OCH_2), 4.01 (dd, 1H, J = 12.03 and 18.00 Hz), 3.54 (t, 4H, J = 4.5 and 9.12 Hz), 3.29 (dd, 1H, J = 5.91 and 18.63 Hz), 3.18-3.11 (q, 2H, CH_2), 2.89-2.72 (m, 2H, CH_2), 2.33-2.27 (m, 6H), 2.16-2.11 (t, 2H, J = 7.26 and 14.43 Hz, CH_2), 1.86-1.77 (p, 2H, CH_2), 1.41 (t, 3H, J = 6.93 and 13.89 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): δ 172.10, 170.54, 160.82, 154.20, 148.63, 138.05, 130.93, 130.47, 129.67, 129.01, 122.54, 120.70, 107.08, 97.88, 66.60, 64.15, 57.99, 53.71, 36.20, 35.12, 33.16, 21.07, 14.88. MS (ESI) m/z = 704.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{31}H_{36}N_5O_4ICl$ $[M + H]^+$ m/z = 704.1501, found 704.1504. HPLC purity: 98.92% (R_t = 4.16 min).

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-iodophenyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(3-morpholinopropyl)-5-oxopentanamide (43). White solid (46 mg, 76% yield). TLC: 10% MeOH in DCM, R_f = 0.37; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 7.98 (s, 1H), 7.94 (d, 1H, J = 9.09 Hz), 7.85 (d, 2H, J = 8.46 Hz), 7.78 (t, 1H), 7.57 (d, 2H, J = 8.49 Hz), 7.34 (d, 1H, J = 2.34 Hz), 7.26-7.23 (dd, 1H, J = 2.43 and 8.97 Hz), 5-84-5.78 (dt, 1H, J = 5.16 and 11.97 Hz), 4.21-4.14 (q, 2H, OCH_2), 4.01 (dd, 1H, J = 12.42 and 18.36 Hz), 3.53 (t, 4H, J = 4.47 and 9.09 Hz), 3.29 (dd, 1H, J = 5.34 and 18.15 Hz), 3.07-3.01 (q, 2H, CH_2), 2.91-2.71 (m, 2H, CH_2), 2.27 (brs, 4H), 2.27-2.19 (m, 2H), 2.15-2.10 (t, 2H, J = 7.29 and 14.49 Hz, CH_2), 1.87-1.77 (p, 2H, CH_2), 1.56-1.49 (p, 2H, CH_2), 1.41 (t, 3H, J = 6.93 and 13.89 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): δ 172.01, 170.52, 160.82, 154.18, 148.63, 138.05, 135.34, 130.92, 130.45, 129.66, 128.99, 128.20, 122.54, 121.18, 120.69, 107.08, 97.87, 66.62, 64.15, 57.85, 56.35, 53.77, 37.26, 35.15, 33.20, 26.57, 21.07, 14.87. MS (ESI) m/z = 718.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{32}H_{38}N_5O_4ICl$ $[M + H]^+$ m/z = 718.1657, found 718.1651. HPLC purity: 97.24% (R_t = 4.28 min).

5-(3-(4-Bromophenyl)-5-(2-chloro-7-ethoxyquinolin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(3-morpholinopropyl)-5-oxopentanamide (44). Off-white solid (49 mg, 80% yield). TLC: 10% MeOH in DCM, R_f = 0.39; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 7.99 (s, 1H), 7.94 (d, 1H, J = 9.09 Hz), 7.83 (t, 1H, J = 5.16 and 9.9 Hz), 7.74-7.65 (m, 4H), 7.34 (d, 1H, J = 2.34 Hz), 7.27-7.23 (dd, 1H, J = 2.49 and 8.97 Hz), 5-85-5.79 (dt, 1H, J = 5.25 and 12.06 Hz), 4.21-4.14 (q, 2H, OCH_2), 4.02 (dd, 1H, J = 12.33 and 18.33 Hz), 3.51 (t, 4H, J = 4.17 and 9.04 Hz), 3.30 (dd, 1H, J = 5.55 and 18.37 Hz), 3.08-3.01 (q, 2H, CH_2), 2.91-2.72 (m, 2H, CH_2), 2.27 (brs, 4H), 2.26-2.20 (m, 2H), 2.16-2.11 (t, 2H, J = 7.41 and 14.58 Hz, CH_2), 1.87-1.77 (p, 2H, CH_2), 1.56-1.49 (p, 2H, CH_2), 1.41 (t, 3H, J = 6.96 and 13.92 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): δ 172.03, 170.54, 160.83, 153.99, 148.64, 132.23, 130.67, 130.46, 129.67, 129.13, 124.24, 122.55, 120.70, 107.09, 66.61, 64.15, 57.91, 56.33, 53.76, 37.24, 35.15, 33.22, 26.58, 21.07, 14.87. MS (ESI) m/z = 670.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{32}H_{38}N_5O_4BrCl$ $[M + H]^+$ m/z = 670.1796, found 670.1793. HPLC purity: 96.61% (R_t = 3.93 min).

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-(6-chloropyridin-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(3-morpholinopropyl)-5-oxopentanamide (45). Light yellow solid (49 mg, 81% yield). TLC: 10% MeOH in DCM, R_f = 0.40; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 8.80 (s, 1H), 8.23 (d, 1H, *J* = 6.78 Hz), 8.01 (s, 1H), 7.95-7.81 (m, 6H), 7.65 (d, 1H, *J* = 8.22 Hz), 7.34 (s, 1H), 7.26 (d, 1H, *J* = 8.16 Hz), 5-87-5.83 (dt, 1H, *J* = 5.30 and 12.16 Hz), 4.20-4.15 (q, 2H, OCH_2), 4.07 (dd, 1H, *J* = 12.87 and 17.82 Hz), 3.51 (brs, 4H), 3.08-3.01 (q, 2H, CH_2), 2.90-2.72 (m, 2H, CH_2), 2.29 (brs, 4H), 2.27-2.22 (m, 2H), 2.16-2.11 (t, 2H, *J* = 7.35 and 14.24 Hz, CH_2), 1.88-1.78 (p, 2H, CH_2), 1.57-1.50 (p, 2H, CH_2), 1.41 (t, 3H, *J* = 6.51 and 12.57 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): δ 174.65, 172.16, 172.08, 170.58, 160.83, 160.41, 154.31, 153.81, 150.51, 150.18, 148.65, 148.31, 140.74, 138.22, 137.70, 135.58, 134.51, 131.57, 129.49, 127.96, 127.64, 124.94, 124.43, 123.21, 120.90, 107.71, 66.50, 64.03, 57.91, 53.64, 36.09, 35.17, 35.07, 33.22, 21.12, 14.91. MS (ESI) *m*/*z* = 703.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{37}H_{41}N_6O_4Cl_2$ $[M + H]^+$ *m*/*z* = 703.2566, found 703.2569. HPLC purity: 95.36% (R_t = 4.27 min).

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-(6-fluoropyridin-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(3-morpholinopropyl)-5-oxopentanamide (46). White solid (47 mg, 77% yield). TLC: 10% MeOH in DCM, R_f = 0.43; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 8.62 (d, 1H, *J* = 2.28 Hz), 8.38-8.31 (m, 1H), 8.01 (s, 1H), 7.95-7.80 (m, 6H),), 7.34-7.32 (m, 1H), 7.30-7.23 (m, 2H), 5-87-5.81 (dt, 1H, *J* = 5.04 and 11.7 Hz), 4.21-4.14 (q, 2H, OCH_2), 4.07 (dd, 1H, *J* = 12.15 and 18.15 Hz), 3.52 (t, 4H, *J* = 4.32 and 8.76 Hz), 3.36 (dd, 1H, *J* = 5.37 and 17.88 Hz), 3.09-3.02 (q, 2H, CH_2), 2.92-2.80 (m, 2H, CH_2), 2.28 (brs, 4H), 2.27-2.21 (m, 2H), 2.17-2.13 (t, 2H, *J* = 7.32 and 14.46 Hz, CH_2), 1.89-1.82 (p, 2H, CH_2), 1.57-1.50 (p, 2H, CH_2), 1.41 (t, 3H, *J* = 6.9 and 13.83 Hz, CH_3); ^{13}C NMR (75 MHz, DMSO): δ 172.04, 170.53, 160.83, 154.35, 148.65, 146.11, 145.91, 140.89, 140.78, 137.94, 131.17, 130.56, 129.68, 127.93, 127.55, 122.57, 120.70, 110.51, 110.01, 107.09, 66.60, 64.15, 57.86, 56.34, 53.75, 37.26, 35.20, 33.28, 26.56, 21.12, 14.87. MS (ESI) *m*/*z* = 687.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{37}H_{41}N_6O_4ClF$ $[M + H]^+$ *m*/*z* = 687.2862, found 687.2859. HPLC purity: 97.05% (R_t = 4.06 min).

5-(5-(2-Chloro-7-ethoxyquinolin-3-yl)-3-(4-(6-(trifluoromethyl)pyridin-3-yl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)-N-(3-morpholinopropyl)-5-oxopentanamide (47). Off-white solid (45 mg, 75% yield). TLC: 10% MeOH in DCM, R_f = 0.37; visualized with UV. ^{1}H NMR (300 MHz, DMSO): δ 9.15 (s, 1H), 8.44 (d, 1H, *J* = 8.01 Hz), 8.02-7.92 (m, 7H), 7.86 (t, 2H, *J* = 4.89 and 10.05 Hz), 7.34 (d, 1H, *J* = 1.74 Hz), 7.27-7.23 (dd, 1H, *J* = 2.16 and 8.91 Hz), 5-88-5.83 (dt, 1H, *J* = 5.07 and 11.85 Hz), 4.21-4.14 (q, 2H, OCH_2), 4.08 (dd, 1H, *J* = 12.06 and 18.06 Hz), 3.53 (t, 4H, *J* = 4.02 and 8.22 Hz), 3.29 (m, 1H), 3.09-3.03 (q, 2H, CH_2), 2.93-2.78 (m, 2H, CH_2), 2.31 (brs, 4H), 2.27-2.23 (m, 2H), 2.18-2.13 (t, 2H, *J* = 7.2 and 14.37 Hz, CH_2), 1.89-1.82 (p, 2H, CH_2), 1.58-1.49 (p, 2H, CH_2), 1.41 (t, 3H, *J* = 6.87 and 13.8 Hz, CH_3); MS (ESI) *m*/*z* = 737.1 $[M + H]^+$; HRMS (ESI): calcd for $C_{38}H_{41}N_6O_4ClF_3$ $[M + H]^+$ *m*/*z* = 737.2830, found 737.2835. HPLC purity: 95.12% (R_t = 4.55 min).

4) Biological and Physiochemical Experimental Details:

A) Purification of Human RPA: Full length, heterotrimeric human RPA (fl-RPA) and DBD-A/B constructs were expressed and purified to near homogeneity as we have previously described.[4-6]

A) DNA Substrate Preparation: The single strand 34-base DNA was obtained from Integrated DNA Technologies and was 5' labeled with [^{32}P], purified and quantified as previously described.[6]

C) Electrophoretic Mobility Shift Assay (EMSA): EMSAs were carried out using previously described procedure with the following modifications.[4-6] Briefly, reactions (20 μL) were performed in buffer containing 20 mM HEPES (pH 7.8), 1 mM DTT, 0.001% NP-40, 50 mM NaCl. Chemical compounds were suspended in DMSO and DMSO concentration in the final reaction mixture was kept constant and below 5%. Purified full length RPA (120 ng) was incubated with inhibitor or DMSO control in reaction buffer for 30 min before the addition of the 34 base [^{32}P]-ssDNA. Reactions were incubated for 5 min at room temperature and products separated via 6% native polyacrylamide gel electrophoresis. The bound and unbound fractions were then quantified by phosphor-imager analysis using ImageQuant software (Molecular Dynamics, CA) and IC_{50} values calculated by non-linear regression using SigmPlot (Sysat).

D) Fluorescent Intercalator Displacement (FID) Assay: The analysis of compound interactions with DNA was determined by inhibition of SYBR-Green intercalation into DNA as we have previously described.[7] Briefly, reactions were performed in 25 mM MOPS (pH 6.5) containing sonicated salmon sperm DNA (8.29 ng/μL), SYBR-Green, and the indicated concentrations of RPA inhibitors. Reactions were conducted in black 96-well plates. Doxorubicin, a known noncovalent DNA binding chemotherapeutic, was used as a positive control. Fluorescence was measured using a BioTek® Synergy™ H1 hybrid multi-mode microplate reader with an excitation wavelength of 485 nm, emission wavelength of 528 nm, and a read height of 7 mm. Data were collected using BioTek® Gen5™ reader software. Reactions were incubated a maximum of 5 min before measurements were collected.

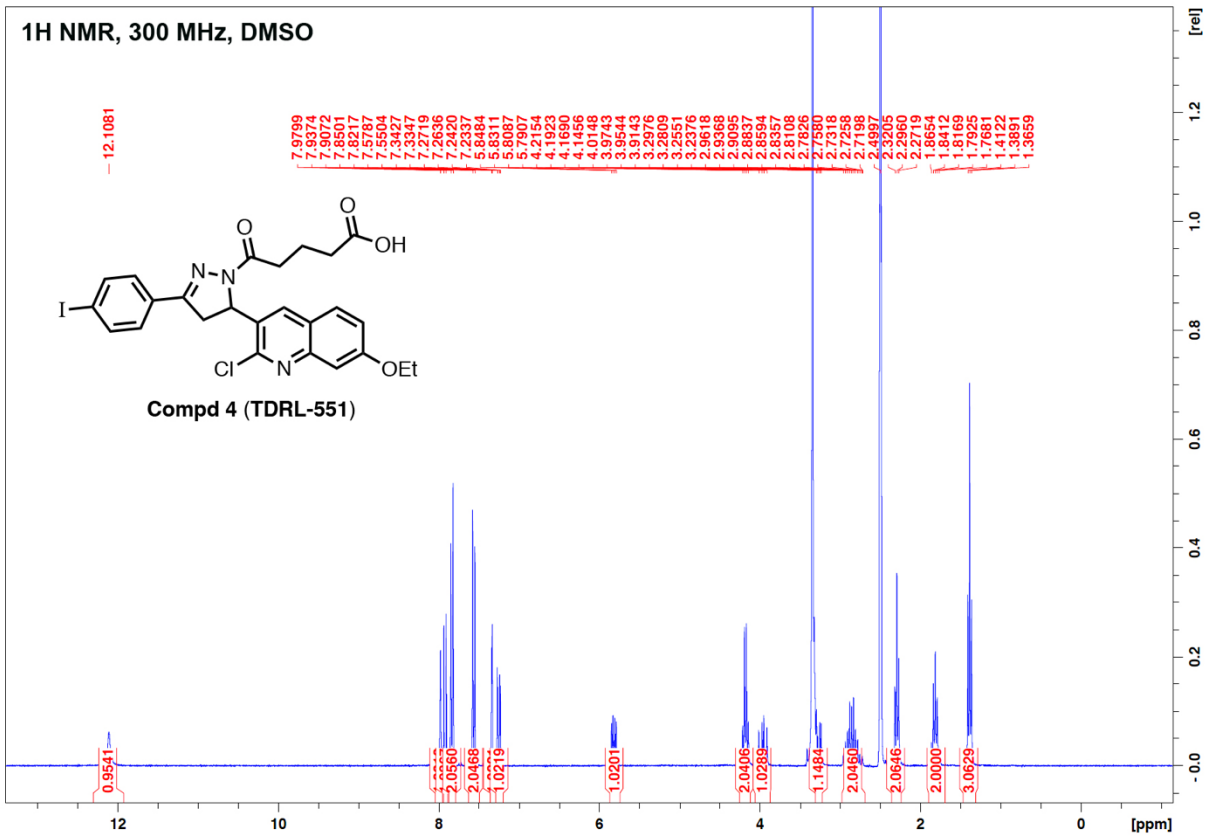
F) Solubility Analysis: Aqueous solubility was determined by suspending compound in un-buffered water with stirring. Insoluble material was removed by sedimentation or filtration and soluble compound quantified by absorbance spectroscopy and LC/MS. pH dependence was determined by suspending compound in 10 mM citrate buffer at pH 4.0 or 10 mM phosphate buffer at pH 7 and carbonate buffer at pH 9.5. The analysis of compound **4** and **43** at various pH demonstrate a dramatic increase in aqueous solubility of the carboxylic acid containing compound **4** at higher pH value while the morpholino containing compound **43** displayed the greater solubility at lower pH value.

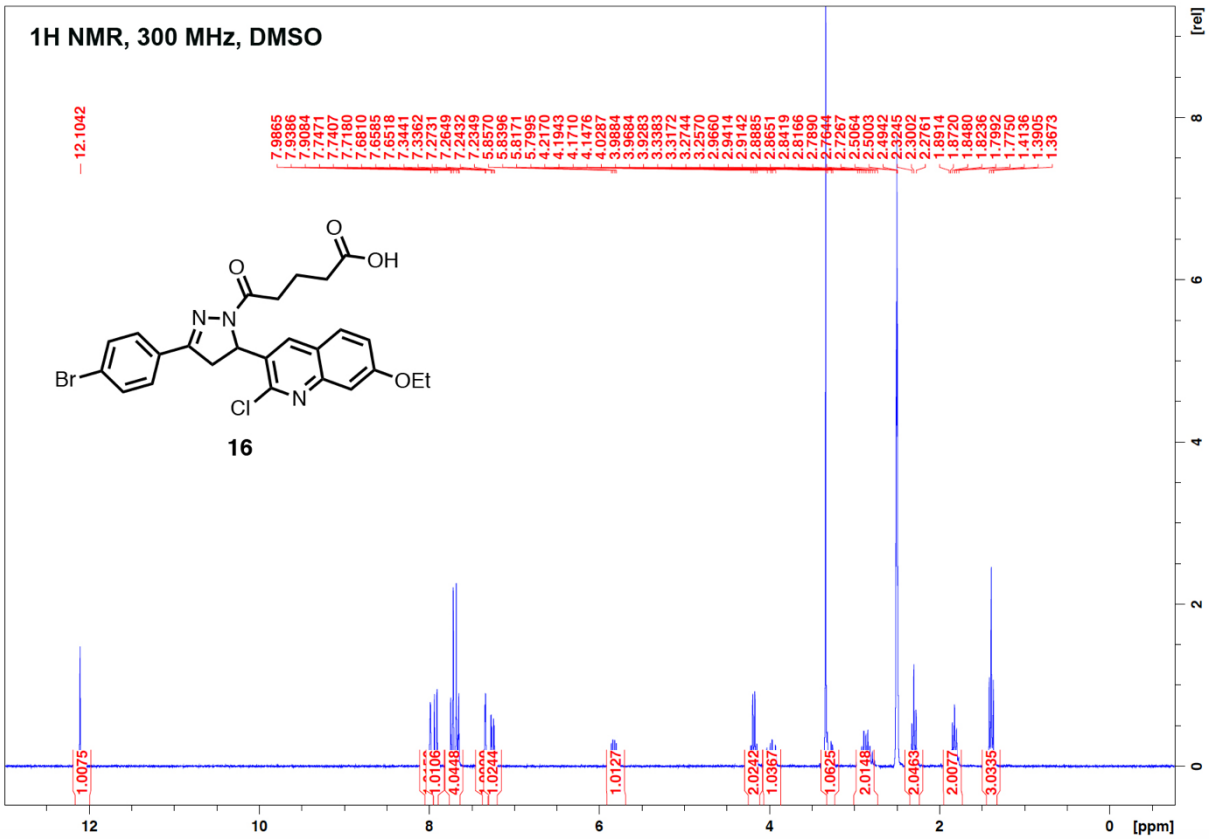
Table S3. Solubility of compound **4** and **43** as a function of pH.

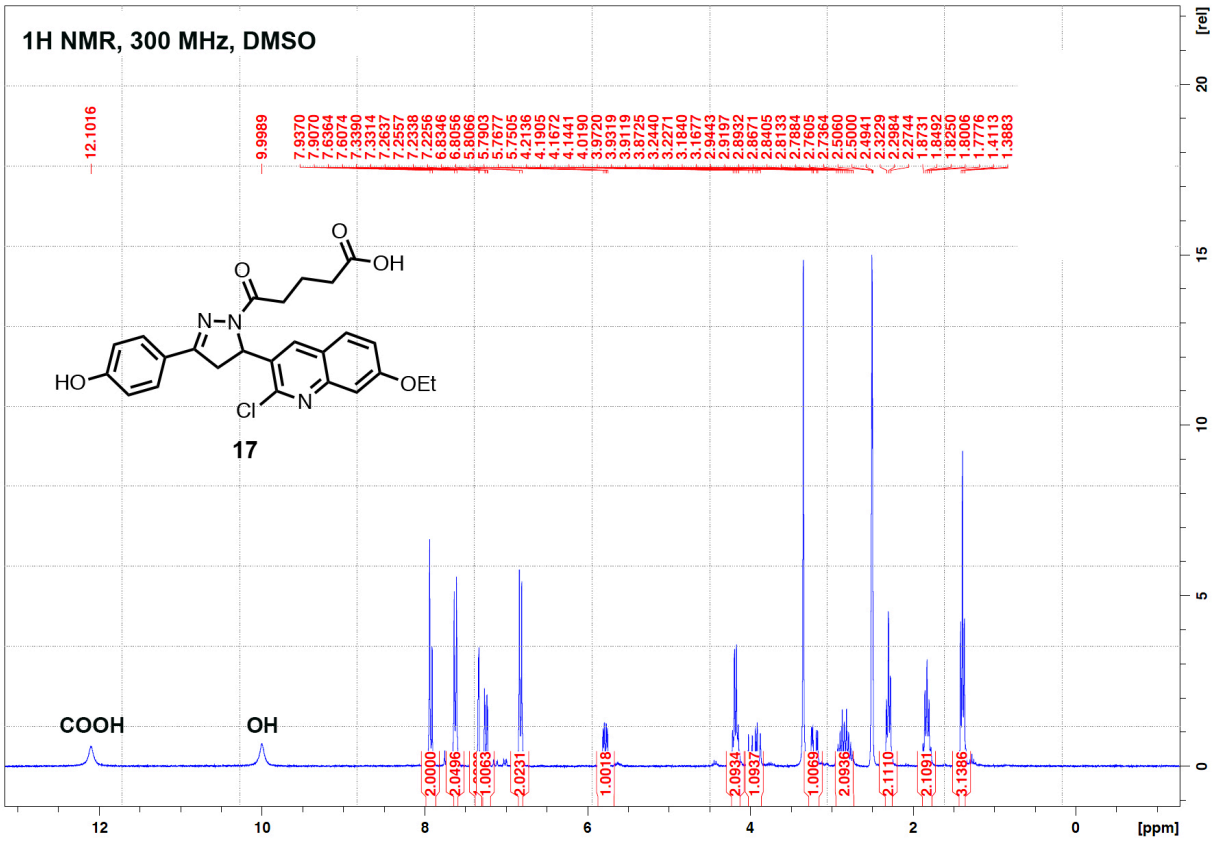
	Aqueous solubility		
pH	4	7	9.5
Compound 4	0.76 ± 0.35 μM	3.3 ± 0.36 μM	112.5 ± 0.74 μM
Compound 43	21.4 ± 5.49 μM	5.7 ± 2.79 μM	3.6 ± 2.22 μM

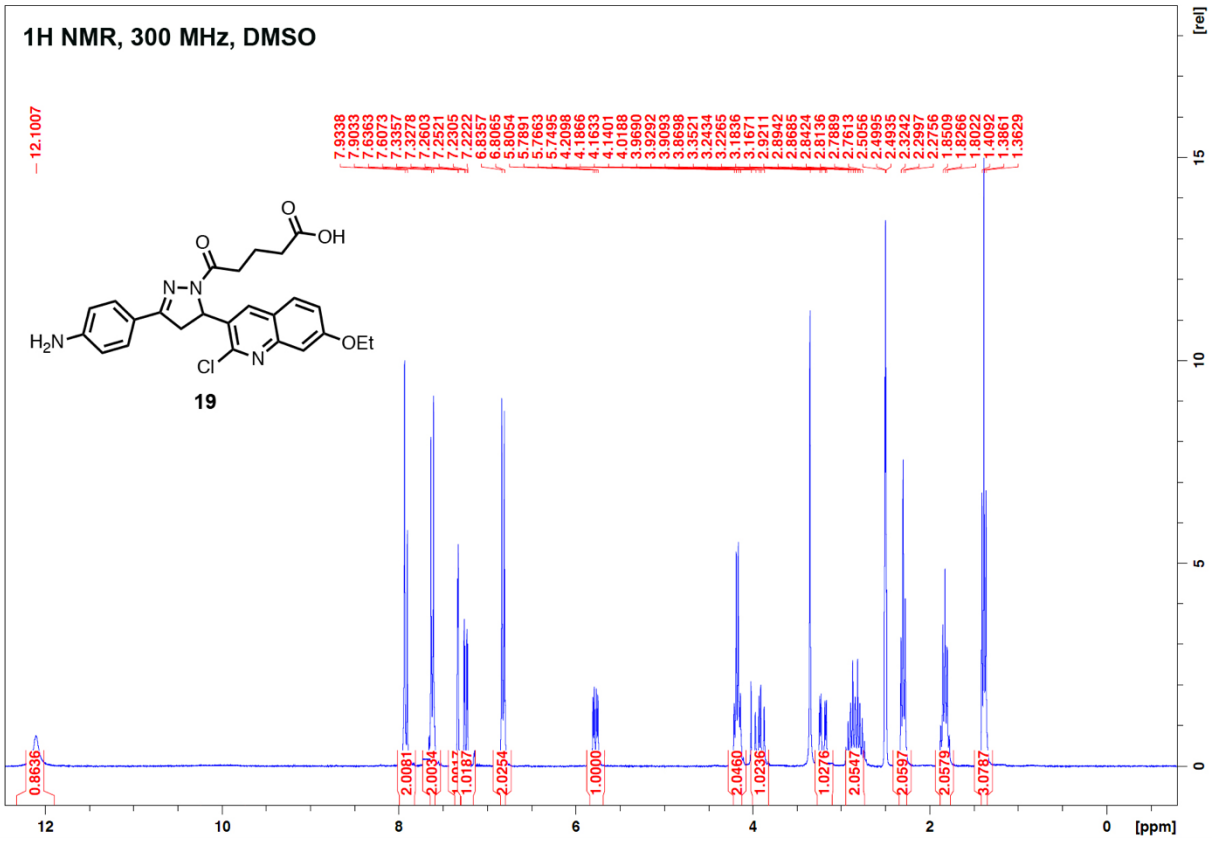
G) Cellular Uptake Measurement: All cells were grown as monolayers at 37°C with 5% CO_2 in media containing 20% fetal bovine serum and 0.1% pen/strep. Cellular uptake was assessed in both H460 NSCLC (Non-Small Cell Lung Cancer) and SKGT4 esophageal adenocarcinoma cells. Similar uptake data was also obtained in the SKGT4 esophageal adenocarcinoma cell line (data not shown). Briefly, cells were plated in 35 mm dishes at 1 x 106 cells well and incubated overnight. Compounds were added to the medium at a concentration of 20 μM incubation continued for 4 hours. Media was removed and cells washed 3 x with PBS. 1 mL of methanol was added per well and cells agitated overnight at 4°C. The methanol was collected, wells washed with an additional 1 mL of methanol and pooled. The compounds were dried under vacuum, suspended in methanol and quantified by LC/MS. The LC/MS signal was quantified and relative level was determined and normalized to compound **4**.

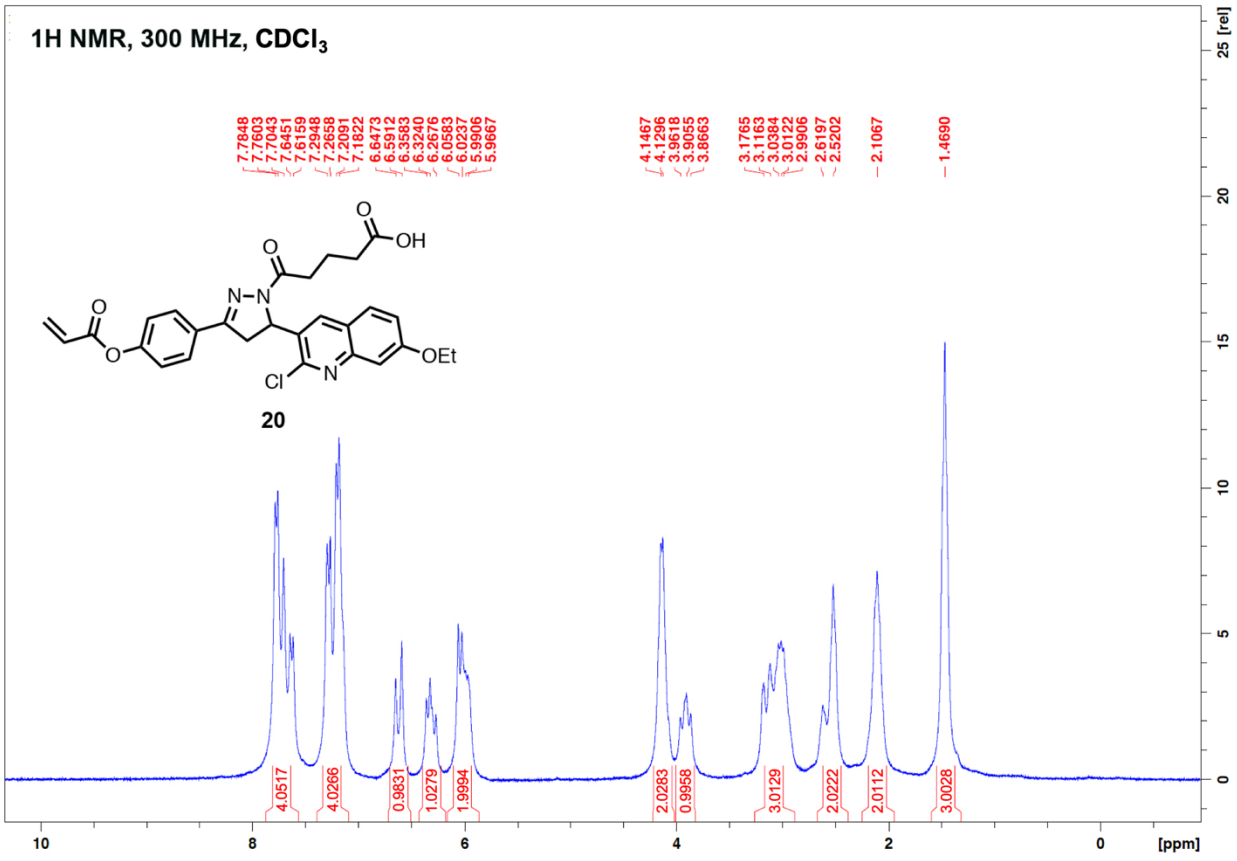
5) ^{1}H NMR Spectra of Final Compounds:

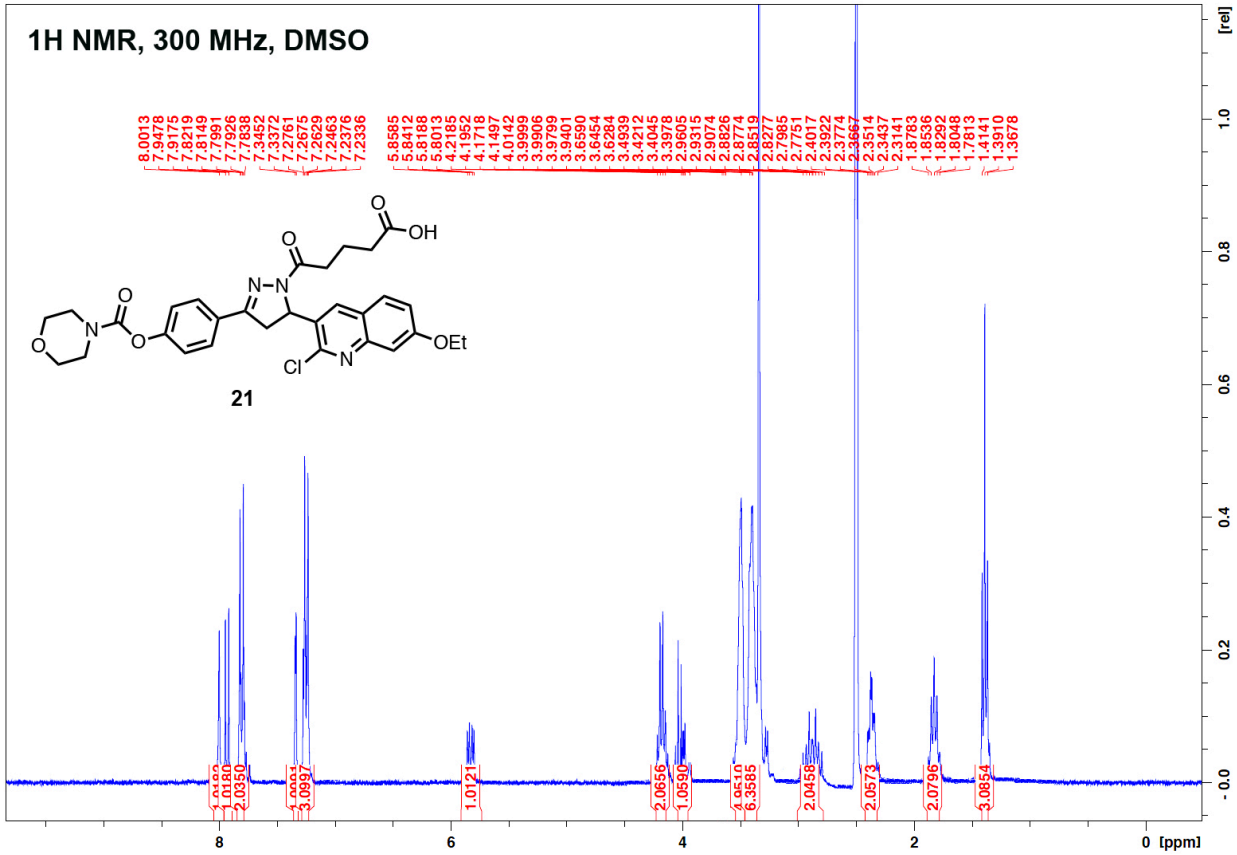


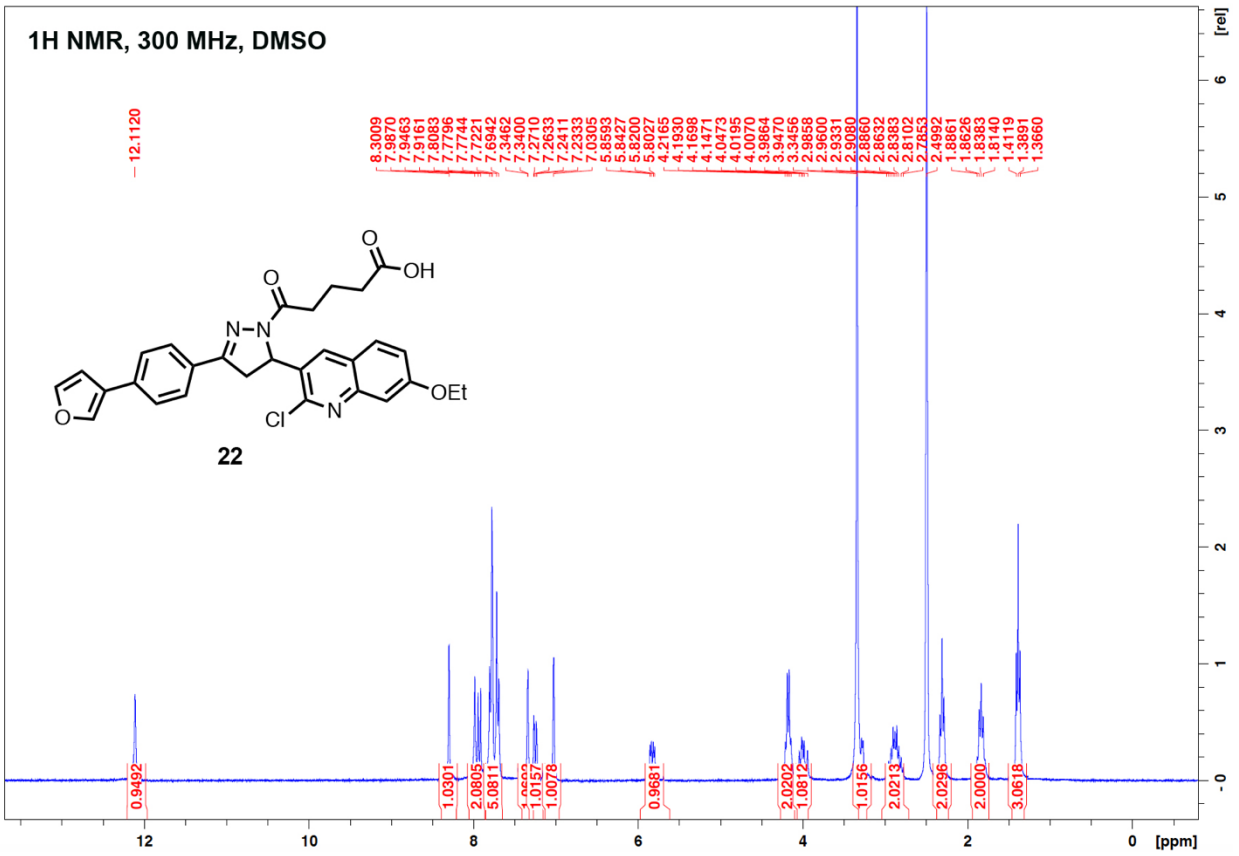


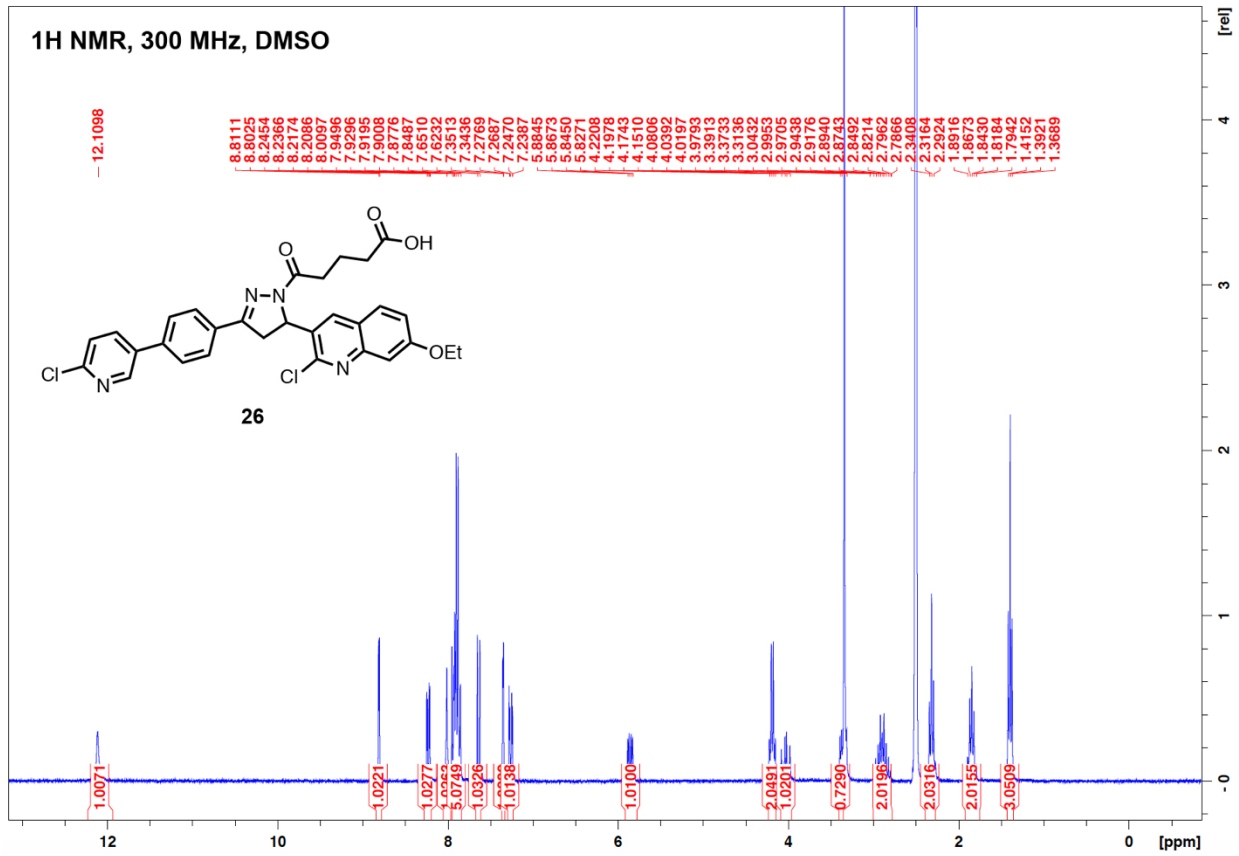

1H NMR, 300 MHz, DMSO
12.1016
9.9989
7.9370
7.9070
7.6364
7.6074
7.3390
7.3314
7.2637
7.2557
7.2338
7.2256
6.8346
6.8056
5.8066
5.7903
5.7677
5.7505
4.2136
4.1905
4.1672
4.1441
4.0190
3.9720
3.9319
3.9119
3.8725
3.2440
3.2271
3.1840
3.1677
2.9443
2.9197
2.8932
2.8671
2.8405
2.8133
2.7884
2.7605
2.7364
2.5060
2.5000
2.4941
2.3229
2.2984
2.2744
1.8731
1.8492
1.8250
1.8006
1.7776
1.4113
1.3883
O
OH
O
N–N
HO
OEt
Cl
N
17
COOH
OH
2.0000
2.0496
1.0063
2.0231
1.0018
2.0934
1.0937
1.0069
2.0936
2.1110
2.1091
3.1386
12
10
8
6
4
2
0
[ppm]
[rel]
20
15
10
5
0

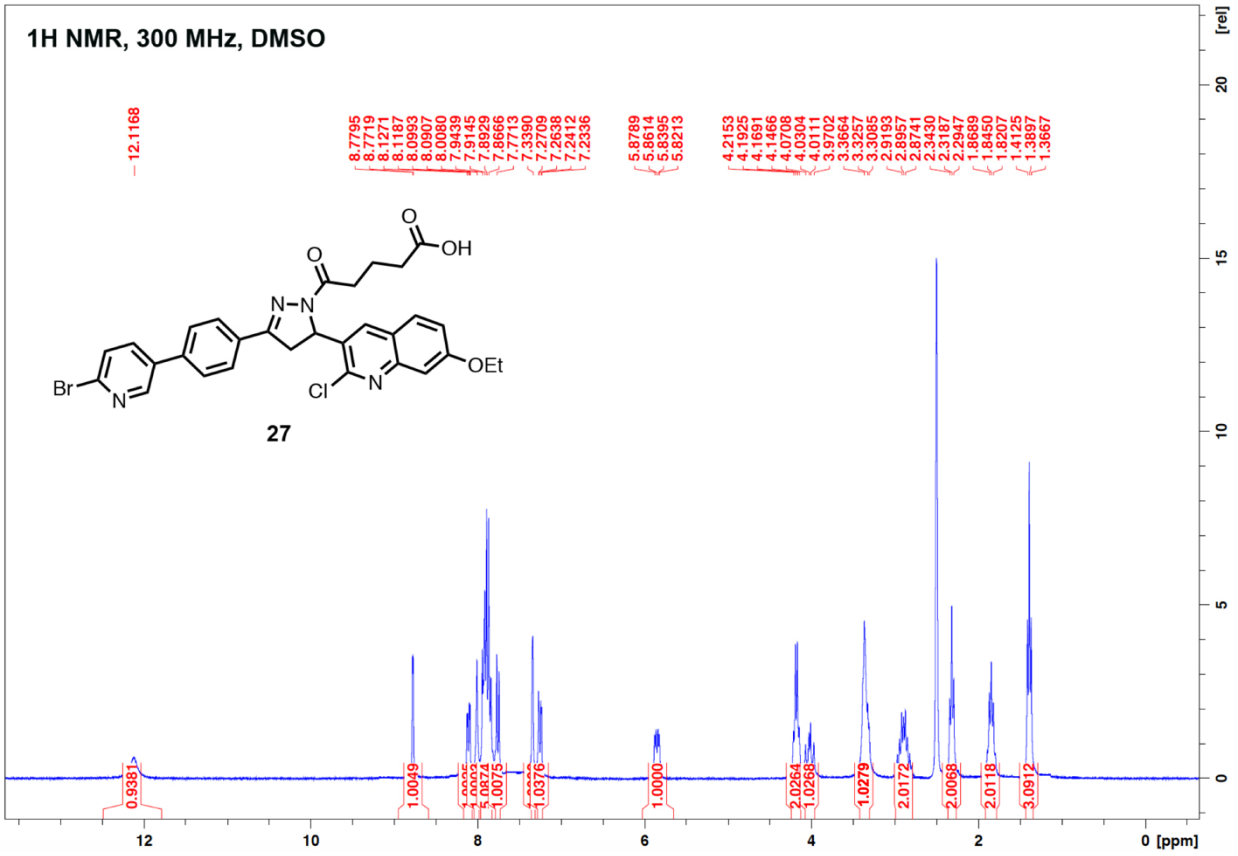

1H NMR, 300 MHz, DMSO
12.1007
7.9338
7.9033
7.6363
7.6073
7.3357
7.3278
7.2603
7.2521
7.2305
7.2222
6.8357
6.8065
5.8054
5.7891
5.7663
5.7495
4.2098
4.1866
4.1633
4.1401
4.0188
3.9690
3.9292
3.9093
3.8698
3.3521
3.3434
3.3265
3.1836
3.1671
2.9211
2.8942
2.8685
2.8424
2.8136
2.7889
2.7613
2.5056
2.4995
2.4935
2.3242
2.2997
2.2756
1.8509
1.8266
1.8022
1.4092
1.3861
1.3629
O
OH
O
N–N
H2N
OEt
Cl
N
19
0.8636
2.0081
2.0034
1.0187
2.0254
1.0000
2.0460
1.0236
1.0276
2.0547
2.0597
2.0579
3.0787
12
10
8
6
4
2
0
[ppm]
[rel]
15
10
5
0

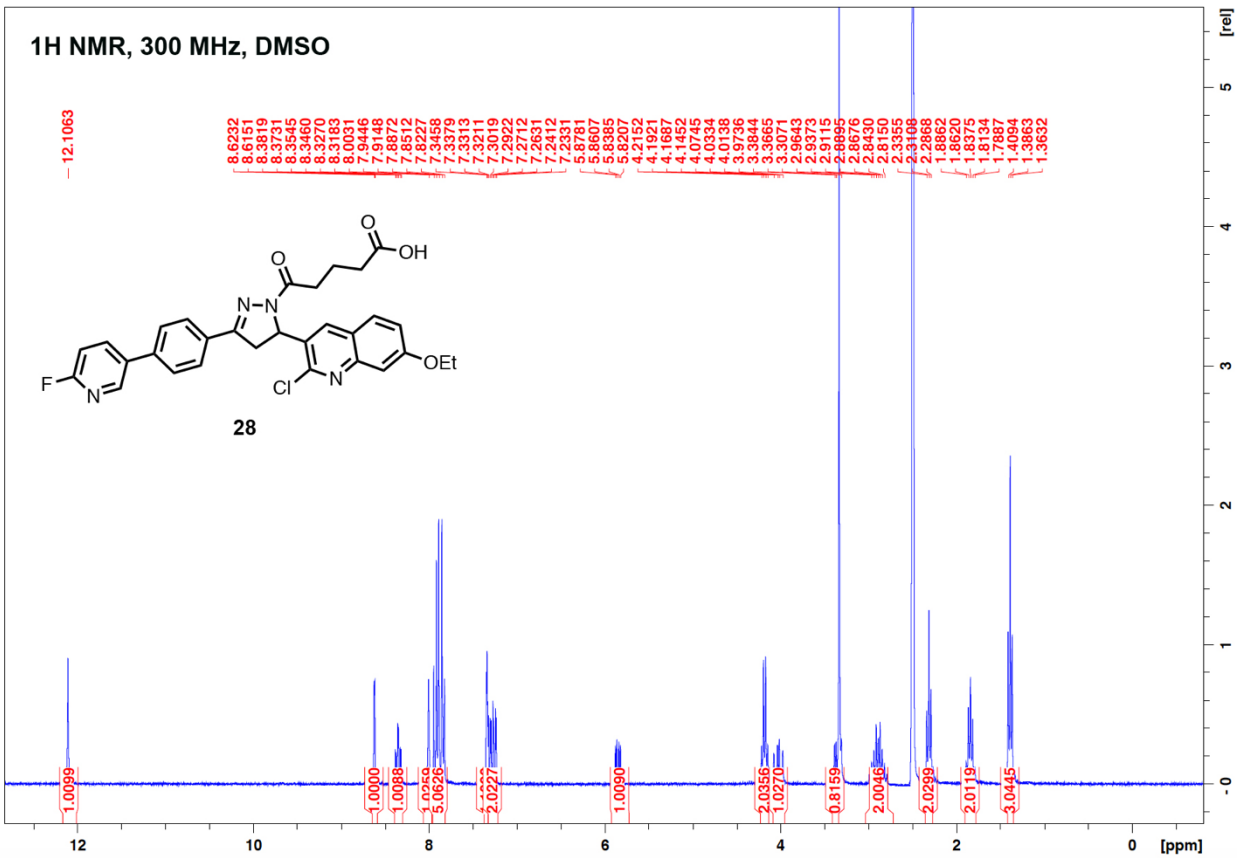

1H NMR, 300 MHz, CDCl3
20
[ppm]

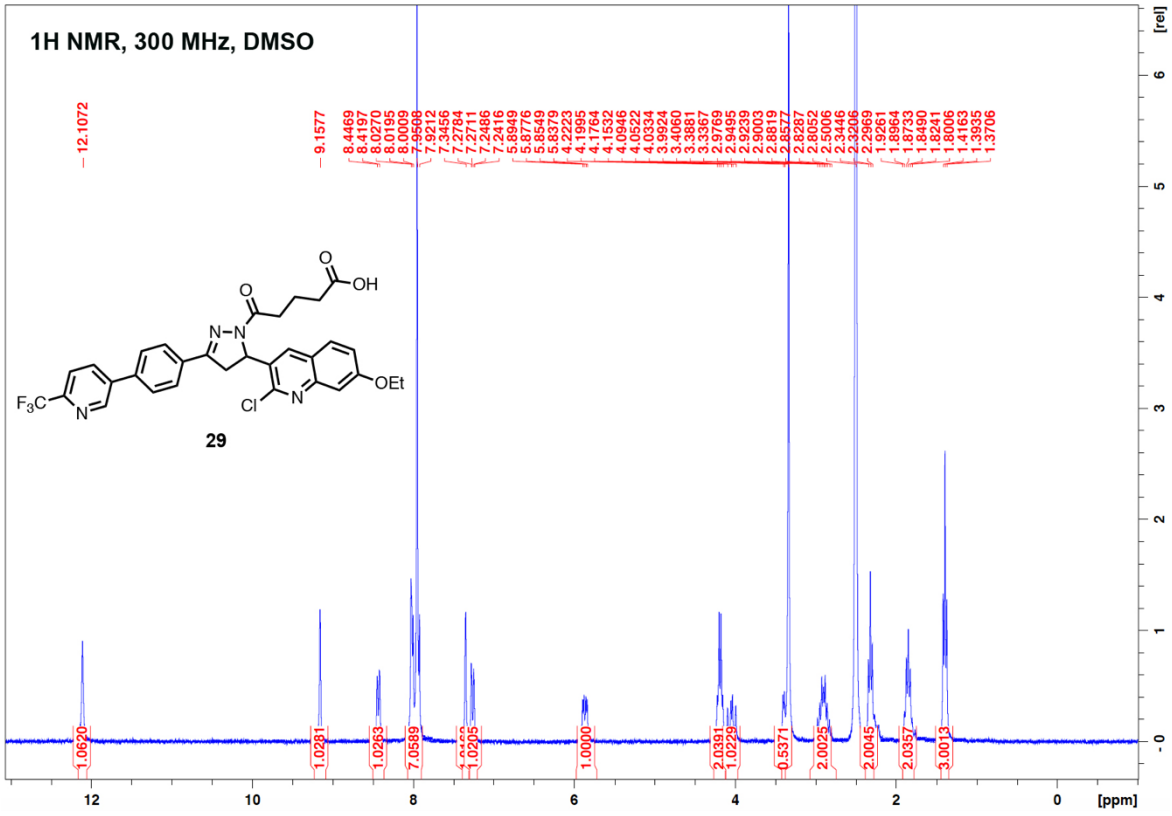

1H NMR, 300 MHz, DMSO
21
[ppm]

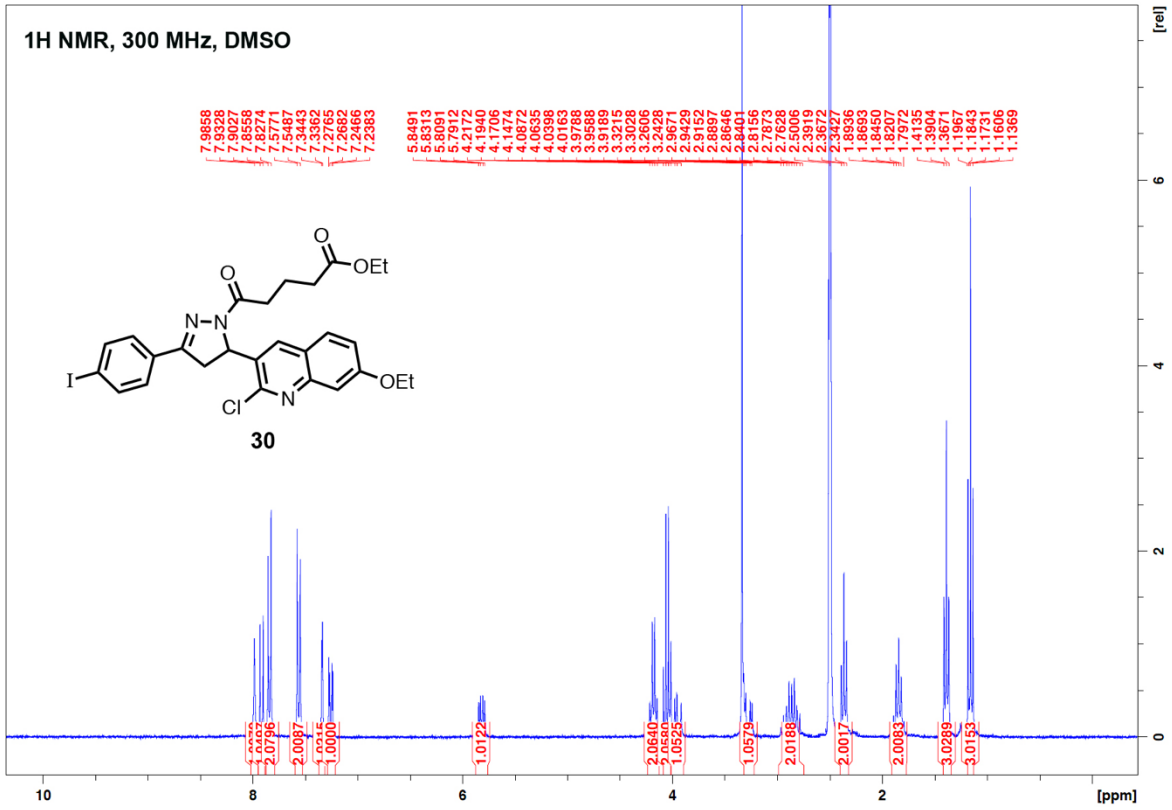

1H NMR, 300 MHz, DMSO
22
[ppm]
[rel]

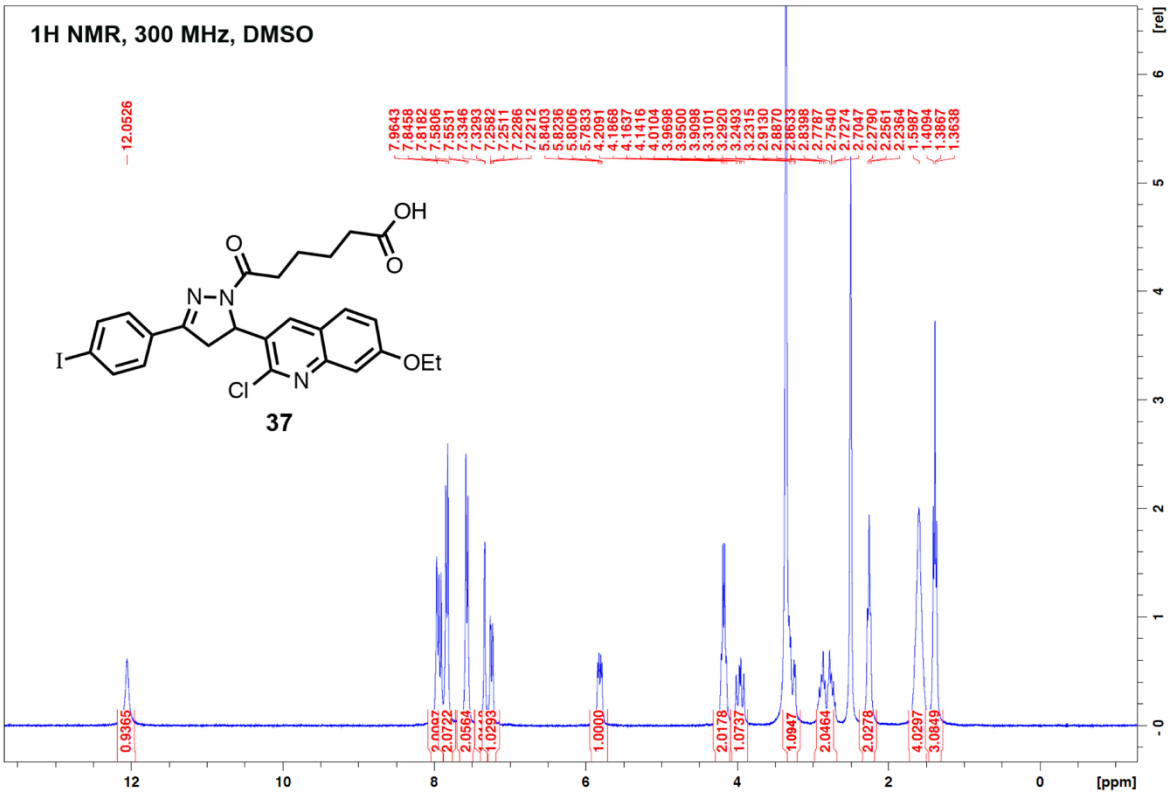

1H NMR, 300 MHz, DMSO
26
[ppm]
[rel]

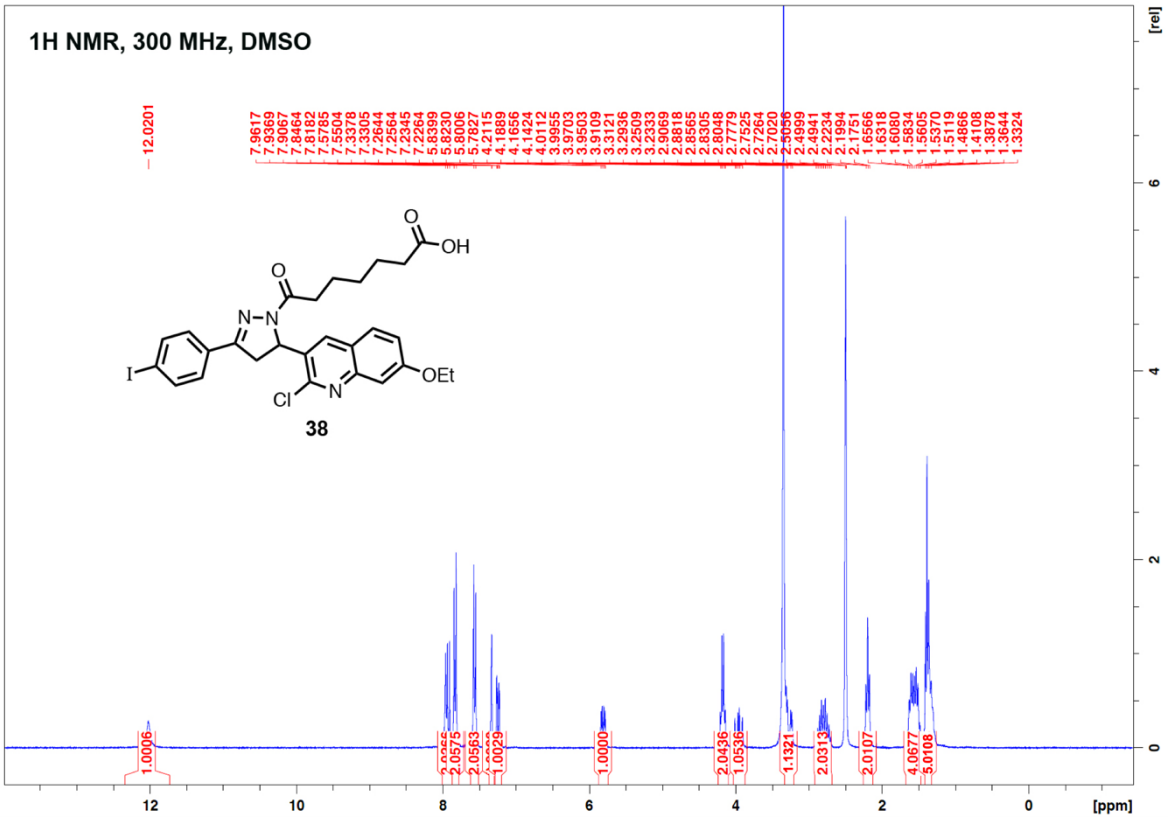

1H NMR, 300 MHz, DMSO
27
[rel]
[ppm]

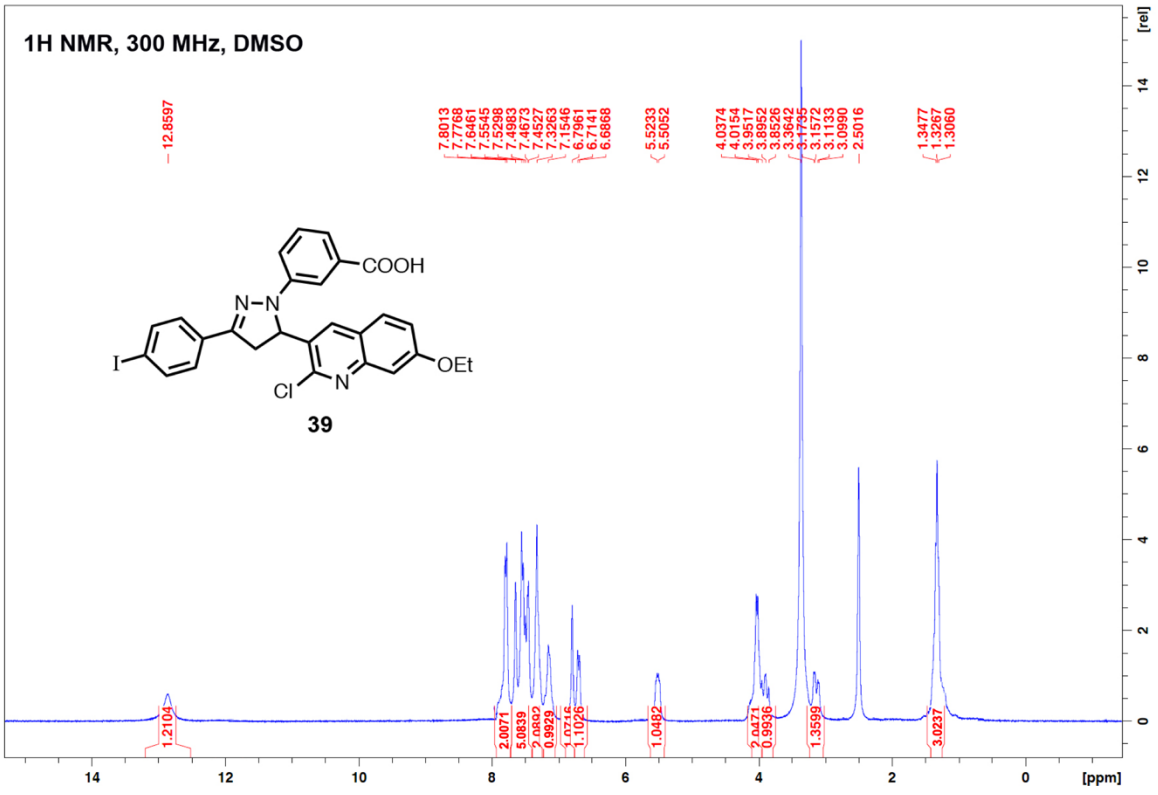

1H NMR, 300 MHz, DMSO
28
[rel]
[ppm]

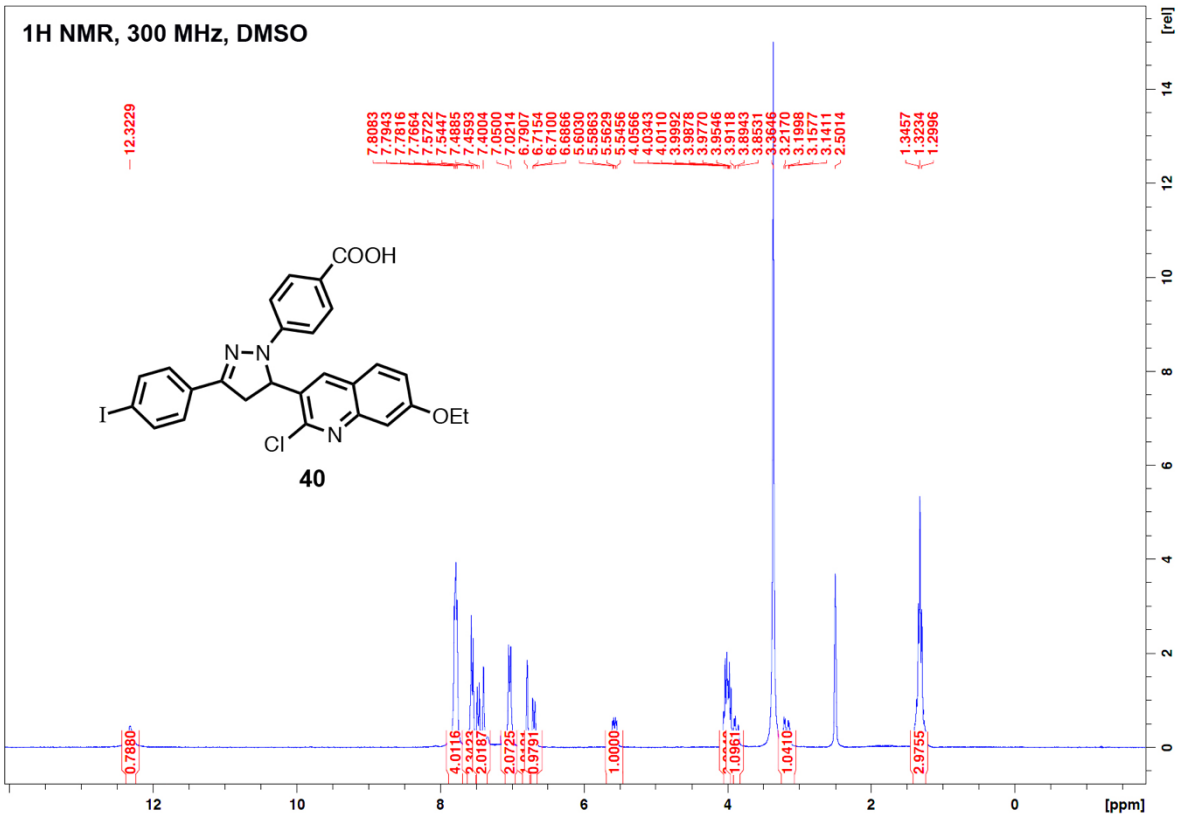

1H NMR, 300 MHz, DMSO
29
[ppm]
[rel]

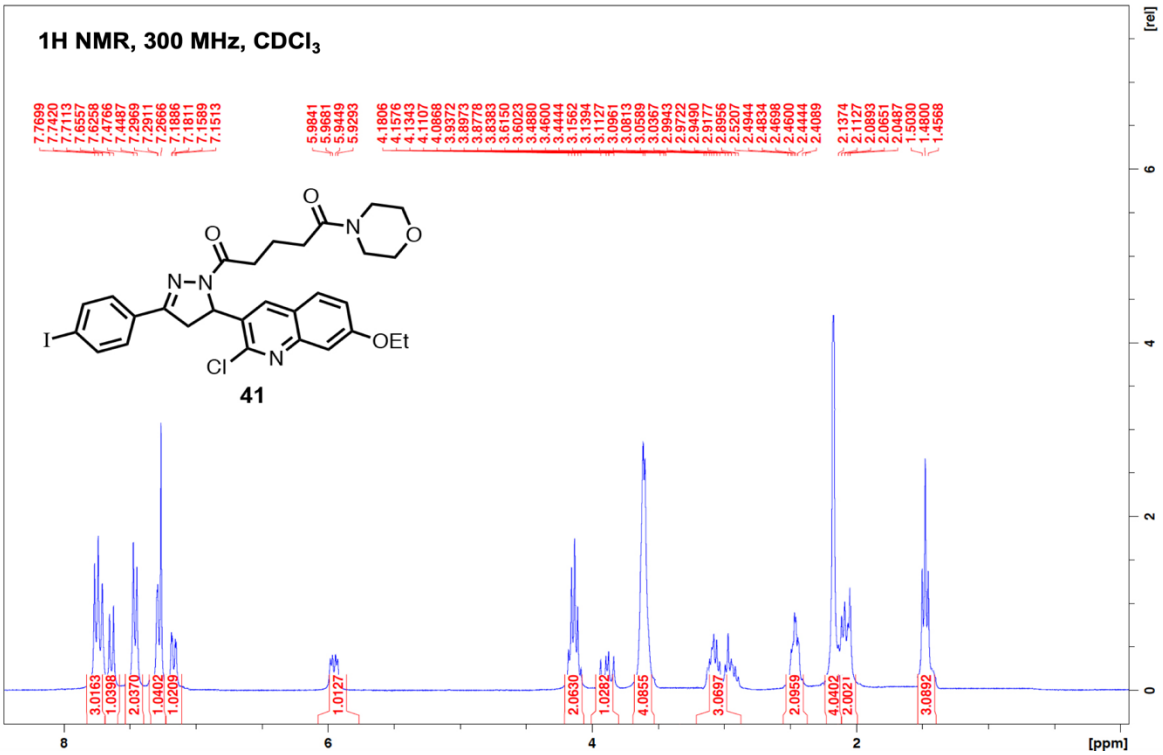

1H NMR, 300 MHz, DMSO
30
[ppm]
[rel]

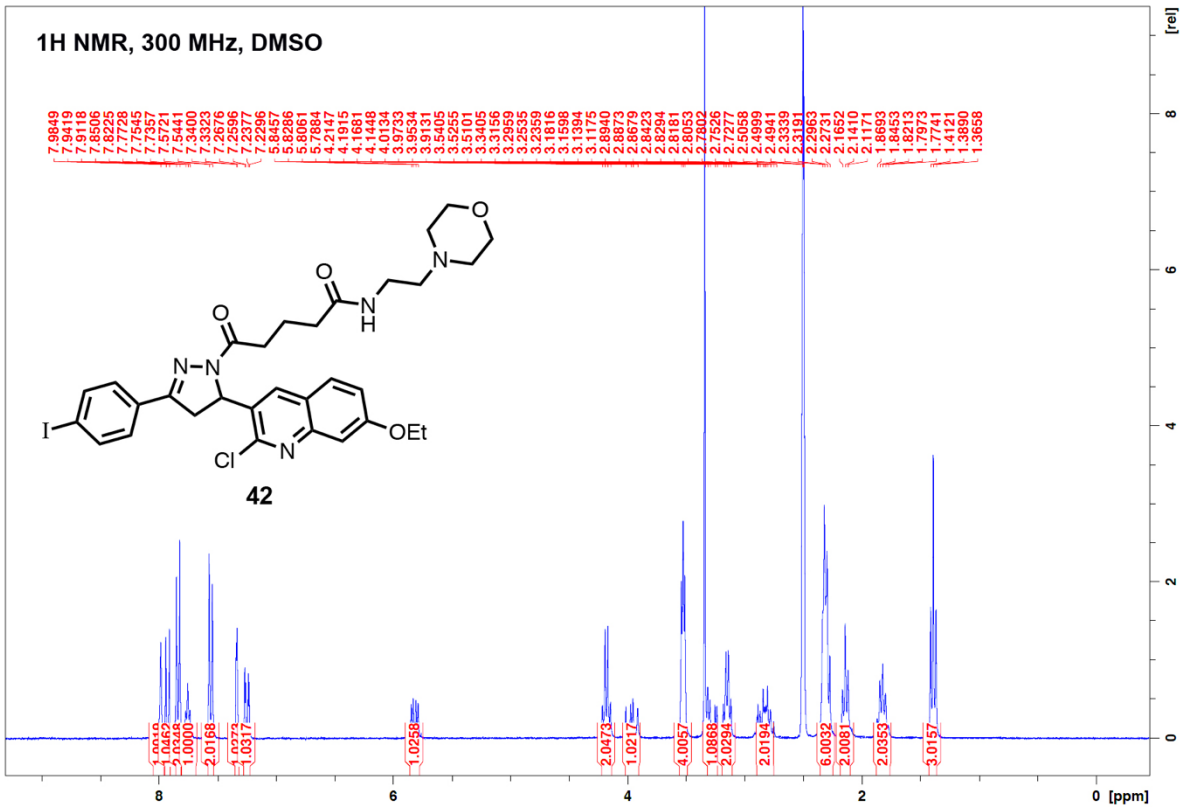

1H NMR, 300 MHz, DMSO
37
[rel]
[ppm]

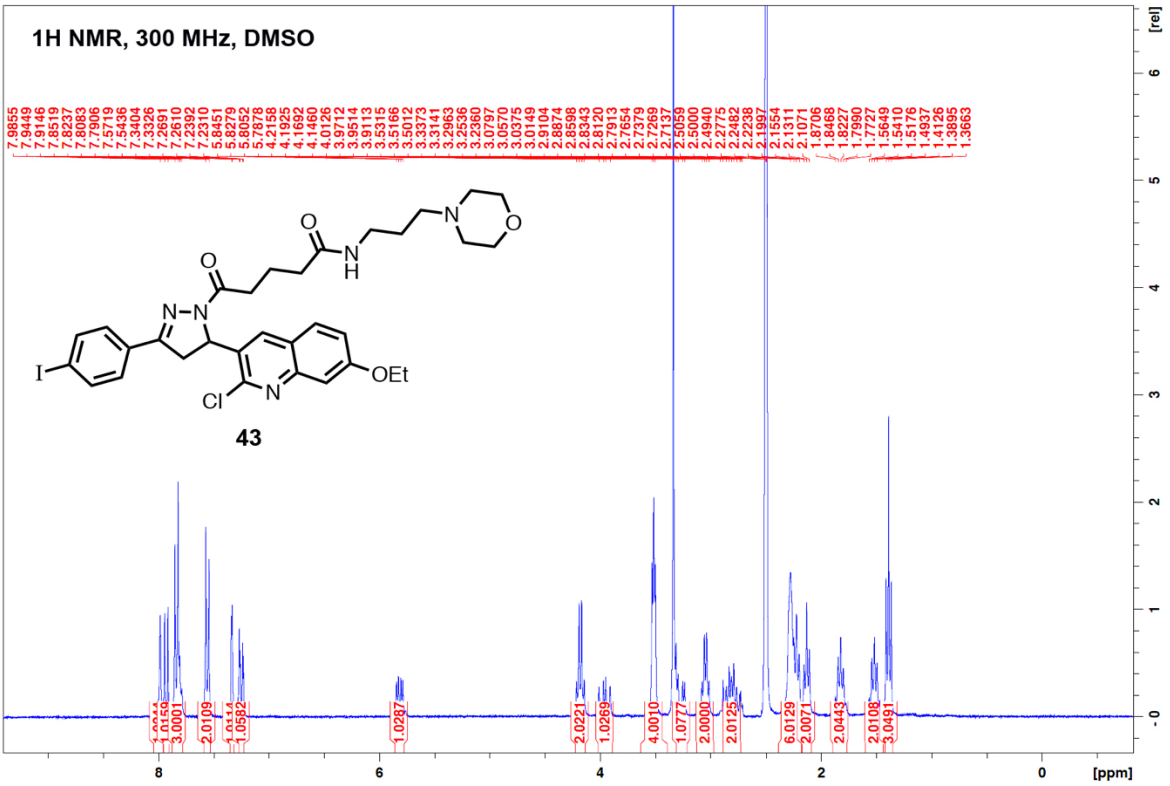

1H NMR, 300 MHz, DMSO
38
[rel]
[ppm]

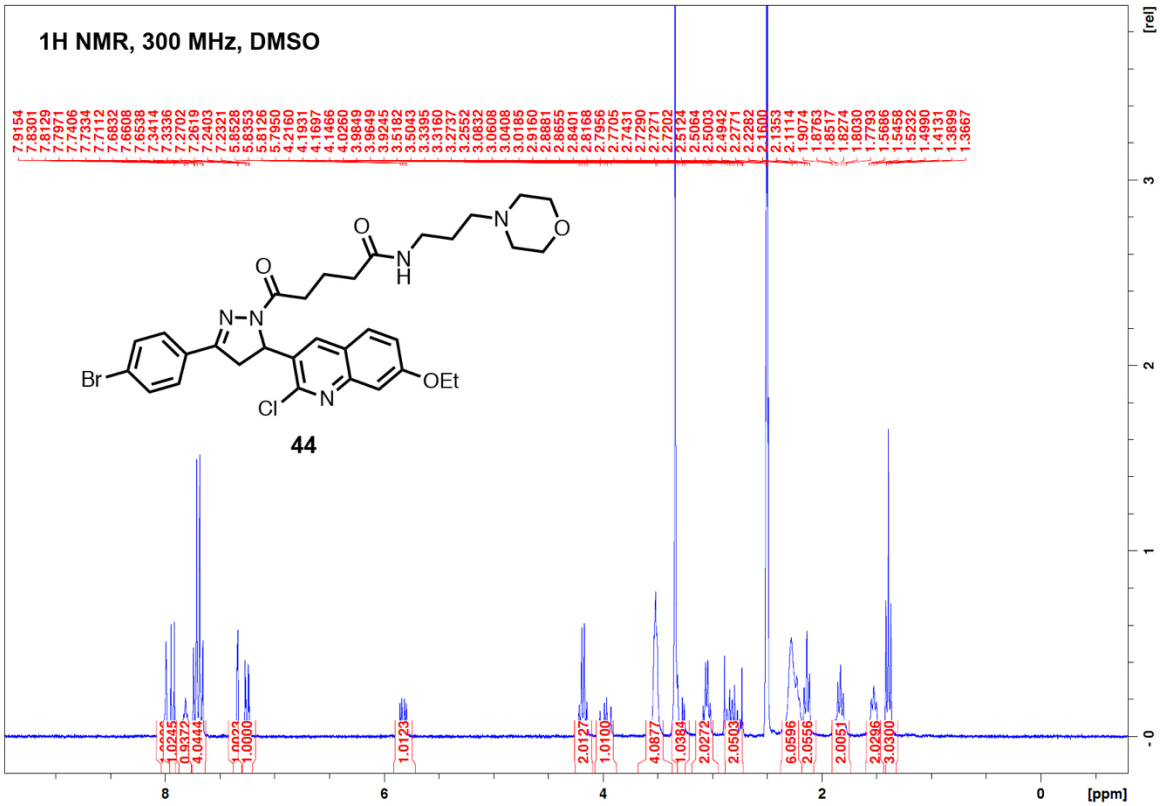

1H NMR, 300 MHz, DMSO
COOH
N–N
I
OEt
Cl
N
39
[rel]
[ppm]

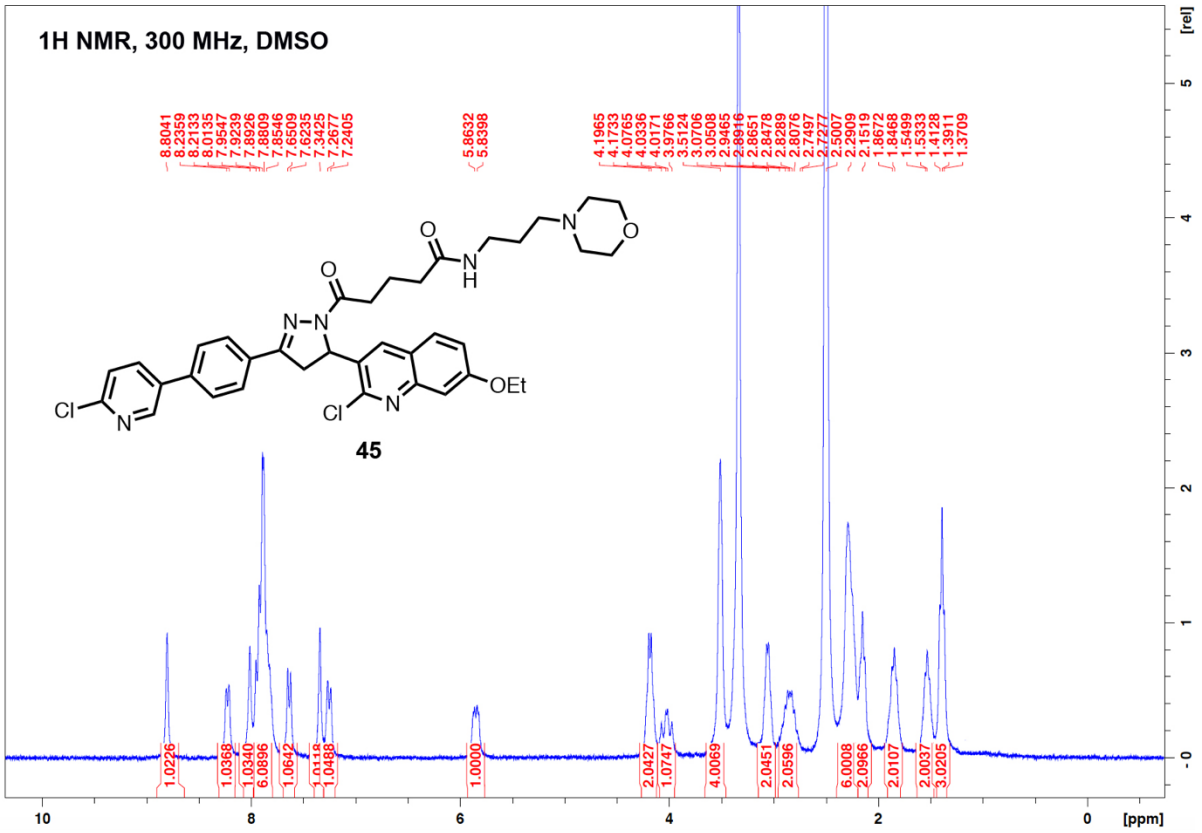

1H NMR, 300 MHz, DMSO
COOH
N–N
I
OEt
Cl
N
40
[rel]
[ppm]

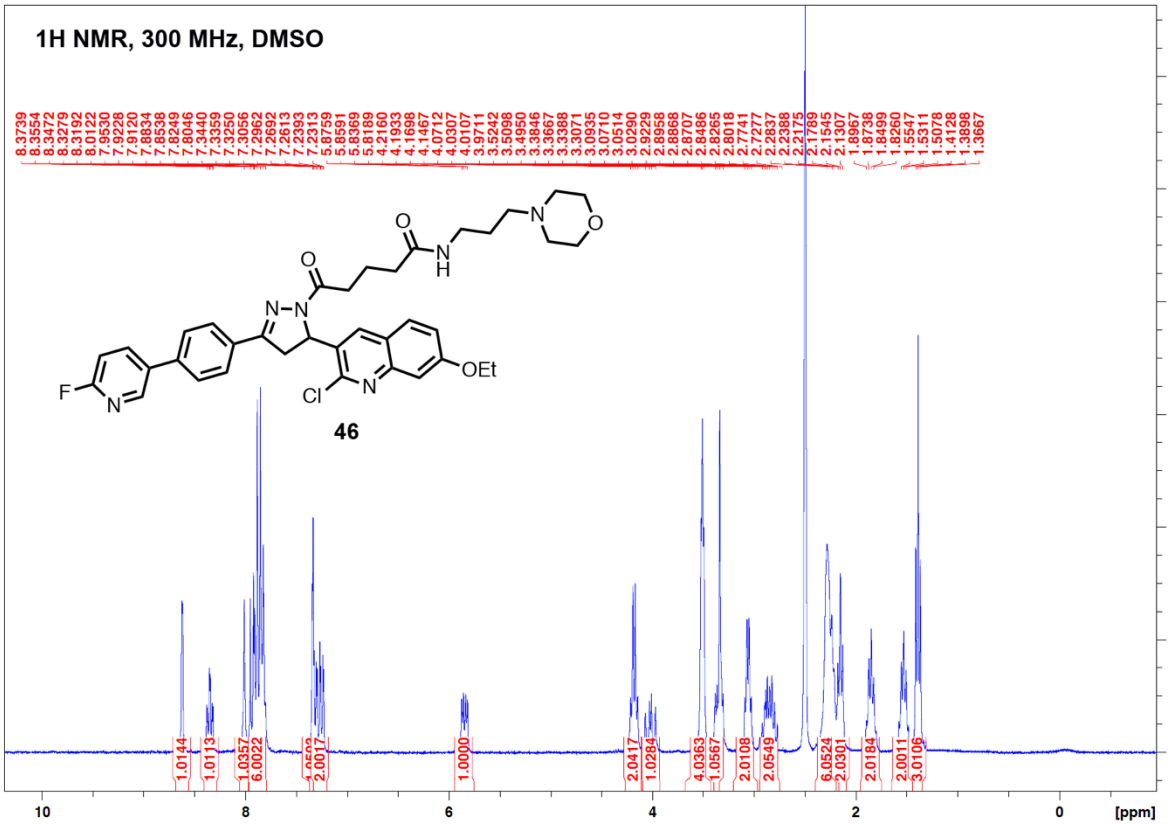

1H NMR, 300 MHz, CDCl3
41
[rel]
[ppm]

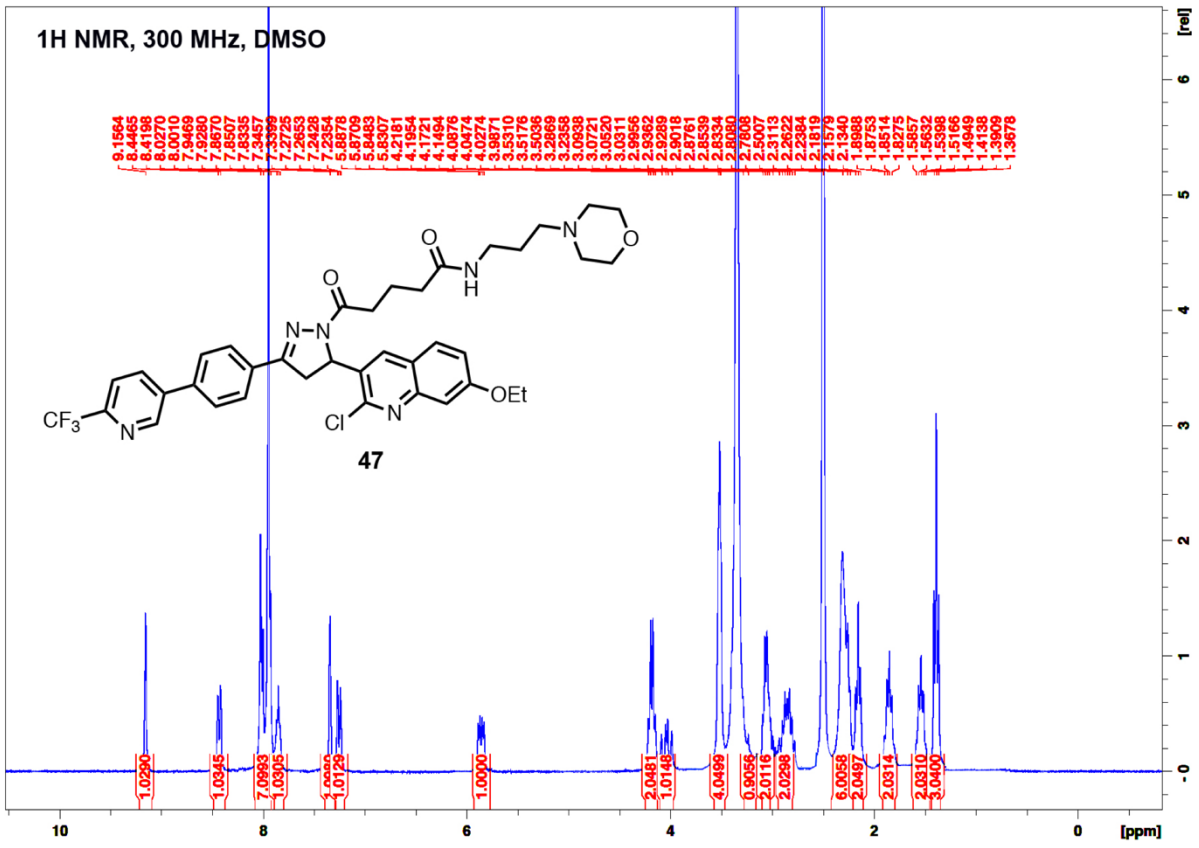

1H NMR, 300 MHz, DMSO
42
[rel]
[ppm]


1H NMR, 300 MHz, DMSO
[rel]
[ppm]
43


1H NMR, 300 MHz, DMSO
[rel]
[ppm]
44


1H NMR, 300 MHz, DMSO
45
[ppm]
[rel]

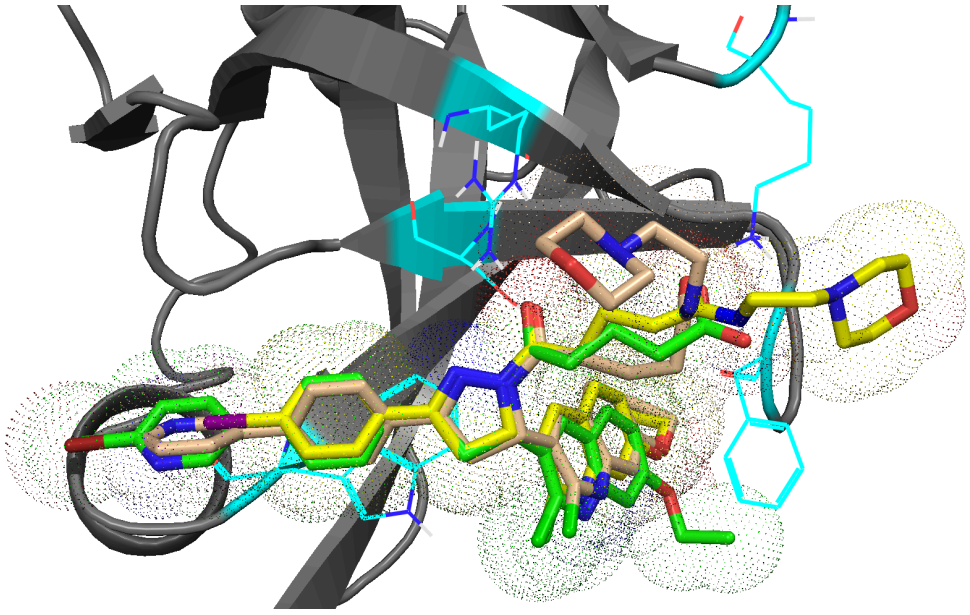

1H NMR, 300 MHz, DMSO
46
[ppm]
[rel]


1H NMR, 300 MHz, DMSO
47
[ppm]
[rel]

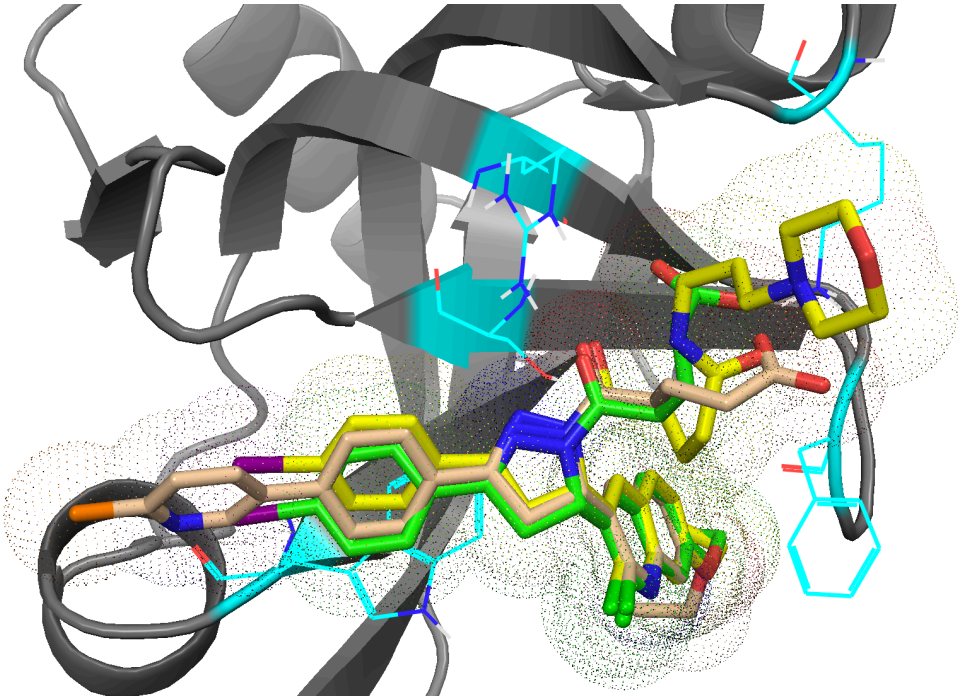
6) Molecular Docking:

We have performed molecular docking studies mainly focusing on the central DNA binding domains A and B of RPA70 by using $RPA70_{181-422}$ X-ray crystal structure[3] and PDB code 1FGU obtained from the Protein Data Bank (PDB)[8] and prepared them using the Protein Preparation Wizard.[9] In this step, force field atom types and bond orders are assigned, missing atoms are added, tautomer/ionization states are assigned, water orientations are sampled, Asn, Gln, and His residues are flipped to optimize the hydrogen bond network, and a constrained energy minimization is performed. RPA inhibitors were drawn in ChemDraw as MDL molfiles and prepared for docking using LigPrep[10] including a minimization with the OPLS3 force field.[11-12] All chiral centers were retained as specified in the literature. One low energy ring conformation per compound was generated. Ionization states and tautomer forms were enumerated at pH 7.0 ± 2.0 with Epik.[13-15] RPA inhibitors were flexibly docked into the domain B binding residues using the Glide SP protocol[16-18] with default settings. Docking poses were evaluated based on visual interrogation and calculated docking score. Potential amino acid interactions were determined based on proximity to each compound as revealed by docking analysis. RPA interactions with small molecules were viewed using Pymol using cartoon, surface, and compounds interaction views. All the molecular modeling within this study was performed using Maestro software, version 11 (Schrödinger),[19] operating in a Linux environment.

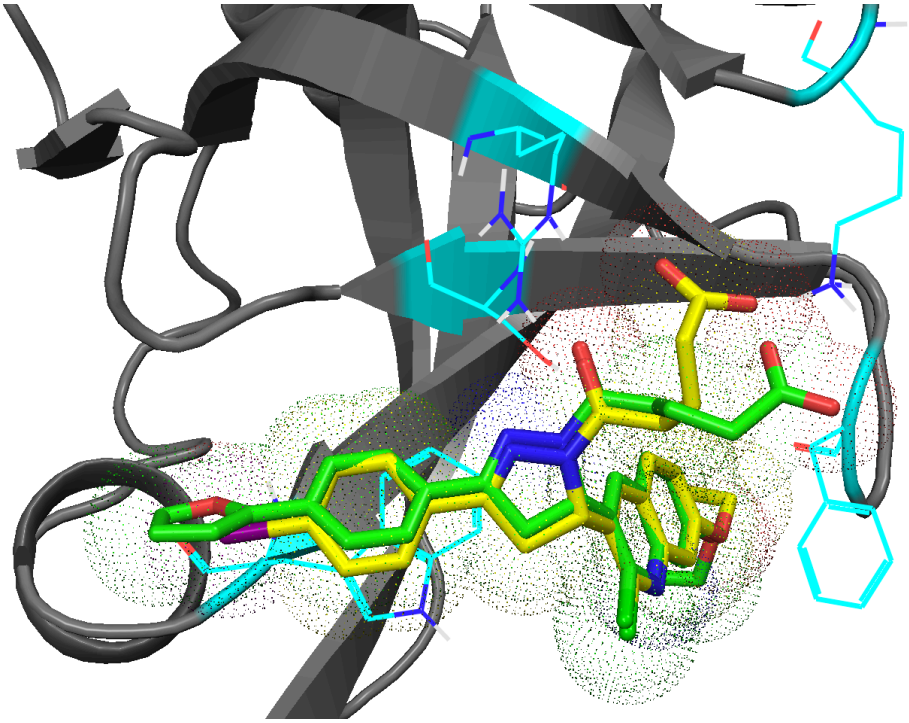
i) Molecular Overlay of compound 26 (Green Carbon), 42 (Yellow Carbon) and 45 (Tan color Carbon) in the RPA structure.



ii) Molecular Overlay of compound 4 (Green Carbon), 27 (Tan color Carbon) and 43 (Yellow Carbon) in the RPA structure.



iii) Molecular Overlay of compound 4 (Yellow Carbon) and 23 (Green Carbon) in the RPA structure.



iv) 2D Interactions of RPA Inhibitors with RPA.

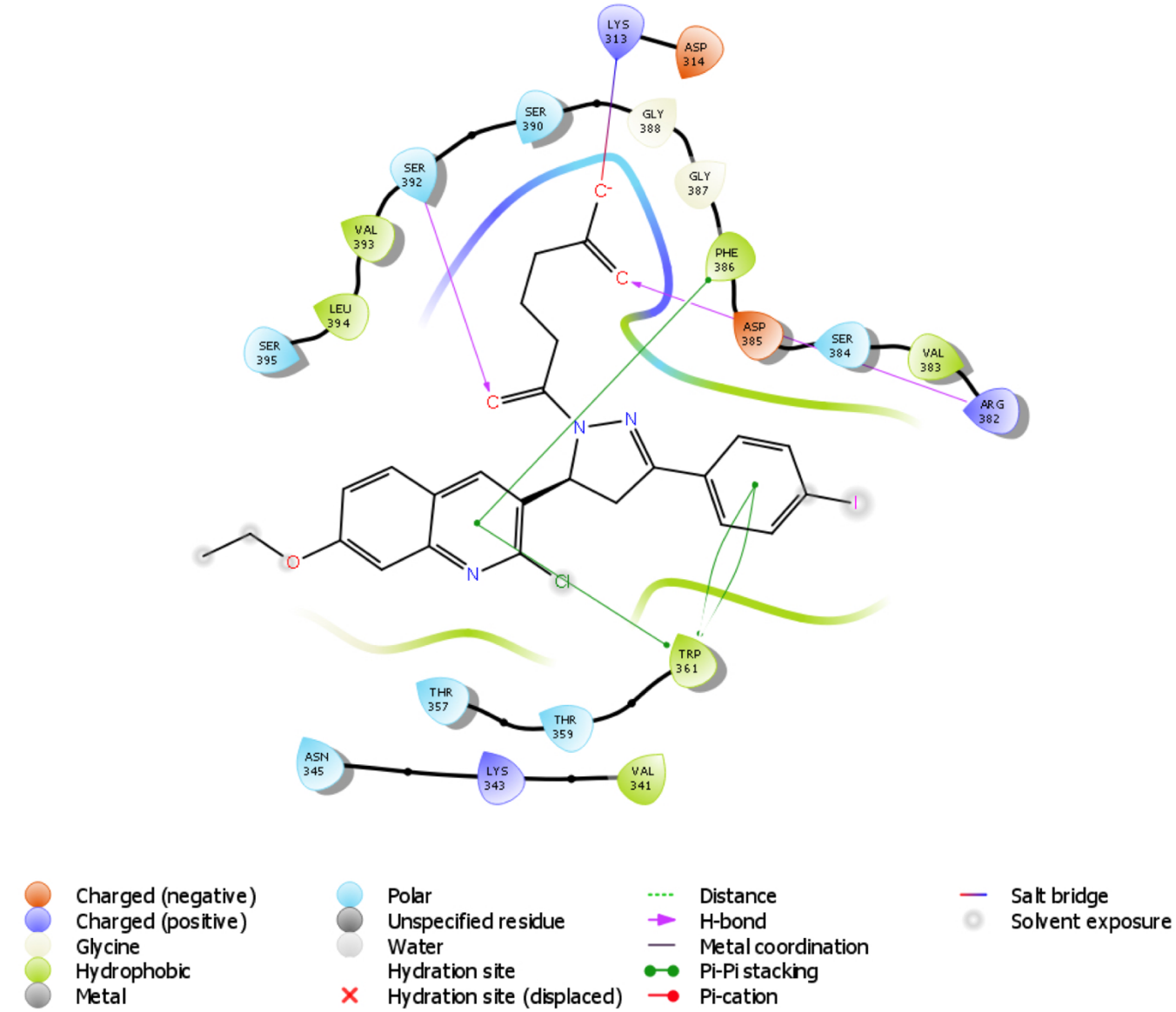


Figure S2: Compound **4** interactions with RPA.

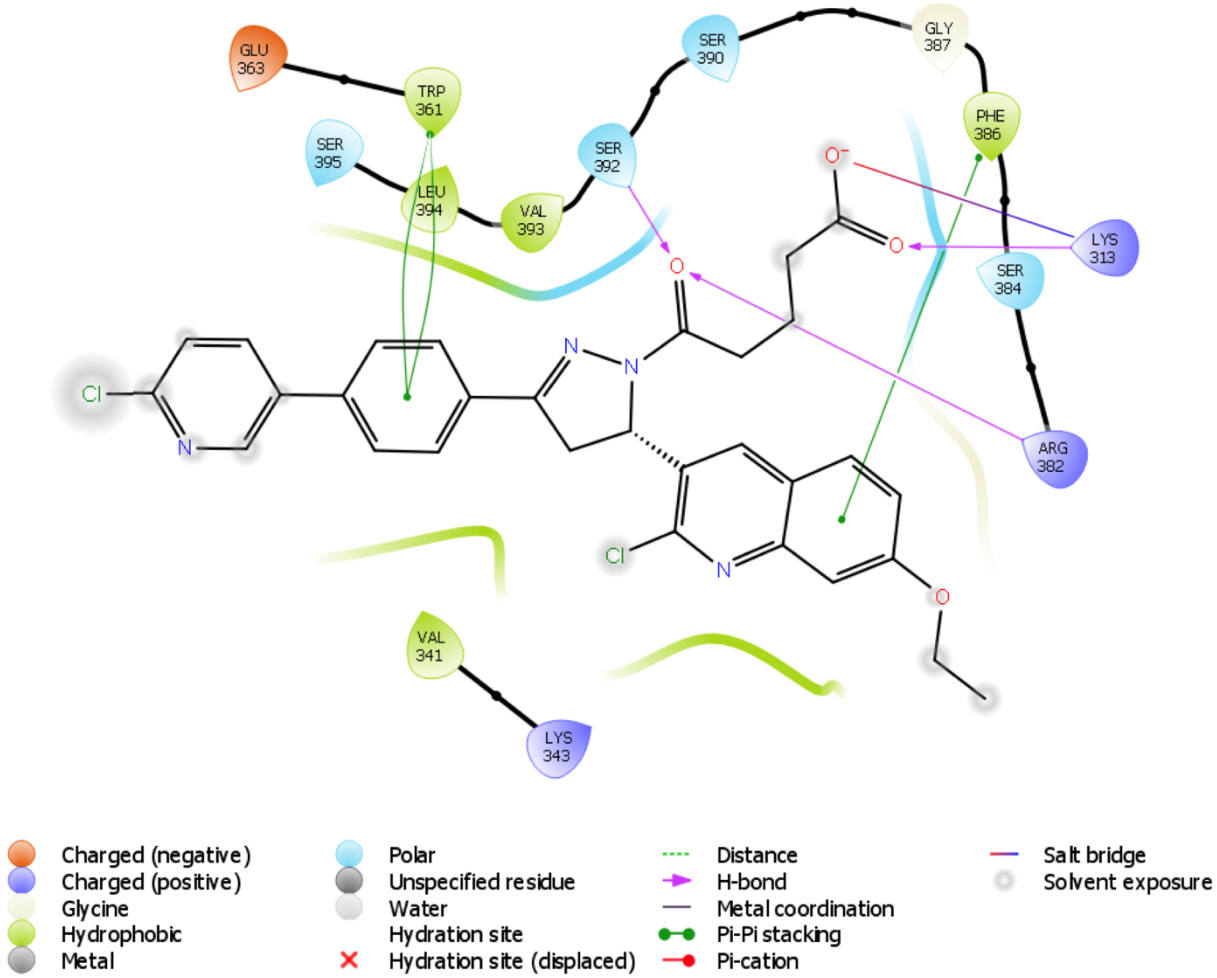


Figure S3: Compound **26** interactions with RPA.

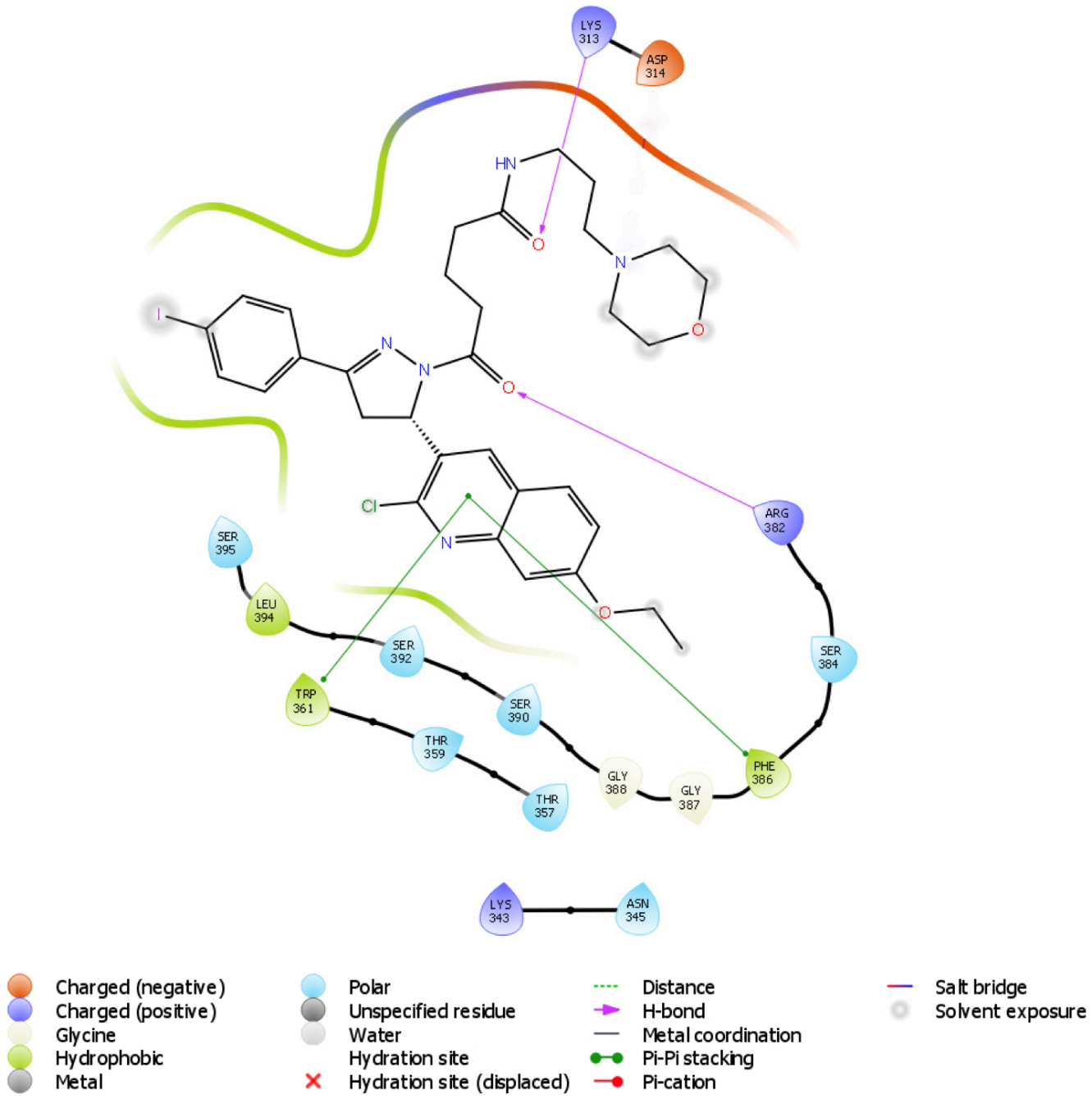


Figure S4: Compound **43** interactions with RPA.

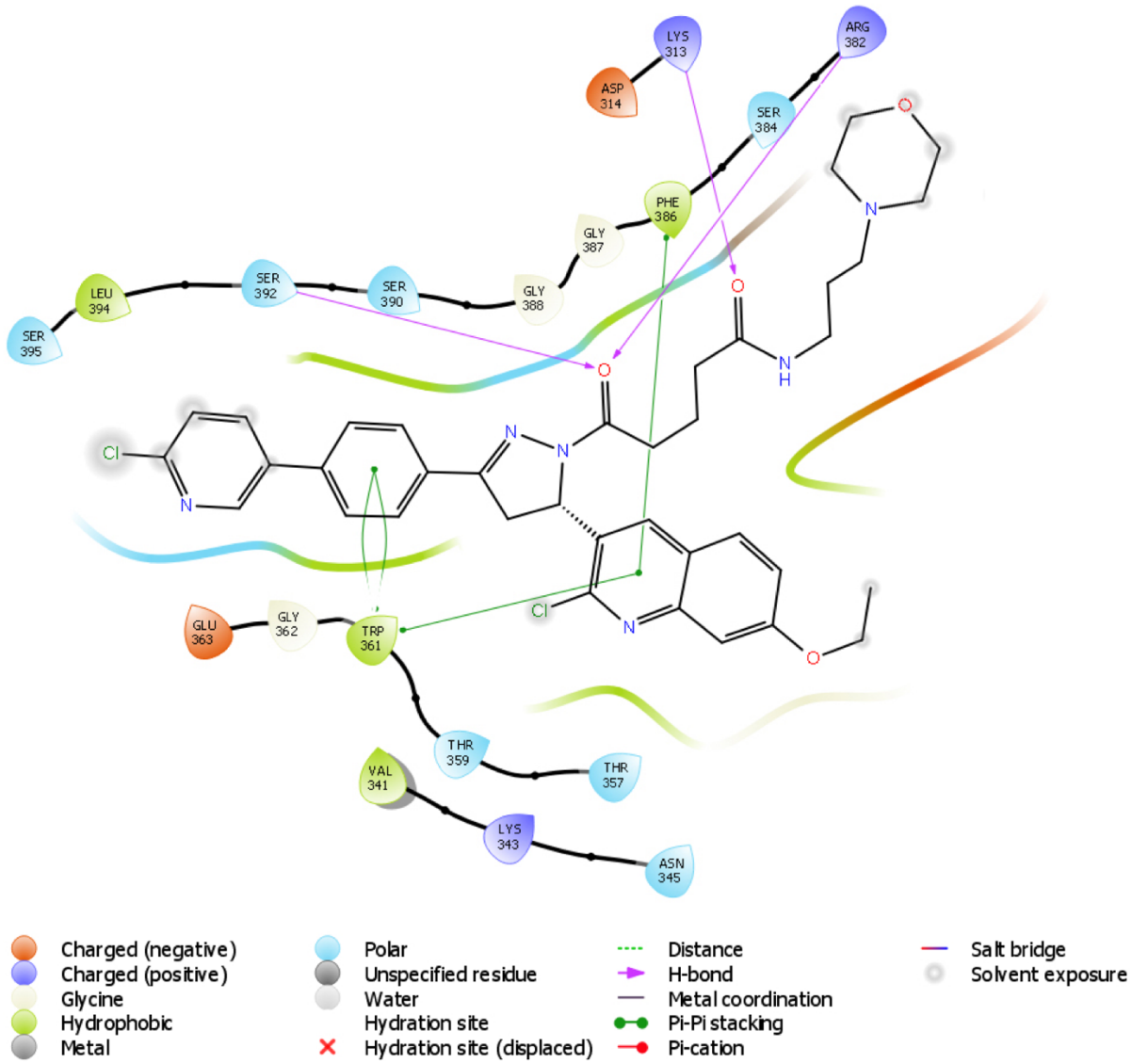


Figure S5: Compound **45** interactions with RPA.

References:

1. Brosey, C. A.; Soss, S. E.; Brooks, S.; Yan, C.; Ivanov, I.; Dorai, K.; Chazin, W. J. Functional dynamics in replication protein a DNA binding and protein recruitment domains. *Structure* **2015**, *23*, 1028-1038. 2.
2. Fan, J.; Pavletich, N. P. Structure and conformational change of a replication protein A heterotrimer bound to ssDNA. *Genes Dev.* **2012**, *26*, 2337-2347.
3. Bochkareva, E.; Belegu, V.; Korolev, S.; Bochkarev, A. Structure of the major single-stranded DNA-binding domain of replication protein A suggests a dynamic mechanism for DNA binding. *EMBO J* **2001**, *20*, 612-618.
4. Patrick, S. M.; Turchi, J. J.; Replication protein A (RPA) binding to duplex cisplatin damaged DNA is mediated through the generation of single-stranded DNA. *J. Biol. Chem.* **1999**, 274, 14972-14978.
5. Andrews, B. J.; Turchi, J. J. Development of a high-throughput screen for inhibitors of replication protein A and its role in nucleotide excision repair. *Mol. Cancer Ther.* **2004**, 3, 385-391.
6. Mishra, A. K.; Dormi, S. S.; Turchi, A. M.; Woods, D. S.; Turchi, J. J. Chemical inhibitor targeting the replication protein A–DNA interaction increases the efficacy of Pt-based chemotherapy in lung and ovarian cancer. *Biochem. Pharmacol.* **2015**, *93*, 25-33.
7. Gavande, N. S.; VanderVere-Carozza, P. Mishra, A. K.; Vernon, T. L.; Pawelczak, K. S.; Turchi, J. J. Design and Structure-Guided Development of Novel Inhibitors of the Xeroderma Pigmentosum Group A (XPA) Protein-DNA Interaction. *J. Med.Chem*. **2017**, *60*, 8055-8070.
8. Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. The Protein Data Bank. *Nucleic Acids Res.* **2000**, *28*, 235-242.
9. Sastry, G. M.; Adzhigirey, M.; Day, T.; Annabhimoju, R.; Sherman, W. Protein and ligand preparation: Parameters, protocols, and influence on virtual screening enrichments. *J. Comput.-Aided Mol. Des.* **2013**, *27*, 221-234.
10. Schrödinger release 2019-2: LigPrep; Schrödinger LLC: New York, NY, 2019.
11. Shivakumar, D.; Harder, E.; Damm, W.; Friesner, R. A.; Sherman, W. Improving the prediction of absolute solvation free energies using the next generation OPLS force field. *J. Chem. Theory Comput.* **2012**, *8*, 2553−2558.
12. Harder, E.; Damm, W.; Maple, J.; Wu, C.; Reboul, M.; Xiang, J. Y.; Wang, L.; Lupyan, D.; Dahlgren, M. K.; Knight, J. L.; Kaus, J. W.; Cerutti, D. S.; Krilov, G.; Jorgensen, W. L.; Abel, R.; Friesner, R. A. OPLS3: A force field providing broad coverage of drug-like small molecules and proteins. *J. Chem. Theory Comput.* **2016**, *12*, 281−296.
13. Shelley, J. C.; Cholleti, A.; Frye, L. L.; Greenwood, J. R.; Timlin, M. R.; Uchimaya, M. Epik: A software program for Pk(a) prediction and protonation state generation for drug-like molecules. *J. Comput.-Aided Mol. Des.* **2007**, *21*, 681−91.
14. Greenwood, J. R.; Calkins, D.; Sullivan, A. P.; Shelley, J. C. Towards the comprehensive, rapid, and accurate prediction of the favorable tautomeric states of drug-like molecules in aqueous solution. *J. Comput.-Aided Mol. Des.* **2010**, *24*, 591−604.
15. Schrödinger release 2019-2: Epik; Schrödinger LLC: New York, NY, 2019.
16. Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J. Med. Chem.* **2004**, *47*, 1739−1349.
17. Halgren, T. A.; Murphy, R. B.; Friesner, R. A.; Beard, H. S.; Frye, L. L.; Pollard, W. T.; Banks, J. L. Glide: A new approach for rapid, accurate docking and scoring. 2. Enrichment factors in database screening. *J. Med. Chem.* **2004**, *47*, 1750−1759.
18. Small-molecule drug discovery suite 2019-2: Glide; Schrödinger LLC: New York, NY, 2019.
19. Maestro, version 11; Schrödinger, LLC, New York, NY, 2017.