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Novel 3-methylindoline inhibitors of EZH2: design synthesis and SAR

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ABSTRACT

EZH2 (enhancer of zeste homologue 2) is the catalytic subunit of the polycomb repressive complex 2 (PRC2) that catalyzes the methylation of lysine 27 of histone H3 (H3K27). Dysregulation of EZH2 activity is associated with several human cancers and therefore EZH2 inhibition has emerged as a promising therapeutic target. Several small molecule EZH2 inhibitors with different chemotypes have been reported in the literature many of which use a bicyclic heteroaryl core. Several small molecule EZH2 inhibitors representing diverse chemotypes have been reported in literature, many of which use a bicyclic heteroaryl core. Herein, we report the design and synthesis of EZH2 inhibitors containing an indoline core. Partial saturation of an indole to an indoline provided lead compounds with nanomolar activity against EZH2, while also improving solubility and oxidative metabolic stability.

Covalent modifications of histones play pivotal roles in the organization of the chromatin structure and the regulation of gene expression.[1,2] A large number of enzymes are known to catalyze the addition or removal of covalent groups from specific amino acids in histone proteins including histone methyltransferases (HMTs).[3] Enhancer of Zeste Homologue 2 (EZH2) is the catalytic subunit of Polycomb repressive complex 2 (PRC2), which catalyzes the methylation of lysine 27 of histone 3 (H3K27).[4] Tri-methylation of the lysine-27 of histone 3 (H3K27) is associated with the silencing of specific genes, including many tumor suppressor genes.[5] EZH2 has been found to be significantly overexpressed in a variety of human cancers and its expression level correlates with cancer progression and poor prognosis.[6,7] In addition, point mutations of residues, such as Y641, A677 and A687, within the catalytic domain of EZH2 have been found in follicular lymphomas and diffuse large cell B lymphomas (DLBCL).[8] Several studies have revealed that EZH2 knockdown in tumor cell lines can cause decreased cell proliferation, migration angiogenesis and increased apoptosis.[9–11] Collectively, this evidence supports EZH2 as an important target for cancer therapy and its inhibitors to be potential anticancer agents. Therefore significant efforts have been made on the discovery and optimization of small molecule EZH2 inhibitors. Through these efforts various small molecule EZH2 inhibitors have been reported with demonstrated efficacy both in vitro and in vivo.[12–14]

An analysis of EZH2 inhibitors reported in the literature[13] led to the recognition that a substituted pyridone-methyl amide fragment constituted a highly optimized moiety for binding to EZH2. Examples of published molecules which have the pyridone group are shown in Figure 1. Of these, EPZ6438[15] (**7**) and GSK126[16] (**2**) are currently being evaluated in human clinical trials. We noted that EPZ6438 and EPZ11989 are exceptions in the pyridone containing EZH2 inhibitors; the pyridone-methyl amide is attached to a phenyl core in place of a bicyclic hetero-aryl core. It has been demonstrated that increased fraction of sp3 carbons (Fsp3 = number of sp3 hybridized carbons/total carbon count) correlates with improved solubility, an experimental physical property important to success in drug discovery.[17] These observations prompted us to use a bicyclic non-planar indoline core for making novel EZH2 inhibitors, where the core consists of a phenyl residue fused with a saturated 5-membered ring. Our design is drawn in Figure 2, where we show that the indoline can be derived from the EPZ6438 (**7**) core by C7-C8 cyclization or by saturation of indole core at C-2 and C-3 present in Ei1 (**1**) and GSK126 (**2**). We envisaged that the new molecules with non-planar indoline core might have improved solubility and pharmacokinetic properties due to higher degree of saturation and non-planarity of the core.

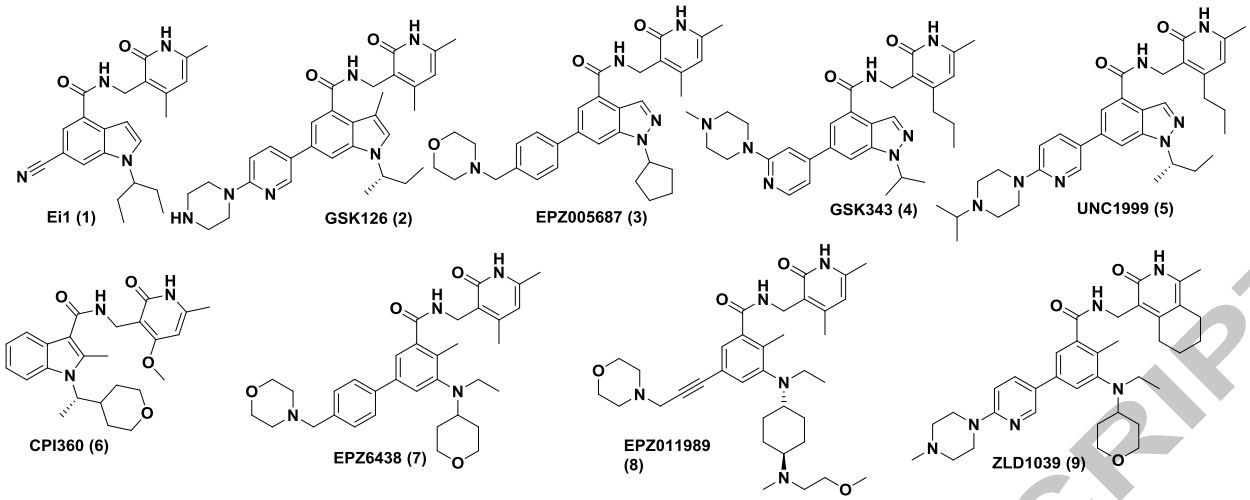


Figure 1. Reported EZH2 inhibitors[13]

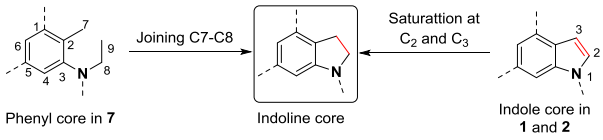
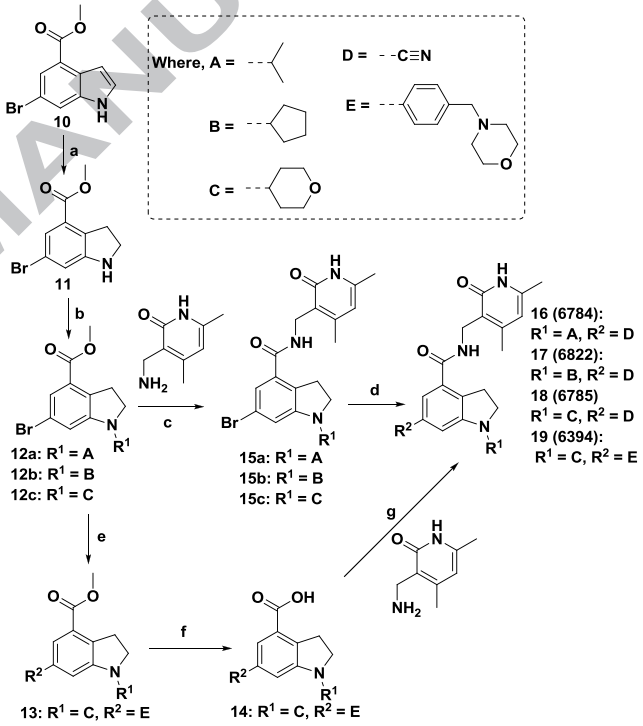


Figure 2. Design of indoline core for making EZH2 inhibitors

We started our lead generation effort by preparing compounds **16**, **17**, **18** and **19** incorporating an indoline core (Scheme 1). Key intermediates **12a-c** were synthesized by a reductive amination of various ketones with **11**, which was obtained by reduction of commercially available indole **10**. Intermediates **12a** and **12b** were then converted to **15a** and **15b** using trimethyaluminium as the coupling agent. Cyanation of **15a**, **15b** and **15c** afforded **16**, **17** and **18** respectively. Alternatively, intermediate **12c** was transformed to **19** via Suzuki coupling followed by hydrolysis and amide bond formation.

Compounds were tested *in vitro* for their ability to inhibit the enzymatic activity of EZH2, mutant EZH2 (Y641F) and the homolog EZH1. The enzymatic activity was determined using the indicated HMT complexes incubated with ^{3}H-SAM (tritiated S-adenosenyl L-methionine) and histone H3 and IC_{50} curves were determined for each compound (see supplemental information) . The IC_{50} results for inhibition of EZH2 are shown in Table 1.

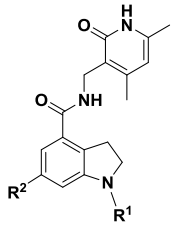


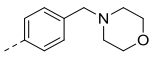
Scheme 1. Synthesis of **16**, **17 18** and **19**. Reagents and conditions: (a) TFA, triethylsilane, CH_2Cl_2, RT; (b) AcOH, ketone, $Na(OAc)_3BH$, CH_2Cl_2, 0-RT, 16 h; (c) 2M $AlMe_3$ in toluene, THF, 80 °C, 18 h; (d) Zn, $Zn(CN)_2$, $PdCl_2(dppf)•CH_2Cl_2$, DMA, 135 °C, 18 h; (e) Boronic ester, Na_2CO_3, $Pd(PPh_3)_4$, dioxane-water, 90 °C, 15 h; (f) 6N HCl, 95 °C, 16 h; (g) PyBOP, TEA, DMSO, RT, 16 h. Further details are in the *Supplemental Information*.

Based on reported compounds and published SAR,[13] we maintained the 4,6-dimethylpyridone methyl amide as a constant. Our first analogs scoped out the effect of substitution at the 1- and 6-positions of the indoline. The isopropyl substituted **16** was inactive (EZH2 IC_{50} = 26.6 μM) while the cyclopentyl substituted **17** had a 47-fold improvement in potency (EZH2 IC_{50} = 571 nM). However, a tetrahydropyran (THP) substitution led to a drastic loss of potency (**18** EZH2 IC_{50} = 15.7 μM). We also made compound **19** with a large phenyl-methyl morpholine at the 6-position, and surprisingly, while this compound has a THP group at the 1-position, its activity improved to EZH2 IC_{50} = 237

nM. With some uncertainty about our SAR conclusions at this point, we turned our attention to substitution at the 3-position.

Table 1 EZH2 inhibitory activity of compounds **16-19**

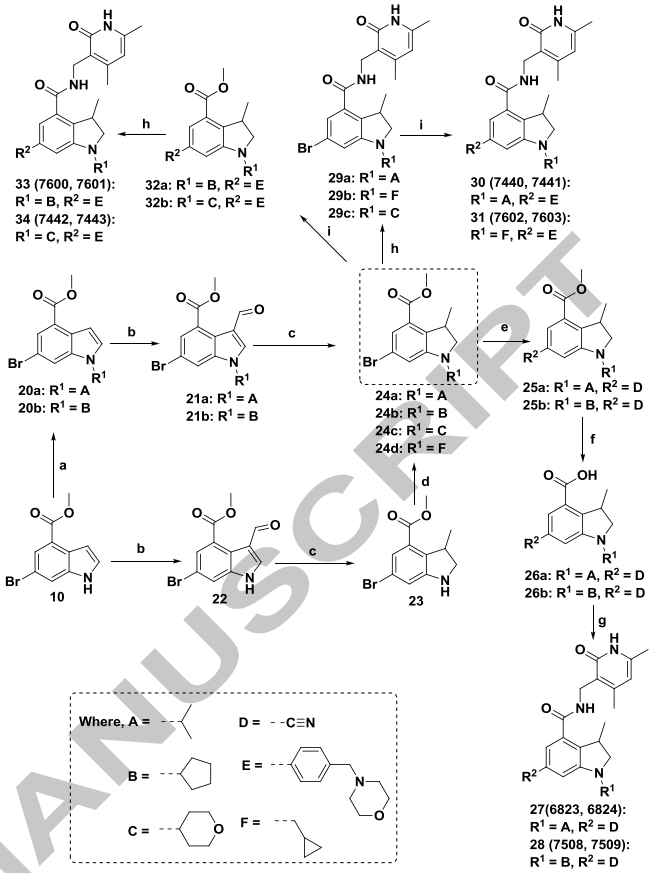


Compound	R^1	R^2	EZH2 IC_{50}[a] (nM)
16		--C≡N	26,600
17		--C≡N	571
18		--C≡N	15,700
19			237

[a]Experimental details are in the *Supplemental Information.*

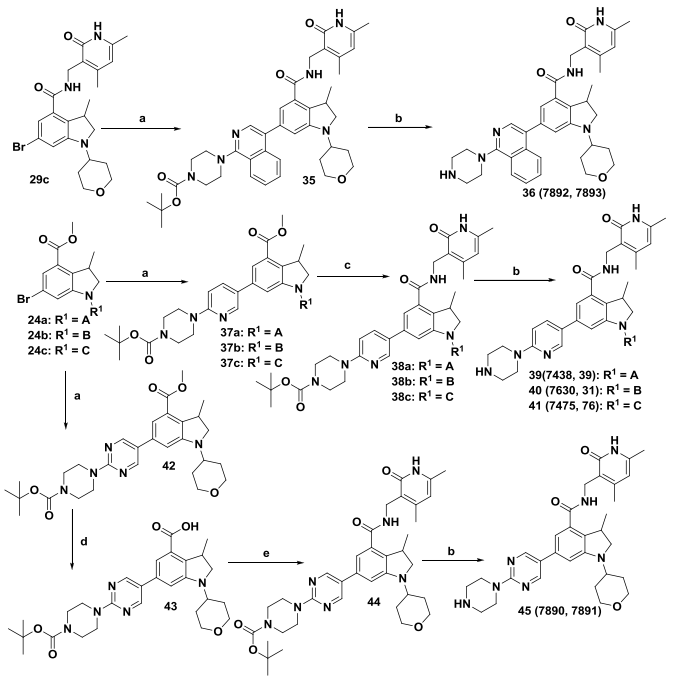
For compounds containing a 3-position methyl substituent, we synthesized several analogs using different R^1 and R^2 groups, including those reported in the literature[13] for molecules having an indole core. R^2 groups included nitrile, phenyl-methyl morpholine, piperazino-pyridine, piperazino-pyrimidine and piperazino-isoquinoline. R^1 groups included isopropyl, cyclopentyl, cyclopropylmethyl and THP. The 3-position methyl group resulted in enantiomeric pairs of compounds after separation by chiral chromatography.

Scheme 2 describes the synthesis of compounds **27**, **28**, **30**, **31**, **33** and **34**. Briefly, intermediate **24a** and **24b** were synthesized from **10** by alkylation followed by formylation and reduction while **24c** and **24d** were synthesized by reductive amination of **23** which was obtained from **10** via **22**. Cyanation of **24a** and **24b** resulted in **25a** and **25b** which after hydrolysis followed by amide bond formation with 3-(aminomethyl)-4,6-dimethylpyridin-2(1*H*)-one gave **27** and **28**, respectively. Compound **29a**, **29b** and **29c** were obtained by amide bond formation of 3-(aminomethyl)-4,6-dimethylpyridin-2(1*H*)-one with **24a**, **24d** and **24c** respectively, using trimethylaluminium as coupling agent. Suzuki coupling of **29a** and **29b** with arylboronic ester yielded **30** and **31** respectively. Suzuki coupling of **24b** and **24c** respectively gave **32a** and **32b** which after amidation afforded **33** and **34** respectively.



Scheme 2. Synthesis of **27**, **28**, **30**, **31**, **33** and **34**. Reagents and conditions: (a) NaH, alkyl bromide, DMF, 0-RT, 16 h; (b) (i) $POCl_3$,DMF, 2.5 h (ii) 2N NaOH; (c) (i) ZnI_2, $NaCNBH_3$, DCE, RT, 16 h (ii) TFA, triethylsilane, DCE, RT, 16 h; (d) AcOH, aldehyde/ketone, $Na(OAc)_3BH$, 0-RT, 16 h (e) Zn, $Zn(CN)_2$, $PdCl_2$(dppf).DCM, DMA, 135 °C, 18 h; (f) LiOH, THF, MeOH, Water, RT, 6 h; (g) 3-(Aminomethyl)-4,6-dimethylpyridin-2(1H)-one, PyBOP, TEA, DMSO, RT, 16 h; (h) 3-(Aminomethyl)-4,6-dimethylpyridin-2(1H)-one, 2M $AlMe_3$ in toluene, THF, 80 °C, 18 h; (i) Boronic ester, Na_2CO_3, $Pd(PPh_3)_4$, dioxane, water, 90 °C, 15 h. Further details are in the *Supplemental Information*.

Scheme 3 describes the synthesis of compounds **36, 39, 40, 41** and **45.** Boc-piperazine-isoquinoline boronic ester (synthesized by a method described in *Supplemental Information*) was coupled with **29c** to give **35** which after Boc-deprotection afforded **36**. Compound **24a**, **24b** and **24c** were coupled with commercially available Boc-piperazine-pyridine boronic ester to afford **37a**, **37b** and **37c** which after amide bond formation followed by Boc-deprotection afforded **39**, **40** and **41** respectively. Suzuki coupling of Boc-piperazine-pyrimidine boronic ester with **24c** resulted **42** which was converted to **45** via **43** and **44**.



Scheme 3. Synthesis of **36**, **39**, **40**, **41** and **45**. Reagents and conditions: (a) $PdCl_2(dppf).dcm$, K_2CO_3, boronic ester, dioxane, water, 90°C, 16 h; (b) TFA, DCM, RT, 16 h; (c) 3-(Aminomethyl)-4,6-dimethylpyridin-2(1H)-one, 2M $AlMe_3$ in toluene, THF, 80 °C, 18 h; (d) LiOH, THF, MeOH, water, RT, 6 h; (e) 3-(Aminomethyl)-4,6-dimethylpyridin-2(1H)-one, PyBOP, TEA, DMSO, RT, 16 h. Further details are in the *Supplemental Information*.

With this set of methyl-substituted compounds in hand, we tested for activity against EZH2; the active analogs were additionally tested for activity against EZH1 and the Y641F EZH2 mutant. The Y641 residue is frequently mutated in certain lymphomas. Moreover, lymphomas with this mutation have increased H3K27 methylation.[16] The SAR is illustrated in Table 2.

The methyl substituent had a dramatic effect on potency in the series. As an illustrative example, **16** has EZH2 IC_{50} of 26.6 μM, while the methyl substituted active enantiomer **27**^{e1} has EZH2 IC_{50} of 88 nM - a 302 fold improvement. The inactive enantiomer **27**^{e2} has no measurable activity against EZH2. This interesting phenomenon is an example of the "magic methyl" effect that has been described in the literature.[18] During the prosecution of this program, a patent application describing indoline core containing EZH2 inhibitors was published.[19] While the broad claims included multiple 3- substituted indolines and some compounds containing 3,3-dimethyl substituted indolines were described, no compounds containing 3-monomethyl substituted indolines were exemplified.

We found that for all R^1 and R^2 groups, the 2 enantiomers of a pair had very disparate activity. This difference in activity in an enantiomeric pair was more pronounced in the case of a small R^2 substituent (-CN, in **27**^{e1}, **27**^{e2}, **28**^{e1} and **28**^{e2}). In these examples, the difference in activity between enantiomers is >100 fold, with the less potent enantiomer (**27**^{e2} and **28**^{e2}) having no measurable IC_{50} against EZH2 up to 100 μM. With the larger R^2 substituents shown in Table 2, the less active enantiomer had measurable activity, albeit in the micromolar range. This indicates that in the 3-methyl substituted indoline series, there appears to be some cross talk between the 3- and 6-position substituents. In an effort to understand the "magic methyl" effect, we used the published crystal structure of EZH2[20] to dock both enantiomers of compound **34** (see *Supplemental Information*). This pair of enantiomers presented the dimethyl pyridone moiety to the protein in a manner identical to the published bound inhibitor, forming 2 H-bonds with the backbone of W624. The active enantiomer (**34**^{e1}, predicted to be the R enantiomer based on docking) indeed has the methyl group sitting in a groove lined by T678, F665, and the face of R685, possibly displacing an isolated water molecule. The inactive enantiomer (**34**^{e2}) is seen to rotate the indoline group by 180^o, while still anchored to the protein through the pyridone. This likely happens in an attempt to avoid a steric clash with the protein. In this state, R685 and F665 interactions with the ligand are lost, and a high entropy stranded water is likely interacting with R685 thus explaining the potency loss.

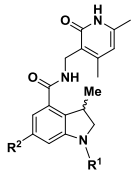
We probed the role of substituent at the N^1 position of indoline (R^1) and found that compounds with cyclopentyl (**28**^{e1}, **33**^{e1}) and THP group (**34**^{e1}) had better potency compared to their corresponding isopropyl analogs **27**^{e1} and **30**^{e1} (Table 2). These results indicated that bulkier groups are needed at this position for better potency. The compound with cyclopropylmethyl group at N^1 (**31**^{e1}) was found to be 8 fold less potent compared to its isopropyl analog (**30**^{e1}) (Table 2). This result highlights the role of α-branching at this position on potency.

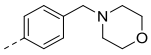
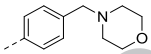
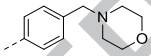
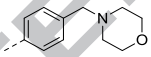
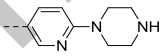
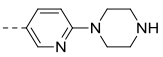
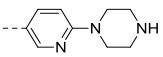
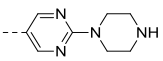
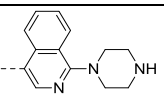
Next, we decided to study effect of substituent at C-6 position of indoline on activity (Table 2). We used different substituents at this position and pyridine-2-yl-piperizine residue was found to be the best substituent at this position as far as the biological activity against WT EZH2 inhibition is concerned (Compounds **39**-**41**, Table 2).

The pyrimidine analog of **41**^{e1} (**45**^{e1}) was found to be 9-fold less potent than **41**^{e1}. We also explored a 3-ethyl substituted analog of **41**^{e1} and found it to be 13-fold less potent (EZH2 IC_{50} = 145 nM, data not shown).

While these compounds maintained relatively good potency for EZH2, they did not display appreciable inhibitory activity against EZH1 (IC_{50} > 1.35 μM), indicating their relative selectivity for EZH2 versus the homolog EZH1. Regarding Y641F EZH2 activity, overall, this series suffered a 7-40 fold loss in potency relative to WT EZH2. Compound **28**^{e1} with a cyano group at the R^2 position had the best potency against Y641F EZH2.

Table 2. SAR of 3-methlindoline based compounds



Compound	R^1	R^2	EZH1 IC_{50}[a] (nM)	EZH2 IC_{50}[a] (nM)	EZH2 (Y641F) IC_{50}[a] (nM)
27[e1]			7,750	88	478
27[e2]			ND	>100,000	ND
28[e1]			4,440	27	185
28[e1]			ND	>100,000	ND
30[e1]			2,710	47	518
30[e2]			ND	4,140	ND
31[e1]			ND	375	ND
31[e2]			ND	15,200	ND
33[e1]			2,650	24	902
33[e2]			ND	448	ND
34[e1]			3,340	29	975
34[e2]			ND	6,980	ND
39[e1]			1,870	17	622
39[e2]			ND	1,082	ND
40[e1]			1,350	21	505
40[e2]			ND	378	ND
41[e1]			1,980	11	578
41[e2]			ND	2,150	ND
45[e1]			ND	98	ND
45[e2]			ND	2,160	ND
36[e1]			1,560	17	304
36[e2]			ND	540	ND

[e1/e2] Active/inactive enantiomer; ND: not determined; [a]Experimental details are in the *Supplemental Information.*

We tested EPZ6438 (**7**, EZH2 IC_{50} = 2 nM in our assay) and two of our lead compounds with the indoline core (**34**[e1] and **41**[e1]) in solubility and microsomal stability assays; the data are shown in Table 3. These two compounds demonstrated superior kinetic solubility in PBS (pH 7.5) and improved oxidative stability in human and mouse liver microsomes (HLM and MLM) compared to EPZ6438 (**7**).

Table 3. In vitro ADME data[a] for **7**, **15**[e1] and **21**[e1]

Compound	Sol (μM)[b]	hLM (% R)[c]	mLM (% R)[c]
7	28	25	39
34[e1]	75	62	58
41[e1]	75	83	95

[a]Experimental details are in the *Supplemental Information*; [b]Kinetic solubility; [c]Percent parent remaining after 30 min.

In conclusion, we describe the indoline as a novel core for making EZH2 inhibitors. These findings provide a foundation for future analoging and SAR; lead compounds will be tested in cell assays, in vivo for optimization of pharmacokinetic properties and evaluation in pharmacology models.

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