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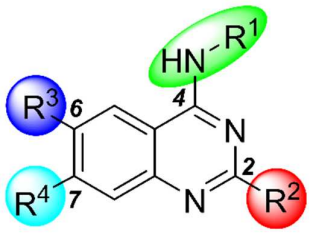

Comprehensive SAR studies of the first substrate-competitive SETD8 inhibitor led to the discovery of interesting SAR trends and novel analogs.

Structure-activity relationship studies of SETD8 inhibitors†‡

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Abstract

SETD8 (also known as SET8, PR-SET7, or KMT5A (lysine methyltransferase 5A)) is the only known lysine methyltransferase that catalyzes monomethylation of histone H4 lysine 20 (H4K20). In addition to H4K20, SETD8 monomethylates non-histone substrates such as the tumor suppressor p53 and proliferating cell nuclear antigen (PCNA). Because of its role in regulating diverse biological processes, SETD8 has been pursued as a potential therapeutic target. We recently reported the first substrate-competitive SETD8 inhibitor, UNC0379 (**1**), which is selective for SETD8 over 15 other methyltransferases. We characterized this inhibitor in a battery of biochemical and biophysical assays. Here we describe our comprehensive structure-activity relationship (SAR) studies of this chemical series. In addition to 2- and 4-substituents, we extensively explored 6- and 7-substituents of the quinazoline scaffold. These SAR studies led to the discovery of several new compounds, which displayed similar potencies as compound **1**, and interesting SAR trends.

Introduction

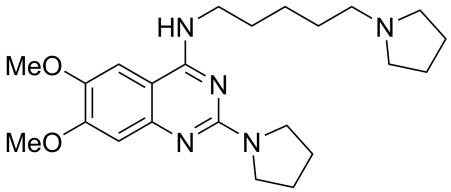
Post-translational modifications (PTMs) of histones are critical in regulating gene expression and transcription.[1-3] Among a myriad of PTMs, histone lysine methylation has been recognized as a major mechanism in chromatin regulation. Histone lysine methylation typically takes place at the N-terminal tails of core histone proteins (H3, H4, H2A, and H2B) and is catalyzed by protein lysine methyltransferases (PKMTs). It is worth noting that PKMTs also methylate many non-histone substrates.[4]

PKMTs have been increasingly recognized as a class of potential therapeutic targets by the medicinal chemistry and drug discovery community. Consequently, a number of selective inhibitors of PKMTs have been discovered during recent years.[5-31] Related to PKMTs, protein arginine methyltransferases (PRMTs) catalyze methylation of arginine residues of histone and non-histone proteins.[32] A number of selective inhibitors of PRMTs have also been reported.[33-35]

SETD8 (also known as SET8, PR-SET7, or KMT5A (lysine methyltransferase 5A)), first characterized in 2002, is the only known PKMT that catalyzes monomethylation of histone H4 lysine 20 (H4K20).[36-38] Monomethylation of H4K20 (H4K20me) and SETD8 have been implicated in the DNA damage response and cell cycle progression.[38] In addition, SETD8 promotes epithelial–mesenchymal transition (EMT) by physically associating with TWIST, a master regulator of EMT.[39] SETD8 also monomethylates lysine 382 (K382) of the tumor suppressor p53 and lysine 248 (K248) of proliferating cell nuclear antigen (PCNA) and plays a potential role in human carcinogenesis.[40, 41]

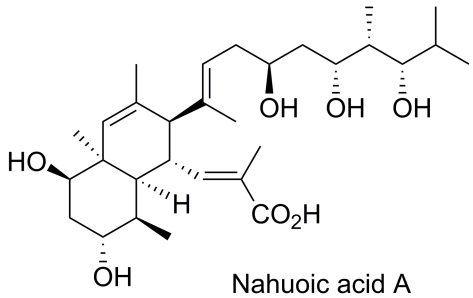
We recently reported UNC0379 (**1**) as the first substrate-competitive small-molecule inhibitor of SETD8 (Figure 1).[42] Compound **1** is active in multiple biochemical (e.g., radioactive

methyl transfer, microfluidic capillary electrophoresis) and biophysical (e.g., isothermal titration calorimetry, surface plasmon resonance) assays, and importantly, selective for SETD8 over 15 other methyltransferases.[42] The only other known selective inhibitor of SETD8 is marine nature product nahuoic acid A, which is competitive with the co-factor *S*-adenosyl-L-methionine (SAM) (Figure 1).[21] In this article, we describe our comprehensive structure-activity relationship (SAR) studies of the quinazoline template represented by compound **1**, which resulted in the discovery of interesting SAR trends and novel analogs with similar potencies as compound **1**.



UNC0379 (**1**)

SETD8: IC_{50} = 7.3 ± 1.0 μM
Competitive with substrate
Selective over 15 other methyltransferases



Nahuoic acid A

SETD8: IC_{50} = 6.5 ± 0.5 μM
Competitive with the cofactor SAM

Figure 1. Structures of the known selective inhibitors of SETD8.

Results and discussion

Our strategy for studying SAR of the UNC0379 series was to extensively explore the 2-, 4-, 6-, and 7-substituents (Figure 2). We previously reported initial SAR results of the 2- and 4-substituents.[42] In these new studies, we investigated not only additional 2- and 4- substituents, but also 6- and 7-substituents, the two regions that were not previously explored for SETD8.

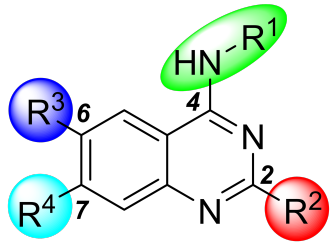
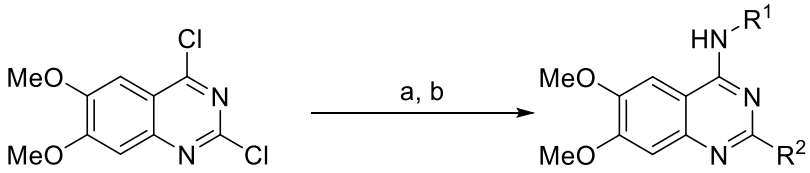


Figure 2. The four highlighted regions were explored for studying SAR of the UNC0379 series.

We first explored the 4-amino moiety of the quinazoline scaffold. Compounds **1** – **15** (Scheme 1 and Table 1) were synthesized from commercially available 2,4-dichloro-6,7-dimethoxyquinazoline and corresponding amines in good yields. As previously reported,[6] we displaced the 4-chloro group with the first set of amines at room temperature. The 2-chloro group was substituted by the second set of amines under microwave heating conditions, yielding the desired 2,4-diamino-6,7-dimethoxyquinazolines (Scheme 1).

Scheme 1. Typical synthesis of 2,4-diamino-6,7-dimethoxyquinazolines.[a]

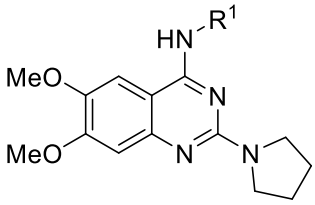


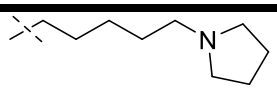
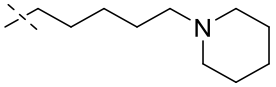
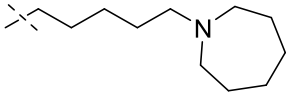
[a] Reagents and conditions: (a) R^1 amines, THF, *N*,*N*-diisopropylethylamine, room temperature; (b) R^2 amines, *n*-BuOH, DIPEA, microwave, heat.

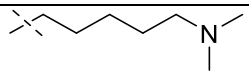
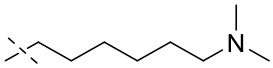
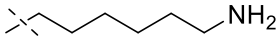
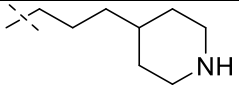
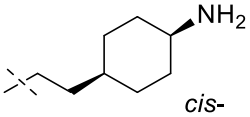
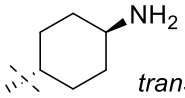
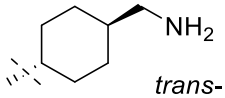
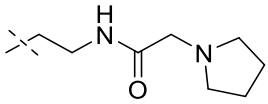
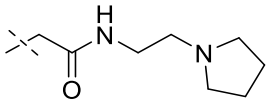
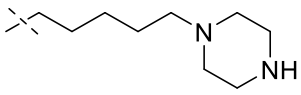
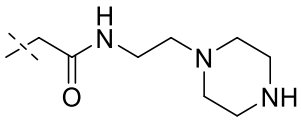
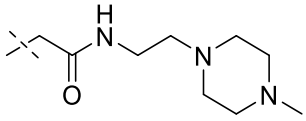
The ring size of the terminal cyclic amino group did not have significant impact on SETD8 potency (Table 1). Pyrrolidine (compound **1**), piperidine (compound **2**), and azepane (compound **3**) resulted in similar potencies. The replacement of the cyclic amino group with an acyclic amino group such as dimethyl amine group (compound **4**) didn't lead to a significant potency change either. However, increasing the length of the side chain from 5 to 6 carbons (compound **4** versus compound **5**) resulted in a decrease in potency. We previously reported that

decreasing the length of the side chain also led to a decrease in potency.[42] Interestingly, replacing the dimethyl amine group with the primary amino group slightly decreased potency (compound **5** versus compound **6**). We next explored various conformation-constrained analogs and found that these compounds (**7** – **10**) were not as potent as compound **1**. In addition to exploring the length of the side chain, we also attempted to replace the straight 5-carbon chain with several amide-containing linkers and found that the amide **11** was significantly less potent than compound **1** and the amide **12** was completely inactive. We previously reported that compound **13** was weakly active against SETD8.[42] Consistent with the result of the amide **12**, the amides **14** and **15** did not display any activity against SETD8. Taken together, these results suggest that: (1) the terminal pyrrolidine group can be modified without potency loss; and (2) the 5-carbon linker is optimal. In addition, we previously demonstrated that the basicity of the pyrrolidine nitrogen was important for maintaining potency for SETD8.[42]

Table 1. SAR of the 4-Amino Moiety.



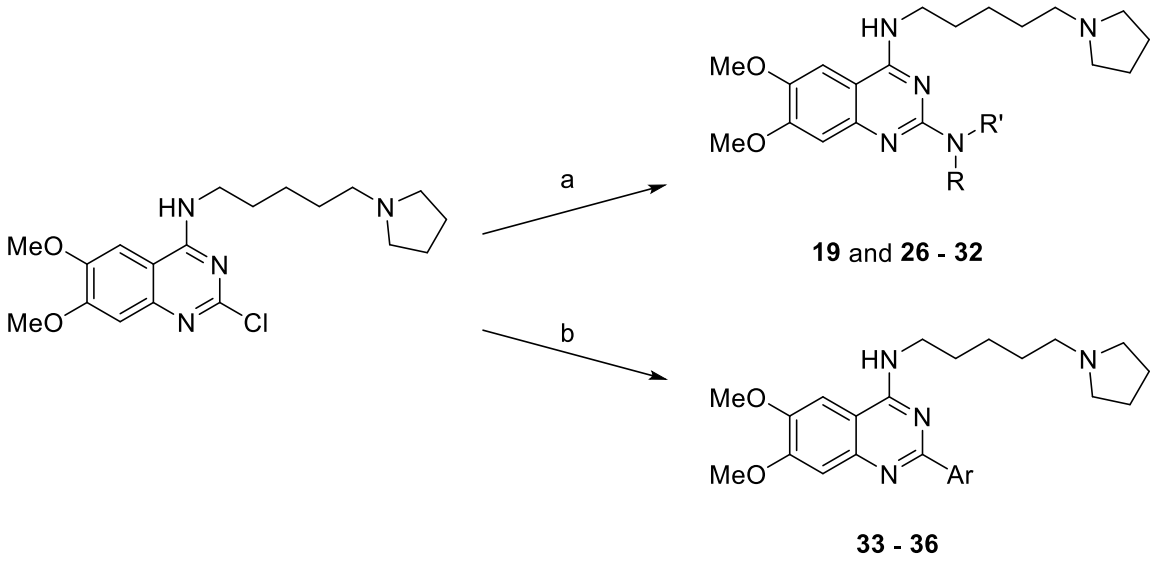
Compound	R^1 Group	SETD8 IC_{50} (μM)[a]
1		7.3 ± 1.0[b]
2		7.9 ± 0.8[b]
3		7.9 ± 1.2

4		7.9 ± 1.4[b]
5		26 ± 5
6		40 ± 1
7		40 ± 6
8	 *cis-*	43 ± 5
9	 *trans-*	> 250
10	 *trans-*	> 250
11		63 ± 19
12		> 250
13		32 ± 8[b]
14		> 250
15		> 250

[a] IC_{50} determination experiments were performed in duplicate. [b] IC_{50} value was reported previously.[42]

We next investigated various 2-substituents at the quinazoline core (Scheme 2 and Table 2). Synthesis of compounds **16** – **18** was described previously.[42] Compounds **20** – **25** were prepared according to the synthetic route illustrated in Scheme 1. Buchwald–Hartwig amination reaction conditions[43] were used to synthesize compounds **19** and **26** – **32** from the known intermediate 2-chloro-6,7-dimethoxy-*N*-(5-(pyrrolidin-1-yl)pentyl)quinazolin-4-amine[42] and commercially available amines (Scheme 2). Compounds **19** and **26** – **32** could not be generated using standard nucleophilic conditions (Scheme 1) in good yields. A Suzuki coupling reaction[44] was used to prepare compounds **33** – **36** from the same intermediate and commercially available aromatic boronic acids (Scheme 2).

Scheme 2. Synthesis of compounds **19** and **26** – **36**.[a]

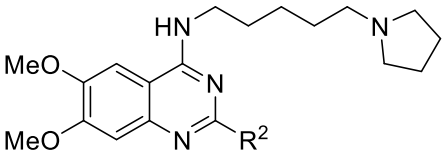


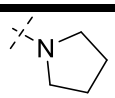
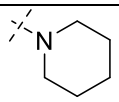
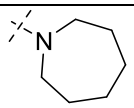
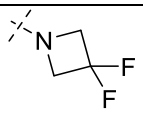
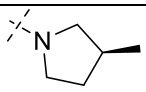
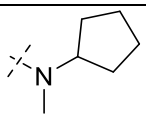
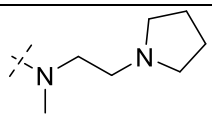
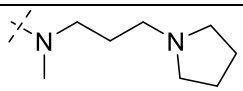
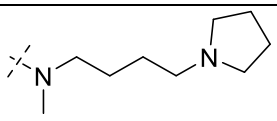
[a] Reagents and conditions: (a) Amines, $Pd(OAc)_2$, (+)-BINAP, Cs_2CO_3, THF, microwave, heat; (b) Aromatic boronic acid, $Pd(PPh_3)_4$, K_2CO_3, dioxane/water, microwave, heat. Ar, aromatic ring.

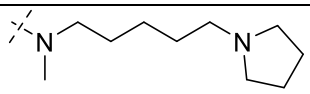
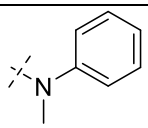
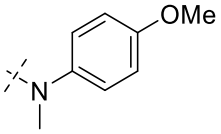
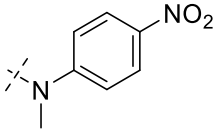
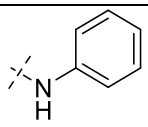
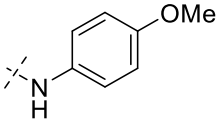
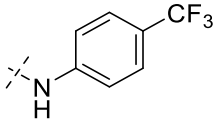
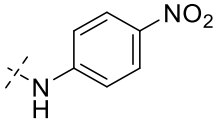
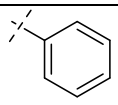
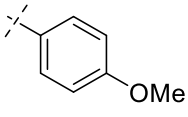
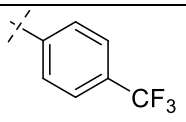
As shown in Table 2, replacing the pyrrolidine (compound **1**) with either the piperidine (compound **16**) or azepane (compound **17**) resulted in a significant loss of the potency, suggesting that a larger group is disfavored. On the other hand, the replacement of the

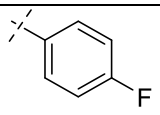
pyrrolidine (compound **1**) with the dimethyl amine group (compound **18**) didn't lead to a significant potency change. These results were reported previously.[42] Interestingly, the 3,3-difluoroazetidine (compound **19**) resulted in a large loss of potency, possibly due to the increase of the compound's polarity. We attempted to synthesize a simple azetidine analog, but found that the target molecule was unstable and could not be isolated. Adding a methyl substituent to the pyrrolidine (compound **20**) led to about two-fold drop in potency. We previously reported that compound **21** displayed some activity for SETD8.[42] Based on this result, we attempted to introduce a pyrrolidine with a 2 – 5-carbon linker and were disappointed to find that these compounds (**22** – **25**) did not exhibit any activity for SETD8. We also explored unsubstituted and substituted *N*-methylanilines and anilines. As shown in Table 2, unsubstituted *N*-methylaniline (compound **26**) and *N*-methylanilines with either an electron-donating group (methoxy, compound **27**) or an electron-withdrawing group (nitro, compound **28**) at the *para*-position were inactive. Similarly, unsubstituted aniline (compound **29**) and anilines with either an electron-donating group (compound **30**) or an electron-withdrawing group (compounds **31** and **32**) at the *para*-position did not display any activity. Lastly, we attempted to replace the pyrrolidine with a phenyl or substituted phenyl group containing an electron-donating or electron-withdrawing group at the *para*-position, but found that none of these compounds (**33** – **36**) were active against SETD8. Taken together, these results suggest that the SAR at 2-substituent is very tight. The vast majority of the modifications we made led to a significant or complete loss of potency for SETD8.

Table 2. SAR of the 2- Substituted Group.



Compound	R^2 Group	SETD8 IC_{50} (μM)[a]
1		7.3 ± 1.0[b]
16		94 ± 18[b]
17		> 250[b]
18		9.2 ± 1.2[b]
19		110 ± 4
20		15 ± 3
21		37 ± 9[b]
22		> 250
23		> 250
24		> 250

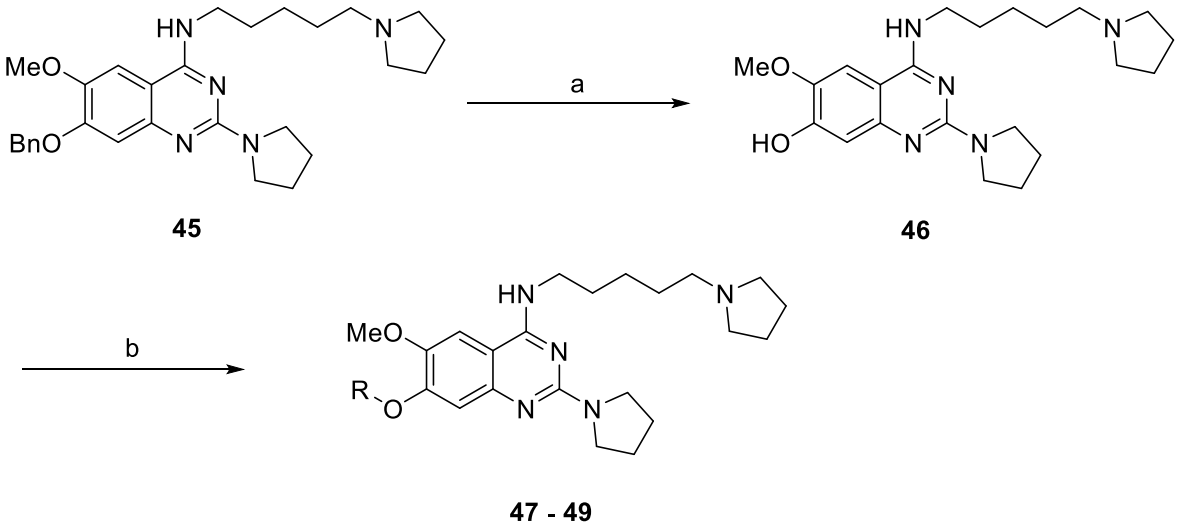
25		> 250
26		> 250
27		> 250
28		> 250
29		> 250
30		> 250
31		> 250
32		> 250
33		> 250
34		> 250
35		> 250

36		> 250

[a] IC_{50} determination experiments were performed in duplicate. [b] IC_{50} value was reported previously.[42]

We also extensively explored the 6- and 7-substituents (Scheme 3 and Table 3), which were not studied previously. Compounds **37** – **45** were prepared from different 6,7-substituted 2,4-dichloroquinazolines (synthesis of these intermediates is detailed in the supplementary information) according to the synthetic route illustrated in Scheme 1. Synthesis of compounds **46** – **49** is outlined in Scheme 3. Briefly, debenzylation of compound **45** via hydrogenation produced compound **46**. Nucleophilic substitution reactions between the phenol **46** and various alkyl bromides afforded compounds **47** – **50**.

Scheme 3. Synthesis of compounds **46** – **49**.[a]



[a] Reagents and conditions: (a) H_2, Pd/C, EtOH, room temperature; (b) RBr, K_2CO_3, DMF, room temperature.

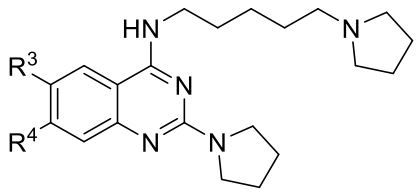
We found that the removal of both methoxy groups (compound **37**) or 6-methoxy group (compound **38**) completely abolished activity (Table 3). Interestingly, the removal of the 7-methoxy group (compound **39**) led to about 7-fold loss in potency, but it retained some activity

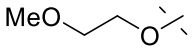
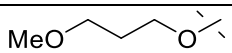
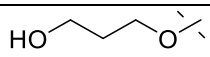
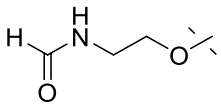
against SETD8. These results suggest that the 6-methoxy group may be more important for maintaining SETD8 potency compared with the 7-methoxy group.

We next investigated several 6-substituents while holding the 7-methoxy group constant and found that the replacement of the 6-methoxy group with the 6-ethoxy group did not result in a significant change in potency (compound **1** versus compound **40**). On the other hand, the 6-isopropoxy group (compound **41**) and 6-chloro group (compound **42**) led to about 8-fold and 60-fold loss in potency, respectively, suggesting that a larger group or a less electron-donating group is disfavored at this position.

Lastly, we explored various 7-substituents while holding the 6-methoxy group constant. Slightly increasing the size of the 7-methoxy group to the 7-ethoxy group (compound **43**) did not significantly change potency. On the other hand, the larger 7-isopropoxy group (compound **44**) and 7-benzyloxy group (compound **45**) led to more than 6-fold and 17-fold potency drops, respectively. Interestingly, the 7-hydroxy group (compound **46**) completely abolished activity against SETD8. We next studied whether a linear chain could be tolerated at the 7-position. We were pleased to find that compound **47**, which contains the 7-methoxyethyloxy group, was as potent as compound **1**. However, the 7-methoxypropoxy group (compound **48**) and 7-hydroxypropoxy group (compound **49**) led to a significant decrease in potency. Interestingly, compound **50**, which contains the 7-formylaminoethyloxy group, retained the same potency as compounds **1** and **47**. Taken together, these results suggest that the 7-position is amenable to modifications and there may be an opportunity to create more potent inhibitors of SETD8 by further exploring this region.

Table 3. SAR of the 6- and 7- Substituted Groups.



Compound	R^3 Group	R^4 Group	SETD8 IC_{50} (μM)[a]
1	MeO-	MeO-	7.3 ± 1.0[b]
37	H-	H-	> 250
38	H-	MeO-	> 250
39	MeO-	H-	52 ± 11
40	EtO-	MeO-	9.5 ± 0.9
41	*i*-PrO-	MeO-	61 ± 12
42	Cl-	MeO-	46 ± 11
43	MeO-	EtO-	11 ± 1
44	MeO-	*i*-PrO-	48 ± 10
45	MeO-	BnO-	130 ± 44
46	MeO-	HO-	> 250
47	MeO-		8.0 ± 0.8
48	MeO-		40 ± 12
49	MeO-		24 ± 3
50	MeO-		8.7 ± 0.4

[a] IC_{50} determination experiments were performed in duplicate. [b] IC_{50} value was reported previously.[42]

Conclusions

We comprehensively studied SAR of the quinazoline scaffold represented by UNC0379 (compound **1**), which was recently discovered as the first substrate-competitive inhibitor of SETD8. We found a number of interesting SAR trends. They include that: (1) at 4-position, the terminal pyrrolidine group can be modified without potency loss and the 5-carbon linker is optimal; (2) at 2-position, modifications are generally not tolerated and pyrrolidine and dimethylamino groups are optimal; (3) at 6-position, the methoxy and ethoxy groups are preferred and a larger group or a less electron-donating group is disfavored; and (4) at 7-position, modifications can be well tolerated and further exploration of this region may result in more potent SETD8 inhibitors. These SAR studies also led to the discovery of several novel compounds (**3**, **40**, **43**, **47** and **50**), which exhibited similar potencies as compound **1**. During the revision of this paper, several novel inhibitors of SETD8 have been reported.[45]

Acknowledgements

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