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Imidazole derivatives as potent inhibitors of sirtuin-1

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Developing of small molecule modulators of SIRT1 activity opens up opportunities for delaying age-related diseases. Therefore, the design of novel modulators is a promising therapeutic approach. Here, we synthesized a series of imidazole derivatives and studied their modulatory activity of against SIRT1 using high-throughput fluorescent assay screening and molecular docking calculations. We found that despite some structural similarity with the known imidazothiazole-based activators, such as SRT1460 and SRT1720, our synthesized derivatives demonstrated an essentially different modulating behavior. In particular, all synthesized derivatives revealed significant inhibiting activity, so that compounds **7a** and **8b** were characterized by the almost complete inhibition (up to 98-100 %) of SIRT1 enzymatic activity. Molecular docking calculations suggest that all studied imidazole derivatives favor a strong binding to the catalytic domain of SITR1, similar to the known inhibitors, such as (*S*)-selisistat. On the opposite, SRT1460 and SRT1720 activators occupied allosteric sites terminal to the catalytic domain of SIRT1. These findings demonstrate the essentially different molecular mechanisms of modulating SIRT1 enzyme activity by these two groups of imidazothiazole derivatives and help further understand SIRT1 action.

Keywords: Sirtuin-1, inhibitor, organic synthesis, imidazole derivatives, molecular docking, high-throughput screening.

Похідні імідазолу як перспективні інгібітори сіртуїну-1. *В.В. Ліпсон, Ф.Г. Яременко, В.В. Вакула, С.В. Коваленко, О.В. Кириченко, С.М. Десенко, В.І. Мусатов, П.О. Бориско, С.О. Зозуля.*

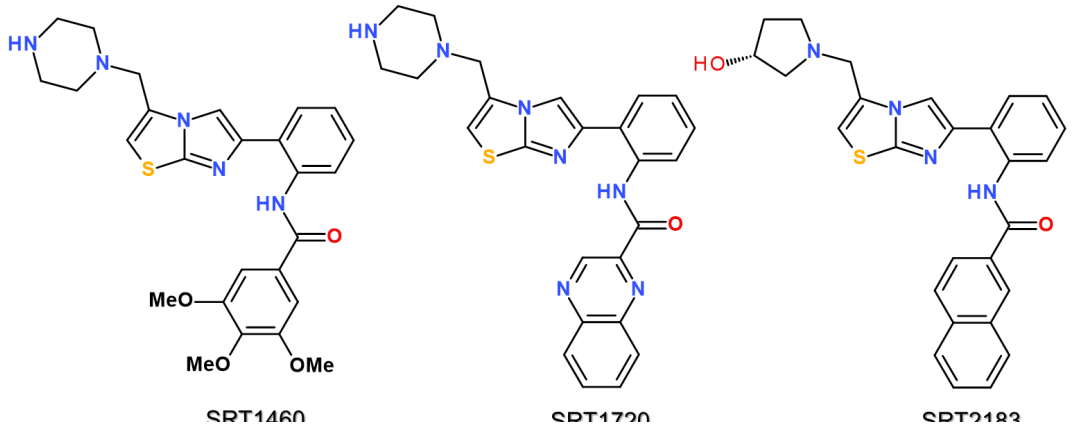
Розробка низькомолекулярних модуляторів активності SIRT1 відкриває можливості для відтермінування вікових захворювань. Тому дизайн нових модуляторів є перспективним терапевтичним підходом. В цій роботі ми синтезували серію похідних імідазолу та вивчили їхню модуляторну активність проти SIRT1 за допомогою скринінгу високопродуктивним флуоресцентним аналізом та розрахунків з використанням молекулярного докінгу. Встановлено, що, незважаючи на деяку структурну подібність з відомими активаторами на

основі імідазотіазолу, такими як SRT1460 і SRT1720, синтезовані похідні продемонстрували істотно іншу модулюючу поведінку. Зокрема, усі синтезовані похідні виявили значну інгібуючу активність, так що сполуки 7a і 8b характеризуються майже повним інгібуванням (до 98-100 %) ферментативної активності SIRT1. Розрахунки молекулярного докінгу показують, що всі вивчені похідні імідазолу сприяють міцному зв'язуванню з каталітичним доменом SITR1, подібно до відомого інгібітора, такого як (S)-селізистат. Навпаки, активатори SRT1460 і SRT1720 займають алостеричні сайти розташовані біля каталітичного домену SIRT1. Ці результати демонструють суттєво різні молекулярні механізми модуляції активності ферменту SIRT1 цими двома групами похідних імідазотіазолу та допомагають у подальшому розумінні дії SIRT1.

1. Introduction

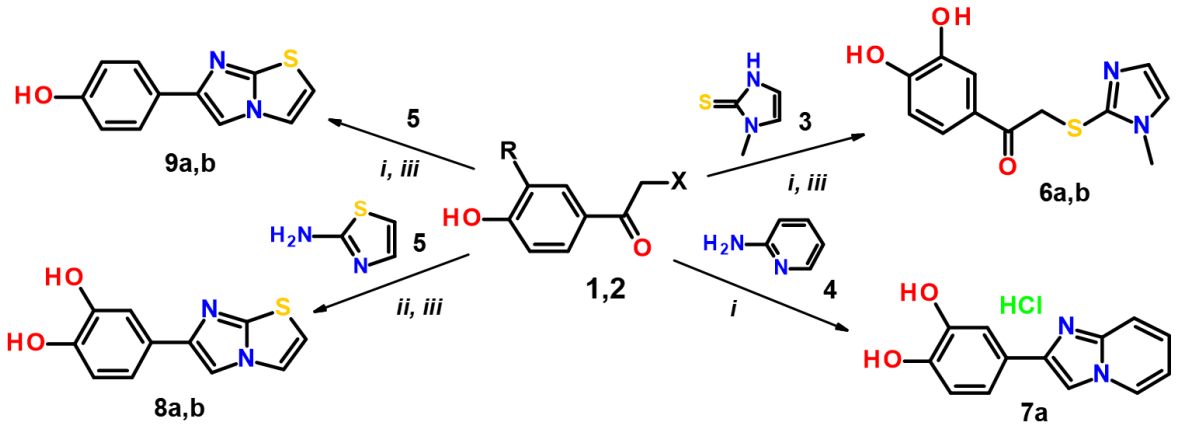
Sirtuins are NAD^+-dependent enzymes that belong to the class III histone deacetylases (HDACs). Their name derives from Silent Information Regulator 2 proteins (Sir2), first discovered as yeast growth factors [1]. In mammals, seven sirtuins (SIRT1-SIRT7) have been identified and are located in different parts of the cell, such as the nucleus, cytoplasm, and mitochondria. SIRT1 (Silent information regulator 2 homologue one) is the closest in structure to Sir2 and the most studied of all seven human sirtuins [2]. This enzyme belongs to epigenetic factors, which affect the functional activity of genes without altering the primary structure of forming their DNA. SIRT1 main function is to transfer an acetyl group from lysine residues in histone proteins to the ADP-ribose NAD^+ fragment. This process contributes to a tighter packing of chromatin and stops the expression of genes, the products of which are not needed by the cells at the moment or may even turn out to be harmful. Even though the primary substrate for sirtuins is histone proteins, most of the proven effects of SIRT1 are associated with its effect on non-histone substrates. Now, more than 35 different target proteins for SIRT1 have been identified, which are involved in cellular processes, such as mitochondrial biogenesis in several tissues, inflammation, carbohydrate/lipid metabolism, autophagy, stress resistance, apoptosis, maintenance of circadian rhythms, and gene silencing. Therefore, modulation of SIRT1 activity can be considered an effective strategy for the treatment of cancer, age-related neurodegenerative disorders, viral and inflammatory diseases, and metabolic disorders accompanying diabetes mellitus type 2 (DM2). In the last decade, many modulators of SIRT1 activity have been discovered among different natural products and synthetic organic molecules [3-6].

Activators of SIRT1 are important for the correction of metabolic disorders associated with DM2. Inhibitors of this enzyme are of great interest for treating cancer, human immunodeficiency virus and neurodegenerative disorders, such as Huntington's disease, Parkinson's disease, and Alzheimer's disease [7]. In connection with the search for new substances with SIRT1 modulation properties, our



SRT1460 SRT1720 SRT2183

Scheme 1. Structure of SIRT1 activators, containing an imidazo[2,1-*b*]thiazol core. 3,4,5-trimethoxy-N-[2-[3-(piperazin-1-ylmethyl)imidazo[2,1-b][1,3]thiazol-6-yl]-phenyl]benzamide (SRT1460, PubChem CID 24180124), N-(2-(3-(piperazin-1-ylmethyl)imidazo[2,1-b]thiazol-6-yl)phenyl)quinoxaline-2-carboxamide (SRT1720, PubChem CID 24180125), (*R*)-N-(2-(3-((3-hydroxypyrrolidin-1-yl)methyl)imidazo[2,1-b]thiazol-6-yl)phenyl)-2-naphthamide (SRT2183, PubChem CID 24180126) [8].



Scheme 2. Synthesis of SIRT1 modulators.

attention was drawn to a series of SIRT1 activators bearing an imidazothiazole core, such as SRT1460, SRT1720 and SRT2183, respectively (Scheme 1) [8].

Therefore, the goal of our study was to synthesize new imidazole analogs of the activators mentioned above, which would have a lower molecular weight and contain hydroxyphenyl substituents (Scheme 2), following the evaluation of their ability to modulate the activity of Sirtuin-1.

2. Experimental

Reagents and analytics. All commercially available reagents and solvents were purchased from commercial vendors and used without purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian MR-400 spectrometer 400 MHz in DMSO-d_6 with TMS as an internal reference. The mass spectra were recorded on a Varian 1200L GC–MS instrument, ionization by EI at 70 eV. Elemental analyses were carried out on an EA 3000 Eurovector elemental analyzer. Melting points were determined on a Kofler hot bench.

Compounds **6a**,**b**, **7a**, **8a**,**b**, **9a**,**b** were synthesized by condensation of 2-chloro- **1** or 2-bromo-1-arylethanone **2** with heterocyclic amines **4**, **5** or with N-methyl-imidazolethione **3** according to Scheme 2.

*Synthesis of 1-(3,4-dihydroxyphenyl)-2-[(1-methyl-1H-imidazol-2-yl)thio]ethanone hydrochloride (**6a**).* N-Methylimidazolethione **3** (20 mmol) was added to a solution of 2-chloro-1-(3,4-dihydroxy-phenyl)ethanone **1** (20 mmol) in a minimal amount of acetone and reaction mixture refluxed until a precipitate formed. The target compound **6a** was filtered off and washed with acetone. Yield 5.41 g (90 %),white needles, mp 215-216 °C.^{1}H NMR spectrum, δ, ppm: 7.78 (d, 1H, *J 1.9 Hz*, C^{5Imd}-H), 7.71 (d, 1H, *J 1.9 Hz*, C^{4Imd}-H), 7.40 (dd, 1H, *J 8.3, 2.0 Hz,* C^{6Ar}-H), 7.36 (d, 1H, *J 2.0 Hz*, C^{2Ar}-H), 6.89 (d, 1H, *J 8.3 Hz*, C^{6Ar}-H), 5.03 (s, 1H, CH_2), 3.82 (s, 1H, NMe).

*General procedure for the preparation of compounds (**7a**), (**8a**).* To a solution of 2-chloro-1-arylethanone **1** (20 mmol) in a minimal amount of BuOH corresponding heterocyclic amine **4** or **5** (20 mmol) was added and reaction mixture refluxed until a precipitate formed. The target compounds were filtered off and washed with BuOH.

*4-Imidazo[1,2-a]pyridin-2-ylbenzene-1,2-diol hydrochloride (**7a**).* Yield 4.10 g (78 %), white needles, mp 290-291 °C. ^{1}H NMR spectrum, δ, ppm: 9.83 (bs, 1H, OH), 9.48 (bs, 1H, OH), 8.85(d, 1H, *J 6.7 Hz*, C^{2Pyr}-H), 8.60 (s, 1H, C^{Imd}-H), 7.85-7.96 (m, 2H, $C^{4,5Pyr}$-H), 7.46 (t, 1H, *J 6.3 Hz*, C^{3Pyr}-H), 7.37 (bs, 1H, C^{2Ar}-H), 7.34 (dd, 1H, *J 8.2, 2.0 Hz,* C^{6Ar}-H), 6.95 (d, 1H, *J 8.2 Hz,* C^{5Ar}-H).

*4-Imidazo[2,1-b][1,3]thiazol-6-ylbenzene-1,2-diol hydrochloride (**8a**).* Yield 3.92 g (63 %), white crystal powder, mp 276-277 °C (from acetone-H_2O). ^{1}H NMR spectrum, δ, ppm: (2H, OH in exchange with H_2O), 8.33 (s, 1H, C^{Imd}-H), 8.19(d, 1H, *J 3.9 Hz*, NCH), 7.64 (d, 1H, *J 4.0 Hz*, SCH), 7.22 (s, 1H, C^{2Ar}-H), 7.16 (d, 1H, *J 8.0 Hz* C^{6Ar}-H), 6.89 (d, 1H, *J 8.1 Hz* C^{5Ar}-H).

*4-Imidazo[2,1-b][1,3]thiazol-6-yl-phenol hydrobromide (**9a**).* To a solution of 2-bromo-1-(4-hydroxyphenyl)ethanone **2** (20 mmol) in a minimal amount of acetone amine **5** (20 mmol) was added and reaction mixture refluxed until a precipitate formed. The target compound **9a**

was filtered off and crystallized from absolute EtOH. Yield 4.46 g (75 %), white crystal powder, mp 245-246 °C. ^{1}H NMR spectrum, δ, ppm: (1H, OH in exchange with H_2O), 8.39 (s, 1H, C^{Imd}-H), 8.24(d, 1H, *J 4.2 Hz*, NCH), 7.66 (d, 1H, *J 4.2 Hz*, SCH), 7.64 (d, 2H, *J 8.5 Hz* $C^{2,6Ar}$-H), 6.91 (d, 2H, *J 8.5 Hz* $C^{3,5Ar}$-H).

General procedure for the preparation of compounds ***(6b), (8b), (9b)***.The conversion of compounds **6a**, **8a**, from hydrochorides and **9a** from hydrobromide (2 mmol) into the corresponding bases was carried out by dissolving them in a minimal amount of water and then adding a solution of potassium carbonate (0.1 M). The resulting precipitates were filtered off and crystallized.

1-(3,4-Dihydroxyphenyl)-2-[(1-methyl-1H-imidazol-2-yl)thio]ethanone ***(6b)***. Yield 0.49 g (93 %), light cream crystals, mp 235-236 °C (from i-PrOH). ^{1}H NMR spectrum, δ, ppm: 9.97 (s, 1H, OH), 9.38 (s, 1H, OH), 7.32-7.36 (m, 2H, C^{6Ar}-H+C^{2Ar}-H), 7.21 (d, 1H, *J 1.5 Hz*, C^{5Imd}-H), 6.89 (d, 1H, *J 1.5 Hz*, C^{4Imd}-H), 6.80 (d, 1H, *J 6.2 Hz*, C^{5Ar}-H), 4.48 (s, 2H, SCH_2), 3.56 (s, 3H, NMe). Mass spectrum, *m/z* (I_{rel}, %): 265.5 $[M+H]^+$ (100). Found, %: C 54.61 H 4.60 N 10.56. $C_{12}H_{12}N_2O_3S$. Calculated, %: C 54.53 H 4.58 N 10.60.

4-Imidazo[2,1-b][1,3]thiazol-6-ylbenzene-1,2-diol ***(8b)***. Yield 0.28 g (61 %), сероватый порошок, mp 261-262 °C. ^{1}H NMR spectrum, δ, ppm: (2H, OH in exchange with H_2O), 8.95 (s, 1H, OH), 8.94 (s, 1H, OH), 7.95 (s, 1H, C^{Imd}-H), 7.86(d, 1H, *J 4.3 Hz*, NCH), 7.23 (d, 1H, *J 1.3 Hz*, C^{2Ar}-H), 7.19 (d, 1H, *J 4.3 Hz*, SCH), 7.08 (dd, 1H, *J 8.0, 1.3 Hz,* C^{6Ar}-H), 6.74 (d, 1H, *J 8.0 Hz* C^{5Ar}-H). Mass spectrum, *m/z* (I_{rel}, %): 233.2 $[M+H]^+$ (100). Found, %: C 56.91 H 3.45 N 12.03. $C_{11}H_8N_2O_2S$. Calculated, %: C 56.88 H 3.47 N 12.06.

4-Imidazo[2,1-b][1,3]thiazol-6-ylphenol ***(9b)***. Yield 0.38 g (87 %), white amorphous powder, mp 257-260 °C. ^{1}H NMR spectrum, δ, ppm: 9.46 (s, 1H, OH), 8.01 (s, 1H, C^{Imd}-H), 7.88(d, 1H, *J 4.2 Hz*, NCH), 7.63 (d, 2H, *J 8.2 Hz* $C^{2,6Ar}$-H), 7.19 (d, 1H, *J 4.2 Hz*, SCH), 6.78 (d, 2H, *J 8.2 Hz* $C^{3,5Ar}$-H). Mass spectrum, *m/z* (I_{rel}, %): 217.2 $[M+H]^+$ (100). Found, %: C 61.15 H 4.16 N 12.89. $C_{11}H_8N_2OS$. Calculated, %: C 61.09 H 4.10 N 12.95.

High-throughput screening. The SIRT1 modulating activity of the studied compounds (Scheme 3) were tested with the recombinant SIRT1 protein using the mode of high-throughput screening by detecting a luminogenic product using the SIRT-Glo™ Assay kit (Cat. G6450) manufactured by Promega (Madison, USA) [9]. Recombinant SIRT1 protein manufactured by SignalChem (Cat. S35-31H-10) was used.

The test compounds were dissolved in dimethylsulfoxide (DMSO) and then added to the reaction buffer in the amount of 80 μM (the final concentration of substances in the reaction mixture was 20 μM, the final concentration of DMSO in the test was 1%). The dissolved compounds were added in 25 μl to a well of a 96-well plate. Nicotinamide (cat. G6540) was used as a reference inhibitor compound at a final concentration of 250 μM (1% DMSO). On the next step, 25 μl of Sirtuin1 protein at a concentration of 0.4 ng/μl (2 ng of protein per well in a reaction volume of 10 μl of a 384-well plate) was added. The pre-reaction mixture was incubated for 30 min at room temperature (25°C). After that, the mixture was transferred from a 96-well plate to a small-volume 384-well white plate manufactured by Corning (cat. 3673) in 10 μl portions, in 4 replicates.

To initiate the enzymatic reaction, 10 μl of SIRT-Glo™ reagent (a mixture of SIRT-Glo™ Substrate, cat. G644A and Developer Reagent, cat. G644B, according to the protocol [9] was added to the pre-reaction mixture. The reaction mixture was incubated at room temperature for 40 min. Luminescence was read using an Omega PolarStar microplate reader. The percentage of inhibition was determined by the Eq. (1):

$$Inhibition(\%) = 100 - ((\frac{X - Aver_{\min}}{Aver_{\max} - Aver_{\min}}) * 100) \quad (1)$$

where X is the luminescence signal at the test point; $Aver_{min}$ is the arithmetic mean of the luminescence of the negative control (reaction without the addition of protein); $Aver_{max}$ is the arithmetic mean value of the luminescence of the positive control (reaction with the addition of protein, but without the addition of modulator compounds).

The inhibition percentage was calculated for each point separately, and then the arithmetic mean of four replicates of the reaction was found for each compound. The inhibition rates of the test compounds are summarized in the Table 1.

Molecular docking setup. The crystallographic structure of SIRT1 (PDB ID: 4I5I [10]) was used as the receptor. The Graphical User

Table 1. The SIRT1 inhibitory activity of the studied imidazole derivatives.

Compound	**6a**	**7a***	**8b***	**9a**
Inhibition of SIRT1 at a concentration of 20 μM, %	92.8±0.8	99.6±0.2	100.8±1.2	76.2±3.3

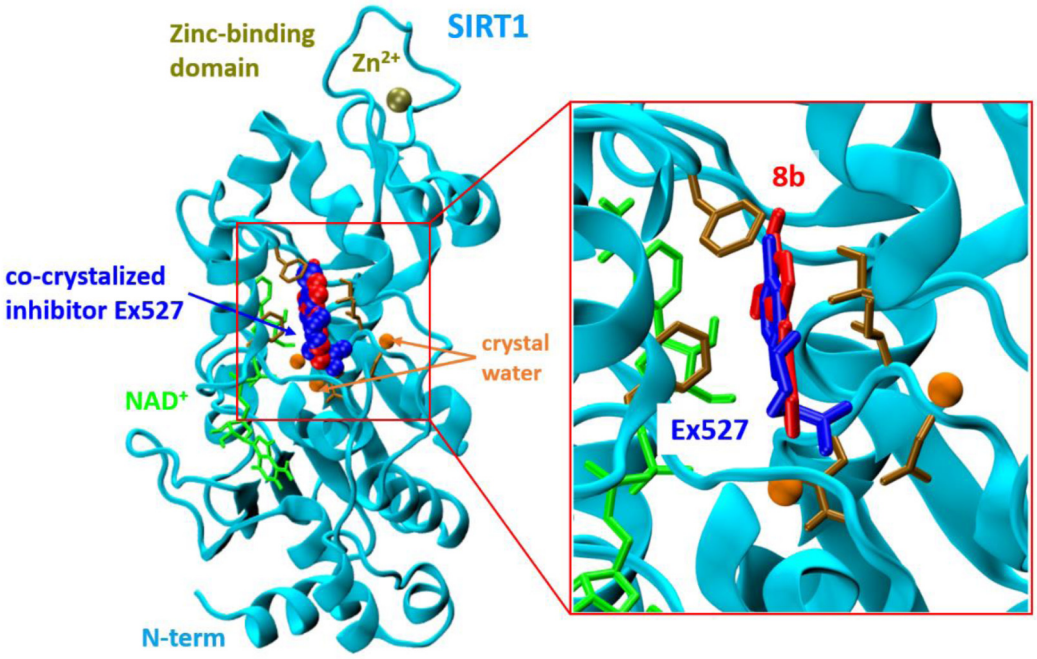


Fig. 1. The 2.5 Å X-ray structure of the catalytic domain of SIRT1 (PDB 4I5I) [10]. The co-crystalized inhibitor Ex527 is shown by the stick representation and coloured blue. The elongated lower pocket of the enzyme active site is occupied by the cofactor NAD^+. Zn^{2+} ion and tree crystalized water molecules are displayed as balls. The Insert: Good overlap of the docked position of **8b** and the X-ray structure of Ex527 is shown for comparison.

Interface of the AutoDock Tools (ADT) was employed to prepare the protein and ligands. A receptor grid box was 40×40×40 Å with a grid spacing of 0.375 Å, and a grid center positioned at Cartesian coordinates x=44.2, y=-20.7, and z=27.0, respectively. The AutoDock Vina 1.1.2 software was utilized for molecular docking calculations [11-12]. The structure of SIRT1 receptor was kept rigid throughout the docking process, while the ligand molecules were conformational flexible. For each docking run, nine docking poses were selected and ranked based on their score values in kcal/mol. Interaction analysis was performed using VMD and Discovery Studio Visualizer. The pose with the lowest binding energy or binding affinity was extracted for further analysis.

3. Results and Discussion

Synthesis. The studied imidazole derivatives **6a**,**b**, **7a**, **8a**,**b**, **9a**,**b** were synthesized by condensation of 2-chloro- **1** or 2-bromo-1-arylethanone **2** with corresponding heterocyclic amines **4**, **5** or with N-methyl-imidazolethione **3** (Scheme 2). The structure and composition of the new compounds were confirmed by ^{1}H NMR spectra, mass spectrometry, and elemental analysis.

Molecular Docking Calculations. To validate our docking protocol, the docking of the studied derivatives was compared with the docking position of the well-known inhibitor of SIRT1 enzyme activity, such as (*S*)-selisistat (Ex527), characterized by IC_{50} 0.1 μM [13-14]. Figure 1 shows that the used molecular docking procedure could correctly reproduce the crystallographic binding mode of the Ex527 inhibitor. Moreover, the best binding modes of the studied derivatives, such as **8b**, overlap essentially with that of Ex527, as seen in the insert of Figure 1.

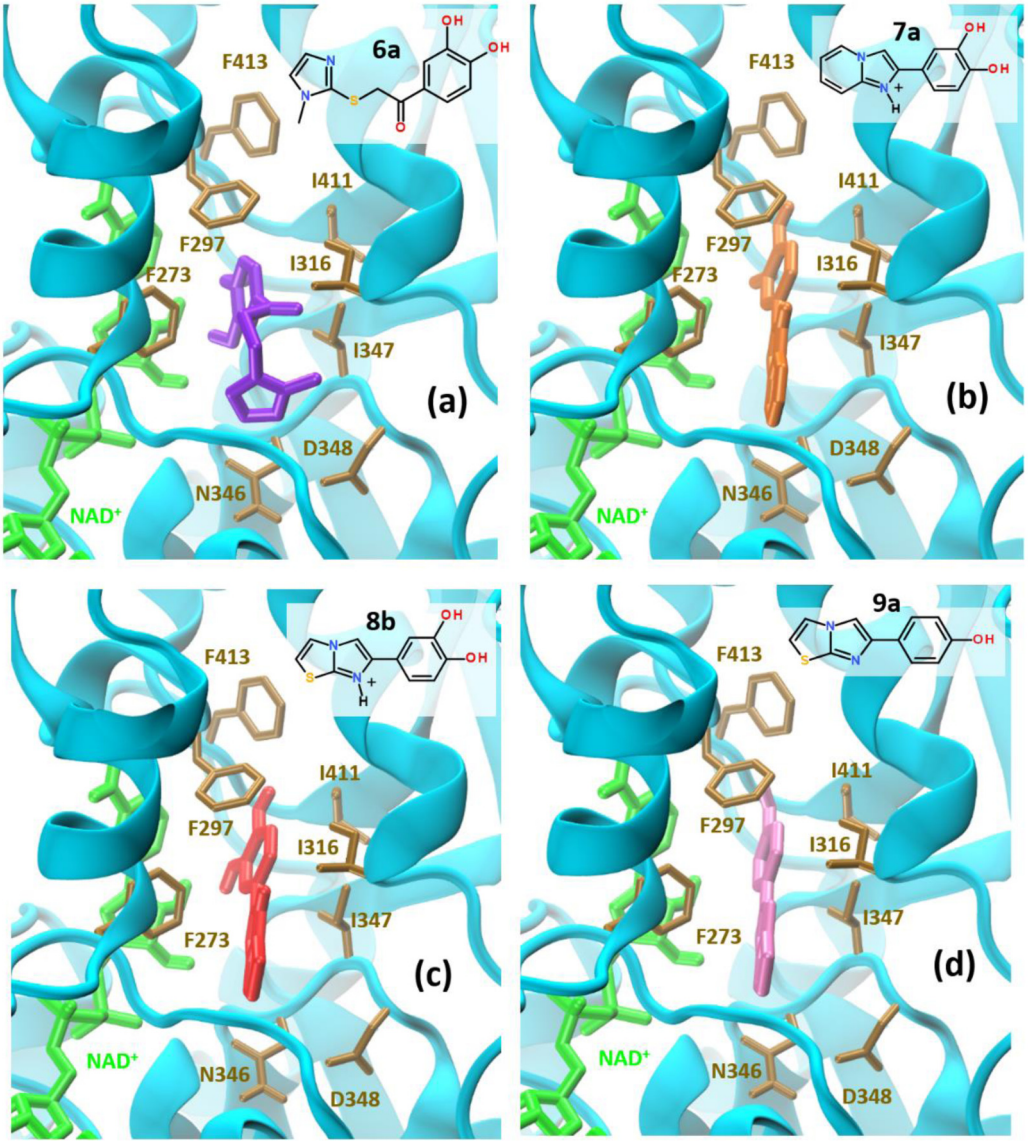


Fig. 2. The best binding modes of **6a** (a), **7a** (b), **8b** (c) and **9a** (d) within the active site of the SIRT1 enzyme estimated by molecular docking calculations.

The binding affinity for the synthesized imidazole derivatives was studied by molecular docking against the X-ray structure of SIRT1. This X-ray structure contains the cofactor NAD^+ and three co-crystallized water molecules (W702, W717 and W732). Therefore, the molecular docking was carried out for two different receptor structures: (i) SIRT1 receptor with the bound cofactor NAD^+ (SIRT1/NAD^+) and (ii) SIRT1 receptor with the bound cofactor NAD^+ and crystal water molecules (SIRT1/NAD^+/3W), as summarized in Table 2. Moreover, taking into account that the high-throughput screening of the modulatory activity of derivatives **7a** and **8b** was performed for their hydrochloride salt (Table 1), molecular docking calculations of these ligands are also carried out for their base and cationic forms, respectively.

Our molecular docking calculations found that the studied imidazole derivatives are all characterized by a binding mode, which is similar in many aspects to the well-known inhibitor Ex527 (Figure 1-2). The nearest residue interaction analysis identified some key residues F273, I347, N346 and D348, which cover the ligand from the front and side faces and are involved in hydrophobic ligand-protein interactions.

Derivatives **7a** and **8b** revealed the highest binding affinity from -8.4 to -8.6 kcal/mol towards the SIRT1/NAD^+ receptor, which is of the same order of the magnitude compared to the available inhibitor (*S*)-selisistat (Table 2).

Table 2. The binding affinity of the studied derivatives and the existing inhibitor Ex527 against the SIRT1 enzyme estimated by molecular docking calculations.

Ligand	Docking Binding Affinity (kcal/mol)	
	SIRT1/NAD$^+$	SIRT1/NAD$^+$/3Waters
6a	–7.9	–8.0
7a	–8.6	–8.2
8a	–8.2	–7.9
8b	–8.4	–8.1
9a	–8.1	–7.9
9b	–8.2	–8.0
(S)-selisistat (Ex527)	–10.7	–11.2

It should also be noticed that the binding energies of the neutral and cationic forms of derivatives **8** and **9** revealed minor differences of 0.1-0.2 kcal/mol towards the cationic structure (Table 2), suggesting that hydrophobic effects drive the major binding interactions of these ligands with the enzyme.

Some recent studies have indicated that both natural and synthetic Sirtuin activators, such as SRT1460, SRT1720 and SRT2183, work via a common allosteric mechanism to stimulate Sirtuin activity [8, 15]. Therefore, we carried out comparative docking studies of these activators against SIRT1 using the same docking protocols described above. Figure 3 shows comparison of the favorable binding modes of the different activators and inhibitors of SIRT1 enzyme.

One can observe essentially different binding behaviors of these two sets of the studied imidazothiazole derivatives. All studied derivatives (Scheme 2) revealed strong binding to the catalytic domain of SITR1. Their binding modes are similar in many aspects to the known inhibitor, such as (*S*)-selisistat (Ex527), shown in Figure 1. It suggests a common inhibiting mechanism for these compounds. In contrast, the same molecular docking procedure demonstrates that the activators SRT1460, SRT1720, and SRT2183 are bound into the SIRT1 enzyme in different fashions, so that they occupy allosteric sites terminal to the catalytic domain of SIRT1. These findings can explain the essentially different modulating activity of structurally similar imidazothiazole derivatives, acting either as activators or inhibitors depending on their binding modes at SIRT1 protein.

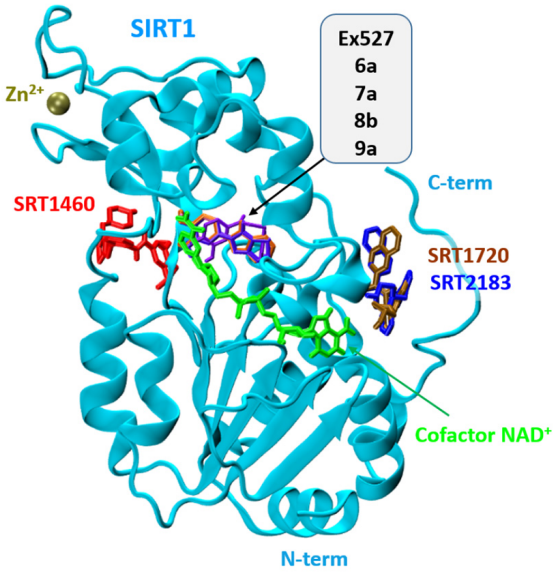


Fig. 3. Comparison of binding modes of the different SIRT1 modulators. The favourable binding modes of the studied inhibitors **6-9** differ essentially from the binding interactions of the known activators, such as SRT1460, SRT1720 and SRT2183, which occupied an allosteric sites terminal to the catalytic domain.

4. Summary and Conclusions

To address the therapeutic potential of SIRT1 modulation for treating age-related diseases, we have synthesized and characterized a series of novel small molecule inhibitors bearing imidazole or imidazothiazole scaffolds. Using high-throughput screening and molecular docking calculations, we found that despite some structural similarity with the known activators, such as SRT1460 and SRT1720 (Scheme 1), our synthesized derivatives **7a** and **8b** (Scheme 2) revealed the significant inhibitory activity of the recombinant SIRT1 protein up to 100 %, as confirmed by the SIRT-Glo™ assay. Molecular docking calculations suggest

that the high inhibitory activity of all studied derivatives is due to their strong binding to the catalytic domain of SITR1. Moreover, their binding modes are essentially similar to the known inhibitor, such as (*S*)-selisistat, suggesting a common inhibiting mechanism. In contrast, using the identical molecular docking protocol, we demonstrate that the well-known activators, such as SRT1460 and SRT1720, favor the binding behavior towards SIRT1, which differs from the studied inhibitors in many aspects. These activators occupied allosteric sites terminal to the catalytic domain of SIRT1, highlighting essentially different molecular mechanisms of modulating the activity of SIRT1 by these two sets of the imidazothiazole derivatives.

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