Supporting Information

Development of an allosteric inhibitor class blocking RNA elongation by the respiratory syncytial virus polymerase complex

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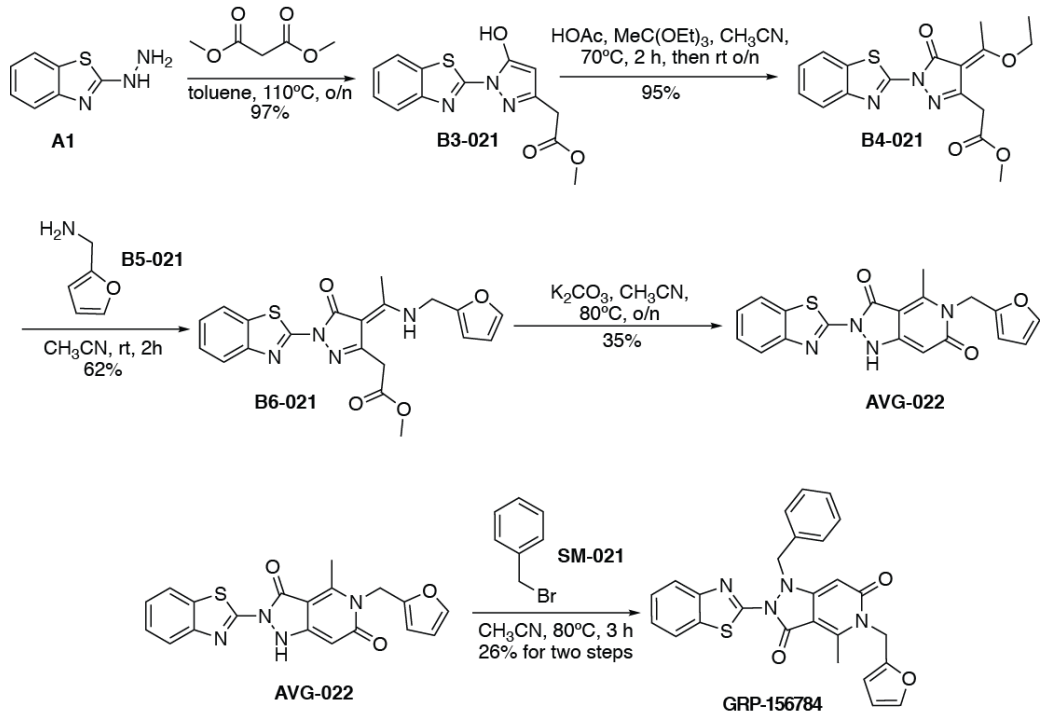
General Synthesis scheme:



The synthesis of methyl 2-(1-(benzo[*d*]thiazol-2-yl)-5-hydroxy-1*H*-pyrazol-3-yl)acetate (B3-021). To a solution of A1 (3.3 g, 19.97 mmol) in toluene (30 mL) was added B2 (3.5 g, 19.97 mmol), then the reaction mixture was stirred at 110 °C overnight. After cooling the reaction mixture to room temperature, the resulting solid was filtered, washed with toluene and dried in vacuum to give B3-021 (5.6 g, 97% yield) as a white solid. B3-021 purity was determined by LCMS using an Agilent 1200-6120 system with a Waters X-Bridge C18 (30mm×4.6 mm×3.5 μm) column (40°C; 2.0 mL/min). Mobile Phase: from 90% [water + 10 mM NH_4HCO_3] and 10% [CH_3CN] to 5% [water + 10 mM NH_4HCO_3] and 95% [CH_3CN] in 0.5 min, then under this condition for 1.5 min, finally changed to 90% [water + 10 mM NH_4HCO_3] and 10% [CH_3CN] in 0.1 min and under this condition for 0.5 min. Purity was found to be 97.2%, Rt = 0.874 min; MS Calcd.: 289.1; MS Found: 290.0 $[M + H]^+$. For synthesis of analogs with modifications to section 1, hydrazine forms of the substitutions were in place of A1.

The synthesis of (*E*)-methyl 2-(1-(benzo[*d*]thiazol-2-yl)-4-(1-ethoxyethylidene)-5-oxo-4,5-dihydro-1*H* –pyrazol-3-yl)acetate (B4-021). HOAc (186 mg, 3.10 mmol) was added to a mixture of B3-021 (4.5 g, 15.49 mmol) and $MeC(Oet)_3$ (7.5 g, 46.46 mmol) in CH_3CN (50 mL) and the reaction mixture was stirred at 70°C for 2 h. Following this, the reaction mixture was stirred at room temperature overnight. After the reaction was complete, the resulting solid was filtered, then

washed with CH_3CN and dried in vacuum to give B4-021 (5.3 g, 95% yield) as a white solid. B4-021 purity was determined by LCMS using an Agilent 1200-6120 system with a Waters X-Bridge C18 (50 mm×4.6 mm×3.5 μm) column (40°C; 2.0 mL/min). Mobile Phase: from 95% [water + 0.05% TFA] and 5% [CH_3CN + 0.05% TFA] to 0% [water + 0.05% TFA] and 100% [CH_3CN + 0.05 % TFA] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 0.05% TFA] and 5% [CH_3CN + 0.05% TFA] in 0.05 min and under this condition for 0.7 min. Purity was found to be 100%. Rt = 1.353 min; MS Calcd.: 359.1; MS Found: 332.1 $[M - 28 + H]^+$. B4-021 NMR analysis: ^1H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.48 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 7.35 (ddd, J = 8.4, 8.0, 1.2 Hz, 1H), 4.47 (q, J = 7.2 Hz, 2H), 3.83 (s, 2H), 3.67 (s, 3H), 2.84 (s, 3H) , 1.33 (t, J = 6.8 Hz, 3H).

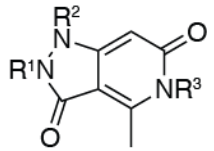
The synthesis of (*E*)-methyl 2-(1-(benzo[*d*]thiazol-2-yl)-4-(1-(furan-2-ylmethylamino)ethylidene) -5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)acetate (B6-021). B5-021 (1.6 g, 16.49 mmol) was added to a solution of B4-021 (4.9 g, 13.75 mmol) in CH_3CN (30 mL), and then the reaction mixture was stirred at room temperature for 2 h. The resulting solid was collected by filtration, washed with CH_3CN and dried in vacuum to give B6-021 (3.5 g, 62% yield) as a white solid. B3-021 purity was determined by LCMS using an Agilent 1200-6120 system with a Waters X-Bridge C18 (50 mm×4.6 mm×3.5 μm) column (40°C; 2.0 mL/min). Mobile Phase: from 95% [water + 0.05% TFA] and 5% [CH_3CN + 0.05% TFA] to 0% [water + 0.05% TFA] and 100% [CH_3CN + 0.05 % TFA] in 1.6 min, then under this condition for 1.4 min, finally changed to 95% [water + 0.05% TFA] and 5% [CH_3CN + 0.05% TFA] in 0.05 min and under this condition for 0.7 min. Purity was found to be 100%. Rt = 1.741 min; MS Calcd.: 410.1; MS Found: 411.1 $[M + H]^+$. For synthesis of analogs possessing modifications to section 3, amine forms of the groups were used similarly to B5-021.

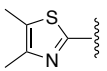
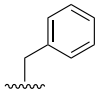
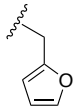
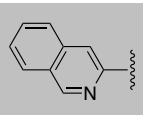
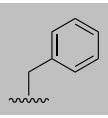
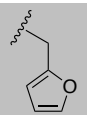
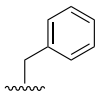
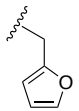
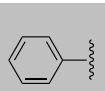
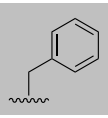
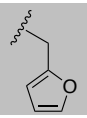
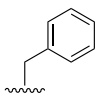
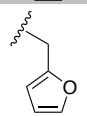
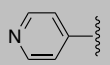
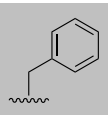
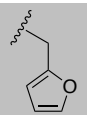
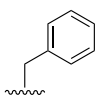
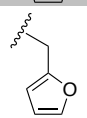
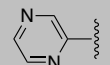
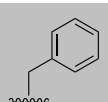
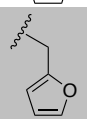
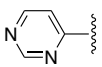
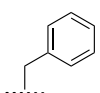
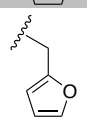
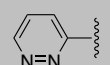
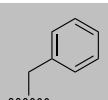
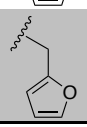
The synthesis of 2-(benzo[*d*]thiazol-2-yl)-5-(furan-2-ylmethyl)-4-methyl-1*H*-pyrazolo[4,3-*c*]pyridine -3,6(2*H*,5*H*)-dione (AVG-022). K_2CO_3 (337 mg, 2.44 mmol) was added to a solution of B6-021 (0.5 g, 1.22 mmol) in CH_3CN (20 mL), then the reaction mixture was stirred at 80 °C overnight. The mixture was concentrated to dryness and the residue was diluted with water (20 mL). The pH value of this mixture was adjusted to 7 with hydrochloric acid (1 N). The resulting solid was filtered, washed with water and dried in vacuum to give AVG-022 (160 mg, 35% yield) as a brown solid. AVG-022 purity was determined by LCMS using an Agilent 1200-6120 system with a Waters X-Bridge C18 (150mm×4.6 mm×3.5 μm) column (40°C; 1.0 mL/min). Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 10 min, then under this condition for 5 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 5 min. Purity is 100.0%, Rt = 6.429 min. AVG-022 NMR analysis: ^1H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 8.07 (d, J = 8.0 Hz,

1H), 7.84 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.50 (dd, J = 7.6, 7.2 Hz, 1H), 7.37 (dd, J = 7.6, 7.6 Hz, 1H), 6.43 (s, 1H), 6.37 (d, J = 2.8 Hz, 1H), 5.73 (s, 1H), 5.34 (s, 2H), 2.96 (s, 3H).

The synthesis of 2-(benzo[*d*]thiazol-2-yl)-1-benzyl-5-(furan-2-ylmethyl)-4-methyl-1*H*-pyrazolo[4,3-*c*] pyridine-3,6(2*H*,5*H*)-dione (GRP-156784). K_2CO_3 (138 mg, 1.00 mmol) was added to a solution of B6-021 (205 mg, 0.50 mmol) in CH_3CN (10 mL), then the reaction mixture was stirred at 80°C overnight. After being cooled to room temperature, SM-021 (85 mg, 0.50 mmol) was subsequently added, and then the mixture was stirred at 80°C for 3 h. After being cooled to room temperature, the reaction system was diluted with water (20 mL) and extracted with ethyl acetate (20 mL×3). The combined organic layers were washed with brine (20 mL×2), dried over sodium sulfate, and concentrated to dryness. The residue was purified by Prep-TLC (petrol ether/EtOAc = 1/1) to give GRP-156784 (60 mg, 26% yield) as a white solid. GRP-156784 purity was determined by LCMS using an Agilent 1200-6120 system with a Waters X-Bridge C18 (150mm×4.6 mm×3.5 μm) column (40°C; 1.0 mL/min). Mobile Phase: from 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] to 0% [water + 10 mM NH_4HCO_3] and 100% [CH_3CN] in 10 min, then under this condition for 5 min, finally changed to 95% [water + 10 mM NH_4HCO_3] and 5% [CH_3CN] in 0.1 min and under this condition for 5 min. Purity is 100.0%, Rt = 10.392 min. GRP-156784 NMR analysis: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 7.6 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.61 (dd, J = 1.8, 1.0 Hz, 1H), 7.54 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H), 7.41 (ddd, J = 8.4, 8.0, 1.2 Hz, 1H), 7.24-7.19 (m, 3H), 7.04-7.01 (m, 2H), 6.48 (s, 1H), 6.43 (dd, J = 3.2, 2.0 Hz, 1H), 6.36 (d, J = 2.4 Hz , 1H), 5.54 (s, 2H), 5.32 (s, 2H), 2.89 (s, 3H). For synthesis of analogs posessing modifications to section 2, bromomethyl- forms of the substitutions were used in place of B6-021.

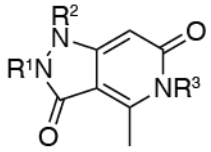
Table S1. Chemical elaboration of scaffolds section 1.

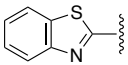
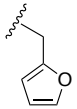
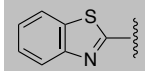
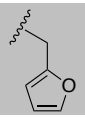
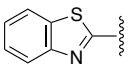
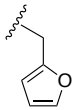
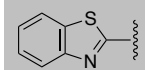
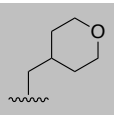
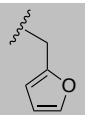
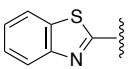
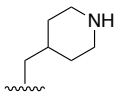
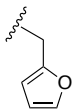
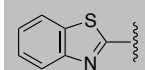
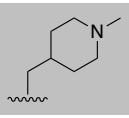
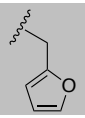
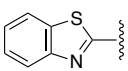
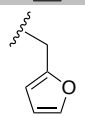
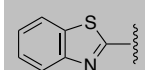
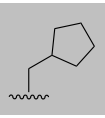
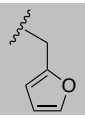
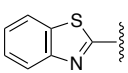
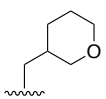
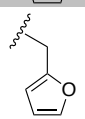
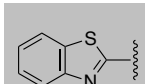
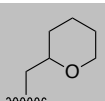
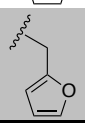


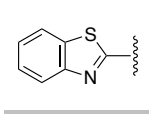
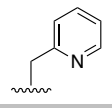
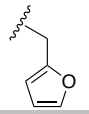
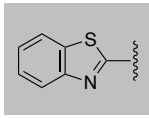
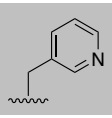
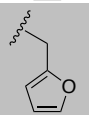
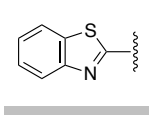
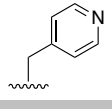
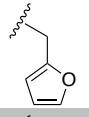
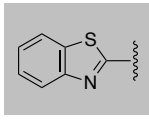
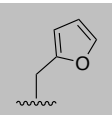
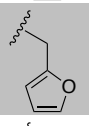
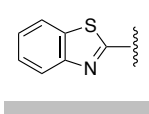
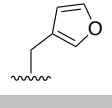
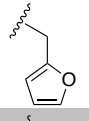
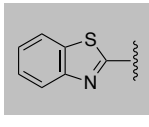
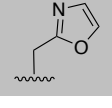
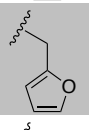
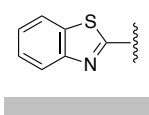
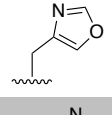
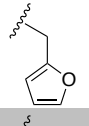
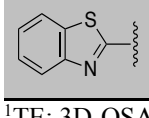
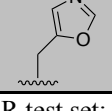
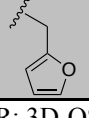
R^1	R^2	R^3	Name	EC_{50} [μM]	CC_{50} [μM]	SI	SMILES	3D-QSAR[1]
			AVG-033	2.8 (2.01 - 4.5)	169.0	60	CC(N1CC2=CC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=NC(C)=C(C)S5)C3=O)=CC1=O	TE
			AVG-034	1.5 (1.1 - 2.2)	300.0	200	CC(N1CC2=CC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=CC(C=CC=C6)=C6C=N5)C3=O)=CC1=O	N/A
			AVG-035	1.49 (0.94 - 2.1)	>300	>201	CC(N1CC2=CC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TR
			AVG-080	2.6 (1.7 - 6.4)	>300	115	CC(N1CC2=CC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=C5)C3=O)=CC1=O	TE
			AVG-081	20	90.0	4.5	CC(N1CC2=CC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CN=C5)C3=O)=CC1=O	N/A
			AVG-082	4.7 (3.2 - 10.8)	190.0	40	CC(N1CC2=CC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=NC=C5)C3=O)=CC1=O	N/A
			AVG-105	>20	>300	N/A	CC(N1CC2=CC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=NC=CC=N5)C3=O)=CC1=O	N/A
			AVG-106	1.6 (1.1 - 2.6)	300.0	188	CC(N1CC2=CC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=CN=CC=N5)C3=O)=CC1=O	TE
			AVG-108	6.9	>300	>45	CC(N1CC2=CC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=NC=N5)C3=O)=CC1=O	TE
			AVG-109	3.5	>300	>86	CC(N1CC2=CC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CN=N5)C3=O)=CC1=O	N/A

[1]TE: 3D-QSAR test set; TR: 3D-QSAR training set; N/A: not applicable

Table S2. Chemical elaboration of scaffolds section 2.

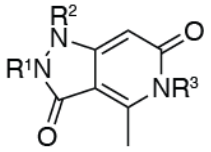


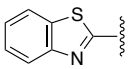
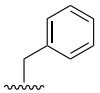
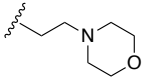
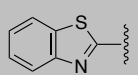
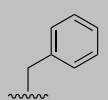
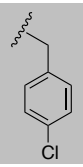
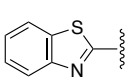
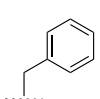
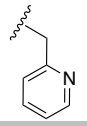
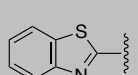
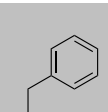
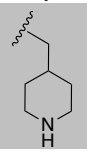
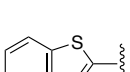
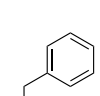
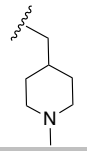
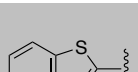
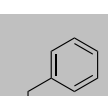
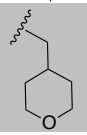
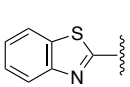
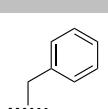
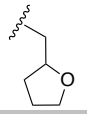
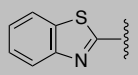
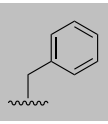
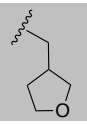
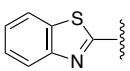
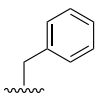
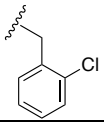
R^1	R^2	R^3	Name	EC_{50} [μM]	CC_{50} [μM]	SI	SMILES	3D-QSAR[1]
	H		AVG-022	0.59 (0.32-1.5)	6.7 (5.4-8.3)	11	O=C1N(C2SC3C(N2)CCCC3)NC=2C1=C(C)N(CC1OCCC1)C(=O)C=2	N/A
			AVG-023	>20	>300	N/A	O=C1N(N(C)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-024	1.21 (0.92 - 1.63)	138.0	114	O=C1N(N(CC2CCCCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	TE
			AVG-025	1.99 (1.37-3.37)	>200	>101	O=C1N(N(CC2CCOCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	TE
			AVG-026	~7.5	13.7	2	O=C1N(N(CC2CCNCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-027	~20	153.0	8	O=C1N(N(CC2CCN(C)CC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-070	3.6	88.0	24	O=C1N(N(CC(C)C)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-071	1.4 (1.1 - 1.8)	60.0	58	O=C1N(N(CC2CCCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-072	1.03 (0.77 - 1.4)	>300	214	O=C1N(N(CC2COCCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	TE
			AVG-073	6.2	96.0	48	O=C1N(N(CC2OCCCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A

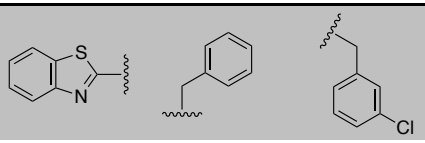
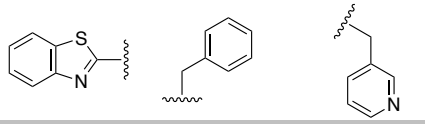
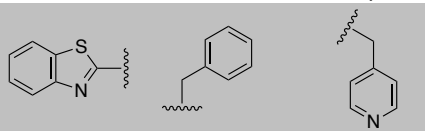
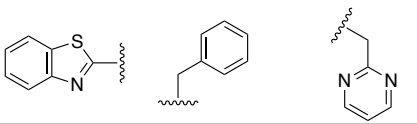
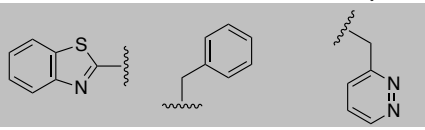
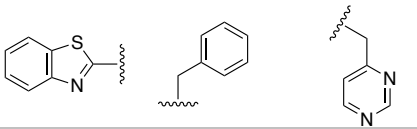
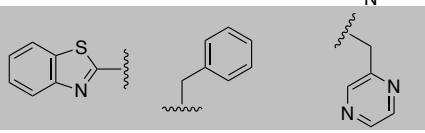
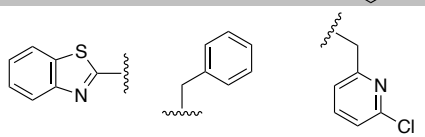
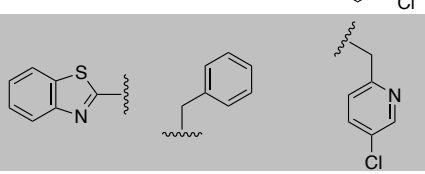
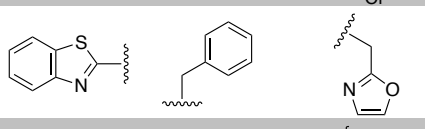
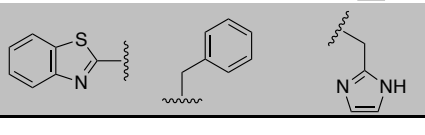
			AVG-119	4.2 (2.14 - 35.3)	>300	>71	O=C1N(N(CC2NCCCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-120	4.0 (2.14 - 35.3)	86.0	21.5	O=C1N(N(CC2CNCCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-121	7	~300	43	O=C1N(N(CC2CCNCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-122	2.5 (1.5 - 8.97)	>300	>120	O=C1N(N(CC2OCCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	TE
			AVG-123	~20	>300	>15	O=C1N(N(CC2COCC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-124	7	>300	43	O=C1N(N(CC2OCCN2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-125	>20	>300	N/A	O=C1N(N(CC2NCOC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	N/A
			AVG-126	6.04	>300	>47	O=C1N(N(CC2OCNC2)C=2C1=C(C)N(CC1OCCC1)C(=O)C=2)C1SC2C(N1)CCCC2	TE

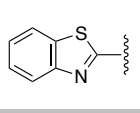
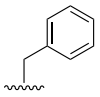
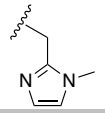
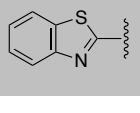
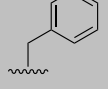
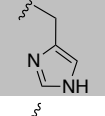
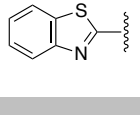
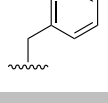
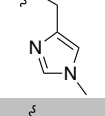
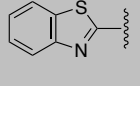
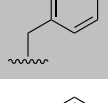
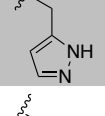
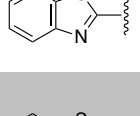
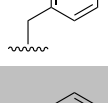
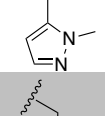
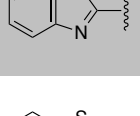
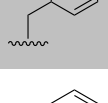
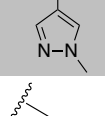
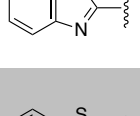
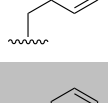
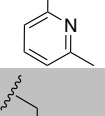
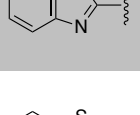
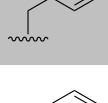
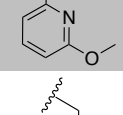
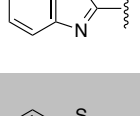
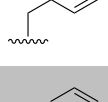
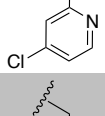
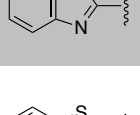
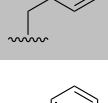
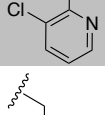
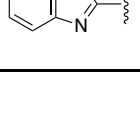
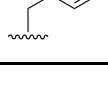
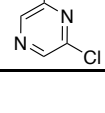
[1]TE: 3D-QSAR test set; TR: 3D-QSAR training set; N/A: not applicable

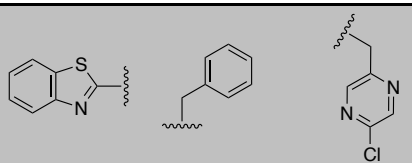
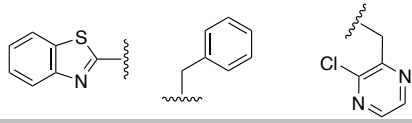
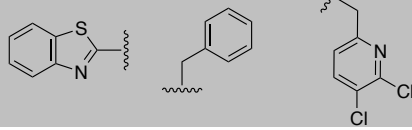
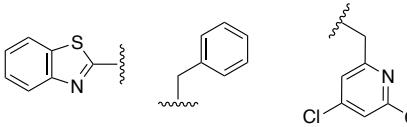
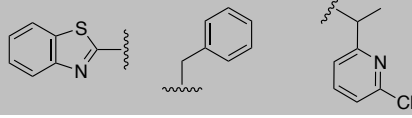
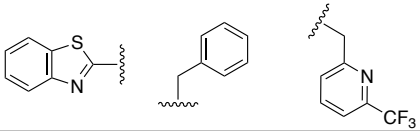
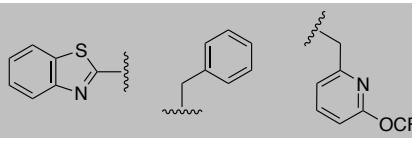
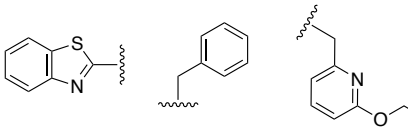
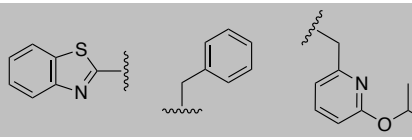
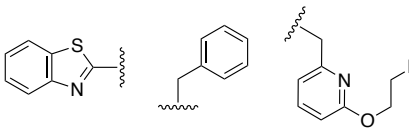
Table S3. Chemical elaboration of scaffolds section 3.

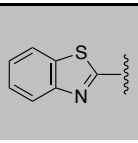
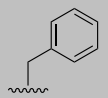
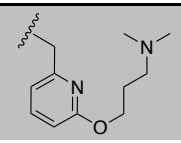
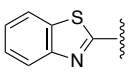
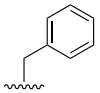
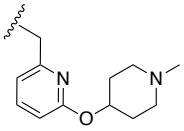
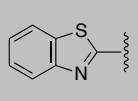
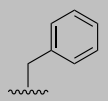
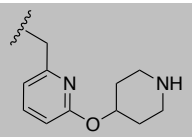
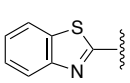
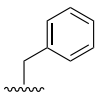
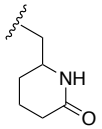
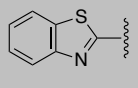
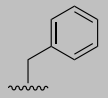
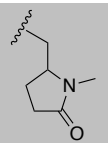
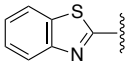
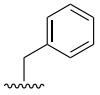
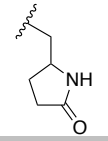
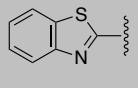
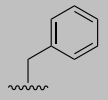
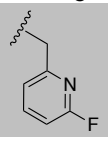
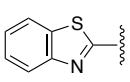
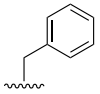
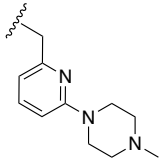
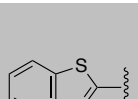
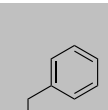
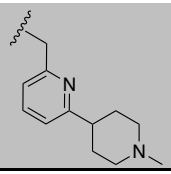


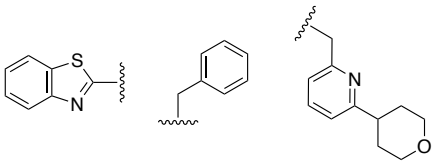
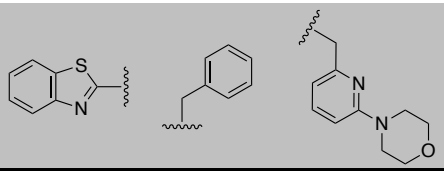
R^1	R^2	R^3	Name	EC_{50} [μM]	CC_{50} [μM]	SI	SMILES	3D-QSAR[1]
			AVG-028	3.97	58.0	15	CC(N1CCN2CCOCC2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-031	0.98 (0.51-4.3)*	288.0	294	CC(N1CC2=CC=C(Cl)C=C2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
			AVG-036	0.89 (069 - 1.17)	~300	337	CC(N1CC2=CC=CC=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
			AVG-038	>20	31.0	N/A	CC(N1CC2CCNCC2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-039	~20	14.2	1	CC(N1CC2CCN(C)CC2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-040	6.06	145.0	24	CC(N1CC2CCOCC2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-074	~20	>300	15	CC(N1CC2OCCC2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-075	2.6 (2.1 - 3.4)	65.0	25	CC(N1CC2COCC2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-076	~20	>300	15	CC(N1CC2=CC=CC=C2Cl)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A

			AVG-077	0.82 (0.68 - 1.05)	23.0	28	CC(N1CC2=CC=CC(Cl)=C2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-088	1.6 (1.2 - 2.1)	26.0	16	CC(N1CC2=CC=CN=C2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-089	1.6 (1.1 - 2.3)	37.0	23	CC(N1CC2=CC=NC=C2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-090	~20	33.0	1.7	CC(N1CC2=NC=CC=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-091	4.6 (3.0 - 36.7)	266.0	58	CC(N1CC2=CC=CN=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-092	2.3 (1.5 - 4.2)	98.0	43	CC(N1CC2=CC=NC=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-093	0.8 (0.6 - 1.1)	43.0	54	CC(N1CC2=CN=CC=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-094	0.11 (0.08 - 1.52)	>300	>2727	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TR
			AVG-095	1.6 (1.14 - 2.18)	68.0	42.5	CC(N1CC2=CC=C(Cl)C=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-096	6.9	13.3	1.9	CC(N1CC2=NC=CO2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-097	5.9	30.0	5.1	CC(N1CC2=NC=CN2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A

			AVG-098	5.7 (4.3 - 8.6)	40.0	7	CC(N1CC2=NC=CN2C)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-099	3.9 (2.8 - 5.7)	33.0	9	CC(N1CC2=CNC=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-100	>20	>300	N/A	CC(N1CC2=CN(C)C=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-101	1.7	102	60	CC(N1CC2=CC=NN2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-102	7.8	60.0	7.7	CC(N1CC2=CC=NN2C)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-103	3.47	>300	>87	CC(N1CC2=NN(C)C=C2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
			AVG-157	0.16 (0.09 - 0.26)	~300	1875	CC(N1CC2=CC=CC(C)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
			AVG-158	0.15 (0.001 - 0.34)	>300	>2000	CC(N1CC2=CC=CC(OC)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TR
			AVG-160	1.67 (0.99 - 3.15)	>300	>180	CC(N1CC2=CC(Cl)=CC=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
			AVG-161	6.1	>300	>49	CC(N1CC2=C(Cl)C=CC=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-162	~20	>300	>15	CC(N1CC2=CN=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A

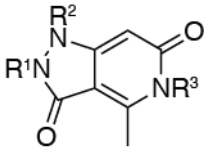
	AVG-163	1.9	>300	>158	CC(N1CC2=CN=C(Cl)C=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
	AVG-164	>20	>300	NA	CC(N1CC2=C(Cl)N=CC=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
	AVG-168	0.21	~300	1429	CC(N1CC2=CC=C(Cl)C(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
	AVG-169	0.72 (0.6 - 0.89)	124	172	CC(N1CC2=CC(Cl)=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
	AVG-170	2.75	>300	>109	CC(N1C(C)C2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
	AVG-201	0.21 (0.16 - 0.26)	>300	>1429	CC(N1CC2=CC=CC(C(F)(F)F)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
	AVG-202	0.12 (0.08 - 0.17)	53	442	CC(N1CC2=CC=CC(OC(F)(F)F)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
	AVG-204	0.29 (0.25 - 0.35)	94	324	CC(N1CC2=CC=CC(OCC)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
	AVG-205	0.87 (0.54 - 1.36)	>300	>345	CC(N1CC2=CC=CC(OC(C)C)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
	AVG-206	4.54	6.5	1.4	CC(N1CC2=CC=CC(OCCN(C)C)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A

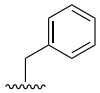
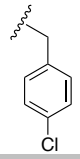
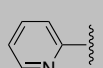
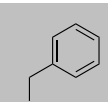
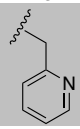
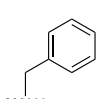
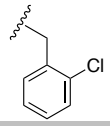
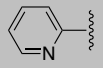
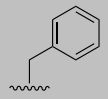
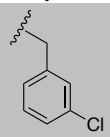
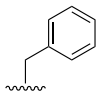
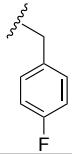
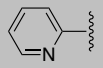
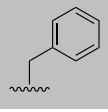
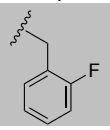
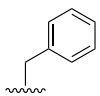
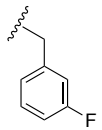
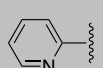
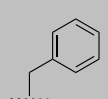
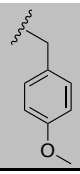
			AVG-207	2.1 (1.7 - 2.58)	4.5	2.1	CC(N1CC2=CC=CC(OCCCN(C)C)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-208	1.57 (0.396 - 2.72)	4.2	2.7	CC(N1CC2=CC=CC(OC3CCN(C)CC3)=N2)=C4C(N(CC5=CC=CC=C5)N(C6=NC7=C(C=CC=C7)S6)C4=O)=CC1=O	N/A
			AVG-209	~10	9.9	1.0	CC(N1CC2=CC=CC(OC3CCNCC3)=N2)=C4C(N(CC5=CC=CC=C5)N(C6=NC7=C(C=CC=C7)S6)C4=O)=CC1=O	N/A
			AVG-210	>10	12	N/A	CC(N1CC2CCCC(N2)=O)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-212	14.4	79	5.5	CC(N1CC2CCC(N2C)=O)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-213	7.3	43	5.9	CC(N1CC2CCC(N2)=O)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-214	0.43 (0.3 - 0.6)	~300	698	CC(N1CC2=CC=CC(F)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	N/A
			AVG-225	0.98 (0.72 - 1.36)	43	44	CC(N1CC2=CC=CC(N3CCN(C)CC3)=N2)=C4C(N(CC5=CC=CC=C5)N(C6=NC7=C(C=CC=C7)S6)C4=O)=CC1=O	N/A
			AVG-226	2.04 (1.8 - 2.24)	4.5	2.2	CC(N1CC2=CC=CC(C3CCN(C)CC3)=N2)=C4C(N(CC5=CC=CC=C5)N(C6=NC7=C(C=CC=C7)S6)C4=O)=CC1=O	N/A

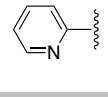
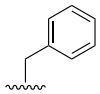
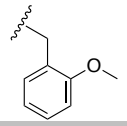
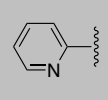
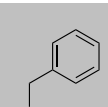
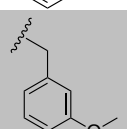
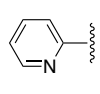
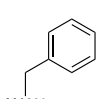
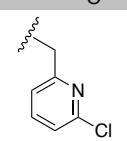
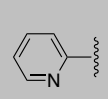
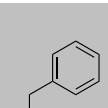
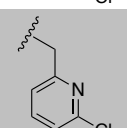
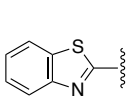
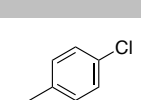
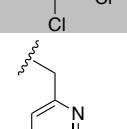
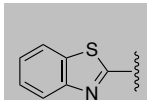
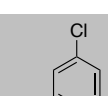
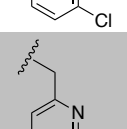
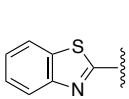
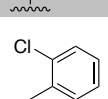
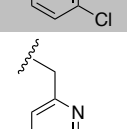
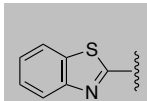
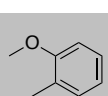
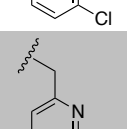
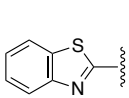
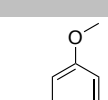
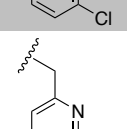
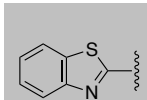
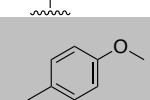
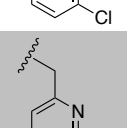
	AVG-227	0.26 (0.22 - 0.35)	145	558	CC(N1CC2=CC=CC(C3CCOCC3)=N2)=C4C(N(CC5=CC=CC=C5)N(C6=NC7=C(C=CC=C7)S6)C4=O)=CC1=O	N/A
	AVG-228	0.28 (0.22 - 0.34)	>300	>1071	CC(N1CC2=CC=CC(N3CCOCC3)=N2)=C4C(N(CC5=CC=CC=C5)N(C6=NC7=C(C=CC=C7)S6)C4=O)=CC1=O	N/A

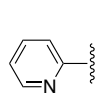
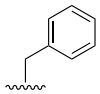
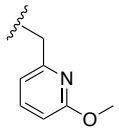
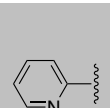
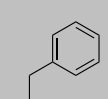
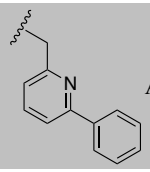
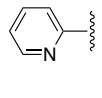
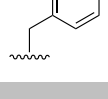
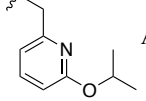
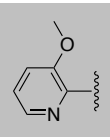
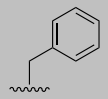
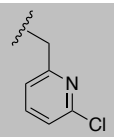
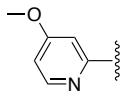
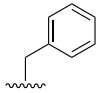
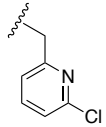
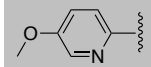
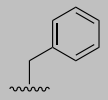
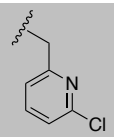
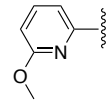
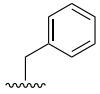
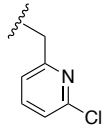
[1]TE: 3D-QSAR test set; TR: 3D-QSAR training set; N/A: not applicable

Table S4. Combinatorial modification of different scaffolds sections.



R^1	R^2	R^3	Name	EC_{50} [μM]	CC_{50} [μM]	SI	SMILES	3D-QSAR[1]
			AVG-078	0.61 (0.54 - 0.68)	67.0	110	CC(N1CC2=CC=C(Cl)C=C2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	N/A
			AVG-104	4.1	27.0	7	CC(N1CC2=CC=CC=N2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	N/A
			AVG-127	0.99	>300	>303	CC(N1CC2=CC=CC=C2Cl)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TE
			AVG-128	0.26 (0.17 - 0.42)	>300	>1154	CC(N1CC2=CC=CC(Cl)=C2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TE
			AVG-129	0.79 (0.63 - 1.02)	>300	>380	CC(N1CC2=CC=C(F)C=C2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TE
			AVG-130	0.87 (0.58 - 1.36)	>300	>345	CC(N1CC2=CC=CC=C2F)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TE
			AVG-131	0.18 (0.14 - 0.22)	~300	1667	CC(N1CC2=CC=CC(F)=C2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TE
			AVG-132	2.20	>300	>136	CC(N1CC2=CC=C(OC)C=C2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TR

			AVG-133	0.72 (0.55 - 0.97)	100	139	CC(N1CC2=CC=CC=C2OC)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TR
			AVG-134	0.6	>300	>500	CC(N1CC2=CC=CC(OC)=C2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TR
			AVG-171	0.08 (0.06 - 0.11)	~300	3750	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TE
			AVG-172	0.12	~300	2500	CC(N1CC2=CC=C(Cl)C(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TE
			AVG-173	0.29 (0.23 - 0.4)	>300	>1035	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=C(Cl)C=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
			AVG-174	2.0	>300	>150	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC(Cl)=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
			AVG-175	1.4	>300	>214	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4Cl)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TE
			AVG-176	0.14 (0.12 - 0.17)	~300	2143	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4OC)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TR
			AVG-177	0.78 (0.3 - 7.6)	>300	>385	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC(OC)=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TR
			AVG-178	0.08 (0.06 - 0.1)	~300	3750	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=C(OC)C=C4)N(C5=NC6=C(C=CC=C6)S5)C3=O)=CC1=O	TR

			AVG-203	0.047 (0.03 - 0.06)	>300	>6383	CC(N1CC2=CC=CC(OC)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	TR
			AVG-229	0.31	~300	968	CC(N1CC2=CC=CC(C3=CC=CC=C3)=N2)=C4C(N(CC5=CC=CC=C5)N(C6=CC=CC=N6)C4=O)=CC1=O	N/A
			AVG-230	0.54 (0.47 - 0.61)	>300	>556	CC(N1CC2=CC=CC(OC(C)C)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC=N5)C3=O)=CC1=O	N/A
			AVG-240	1.23 (0.98 - 1.57)	>300	>244	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=C(OC)C=CC=N5)C3=O)=CC1=O	N/A
			AVG-241	0.039 (0.032 - 0.047)	121	3103	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=CC(OC)=CC=N5)C3=O)=CC1=O	TR
			AVG-242	0.15 (0.12 - 0.18)	~300	2000	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=C(OC)C=N5)C3=O)=CC1=O	TR
			AVG-243	0.96 (0.77 - 1.19)	~300	313	CC(N1CC2=CC=CC(Cl)=N2)=C3C(N(CC4=CC=CC=C4)N(C5=CC=CC(OC)=N5)C3=O)=CC1=O	TR

[1]TE: 3D-QSAR test set; TR: 3D-QSAR training set; N/A: not applicable

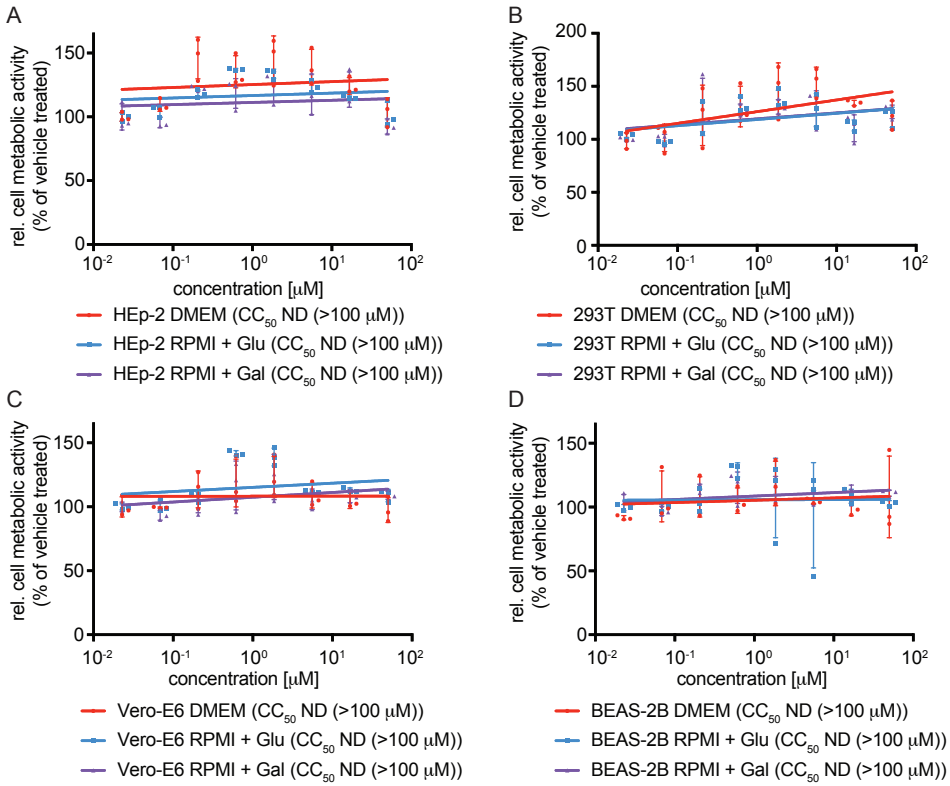


Figure S1. Cytotoxicity testing of established cell lines against AVG-233. Assays were performed after incubation of cells in high-glucose DMEM (red) or RPMI containing 11 mM glucose (blue),or 10 mM galactose, respectively. Cells were exposed to AVG-233 in the respective media for 48 hours. Under all conditions tested, AVG-233 lacked appreciable cytotoxicity on HEp-2 (A), 293T (B), Vero-E6 (C), and BEAS-2B (D) cell lines. Symbols in (A) to (D) represent individual biological repeats (N = 3 each), error bars show SD.