Electronic Supplementary Information

Theoretical models of inhibitory activity for inhibitors of protein-protein interactions: targeting menin-Mixed Lineage Leukemia with small molecules

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Characterization of menin-MLL inhibitors

Compounds **1**, **2**, **3**, **4**, **5**, **6**, and **7** were obtained from synthesis on demand from the contract research organization. All compounds were provided with the certificate of analysis and in addition were fully characterized in house by HR MS and NMR.

6-(2-chloroethyl)-4-(4-(5,5-dimethyl-4,5-dihydrothiazol-2-yl)piperazin-1-yl)thieno-[2,3-d]pyrimidine (1): ^{1}H NMR (600 MHz, METHANOL-d$_4$) δppm 8.40 (s, 1H), 7.44 (s, 1H), 4.20 (m, 4H), 3.83 - 3.98 (m, 8H), 3.39 (t, J = 6.42 Hz, 2H), 1.69 (s, 6H); ^{13}C NMR (151 MHz, DMSO-d6)δppm 170.5, 166.2, 156.2, 150.2, 136.7, 117.9, 115.6, 59.9, 56.4, 48.9, 44.1, 42.4, 32.2, 25.0; HR-MS calc. for [M+H$^+$] C$_{17}$H$_{22}$ClN$_5$S$_2$: 396.1083, found: 396.1079.

6-propyl-4-(4-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)piperazin-1-yl)thieno[2,3-d]pyrimidine (2): ^{1}H NMR (600 MHz, CDCl$_3$) δppm 1.02 (t, J = 7.3 Hz, 3H), 1.77 (q, J = 8.07 Hz, 2H), 2.89 (t, J = 7.5 Hz, 2H), 3.78 - 3.85 (m, 4H), 4.01 - 4.10 (m, 4H), 6.98 (s, 1H), 8.51 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δppm 13.6, 15.3, 24.4, 33.1, 46.1, 49.4, 65.9, 116.0, 117.7, 120.3, 143.8, 146.7, 151.8, 157.8, 168.3, 173.7; LR-MS [M+H$^+$] calc. for C$_{16}$H$_{18}$F$_3$N$_6$S$_2$: 415.09, found: 415.1.

6-ethyl-4-(4-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)piperazin-1-yl)thieno[2,3-d]pyrimidine (3): ^{1}H NMR (600 MHz, DMSO-d$_6$) δppm 1.32 (t, J = 7.3 Hz, 3H), 2.94 (q, J = 7.3 Hz, 2H), 3.75 - 3.89 (m, 4H), 4.05 - 4.14 (m, 4H) 7.40 (m, 1H) 8.45 (s, 1H). LR-MS [M+H$^+$] calc. for C$_{15}$H$_{16}$F$_3$N$_6$S$_2$: 401.08, found: 401.0.

2-(4-(6-(2,2,2-trifluoroethyl)thieno[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-5-(trifluoromethyl)-1,3,4-oxadiazole (4): ^{1}H NMR (600 MHz, CDCl$_3$) δppm 3.69 (q, J = 9.9 Hz, 2H), 3.78 - 3.86 (m, 4H), 4.06 - 4.14 (m, 4H), 7.26 (m, 1H), 8.58 (m, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δppm 35.7, 45.5, 46.0, 117.1, 121.2, 128.8, 128.8, 152.4, 158.3, 164. 4, 168.2; LR-MS [M+H$^+$] calc. for C$_{15}$H$_{15}$F$_6$N$_6$OS: 439.07, found: 439.1.

6-cyclopropyl-4-(4-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)piperazin-1-yl) thieno[2,3-d]pyrimidine (5): ^{1}H NMR (600 MHz, DMSO-d$_6$) δppm 0.81 - 0.88 (m, 2H),

1.07 - 1.12 (m, 2H), 1.17 (t, J = 7.3 Hz, 1H), 3.77 - 3.83 (m, 4H), 4.02 - 4.07 (m, 4H), 7.25 - 7.38 (m, 1H), 8.32 - 8.44 (m, 1H); LR-MS [M+H$^+$] calc. for $C_{16}H_{18}F_3N_6S_2$: 413, found: 413.

6-(methylthio)-4-(4-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl)piperazin-1-yl)thieno[2,3-d]pyrimidine (6): ^{1}H NMR (600 MHz, DMSO-d$_6$) δppm 2.64 (s, 3H), 3.80 - 3.85 (m, 4H), 4.06 - 4.20 (m, 4H), 7.55 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d$_6$) δppm 19.1, 45.0, 48.8, 116.7, 121.3, 132.9, 134.4, 152.2, 156.5, 158.5, 168.8, 173.9; LR-MS [M+H$^+$] calc. for $C_{14}H_{14}F_3N_6S_3$: 419.03, found: 419.0.

6-propyl-4-(4-(5-(trifluoromethyl)-4H-1,2,4-triazol-3-yl)piperazin-1-yl)thieno[2,3-d]pyrimidine (7): ^{1}H NMR (600 MHz, DMSO-d$_6$) δppm 0.96 (t, J = 7.3 Hz, 3H), 1.06 (q, J = 7.0 Hz, 2H), 1.71 (q, J = 7.3 Hz, 2H), 3.95 - 3.99 (m, 4H), 4.26 - 4.41 (m, 4H), 7.30 - 7.42 (m, 1H), 8.36 - 8.44 (m, 1H); LR-MS [M+H$^+$] calc. for $C_{16}H_{18}F_3N_7S$: 398.13, found: 398.1.

Table S1: Amino acid residues and their closest distances[a] from inhibitor **MI-2-2**.

Residue	Residue type	Distance from inhibitor **MI-2-2**
Glu179		4.0
Asp285	Negatively charged	4.9
Glu363		3.9
Asp180–His199	Neutral dimer	3.5
Ser178	Polar and neutral	3.4
Asn282		3.1
His181		3.5
Ala182		3.5
Phe238		3.6
Cys241	Nonpolar and neutral	3.8
Tyr276		2.8
Met278		3.5
Tyr319		3.4
Tyr323		3.3

[a]The shortest distance between heavy atoms, in units of Å.

Table S2: Interaction energy values in $\text{kcal} \cdot \text{mol}^{-1}$ at the consecutive levels of theory for each amino acid residue-inhibitor pair.

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
	Tyr276	-11.4	-15.5	1.7	-3.8	-7.0	-18.9
	Asn282	-5.7	-8.1	0.6	-1.9	-4.9	-11.6
	Met278	-1.5	-6.3	5.2	3.9	-4.2	-14.7
	Glu179	-4.4	-4.8	-4.1	-5.4	-6.3	-7.1
	Tyr323	-0.3	-3.1	4.5	3.6	-2.9	-11.0
	Tyr319	1.3	-2.7	7.3	6.2	-1.0	-11.1
	Ser178	-1.6	-2.2	-0.6	-1.2	-2.4	-3.9
MI-2-2	Glu363	-1.8	-1.9	-1.6	-3.5	-4.0	-2.5
	His181	-0.7	-1.8	2.6	2.0	0.0	-7.1
	Phe238	-0.8	-1.5	0.7	0.3	-1.8	-4.7
	Asp285	1.4	1.4	1.4	0.2	-0.2	1.2
	Cys241	-0.4	-1.0	1.2	0.8	-1.0	-3.3
	Ala182	-0.2	-0.5	0.7	0.5	-0.3	-2.3
	D180–H199	0.0	-0.3	0.8	0.4	-1.5	-3.2
	Tyr276	-10.5	-14.5	2.6	-2.7	-6.1	-17.9
	Asn282	-4.9	-6.7	-0.2	-2.2	-5.1	-10.9
	Met278	-1.5	-6.8	5.5	4.1	-4.2	-14.7
	Glu179	-3.3	-3.5	-3.0	-4.2	-5.2	-5.9
MI-859	Tyr323	-1.1	-3.3	3.8	2.8	-3.4	-11.8
	Tyr319	1.5	-4.8	10.2	8.6	0.0	-11.0
	Ser178	-1.5	-2.2	-0.3	-0.9	-2.2	-3.8
	Glu363	-1.9	-1.9	-1.9	-3.0	-3.5	-2.6
	His181	-1.1	-2.5	1.9	1.3	-0.7	-6.8

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
MI-859	Phe238	-0.7	-1.4	1.2	0.8	-1.5	-4.5
	Asp285	1.0	1.0	1.0	-0.2	-0.6	0.8
	Cys241	-0.5	-1.0	0.9	0.6	-1.1	-3.4
	Ala182	0.5	0.0	1.3	1.1	0.2	-1.5
	D180–H199	-1.0	-1.2	-0.2	-0.6	-2.1	-4.2
MI-319	Tyr276	-11.5	-15.2	1.4	-3.9	-7.0	-18.6
	Asn282	-5.2	-7.4	0.7	-1.6	-4.6	-11.8
	Met278	-1.9	-6.9	4.5	3.0	-4.8	-14.5
	Glu179	-5.9	-6.2	-5.6	-6.8	-7.8	-8.6
	Tyr323	-1.5	-4.8	3.7	2.7	-3.8	-13.8
	Tyr319	0.6	-2.4	5.8	4.7	-2.1	-9.5
	Ser178	-1.8	-2.4	-0.7	-1.3	-2.3	-4.0
	Glu363	2.0	2.0	2.0	1.3	0.9	1.7
	His181	-1.8	-3.0	1.1	0.6	-1.2	-7.4
	Phe238	-0.8	-1.5	1.1	0.8	-1.5	-4.7
	Asp285	3.7	3.7	3.7	2.5	2.3	3.5
	Cys241	-0.9	-1.4	0.9	0.5	-1.2	-4.0
	Ala182	0.2	-0.1	0.8	0.7	-0.1	-1.6
	D180–H199	-0.8	-1.2	-0.1	-0.5	-2.4	-4.2
MI-2-3	Tyr276	-11.4	-15.1	1.5	-3.8	-6.9	-18.6
	Asn282	-5.2	-7.4	0.7	-1.6	-4.6	-11.8
	Met278	-1.9	-6.9	4.5	3.0	-4.9	-14.5
	Glu179	-6.9	-7.2	-6.6	-7.8	-8.6	-9.6
	Tyr323	-2.3	-5.5	3.6	2.5	-4.1	-15.5
	Tyr319	0.5	-2.5	5.7	4.6	-2.2	-9.7

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
MI-2-3	Ser178	-1.8	-2.5	-0.7	-1.4	-2.3	-4.0
	Glu363	1.8	1.8	1.8	1.2	0.7	1.5
	His181	-1.8	-3.0	1.1	0.5	-1.3	-7.5
	Phe238	-0.8	-1.5	1.1	0.8	-1.5	-4.7
	Asp285	5.4	5.4	5.4	4.7	3.7	5.2
	Ala182	0.2	-0.1	0.8	0.7	-0.1	-4.0
	Cys241	-0.9	-1.4	0.9	0.5	-1.1	-1.6
	D180–H199	-1.0	-1.4	-0.3	-0.7	-2.5	-4.4
MI-836	Tyr276	-10.7	-14.8	2.5	-2.9	-6.3	-18.1
	Asn282	-5.1	-6.9	-0.3	-2.4	-5.3	-11.1
	Met278	-1.5	-6.8	5.5	4.0	-4.2	-14.7
	Glu179	-2.6	-2.9	-2.3	-3.6	-4.7	-5.2
	Tyr323	-1.0	-3.2	3.9	2.9	-3.3	-11.7
	Tyr319	1.4	-4.8	10.1	8.6	0.0	-11.0
	Ser178	-1.0	-1.7	0.2	-0.4	-1.9	-3.3
	Glu363	-1.7	-1.7	-1.7	-2.8	-3.3	-2.4
	His181	-2.1	-3.1	-0.4	-0.9	-2.8	-6.2
	Phe238	-0.7	-1.4	1.1	0.7	-1.6	-4.4
	Asp285	1.5	1.5	1.5	0.3	-0.2	1.3
	Ala182	-0.6	-1.1	0.8	0.5	-1.2	-3.5
	Cys241	-1.2	-1.6	-0.4	-0.6	-1.3	-2.9
	D180–H199	-0.7	-1.0	-0.1	-0.4	-1.9	-3.5
MI-2	Tyr276	-13.1	-17.4	1.3	-4.9	-7.8	-20.5
	Asn282	-4.5	-7.2	0.8	-1.5	-4.7	-10.4
	Met278	-1.6	-6.6	4.8	3.5	-4.6	-14.9

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
MI-2	Glu179	-2.9	-3.3	-2.5	-3.8	-5.0	-5.7
	Tyr323	-0.2	-2.6	3.9	3.1	-3.1	-10.4
	Tyr319	1.2	-2.7	7.0	6.0	-1.2	-11.3
	Ser178	-0.5	-1.3	1.2	0.5	-1.0	-3.0
	Glu363	1.7	-1.8	-1.5	-3.5	-4.0	-2.4
	His181	-0.2	-1.2	1.7	1.3	-0.7	-4.6
	Phe238	-0.5	-1.3	1.3	0.9	-1.5	-4.2
	Asp285	2.0	2.1	2.1	0.8	0.2	1.8
	Ala182	-0.1	-0.1	-0.1	-0.1	-0.4	-3.9
	Cys241	-0.8	-1.4	1.1	0.7	-1.1	-1.1
	D180–H199	-0.8	-1.1	0.1	-0.2	-1.9	-4.0
MI-273	Tyr276	-10.4	-14.4	3.0	-2.3	-5.7	-17.9
	Asn282	-4.6	-6.5	0.1	-1.9	-4.8	-10.6
	Met278	-1.8	-6.9	5.3	3.8	-4.3	-15.0
	Glu179	-2.7	-3.2	-2.1	-3.4	-4.3	-5.9
	Tyr323	-1.2	-3.4	3.7	2.7	-3.5	-11.9
	Tyr319	1.3	-4.9	10.0	8.4	-0.2	-11.2
	Ser178	0.7	-0.9	3.4	2.8	0.6	-2.6
	Glu363	-1.9	-1.9	-1.9	-3.1	-3.5	-2.6
	His181	0.8	-2.3	6.6	5.9	3.0	-7.1
	Phe238	-0.6	-1.4	1.4	1.1	-1.3	-4.7
	Asp285	0.4	0.4	0.4	-0.9	-1.2	0.2
	Ala182	-0.4	-0.9	1.0	0.7	-1.0	-3.3
	Cys241	0.3	-0.2	1.2	1.0	0.0	-2.0
	D180–H199	-1.9	-2.8	0.0	-0.5	-1.9	-7.0

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
	Tyr276	-11.8	-15.9	1.4	-4.2	-7.4	-19.2
	Asn282	-5.8	-8.2	0.5	-2.0	-5.1	-11.8
	Met278	-1.5	-6.3	5.2	3.8	-4.3	-14.7
	Glu179	-2.3	-2.7	-2.0	-3.3	-4.6	-5.3
	Tyr323	-0.3	-3.1	4.5	3.6	-2.9	-10.9
	Tyr319	1.1	-2.9	7.0	6.0	-1.2	-11.3
MI-20	Ser178	-0.4	-1.1	0.7	0.2	-1.4	-2.7
	Glu363	-1.2	-1.3	-1.0	-2.9	-3.6	-1.8
	His181	-0.2	-1.4	2.3	1.8	-0.7	-5.2
	Phe238	-0.4	-1.1	0.8	0.6	-1.7	-3.8
	Asp285	1.9	1.9	1.9	0.6	0.1	1.7
	Ala182	0.1	0.0	0.6	0.5	-0.3	-3.3
	Cys241	-0.4	-1.0	1.1	0.8	-1.0	-1.1
	D180–H199	-0.6	-1.0	0.4	-0.0	-2.2	-4.7
	Tyr276	-3.5	-5.8	1.8	-0.2	-3.5	-9.4
	Asn282	-3.9	-4.9	-1.2	-2.5	-4.7	-8.5
	Met278	-2.5	-9.5	8.6	6.4	-3.0	-18.3
	Glu179	-2.9	-3.5	-2.5	-4.0	-5.2	-5.9
	Tyr323	-1.1	-3.3	3.8	2.8	-3.3	-11.8
MI-2-4	Tyr319	1.3	-4.9	10.0	8.4	-0.2	-11.2
	Ser178	-0.1	-0.6	0.8	0.2	-1.2	-2.0
	Glu363	-2.3	-2.3	-2.3	-3.5	-3.8	-3.0
	His181	-2.7	-5.8	3.2	2.0	-1.1	-11.6
	Phe238	-0.7	-0.9	0.1	-0.1	-1.8	-3.6
	Asp285	0.5	0.5	0.5	-0.7	-1.1	0.3

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
MI-2-4	Ala182	-0.5	-0.6	-0.4	-0.4	-1.3	-1.8
	Cys241	-0.1	-1.7	3.8	3.2	1.8	-4.0
	D180–H199	-1.4	-4.9	7.1	5.4	1.5	-9.9
MI-326	Tyr276	-11.5	-15.2	1.4	-4.0	-7.1	-18.7
	Asn282	-4.7	-7.0	1.2	-1.2	-4.3	-11.3
	Met278	-1.7	-6.7	4.7	3.2	-4.7	-14.3
	Glu179	-6.6	-6.9	-6.3	-7.5	-8.2	-9.3
	Tyr323	-1.2	-4.0	3.3	2.2	-4.1	-12.0
	Tyr319	0.4	-2.7	5.4	4.4	-1.9	-8.6
	Ser178	-1.6	-2.3	-0.5	-1.2	-2.2	-3.8
	Glu363	-1.4	-1.4	-1.4	-2.1	-2.2	-1.6
	His181	-1.7	-3.0	1.2	0.6	-1.2	-7.4
	Phe238	-0.8	-1.5	1.2	0.8	-1.5	-4.6
	Asp285	6.1	6.1	6.1	4.9	4.2	5.9
	Ala182	0.3	-0.1	0.8	0.7	-0.1	-4.0
	Cys241	-0.8	-1.4	1.0	0.6	-1.1	-1.6
	D180–H199	-0.9	-1.3	-0.2	-0.6	-2.4	-4.3
MI-19	Tyr276	-11.8	-15.5	1.2	-4.3	-7.3	-19.2
	Asn282	-5.3	-7.6	0.6	-1.8	-4.7	-11.8
	Met278	-1.9	-6.9	4.5	3.0	-4.9	-14.6
	Glu179	-5.1	-5.5	-4.8	-6.0	-7.0	-5.1
	Tyr323	-2.2	-5.4	3.7	2.6	-4.0	-11.0
	Tyr319	0.3	-2.7	5.5	4.4	-2.3	-11.3
	Ser178	-0.5	-1.3	0.7	0.1	-1.3	-2.8
	Glu363	2.4	2.4	2.4	1.7	1.1	-1.9

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
MI-19	His181	-1.1	-2.1	0.2	-0.2	-1.8	-4.7
	Phe238	-0.6	-1.2	1.1	0.8	-1.4	-3.6
	Asp285	6.1	6.1	6.1	5.0	4.3	1.6
	Ala182	-0.3	-0.4	-0.1	-0.2	-0.7	-3.3
	Cys241	-0.9	-1.4	0.9	0.6	-1.1	-1.0
	D180–H199	-1.5	-1.8	-0.7	-1.1	-2.5	-3.6
MI-333	Tyr276	-11.5	-15.2	1.4	-4.0	-7.1	-18.6
	Asn282	-5.1	-7.4	0.7	-1.6	-4.6	-11.7
	Met278	-1.8	-6.8	4.6	3.1	-4.8	-14.4
	Glu179	-6.0	-6.3	-5.6	-6.9	-7.7	-8.7
	Tyr323	-1.7	-4.8	3.1	1.9	-4.7	-13.1
	Tyr319	0.1	-3.1	5.4	4.3	-2.1	-9.5
	Ser178	-1.7	-2.4	-0.6	-1.2	-2.3	-3.9
	Glu363	1.1	1.1	1.1	0.5	0.2	0.8
	His181	-1.7	-3.0	1.2	0.6	-1.2	-7.4
	Phe238	-0.8	-1.5	1.2	0.8	-1.5	-4.7
	Asp285	3.8	3.8	3.8	2.7	2.4	3.6
	Ala182	-0.9	-1.4	0.9	0.5	-1.2	-4.1
	Cys241	0.3	-0.1	0.8	0.7	-0.1	-1.5
	D180–H199	-0.8	-1.2	-0.1	-0.5	-2.3	-4.2
MI-12	Tyr276	-11.0	-15.1	2.2	-3.2	-6.7	-18.4
	Asn282	-6.4	-8.4	-1.7	-3.9	-6.5	-12.3
	Met278	-1.5	-6.8	5.5	4.1	-3.9	-14.5
	Glu179	-3.1	-3.5	-2.9	-4.0	-5.2	-5.6
	Tyr323	-0.1	-1.8	2.4	1.8	-1.2	-5.2

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
	Tyr319	0.0	-1.4	2.9	2.4	-0.8	-4.9
	Ser178	-0.5	-1.2	0.8	0.1	-1.4	-2.7
	Glu363	0.7	0.7	0.7	0.0	-0.5	0.5
	His181	-0.8	-1.9	0.7	0.3	-1.5	-4.6
MI-12	Phe238	-0.4	-1.1	1.3	0.9	-1.3	-3.7
	Asp285	-1.0	-1.0	-1.0	-1.9	-1.8	-1.2
	Ala182	-0.6	-1.2	0.8	0.5	-1.2	-3.5
	Cys241	-0.4	-0.5	-0.1	-0.2	-0.8	-1.5
	D180–H199	-0.7	-0.9	0.0	-0.3	-1.7	-3.4
	Tyr276	-10.9	-14.9	2.4	-3.1	-6.5	-18.3
	Asn282	-5.0	-6.8	-0.1	-2.3	-5.1	-10.9
	Met278	-1.5	-6.8	5.5	4.0	-4.2	-14.6
	Glu179	-2.6	-2.9	-2.4	-3.5	-4.9	-5.1
	Tyr323	1.4	-1.1	2.9	2.3	-1.8	-5.1
	Tyr319	0.8	-4.3	9.0	7.5	0.3	-9.0
	Ser178	-0.7	-1.4	0.6	-0.1	-1.6	-2.9
MI-16	Glu363	-0.2	-0.2	-0.2	-0.9	-1.2	-0.4
	His181	-0.9	-1.9	0.6	0.2	-1.6	-4.7
	Phe238	-0.4	-1.1	1.3	0.9	-1.3	-3.7
	Asp285	2.1	2.2	2.2	1.1	1.1	1.9
	Ala182	-0.5	-1.0	0.9	0.6	-1.1	-3.4
	Cys241	-0.4	-0.5	-0.1	-0.2	-0.8	-1.5
	D180–H199	-0.6	-0.9	0.0	-0.3	-1.7	-3.3
MI-4	Tyr276	-11.1	-15.1	2.2	-3.3	-6.7	-18.5
	Asn282	-6.2	-8.2	-1.5	-3.8	-6.4	-12.1

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
MI-4	Met278	-1.3	-6.7	5.6	4.2	-3.8	-14.3
	Glu179	-2.2	-2.5	-1.9	-3.0	-4.3	-4.7
	Tyr323	0.1	-1.6	2.6	2.0	-1.0	-5.0
	Tyr319	0.1	-1.3	3.0	2.5	-0.7	-4.8
	Ser178	-0.4	-1.1	0.8	0.2	-1.4	-2.6
	Glu363	0.4	0.4	0.4	-0.3	-0.7	0.2
	His181	-0.8	-1.8	0.7	0.3	-1.5	-4.6
	Phe238	-0.4	-1.1	1.3	0.9	-1.3	-3.7
	Asp285	-0.1	-0.1	-0.1	-1.0	-1.0	-0.3
	Ala182	-0.6	-1.2	0.8	0.5	-1.2	-3.5
	Cys241	-0.4	-0.5	-0.1	-0.2	-0.8	-1.5
	D180–H199	-0.5	-0.8	0.2	-0.1	-1.6	-3.2
MI-10	Tyr276	-11.8	-15.8	1.4	-4.2	-7.3	-19.2
	Asn282	-5.8	-8.2	0.4	-2.0	-5.1	-11.8
	Met278	-1.4	-6.2	5.3	3.9	-4.2	-14.6
	Glu179	-4.2	-4.5	-3.8	-5.0	-6.4	-6.8
	Tyr323	1.1	-1.1	4.2	3.6	-1.7	-6.8
	Tyr319	0.0	-3.5	7.2	5.9	-1.1	-13.2
	Ser178	-0.4	-1.1	0.8	0.2	-1.3	-2.6
	Glu363	0.6	0.6	0.6	-0.1	-0.4	0.4
	His181	-0.2	-1.3	2.1	1.7	-0.4	-4.8
	Phe238	-0.4	-1.1	0.9	0.6	-1.5	-3.6
	Asp285	2.5	2.5	2.5	1.5	1.5	2.4
	Ala182	0.2	0.0	0.6	0.5	-0.2	-3.3
	Cys241	-0.4	-1.0	1.2	0.8	-0.9	-1.0

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
MI-10	D180–H199	-0.8	-1.1	0.0	-0.3	-1.9	-3.7
MI-11	Tyr276	-11.9	16.0	1.3	-4.3	-7.5	-19.3
	Asn282	-6.2	-8.6	0.1	-2.4	-5.4	-12.1
	Met278	-1.3	-6.1	5.3	4.0	-4.1	-14.4
	Glu179	-2.0	-2.3	-1.6	-2.7	-4.2	-4.5
	Tyr323	1.0	-0.9	3.9	3.4	-1.6	-6.6
	Tyr319	1.3	-1.7	6.4	5.3	-0.5	-9.9
	Ser178	-0.3	-1.0	0.9	0.3	-1.3	-2.5
	Glu363	-0.7	-0.7	-0.7	-1.4	-1.5	-0.8
	His181	-0.2	-1.2	2.2	1.7	-0.3	-4.7
	Phe238	-0.4	-1.1	0.8	0.5	-1.5	-3.6
	Asp285	0.5	0.5	0.5	-0.5	-0.3	0.3
	Ala182	0.1	0.0	0.6	0.5	-0.2	-3.3
	Cys241	-0.4	-1.1	1.1	0.8	-1.0	-1.0
	D180–H199	-0.5	-0.8	0.3	0.0	-1.6	-3.4
MI-6	Tyr276	-10.8	-14.8	2.5	-2.9	-6.3	-18.2
	Asn282	-4.8	-6.7	0.0	-2.1	-5.0	-10.7
	Met278	-1.6	-6.8	5.4	3.9	-4.3	-14.7
	Glu179	-4.7	-5.0	-4.4	-5.6	-6.7	-7.2
	Tyr323	0.3	-1.9	2.0	1.4	-2.6	-6.1
	Tyr319	0.3	-4.3	8.0	6.5	-0.3	-9.3
	Ser178	-0.8	-1.5	0.5	-0.2	-1.7	-3.0
	Glu363	-0.2	-0.2	-0.2	-0.8	-0.9	-0.4
	His181	-1.0	-2.0	0.5	0.1	-1.7	-4.8
	Phe238	-0.4	-1.1	1.3	0.9	-1.3	-3.7

Inhibitor	Residue	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
MI-6	Asp285	6.0	6.0	6.0	5.1	4.4	5.8
	Ala182	-0.4	-1.0	1.0	0.7	-1.0	-3.3
	Cys241	-0.4	-0.5	-0.1	-0.2	-0.8	-1.5
	D180–H199	-0.9	-1.2	-0.3	-0.6	-2.0	-3.6

Table S3: Correlation between the experimental data and the interaction energy calculated at the consecutive levels of theory upon removal of a given amino acid residue from the binding site model.

Removed residue	R^a at a given level of theory					
	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
Tyr276	-0.64	-0.66	0.19	0.02	-0.67	-0.81
Tyr323	-0.43	-0.74	0.10	-0.02	-0.36	-0.80
Tyr319	-0.74	-0.88	0.09	-0.10	-0.54	-0.90
Asn282	-0.72	-0.80	0.11	-0.04	-0.62	-0.85
Met278	-0.58	-0.89	0.21	0.06	-0.56	-0.89
Glu179	-0.51	-0.73	0.28	0.14	-0.46	-0.85
Ser178	-0.60	-0.82	0.25	0.11	-0.56	-0.85
Glu363	-0.42	-0.80	0.19	0.11	-0.34	-0.87
His181	-0.57	-0.88	0.14	-0.02	-0.64	-0.88
Phe238	-0.60	-0.86	0.18	0.04	-0.54	-0.87
Asp285	-0.51	-0.76	0.13	0.02	-0.43	-0.84
Cys241	-0.63	-0.86	0.17	0.03	-0.55	-0.86
Ala182	-0.65	-0.89	0.13	-0.03	-0.65	-0.88
Asp180–His191	-0.59	-0.89	0.17	0.01	-0.61	-0.90
All included	-0.63	-0.87	0.17	0.03	-0.55	-0.87

[a]Correlation coefficient between the energy obtained at a given level of theory and the experimental inhibitory activity.

Table S4: Total menin-inhibitor interaction energy[a] at the consecutive levels of theory calculated for novel menin-MLL inhibitors.

inhibitor	pIC_{50}	$E_{EL,MTP}^{(10)}$	$E_{EL}^{(10)}$	$E^{(10)}$	E_{SCF}	E_{MP2}	$E_{EL,MTP}^{(10)} + E_{Das}$
1	6.72	-20.2	-43.9	26.5	9.0	-33.4	-92.1
2	6.19	-22.1	-43.7	22.3	5.5	-33.8	-92.4
3	5.89	-22.5	-43.2	21.3	4.7	-33.6	-91.4
4	5.85	-24.6	-44.2	18.2	2.0	-33.5	-93.9
5	5.70	-22.4	-44.1	22.2	5.1	-34.5	-93.2
6	4.70	-20.2	-43.1	26.2	8.9	-30.6	-90.6
7	3.70	-17.5	-35.5	18.8	4.6	-32.1	-83.4
N_{pred}[b]		61.9	71.4	33.3	33.3	61.9	66.7
R[c]		-0.63	-0.83	0.33	0.10	-0.65	-0.84
SE[d]		1.9	1.9	3.4	2.7	1.1	2.1

[a]In units of $kcal \cdot mol^{-1}$.

[b]Percentage of successful predictions [%].

[c]Correlation coefficient between the energy obtained at a given level of theory and the experimental inhibitory activity.

[d]Standard error of estimate, in units of $kcal \cdot mol^{-1}$.

Table S5: Performance of empirical scoring methods for ranking the novel menin-MLL inhibitors.

Scoring function	R^a	$N_{pred}{}^b$
$E_{EL,MTP}^{(10)} + E_{Das}$	-0.84	66.7
LigScore2	-0.84	66.7
Jain	-0.76	76.2
Ludi1	-0.74	71.4
Ludi2	-0.69	61.9
Ludi3	-0.55	61.9
LigScore1	-0.54	52.4
PLP2	-0.40	57.1
PLP1	-0.40	47.6
PMF	-0.33	61.9
PMF04	$+0.30$	47.6
$E_{binding}$ (Discovery Studio 3.5)	$+0.45$	42.9
Chemscore	-0.71	81.0
Goldscore	-0.53	47.6
ASP	$+0.05$	52.4
Binding affinity (AutoDock Vina)	-0.63	61.9

[a] Correlation coefficient between the calculated binding affinity estimate and the experimental inhibitory activity expressed as $p\text{IC}_{50}$.
[b] Percentage of successful predictions [%].