

## Drug Design

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## Design of the First-in-Class, Highly Potent Irreversible Inhibitor Targeting the Menin-MLL Protein–Protein Interaction

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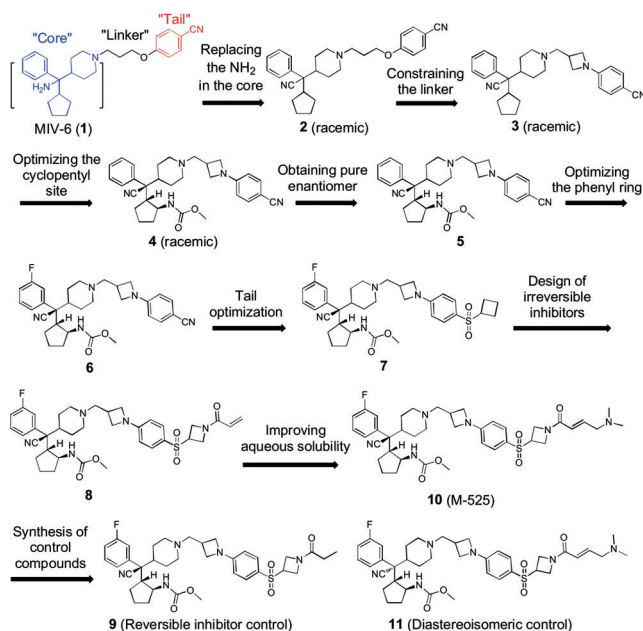
**Abstract:** The structure-based design of M-525 as the first-in-class, highly potent, irreversible small-molecule inhibitor of the menin-MLL interaction is presented. M-525 targets cellular menin protein at sub-nanomolar concentrations and achieves low nanomolar potencies in cell growth inhibition and in the suppression of MLL-regulated gene expression in MLL leukemia cells. M-525 demonstrates high cellular specificity over non-MLL leukemia cells and is more than 30 times more potent than its corresponding reversible inhibitors. Mass spectrometric analysis and co-crystal structure of M-525 in complex with menin firmly establish its mode of action. A single administration of M-525 effectively suppresses MLL-regulated gene expression in tumor tissue. An efficient procedure was developed to synthesize M-525. This study demonstrates that irreversible inhibition of menin may be a promising therapeutic strategy for MLL leukemia.

MLL leukemia, which is characterized by chromosomal translocations at 11q23 and expression of MLL fusion proteins, has a very poor prognosis and is resistant to current therapies.<sup>[1]</sup> MLL fusion proteins directly interact with menin, a protein encoded by the *MEN1* gene, to regulate the expression of *MEIS1* and *HOX* genes, which drive leukemogenesis in MLL leukemia.<sup>[2]</sup> Consequently, targeting the menin-MLL protein–protein interaction using small-molecule inhibitors (hereafter called menin inhibitors) represent a promising therapeutic strategy for MLL leukemia.<sup>[2c,3]</sup>

Several classes of peptidomimetics and non-peptide small-molecule menin inhibitors were reported in recent years.<sup>[4]</sup> To date, all reported menin inhibitors are reversible in nature. Preclinical data showed that extended drug exposure is

required for menin inhibitors to achieve anti-leukemia activity in vitro.<sup>[4d]</sup> Therefore, we hypothesize that irreversible menin inhibitors may achieve much greater antileukemia activity than reversible menin inhibitors in MLL leukemia. Herein, we report the design and characterization of the first-in-class, highly potent and irreversible menin inhibitors.

For the design of irreversible menin inhibitors, we sought to first obtain a highly potent reversible menin inhibitor. We used MIV-6 (**1**), a previously reported, moderately potent, reversible inhibitor,<sup>[4c]</sup> as the starting point for our structure-based optimization efforts, which is summarized in Figure 1.



**Figure 1.** Structure-guided design of irreversible menin inhibitors and control compounds. Compounds 5–11 are enantiopure.

The primary amine group in MIV-6 was shown to be a major metabolic soft spot and the synthetic yield for the core structure bearing this primary amine group was very low.<sup>[4c]</sup> We thus replaced this free amine in MIV-6 with a metabolically stable nitrile group, which led to compound **2** that binds to menin with an IC<sub>50</sub> value of 3.1 μM (Table 1). Although compound **2** is 17 times less potent than MIV-6 in binding to menin, its synthetic yield is high, representing a reasonable starting point for further optimization.

MIV-6 and compound **2** have a flexible linker connecting their respective core structure to the same “tail” group.

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**Table 1:** Binding affinity and cell growth inhibition of menin inhibitors.

ID	Binding affinity to menin in FP assay (IC <sub>50</sub> , nM)	Cell growth inhibition assay (4 days, IC <sub>50</sub> , μM)	
		MV4;11 (MLL fusion)	HL60 (no MLL fusion)
1 (MIV-6)	185 ± 24	3.6 ± 0.2	4.9 ± 0.8
2	3100 ± 200	2.8 ± 0.32	> 10
3	3000 ± 200	> 10	> 10
4	29 ± 2	0.83 ± 0.04	> 10
5	15 ± 1	0.20 ± 0.01	> 10
6	9 ± 1	0.16 ± 0.03	> 10
7	7 ± 1	0.21 ± 0.02	> 10
8	3.0 ± 1.0	0.006 ± 0.002	3.2 ± 0.7
9	8.0 ± 1.0	0.263 ± 0.039	> 10
10 (M-525)	3.3 ± 0.4	0.0027 ± 0.0005	2.0 ± 0.4
11	> 2000	1.01 ± 0.14	1.5 ± 0.3

Because restriction of rotatable bonds is an effective means of reducing conformational space and improving target selectivity for small-molecule drugs, we have identified 3-methylazetidine as a suitable, conformationally constrained linker, which led to compound **3**. Compound **3** binds to menin with IC<sub>50</sub> = 3.0 μM and is as potent as compound **2**.

Analysis of the co-crystal structure of MIV-6 complexed with menin shows that there is a well-defined pocket around the cyclopentyl group of MIV-6.<sup>[4c]</sup> We reasoned that installation of an appropriate group onto the cyclopentyl ring to optimize the interactions at this site could greatly enhance the binding affinity to menin. Our extensive modifications at this site showed that installation of a reverse carbamate at the 2-position of the cyclopentyl ring dramatically improves the binding affinity to menin, which yielded compound **4**. Compound **4** binds to menin with an IC<sub>50</sub> value of 29 nM, and is thus more than 100-times more potent than compounds **2** and **3**.

Compound **4** was initially synthesized as a racemic compound. To determine its stereospecificity for binding to menin, we developed an efficient synthetic route to obtain compound **5**, a pure enantiomer of **4**. Compound **5** binds to menin with an IC<sub>50</sub> value of 15 nM, and is twice as potent as **4**.

Introduction of a fluorine substituent into the phenyl ring group was shown to modestly improve the binding affinity of previous menin inhibitors<sup>[4c,5]</sup> and accordingly, we systematically investigated the effect of a fluorine substituent in the phenyl group of **5**. This effort resulted in **6**, which binds to menin with an IC<sub>50</sub> value of 9 nM ( $K_i < 1$  nM).

These potent menin inhibitors were tested for their activity and selectivity in a 4-day cell growth inhibition assay in MV4;11 (MLL-AF4) and HL-60 (no MLL fusion) cell lines and the resulting data are summarized in Table 1. Compounds **4**, **5** and **6** achieve IC<sub>50</sub> values of 0.83, 0.20, and 0.16 μM, respectively, in the MV4;11 cell line. Significantly, these three compounds have IC<sub>50</sub> values of > 10 μM in the HL-60 cell line, demonstrating excellent cellular selectivity for MLL leukemia.

Although compounds **5** and **6** bind to menin with very high affinities ( $K_i < 1$  nM), they achieve only submicromolar IC<sub>50</sub> values in the MV4;11 cell line carrying an MLL fusion.

Since irreversible inhibitors can achieve enhanced target inhibition over reversible inhibitors,<sup>[6]</sup> we next explored the possibility of designing covalent, irreversible menin inhibitors based upon the potent reversible inhibitor **6**.

Analysis of the co-crystal structure of the MIV-6/menin complex shows that the Cys329 residue in menin is close to the inhibitor and may be used for the design of covalent menin inhibitors. Our modeled structure of **6** in a complex with menin shows that the terminal nitrile group of **6** is the closest to the sulfur atom of Cys329 but is still 6.7 Å away, suggesting that the nitrile group needs to be extended to form a covalent bond with Cys329 (Supporting Information, Figure S1a). We thus replaced the nitrile group in **6** with a cyclobutylsulfonyl group, yielding **7**. Modeling suggests that the sulfonyl group can maintain the hydrogen bond with the indole group of Trp341 and the cyclobutyl moiety lodges in the surface hydrophobic pocket formed by Cys329, Val367, Val371, and Trp341 (Supporting Information, Figure S1b). Indeed, **7** binds to menin with an IC<sub>50</sub> value of 7 nM ( $K_i < 1$  nM).

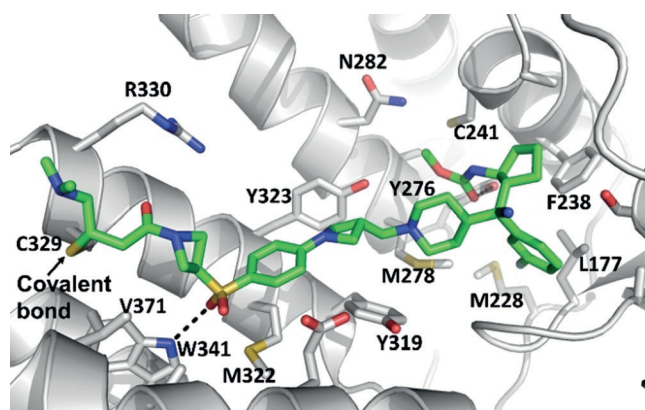
We next designed and synthesized **8** as a potential covalent inhibitor by installation of an acrylamide group, a Michael acceptor, in the 4-membered ring of **7**. We also synthesized **9** as a reversible inhibitor control by reducing the ethenyl moiety in **8** to an ethyl group.

To establish the mode of action of **8** and **9**, we performed mass spectroscopic analyses (Supporting Information, Table S1), which showed that **8** forms a covalent complex upon incubation with recombinant human menin protein, but **9**, lacking the Michael acceptor group fails to do so. Using bio-layer interferometry (BLI) by Octet Red, we demonstrated that while **8** binds to menin protein irreversibly, **9** binds to menin protein reversibly (Supporting Information, Figure S2). Taken together, these data clearly show that **8** is a covalent and irreversible menin inhibitor, while **9** is a non-covalent, reversible menin inhibitor.

In the cell growth inhibition assay, the irreversible menin inhibitor **8** achieves an IC<sub>50</sub> value of 6 nM in the MV4;11 cell line, and its corresponding reversible inhibitors, **7** and **9**, have IC<sub>50</sub> values of 210 and 263 nM respectively (Table 1). Hence, **8** is more than 30 times more potent than the corresponding reversible inhibitors **7** and **9**. In the same cell growth inhibition assay, **8** has an IC<sub>50</sub> value of 3.2 μM in the HL-60 cell line lacking an MLL fusion, thus displaying more than 500-fold cellular selectivity in the MV4;11 cell line harboring an MLL fusion over the HL-60 cell line lacking an MLL fusion.

To improve the solubility of compound **8**, we installed a dimethylaminomethyl group onto the acrylamide group, yielding **10**. Compound **10** binds to menin with an IC<sub>50</sub> value of 3 nM. In the cell growth inhibition assay, **10** achieves an IC<sub>50</sub> value of 3 nM in the MV4;11 cell line and has an IC<sub>50</sub> value of 2.0 μM in the HL-60 cell line, again displaying > 500-fold cellular selectivity for the MV4;11 cell line over the HL-60 cell line.

To precisely establish the mode of interactions of **10** with menin, we determined its co-crystal structure complexed with human menin protein at 2.61 Å resolution (Figure 2; Supporting Information, Figure S3). This co-crystal structure



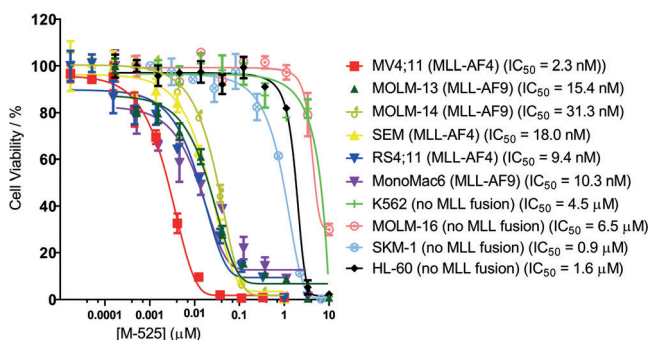
**Figure 2.** Co-crystal structure of compound **10** (green) complexed with menin (gray) at 2.61 Å resolution (PDB: 6B41). A covalent bond between Cys329 and inhibitor **10** was detected.

clearly shows that, consistent with our design, **10** through its acrylamide group forms a covalent bond with the sulfur atom of Cys329. The reverse carbamate group on the cyclopentyl ring inserts nicely into the available pocket in menin, with its carbonyl group forming a strong hydrogen bond with the hydroxyl group of Tyr276, and the methyl group enjoys hydrophobic contacts with the side chains of Met278 and Cys241. The fluorine substituent on the phenyl ring inserts into a hydrophobic pocket formed by Met228, Met278 and Leu177. This co-crystal structure provides a solid structural basis for the high-affinity, covalent binding of **10** with menin. Additionally, our mass spectroscopic and BLI data further confirmed that **10** is a covalent and irreversible inhibitor (Supporting Information, Table S1 and Figure S2).

To investigate the binding stereospecificity of **10** with menin, we synthesized **11**, a diastereoisomer of **10**, by inverting the chiral center on the quaternary carbon (Figure 1). Compound **11** binds to menin with an  $IC_{50}$  value of more than 2000 nM, and is thus more than 500 times less potent than **10**, indicating a high binding stereospecificity of **10** to menin. Furthermore, **11** has an  $IC_{50}$  value of 1.0  $\mu$ M in inhibition of cell growth of the MV4;11 cell line, and is more than 300 times less potent than **10**. These data provide further evidence that the potent cellular activity achieved by **10** in the MV4;11 cell line is attributed to its binding to menin.

The cellular thermal shift assay (CETSA) is a recently developed, powerful assay to assess engagement of small-molecule inhibitors with their specific protein target in cells.<sup>[7]</sup> Our CETSA data (Supporting Information, Figure S4) demonstrated that **10** enhances the thermal stability of cellular menin protein in both the MV4;11 and MOLM-13 cells at concentrations as low as 0.4–1.2 nM over the control treatment and reaches a maximum effect at 30–100 nM. In comparison, **10** has no effect on WD repeat-containing protein 5 (WDR5),<sup>[8]</sup> which also binds to MLL. Since the MV4;11 and MOLM-13 cells were treated with **10** for only 1 h, the thermal stabilization of cellular menin protein by **10** is evidently a direct effect. Hence, the CETSA data provide clear evidence that **10** effectively targets the cellular menin protein at subnanomolar concentrations.

Compound **10** was further evaluated for its activity and specificity in a panel of human acute leukemia cell lines with or without MLL fusions. Similar to inhibitors of other epigenetic regulators such as EZH2 and DOT1L,<sup>[9]</sup> menin inhibitors exert their cell growth inhibitory activity more slowly than traditional cytotoxic agents and kinase inhibitors.<sup>[4d]</sup> Accordingly, we evaluated the growth inhibitory activity of **10** in a panel of leukemia cell lines with a 7-day treatment, with the results summarized in Figure 3. Our data



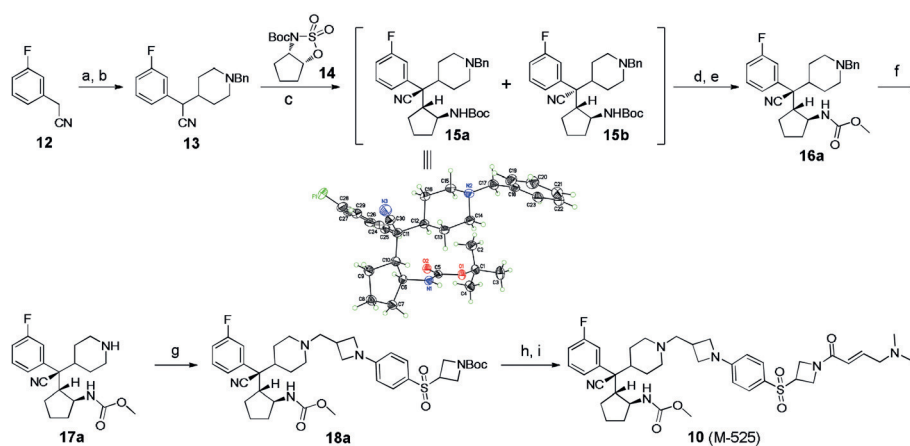
**Figure 3.** Cell growth inhibition in acute leukemia cell lines with or without MLL fusion. Cells were treated with compound **10** for 7 days and cell viability was determined using a WST-8 assay. Data are representative of three independent experiments.

show that **10** achieves  $IC_{50}$  values of 2.3–31.3 nM in six leukemia cell lines harboring MLL fusions. In comparison, **10** has  $IC_{50}$  values of 0.9–6.5  $\mu$ M in four leukemia cell lines lacking MLL fusion and is 25–2000 times less potent than in leukemia cell lines carrying an MLL fusion. Thus, **10** achieves potent cellular activity in human leukemia cell lines carrying MLL fusions, independent of the MLL fusion partner, and demonstrates excellent cellular selectivity over leukemia cell lines carrying no MLL fusion.

Reversible menin inhibitors have been shown to down-regulate *MEIS1* and *HOX* genes in MV4;11 and other leukemia cell lines carrying a MLL fusion.<sup>[4d]</sup> We tested **10** for its ability to regulate expression of *MEIS1* and *HOX* genes in MV4;11 and MOLM-13 cell lines. In the MV4;11 cell line, treatment for 6 or 24 h with **10** significantly down-regulates the expression of *MEIS1*, *HOXA9*, and *HOXA11* genes in a dose-dependent manner (Supporting Information, Figure S5a,b) and is effective at low nanomolar concentrations. Compound **10** also effectively suppresses the expression of *MEIS1* and *HOX* genes in the MOLM-13 cell line at concentrations as low as 3 nM (Supporting Information, Figure S5c). Compound **10** is therefore potent and effective in suppressing the expression of *MEIS1* and *HOX* genes in MV4;11 cells carrying MLL-AF4 fusion and in MOLM-13 cells carrying MLL-AF9 fusion.

We further examined the ability of **10** to down-regulate *MEIS1* and *HOX* genes in the MV4;11 xenograft tumor tissue in mice in a pharmacodynamic (PD) experiment (Supporting Information, Figure S6a,b). In contrast to the requirement for repeated dosing with reversible menin inhibitors,<sup>[4d]</sup> a single, intravenous administration of **10** effectively down-regulates *MEIS1*, *HOXA9*, and *HOXA11* genes at 24 h with the effect





**Scheme 1.** Reagents and conditions: a) 1-benzylpiperidin-4-one, MeONa, MeOH, reflux; b) NaBH<sub>4</sub>, MeOH, RT; c) KHMDS, 18-crown-6, THF, 0 °C to RT, and then H<sub>2</sub>SO<sub>4</sub>; d) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to RT; e) dimethyl dicarbonate, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to RT; f) 10% Pd/C, H<sub>2</sub>, MeOH, RT; g) K<sub>2</sub>CO<sub>3</sub>, KI, CH<sub>3</sub>CN, 80 °C; h) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to RT; i) (2*E*)-4-(dimethylamino)but-2-enoyl chloride hydrochloride, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to RT. HMDS = hexamethyldisilazide, TFA = trifluoroacetic acid. The absolute stereochemistry of **15a** was confirmed by X-ray crystallography.<sup>[10]</sup>

persisting for at least 48 h. The long-lasting PD effect of a single dose of **10** on down-regulation of *MEIS1* and *HOX* genes in vivo suggests that infrequent administration of an irreversible menin inhibitor may be sufficient to achieve a strong anti-leukemia activity against MLL leukemia in patients, and this would represent a significant advantage over reversible menin inhibitors.

The synthesis of **10** is summarized in Scheme 1. The critical step was the construction of the key intermediate **15a**, which consists of three chiral centers and a highly hindered quaternary carbon with four distinct substituents. The synthesis of **15a** was achieved using an efficient method that generates the three chiral centers in one step. The absolute stereochemistry of **15a** was confirmed by determination of its single crystal structure. The detailed synthesis of **10** and other compounds are provided in the Supporting Information.

In summary, we report the design and extensive evaluation of the first-in-class irreversible inhibitors of menin, exemplified by **10** (M-525). Our data clearly demonstrate that irreversible inhibitors of menin are highly potent and effective in targeting the menin-MLL interaction and should be extensively evaluated as a new class of targeted therapy for MLL leukemia.

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## Conflict of interest

The University of Michigan has filed a number of patents on these menin inhibitors disclosed in this study. Shaomeng Wang, Shilin Xu, Angelo Aguilar, Tianfeng Xu, Ke Zheng, Liyue Huang, Jeanne Stuckey are co-inventors on these patent applications. The patents have been licensed by Medsyn Biopharma. Shaomeng Wang is a co-founder of Medsyn Biopharma and owns stocks in Medsyn.

**Keywords:** drug design · irreversible inhibitors · menin-MLL protein–protein interaction · MLL leukemia

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- [10] CCDC 1581872 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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