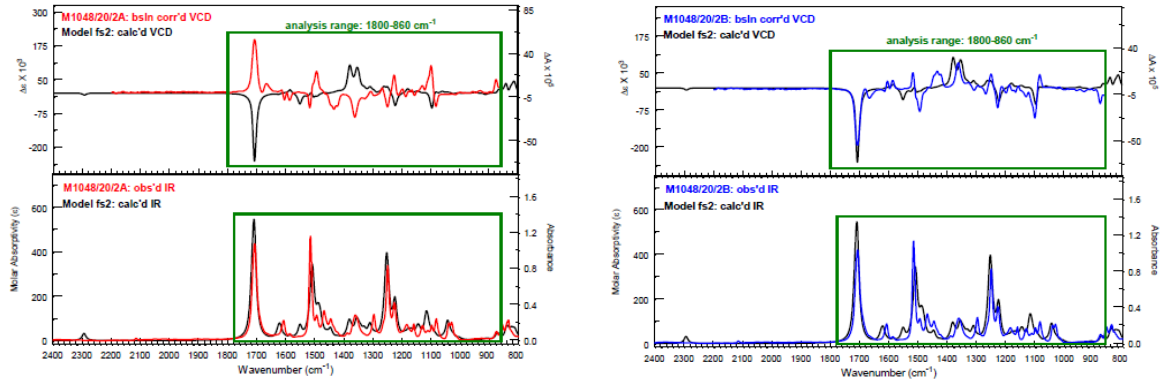
Supplementary Material

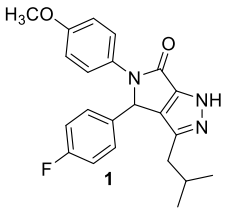
1 Supplementary Figures and Tables

1.1 Supplementary Figures

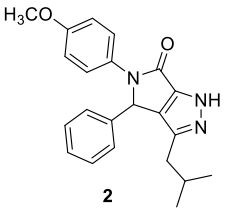


Red = predicted for (*R*) **Black = measured** **Blue = predicted for (*S*)**

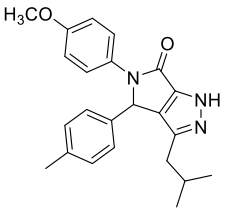
Supplementary Figure 1. Vibrational circular dichroism to determine absolute configuration of bioactive (*S*)-enantiomer of compound **1**.



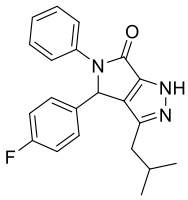
CMLD007431
99% growth inhibition at 10 μM
13% growth inhibition of THP-1 cells



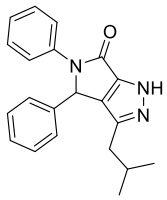
CMLD007427
100% growth inhibition at 10 μM
11% growth inhibition of THP-1 cells



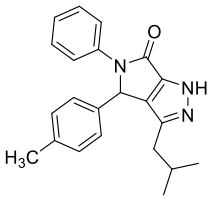
CMLD007430
0% growth inhibition at 10 μM



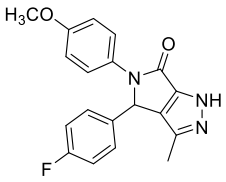
CMLD007425
15% growth inhibition at 10 μM
13% growth inhibition of THP-1 cells



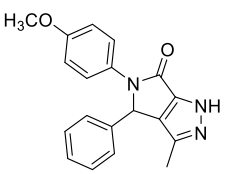
CMLD007421
0% growth inhibition at 10 μM



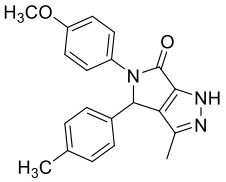
CMLD007424
81% growth inhibition at 10 μM
35% growth inhibition of THP-1 cells



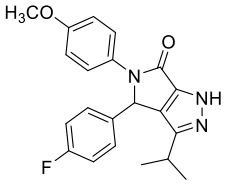
CMLD007221
0% growth inhibition at 10 μM



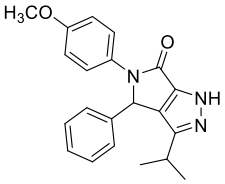
CMLD007219
0% growth inhibition at 10 μM



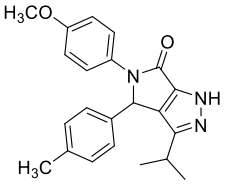
CMLD007247
0% growth inhibition at 10 μM



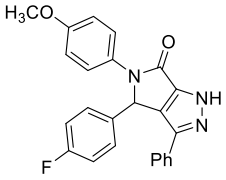
CMLD007188
0% growth inhibition at 10 μM



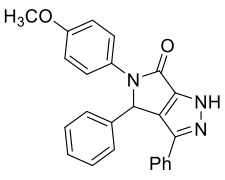
CMLD007286
0% growth inhibition at 10 μM



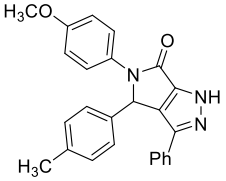
CMLD007169
0% growth inhibition at 10 μM



CMLD007235
0% growth inhibition at 10 μM
30% growth inhibition of THP-1 cells

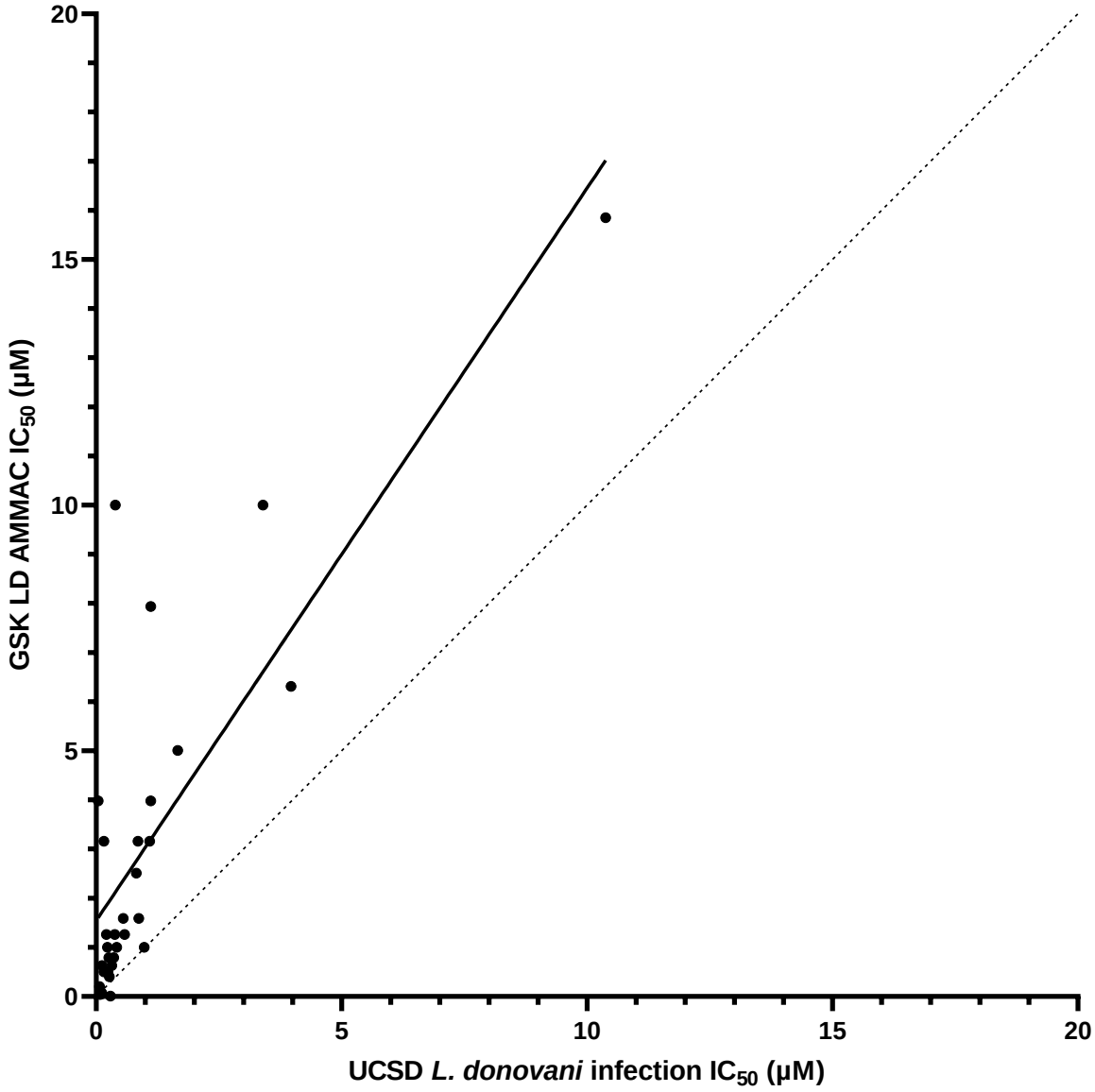


CMLD007203
0% growth inhibition at 10 μM



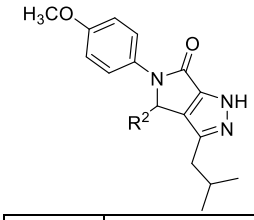
CMLD007262
0% growth inhibition at 10 μM

Supplementary Figure 2: Nascent structure-activity relationships from near-neighbor analogues to compounds **1** and **2** from the primary *L. donovani* intracellular amastigote screen (UCSF).

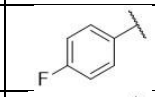
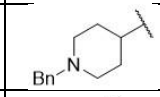
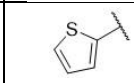
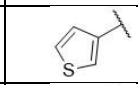
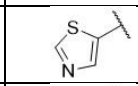
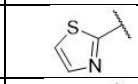
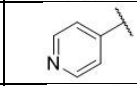
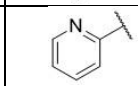
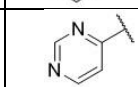
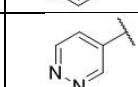
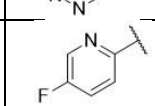
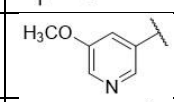
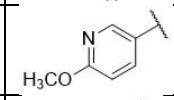
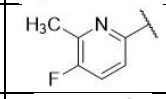
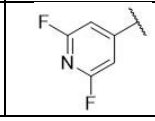


Supplementary Figure 3. Plot of comparative potencies of select compounds in the GSK and UCSD *L. donovani* infection assays shows higher comparative potency in the UCSD assay, with good overall correlation (*see Supplementary Table S2*). Solid line: simple linear regression ($r^2 = 0.5529$); dashed line: x = y.

1.2 Supplementary Tables



Supplementary Table S1: Surveying effects of heterocycles at R^2. Values highlighted in red are considered improved in comparison to initial lead compound 1. "nd" = not determined.

Cpd	R^2	LD AMMAC EC_{50} (µM)[a]	LD MAC EC_{50} (µM)[b]	SI MAC[c]	HEPG2 EC_{50} (µM)	Solubility[d] (µM)	Permeability[e] (nm/sec)	HSA[f] Binding (%)	PFI[g]
***rac*-1**		2.5	15.9	6.3	63.1	107	345	96.4	8.4
S1		15.8	20.0	1.3	63.1	188	290	94.8	9.0
S2		7.9	>50	>6.3	>100	8	300	95.9	8.2
S3		6.3	>50	>7.9	>100	149	470	95.4	8.3
S4		15.8	>50	>3.1	>100	≥534	320	89.3	6.5
S5		20.0	>50	>2.5	>100	143	420	89.5	7.2
S6		>50	>50	1.0	>100	≥432	230	87.9	6.3
S7		31.6	>50	>1.6	>100	≥450	420	86.8	7.1
S8		>50	>50	1.0	>100	273	340	76.8	6.3
S9		>50	>50	1.0	>100	≥340	50	70.5	5.5
S10		10.0	>50	>5.0	>100	≥343	490	90.2	7.7
S11		10.0	20.0	2.0	>100	386	470	91.2	6.6
S12		>50	>50	1.0	>100	272	440	92.6	7.5
S13		12.6	>50	>4.0	>100	305	380	94.4	8.3
S14		>50	>50	1.0	>100	367	540	93	7.4

(a) EC_{50} for growth inhibition of *L. donovani* intracellular amastigotes infecting THP-1 macrophages; (b) EC_{50} for cytotoxicity against host THP-1 macrophages; (c) SI MAC = selectivity index in macrophages, calculated as SI MAC = (LD MAC EC_{50})/(LD AMMAC EC_{50}); (d) kinetic aqueous solubility as determined by high-throughput CLND (chemoluminescent nitrogen detection); (e) artificial membrane permeability; (f) human serum albumin binding; (g) PFI = $ChromLogD_{7.4}$ + Aromatic rings

Supplementary Table S2. Comparative antileishmanial potencies for select compounds in the UCSD vs. GSK infection assays. Pearson correlation $r = .7429$, n = 34, $p < 0.10$. A single outlier compound (**70**) did not demonstrate a measurable IC_{50} value in the GSK LD AMMAC assay and was omitted from this analysis.

Compound	UCSD *L. donovani* infection IC_{50} (μM)	GSK LD AMMAC IC_{50} (μM)
(*S*)-**1**	0.4	0.79
rac-**1**	0.8	2.5
2	1.1	3.2
21	0.2	1.0
39	10.4	15.9
42	0.6	1.3
44	0.3	0.6
45	0.9	3.2
46	1.7	5.0
55	0.2	1.3
67	0.2	0.5
68	0.3	0.0
69	0.3	0.4
70	0.1	>100
71	0.4	1.0
72	0.4	1.3
73	0.2	3.2
74	0.4	10.0
75	0.2	0.5
76	0.1	0.6
77	0.1	0.1
78	0.3	0.8
79	0.1	0.0
80	0.1	0.2
81	0.1	0.1
82	0.0	4.0
83	1.1	4.0
84	1.0	1.0
85	1.1	7.9
86	0.4	10.0
87	0.3	0.8
88	0.6	1.6
89	0.9	1.6
S3	4.0	6.3
S10	3.4	10.0

2 Supplementary Methods: Chemical Synthesis

2.1 General methods.

All ^{1}H NMR spectra were obtained at 400 or 500 MHz and referenced to the $CHCl_3$ singlet at 7.26 ppm, or the center peak of the quintet from the residual ^{1}H resonance of DMSO-d_6 at 2.50 ppm. ^{13}C NMR spectra were obtained at 125 or 100 MHz, and referenced to the center peak of the $CDCl_3$ triplet at 77.16 ppm, or the center peak of the DMSO-d_6 heptet at 39.52 ppm. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, h=heptet m = multiplet, br = broad), coupling constant, and integration. Optical rotations were recorded on a Rudolph AUTOPOL II digital polarimeter at 589 nm, and were reported as $[\alpha]_D$ (concentration in grams/100 mL solvent). Analytical thin layer chromatography was performed using EMD 0.25 mm silica gel 60-F plates. Flash column chromatography was performed on Sorbent Technologies 60 Å silica gel. Chiral HPLC analysis was performed using an Agilent 1100 series HPLC with a multiple wavelength detector. Chiral columns include Chiralcel®OD (Chiral Technologies Inc., 25 cm × 4.6 mm I.D.), Chiralpak®IA (Chiral Technologies Inc., 25cm × 4.6 mm I.D.). High resolution mass spectrometry data was obtained on a Waters Qtof (hybrid quadrupolar/time-of-flight) API US system by electrospray (ESI) in the positive mode. Mass correction was done by an external reference using a Waters Lockspray accessory. Mobile phases were water and acetonitrile with 0.1% formic acid. The MS settings were: capillary voltage = 3kV, cone voltage = 35, source temperature = 120 °C and desolvation temperature = 350 °C. UPLC-MS analysis was performed on a XBridge C18 column (1.7mm, 2.1 X 50 mm) with CH_3CN:H_2O gradient as eluent with UV, ELSD and electrospray ionization (ESI) positive ion detection. Purity analysis was performed by HPLC and quantified by UV peak area at the indicated wavelength.

2.2 Detailed Synthetic Methods.

Methyl keto-enol esters (**5**) were prepared analogously to literature precedents (1) *via* the following representative procedure: An oven dried 250 mL round-bottom flask equipped with a stir bar was charged with methanol (75 mL) and cooled to 0 °C in an ice-water bath. Sodium metal (5.75 g, 250 mmol, 1.00 equiv.) was added portion-wise, and the flask was stirred and allowed to warm to room temperature. A separate flame-dried 100 mL flask was charged with dimethyl oxalate (29.5 g, 250 mmol, 1.00 equiv.) and 4-methylpentan-2-one (31.3 mL, 250 mmol, 1.00 equiv) and methanol (75 mL). After the sodium metal had completely dissolved, the contents of the 100 mL flask were transferred by cannula to the freshly prepared sodium methoxide solution. The 250 mL flask was fitted with an Ar balloon, and the reaction was stirred at 22 °C for 16 h, at which time the reaction was cooled to 0 °C in an ice-water bath, and quenched by the addition of 80 mL 4 M aq. sulfuric acid. The solution was poured into a 1 L separatory funnel, diluted with 250 mL water, and extracted 3x 250 mL dichloromethane. The combined organics were dried over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude oil was distilled under reduced pressure (8 mbar, 105 °C) to yield methyl (*Z*)-2-hydroxy-6-methyl-4-oxohept-2-enoate as a light yellow oil. Yield: 27.2 g, 59.5%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.34 (s, 1H), 3.89 (s, 3H), 2.34 (d, *J* = 7.1 Hz, 2H), 2.14 (dh, *J* = 7.1, 6.6 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 7H).

Pyrrolidinones of general structure **4** (Figure 1) were prepared based on a modified literature precedent (2) at at ~0.5 mmol scales according to the following representative procedure: A 2 dram vial equipped with a stir bar was charged with 4-fluorobenzaldehyde (57.6 µL, 536 µmol, 1.00 equiv.), *N*1,*N*1-dimethylbenzene-1,4-diamine (73.1 mg, 536 µmol, 1.00 equiv.), and (*Z*)-2-hydroxy-

6-methyl-4-oxohept-2-enoate (300 mg, 1.61 mmol, 3.00 equiv.). The reactants were suspended in dichloromethane (5.00 mL), the vial was capped and stirred at 22 °C for 3 days, at which point the vial was concentrated under reduced pressure (typically Genevac evaporator with multiple reactions in parallel). The crude residue was dissolved in a minimal amount of chloroform, and solid 1-[4-(dimethylamino)phenyl]-2-(4-fluorophenyl)-4-hydroxy-3-(3-methylbutanoyl)-2*H*-pyrrol-5-one (**S21**) was precipitated as an off-white solid by the addition of excess hexanes. The solid was collected by vacuum filtration, and carried forward to the next step without further purification. Yield: 154 mg, 72.6%. Purity: >95% @ 254 nm by HPLC. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 9.1 Hz, 2H), 6.9 (dd, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 9.1 Hz, 2H), 5.67 (s, 1 H), 2.90 (s, 6H) 2.44 (dd, *J* = 15.3, 6.4 Hz, 1H), 2.15 (m, 1H), 2.05 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H). LCMS: (ESI+) m/z calc' for $(C_{23}H_{25}FN_2O_3+H)^+$ 397.48; found 397.10.

Pyrazolopyrrolidinones (**1**, **9**-**89**) were synthesized on a ~60 mg scale, as a modification of a literature precedent, according to the following representative procedure:

5-(4-(dimethylamino)phenyl)-4-(4-fluorophenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (21). A 1 dram vial equipped with a stir bar was charged with 1-[4-(dimethylamino)phenyl]-2-(4-fluorophenyl)-4-hydroxy-3-(3-methylbutanoyl)-2*H*-pyrrol-5-one **S21** (60.0 mg, 151 µmol, 1.00 equiv.) and acetic acid (1.5 mL). Hydrazine monohydrate (23 µL, 454 µmol, 3.00 equiv) was added to the vial by microsyringe. The vial was capped with a Teflon-backed screw cap, and heated in a 120 °C metal heating block for 1 h, at which point the mixture was concentrated under reduced pressure (typically Genevac evaporator with multiple reactions in parallel). The residue was dissolved in 1.0 mL DMSO, and purified by reverse-phase preparative HPLC (XBridge C18 column, basic conditions, 40-100% CH_3CN gradient in water). Fractions containing the desired product were concentrated under reduced pressure (Genevac evaporator or lyophilizer) to yield 2.22 as an off-white solid. Yield: 26.9 mg, 41.1% yield. Purity: >95% @ 254 nm by HPLC. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 10.65 (br. s., 1H), 7.14-7.11 (overlap, 4H), 6.95 (m, 2H), 6.62 (d, *J* = 9.1 Hz, 2H), 5.77 (s, 1H), 2.90 (s, 6H), 2.40 (m, 1H), 2.28 (m, 1H), 1.65 (m, 2H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H). LCMS: (ESI+) m/z = 393 $[M+H]^+$.

2.3 Full characterization of select pyrazolopyrrolidinones 1, 24, 42, 44, 46, 55, 57, 64, 65, 67, 70, 72-78, 80-82, 85, 86 and 89, and corresponding pyrrolidinone precursors S1, S24, S42, S44, S46, S55, S57, S64, S65, S67, S70, S72-S78, S80-S82, S85, S86 and S89.

5-(4-fluorophenyl)-3-hydroxy-1-(4-methoxyphenyl)-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S1). Yield: 13.3 g, 89.3%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 9.0 Hz, 2H), 7.17 (m, 2H), 6.97 (dd, *J* = 8.6, 8.6 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.71 (s, 1H), 3.75 (s, 3H), 2.42 (dd, *J* = 15.4, 6.6 Hz, 1H), 2.22 (dd, *J* = 15.4, 6.7 Hz), 2.06 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H). LCMS: (ESI+) m/z = 384.20 $[M+H]^+$.

4-(4-fluorophenyl)-3-isobutyl-5-(4-methoxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (1). Yield: 313 mg, 77.9% yield from **S1**. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 11.36 (br s, 1H), 7.23(d, *J* = 9.1 Hz, 2H), 7.13 (m, 2H), 6.96 (dd, *J* = 8.6, 8.6 Hz, 2H), 6.82 (d, *J* = 9.1 Hz, 2H), 5.83 (s, 1H), 3.76 (s, 3H), 2.50 (dd, *J* = 14.5, 6.8 Hz, 1H), 2.33 (dd, *J* = 14.5, 7.2 Hz, 1H), 1.67 (m, 1H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H). LCMS: (ESI+) m/z = 380 $[M+H]^+$.

1-(4-bromophenyl)-5-(4-fluorophenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S24). Yield: 162 mg, 37.5%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.9 Hz, 2H), 7.33 (d, *J* = 8.9 Hz, 2H), 7.21 (dd, *J* = 8.6, 5.1 Hz, 2H), 6.96 (dd, *J* = 8.6, 8.5 Hz, 2H), 5.79 (s, 1H), 2.52 (dd,

J = 15.5, 6.4 Hz, 1H), 2.33 (dd, *J* = 15.5, 7.5 Hz, 1H), 2.05 (ddqq, *J* = 7.5, 6.7, 6.7, 6.4 Hz, 1H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.1, 164.4, 163.8, 161.8, 154.3, 134.9, 132.3, 130.8, 130.7, 129.5, 129.4, 124.1, 120.5, 119.9, 116.3, 116.1, 61.7, 50.3, 24.9, 22.7, 22.3. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -112.07 (tt, 8.5, 5.1 Hz). HRMS: (ESI+) *m/z* calc'd for $(C_{21}H_{19}BrFNO_3+H)^+$ 432.0611; found: 432.0611.

5-(4-bromophenyl)-4-(4-fluorophenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (24). Yield: 99.0 mg, 99.9% yield from **S24**. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.15 (dd, *J* = 8.5, 5.2 Hz, 2H), 6.96 (t, *J* = 8.5, 8.5 Hz, 2H), 5.96 (s, 1H), 2.71 (dd, *J* = 14.5, 7.1 Hz, 1H), 2.46 (dd, *J* = 14.5, 7.1 Hz, 1H), 1.66 (m, 1H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 163.7, 161.8, 161.7, 148.0, 139.9, 136.8, 132.54, 132.51, 132.1, 128.9, 128.8, 127.2, 124.8, 118.8, 116.3, 116.2, 60.7, 33.7, 28.9, 22.21, 22.19. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -112.56 (tt, *J* = 8.5, 5.5 Hz). HRMS: (ESI+) *m/z* calc'd for $(C_{21}H_{19}BrFN_3O+H)^+$ 428.0774; found: 428.0763.

1-(3-fluoro-4-methoxy-phenyl)-2-(4-fluorophenyl)-4-hydroxy-3-(3-methylbutanoyl)-2H-pyrrol-5-one (S42). Yield: 60.2 mg, 23.3%; Purity: 94.7% @ 210 nm by HPLC. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 2.53 Hz, 1 H), 7.17-7.23 (overlap, 3H), 7.03-7.09 (m, 1H), 6.99 (t, *J* = 8.6 Hz, 2H), 6.86 (t, *J* = 9.0 Hz, 1H), 5.69 (s, 1H), 3.84 (s, 4H), 2.42 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.22 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.05 (m, 1 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.73 (d, *J* = 6.6 Hz, 3 H). LCMS: (ESI+) m/z = 401.0 $[M+H]^+$.

5-(3-fluoro-4-methoxyphenyl)-4-(4-fluorophenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(2*H*)-one (42). Yield: 29.4 mg, 59.4% from **S42**; Purity: >95% @ 240 nm by HPLC. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 10.70 (br. s., 1H), 7.21 (dd, *J* = 12.63, 2.53 Hz, 1H), 7.14 (dd, *J* = 8.72, 5.18 Hz, 2H), 7.07 (m, 1H), 6.98 (m, 2 H), 6.87 (m, 1H), 5.84 (s, 1H), 3.84 (s, 3H), 2.44 (dd, *J* = 10.0, 6.0, 1H), 2.30 (dd, *J* = 10.0, 6.0 Hz, 1H), 1.66 (m, 1H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H). LCMS: (ESI+) m/z = 398 $[M+H]^+$.

1-(benzo[*d*][1,3]dioxol-5-yl)-5-(4-fluorophenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S44). Yield: 310 mg, 78.1%. ^{1}H NMR: (500 MHz, CD_3OD) δ 7.15 (dd, *J* = 8.5, 5.3 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.87 (m, 1H), 6.71 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.87 (d, *J* = 6.7 Hz, 2H), 5.66 (s, 1H), 2.72 (dd, *J* = 14.8, 6.2 Hz, 1H), 2.48 (dd, *J* = 14.8, 7.8 Hz, 1H), 2.04 (m, 1H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.72 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR: (126 MHz, CDC_3OD) δ 196.7, 164.7, 163.2, 161.2, 152.9, 147.7, 145.8, 131.5, 131.4, 129.4, 129.1, 129.0, 120.3, 116.8, 115.1, 115.0, 107.7, 104.9, 101.3, 61.9, 50.7, 24.8, 22.1, 21.6. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -110.23 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{20}FNO_5+H)^+$ 398.1402; found: 398.1411.

5-(benzo[*d*][1,3]dioxol-5-yl)-4-(4-fluorophenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (44). Yield: 104 mg, quant. yield from **S44**. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.02 (m, 2H), 6.86 (dd, *J* = 8.5, 8.5 Hz, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 2H), 5.81 (m, 2H), 5.71 (s, 1H), 5.22 (s, 1H), 2.31 (dd, *J* = 14.5, 7.2 Hz, 1H), 2.16 (dd, *J* = 14.5, 7.2 Hz, 1H), 1.53 (dt, *J* = 13.4, 6.7, 6.7 Hz, 1H), 0.68 (d, *J* = 6.6 Hz, 3H), 0.64 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 163.6, 162.1, 161.6, 147.8, 145.9, 139.1, 132.31, 132.29, 130.9, 129.1, 129.0, 127.0, 118.4, 115.9, 115.7, 108.0, 106.6, 101.4, 61.7, 53.4, 34.0, 28.4, 21.97, 21.96. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -109.12 (tt, *J* = 8.4, 5.0 Hz). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{20}FN_3O_3)^+$ 396.1479; found: 396.1481.

1-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(4-fluorophenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S46). Yield: 394 mg, 62.5%. ^{1}H NMR: (500 MHz, DMSO) δ 9.29 (dd, *J* = 2.0, 0.6 Hz, 1H), 8.48 (s, 1H), 7.89 (dd, *J* = 9.6, 2.0 Hz, 1H), 7.81 (dd, *J* = 9.6, 0.6 Hz, 1H), 7.39 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.02 (dd, *J* = 8.8, 8.8 Hz, 2H), 6.20 (s, 1H), 2.72 (dd, *J* = 15.0, 6.2 Hz, 1H), 2.51 (m, 1H), 1.98 (m, 1H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, DMSO) δ 165.0, 162.5, 160.6, 154.5, 147.9, 132.4, 129.92, 129.85, 127.2, 125.2, 123.8, 115.7, 115.2, 115.0, 60.3, 50.6, 24.5, 22.5, 22.0. ^{19}F NMR: (470 MHz, DMSO) δ -114.06 (tt, *J* = 8.8, 5.5 Hz). HRMS: (ESI+) *m/z* calc'd for $(C_{21}H_{19}FN_4O_3)^+$ 395.1519; found: 395.1515.

(5-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-4-(4-fluorophenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one) (46). Yield: 95.6 mg, 88.0% yield from **S46**. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.80 (d, *J* = 1.9 Hz, 1H), 8.17 (s, 1H), 7.60 (dd, *J* = 9.6, 1.9 Hz, 1H), 7.54 (d, *J* = 9.6 Hz, 1H), 7.09 (dd, *J* = 8.6, 5.1 Hz, 2H), 6.86 (t, *J* = 8.5, 8.5 Hz, 2H), 5.92 (s, 1H), 2.29 (dd, *J* = 14.6, 7.2 Hz, 1H), 2.14 (dd, *J* = 14.6, 7.2 Hz, 1H), 1.50 (m, 1H), 0.65 (d, *J* = 6.6 Hz, 3H), 0.60 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 163.7, 161.8, 153.6, 131.6, 128.9, 128.8, 127.7, 127.1, 123.8, 116.4, 116.2, 115.7, 60.9, 33.7, 28.4, 21.9, 21.8. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -108.16 (tt, *J* = 8.5, 5.2 Hz). HRMS: (ESI+) *m/z* calc'd for $(C_{21}H_{19}FN_6O+H)^+$ 391.1683; found: 391.1675.

5-(2-chlorophenyl)-3-hydroxy-1-(4-methoxyphenyl)-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S55). Yield: 170 mg, 42.4%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 9.0 Hz, 2H), 7.31 (d, *J* = 2.3 Hz, 1H), 7.16–7.14 (overlap, 2H), 6.98 (dd, *J* = 6.0, 3.4 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.43 (s, 1H), 3.72 (s, 3H), 2.45 (dd, *J* = 15.4, 6.8 Hz, 1H), 2.21 (dd, *J* = 15.4, 7.1 Hz, 1H), 2.02 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.5, 163.5, 159.4, 158.1, 134.9, 133.2, 130.1, 128.6, 127.8, 127.5, 124.9, 124.6, 119.7, 114.4, 57.6, 55.4, 48.9, 25.0, 22.6, 22.4. HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{22}ClNO_4+H)^+$ 400.1316; found: 400.1308.

4-(2-chlorophenyl)-3-isobutyl-5-(4-methoxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (55). Yield: 106 mg, 86.3% yield from **S55**. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.9 Hz, 2H), 7.35 (br d, *J* = 7.9 Hz, 1H), 7.14 (ddd, *J* = 7.9, 7.4, 1.0 Hz, 1H), 7.09 (br dd, *J* = 7.4, 7.4 Hz, 1H), 6.99 (br d, *J* = 7.6 Hz, 1H), 6.81 (br d, *J* = 9.0 Hz, 2H), 6.62 (s, 1H), 3.72 (s, 3H), 2.73 (dd, *J* = 14.3, 7.3 Hz, 1H), 2.58 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.64 (m, 1H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 162.1, 157.1, 148.4, 139.8, 134.8, 133.3, 130.9, 129.7, 129.5, 127.9, 127.8, 127.0, 124.3, 114.3, 57.1, 55.4, 33.9, 29.1, 22.2, 22.0. HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{22}ClN_2O_2+H)^+$ 394.1567; found: 394.1568.

3-hydroxy-5-(2-methoxyphenyl)-1-(4-methoxyphenyl)-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S57). Yield: 124 mg, 58.5%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 9.1 Hz), 7.22 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.83–6.90 (overlap, 2H), 6.78 (d, *J* = 9.1 Hz, 2H), 6.34 (br s, 1H), 3.90 (br s , 3H), 3.74 (s, 3 H), 2.31 (dd, *J* = 14.0, 6.0 Hz, 1 H), 2.02 (dd, *J* = 14.0, 6.0 Hz, 1 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.67 (d, *J* = 6.3 Hz, 3 H). LCMS: (ESI+) m/z = 396.10 $[M+H]^+$.

3-isobutyl-4-(2-methoxyphenyl)-5-(4-methoxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (57). Yield: 48.4 mg, 81.5% yield from **S57**. Purity: >95% @ 272 nm by HPLC. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 9.1 Hz, 2 H), 7.19 (ddd, *J* = 8.3, 7.1, 1.7 Hz, 1H), 6.95 (m, 1H), 6.88 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.81 (d, *J* = 9.1 Hz, 3H), 6.50 (br. s., 1H), 3.88 (br. s., 3H), 3.75 (s, 3H), 2.40 (m, 1H), 2.30 (m, 1H), 1.68 (m, 1H), 0.80 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H). LCMS: (ESI+) m/z = 392 $[M+H]^+$.

5-(4-fluoro-2-methylphenyl)-3-hydroxy-1-(4-methoxyphenyl)-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S64). Yield: 114 mg, 53.2%. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.09(d, *J* = 8.8 Hz, 2H), 6.90 (m, 1H), 6.75-6.85 (overlap, 4H), 5.93 (s, 1H), 3.76 (s, 3H), 2.41-2.51 (overlap, 4H), 2.27 (dd, *J* = 8.0, 4.0 Hz, 1H), 2.06 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H). LCMS: (ESI+) m/z = 398.2 $[M+H]^+$.

4-(4-fluoro-2-methylphenyl)-3-isobutyl-5-(4-methoxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (64). Yield: 61.0 mg, 93.4 % yield from **S64**; Purity: >95% @ 254 nm by HPLC. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.0 Hz, 1H), 7.45 (d, *J* = 9.1 Hz, 2H), 7.28-7.24 (overlap, 2H), 7.05 (dd, *J* = 8.8, 4.0 Hz, 1H), 6.84 (d, *J* = 9.1 Hz, 2H), 6.17 (s, 1H), 3.76 (s, 3H), 2.48 (m, 1H), 2.39 (m, 1H), 1.72 (m, 1H), 1.44 (s, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H). LCMS: (ESI+) m/z = 394 $[M+H]^+$.

5-(3,4-difluorophenyl)-3-hydroxy-1-(4-methoxyphenyl)-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S65). Yield: 404 mg, 71.4%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.06–6.98 (overlap, 3H), 6.83 (m, 2H), 5.71 (s, 1H), 3.75 (s, 3H), 2.59 (dd, *J* = 15.5, 6.4 Hz, 1H), 2.44 (dd, *J* = 15.5, 7.5 Hz, 1H), 2.09 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 196.4, 164.5, 158.3, 153.9, 151.6, 151.5, 151.4, 151.3, 149.6, 149.5, 149.4, 149.3, 132.74, 132.70, 132.67, 128.3, 124.7, 124.23, 124.20, 124.18, 124.15, 120.2, 117.8, 117.7, 116.7, 116.5, 114.6, 62.1, 55.5, 50.5, 24.9, 22.8, 22.4. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -136.14 (m), -136.91 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{21}F_2NO_4+H)^+$ 402.1517; found: 402.1516.

4-(3,4-difluorophenyl)-3-isobutyl-5-(4-methoxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (65). Yield: 99.0 mg, quant. yield from **S65**. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 9.0 Hz, 2H), 7.05 (ddd, *J* = 8.2, 8.2, 8.1 Hz, 1H), 6.95–6.92 (overlap, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.84 (s, 1H), 3.74 (s, 3H), 2.72 (dd, *J* = 14.5, 7.1 Hz, 1H), 2.46 (dd, *J* = 14.5, 7.1 Hz, 1H), 1.68 (dt, *J* = 13.4, 6.7, 6.7 Hz, 1H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 161.9, 157.8, 151.7, 151.6, 151.3, 151.2, 149.7, 149.6, 149.4, 149.3, 139.8, 134.3, 130.2, 126.6, 126.0, 123.7, 117.9, 117.8, 116.4, 116.2, 114.4, 61.2, 55.5, 33.8, 28.9, 22.24, 22.21. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -136.08 (m), -137.16 (dddd, *J* = 17.9, 13.4, 8.9, 4.4 Hz). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{21}F_2N_3O_2+H)^+$ 398.1680; found: 398.1679.

1-(benzo[*d*][1,3]dioxol-5-yl)-5-(2-chlorophenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S67). Yield: 259 mg, 62.7%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.34 (m, 1H), 7.17 (m, 2H), 6.99–6.96 (overlap, 2H), 6.82 (d, *J* = 7.2 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.38 (s, 1H), 5.90 (d, *J* = 7.6 Hz, 2H), 2.43 (dd, *J* = 15.5, 6.8 Hz, 1H), 2.19 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.00 (m, 1H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.6, 163.6, 159.2, 148.0, 146.3, 134.9, 133.0, 130.2, 130.1, 129.7, 127.9, 127.4, 119.6, 116.8, 108.3, 105.2, 101.7, 57.9, 48.9, 24.9, 22.6, 22.4. HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{20}ClNO_5+H)^+$ 414.1108; found 414.1108.

5-(benzo[*d*][1,3]dioxol-5-yl)-4-(2-chlorophenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (67). Yield: 118 mg, quant. yield from **S67**. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers – major rotamer) δ 7.36 (d, *J* = 7.9 Hz, 1H), 7.16 (ddd, *J* = 9.1, 7.8, 1.4 Hz, 1H), 7.12–7.09 (overlap, 2H), 6.97 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.82 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.58 (s, 1H), 5.90 (dd, *J* = 5.6, 1.4 Hz, 2H), 2.69 (dd, *J* = 14.4, 7.3 Hz, 1H), 2.54 (dd, *J* = 14.4, 7.2

Hz, 1H), 1.63 (m, 1H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) δ 161.9, 148.0, 145.3, 140.0, 134.6, 133.4, 131.9, 129.8, 129.6, 127.9, 127.1, 116.4, 108.2, 105.3, 101.5, 57.3, 34.8, 34.7, 34.0, 31.7, 29.2, 29.1, 27.0, 25.4, 22.8, 22.2, 22.0, 20.8, 14.2, 11.6. HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{20}ClN_3O_3+H)^+$ 410.1271; found: 410.1263.

1-(benzo[*d*][1,3]dioxol-5-yl)-5-(4-fluoro-2-methylphenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S70). Yield: 442 mg, 29.9%. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers – major rotamer) δ 6.86 (dd, *J* = 8.5, 5.8 Hz, 1H), 6.82–6.76 (overlap, 2H), 6.74 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 6.60 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.92 (m, 3H), 2.54 (dd, *J* = 15.4, 6.4 Hz, 1H), 2.50 (s, 3H), 2.34 (dd, *J* = 15.4, 7.5 Hz, 1H), 2.05 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) δ 196.8, 164.9, 163.2, 161.3, 148.2, 146.8, 139.9, 139.8, 129.7, 129.14, 129.12, 127.2, 127.1, 121.2, 117.8, 117.7, 117.5, 116.8, 114.0, 113.9, 108.4, 106.0, 105.0, 101.8, 64.5, 58.5, 50.3, 49.4, 25.0, 24.9, 22.8, 22.5, 22.4, 22.2, 19.7, 18.8. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -113.63 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{23}H_{22}FNO_5+H)^+$ 412.1560; found 412.1570.

5-(benzo[*d*][1,3]dioxol-5-yl)-4-(4-fluoro-2-methylphenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (70). Yield: 99.0 mg, quant. yield from **S70**. ^{1}H NMR: (500 MHz, $CDCl_3$) (Mixture of rotamers – major rotamer) 6.88–6.81 (overlap, 3H), 6.76 (m, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.11 (s, 1H), 5.90 (d, *J* = 3.5 Hz, 2H), 2.62 (dd, *J* = 14.5, 7.1 Hz, 1H), 2.48 (dd, *J* = 14.4, 7.1 Hz, 1H), 2.42 (s, 2H), 1.57 (m, 1H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) δ 163.1, 162.3, 161.1, 148.0, 146.1, 139.5, 137.9, 131.7, 130.7, 128.5, 127.6, 118.3, 117.2, 117.0, 114.3, 114.2, 108.2, 106.8, 105.7, 101.5, 63.3, 57.5, 34.8, 34.6, 34.1, 31.7, 29.2, 28.9, 25.4, 22.8, 22.20, 22.18, 20.8, 19.5, 14.2. ^{19}F NMR: (470 MHz, $CDCl_3$) (minor rotamer) δ -113.83 (m); (major rotamer) δ -113.97 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{23}H_{22}FN_3O_3+H)^+$ 408.1723; found 408.1719.

1-(3-fluoro-4-methoxyphenyl)-3-hydroxy-5-(2-methoxyphenyl)-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S72). Yield: 413 mg, 80.3%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 12.9, 2.0 Hz, 1H), 7.29 (d, *J* = 6.4 Hz, 1H), 7.21 (ddd, *J* = 8.5, 8.4, 1.7 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 7.4 Hz, 1H), 6.81 (dd, *J* = 9.1, 9.1 Hz, 1H), 3.94 (s, 2H), 3.78 (s, 3H), 2.33 (dd, *J* = 15.2, 6.8 Hz, 1H), 2.07 (dd, *J* = 15.2, 7.2 Hz, 1H), 1.98 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 163.2, 157.4, 152.8, 150.9, 145.6, 145.5, 130.3, 129.7, 129.6, 122.9, 121.6, 117.9, 113.3, 111.5, 110.5, 56.4, 55.8, 48.1, 24.9, 22.6, 22.3. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -133.14 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{23}H_{24}FNO_5+H)^+$ 414.1717 Found 414.1722.

5-(3-fluoro-4-methoxyphenyl)-3-isobutyl-4-(2-methoxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (72). Yield: 99.9 mg, quant. yield from **S72**. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 13.4, 2.1 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.19 (m, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.83 (dd, *J* = 9.1, 9.1 Hz, 1H), 6.78 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.50 (s, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 2.64 (dd, *J* = 14.4, 7.4 Hz, 1H), 2.47 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.69 (m, 1H), 0.80 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 162.1, 157.0, 153.0, 151.0, 144.8, 144.7, 139.6, 131.9, 131.8, 129.5, 124.7, 121.4, 118.0, 113.44, 113.42, 110.8, 56.5, 55.6, 33.9, 28.8, 22.3, 22.2, 22.1. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -133.59 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{23}H_{24}FN_3O_3+H)^+$ 410.1880; found 410.1873.

5-(4-fluoro-2-methylphenyl)-1-(3-fluoro-4-methoxyphenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S73). Yield: 415 mg, 26.8%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.12

(dd, *J* = 12.2, 2.4 Hz, 1H), 6.92 (m, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.85–6.80 (overlap, 3H), 6.76 (ddd, *J* = 8.5, 8.3, 2.5 Hz, 1H), 5.93 (s, 1H), 3.82 (s, 4H), 2.60 (dd, *J* = 15.4, 6.3 Hz, 2H), 2.56 (s, 3H), 2.40 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.06 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 4H), 0.74 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 196.7, 165.2, 163.2, 161.2, 153.4, 153.0, 151.0, 146.7, 146.6, 139.9, 139.8, 129.01, 128.98, 128.84, 128.77, 127.0, 126.9, 121.7, 119.5, 119.4, 117.7, 117.6, 114.0, 113.9, 113.48, 113.46, 112.4, 112.3, 64.2, 58.2, 56.4, 50.5, 49.7, 25.0, 24.9, 22.8, 22.4, 22.2, 19.7, 18.7. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -113.56 (m), -132.18 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{23}H_{23}F_2NO_4+H)^+$ 416.1673; found 416.1666.

4-(4-fluoro-2-methylphenyl)-5-(3-fluoro-4-methoxyphenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (73). Yield: 103 mg, quant. yield from **S73**. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers – major rotamer) δ 7.17 (d, *J* = 12.1 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.85–6.82 (overlap, 3H), 6.75 (s, 1H), 6.14 (s, 1H), 3.81 (s, 3H), 2.62 (dd, *J* = 14.5, 7.1 Hz, 1H), 2.54–2.48 (overlap, 3H), 1.56 (m, 1H), 0.75 (d, *J* = 6.4 Hz, 3H), 0.72 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) ^{13}C NMR (126 MHz, $cdcl_3$) δ 163.2, 162.1, 161.2, 153.0, 151.0, 137.8, 130.9, 130.6, 128.3, 119.8, 117.3, 117.2, 114.5, 114.3, 113.5, 112.8, 112.6, 57.1, 56.4, 34.1, 29.0, 22.3, 22.17, 22.16, 19.5. ^{19}F NMR: (470 MHz, $CDCl_3$) (major rotamer) δ -113.79 (m), -132.93 (m); (minor rotamer) δ -113.60 (m), -133.07 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{23}H_{23}F_2N_3O_2+H)^+$ 412.1837; found 412.1827.

5-(2-bromophenyl)-1-(4-bromophenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S74). Yield: 406 mg, 82.3%. ^{1}H NMR: (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $cdcl_3$) δ 7.53 (br d, *J* = 7.8 Hz, 1H), 7.43–7.36 (overlap, 4H), 7.20 (br dd, *J* = 7.4, 7.4 Hz, 1H), 7.11 (br dd, *J* = 7.6, 7.6 Hz, 1H), 6.95 (br d, *J* = 7.8 Hz, 1H), 6.42 (s, 1H), 2.49 (dd, *J* = 15.6, 6.9 Hz, 1H), 2.20 (dd, *J* = 15.6, 7.0 Hz, 1H), 2.00 (m, 1H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, $cdcl_3$) δ 198.0, 163.6, 158.7, 134.9, 134.3, 133.6, 132.25, 132.16, 130.6, 128.7, 127.6, 125.5, 124.3, 120.0, 119.9, 60.0, 49.1, 24.9, 22.6, 22.4. HRMS: (ESI+) *m/z* calc'd for $(C_{21}H_{19}Br_2NO_3+H)^+$ 491.9810; found 491.9993.

4-(2-bromophenyl)-5-(4-bromophenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (74). Yield: 112 mg, quant. yield from **S74**. ^{1}H NMR: (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $cdcl_3$) δ 7.57 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.13 (ddd, *J* = 7.6, 7.6, 1.4 Hz, 1H), 7.09 (ddd, *J* = 7.6, 7.4, 1.9 Hz, 1H), 6.92 (dd, *J* = 7.6, 1.9 Hz, 1H), 6.62 (s, 1H), 2.73 (dd, *J* = 14.4, 7.4 Hz, 1H), 2.60 (dd, *J* = 14.4, 7.3 Hz, 1H), 1.61 (m, 1H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.70 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) ^{13}C NMR (126 MHz, $cdcl_3$) δ 161.8, 137.1, 136.0, 133.2, 132.1, 130.2, 128.7, 127.8, 123.4, 118.2, 59.4, 34.8, 34.1, 31.7, 29.2, 25.4, 22.8, 22.2, 22.0, 20.8, 14.3. HRMS: (ESI+) *m/z* calc'd for $(C_{21}H_{19}Br_2N_3O+H)^+$ 489.9973; found 489.9964.

1-(4-bromophenyl)-3-hydroxy-5-(2-methoxyphenyl)-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S75). Yield: 365 mg, 82.3%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 8.9 Hz, 2H), 7.22 (m, 1H), 6.88 (br d, *J* = 8.3 Hz, 1H), 6.84 (br dd, *J* = 7.4, 7.4 Hz, 1H), 6.38 (s, 1H), 3.94 (s, 3H), 2.34 (dd, *J* = 15.2, 6.8 Hz, 1H), 2.07 (dd, *J* = 15.2, 7.1 Hz, 1H), 1.98 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 163.3, 157.3, 135.6, 132.0, 130.4, 123.3, 122.7, 121.7, 119.0, 111.5, 77.4, 77.2, 76.9, 55.9, 48.2, 24.9, 22.7, 22.3. HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{22}BrNO_4+H)^+$ 444.0810; found 444.0820.

5-(4-bromophenyl)-3-isobutyl-4-(2-methoxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (75). Yield: 111 mg, quant. yield from **S75**. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers –

major rotamer) δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.9 Hz, 2H), 7.18 (m, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.76 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.57 (s, 1H), 3.93 (s, 3H), 2.72 (dd, *J* = 14.3, 7.3 Hz, 1H), 2.53 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.69 (m, 1H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) δ 162.2, 156.9, 148.3, 139.6, 137.6, 131.8, 129.5, 127.6, 127.0, 124.6, 123.3, 121.5, 117.6, 110.8, 55.6, 34.8, 33.7, 29.2, 28.9, 27.0, 25.4, 22.8, 22.2, 22.1, 20.8, 14.2. HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{22}BrN_3O_2+H)^+$ 440.0974; found 440.0961.

1-(4-bromophenyl)-5-(4-fluoro-2-methylphenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S76). Yield: 211 mg, 47.3%. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers – major rotamer) δ 7.41 (d, *J* = 8.9 Hz, 2H), 7.19 (d, *J* = 8.9 Hz, 2H), 6.84–6.81 (overlap, 2H), 6.76 (m, 1H), 5.99 (s, 1H), 2.63–2.59 (overlap, 4H), 2.41 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.07 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) δ 196.7, 165.2, 163.2, 161.3, 139.8, 139.8, 135.0, 132.4, 132.3, 128.84, 128.81, 126.9, 126.8, 124.7, 123.9, 121.8, 120.4, 117.8, 117.7, 114.1, 113.9, 63.8, 57.8, 50.6, 49.8, 25.0, 24.9, 22.8, 22.4, 22.2, 19.7, 18.7. ^{19}F NMR: (470 MHz, $CDCl_3$) (major rotamer) δ -113.40 (m); (minor rotamer) δ -112.87 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{21}BrFNO_3+H)^+$ 446.0767; found 446.0762.

5-(4-bromophenyl)-4-(4-fluoro-2-methylphenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (76). Yield: 108 mg, quant. yield from **S76**. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers – major rotamer) δ 7.40–7.38 (overlap, 3H), 7.26 (m, 1H), 6.86 (m, 1H), 6.74 (m, 1H), 6.21 (br s, 1H), 2.58 (dd, *J* = 14.5, 7.2 Hz, 1H), 2.55–2.50 (overlap, 2H), 1.56 (d, *J* = 5.6 Hz, 1H), 0.76 (d, *J* = 6.4 Hz, 3H), 0.72 (d, *J* = 6.6 Hz, 3H). ^{19}F NMR: (470 MHz, $CDCl_3$) (major rotamer) δ -113.59 (m); (minor rotamer) δ -113.32 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{21}BrFN_3O+H)^+$ 442.0930; found 442.0924.

1-(4-bromophenyl)-5-(4-fluoro-2-methoxyphenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S77). Yield: 194 mg, 39.1%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 9.0 Hz, 2H), 7.37 (d, *J* = 9.0 Hz, 2H), 6.90 (br s, 1H), 6.60 (br d, *J* = 10.5 Hz, 1H), 6.56 (ddd, *J* = 8.3, 8.3, 2.4 Hz, 1H), 6.29 (br s, 1H), 3.92 (s, 3H), 2.38 (dd, *J* = 15.3, 6.7 Hz, 1H), 2.13 (dd, *J* = 15.2, 7.2 Hz, 1H), 2.02 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 164.8, 163.5, 162.8, 158.9, 158.6, 135.3, 132.1, 123.4, 119.3, 118.6, 108.5, 100.0, 99.8, 56.2, 48.7, 24.9, 22.7, 22.4.^{19}F NMR: (470 MHz, $CDCl_3$) δ -108.71 (br s). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{21}BrFNO_4+H)^+$ 462.0716; found 462.0711.

5-(4-bromophenyl)-4-(4-fluoro-2-methoxyphenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (77). Yield: 71.0 mg, 71.6% yield from **S77**. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers – major rotamer) δ 7.45 (d, *J* = 8.9 Hz, 2H), 7.37 (d, *J* = 8.9 Hz, 2H), 6.84 (br s, 1H), 6.62 (br d, *J* = 9.8 Hz, 1H), 6.50–6.47 (overlap, 2H), 3.91 (s, 3H), 2.72 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.52 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.70 (m, 1H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) δ 164.4, 162.4, 162.2, 158.1, 139.5, 137.3, 131.9, 123.6, 121.5, 120.5, 117.9, 108.2, 108.1, 99.5, 99.2, 56.0, 36.2, 34.8, 34.6, 33.8, 31.7, 29.2, 28.9, 27.0, 25.4, 22.8, 22.20, 22.15, 20.8, 18.9, 14.2, 11.5. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -110.19 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{21}BrFN_3O_2+H)^+$ 458.0879; found 458.0874.

5-(2-chlorophenyl)-1-(4-(dimethylamino)phenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S78). Yield: 246 mg, quant. yield. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 6.1, 3.3 Hz, 1 H), 7.26 (m, 2H), 7.19–7.16 (overlap, 2H), 7.03 (m, 1H), 6.60 (d, *J* = 9.1 Hz, 2H), 6.41 (s,1 H), 2.90 (s, 6H), 2.40 (dd, *J* = 15.3, 7.0 Hz, 1H), 2.15 (dd, *J* = 15.3, 6.7 Hz,1H), 2.00 (m, 1H),

0.90 (d, *J* = 6.8 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H). LCMS: (ESI+) *m/z* calc'd for $(C_{23}H_{25}ClN_2O_3+H)^+$ 413.16; found 413.10.

4-(2-chlorophenyl)-5-(4-(dimethylamino)phenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (78). Yield: 25.0 mg, 43.6% yield from **S78**. ^{1}H NMR: (400 MHz, $CDCl_3$) δ 10.36 (br s, 1H), 7.29 - 7.38 (overlap, 3H), 7.17–7.09 (overlap, 2H), 7.03 (dd, *J* = 7.6, 2.3 Hz, 1H), 6.64 (d, *J* = 9.4 Hz, 2H), 6.57 (s, 1H), 2.89 (s, 6H), 2.45 (m, 1H), 2.38 (m, 1H), 1.59 (m, 1H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H). LCMS: (ESI+) *m/z* calc'd for $(C_{23}H_{25}ClN_4O+H)^+$ 409.18; found 409.10.

1-(4-(dimethylamino)phenyl)-3-hydroxy-5-(2-methoxyphenyl)-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S80). Yield: 292 mg, 71.5%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.7 Hz, 2H), 7.18 (m, 1H), 6.95 (s, 1H), 6.83 (dd, *J* = 7.5, 7.5 Hz, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 6.32 (s, 1H), 3.88 (s, 3H), 2.86 (s, 6H), 2.33 (dd, *J* = 15.1, 6.8 Hz, 1H), 2.09 (dd, *J* = 15.1, 7.2 Hz, 1H), 1.98 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 163.0, 157.6, 148.7, 129.9, 125.9, 123.7, 121.4, 112.5, 111.4, 55.8, 47.9, 40.6, 25.0, 22.7, 22.3. HRMS: (ESI+) *m/z* calc'd for $(C_{24}H_{28}N_2O_4+H)^+$ 409.2127; found 409.2125.

5-(4-(dimethylamino)phenyl)-3-isobutyl-4-(2-methoxyphenyl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (80). Yield: 98.1 mg, 99.1% yield from **S80**. ^{1}H NMR: (500 MHz, DMSO) (mixture of rotamers – major rotamer) δ 7.29 (d, *J* = 9.0 Hz, 2H), 7.17 (m, 1H), 7.00 (s, 1H), 6.77 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.64 (d, *J* = 9.0 Hz, 2H), 6.46 (d, *J* = 8.6 Hz, 1H), 3.84 (s, 3H), 2.82 (s, 6H), 2.33 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.23 (dd, *J* = 13.9, 7.1 Hz, 1H), 1.57 (m, 1H), 0.70 (d, *J* = 6.5 Hz, 3H), 0.58 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, DMSO) (mixture of rotamers) δ 161.9, 156.8, 149.3, 147.7, 136.1, 128.9, 127.5, 125.4, 124.7, 124.2, 120.7, 112.3, 111.3, 55.6, 53.0, 40.2, 33.1, 29.9, 28.0, 22.0, 21.7. HRMS: (ESI+) *m/z* calc'd for $(C_{24}H_{28}N_4O_2+H)^+$ 405.2291; found 405.2301.

1-(4-(dimethylamino)phenyl)-5-(4-fluoro-2-methylphenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S81). Yield: 208 mg, 50.6%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 9.0 Hz, 2H), 6.89 (dd, *J* = 8.4, 5.8 Hz, 1H), 6.76 (m, 2H), 6.59 (d, *J* = 9.0 Hz, 2H), 5.92 (s, 1H), 2.89 (s, 7H), 2.62 (dd, *J* = 15.4, 6.3 Hz, 1H), 2.49 (s, 3H), 2.43 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.08 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 196.5, 165.2, 163.0, 161.1, 154.1, 149.4, 139.94, 139.89, 129.7, 127.1, 127.0, 125.2, 124.7, 124.1, 121.4, 117.4, 117.3, 113.7, 113.5, 112.5, 58.4, 50.5, 40.5, 25.0, 24.9, 22.8, 22.4, 19.7. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -114.32 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{24}H_{27}FN_2O_3+H)^+$ 411.2084; found 411.2083.

5-(4-(dimethylamino)phenyl)-4-(4-fluoro-2-methylphenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (81). Yield: 105 mg, quant. yield from **S81**. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers – major rotamer) δ 7.06 (d, *J* = 8.2 Hz, 2H), 6.90 (m, 1H), 6.79–6.75 (overlap, 2H), 6.59 (d, *J* = 8.5 Hz, 2H), 6.44 (m, 1H), 6.08 (s, 1H), 2.88 (s, 6H), 2.59 (dd, *J* = 14.4, 7.0 Hz, 1H), 2.45 (m, 1H), 2.37 (s, 3H), 1.57 (m, 1H), 0.75 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) δ 163.0, 162.2, 161.0, 149.1, 138.1, 131.1, 128.7, 126.9, 126.2, 124.9, 117.0, 116.8, 114.1, 113.9, 112.7, 57.4, 40.6, 34.8, 34.6, 34.3, 31.7, 29.2, 28.8, 28.5, 27.0, 25.4, 22.8, 22.3, 22.23, 22.20, 20.8, 19.5, 18.9, 14.2, 11.5. ^{19}F NMR: (470 MHz, $CDCl_3$) (major rotamer) δ -114.48 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{24}H_{27}FN_4O+H)^+$ 407.2247; found 407.2249.

1-(4-(dimethylamino)phenyl)-5-(4-fluoro-2-methoxyphenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S82). Yield: 269 mg, 63.1%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.93 (br s, 1H), 6.59 (d, *J* = 8.6 Hz, 2H), 6.55–6.52 (overlap, 2H), 6.23 (br s, 1H), 3.86 (s, 3H), 2.88 (s, 6H), 2.38 (dd, *J* = 15.1, 6.7 Hz, 1H), 2.15 (dd, *J* = 15.1, 7.3 Hz, 1H), 2.02 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 164.5, 163.2, 162.6, 158.8, 148.8, 123.9, 119.6, 112.5, 99.9, 99.7, 56.2, 48.4, 40.6, 25.0, 22.7, 22.4. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -109.79 (br s). HRMS: (ESI+) *m/z* calc'd for $(C_{24}H_{27}FN_2O_4+H)^+$ 427.2033; found 427.2025.

5-(4-(dimethylamino)phenyl)-4-(4-fluoro-2-methoxyphenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (82). Yield: 100 mg, quant. yield from **S82**. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 9.0 Hz, 2H), 6.91 (m, 1H), 6.63 (d, *J* = 9.0 Hz, 2H), 6.56 (dd, *J* = 10.7, 2.2 Hz, 1H), 6.48 (ddd, *J* = 8.4, 8.3, 2.3 Hz, 1H), 6.40 (s, 1H), 3.82 (s, 3H), 2.88 (s, 6H), 2.63 (dd, *J* = 14.3, 7.3 Hz, 1H), 2.46 (dd, *J* = 14.3, 7.2 Hz, 1H), 1.68 (m, 1H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 164.2, 162.2, 162.1, 158.3, 148.4, 139.6, 128.6, 127.7, 127.4, 124.6, 121.1, 112.8, 107.9, 107.7, 99.3, 99.1, 55.9, 40.8, 34.1, 28.8, 22.24, 22.19. ^{19}F NMR: (470 MHz, $CDCl_3$) δ -111.17 (br s). HRMS: (ESI+) *m/z* calc'd for $(C_{24}H_{27}FN_4O_2+H)^+$ 423.2196; found 423.2191.

3-hydroxy-5-(2-methoxyphenyl)-1-(6-methoxypyridin-3-yl)-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S85). Yield: 280 mg, 70.6%. ^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 2.4 Hz, 1H), 7.76 (br d, *J* = 7.8 Hz, 1H), 7.22 (ddd, *J* = 8.4, 8.4, 1.7 Hz, 1H), 6.94 (br s, 1H), 6.85 (dd, *J* = 7.2, 7.2 Hz, 2H), 6.63 (d, *J* = 9.0 Hz, 1H), 6.38 (br s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 2.33 (dd, *J* = 15.2, 6.8 Hz, 1H), 2.07 (dd, *J* = 15.2, 7.2 Hz, 1H), 1.98 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.66 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) δ 163.5, 161.9, 157.5, 141.0, 133.8, 130.5, 127.2, 122.6, 121.6, 111.5, 110.8, 55.9, 53.7, 48.2, 24.9, 22.7, 22.3. HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{24}N_2O_5+H)^+$ 397.1763; found 397.1761.

3-isobutyl-4-(2-methoxyphenyl)-5-(6-methoxypyridin-3-yl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (85). Yield: 111 mg, quant. yield from **S85**. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers – major rotamer) δ 8.17 (d, *J* = 2.6 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.19 (ddd, *J* = 8.8, 7.7, 1.7 Hz, 1H), 6.91 (br s, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.79 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.67 (d, *J* = 8.9 Hz, 1H), 6.51 (br s, 1H), 3.86 (s, 6H), 2.66 (dd, *J* = 14.3, 7.3 Hz, 1H), 2.48 (dd, *J* = 14.4, 7.1 Hz, 1H), 1.69 (m, 1H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) δ 162.3, 161.3, 157.1, 140.9, 134.2, 129.6, 129.2, 124.3, 121.4, 110.9, 110.7, 55.6, 53.7, 34.8, 33.9, 31.7, 29.2, 28.8, 25.4, 22.8, 22.2, 22.1, 20.8, 14.2, 11.6. HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{24}N_4O_3+H)^+$ 393.1927; found 292.1920.

5-(4-fluoro-2-methylphenyl)-3-hydroxy-1-(6-methoxypyridin-3-yl)-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S86). Yield: 119 mg, 29.9%. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers – major rotamer) δ 7.98 (d, *J* = 2.5 Hz, 1H), 7.45 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.88 (dd, *J* = 8.5, 5.8 Hz, 1H), 6.82–6.77 (overlap, 2H), 6.66 (d, *J* = 8.9 Hz, 1H), 5.94 (s, 1H), 3.87 (s, 3H), 2.57 (dd, *J* = 15.5, 6.3 Hz, 1H), 2.50 (s, 3H), 2.38 (dd, *J* = 15.5, 7.6 Hz, 1H), 2.07 (dd, *J* = 14.5, 7.7 Hz, 2H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.75 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) δ 196.8, 165.3, 163.3, 162.8, 161.3, 142.5, 141.4, 140.6, 139.93, 139.87, 135.0, 133.8, 128.81, 128.79, 127.1, 127.0, 126.5, 121.7, 117.8, 117.7, 114.2, 114.0, 111.4, 111.3, 111.0, 100.5, 64.3, 58.2, 53.9, 53.0, 52.3, 50.4, 50.1, 26.2, 25.0, 24.9, 22.81, 22.79, 22.6, 22.4, 22.2, 19.7, 18.7. ^{19}F NMR: (470 MHz, $CDCl_3$) (major rotamer) δ -113.29 (m); (minor rotamer) δ -112.82 (br s). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{23}FN_2O_4+H)^+$ 399.1720; found 399.1729.

4-(4-fluoro-2-methylphenyl)-3-isobutyl-5-(6-methoxypyridin-3-yl)-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (86). Yield: 112 mg, quant. yield from **S86**. ^{1}H NMR: (500 MHz, $CDCl_3$) (mixture of rotamers – major rotamer) δ 7.88 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 6.83–6.77 (overlap, 2H), 6.72 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 6.08 (s, 1H), 3.80 (s, 3H), 2.36–2.32 (overlap, 4H), 2.24 (dd, *J* = 14.4, 7.3 Hz, 1H), 1.50 (m, 1H), 0.69 (d, *J* = 6.6 Hz, 3H), 0.65 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: (126 MHz, $CDCl_3$) (mixture of rotamers) δ 163.1, 162.2, 161.2, 142.6, 141.6, 137.9, 136.0, 134.8, 132.9, 130.1, 128.5, 128.4, 128.2, 117.3, 117.1, 114.4, 114.2, 111.0, 63.0, 57.2, 53.7, 34.3, 31.6, 28.6, 22.6, 22.04, 22.03, 19.3, 14.0. ^{19}F NMR: (470 MHz, $CDCl_3$) (major rotamer) δ -113.62 (m); (minor rotamer) δ -113.45(br s). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{23}FN_4O_2+H)^+$ 395.1883; found 395.1893.

1-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-5-(4-fluoro-2-methylphenyl)-3-hydroxy-4-(3-methylbutanoyl)-1,5-dihydro-2*H*-pyrrol-2-one (S89). Yield: 284 mg, 64.7%. ^{1}H NMR: (500 MHz, CD_3OD) (mixture of rotamers – major rotamer) δ 8.95 (m, 1H), 8.29 (s, 1H), 7.65 (d, *J* = 9.5 Hz, 1H), 7.53 (dd, *J* = 9.6, 2.0 Hz, 1H), 6.85 (dd, *J* = 8.7, 5.7 Hz, 1H), 6.80 (dd, *J* = 9.6, 2.4 Hz, 1H), 6.73 (ddd, *J* = 8.4, 8.4, 2.5 Hz, 1H), 6.05 (s, 1H), 2.79 (dd, *J* = 14.8, 6.2 Hz, 1H), 2.64 (s, 2H), 2.54 (dd, *J* = 14.8, 7.9 Hz, 1H), 2.05 (m, 1H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR: (126 MHz, CD_3OD) (mixture of rotamers) δ 197.4, 166.5, 163.6, 161.6, 154.3, 150.3, 148.6, 140.7, 140.6, 129.7, 127.1, 127.03, 126.96, 126.7, 124.0, 122.9, 118.0, 117.9, 116.4, 115.0, 114.2, 114.1, 112.2, 58.0, 51.7, 25.6, 22.9, 22.4, 19.7. ^{19}F NMR: (470 MHz, CD_3OD) (major rotamer) δ -114.42 (ddd, *J* = 10.0, 8.6, 5.7 Hz); (minor rotamer) - δ 114.25 (m). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{21}FN_4O_3+H)^+$ 409.1676; found 409.1678.

5-([1,2,4]triazolo[1,5-*a*]pyridin-6-yl)-4-(4-fluoro-2-methylphenyl)-3-isobutyl-4,5-dihydropyrrolo[3,4-*c*]pyrazol-6(1*H*)-one (89). Yield: 99.9 mg, quant. yield from **S89**. ^{1}H NMR: (500 MHz, DMSO) (mixture of rotamers) δ 13.49 (s, 1H), 9.24 (s, 1H), 8.48 (s, 1H), 7.87–7.84 (overlap, 2H), 7.07–6.99 (overlap, 2H), 6.84 (m, 1H), 6.69 (s, 1H), 2.56 (s, 3H), 2.37 (m, 2H), 2.27 (dd, *J* = 14.1, 7.2 Hz, 1H), 1.49 (m, 1H), 0.68 (d, *J* = 6.6 Hz, 3H), 0.59 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR: (126 MHz, DMSO) (mixture of rotamers) δ 162.2, 160.2, 154.5, 147.9, 138.5, 131.0, 128.4, 127.5, 126.7, 124.7, 123.3, 116.9, 116.7, 115.6, 113.9, 113.7, 60.6, 56.2, 33.3, 28.2, 28.0, 21.9, 21.7, 18.8, 17.6. ^{19}F NMR: (470 MHz, DMSO) (major rotamer) δ -114.51 (br s); (minor rotamer) δ -113.89 (br s). HRMS: (ESI+) *m/z* calc'd for $(C_{22}H_{21}FN_6O+H)^+$ 405.1839; found 405.1834.

3 Supplementary References

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