Article

Discovery of (5-Phenylfuran-2-yl)methanamine Derivatives as New Human Sirtuin 2 Inhibitors

Lijiao Wang 1, Chao Li 1, Wei Chen 1, Chen Song 1, Xing Zhang 2, Fan Yang 1, Chen Wang 1, Yuanyuan Zhang 2, Shan Qian 1, Zhouyu Wang 2, * and Lingling Yang 1, *

1 College of Food and Bioengineering, Xihua University, Sichuan 610039, China
2 College of Science, Xihua University, Sichuan 610039, China
* Correspondence: zhouyuwang77@gmail.com (Z.W.); yangll0808@sina.com (L.Y.); Tel.: +86-28-7725898 (L.Y.)

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Abstract: Human sirtuin 2 (SIRT2), a member of the sirtuin family, has been considered as a promising drug target in cancer, neurodegenerative diseases, type II diabetes, and bacterial infections. Thus, SIRT2 inhibitors have been involved in effective treatment strategies for related diseases. Using previously established fluorescence-based assays for SIRT2 activity tests, the authors screened their in-house database and identified a compound, 4-(5-((3-(quinolin-5-yl)ureido)methyl)furan-2-yl)benzoic acid (20), which displayed 63 ± 5% and 35 ± 3% inhibition against SIRT2 at 100 µM and 10 µM, respectively. The structure-activity relationship (SAR) analyses of a series of synthesized (5-phenylfuran-2-yl)methanamine derivatives led to the identification of a potent compound 25 with an IC_{50} value of 2.47 µM, which is more potent than AGK2 (IC_{50} = 17.75 µM). Meanwhile, 25 likely possesses better water solubility (cLogP = 1.63 and cLogS = −3.63). Finally, the molecular docking analyses indicated that 25 fitted well with the induced hydrophobic pocket of SIRT2.

Keywords: histone deacetylases; sirtuins; SIRT2; SAR studies; molecular docking

1. Introduction

Histone deacetylases (HDACs) are enzymes that catalyze the removal of acyl groups from ε-N-acyl-lysine amino groups on histones and non-histone substrates. These have been identified and grouped into four classes [1–3]: Classes I, II, and IV HDACs are Zn^{2+}-dependent metalloproteases; class III HDACs, namely sirtuins (SIRTs), use NAD^{+} as a cofactor for catalysis [4–6]. There are seven isotypes of sirtuins (SIRT1–7), which differ in their catalytic activity and subcellular localization [7]. The isotype SIRT2, which is located in both cytoplasm and nucleus [8], mainly catalyzes deacetylation and defatty-acylation for a variety of protein substrates, including histones H3 and H4 [9,10], and nonhistone proteins α-tubulin [11], p53 [12], Foxo1 [13], p300 [14], NFκB [15], PAR3 and PRLR [16]. Thus, SIRT2 has been shown to be involved in cell cycle regulation [11,17,18], autophagy [19], peripheral myelination [20], and immune and inflammatory responses [21–23]. Recently, many studies revealed that the dysregulation of SIRT2 activity is a key factor contributing to the pathogenesis of cancer [24], neurodegenerative diseases [25,26], type II diabetes [27], and bacterial infections [21,23], which makes SIRT2 a promising target for pharmaceutical intervention.

To date, except for some substrate analogues [7], a number of small molecule inhibitors targeting SIRT2 have been reported. The representative inhibitors are shown in Figure 1: The moderate potency or non-specific inhibitors Sirtinol (46 µM) [28], EX-527 (46 µM) [29,30], AGK2 (3.5 µM) [31,32], AEM1 (18.5 µM) [33], AK-7 (15.5 µM) [34], and AC-93253 (6 µM) [35], the highly potent but unselective inhibitors VII (0.048 µM) and VIII (0.001 µM) [36], and the potent and highly isotype-selective SIRT2 inhibitor SirReal2 (0.4 µM) [23,37]. However, there remains a shortage of novel SIRT2 inhibitors as lead candidates for drug discovery and development.
by using Suzuki cross-coupling reaction between commercially available substituted iodobenzenes in the presence of triphosgene, in 82–93% yields (Scheme 1). The intermediates 5a–5i were obtained through the condensation reaction between the key intermediate 5a and the focus of structural modifications.

The authors previously established a fluorescence-based method for SIRT2 inhibition tests [38–40], and identified a series of N-(3-(phenoxy)methyl)phenyl)acetamide derivatives as highly selective SIRT2 inhibitors [38,41], some of which showed inhibitory activities against SIRT2 highly-expressed human breast cancer cells and non-small cell lung cancer cells. Recently, the in-house compound collection using the fluorescence-based method was screened, and a new compound was identified, 4-(5-((3-(quinolin-5-yl)ureido)methyl)furan-2-yl)benzoic acid (20, Figure 2), which displayed 63 ± 5% and 35 ± 3% inhibition against SIRT2 at 100 μM and 10 μM, respectively (Table 1). The scaffold of compound 20 is novel for SIRT2 inhibitors, and 20 has a relatively low molecular weight (387 Da) with moderate physicochemical properties (cLogP = 3.05, cLogS = –4.04). Thus, in this study, the authors used 20 as a starting point for further structural modifications (Linker, A, B, Figure 2) to improve the inhibitory potency against SIRT2.

![Chemical structures and inhibition potencies of selected examples SIRT2 inhibitors.](image1)

**Figure 1.** Chemical structures and inhibition potencies of selected examples SIRT2 inhibitors.

![Chemical structure of 20 and the focus of structural modifications.](image2)

**Figure 2.** Chemical structure of 20 and the focus of structural modifications.

### 2. Results and Discussion

#### 2.1. Chemistry

This study synthesized a series of (5-phenylfuran-2-yl)methanamine derivatives using the synthetic routes outlined in Schemes 1–3. Firstly, urea-based compounds 11–19 were acquired through the condensation reaction between the key intermediate 5a–5i with aromatic-amine compounds 6–10 in the presence of triphosgene, in 82–93% yields (Scheme 1).
1a–1i with (5-formylfuran-2-yl)boronic acid (2), respectively. Then, the condensation reaction and reduction reaction were performed in sequence to produce the intermediates 5a–5i. The carboxylic acid compounds 20–26 were subsequently produced through the hydrolysis reaction from the corresponding esters.

Scheme 1. The preparation of target compounds 12, 17, 18 and 20–26. Reagents and conditions: (i) Pd(PPh₃)₂Cl₂, Na₂CO₃, MeCN/H₂O = 1:1, 60 °C, 1 h, 80–85% [42]; (ii) NH₂OH·HCl, NaOAc, EtOH, Ref., 0.5 h, 100% [43]; (iii) Zn, HCl, EtOH, 80 °C; 62–83%; (iv) BTC, Et₃N, DCM, RT., 0.5 h, 6 h, 82–93%; (v) NaOH, EtOH/H₂O = 1:1, 80 °C, 2 h, 86–95%.

Next, the desired target compound 30, a hydroxamic acid derivative, was prepared by a three-step sequence starting from the synthesized intermediate 4a (Scheme 2). Sodium cyanoborohydride (NaBH₃CN)-mediated reduction reaction was firstly performed to reduce the aldoxime group of intermediate 4a to the hydroxylamine of intermediate 27 (54% yield), followed by condensation with 2-phenylacetyl chloride in the presence of NaHCO₃ to give the compound 29. Further, hydrolysis of compound 29 using 3.0 equiv NaOH led to the white solid target compound 30. The synthesis of target compounds 32–37 are also depicted in Scheme 2. The reactions of commercially available amines (aniline, phenylmethanamine, and pyridin-3-ylmethanamine) or hydrazide (nicotinohydrazide) with intermediates 3a or 3i in the presence of hantzschester (1.2 equiv), catalytic amount of molecular sieve and trifluoroacetic acid, resulted in the reductive amination products 31–34. The resulting compounds 31–33 were subsequently hydrolyzed to give the desired compounds 35–37 in high yields.
Scheme 2. The preparation of target compounds 30 and 32–37. Reagents and conditions: (i) NaBH₃CN, HCl, MeOH, 0–60 °C, 4 h, 54%; (ii) NaHCO₃, diethyl ether, RT, 6 h, 78%; (iii) NaOH, EtOH/H₂O = 1:1, 80 °C, 2 h, 89%; (iv) hantzschester, TFA, molecular sieve, DCM, 45 °C, 6–12 h, 56–95%; (v) NaOH, EtOH/H₂O = 1:1, 80 °C, 2 h, 92–96%.

Scheme 3. The preparation of target compounds 39, and 43–52. Reagents and conditions: (i) benzene sulfonyl chloride, Et₃N, DCM, RT, 2 h, 91%; (ii) NaOH, EtOH/H₂O = 1:1, 80 °C, 2 h, 90%; (iii) HOBT, EDCI, DIPEA, DCM, RT, 12 h, 73–91%; (iv) NaOH, EtOH/H₂O = 1:1, 80 °C, 2 h, 90–95%.

Finally, Scheme 3 presents the synthetic routes for compounds 39 and 43–52, which contain a sulfonamide or amide linker. For sulfonamide linker compound 39, intermediate 5a was used to react with benzene sulfonyl chloride in the presence of Et₃N at room temperature, and the resulting compound 38 underwent a hydrolysis reaction to give the desired target compound 39, in 80% yield for two steps. The synthetic access to structurally diverse amide linker compounds 41–48 was achieved using a condensation reaction of carboxylic acid (40) with amine (5a, 5c–5f) in the presence of 1-hydroxybenzotriazole (HOBT), 1-(3-dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDCI), and N,N-disopropylethylamine (DIPEA). The resulting ester-contained compounds 41, 42, 46 and 47 were subjected to hydrolyzation to afford the target compounds 49–52 in good yields.
2.2. SAR Studies with SIRT2

The enzyme activity assays were performed using a fluorogenic-based method [38–40], and Ac-Glu-Thr-Asp-Lys(Dec)-AMC, termed p2270, was used as the substrate. The SAR studies with all of the synthesized (5-phenylfuran-2-yl)methanamine derivatives (Tables 1 and 2) were carried out. The compounds bearing various linkers or different substituents (A moiety) at 3- or 4-position of the phenyl of (5-phenylfuran-2-yl)methanamine scaffold (Table 1) were firstly investigated. Compared with the hit compound 20, compounds 12 and 21, containing a urea as linker, showed comparable or slightly lower SIRT2 inhibitory activities at 100 μM or 10 μM; Carboxyl acid which contained compounds 20 and 21, appeared to have better clogP and clogS properties than 12 (with clogP of 5.14 and clogS of −4.43). Compound 22 (23 ± 3%), bearing a thiourea linker, displayed lower inhibitory activity to SIRT2 than the corresponding compound 21 (33 ± 3%) at 10μM. Further comparison of the different linkers, including hydroxamic acid (30), secondary amine (35, 36), sulfonamide (39) and amide (49, 50) revealed that urea linker derivatives were likely to have more potent SIRT2 inhibition than other linker derivatives. The additional compounds with the 4-ethyl formate (32), 4-methyl (43), 4-methoxy group (44) replaced the 4-carboxyl of the phenyl of (5-phenylfuran-2-yl)methanamine scaffold or changed to 3-position substituents (45–47, 51, and 52) did not show improved inhibitory activity against SIRT2. These results indicate that the urea linker and 4-carboxyl of the phenyl of (5-phenylfuran-2-yl)methanamine scaffold may be beneficial to fit with the binding pocket of SIRT2.

Table 1. The inhibitory activities and calculated clogP/clogS values of compounds 12, 20–22, 30, 32, 35–36, 39, 43–47 and 49–52 against human SIRT2.

| ID | Structure | Inhibition% 1/SIRT2-p2270 @ 100 μM | Inhibition% 1/SIRT2-p2270 @ 10 μM | cLogP | cLogS |
|----|-----------|---------------------------------|---------------------------------|-------|-------|
| 20 | ![Structure](image) | 63 ± 5                          | 35 ± 3                          | 3.05  | −4.04 |
| 12 | ![Structure](image) | 60 ± 3                          | 33 ± 3                          | 5.14  | −4.43 |
| 21 | ![Structure](image) | 46 ± 4                          | 33 ± 3                          | 2.85  | −3.98 |
| 22 | ![Structure](image) | 44 ± 5                          | 23 ± 3                          | 3.60  | −4.22 |
| 30 | ![Structure](image) | 13 ± 2                          | −2 ± 3                          | 2.99  | −4.05 |
| 35 | ![Structure](image) | 24 ± 3                          | 1 ± 2                           | 4.27  | −4.13 |
| 39 | ![Structure](image) | 38 ± 3                          | 11 ± 2                          | 1.85  | −4.13 |
| 49 | ![Structure](image) | 32 ± 3                          | 8 ± 1                           | 3.12  | −4.14 |
whereas compounds 50 and 25 inhibition to SIRT2, whereas compounds further synthesized. Comparing with structurally similar compound AGK2 (80 ± 6% @ 100 µM), which both contained a urea linker, displayed low SIRT2 inhibition compared to 38 ± 13.12% and 3.12 µM, respectively. 33 The additional compounds with the 4-ethyl formate (32 ± 3% @ 100 µM) shows potent inhibition against SIRT2, which is substantially more potent than the hit compound M, 23 ± 2% @ 100 µM (37, 25, 34, and 37) were almost no SIRT2 inhibitory activities (Table 2). Compared with 25, only compounds 17 (50 ± 4% @ 100 µM, 37 ± 3% @ 10 µM) and 18 (40 ± 5% @ 100 µM, 23 ± 2% @ 10 µM), which both contained a urea linker, displayed low inhibition to SIRT2, whereas compounds 33, 34, 37 and 48 had also almost no SIRT2 inhibitory activities (Table 2).

Collectively, the structural optimization and SAR studies led to the discovery of compound 25, which exhibited high potency against SIRT2, better than the hit compound 20 and positive control AGK2. Subsequently, the IC50 value of 25 was then measured against SIRT2, and the IC50 curve

| ID | Structure | Inhibition% 1/SIRT2-p2270 | cLogP | cLogS |
|----|-----------|---------------------------|-------|-------|
|    |           | @ 100 µM                  |       |       |
| 50 |           | 30 ± 2                    | 3.34  | −4.25 |
| 32 |           | 9 ± 2                     | 4.17  | −4.54 |
| 36 |           | 15 ± 2                    | 2.48  | −4.29 |
| 43 |           | 3 ± 2                     | 4.18  | −4.46 |
| 44 |           | 20 ± 3                    | 3.79  | −4.36 |
| 45 |           | 19 ± 2                    | 3.76  | −4.36 |
| 46 |           | 15 ± 2                    | 3.46  | −4.3  |
| 51 |           | 18 ± 3                    | 3.09  | −4.12 |
| 47 |           | 16 ± 3                    | 3.67  | −4.4  |
| 52 |           | 18 ± 2                    | 3.31  | −4.24 |
| AGK2 |       | 80 ± 6                    | 5.65  | −4.25 |

1 Each compound was tested in triplicate; the data are presented as the mean ± SD (n = 2).

The authors next synthesized compounds 23–26, which contain a urea linker and 4-carboxyl of the phenyl of (5-phenylfuran-2-yl)methanamine. The tested inhibitory activities and calculated clogP and clogS values are shown in Table 2. Compounds 23, 24, and 26 appear to have moderate physiochemical properties, but compound 25, with the pyridine moiety, likely possesses better water solubility (cLogP = 1.63 and cLogS = −3.63). Notably, compound 25 (99 ± 2% @ 100 µM, 90 ± 3% @ 10 µM) shows potent inhibition against SIRT2, which is substantially more potent than the structurally similar compound AGK2 (80 ± 6% @ 100 µM, 30 ± 5% @ 10 µM). Considering the fact that the introduction of pyridine at the skeleton has improved SIRT2 inhibition, a series of pyridine-containing (5-phenylfuran-2-yl)methanamine derivatives (17, 18, 33, 34, and 48) were further synthesized.
has been presented in Figure 3. The study observed that compound 25 inhibited SIRT2 via a dose dependent manner with an IC\textsubscript{50} value of 2.47 μM, which is more potent than AGK2 (with an IC\textsubscript{50} value of 17.75 μM). Molecular docking was then used to investigate the possible binding mode of 25 with SIRT2. The results indicated that 25 appeared to fit well with the induced hydrophobic pocket (Figure 4) [44,45]. The carboxyl acid group of 25 is likely positioned to make hydrogen-bonding interactions with the main chain of Asp170 and the side chain of Thr171 and Tyr139. The furan and pyridine moiety likely have hydrophobic contacts with hydrophobic residues Phe119, Phe234, Phe131, Leu138, and Ile169 (Figure 4). Notably, the pyridine appears to form edge-to-face aromatic interactions with Phe119, and fits well with the pocket around Phe119, Phe131, and Phe234, suggesting that introducing substituents on pyridine may result in a clash with these three residues. Together, these docking results may explain why the replacement of the carboxyl acid group or the introduction of substituents on pyridine leads to a decrease in SIRT2 inhibition, and indicates the possible inhibition mode for this series of compounds.

| ID | Structure | Inhibition% \textsuperscript{1}/SIRT2-p2270 | cLogP | cLogS |
|----|-----------|------------------------------------------|-------|-------|
| 23 | ![Structure](image1.png) | 35 ± 4 / 10 ± 3 | 3.15 | -3.58 |
| 24 | ![Structure](image2.png) | 43 ± 2 / 13 ± 2 | 3.21 | -3.82 |
| 25 | ![Structure](image3.png) | 99 ± 2 / 90 ± 3 | 1.63 | -3.63 |
| 26 | ![Structure](image4.png) | 9 ± 2 / -5 ± 3 | 3.05 | -3.83 |
| 17 | ![Structure](image5.png) | 50 ± 4 / 37 ± 3 | 2.85 | -3.83 |
| 18 | ![Structure](image6.png) | 40 ± 5 / 23 ± 2 | 3.54 | -4.12 |
| 33 | ![Structure](image7.png) | 20 ± 3 / 3 ± 2 | 3.28 | -4.08 |
| 37 | ![Structure](image8.png) | 30 ± 5 / 5 ± 2 | 2.56 | -3.83 |
| 48 | ![Structure](image9.png) | 18 ± 2 / 0 ± 2 | 2.82 | -4.11 |
| 34 | ![Structure](image10.png) | 3 ± 2 / -2 ± 3 | 3.19 | -4.12 |
| AGK2 | ![Structure](image11.png) | 80 ± 6 / 30 ± 5 | 5.65 | -4.25 |

\textsuperscript{1} Each compound was tested in triplicate; the data are presented as the mean ± SD (n = 2).
3. Materials and Methods

3.1. Synthesis

As previously reported, proton ($^1$H) and carbon ($^{13}$C) NMR spectra were recorded on a Bruker AV-400 (Bruker Company, Billerica, Germany) instrument and are reported in ppm relative to tetramethylsilane (TMS) and referenced to the solvent in which the spectra were collected. Unless otherwise noted, all of the commercially available starting materials, reagents, and solvents and reagents were used without further purification. The analytical thin-layer chromatography (TLC) was run on Merck silica gel 60 F-254 (Qingdao Haiyang, Qingdao, China). The spots on the plates were visualized under UV light ($\lambda = 254$ nm). Purification was performed on silica gel chromatography with EtOAc—petroleum ether or CH$_2$Cl$_2$-MeOH solvent systems. The melting points were measured on an electrothermal melting point apparatus without correction (JIAHANG, Shanghai, China). ESI-MS was obtained on a Shimadzu-2010EV series liquid chromatograph mass spectrometer (Shimadzu, Tokyo, Japan). High-resolution mass spectra (HRMS) were determined using a SCIEX
X500 QTOF mass spectrometer (Shanghai Sciex Analytical Instrument Trading Co., Shanghai, China). All target compounds were purified to >95% purity, as determined by the high-performance liquid chromatography (HPLC). The HPLC analysis was performed on a Waters 2695 HPLC system equipped with a Kromasil C18 column (4.6 mm × 250 mm, 5 µm, Waters, Milford, MA, USA).

3.1.1. General Procedure for the Preparation of Key Intermediates 5a–5i

A mixture of substituted iodobenzenes (1a–1i, 15 mmol), (5-formylfuran-2-yl)boronic acid (2, 15 mmol), bis(triphenylphosphine)palladium(II) chloride (Pd(PPh₃)₂Cl₂, 0.6 mmol) and sodium carbonate (Na₂CO₃, 30 mmol) in MeCN/H₂O (10 mL/10 mL) was stirred for 1 h at 60 °C. Upon completion of the reaction as determined by TLC, MeCN was removed by a rotary evaporator under reduced pressure, and the residue was acidified with 1 M HCl solution (pH 7) and filtered. Next, the filtrate was partitioned between water (60 mL) and ethyl acetate (3 × 50 mL). The organic layer was dried over magnesium sulfate anhydrous (MgSO₄), filtered and concentrated in vacuo. The crude products were purified by column chromatography with appropriate eluents to give the coupling products 3a–3i, in 80–86% yields.

To a solution of the coupling products 3a–3i (12 mmol) in EtOH (25 mL), hydroxylamine hydrochloride (NH₂OH.HCl, 14.4 mmol) and sodium acetate (NaOAc, 14.4 mmol) were added and the mixture was stirred at reflux for 0.5 h. When TLC indicated that the reaction was finished, the reaction solution was concentrated and the residue was partitioned between water (50) and ethyl acetate (3 × 50 mL). The combined organic layer was dried over MgSO₄, filtered and concentrated in vacuo to give the crude products 4a–4i, which were used without further purification. Subsequently, to a stirring solution of condensation products, 4a–4i (12 mmol) in EtOH (25 mL) was added to zinc powder (Zn, 12 mmol) and 3 M hydrochloric acid (HCl, 8.0 mL) at ambient temperatures. The reaction mixture was stirred at reflux for 0.5 h. When TLC indicated that the reaction was finished, the reaction mixture was cooled to room temperature (RT). After evaporation of the solvent, the residue was taken up in DCM (30 mL), dried over magnesium sulfate anhydrous (MgSO₄), and the filtrate was partitioned between water (60 mL) and ethyl acetate (3 × 30 mL). The combined extracts were dried, concentrated and purified by column chromatography with appropriate eluents with ethyl acetate and ethyl acetate (3 × 50 mL). The combined extracts were dried, concentrated and purified by column chromatography with appropriate eluents with ethyl acetate (Et₂N, TEA) to afford the desired intermediates 5a–5i in high yields.

1-(5-(2,5-Dichlorophenyl)furan-2-yl)methyl)-3-(quinolin-5-yl)urea (12). A solution of quinolin-5-amine (7, 250 mg, 1.73 mmol) and TEA (200 µL, 2.03 mmol) dissolved in CH₂Cl₂ (DCM, 15 mL) was slowly dripped into a stirred solution of triphosgene (BTC, 256 mg, 0.85 mmol) in DCM (10 mL) by using a constant-pressure dropping funnel. Then, the mixture was stirred for another 0.5 h at room temperature (RT). After evaporation of the solvent, the residue was taken up in DCM (30 mL), and (5-(2,5-dichlorophenyl)furan-2-yl)methanamine (5b, 230 mg, 0.95 mmol) was added directly to the residue. The reaction mixture was stirred at RT for 6 h, and the solvent was subsequently removed in vacuo. The residue obtained was purified by column chromatography (V(PE):V(EA) = 1:1) to give the desired target compound 12 (343 mg, 0.84 mmol) in 88% yield. 96.8% HPLC purity. Mp: 245–246 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ 8.92 (s, 1H), 8.89 (dd, J = 4.0 Hz, J = 4.0 Hz, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.06–8.04 (m, 1H), 7.86 (d, J = 2.8 Hz, 1H), 7.69 (s, 1H), 7.68 (d, J = 2.8 Hz, 1H), 7.60–7.53 (m, 2H), 7.39 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 7.20 (d, J = 3.2 Hz, 2H), 6.53 (d, J = 3.2 Hz, 1H), 4.47 (d, J = 5.6 Hz, 2H) ppm. ¹³C-NMR (101 MHz, DMSO-d₆) δ 155.9, 154.7, 150.7, 148.7, 147.3, 135.8, 133.0, 132.7, 130.8, 130.3, 129.9, 128.6, 127.7, 126.9, 123.8, 121.3, 121.0, 117.4, 113.6, 109.5, 36.90 ppm. HRMS: m/z calcd for C₂₁H₁₆N₅O₂ [M + H]⁺ 412.0577, found 412.0573.

Ethyl 4-(5-((3-pyridin-3-yl)ureido)methyl)furan-2-yl)benzoate (17). The title compound was prepared from pyridin-3-amine (9) and ethyl 4-((aminomethyl)furan-2-yl)benzoate (5a) using the same method as compound 12, purified by column chromatography (V(DCM):V(MeOH) = 30:1). Yield: 82%. HPLC purity: 98.6%. Mp: 182–184 °C. ¹H-NMR (400 MHz, DMSO-d₆) δ 9.45 (s, 1H), 8.59 (d, J = 2.4 Hz, 1H), 8.12 (dd, J = 4.4, 1.2 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.93–7.88 (m, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.26 (dd, J = 8.4, 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H) ppm.
1H), 7.18 (s, 1H), 7.10 (d, J = 3.2 Hz, 1H), 6.46 (d, J = 3.2 Hz, 1H), 4.40 (d, J = 5.6 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 165.8, 155.6, 155.0, 151.5, 142.6, 139.9, 137.5, 134.8, 130.3, 128.5, 124.8, 124.0, 123.6, 114.6, 109.8, 61.2, 45.8, 31.2 ppm. HRMS: m/z calcld for C20H20N3O4 [M + H]+ 366.1448 found 366.1444.

1-(Pyridin-3-yl)-3-(5-(4-(trifluoromethyl)phenyl)furan-2-yl)methylurea (18). The title compound was prepared from pyridin-3-amine (9) and (5-(4-(trifluoromethyl)phenyl)furan-2-yl)methyl-l2-azene (5h) using the same method as compound 12, purified by column chromatography (V:PE):V(EA) = 3:1. Yield: 83%. HPLC purity: 98.0%. Mp: 183–187 °C. 1H-NMR (400 MHz, DMSO-d6) δ 8.87 (s, 1H), 8.58 (s, 1H), 8.14 (s, 1H), 7.91 (d, J = 12.8 Hz, 2H), 7.87 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.27 (dd, J = 12.8 Hz, J = 2.8 Hz, 1H), 7.11 (d, J = 3.2 Hz, 1H), 6.89 (t, J = 5.6 Hz, 1H), 6.46 (d, J = 3.2 Hz, 1H), 4.41 (d, J = 5.6 Hz, 2H) ppm. 13C-NMR (10 MHz, DMSO-d6) δ 155.5, 154.9, 154.1, 151.0, 143.6, 142.1, 139.3, 137.9, 134.3, 130.0, 126.4, 126.3, 125.5, 124.0, 109.7, 45.8 ppm. HRMS: m/z calcld for C16H15N2O2 [M + H]+ 362.1061, found 362.1070.

4-(5-(((3-(Quinolin-5-yl)ureido)methyl)furan-2-yl)benzoic Acid (20). A mixture of ethyl 4-(5-((3-(quinolin-5-yl)ureido)methyl)furan-2-yl)benzoate (11, 415 mg, 1.0 mmol), which was prepared from quinolin-5-amine (9) and ethyl 4-(5-(aminomethyl)furan-2-yl)benzoate (5a) using the same method as compound 12, and NaOH (127 mg, 3.0 mmol) reacted for 2 h in the solution of EtOH/H2O (10 mL/10 mL) at 80 °C. After evaporation of the organic solvent, the residue was treated with 50 mL of ice water, and the residue was used to adjust the pH to 6–7 with diluted HCl. Next, the mixture was extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine, dried, and concentrated. The residue obtained was purified by column chromatography (V:PE):V(EA) = 2:1 to give the final compound 20 (344 mg) in 89% yield. HPLC purity: 98.2%.Mp: 285–287 °C. 1H-NMR (400 MHz, DMSO-d6) δ 9.84 (s, 1H), 9.01 (d, J = 8.4 Hz, 1H), 8.86 (d, J = 4.0 Hz, 1H), 8.20 (t, J = 5.6 Hz, 1H), 8.14 (q, J = 5.6 Hz 1H), 7.94 (s, 1H), 7.92 (s, 1H), 7.68–7.62 (m, 4H), 7.50 (q, J = 4.0 Hz, 1H), 6.89 (d, J = 3.2 Hz, 1H), 6.45 (d, J = 3.2 Hz, 1H), 4.43 (d, J = 5.2 Hz, 1H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 170.8, 156.2, 153.7, 152.8, 150.5, 148.7, 136.5, 131.6, 130.1, 129.9, 123.0, 122.7, 121.0, 117.6, 110.2, 101.7, 99.6, 36.9 ppm. HRMS: m/z calcld for C22H18N2O4 [M + Na]+ 388.1252, found 388.1254.

4-(5-(((3-Phenylureido)methyl)furan-2-yl)benzoic Acid (21). The title compound was prepared from ethyl 4-(5-((3-phenylureido)methyl)furan-2-yl)benzoate (13) using the same method as compound 20, purified by column chromatography (V:PE):V(EA) = 2:1. Yield: 86%. HPLC purity: 97.6%. Mp: 285–288 °C. 1H-NMR (400 MHz, DMSO-d6) δ 9.28 (s, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 7.38 (s, 1H), 7.21 (t, J = 7.6 Hz, 2H), 6.95 (d, J = 3.2 Hz, 1H), 6.88 (t, J = 7.2 Hz, 1H), 6.40 (d, J = 2.8 Hz, 1H), 4.37 (d, J = 5.2 Hz, 2H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 168.9, 155.8, 154.6, 152.0, 141.2, 133.1, 130.3, 129.0, 123.1, 121.3, 118.0, 109.4, 108.5, 36.8 ppm. HRMS: m/z calcld for C19H16N2O4Na [M + Na]+ 359.0968, found 359.0965.

4-(5-(((3-Phenylthiourea)methyl)furan-2-yl)benzoic Acid (22). The title compound was prepared from ethyl 4-(5-((3-phenylthiourea)methyl)furan-2-yl)benzoate (14) using the same method as compound 20, purified by column chromatography (V:PE):V(EA) = 4:1. Yield: 87%. HPLC purity: 97.6%. Mp: 281–282 °C. 1H-NMR (400 MHz, DMSO-d6) δ 11.04 (s, 1H), 9.44 (s, 1H), 7.95 (d, J = 8.4 Hz, 3H), 7.70 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 4.0 Hz, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 3.2 Hz, 1H), 6.48 (d, J = 3.2 Hz, 1H), 4.82 (d, J = 5.6 Hz, 2H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 207.0, 181.4, 169.6, 152.9, 152.4, 140.7, 132.7, 130.3, 128.7, 124.0, 123.1, 123.0, 110.1, 108.1, 31.2 ppm. HRMS: m/z calcld for C19H17N2O5S [M + H]+ 353.0954, found 353.0962.

4-(5-(((3-(4-Cyano-3-fluorophenyl)ureido)methyl)furan-2-yl)benzoic Acid (23). The title compound was prepared from ethyl 4-(5-((3-(4-cyano-3-fluorophenyl)ureido)methyl)furan-2-yl)benzoate (15) using the same method as compound 20, purified by column chromatography (V:DCM):V(MeOH) = 30:1. Yield: 92%. HPLC purity: 97.2%. Mp: 192–193 °C. 1H-NMR (400 MHz, DMSO-d6) δ 10.97 (s, 1H), 8.53 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.83 (dd, J = 12.8 Hz, J = 2.0 Hz 1H), 7.70 (d, J = 8.4 Hz, 3H),
2-Hydroxy-4-(5-(3-phenylureido)methyl)furan-2-yl)benzoic Acid (24). The title compound was prepared from ethyl 2-hydroxy-4-(5-(3-phenylureido)methyl)furan-2-yl)benzoate (16) using the same method as compound 20, purified by column chromatography (V(PE):V(MeOH) = 3:1). Yield: 95%. HPLC purity: 98.6%. Mp: 218–220 °C. 1H-NMR (400 MHz, DMSO-d6) δ 12.05 (s, br, 2H), 8.60 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.29 (q, J = 4.8 Hz, 1H), 7.08 (d, J = 3.2 Hz, 1H), 6.87 (t, J = 5.6 Hz, 1H), 6.45 (d, J = 3.2 Hz, 1H), 4.41 (d, J = 5.6 Hz, 2H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 167.5, 155.4, 154.7, 151.6, 142.7, 140.1, 137.5, 134.5, 130.5, 129.5, 125.2, 124.1, 123.5, 109.8, 109.5, 31.2 ppm. HRMS: m/z calcd for C_{19}H_{17}N_{2}O_{5} [M + H]^+ 353.1132, found 353.1140.

4-(5-((3-phenylureido)methyl)furan-2-yl)benzoic Acid (25). The title compound was prepared from ethyl 4-(5-((3-phenylureido)methyl)furan-2-yl)benzoate (17) using the same method as compound 20, purified by column chromatography (V(PE):V(MeOH) = 3:1). Yield: 95%. HPLC purity: 98.6%. Mp: 218–220 °C. 1H-NMR (400 MHz, DMSO-d6) δ 12.98 (s, br, 1H), 8.84 (s, 1H), 8.58 (s, 1H), 8.14 (d, J = 4.0 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.29 (q, J = 4.8 Hz, 1H), 7.08 (d, J = 3.2 Hz, 1H), 6.87 (t, J = 5.6 Hz, 1H), 6.45 (d, J = 3.2 Hz, 1H), 4.41 (d, J = 5.6 Hz, 2H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 167.5, 155.4, 154.7, 151.6, 142.7, 140.1, 137.5, 134.5, 130.5, 129.5, 125.2, 124.1, 123.5, 109.8, 109.5, 31.2 ppm. HRMS: m/z calcd for C_{19}H_{17}N_{2}O_{5} [M + H]^+ 338.1135, found 338.1138.

4-(5-((3-bromo-2-methylpyridin-3-yl)ureido)methyl)furan-2-yl)benzoic acid (26). The title compound was prepared from ethyl 4-(5-((3-bromo-2-methylpyridin-3-yl)ureido)methyl)furan-2-yl)benzoate (19) using the same method as compound 20, purified by column chromatography (V(PE):V(MeOH) = 10:1). Yield: 90%. HPLC purity: 97.6%. Mp: 250–254 °C. 1H-NMR (400 MHz, DMSO-d6) δ 12.96 (s, 1H), 8.56 (d, J = 2.8 Hz, 1H), 8.35 (s, 1H), 8.14 (d, J = 2.8 Hz, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.58 (s, 1H), 7.09 (d, J = 3.2 Hz, 1H), 6.49 (d, J = 3.2 Hz, 1H), 4.42 (d, J = 5.6 Hz, 2H), 2.40 (s, 3H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 167.4, 155.4, 154.4, 151.8, 146.2, 142.0, 136.2, 134.4, 130.5, 129.6, 127.9, 123.5, 117.5, 110.0, 109.5, 36.8, 21.38 ppm. LCMS m/z: 428.0 [M – H]−.

4-(5-((N-hydroxy-2-phenylacetamido)methyl)furan-2-yl)benzoic Acid Ethyl (30). To a solution of (E)-4-(5-((hydroxyiminomethyl)furan-2-yl)benzoate (4a, 610 mg, 2.35 mmol) in methyl alcohol (10 mL), sodium cyanoborohydride (440 mg, 1.5 mmol) and 12 M hydrochloric acid (780 μL, 9.4 mmol) were added at 0 °C. Then, the mixture was stirred at room temperature for 4 h. When TLC indicated that the reaction was finished, the reaction solution was concentrated and the residue was basified with 6 N sodium hydroxide solution (pH 8) and extracted several times with ethyl acetate. The combined organic extracts were dried (Na₂SO₄), and concentrated under reduced pressure to yield the reduction product ethyl 4-(5-(hydroxyiminomethyl)furan-2-yl)benzoate (27, 328 mg) in 54% yield. Next, 2-phenylacetyl chloride (28, 195 mg, 1.27 mmol) and NaHCO₃ (106 mg, 1.27 mmol) were added to the solution of 27 (328 mg, 1.27 mmol) in diethyl ether (15 mL) and the reaction was stirred at room temperature for 6 h. Upon completion of the reaction as determined by TLC, the resulting solution was concentrated under reduced pressure to dryness and the residue was purified by silica gel column chromatography to give the light yellow compound 29 in 78% yield. The target compound 30 was gained from ethyl 4-(5-(N-hydroxy-2-phenylacetamido)methyl)furan-2-yl)benzoate (29) using the same method as compound 20, purified by column chromatography (V(PE):V(MeOH) = 3:1). Yield: 89%. HPLC purity: 97.0%. Mp: 162–163 °C. 1H-NMR (400 MHz, DMSO-d6) δ 12.95 (s, 1H), 10.15 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.32–7.21 (m, 5H), 7.08 (d, J = 3.2 Hz, 1H), 6.49 (d, J = 3.2 Hz, 1H), 4.80 (s, 2H), 3.79 (s, 2H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 171.9, 167.4, 152.0, 151.8, 136.1, 134.4, 130.5, 129.9, 129.6, 128.6, 126.8, 123.6, 111.7, 109.4, 45.07, 38.9 ppm. HRMS: m/z calcd for C_{20}H_{16}NO_{3} [M + H]^+ 350.1034, found 350.1066.
3.1.2. Hantzsch-Involved Reductive Amination Used for Compounds 31–34

To a solution of substituted 5-phenylfuran-2-carbaldehydes (3a and 3i, 1.5 mmol), different amines (1.8 mmol) and diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (hantzschest, 1.8 mmol) in DCM (25 mL), catalytic amount of molecular sieve and trifluoroacetic acid were added at room temperature, and the reaction was warmed to 45 °C and reacted for 6–12 h. After completion (monitored by TLC), the reaction was filtered, and the crude residue was obtained by concentrating the filtrate in vacuo. Finally, the crude residue was purified by column chromatography to give the desired compounds 31–34 in high yields.

Ethyl 4-(5-((Benzylationo)methyl)furan-2-yl)benzoate (32). Yield: 56%. HPLC purity: 98.1%. Mp: 250–251 °C. 1H-NMR (400 MHz, DMSO-d6) δ 7.98 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.37–7.30 (m, 4H), 7.23 (t, J = 8.4 Hz, 1H), 7.08 (d, J = 3.2 Hz, 1H), 6.44 (d, J = 3.2 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.74 (s, 4H), 2.80 (s, br, 1H), 1.33 (t, J = 7.2 Hz, 3H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 165.9, 156.4, 151.3, 140.9, 135.0, 130.3, 128.6, 128.5, 128.3, 127.1, 123.5, 110.0, 109.7, 61.2, 52.5, 45.3, 14.67 ppm. LCMS m/z: 335.2 [M + H]+.

Ethyl (E)-4-(5-(2-nicotinoylhydrazono)methyl)furan-2-yl)benzoate (33). Yield: 72%. HPLC purity: 97.5%. Mp: 201–204 °C. 1H-NMR (400 MHz, DMSO-d6) δ 12.10 (s, 1H), 9.09 (d, J = 1.2 Hz, 1H), 8.79 (d, J = 3.6 Hz, 1H), 8.41 (s, 1H), 8.28 (dt, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H), 7.62–7.58 (m, 1H), 7.36 (d, J = 3.6 Hz, 1H), 7.16 (d, J = 3.6 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 165.7, 162.2, 154.2, 152.9, 150.4, 149.0, 138.2, 136.0, 133.9, 130.4, 129.5, 129.4, 124.5, 124.1, 117.3, 111.3, 61.3, 14.7 ppm. HRMS: m/z calc for C26H18N3O4 [M + H]+ 364.1260, found 364.1264.

1-(5-(4-Bromophenyl)furan-2-yl)-N-(pyridin-3-ylmethyl)methanamine (34). Yield: 95%. HPLC purity: 97.8%. Mp: 146–150 °C. 1H-NMR (400 MHz, DMSO-d6) δ 8.53 (s, 1H), 8.44 (d, J = 3.6 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.64–7.58 (m, 5H), 7.35–7.32 (m, 1H), 6.93 (d, J = 3.2 Hz, 1H), 6.39 (d, J = 3.2 Hz, 1H), 3.75 (s, 2H), 3.72 (s, 2H), 1.23 (s, 1H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 155.1, 151.3, 149.9, 148.4, 136.3, 136.2, 132.2, 130.1, 125.6, 123.8, 120.4, 109.8, 107.8, 49.9, 45.4 ppm. HRMS: m/z calc for C17H13BrN2O [M + H]+ 342.0368, found 343.0397 and 345.0387.

4-(5-((phenylamino)methyl)furan-2-yl)benzoic Acid (35). The title compound was prepared from ethyl 4-(5-((phenylamino)methyl)furan-2-yl)benzoate (31) using the same method as compound 20, purified by column chromatography (V(PE)/V(EA) = 2:1). Yield: 96%. HPLC purity: 98.3%. Mp: 207–210 °C. 1H-NMR (400 MHz, DMSO-d6) δ 12.96 (s, 1H), 7.98 (d, J = 7.6 Hz, 2H), 7.78 (d, J = 7.6 Hz, 2H), 7.09 (t, J = 7.6 Hz, 2H), 7.05 (d, J = 3.2 Hz, 1H), 6.70 (d, J = 7.6 Hz, 2H), 6.57 (t, J = 7.2 Hz, 1H), 6.47 (d, J = 3.2 Hz, 1H), 6.18 (s, br, 1H), 4.34 (s, 2H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 167.4, 155.2, 151.5, 148.7, 134.6, 130.5, 129.4, 129.3, 123.4, 116.7, 112.9, 110.1, 109.4, 40.5 ppm. LCMS m/z: 294.1 [M + H]+.

4-(5-((Benzylationo)methyl)furan-2-yl)benzoic Acid (36). The title compound was prepared from ethyl 4-(5-((benzylationo)methyl)furan-2-yl)benzoate (32) using the same method as compound 20, purified by column chromatography (V(PA)/V(EA) = 2:1). Yield: 92%. HPLC purity: 98.0%. Mp: 248–250 °C. 1H-NMR (400 MHz, DMSO-d6) δ 10.96 (s, br, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 6.4 Hz, 2H), 7.44–7.38 (m, 3H), 7.17 (d, J = 3.2 Hz, 1H), 6.81 (d, J = 3.2 Hz, 1H), 4.27 (s, 2H), 4.19 (s, 2H) ppm. 13C-NMR (101 MHz, DMSO-d6) δ 167.4, 153.3, 147.3, 134.0, 132.5, 130.6, 130.5, 130.1, 129.3, 129.1, 124.0, 115.0, 109.5, 50.0, 42.6 ppm. HRMS: m/z calc for C19H17O3N [M + H]+ 308.1265, found 308.1260.

(E)-4-(5-(2-nicotinoylhydrazono)methyl)furan-2-yl)benzoic Acid (37). The title compound was prepared from ethyl (E)-4-(5-(2-nicotinoylhydrazono)methyl)furan-2-yl)benzoate (33) using the same method as compound 20, purified by column chromatography (V(PE)/V(EA) = 2:1). Yield: 92%. HPLC purity: 97.2%. Mp: 237–240 °C. 1H-NMR (400 MHz, DMSO-d6) δ 12.10 (s, 1H), 9.09 (s, 1H), 8.79 (d, J = 3.6 Hz, 1H), 8.41 (s, 1H), 8.28 (dt, J = 8.4 Hz, J = 2.0 Hz, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.4 Hz,
2H), 7.62–7.58 (m, 1H), 7.34 (d, J = 3.6 Hz, 1H), 7.16 (d, J = 3.6 Hz, 1H) ppm. $^{13}$C-NMR (101 MHz, DMSO-$d_6$) δ 164.7, 162.2, 154.6, 152.8, 150.9, 149.1, 138.4, 137.2, 136.0, 130.5, 129.6, 129.5, 124.2, 124.1, 117.1, 110.7 ppm. HRMS: m/z calc for C$_{18}$H$_{14}$N$_3$O$_4$ [M + H]$^+$ 336.0975, found 336.0952.

4-(5-(Phenylsulfonamidomethyl)furan-2-yl)benzoic Acid (39). The intermediate 5a (100 mg, 0.43 mmol) reacted with benzenesulfonyl chloride (90 mg, 0.50 mmol) in the presence of Et$_3$N (179 µL, 1.30 mmol) at room temperature, in DCM (15 mL). When TLC indicated that the reaction was finished, the reaction was concentrated in vacuo and the pH was adjusted to 7–8 with saturated NaHCO$_3$. Then, the water solution was extracted with ethyl acetate (3 x). The combined extracts were concentrated to give brown crude product ethyl 4-(5-(phenylsulfonamidomethyl)furan-2-yl)benzoate (38) in 91% yield, which was used to synthesize the target compound 39, in 90% yield. HPLC purity: 97.5%. Mp: 222–223°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 3.13 (s, 1H), 8.36 (d, J = 6.0 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 6.8 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.62–7.55 (m, 3H), 6.98 (d, J = 3.6 Hz, 1H), 6.38 (d, J = 3.2 Hz, 1H) 4.19 (d, J = 6.0 Hz, 2H) ppm. $^{13}$C-NMR (101 MHz, DMSO-$d_6$) δ 167.4, 152.1, 152.0, 141.2, 134.2, 132.7, 130.4, 129.5, 129.5, 126.9, 123.6, 111.1, 109.1, 39.9 ppm. HRMS: m/z calc for C$_{18}$H$_{16}$N$_3$O$_5$S [M + H]$^+$ 358.0671, found 358.0670.

2-Phenyl-N-((5-(p-tolyl)furan-2-yl)methyl)acetamide (43). (5-(p-tolyl)furan-2-yl)methanamine (5c, 378 mg, 1.49 mmol) reacted with 2-phenylacetic acid (200 mg, 1.47 mmol) in the presence of 1-hydroxybenzotriazole (HOBT, 214 mg, 1.47 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 282 mg, 1.47 mmol), and N,N-diisopropylethylamine (DIPEA, 0.21 mL, 4.3 mmol) in DCM (20 mL). The mixture was stirred at room temperature for 12 h. Then, the mixture was concentrated and partitioned between water (60 mL) and ethyl acetate (3 x 60 mL). The organic layer was dried over MgSO$_4$, filtered, concentrated and purified by column chromatography (V:PE):V(EA) = 6:1) to give the target compound 43 (327 mg) in 73% yield. HPLC purity: 99.2%. Mp: 193–194°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8.60 (t, J = 5.6 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 4.4 Hz, 4H), 7.24–7.21 (m, 3H), 6.28 (d, J = 3.2 Hz, 1H), 6.30 (d, J = 3.2 Hz, 1H), 4.33 (d, J = 5.6 Hz, 2H), 3.48 (s, 2H), 2.32 (s, 2H) ppm. $^{13}$C-NMR (101 MHz, DMSO-$d_6$) δ 710.5, 152.8, 152.2, 137.1, 136.8, 129.9, 129.4, 128.7, 128.2, 126.8, 123.7, 109.4, 106.1, 42.7, 36.3, 21.3 ppm. HRMS: m/z calc for C$_{20}$H$_{19}$NO$_2$ Na [M + Na]$^+$ 328.1231, found 328.1228.

N-((5-(4-methoxyphenyl)furan-2-yl)methyl)-2-phenylacetamide (44). The title compound was prepared from intermediate 5d using the same method as compound 43, purified by column chromatography (V:PA):V(EA) = 7:1). Yield: 86%. HPLC purity: 98.2%. Mp: 196–197°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8.59 (t, J = 5.6 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 4.4 Hz, 4H), 7.25–7.21 (m, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 3.2 Hz, 1H), 6.28 (d, J = 3.2 Hz, 1H), 4.33 (d, J = 5.6 Hz, 2H), 3.79 (s, 3H), 3.49 (s, 2H) ppm. $^{13}$C-NMR (101 MHz, DMSO-$d_6$) δ 170.5, 159.1, 152.8, 151.8, 136.8, 129.4, 128.7, 126.8, 125.2, 123.8, 114.8, 109.4, 105.1, 55.6, 42.7, 36.3 ppm. HRMS: m/z calc for C$_{20}$H$_{19}$NO$_2$ Na [M + Na]$^+$ 344.1170, found 344.1175.

N-((5-(3-methoxyphenyl)furan-2-yl)methyl)-2-phenylacetamide (45). The title compound was prepared from intermediate 5e using the same method as compound 43, purified by column chromatography (V:PE):V(EA) = 7:1). Yield: 91%. HPLC purity: 97.8%. Mp: 182–184°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8.61 (t, J = 5.6 Hz, 1H), 7.35–7.29 (m, 5H), 7.25–7.23 (m, 2H), 7.21–7.20 (m, 1H), 6.89 (d, J = 3.2 Hz, 1H), 6.86 (dd, J = 8.0 Hz, J = 3.2 Hz, 1H), 6.32 (d, J = 3.6 Hz, 1H), 4.34 (d, J = 5.6 Hz, 2H), 3.80 (s, 3H), 3.50 (s, 2H) ppm. $^{13}$C-NMR (101 MHz, DMSO-$d_6$) δ 170.6, 160.1, 152.7, 152.5, 136.8, 132.1, 130.5, 129.4, 128.7, 126.8, 116.2, 113.4, 109.5, 109.1, 107.4, 55.6, 42.7, 36.3 ppm. HRMS: m/z calc for C$_{20}$H$_{19}$NO$_2$ Na [M + Na]$^+$ 344.1170, found 344.1174.

Methyl 3-((benzamidomethyl)furan-2-yl)benzoate (46). The title compound was prepared from intermediate 5f and benzoic acid using the same method as compound 43, purified by column chromatography (V:PE):V(EA) = 8:1). Yield: 90%. HPLC purity: 97.9%. Mp: 197–198°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 8.09 (t, J = 6.4 Hz, 1H), 8.22 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 7.6 Hz, 2H),
Methyl 3-(5-(2-Phenylacetamido)methyl)furan-2-yl)benzoate (47). The title compound was prepared from intermediate 5f and phenylacetic acid using the same method as compound 43, purified by column chromatography (V(P(E):V(EA)) = 8:1). Yield: 90%. HPLC purity: 97.2%. Mp: 183–184 °C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.66 (t, $J = 5.6$ Hz, 1H), 8.21 (s, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.57 (t, $J = 8.0$ Hz, 1H), 7.30 (d, $J = 4.4$ Hz, 4H), 7.25–7.20 (m, 1H), 7.01 (d, $J = 3.2$ Hz, 1H), 6.36 (d, $J = 3.2$ Hz, 1H), 6.52 (d, $J = 5.6$ Hz, 2H), 4.61 (s, 3H), 4.30 (q, $J = 6.6$ Hz, 2H). 13C-NMR (101 MHz, DMSO-$d_6$) $\delta$ 170.6, 166.5, 153.4, 151.5, 136.8, 131.2, 130.8, 129.9, 129.4, 128.7, 128.3, 126.8, 123.8, 109.8, 108.2, 52.8, 42.7, 36.2 ppm. HRMS: m/z calcd for C$_{20}$H$_{17}$NO$_4$ [M + H]$^+$ 356.1210, found 356.1211; C$_{20}$H$_{16}$NO$_4$Na [M + Na]$^+$ 358.1010, found 358.1015.

Ethyl 4-(5-(Nicotinamidomethyl)furan-2-yl)benzoate (48). The title compound was prepared from intermediate 5a and nicotinic acid using the same method as compound 43, purified by column chromatography (V(P(E):V(EA)) = 6:1). Yield: 78%. HPLC purity: 97.8%. Mp: 182–183 °C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.30 (t, $J = 2.0$ Hz, 1H), 9.07 (d, $J = 1.6$ Hz, 1H), 8.73 (d, $J = 6.0$ Hz, 1H), 8.25 (t, $J = 8.0$ Hz, 1H), 8.00 (d, $J = 8.4$ Hz, 2H), 7.90 (d, $J = 1.6$ Hz, 2H), 7.79 (d, $J = 8.8$ Hz, 2H), 7.77–7.49 (m, 3H), 7.08 (d, $J = 2.4$ Hz, 1H), 6.47 (d, $J = 3.2$ Hz, 1H), 4.58 (d, $J = 5.6$ Hz, 2H). 13C-NMR (101 MHz, DMSO-$d_6$) $\delta$ 167.5, 166.7, 154.2, 151.6, 134.5, 134.5, 131.9, 130.5, 129.5, 128.8, 127.8, 123.5, 110.1, 109.5, 36.8 ppm. LCMS m/z: 351.1 [M + H]$^+$.

4-(5-(Benzamidomethyl)furan-2-yl)benzoic Acid (49). Using the intermediate 5a and benzoic acid, the title compound 49 was synthesized via condensation reaction (87% yield), and hydrolysis reaction (92% yield) in turn. HPLC purity: 97.6%. Mp: 183–186 °C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.09 (t, $J = 5.6$ Hz, 1H), 7.98 (d, $J = 8.4$ Hz, 2H), 7.90 (d, $J = 1.6$ Hz, 2H), 7.79 (d, $J = 8.8$ Hz, 2H), 7.77–7.49 (m, 3H), 7.08 (d, $J = 2.4$ Hz, 1H), 6.47 (d, $J = 3.2$ Hz, 1H), 4.58 (d, $J = 5.6$ Hz, 2H). 13C-NMR (101 MHz, DMSO-$d_6$) $\delta$ 167.5, 166.7, 154.0, 151.7, 136.8, 134.5, 133.0, 130.6, 129.5, 128.8, 127.8, 123.5, 110.1, 109.5, 36.8 ppm. LCMS m/z: 320.1 [M − H]$^−$.

4-(5-(2-Phenylacetamido)methyl)furan-2-yl)benzoic Acid (50). Using the intermediate 5a and phenylacetic acid, the title compound 49 was synthesized via condensation reaction (82% yield), and hydrolysis reaction (95% yield) in turn. HPLC purity: 97.1%. Mp: 228–230 °C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.98 (s, 1H), 8.65 (t, $J = 5.4$ Hz, 1H), 7.98 (d, $J = 8.8$ Hz, 2H), 7.75 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 4.4$ Hz, 4H), 7.26–7.22 (m, 1H), 7.05 (d, $J = 3.2$ Hz, 1H), 6.38, (d, $J = 3.2$ Hz, 1H), 4.37 (d, $J = 5.6$ Hz, 2H), 3.49 (s, 2H) ppm. 13C-NMR (101 MHz, DMSO-$d_6$) $\delta$ 170.6, 167.4, 154.0, 151.7, 136.8, 134.5, 133.0, 129.5, 128.7, 126.9, 123.5, 109.9, 109.4, 42.7, 36.3 ppm. HRMS: m/z calcd for C$_{19}$H$_{15}$NO$_4$ [M + Na]$^+$ 344.0852, found 344.0855.

3-(5-(Benzamidomethyl)furan-2-yl)benzoic Acid (51). The title compound was prepared from compound 46 via hydrolysis reaction (90% yield), purified by column chromatography (V(P(E):V(EA)) = 3:1). HPLC purity: 97.0%. Mp: 190–191 °C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ 13.15 (s br, 1H), 9.20 (t, $J = 6.4$ Hz, 1H), 8.22 (s, 1H), 7.94–7.91 (m, 3H), 7.83 (d, $J = 7.6$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 2H), 7.47 (t, $J = 8.0$ Hz, 2H), 7.00 (d, $J = 3.2$ Hz, 1H), 6.42 (d, $J = 3.2$ Hz, 1H), 4.55 (d, $J = 5.6$ Hz, 2H) ppm. 13C-NMR (101 MHz, DMSO-$d_6$) $\delta$ 167.5, 166.7, 153.5, 151.5, 134.5, 132.0, 131.8, 131.1, 129.8, 128.8, 128.4, 127.8, 124.1, 109.8, 108.1, 36.7 ppm. HRMS: m/z calcd for C$_{19}$H$_{15}$NO$_4$ [M + Na]$^+$ 344.0852, found 344.0855.

3-(5-(2-Phenylacetamido)methyl)furan-2-yl)benzoic Acid (52). The title compound was prepared from compound 47 via hydrolysis reaction (91% yield), purified by column chromatography (V(P(E):V(EA)) = 3:1). HPLC purity: 97.2%. Mp: 220–221 °C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.85 (t, $J = 5.6$ Hz, 1H), 8.27 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 2H), 7.58 (t, $J = 8.0$ Hz, 1H), 7.36–7.34 (m, 4H), 7.29–7.25 (m, 1H), 7.02 (d, $J = 3.2$ Hz, 1H), 6.40 (d, $J = 3.2$ Hz, 1H), 4.41 (d, $J = 5.6$ Hz, 2H), 3.55 (s, 2H) ppm. 13C-NMR (101 MHz,
DMSO-d$_6$ $\delta$ 170.7, 167.8, 153.2, 151.8, 136.8, 131.0, 129.6, 129.5, 128.7, 128.4, 127.6, 126.8, 124.1, 109.7, 107.8, 42.7, 36.2 ppm. HRMS: $m/z$ calcd for C$_{20}$H$_{17}$NO$_4$Na $[M + Na]^+$ 358.1011, found 358.105.

3.2. Inhibition Assays

This study tested the inhibitory activities of the synthesized compounds against recombinant human SIRT2 proteins using a fluorogenic substrate p2270(Ac-Glu-Thr-Asp-Lys(Dec)-AMC)-coupled trypsin assay. The assay buffer is 25 mM Tris–HCl pH 8.0, 150 mM NaCl, and 10% glycerol. The test compounds were added to 60 µL of reaction mixture containing SIRT2 enzymes (0.2 µM), and each compound was prepared in a 3-fold dilution series (300 µM–15 nM) with the final DMSO concentration < 1%. After incubation at 25 °C for 30 min, the reaction started by the addition of the substrate p2270 (10 mM) and NAD$^+$ (400 mM) at 25 °C. After 2 h, 50 µL 3–4 U/µL trypsin and 4 mM nicotinamide were added to terminate the reaction, followed by further incubation for 30 min at 25 °C. The fluorescence intensity was measured using a microplate reader ($\lambda_{ex}$ = 380 nm, $\lambda_{em}$ = 460 nm). All determinations were performed in triplicate. The IC$_{50}$ values were obtained using GraphPad Prism software as described previously.

3.3. Molecular Docking Assays

All the docking simulations were performed using AutoDock Vina. The crystal structure of SIRT2 complexed with an N-(3-(phenoxyethyl)phenyl)acetamide derivative (24a) (PDB ID: 5YQO) and was used as the docking template. All the water and solvent molecules, as well as 24a were removed, and clean protein structure coordinates were obtained. AutoDockTools was used to assign Gasteiger-Marsili charges to the protein structure model, and merge non-polar hydrogens onto their respective heavy atoms of the protein structure (saved as pdbqt format). The 3D coordinates of the compound structures were prepared using the Discovery Studio viewer, followed by assigning atom types and partial charges using AutoDockTools (saved as pdbqt format). The binding site was defined as a rectangular grid, with the grid center coordinates of [x, y, z = −13.5, −10.1, −18.4] and the grid size of [25, 25, 25], to encompass the entire binding site. The number of possible docking poses were set as 10, and the other docking parameters were set as default. The docking results were inspected using PyMOL.

4. Conclusions

In this study, a series of (5-phenylfuran-2-yl)methanamine derivatives were synthesized. The SAR analyses of these compounds with SIRT2 led to the identification of compound 25 with 99 ± 2% @ 100 µM and 90 ± 3 % @ 10 µM inhibition against SIRT2. Meanwhile, 25 likely possesses better water solubility (cLogP = 1.63 and cLogS = −3.63). The IC$_{50}$ measurements revealed that 25 had considerable potency against SIRT2 with an IC$_{50}$ value of 2.47 µM, which is more potent than AGK2. The molecular docking analyses indicated that 25 fits well with the induced hydrophobic pocket of SIRT2. This study will aid future investigations to discover new potent and selective SIRT2 inhibitors to provide potential treatments for relevant diseases.

**Author Contributions:** L.W., C.L., C.S. and X.Z. designed and synthesized the target compounds. W.C., F.Y., C.W. and Y.Z. performed the biological evaluation. S.Q. performed the molecular docking. Z.W. and L.Y. interpreted the data and wrote the paper. All authors have approved the final manuscript.

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**Sample Availability:** Samples of all the compounds are available from the authors.