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Derivatives contain dimethylaminopyridine as SIRT2 inhibitors: A mini review

Mostafa M. Badran[1,2,3], Samar H Abbas[*2], Mikako Fujita[3], Mohamed Abdel-Aziz[2]

[1] Department of Medicinal Chemistry, Faculty of Pharmacy, South Valley University, Qena, 83523, Egypt.
[2] Department of Medicinal Chemistry, Faculty of Pharmacy, Minia University, 61519-Minia, Egypt.
[3] Medicinal and Biological Chemistry Science Farm Joint Research Laboratory, Faculty of Life Sciences, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto, 862-0973, Japan

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Abstract

The development of new compounds inhibiting SIRT2, a protein that regulates various biological processes, has attracted significant attention in recent years. This study reported dimethylaminopyridine (DMAP) synthesis and evaluation as a new scaffold for SIRT2 inhibition. DMAP derivatives were designed and synthesized using a combination of computational modeling and synthetic chemistry approaches. A high-throughput screening assay was used to evaluate the ability of compounds to inhibit SIRT2. The most potent compounds were identified and further characterized using cellular and enzymatic assays. This review suggests that DMAP could be a promising scaffold for developing novel SIRT2 inhibitors with potential anticancer activity.

Keywords:

Dimethyl aminopyridine; HDACs, SiRT2 inhibitors

1.Introduction

Histone deacetylases HDACs are a class of enzymes that remove acetyl groups from histone proteins. Histones are responsible for DNA package into a compact structure called chromatin, which regulates gene expression. Acetylation of histones is proceeded by histone acetyltransferases (HATs) which are generally associated with gene activation. Conversely, deacetylation is run by HDACs associated with gene repression. [1-4]

There are four classes of HDACs:

- Class I HDACs - HDAC1, HDAC2, HDAC3, and HDAC8. They are mainly localized in the nucleus and are critical in gene expression regulation.
- Class II HDACs - HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10**.** They have nuclear and cytoplasmic localization and are involved in diverse biological processes.
- Class III HDACs are also known as sirtuins (SIRT1-SIRT7) and require NAD+ as a cofactor to deacetylate lysine residues. They are implicated in energy metabolism, stress response, and aging.
- Class IV HDACs comprise only one member, HDAC11, and have features of both Class I and Class II enzymes.[5]

Sirtuins utilize NAD^+ as a co-factor for deacetylation process (**Figure 1**).[6] Sirtuins constitute seven isozymes Sirt 1-7. They share the catalytic domain of 260 amino acids and were differentiated by the length of N and C amino acids.[7]

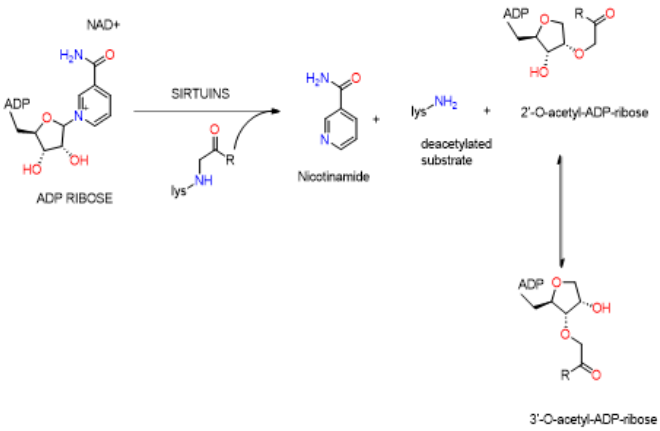


Figure 1. The proposed catalytic mechanism of deacetylation of *N*- terminal lysine acids by Sirtuins.[6]

Sirtuins mediate a vast array of physiological processes such as gene transcription, inflammation, cell cycle progression, apoptosis, autophagy, metabolism, aging, and mitochondrial function.[8,9] SIRT1 is considered the most well-studied sirtuin member and plays an important role in aging, metabolism, and cancer.[10] SIRT2 participates in DNA repair and cell survival. SIRT3 mediates mitochondrial function and aging.[11] SIRT4 is involved in inflammation and insulin resistance.[12] SIRT5 is involved in ammonia disposal and regulation.[13] SIRT6 is involved in the regulation of ribosomes and aging.[14] SIRT7 helps in DNA repair by promoting ribosomal RNA and aging.[15]

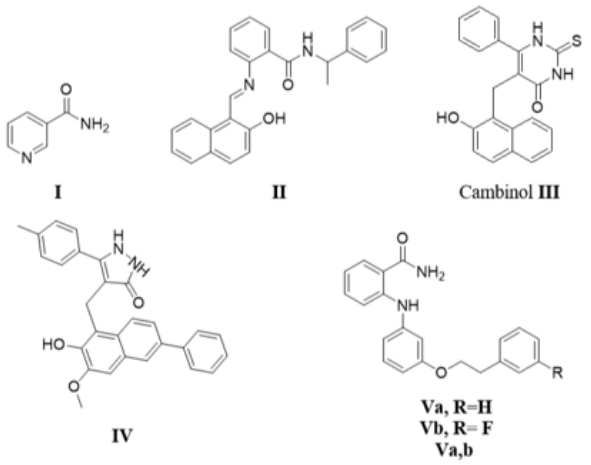
**** Correspondence:*** *Samar H. Abbas*
Tel.: *(+20) 100-542-4005* ***Fax:*** *(+20) 086-236-9075*
Email Address: *samar_hafez@mu.edu.eg*

SIRT2 isozyme was reported to deacetylate histone H4 substrate and non-histone substrates as p46, FOXO1, and α-tubulin.[16-18] SIRT2 has a crucial role in cancer due to its cellular activity. Its activity varied between suppressing tumors as glioma cells or promotion as in neuroblastoma or pancreas cancer cells.[19,20] In addition, it showed oncogenic activity as it stabilizes the Myc-oncoprotein.[20] Additionally, SIRT2 protein promotes mTOR activation and it increases cell growth of colorectal carcinoma cells.[21] SIRT2 protein was overexpressed in renal cell carcinoma stem-like cells and regulated cancer metastasis.[22] Other findings demonstrated a role of SIRT2 and HDAC6 in cell migration and invasion to bladder cancer cells *via* targeting actin cytoskeleton.[23] The crystal structure of SIRT2 comprises two domains. The small domain conserved zinc ion. The large domain constitutes Rossman fold for NAD^+ binding. Between the two domains, the active site was located.[24] The active site contains many hydrophobic pockets including A, B, and C, selectivity, and acetyl lysine (**Figure 2**).

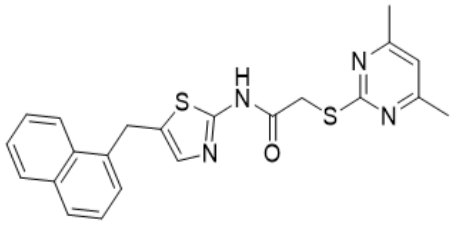
Figure 2. Crystal structure of human SIRT2 enzymes (PDB ID: 4rmg) containing the active site

2.SIRT2 inhibitors

The natural pan inhibitor for Sirtuin isozymes, nicotinamide (NAM) **I**, showed no selectivity towards SIRT1 and 2.[25] Furthermore, Sirtinol **II** was the 1st synthesized SIRT inhibitor that possessed moderate selectivity towards SIRT2. It had IC_{50} values of 68 μM and 38 μM against SIRT1 and SIRT2, respectively. The *meta* and *para* analogues of sirtinol possessed 2-10 folds more potent than *o*-isomer as SIRT1 and 2 inhibitors.[26] The drug showed potent cytotoxicity against MCF-7 breast cancer and H1299 lung cancer cell lines.[27] Further investigations were being conducted on the utilization of the hydroxy naphthyl group as cambinol **III** and compound **IV**.[28-30] Cambinol **III** showed potent inhibitory activity in the mice Burkitt lymphoma xenograft model. It induced apoptosis *via* hyperacetylation of p53 and BCL6 oncoprotein.[29] But the two compounds **III** and **IV** showed no selectivity towards SIRT1 and 2. On the other side, the highly potent SIRT2 inhibitors, compounds **Va** and **Vb**, were innovated by Suzuki *et al*. based on the modification of 2-anilinobenzamide, and they possessed submicromolar inhibitory activity. Compounds **Va, b** showed high selectivity toward SIRT2 with IC_{50} values equal to 1 μM and 0.57 μM, respectively, against SIRT2. In contrast, their IC_{50} values versus SIRT1 were more than 300 μM. Additionally, Compound **Va** induced the hyperacetylation of tubulin in human colon cancer HCT116 cells. [31,32]



The naphthyl group had a pivotal role in the binding of Sirtuin inhibitors, and it forms hydrophobic interactions with the hydrophobic binding site. Another lead compound harnessing the naphthyl group was SirReal2 **VI**.[33] The compound **VI** showed the most potent inhibitory activity among a series of six derivatives with an IC_{50} value of 0.4 μM against SIRT2.



Sireal2, **VI**

The SAR study of compound **VI** revealed the importance of the dimethyl pyrimidine moiety in the binding with the selectivity pocket as well as the adaption of the naphthyl group in the acetyl-lysine hydrophobic pocket (**Figure 3**).

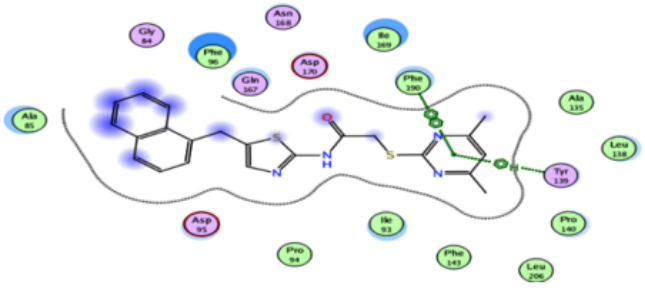
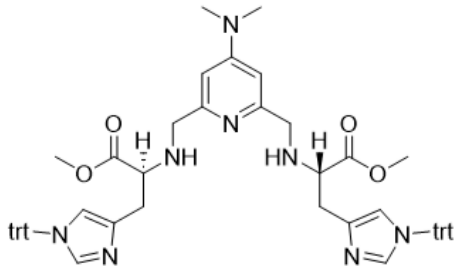


Figure 3. The 2*D* of compound VI within the active site of SIRT2 enzyme (PDB code 4RMG)

Substituted aminopyridine as cytotoxic agents

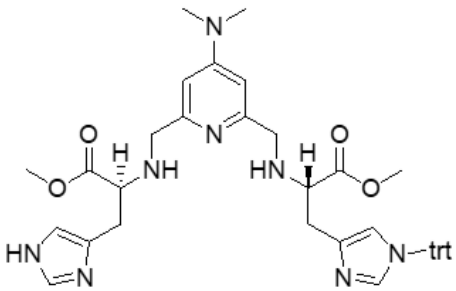
Compound **VII** bearing a dimethylaminopyridyl histidine fragment, was designed as a Bleomycin-like ligand [32] to induce apoptosis in human pancreatic carcinoma cells. The results revealed that compound **VII** was proficient in inducing apoptosis in these cancer cells. The mechanism of action was observed as the activation of reactive oxygen species (ROS) and the downregulation of anti-apoptotic proteins like Bcl-**2.** Additional experiments confirmed that compound **VII**-induced apoptosis

was independent of the p53 pathway and had no cytotoxic effect on non-cancerous cells.



VII

Further development of the previous compound was performed by T. Ali and coworkers. The authors synthesized a series of compounds by modifying substituents of the imidazole rings.[33] The modifications included the addition of mono- and dibenzyl, trityl, or methyl groups. They evaluated the cytotoxicity of these compounds against three human cancer cell lines: breast, colon, and lung. The results showed that the imidazole-substituted derivatives exhibited higher cytotoxicity than the non-substituted ones. The two most active compounds were **VII** and **VIII**. Also, the researchers investigated the mechanism of action of the imidazole-substituted compounds. They found that these compounds induced cell death by apoptosis and inhibited the migration and invasion of cancer cells. Additionally, the compounds were found to chelate metal ions, which may contribute to their anticancer activity.



VIII

Substituted aminopyridine as SIRT2 inhibitors

Compounds **VII**, **VIII,** and fifteen compounds were screened as SIRT2 inhibitors from the chemical library of T. Ali *et al*. The compound's design is based on linking the tritylhistdine group to the dimethylaminopyridine scaffold. The examined compounds **VII** and **VIII** showed potent activity with IC_{50} values of 5.5 µM and 8.8 µM, respectively. Firstly, compound **X** was prepared by simplification of the original previously mentioned two compounds. Compound **X** was synthesized *via* reductive amination of *N,N*-dimethyl-4-aminopyridin-2-carbaldehyde with trityl histidine intermediate compound **IX**. The inhibition activity of compounds **IX** and **X** was screened, and the results indicated that the trityl histidine intermediate compound **IX** showed negligible low SIRT2 enzyme activity, recording an IC_{50} value of 43 µM. While compound **X** exhibited higher potency than the previous lead compounds **VII** and **VIII** against SIRT2, showing an IC_{50} value equal to 1.7 µM. Therefore, they synthesized thirteen derivatives **XI**-**XXIII** to enhance the activity of **X**. Worthily, compounds bearing dimethyl and diethylamino pyridine motif exhibited higher activity and had IC_{50} of 1.3 µM and 1.7 µM, respectively. While compound **XXII** had lower activity (IC_{50}: 20 µM) and compound **XXIII** with bis benzyl groups had negligible inhibitory activity (IC_{50} >100 µM). In addition, the cytotoxicity activities of some selected compounds were evaluated against MCF7, K562, and MT-2 cell lines (**Table 1**). All the examined compounds have more potent cytotoxicity against SIRT-2 sensitive MCF-7 than Sireal2 **VI**. On the other side, the higher cytotoxicity of the selected compounds against K562 and MT-2 versus the lower potency of Sireal2 might be related to the activity of these compounds through DNA cleavage as **VII** and **VIII**.[34] The docking study of **XI** matches with the *in vitro* results. The docking Study revealed that the diethylamino pyridine moiety interacted with Ile 169 of the selectivity pocket in a pattern like that of the Sireal2 **VI** dimethyl pyrimidine group. Also, the trityl group occupied the acetyl-lysine pocket (**Figure 4**).[34]

Table 1. Cytotoxicity of selected trityl histidine derivatives against MCF-7, K562, and MT-2 cell lines (IC_{50} (µM)).

Compound	IC_{50} (µM)		
	MCF-7	K562	MT-2
VII	1.72 ± 0.51	7.91 ± 1.12	8.86 ± 1.38
VIII	2.29 ± 0.43	6.51 ± 0.89	8.61 ± 1.0
X	0.77 ± 0.08	7.53 ± 0.55	3.53 ± 0.44
XI	0.71 ± 0.06	6.27 ± 0.91	4.36 ± 0.62
XIII	11.9 ± 1.2	10.4 ± 1.1	6.81 ± 0.42
XV	8.96 ± 1.03	6.36 ± 0.73	1.75 ± 0.11
XVIII	9.87 ± 1.27	5.35 ± 0.59	1.37 ± 0.08
SirReal2 **VI**	13.7 ± 2.2	>100	>100

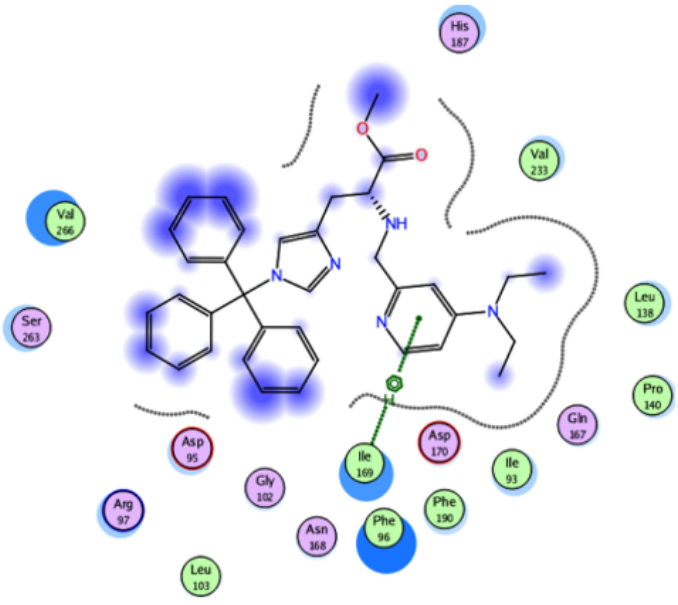
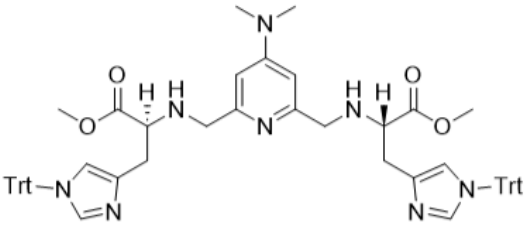


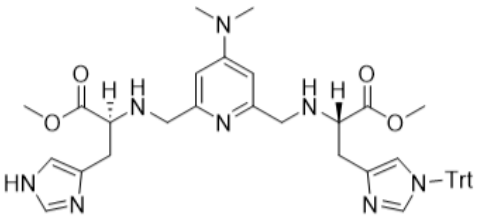
Figure 4. 2D interaction of X with the active site of SIRT2 enzyme (PDB code 4RMG)

SirReal2

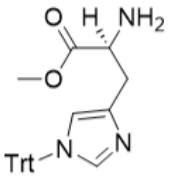
VI (IC_{50}= 0.21 ± 0.02)



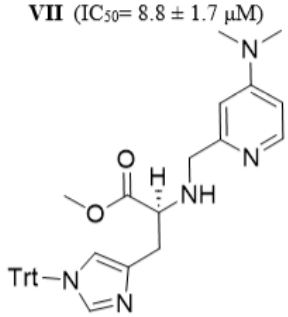
VII (IC_{50}= 8.8 ± 1.7 μM)



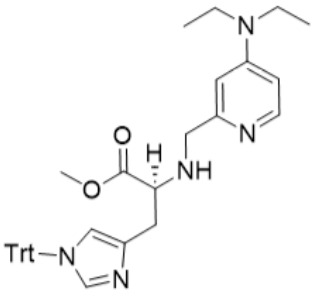
VIII (IC_{50}= 5.5 ± 0.5 μM)



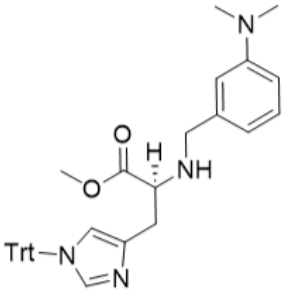
IX (IC_{50}= 43.0 ± 0.8 μM)



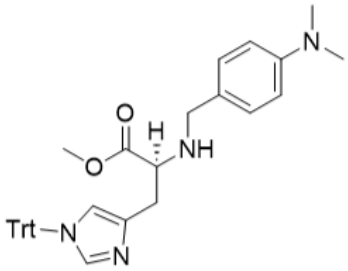
X (IC_{50}= 1.7 ± 0.0 μM)



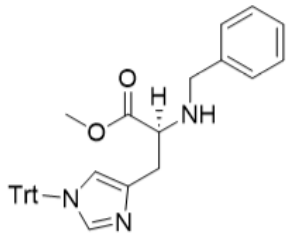
XI (IC_{50}= 1.3 ± 0.2 μM)



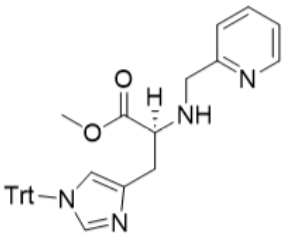
XII (IC_{50}= 5.6 ± 0.1 μM)



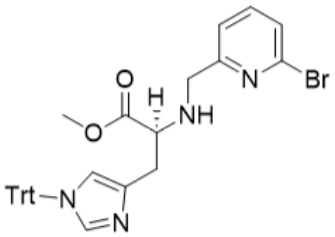
XIII (IC_{50}= 11.8 ± 0.3 μM)



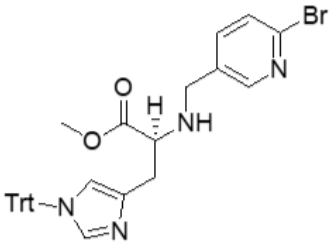
XIV (IC_{50}= 16.4 ± 1.1 μM)



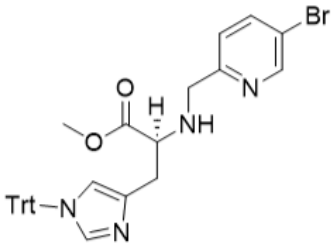
XV (IC_{50}= 21.8 ± 1.0 μM)



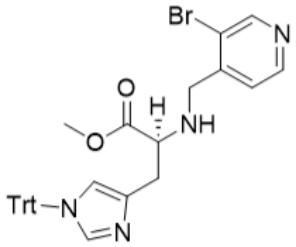
XVI (IC_{50}= 10.2 ± 0.3 μM)



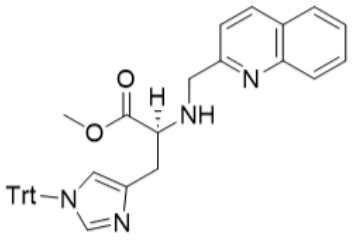
XVII (IC_{50}= 6.7 ± 1.5 μM)



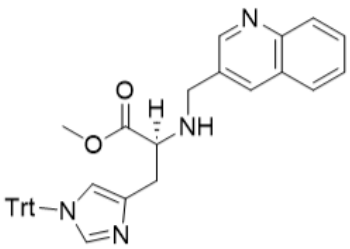
XVIII (IC_{50}= 5.9 ± 0.4 μM)



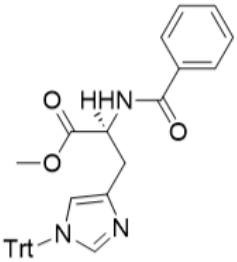
XIX (IC_{50}= 7.5 ± 1.6 μM)



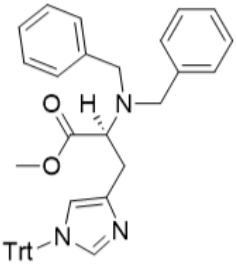
XX (IC_{50}= 2.5 ± 0.3 μM)



XXI (IC_{50}= 3.3 ± 0.8 μM)



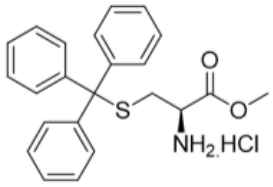
XXII (IC_{50}= 20.4 ± 3.1 μM)



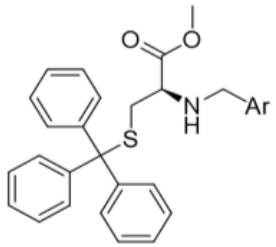
XXIII (IC_{50}= >100 μM)

Radwan and his co-workers developed new series of cysteine methyl esters containing SIRT2 inhibitors. The structure development was achieved through structural modification of the previous potent compound **XI** by conserving the essential trityl group and replacing methyl histidine linker with methyl cysteine. Also, the design includes the incorporation of different terminal aryl groups. SIRT2 screening of the synthesized compounds revealed the high potency of compounds **XXVIII**, **XXXII**, and **XXXV** (**Table 2**). They possessed IC_{50} values of 17.2 μM, 10.8 μM, and 9.5 μM, respectively. These results confirmed the importance of diethyl and dimethyl aminopyridine for the activity. Moreover, they proposed the loss of the activity of **XXXIV** may be related to the free rotation of **XXVIII** compared with **XXXIV**. Additionally, the cytotoxicity of these three compounds, **XXVIII**, **XXXII**, and **XXXV**, was tested versus five different cancer cell lines compared to the cytotoxicity of compound **XI** and Sireal2 **VI**. Compounds **XXVIII** and **XXXIII** had high and close cytotoxicity values, especially against HL-60 leukemia cell lines (**Table 3**).

Notably, the hydrazide derivative showed less relative cytotoxicity owing to its higher polarity and lower cellular penetration ability. The higher cytotoxicity of the active compounds than Sireal2 was explained by DNA cleavage screening at one micromole concentration. Compounds **XXVIII**, **XXXIII**, and **XXXV** showed strong DNA cleavage, like compound **XI**. So, they acted by dual SIRT2 inhibition/DNA cleavage activities. The docking study of the most active compound **XXVIII** showed a similar binding mode to **XXIV** except for adaption in the selectivity pocket. The long histidine moiety of **XI** seemed to be more adaptable in the selectivity pocket than the short methyl cysteine of **XXVIII**. In addition, the dimethylamino group linked to the pyridine ring is not adapted correctly with **XXVIII** than **XI**. Furthermore, the replacement of the dimethylamino group with ling diethyl caused interference interaction with Leu 138; this indicated the higher potency of **XXVIII** over **XXXIII**. The inhibition activity of **XXXV** was attributed to the hydrogen bonding of Asn 168 forms with the hydrazide group.[35]



XXIV



XXV-XXXIII

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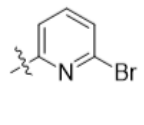
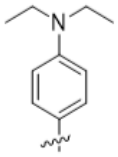
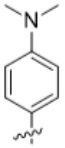


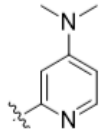
XXV



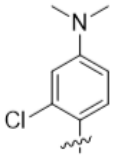
XXVI



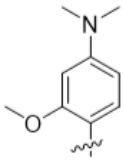
XXVII



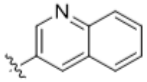
XXVIII



XXIX

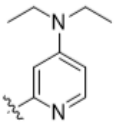


XXX

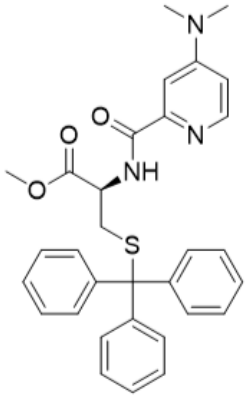


XXXI

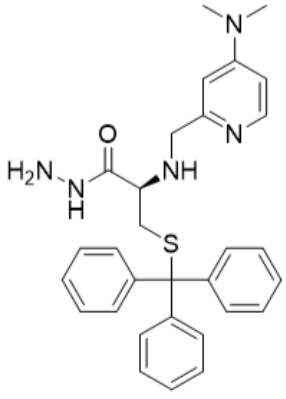
XXXII



XXXIII



XXXIV



XXXV

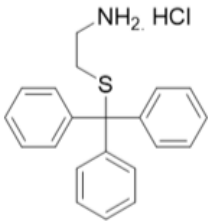
Table 2. The *in vitro* SIRT2 inhibitory activity of compounds **XXIV-XXXV** versus **XI**

Compound	IC_{50} against SIRT2 (μM)	Compound	IC_{50} against SIRT2 (μM)
XXIV	> 100	**XXXI**	> 100
XXV	> 100	**XXXII**	> 100
XXVI	> 100	**XXXIII**	17.2 ±1.2
XXVII	> 100	**XXXIV**	> 100
XXVIII	10.8 ±1.9	**XXXV**	9.5±1.2
XXIX	> 100	**XI**	1.3±0.2
XXX	> 100		

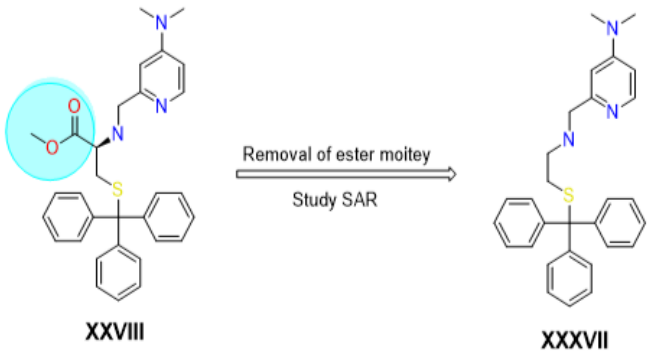
Table 3. IC_{50} values of selected compounds against multiple cancer cell lines.

	MCF-7	**HeLa**	**K562**	**MT-2**	**HL-60**
SirReal2 **VI**	17.08±2.15	10.37±0.94	13.65± 0.44	17.86± 1.52	90.6 ± 8.77
XXVIII	3.16 ± 0.26	1.56 ± 0.17	2.17 ± 0.25	3.15 ± 0.13	0.45 ± 0.05
XXXIII	3.32 ± 0.41	2.72 ± 0.19	2.53 ± 0.31	2.55 ± 0.28	1.19 ± 0.09
XXXV	10.03±1.12	7.95 ± 0.81	14.99± 1.17	16.82± 1.04	12.78±0.95
XI	0.71 ± 0.08	0.37 ± 0.04	0.30 ± 0.02	0.17 ± 0.02	0.28 ± 0.04

Another approach was carried out by the previous team utilizing a cysteamine linker instead of a methyl cysteine ester linker. The synthesized compounds were tested as SIRT2 inhibitors using an electrophoretic mobility test. Firstly, the parent compound **XXXVI** showed no activity (**Table 4**).



XXXVI

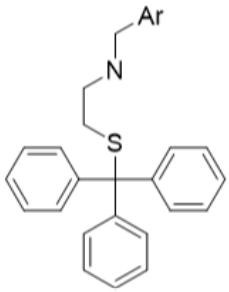


XXVIII **XXXVII**

Compound **XXXVII** devoid of the ester group displayed higher activity than **XXVIII**, with an IC_{50} value of 7.5 μM. The activity was dramatically decreased by removing the dimethylamino group (**IXL** had an IC_{50} value of 39.3 μM). Moreover, removing the dimethyl aminopyridine moiety or its replacement with other aromatic groups abolishes the activity (e.g., **XXXVIII**, **IXL**, and **XLI**). The results reflected the pivotal role of the basic pyridine ring (which is enhanced by a 4-dimethyl amino group) in the activity. **XLII**-bearing diethylaminopyridine has comparable inhibition activity to **XXXVII** (IC_{50} = 7.5 μM). Interestingly, the docking study of **XXXVII, XXVIII**, and Sireal2 with SIRT2 revealed a high degree of alignment of **XXXVII** with Sireal2 compared to **XXVIII**. Moreover, removing carboxymethyl ester from **XXVIII** allowed the protonation of pyrimidine NH of **XXXVII** to form an H-bonding with Ala135 in the selectivity pocket.[36]

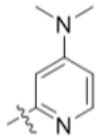
Table 4. In vitro SIRT2 inhibitory activity of cysteamine derivatives versus XXVIII.

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
XXXVI	> 100	**XLII**	7.6 ± 0.7
XXXVII	7.5 ± 0.3	**XLIII**	> 100
XXXVIII	> 100	**XLIV**	> 100
IXL	> 100	**XLV**	> 100
XL	39.3 ± 7.7	**XXVIII**	10.8 ± 1.9
XLI	> 100		

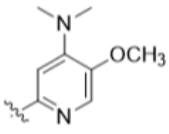


XXXVII- XLII

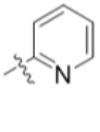
Ar=



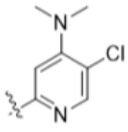
XXXVII



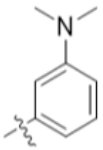
XXXVIII



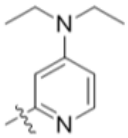
IXL



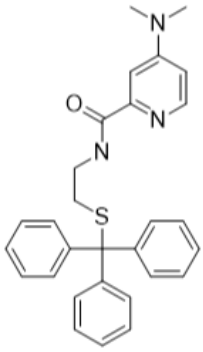
XL



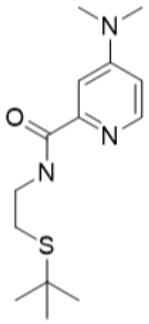
XLI



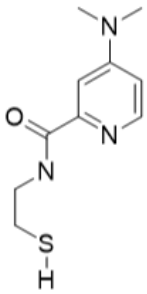
XLII



XLIII



XLIV



XLV

Conclusion

In this review, dimethylamino pyridine (DMAP) development as a new scaffold for SIRT2 inhibition has shown promising results. The combination of molecular modeling and synthetic chemistry approaches allowed the design and synthesis of several DMAP derivatives, which were then evaluated for their ability to inhibit SIRT2. The most potent compound, **XI**, was further assessed as a cytotoxic drug providing essential insights into the mechanism of action of DMAP as a new building block for SIRT2 inhibitors. These findings suggest that DMAP could be a valuable tool for developing novel SIRT2 inhibitors with potential therapeutic applications in various diseases. Further studies are warranted to explore the full potential of DMAP and its derivatives in this context.

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