Supporting information
**MIC determination.** MICs against replicating M. tuberculosis were determined by the microplate Alamar blue assay (MABA). PBTZ169 (synthesized by our lab), RIF and INH were included as positive controls. M. tuberculosis H37Rv (ATCC27294) and clinical isolate strains were grown to late log phase (70 to 100 Klett units) in Difco Middlebrook 7H9 Broth (catalog no. 271310) supplemented with 0.2% (vol/vol) glycerol, 0.05% Tween 80, and 10% (vol/vol) albumin-dextrosecatalase (BBL Middlebrook ADC Enrichment, catalog no. 212352) (7H9-ADCTG). Cultures were centrifuged, washed twice, and then suspended in phosphate phosphate-buffered saline. Suspensions were then passed through an 8 µm-pore-size filter to remove clumps, and aliquots were frozen at -80 °C. Two fold dilutions of test compounds and positive controls were prepared in 7H9-ADC-TG in a volume of 100 µl in 96-well, black, clear-bottom microplates (BD Biosciences, Franklin Lakes, NJ). M. tuberculosis (100 µl containing $2 \times 10^5$ CFU) was added, yielding a final testing volume of 200 µl. The plates were incubated at 37°C; on day 7 of incubation, 12.5 µl of 20% Tween 80 and 20 µl of Alamar blue were added to all wells. After incubation at 37 °C for 16 to 24 h, the fluorescence was read at an excitation of 530 nm and an emission of 590 nm. The MIC was defined as the lowest concentration effecting a reduction in fluorescence of ≥90% relative to the mean of replicate bacterium-only controls.

**Aqueous solubility determination.** Solubility was measured at pH 2.0 by using an HPLC-UV method. Test compounds were initially dissolved in 0.01 M HCl (approximately pH 2.0, 1 mL). The mixture was stirred for 12 h at room temperature and then filtered. The saturated solutions were transferred to other vials for analysis by HPLC-UV. Each sample was performed in triplicate. Aqueous concentration was determined by comparison of the peak area of the saturated solution with a standard curve plotted peak area versus known concentrations, which were prepared by solutions of test compound in ACN at 1.0, 0.1, 0.01, 0.001 mg/mL.

All samples were performed on an Agilent 1260 HPLC-UV system. Conditions (solvent A = methanol, solvent B = 0.1% TFA + H$_2$O): Zorbax SB-C18 column (250 mm × 4.6 mm, 5 µm, PN: 883975-902). Injection volum: 10 µL. Flow: 0.5 mL/min. Gradient elution: 0.00 min, 40% A; 3 min, 50% A; 15 min, 100% A; 16 min, 40% A; 25 min 40%A. UV at 254 nm.
Cytotoxicity determination. Compounds were examined for toxicity (CC\textsubscript{50}) in a mammalian Vero cell line at concentrations from 1000 to 4 \(\mu\)g/ml. The Vero cells were maintained in culture medium (Minimum Essential Medium with Earle’s salt, supplemented with 10% fetal bovine serum) at 37 °C under 5% CO\textsubscript{2}. Cells were seeded in 96-well plates at the plating density of 1 \(\times\) 10\(^4\) cells per well and allowed to recover for 24 h. Culture medium was replaced by assay medium containing the compound to be tested or drug-free. After 72 h of exposure, cells were harvested and cell viability was assessed by MTT assay. The CC\textsubscript{50} values were calculated by Bliss analyses.

General Chemical Methods. All commercially available solvents and reagents were used without further purification. All moisture sensitive reactions were carried out under Argon atmosphere in commercially available anhydrous solvents. \(^1\)H NMR spectra were determined on a Varian Mercury-400 or Bruker 500 M spectrometer in MeOD, CDCl\(_3\), or DMSO-\(d_6\) using tetramethylsilane as an internal standard. Electrospray ionization (ESI) mass spectra was obtained on an Agilent 1260-6420 Mass spectrum instruments. The reagents were all of analytical grade or chemically pure. TLC was performed on silica gel plates (Merck, ART5554 60F254).

Purity was determined by HPLC, and all target compounds were confirmed to have >95% purity.

Standard Drug. Rifampicin (RFP) and isoniazid (INH) were purchased from Sigma. PBTZ169 was synthesized according to the published procedure (EMBO Mol. Med.2014, 6 (3), 372–83.).

Purity determination. All samples were performed on an Agilent 1260 HPLC-UV system. Conditions (solvent A = methanol, solvent B = 0.1% TFA + H\(_2\)O): Zorbax SB-C18 column (250 mm \times 4.6 mm, 5 \(\mu\)m, PN: 883975-902). Injection volumn: 10 \(\mu\)L. Flow: 0.5 mL/min. Gradient elution: 0.00 min, 40% A; 3 min, 50% A; 15 min, 100% A; 16 min, 40% A; 25 min 40%A. UV at 254 nm.

General synthesis procedure for synthesis of compounds 1-34. To a stirring solution of A (0.3 mmol) in MeOH (5 mL) was added the corresponding aldehyde (0.4 mmol) and NaCNBH\(_3\) (0.5 mmol) at room temperature. The mixture was adjusted to pH 6-7, stirred
overnight at room temperature, and quenched by 1 M NaOH solution (5 mL). The mixture was diluted by H₂O (15 mL), and extracted by DCM (10 mL × 3). The combined organic layer was washed by brine, dried over anhydrous MgSO₄, filtered, and concentrated. The residue was purified over silica gel column (DCM : MeOH = 20 : 1) to yield oils B1-B34.

To a stirred solution of B1-B34 (0.2 mmol) in DCM (5 mL) was added TFA (1 mL) at room temperature. The mixture was stirred for 2 hours and concentrated to afford the crude product B1-34 which was used directly in the next step without further purification.

To a stirred solution of above crude B1-34 in anhydrous MeOH (10 mL) was added BTZ core compound D (0.2 mmol) and Et₃N (0.6 mmol) at room temperature. The mixture was stirred overnight at 40 °C, and concentrated. The residue was purified by silica gel column (DCM : MeOH = 20 : 1) to yield the yellow solids 1-34. (The data and NMR copies of compounds 1-34 were listed in the supporting information.)

2-(5-(cyclohexylmethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (1). According to above general procedure, employing cyclohexanecarbaldehyde afforded compound 1 as a yellow solid. 

\[
\begin{align*}
1^H \text{NMR} & (500 \text{ MHz, CDCl}_3) \delta 9.21 (s, 1H), 8.81 (s, 1H), 4.23 (s, 1H), 4.02-3.96 (m, 2H), \\
& 3.66 (s, 1H), 3.14-3.02 (brs, 2H), 2.72-2.54 (brs, 4H), 2.29 (s, 2H), 1.79-1.71 (m, 6H), 1.26-1.17(m, 3H), 0.91(s, 2H); \\
13^C \text{NMR} & (125 \text{ MHz, CDCl}_3) \delta 165.97, 159.88, 143.59, 134.62, 133.76 (q, J = 3.46 Hz), 129.59(q, J = 34.41 Hz), 126.87, 126.51, 125.90(q, J = 3.34 Hz), \\
& 122.54 (q, J = 274.1 Hz), 62.13, 60.23, 56.37, 53.44, 41.80, 39.94, 36.81, 31.78, 26.72, 26.05; \\
\text{ESI-MS:} & 483 (M + H)^+. \text{HRMS-ESI (m/z): Calcd. For C}_{22}\text{H}_{26}\text{F}_3\text{N}_4\text{O}_3\text{S} (M+H)^+: 483.1672; \text{Found: 483.1675.}
\end{align*}
\]

2-(5-(4-fluorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (2). According to above general procedure, employing 4-fluorobenzaldehyde afforded compound 2 as a yellow solid. 

\[
\begin{align*}
\text{mp:} & 178-180 ^\circ C; \\
1^H \text{NMR} & (500 \text{ MHz, CDCl}_3) \delta 9.21 (s, 1H), 8.82(s, 1H), 7.31 (s, 1H), 7.05-7.04 (s, 2H), \\
& 4.23 (s, 1H), 4.04-3.96 (m, 2H), 3.78-3.75 (m, 1H), 3.65(brs, 2H), 3.18-3.04(brs, 2H), 2.73-2.61 (brs, 3H), 1.64 (s, 1H), 1.30-1.27 (m, 3H); \\
13^C \text{NMR}(125 \text{ MHz, CDCl3}) & \delta 165.97, 143.61, 134.53, 133.79 (q, J=3.42 Hz), 130.02 (q, J = 35.30 Hz), 126.87, 125.93(q, J = 3.56 Hz), 123.78(q, J=272.01Hz), 115.42, 115.22, 59.60, 58.51, 58.35, 56.17,
\end{align*}
\]
53.22, 41.81, 39.99; ESI-MS: 495 (M + H)+; HRMS-ESI (m/z): Calcd. For C$_{22}$H$_{19}$F$_{4}$N$_{4}$O$_{3}$S (M+H)$^+$: 495.1109; Found: 495.1106.

2-(5-(4-chlorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (3). According to above general procedure, employing 4-chlorobenzaldehyde afforded compound 3 as a yellow solid. mp: 228-230 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.21 (s, 1H), 8.81 (s, 1H), 7.30 (s, 1H), 7.21-7.15 (m, 3H), 4.25-4.20 (brs, 1H), 4.03-3.95 (brs, 2H), 3.66 (brs, 3H), 3.17-3.04 (brs, 2H), 2.74-2.64 (brs, 3H), 2.37 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.97, 159.92, 143.60, 134.60, 133.78 (q, J = 3.42 Hz), 129.33 (q, J = 34.20 Hz), 128.64, 126.86, 125.90 (q, J = 3.41 Hz), 122.40 (q, J = 270.12 Hz), 121.08, 59.57, 58.80, 56.20, 53.46, 53.21, 41.84, 40.01, 21.13; ESI-MS: 511 (M + H)$^+$; HRMS-ESI (m/z): Calcd. For C$_{22}$H$_{19}$ClF$_{3}$N$_{4}$O$_{3}$S (M+H)$^+$: 511.0813; Found: 511.0817.

2-(5-(4-bromobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (4). According to above general procedure, employing 4-bromobenzaldehyde afforded compound 4 as a yellow solid. mp: 237-239 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.20 (s, 1H), 8.81 (s, 1H), 7.48 (s, 2H), 7.30-7.23 (brs, 2H), 4.22 (s, 1H), 4.01 (brs, 2H), 3.76-3.65 (brs, 3H), 3.18-3.05 (brs, 2H), 2.75-2.61 (brs, 2H), 1.64 (s, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.15, 159.52, 144.61, 138.93, 132.14, 131.55, 130.95, 130.12, 128.11 (q, J = 33.92 Hz), 126.71, 126.57, 123.45 (q, J = 253.41 Hz), 120.25, 59.98, 59.86, 58.09, 56.35, 53.52, 41.74; ESI-MS: 555 (M + H)$^+$; HRMS-ESI (m/z): Calcd. For C$_{22}$H$_{19}$BrF$_{3}$N$_{4}$O$_{3}$S (M+H)$^+$: 555.0308; Found: 555.0310.

2-(5-(4-cyanobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (5). According to above general procedure, employing 4-formylbenzonitrile afforded compound 5 as a yellow solid. mp: 232-234 °C; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.20 (s, 1H), 8.81 (s, 1H), 7.65 (s, 2H), 7.45 (s, 1H), 7.30 (s, 1H), 4.24 (s, 1H), 4.05-3.96 (m, 2H), 3.71-3.67 (m, 3H), 3.19-3.05 (m, 2H), 2.75-2.63 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.96, 159.99, 144.18, 143.60, 134.47, 133.78, 133.75 (q, J = 3.60 Hz), 132.93, 129.70 (q, J = 35.43 Hz), 129.04, 125.97 (q, J = 3.60 Hz), 122.35 (q, J = 273.50 Hz), 120.25, 118.76, 118.33, 111.17, 59.89, 58.71, 58.47,
8-nitro-2-(5-(4-nitrobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (6). According to above general procedure, employing 4-nitrobenzaldehyde afforded compound 6 as a yellow solid. mp: 230-232 °C; 1H NMR (500 MHz, CDCl₃) δ 9.21 (s, 1H), 8.82 (s, 1H), 8.22-8.20 (m, 2H), 7.52-7.51 (m, 2H), 4.28-4.23 (m, 1H), 4.06-4.03 (m, 2H), 3.97-3.96 (m, 3H), 3.20-3.07 (m, 2H), 2.77-2.65 (m, 4H); 13C NMR (125 MHz, CDCl₃) δ 165.95, 160.01, 147.29, 146.29, 143.60, 134.46, 133.77 (q, J = 3.34 Hz), 129.25 (q, J = 35.40 Hz), 126.77, 126.47, 126.00, 125.96, 122.35 (q, J = 270.12 Hz), 59.94, 58.44, 53.35, 41.86, 40.05; ESI-MS: 522 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C₂₂H₁₉F₃N₅O₅S (M+H)⁺: 522.1054; Found: 522.1057.

8-nitro-6-(trifluoromethyl)-2-(5-(4-(trifluoromethyl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-4H-benzo[e][1,3]thiazin-4-one (7). According to above general procedure, employing 4-trifluorobenzaldehyde afforded compound 7 as a yellow solid. mp: 215-217 °C; 1H NMR (500 MHz, CDCl₃) δ 8.88-8.87 (m, 2H), 7.68-7.66 (m, 2H), 7.55-7.54 (m, 2H), 4.05-3.97 (m, 2H), 3.75-3.61 (m, 4H), 3.34-3.31 (m, 1H), 3.10 (s, 1H), 2.97 (s, 1H), 2.72-2.65 (m, 2H); 13C NMR (125 MHz, CDCl₃) δ 165.14, 159.52, 144.59, 144.47, 135.18, 132.13, 132.11 (q, J = 3.34 Hz), 129.38, 127.87 (q, J = 31.82 Hz), 126.70, 126.55, 126.52, 126.16, 125.54 (q, J = 3.36 Hz), 123.96 (q, J = 275.64 Hz), 60.04, 59.91, 58.29, 56.48, 53.51, 49.06, 41.77; ESI-MS: 545 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C₂₃H₁₉F₆N₄O₃S (M+H)⁺: 545.1077; Found: 545.1081.

2-(5-(4-methoxybenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (8). According to above general procedure, employing 4-methoxybenzaldehyde afforded compound 8 as a yellow solid. mp: 192-194 °C; 1H NMR (500 MHz, CDCl₃) δ 9.21 (s, 1H), 8.81 (s, 1H), 7.24-7.23 (m, 2H), 6.89-6.87 (m, 2H), 4.22-4.20 (m, 1H), 4.02-3.94 (m, 2H), 3.84 (s, 3H), 3.77-3.75 (m, 2H), 3.66-3.61 (m, 2H), 3.15-3.02 (m, 2H), 2.72-2.61 (m, 4H); 13C NMR (125 MHz, CDCl₃) δ 165.97, 159.87, 158.82, 143.59, 134.62, 133.76 (q, J = 3.40 Hz), 129.07 (q, J = 35.13 Hz), 126.87, 125.91 (q, J = 3.58 Hz), 122.47 (q, J = 270.82 Hz), 114.14, 113.76,
59.68, 59.57, 58.47, 56.30, 55.28, 53.36, 41.84, 40.01; ESI-MS: 507 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C_{23}H_{22}F_{3}N_{4}O_{4}S (M+H)⁺: 507.1308; Found: 507.1305.

2-(5-(4-(tert-butyl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (9). According to above general procedure, employing 4-tert-butylbenzaldehyde afforded compound 9 as a yellow solid.

mp: 81-83 °C; ¹H NMR (500 MHz, DMSO) δ 8.88-8.87 (m, 2H), 7.32-7.31 (m, 2H), 7.22-7.21 (m, 2H), 4.01-3.95 (m, 2H), 3.76-3.73 (m, 1H), 3.63-3.56 (m, 3H), 3.34 (s, 2H), 3.08-2.96 (brs, 2H), 2.69-2.62 (m, 2H), 1.27 (s, 9H); ¹³C NMR (125 MHz, DMSO) δ 165.11, 159.49, 149.56, 144.58, 136.34, 135.18, 132.10 (q, J = 3.47 Hz), 128.45, 127.77 (q, J = 34.40 Hz), 126.53 (q, J = 3.40 Hz), 125.36, 123.15 (q, J = 272.95 Hz), 60.15, 59.99, 58.61, 56.40, 53.56, 41.75, 34.59, 31.63; ESI-MS: 533 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C_{26}H_{28}F_{3}N_{4}O_{3}S (M+H)⁺: 533.1829; Found: 533.1833.

2-(5-(4-methylbenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (10). According to above general procedure, employing 4-methylbenzaldehyde afforded compound 10 as a yellow solid.

mp: 223-225 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.21 (s, 1H), 8.81 (s, 1H), 7.22-7.17 (m, 4H), 4.61 (s, 1H), 4.00-3.98 (m, 2H), 3.67 (brs, 3H), 3.18-3.05 (m, 2H), 2.75 (brs, 4H), 2.37 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 165.97, 159.98, 143.60, 134.57, 133.78 (q, J = 3.41 Hz), 129.46 (q, J = 35.52 Hz), 129.18, 128.70, 128.59, 126.85, 126.50, 126.15, 125.91 (q, J = 3.61 Hz), 122.54 (q, J = 273.08 Hz), 59.44, 58.77, 56.10, 46.31, 41.81, 39.98, 21.13; ESI-MS: 491 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C_{23}H_{22}F_{3}N_{4}O_{3}S (M+H)⁺: 491.1359; Found: 491.1360.

8-nitro-2-(5-(4-(trifluoromethoxy)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (11). According to above general procedure, employing 4-(trifluoromethoxy)benzaldehyde afforded compound 11 as a yellow solid.

mp: 188-189 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.21 (s, 1H), 8.81 (s, 1H), 7.35-7.20 (m, 4H), 4.24 (s, 1H), 4.02-3.96 (m, 2H), 3.66 (brs, 3H), 3.17-3.04 (m, 1H), 2.75-2.61 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ 165.95, 160.33, 143.60, 134.42, 133.78 (q, J = 3.74 Hz), 127.80 (q, J = 35.40 Hz), 126.77, 125.98, 124.28, 122.40 (q, J = 273.50 Hz),
58.50, 58.28, 53.46, 41.78, 39.96; ESI-MS: 561 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{23}H_{19}F_{6}N_{4}O_{4}S (M+H)^+: 561.1026; Found: 561.1028.

2-(5-benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (12). According to above general procedure, employing benzaldehyde afforded compound 12 as a yellow solid. "H NMR (500 MHz, DMSO) δ 8.88-8.87 (m, 2H), 7.30-7.24 (m, 5H), 4.03-3.96 (m, 2H), 3.74-3.72 (m, 1H), 3.60 (brs, 3H), 3.34 (brs, 1H), 3.09 (brs, 1H), 2.96 (brs, 1H), 2.69-2.62 (m, 2H); "C NMR (125 MHz, DMSO) δ 165.11, 159.48, 144.56, 139.39, 135.18, 132.11 (q, J = 3.60 Hz), 128.74, 128.65, 127.47 (q, J = 33.34 Hz), 127.27, 126.68, 126.52 (q, J = 3.46 Hz), 123.20 (q, J = 271.54 Hz), 60.07, 59.95, 58.94, 56.48, 56.38, 53.54, 41.75; ESI-MS: 477 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{22}H_{20}F_{3}N_{4}O_{3}S (M+H)^+: 477.1203; Found: 477.1200.

2-(5-(3-fluorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (13). According to above general procedure, employing 3-fluorobenzaldehyde afforded compound 13 as a yellow solid. mp: 176-178 °C; "H NMR (500 MHz, DMSO) δ 8.88-8.87 (m, 2H), 7.34-7.21 (m, 4H), 3.99-3.97 (m, 2H), 3.77-3.75 (m, 1H), 3.61 (brs, 3H), 3.34 (brs, 2H), 3.08 (brs, 1H), 2.96 (brs, 1H), 2.68-2.62 (m, 2H); "C NMR (125 MHz, DMSO) δ 165.11, 159.49, 144.56, 142.61, 142.54, 135.17, 132.11 (q, J = 3.53 Hz), 130.58, 130.50, 130.10, 127.79 (q, J = 34.29 Hz), 126.69, 126.53 (q, J = 3.36 Hz), 124.64, 124.62, 123.24 (q, J = 272.89 Hz), 115.30, 115.08, 114.14, 113.93, 60.03, 59.89, 58.20, 56.32, 53.51, 41.75; ESI-MS: 495 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{22}H_{19}F_{4}N_{4}O_{3}S (M+H)^+: 495.1109; Found: 495.1111.

2-(5-(3-chlorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (14). According to above general procedure, employing 3-chlorobenzaldehyde afforded compound 14 as a yellow solid. mp: 177-180 °C; "H NMR (500 MHz, DMSO) δ 8.87 (s, 2H), 7.34-7.21 (m, 4H), 3.99-3.97 (m, 2H), 3.77-3.75 (m, 1H), 3.61 (brs, 3H), 3.34 (brs, 2H), 3.08 (brs, 1H), 2.96 (brs, 1H), 2.68-2.62 (m, 2H); "C NMR (125 MHz, DMSO) δ 165.11, 159.47, 144.56, 142.14, 135.16, 133.37, 132.12, 132.09, 130.54, 128.41, 127.76 (q, J = 34.66 Hz), 126.70, 126.52 (q, J = 34.66 Hz), 124.66, 124.62, 123.24 (q, J = 272.89 Hz), 115.30, 115.08, 114.14, 113.93, 60.03, 59.89, 58.20, 56.32, 53.51, 41.75; ESI-MS: 495 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{22}H_{19}F_{4}N_{4}O_{3}S (M+H)^+: 495.1109; Found: 495.1111.
3.54 Hz), 123.23 (q, J = 273.27 Hz), 60.04, 59.90, 58.07, 56.29, 53.51; ESI-MS: 511 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{22}H_{19}ClF_{3}N_{4}O_{3}S(M+H)^+: 511.0813; Found: 511.0815.

2-(5-(3-bromobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (15). According to above general procedure, employing 3-bromobenzaldehyde afforded compound 15 as a yellow solid. mp: 172-174 ºC; $^1$H NMR (500 MHz, DMSO) δ 8.88-8.87 (m, 2H), 7.48-7.42 (m, 2H), 7.32-7.28 (m, 2H), 4.01-3.95 (m, 2H), 3.78-3.75 (m, 1H), 3.63-3.60 (m, 3H), 3.34 (s, 1H), 3.09 (brs, 1H), 2.96 (brs, 1H), 2.69-2.62 (m, 2H); ESI-MS: 555 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{22}H_{19}BrF_{3}N_{4}O_{3}S(M+H)^+: 555.0308; Found: 555.0306.

3-((5-(8-nitro-4-oxo-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-2-yl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)benzonitrile (16). According to above general procedure, employing 3-formylbenzonitrile afforded compound 16 as a yellow solid. $^1$H NMR (500 MHz, DMSO) δ 8.88-8.87 (m, 2H), 7.74-7.66 (m, 3H), 7.55-7.52 (m, 1H), 4.00-3.96 (m, 2H), 3.77-3.75 (m, 1H), 3.66-3.62 (m, 3H), 3.34 (s, 1H), 3.09 (brs, 1H), 2.97 (brs, 1H), 2.71-2.64 (m, 2H); $^{13}$C NMR (125 MHz, DMSO) δ 165.11, 159.47, 144.56, 141.26, 135.17, 133.67, 132.13, 131.19, 129.95, 127.79 (q, J = 35.18 Hz), 126.68, 126.53 (q, J = 3.61 Hz), 124.48 (q, J = 270.99 Hz), 119.32, 111.68, 60.01, 59.82, 57.81, 56.28, 53.47, 41.76; ESI-MS: 502 (M + H)^+ HRMS-ESI (m/z): Calcd. For C_{23}H_{19}F_{4}N_{5}O_{3}S(M+H)^+: 502.1155; Found: 502.1151.

8-nitro-2-(5-(3-nitrobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (17). According to above general procedure, employing 3-nitrobenzaldehyde afforded compound 17 as a yellow solid. mp: 199-200 ºC; $^1$H NMR (500 MHz, DMSO) δ 8.87-8.86(m, 2H), 8.13-8.09(m, 2H), 7.75-7.76(m, 1H), 7.63-7.59(m, 1H), 4.01-3.95(m, 2H), 3.79-3.74(m, 3H), 3.64-3.62(m, 1H),3.09(brs, 1H),2.97(brs, 1H),2.72-2.65(m, 2H); $^{13}$C NMR(125 MHz, DMSO) δ 165.13, 159.49, 148.30, 144.57, 142.00, 135.42, 135.17, 132.12(q, J=3.52Hz), 130.22, 130.11, 127.95, 127.24 (q, J = 35.21 Hz), 126.54 (q, J = 3.47 Hz), 124.49, 122.02 (q, J = 270.12 Hz), 60.02, 59.87, 57.69, 56.29, 53.50, 41.77; ESI-MS: 522 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{22}H_{19}F_{3}N_{5}O_{3}S(M+H)^+: 522.1054; Found: 522.1051.
8-nitro-6-(trifluoromethyl)-2-(5-(3-(trifluoromethyl)benzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-4H-benzo[e][1,3]thiazin-4-one (18). According to above general procedure, employing 3-(trifluoromethyl)benzaldehyde afforded compound 18 as a yellow solid. mp: 135-136 °C; ¹H NMR (500 MHz, DMSO) δ 8.88-8.87 (m, 2H), 7.62-7.56 (m, 4H), 4.01-3.97 (m, 3H), 3.79-3.62 (m, 5H), 3.34 (s, 1H), 3.10 (brs, 1H), 2.97 (brs, 1H), 2.70-2.63 (m, 2H); ESI-MS: 545 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C₂₃H₁₉F₆N₄O₃S (M+H)⁺: 545.1077; Found: 545.1080.

2-(5-(3-methoxybenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (19). According to above general procedure, employing 3-methoxybenzaldehyde afforded compound 19 as a yellow solid. mp: 101-102 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.18 (s, 2H), 8.80 (s, 1H), 6.97-6.86 (m, 4H), 4.19-3.88 (m, 9H), 3.28-2.84 (m, 6H); ESI-MS: 507 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C₂₃H₂₁F₃N₄O₄S (M+H)⁺: 507.1308; Found: 507.1305.

2-(5-(2-fluorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (20). According to above general procedure, employing 2-fluorobenzaldehyde afforded compound 20 as a yellow solid. mp: 154-156 °C; ¹H NMR (500 MHz, DMSO) δ 8.88-8.86 (m, 2H), 7.43-7.40 (m, 1H), 7.32-7.31 (m, 1H), 7.18-7.14 (m, 2H), 4.02 (m, 2H), 3.73-3.59 (m, 5H), 3.34 (s, 1H), 3.08 (brs, 1H), 2.96 (brs, 1H), 2.71-2.64 (m, 4H); ¹³C NMR (125 MHz, DMSO) δ 165.10, 162.09 (q, J = 3.53 Hz), 159.67, 159.50, 144.56, 135.17, 132.10 (q, J = 3.53 Hz), 131.58, 131.53, 130.10, 129.42, 129.34, 127.93 (q, J = 3.53 Hz), 127.25, 126.53 (q, J = 3.53 Hz), 125.65, 125.50, 124.70 (q, J = 3.25 Hz), 123.24 (q, J = 272.51 Hz), 115.66, 115.44, 59.86, 59.72, 56.33, 53.48, 51.31, 41.74; ESI-MS: 495 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C₂₂H₁₉F₄N₄O₄S (M+H)⁺: 495.1109; Found: 495.1110.

2-(5-(3,4-difluorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (21). According to above general procedure, employing 3,4-difluorobenzaldehyde afforded compound 21 as a yellow solid. mp: 151-155 °C; ¹H NMR (500 MHz, CDCl₃) δ 9.20 (s, 1H), 8.81 (s, 1H), 7.31 (brs, 1H), 6.88-6.84 (m, 2H), 4.23 (brs, 1H), 4.03-3.94 (m, 2H), 3.69 (brs, 3H), 3.15 (brs, 1H), 3.03 (brs, 1H), 2.74 (brs, 2H), 2.67 (brs, 2H); ¹³C NMR (125 MHz, DMSO) δ 165.11, 161.80 (q,
(J = 247.5 Hz), 160.85 (q, J = 3.7 Hz), 127.77 (q, J = 3.7 Hz), 126.68, 126.53 (q, J = 3.7 Hz), 123.13 (q, J = 272.7 Hz), 122.05 (d, J = 3.5 Hz), 121.90 (d, J = 3.5 Hz), 111.82 (d, J = 3.8 Hz), 104.05 (t, J = 26.3 Hz), 59.66 (d, J = 14.7 Hz), 56.32, 53.46, 50.86, 41.72; ESI-MS: 513 (M + H); HRMS-ESI (m/z): Calcd. For C_{22}H_{18}F_{3}N_{4}O_{5}S (M+H)^+: 513.1014; Found: 513.1017.

2-(5-(3,4-dichlorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (22). According to above general procedure, employing 3,4-dichlorobenzaldehyde afforded compound 22 as a yellow solid. mp: 113-115 °C; ¹H NMR (500 MHz, DMSO) δ 8.89 (s, 1H), 8.87 (s, 1H), 7.58 (s, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 4.03-4.00 (m, 2H), 3.75-3.72 (m, 1H), 3.69 (s, 2H), 3.63-3.60 (m, 1H), 3.10 (b.s., 1H), 2.97 (b.s., 1H), 2.72 (d, J = 8.4 Hz, 1H), 2.69 (d, J = 8.4 Hz, 1H), 2.60-2.56 (m, 2H); ¹³C NMR (125 MHz, DMSO) δ 165.13, 159.51, 144.58, 135.90, 135.18, 134.16, 132.52, 132.13 (q, J = 3.7 Hz), 129.05, 127.95, 127.74, 127.61, 127.26, 126.69, 126.54 (q, J = 3.7 Hz), 124.49, 121.78, 59.90, 56.28, 55.10, 53.49, 41.77; ESI-MS: 545 (M + H); HRMS-ESI (m/z): Calcd. For C_{22}H_{18}Cl_{2}F_{3}N_{4}O_{5}S (M+H)^+: 545.0423; Found: 545.0425.

2-(5-(3-chloro-4-fluorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (23). According to above general procedure, employing 3-chloro-4-fluorobenzaldehyde afforded compound 23 as a yellow solid. mp: 73-75 °C; ¹H NMR (500 MHz, DMSO) δ 8.85 (d, J = 7.11 Hz, 2H), 7.4 (d, J = 6.77 Hz, 1H), 7.35-7.31 (m, 2H), 3.99-3.93 (m, 2H), 3.74 (d, J = 12.78 Hz, 1H), 3.61-3.58 (m, 4H), 3.06 (b.s., 1H), 2.94 (b.s., 1H), 2.68-2.66 (m, 1H), 2.62-2.61 (m, 1H), 2.53 (b.s., 1H); ¹³C NMR (125 MHz, DMSO) δ 165.12, 159.49, 156.622 (d, J = 246.52 Hz), 144.57, 137.38, 135.16, 132.23 (q, J = 3.79 Hz), 130.58, 129.31 (d, J = 7.05 Hz), 127.79 (q, J = 34.30 Hz), 126.70, 126.55 (q, J = 3.55 Hz), 123.13 (q, J = 272.73 Hz), 119.56 (d, J = 17.68 Hz), 117.08 (d, J = 20.80 Hz), 59.83, (d, J = 14.98 Hz), 57.34, 56.25, 53.45, 41.72; ESI-MS: 529 (M + H); HRMS-ESI (m/z): Calcd. For C_{22}H_{18}ClF_{4}N_{4}O_{5}S (M+H)^+: 529.0719; Found: 529.0716.
2-(5-(4-chloro-3-fluorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (24). According to above general procedure, employing 4-chloro-3-fluorobenzaldehyde afforded compound 24 as a yellow solid. mp: 204-206 °C; \( ^1H \) NMR (500 MHz, DMSO) \( \delta \) 9.16 (s, 1H), 8.77 (s, 1H), 7.30 (t, \( J = 7.81 \) Hz, 1H), 7.08 (d, \( J = 9.73 \) Hz, 1H), 7.00 (d, \( J = 7.85 \) Hz, 1H), 4.22-4.17 (m, 1H), 3.98 (t, \( J = 9.90 \) Hz, 1H), 3.91-3.89 (m, 1H), 3.60-3.54 (m, 3H), 3.12 (brs, 1H), 2.99 (brs, 1H), 2.69 (brs, 2H), 2.58-2.56 (m, 2H); \( ^{13}C \) NMR (125 MHz, DMSO) \( \delta \) 166.09, 160.10, 159.45, 156.97, 143.72, 134.62, 133.90 (q, \( J = 3.35 \) Hz), 130.63, 129.78 (q, \( J = 35.51 \) Hz), 126.95, 126.05 (q, \( J = 3.65 \) Hz), 124.81, 122.54 (q, \( J = 273.48 \) Hz), 116.64 (d, \( J = 21.46 \) Hz), 59.87 (d, \( J = 14.46 \) Hz), 58.24, 56.29, 53.39, 41.96, 40.14; ESI-MS: 529 (M + H)\(^+\); HRMS-ESI (m/z): Calcd. For \( C_{22}H_{18}ClF_4N_4O_3S \) (M+H)\(^+\): 529.0719; Found: 529.0721.

2-(5-(2-chloro-4-fluorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (25). According to above general procedure, employing 2-chloro-4-fluorobenzaldehyde afforded compound 25 as a yellow solid. mp: 149-151 °C; \( ^1H \) NMR (500 MHz, DMSO) \( \delta \) 8.85 (s, 1H), 8.83 (s, 1H), 7.49 (t, \( J = 7.10 \) Hz, 1H), 7.36 (d, \( J = 8.57 \) Hz, 1H), 7.17 (t, \( J = 8.05 \) Hz, 1H), 4.14-3.94 (m, 2H), 3.71 (d, \( J = 12.75 \) Hz, 1H), 3.66 (s, 1H), 3.58 (d, \( J = 10.19 \) Hz, 1H), 3.07 (brs, 1H), 3.07 (brs, 1H), 2.95 (brs, 1H), 2.71 (d, \( J = 8.69 \) Hz, 1H), 2.65 (d, \( J = 8.69 \) Hz, 1H), 2.57 (brs, 2H); \( ^{13}C \) NMR (125 MHz, DMSO) \( \delta \) 164.64, 160.80 (d, \( J = 246.23 \) Hz), 159.03, 144.10, 134.70, 133.44 (d, \( J = 10.57 \) Hz), 132.57 (d, \( J = 3.33 \) Hz), 131.80, 131.72, 131.64 (q, \( J = 3.71 \) Hz), 127.31 (q, \( J = 34.65 \) Hz), 126.21, 126.07 (q, \( J = 3.50 \) Hz), 122.66 (q, \( J = 272.59 \) Hz), 116.36 (d, \( J = 24.63 \) Hz), 114.20 (d, \( J = 20.61 \) Hz), 59.39 (d, \( J = 11.95 \) Hz), 55.83, 54.55, 53.01, 41.30; ESI-MS: 529 (M + H)\(^+\); HRMS-ESI (m/z): Calcd. For \( C_{22}H_{18}ClF_4N_4O_3S \) (M+H)\(^+\): 529.0719; Found: 529.0721.

2-(5-(2,4-difluorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (26). According to above general procedure, employing 2,4-difluorobenzaldehyde afforded compound 26 as a yellow solid. mp: 144-146 °C; \( ^1H \) NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.20 (s, 1H), 8.81 (s, 1H), 7.31 (brs, 1H), 6.88-6.84 (m, 2H), 4.23 (brs, 1H), 4.03-3.94 (m, 2H), 3.69 (brs, 3H), 3.15 (brs, 1H), 3.03 (brs, 1H), 2.74 (brs, 2H), 2.67 (brs, 2H); \( ^{13}C \) NMR (125 MHz, DMSO) \( \delta \) 165.11, 161.80 (q, \( J = 247.5 \) Hz), 160.85 (q, \( J = 250.6 \) Hz), 159.51, 144.58, 135.17, 132.80 (d, \( J = 3.3 \) Hz),
132.11 (q, J = 3.7 Hz), 127.77 (q, J = 36.0 Hz), 126.68, 126.53 (q, J = 3.7 Hz), 123.13 (q, J = 272.7 Hz), 122.05 (d, J = 3.5 Hz), 121.90 (d, J = 3.5 Hz), 111.82 (d, J = 3.8 Hz), 111.61 (d, J = 3.9 Hz), 104.05 (t, J = 26.3 Hz), 59.66 (d, J = 14.7 Hz), 56.32, 53.46, 50.86, 41.72; ESI-MS: 513 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{22}H_{19}F_{4}N_{4}O_{3}S (M+H)^+: 513.1014; Found: 513.1016.

2-(5-(2,4-dichlorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (27). According to above general procedure, employing 2,4-dichlorobenzaldehyde afforded compound 27 as a yellow solid. mp: 106-108 °C; ^1H NMR (500 MHz, DMSO) δ 8.89 (s, 1H), 8.87 (s, 1H), 7.58 (s, 1H), 7.50 (d, J = 8.2Hz, 1H), 7.40 (d, J = 8.2Hz, 1H), 4.03-4.00 (m, 2H), 3.75-3.72 (m, 1H), 3.69 (s, 2H), 3.63-3.60 (m, 1H), 3.10 (brs, 1H), 2.97 (brs, 1H), 2.72 (d, J = 8.4 Hz, 1H), 2.69 (d, J = 8.4 Hz, 1H), 2.60-2.56 (m, 2H); ^13C NMR (125 MHz, DMSO) δ 165.13, 159.51, 144.58, 135.90, 135.18, 134.16, 132.52, 132.13 (q, J = 3.7 Hz), 129.05, 127.95, 127.74, 127.61, 127.26, 126.69, 126.54 (q, J = 3.7 Hz), 124.49, 121.78, 59.90, 56.28, 55.10, 53.49, 41.77; ESI-MS: 545 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{22}H_{19}F_{4}N_{4}O_{3}S (M+H)^+: 545.0423; Found: 545.0422.

2-(5-(2-bromo-4-fluorobenzyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (28). According to above general procedure, employing 2-bromo-4-fluorobenzaldehyde afforded compound 28 as a yellow solid. mp: 150-151 °C; ^1H NMR (500 MHz, DMSO) δ 8.88 (s, 1H), 8.87 (s, 1H), 7.55-7.49 (m, 2H), 7.25-7.24 (m, 1H), 4.02-3.98 (m, 2H), 3.75-3.61 (m, 4H), 3.10 (brs, 1H), 2.98 (brs, 1H), 2.76-2.68 (m, 2H), 2.60-2.59 (m, 2H); ^13C NMR (125 MHz, DMSO) δ 165.12, 161.17 (d, J = 247.45 Hz), 159.49, 144.57, 135.18, 134.68 (d, J = 3.26 Hz), 132.12 (d, J = 8.29 Hz), 127.78 (q, J = 34.50 Hz), 127.26, 127.20, 126.68, 126.56, 123.90 (d, J = 9.64 Hz), 123.13 (q, J = 272.48 Hz), 119.91 (d, J = 24.48 Hz), 115.10, 59.84, 57.47, 56.48, 56.32, 53.51, 41.78; ESI-MS: 573 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{22}H_{19}F_{4}N_{4}O_{3}S (M+H)^+: 573.0214; Found: 573.0216.

8-nitro-2-(5-(pyridin-2-ylmethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (29). According to above general procedure, employing picolinaldehyde afforded compound 29 as a yellow solid. mp: 18-
174 °C; \(^1\)H NMR (500 MHz, DMSO) \(\delta\) 8.88 (s, 1H), 8.87 (s, 1H), 8.50 (s, 1H), 7.76 (brcs, 1H), 7.44-7.42(m, 1H), 7.28 (s, 1H), 4.05-3.98 (m, 2H), 3.79-3.63 (m, 4H), 3.13 (brcs, 1H), 3.00 (brcs, 1H), 2.80-2.57 (m, 4H); \(^{13}\)C NMR (125 MHz, DMSO) \(\delta\) 165.97, 160.18, 149.30, 143.59, 137.00, 134.50, 133.75, 133.72, 129.68 (q, \(J = 35.54\) Hz), 126.78, 125.95 (q, \(J = 3.72\) Hz), 125.89, 123.41, 122.76, 122.41 (q, \(J = 272.14\) Hz), 60.27, 59.48, 55.72, 52.79, 41.85, 40.05; ESI-MS: 478 (M + H); HRMS-ESI (m/z): Calcd. For C\(_{21}\)H\(_{19}\)F\(_4\)N\(_5\)O\(_3\)S (M+H): 478.1155; Found: 478.1157.

8-nitro-2-(5-(pyridin-3-ylmethyl)hexahydropyrrolo[3,4-c]pyrro-2(1H)-yl)-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (30). According to above general procedure, employing nicotinaldehyde afforded compound 30 as a yellow solid. mp: 124-130 °C; \(^1\)H NMR (500 MHz, DMSO) \(\delta\) 9.14 (s, 1H), 8.76 (s, 1H), 8.62-8.53 (m, 3H), 7.70 (brcs, 1H), 4.17 (brcs, 1.5H), 3.97-3.93 (m, 2.5H), 3.75-3.65 (m, 4H), 3.17 (brcs, 1H), 3.04 (brcs, 1H), 2.76 (brcs, 3H); ESI-MS: 478 (M + H); HRMS-ESI (m/z): Calcd. For C\(_{21}\)H\(_{19}\)F\(_4\)N\(_5\)O\(_3\)S (M+H): 478.1155; Found: 478.1153.

8-nitro-2-(5-(pyridin-4-ylmethyl)hexahydropyrrolo[3,4-c]pyrro-2(1H)-yl)-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (31). According to above general procedure, employing isonicotinaldehyde afforded compound 31 as a yellow solid. mp: 83-90 °C; \(^1\)H NMR (500 MHz, DMSO) \(\delta\) 8.88 (d, \(J = 6.0\)Hz, 2H), 8.51 (d,J=3.6Hz, 2H), 7.34 (d, \(J = 3.8\)Hz, 2H), 4.06-3.98 (m, 2H), 3.76-3.65 (m, 4H), 3.12 (brcs, 1H), 3.02 (brcs, 1H), 2.75-2.53 (m, 2H); \(^{13}\)C NMR (125 MHz, DMSO) \(\delta\) 165.10, 159.50, 150.40, 149.97, 148.54, 144.55, 135.17, 132.12 (q, \(J = 3.61\) Hz), 127.79 (q, \(J = 34.71\) Hz), 126.66, 126.54 (q, \(J = 3.56\) Hz), 123.80, 123.13 (q, \(J = 272.56\) Hz), 121.69, 60.06, 59.91, 57.62, 56.32, 53.47, 41.80; ESI-MS: 478 (M + H); HRMS-ESI (m/z): Calcd. For C\(_{21}\)H\(_{19}\)F\(_4\)N\(_5\)O\(_3\)S (M+H): 478.1155; Found: 478.1158.

2-(5-(naphthalen-2-ylmethyl)hexahydropyrrolo[3,4-c]pyrro-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (32). According to above general procedure, employing 2-naphthaldehyde afforded compound 32 as a yellow solid. mp: 126-128 °C; \(^1\)H NMR (500 MHz, DMSO) \(\delta\) 8.87 (s, 2H), 7.86-7.83 (m, 3H), 7.28 (s, 1H), 7.48-7.47 (s, 3H), 4.02-3.95 (m, 2H), 3.77-3.75 (m, 3H), 3.63-3.61 (m, 1H), 3.09 (brcs, 1H), 2.97 (brcs, 1H), 2.72-2.65 (m, 2H), 2.59-2.56 (m, 2H); \(^{13}\)C NMR (125 MHz, DMSO)
δ 165.12, 159.49, 144.56, 137.17, 133.36, 132.67, 132.10 (q, J = 3.5 Hz), 130.11, 128.15, 127.94 (q, J = 5.3 Hz), 127.59, 127.38, 127.20, 126.96, 126.70, 126.52 (q, J = 3.6 Hz), 126.44, 123.14 (q, J = 273.2 Hz), 121.78, 119.07, 60.13, 59.07, 56.35, 53.55, 41.78; ESI-MS: 527 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C₂₆H₂₂F₃N₄O₃S (M+H)⁺: 527.1359; Found: 527.1361.

2-(5-(naphthalen-1-ylmethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (33). According to above general procedure, employing 1-naphthaldehyde afforded compound 33 as a yellow solid. mp: 111-113 °C; ¹H NMR (500 MHz, DMSO) δ 8.87 (s, 1H), 8.85 (s, 1H), 8.265 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.45-7.42 (m, 2H), 7.38-7.31 (m, 2H), 4.05-3.86 (m, 4H), 3.77 (d, J = 13.0 Hz, 1H), 3.54 (d, J = 11.1 Hz, 1H), 3.05 (brs, 1H), 3.94 (d, J = 8.9 Hz, 2H), 2.60-2.55 (m, 2H); ¹³C NMR (125 MHz, DMSO) δ 165.06, 159.32, 144.51, 135.29, 135.13, 133.80, 132.18, 132.08 (q, J = 3.7 Hz), 128.59, 128.09, 127.76 (q, J = 34.5 Hz), 126.87, 126.69, 126.52 (q, J = 3.6 Hz), 126.94 (q, J = 5.8 Hz), 125.75, 124.94, 123.14 (q, J = 272.6 Hz), 60.25 (d, J = 22.4 Hz), 57.29, 56.34, 53.60, 41.72; ESI-MS: 527 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C₂₆H₂₂F₃N₄O₃S (M+H)⁺: 527.1359; Found: 527.1362.

2-(5-((5-methoxy-1H-indol-3-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (34). According to above general procedure, employing 5-methoxy-1H-indole-3-carbaldehyde afforded compound 34 as a yellow solid. mp: 225-228 °C; ¹H NMR (500 MHz, DMSO) δ 10.69 (s, 1H), 8.86 (s, 2H), 7.19 (d, J = 8.74 Hz, 1H), 7.15 (s, 1H), 7.06 (s, 1H), 6.66 (d, J = 8.57 Hz, 1H), 3.94 (q, J = 9.54 Hz, 2H), 3.74-3.70 (m, 3H), 3.57 (s, 4H), 3.04 (brs, 1H), 2.91 (brs, 1H), 2.72 (d, J = 8.84 Hz, 1H), 2.67 (d, J = 8.84 Hz, 1H), 2.45 (brs, 2H); ESI-MS: 546 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C₂₅H₂₃F₃N₅O₄S (M+H)⁺: 546.1417; Found: 546.1420.

Synthesis of compound 35. To a stirred solution of A (42 mg, 0.2 mmol) in anhydrous MeOH (10 mL) was added BTZ core compound D (64 mg, 0.2 mmol) and Et₃N (0.6 mmol) at room temperature. The mixture was stirred overnight at 40 °C, and concentrated. The residue was purified by silica gel column (DCM : MeOH = 20 : 1) to yield the yellow solids 35 (53 mg, 54% yield), mp: 204-205 °C; ¹H NMR (125 MHz, DMSO) δ 8.88 (s, 1H), 8.87...
(s, 1H), 3.98 (brs, 2H), 3.97-3.57 (m, 4H), 3.34-3.29 (m, 1H), 3.25-3.22 (m, 1H), 3.14 (brs, 1H), 3.03 (brs, 1H); ESI-MS: 487 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{20}H_{21}F_{3}N_{4}O_{5}S (M+H)^+: 487.1258; Found: 487.1261.

**Synthesis of compound 36.** To a stirred solution of 35 (97 mg, 0.2 mmol) in DCM (5 mL) was added TFA (1 mL) at room temperature. The mixture was stirred for 2 hours and concentrated. The residue was diluted by DCM, and washed by NaHCO_3 solution (1 M), and saturated saline, dried over anhydrous MgSO_4, filtered and concentrated. The residue was purified over silica gel column (DCM : MeOH = 20 : 1) to compound 36 as a yellow solid (43 mg, 56% yield), mp: 219-221 °C; ^1H NMR (500 MHz, DMSO) δ 8.90 (s, 1H), 8.89 (s, 1H), 4.00-3.96 (m, 2H), 3.86 (d, J = 10.7 Hz, 1H), 3.77 (d, J = 8.50 Hz, 1H), 3.50-3.46 (m, 2H), 3.33 (d, J = 9.00 Hz, 3H), 3.25-3.20 (m, 2H); ESI-MS: 387 (M + H)^+; HRMS-ESI (m/z): Calcd. For C_{15}H_{13}F_{3}N_{4}O_{3}S (M+H)^+: 387.0733; Found: 387.0735.

**General synthesis procedure of compounds 37-43.** A mixture of compound A (0.3 mmol) and corresponding ketones (0.4 mmol) in Ti(OPr)_4 was stirred at 70 °C for 8 hours and cooled to room temperature. MeOH (5 mL) and NaCNBH_3 (1.6 mmol) was added to the mixture, and stirred for 5 hours at 40 °C. The mixture was quenched by 1 N NaOH (10 mL), filtered by celite, and washed by MeOH. The MeOH was evaporated under vacuo. The residue was diluted by H_2O, and extracted by Et_2O. The combined organic layer was washed by brine, dried over anhydrous MgSO_4, filtered, and concentrated. The residue was purified over silica gel column (DCM : MeOH = 30 : 1) to yield oils B37-B43 (yield, 30-55%).

To a stirred solution of B37-B43 in DCM (5 mL) was added TFA (1 mL) at room temperature. The mixture was stirred for 2 hours and concentrated to afford the crude product C37-C43 which was used directly in the next step without further purification. To a stirred solution of above crude C37-C43 in anhydrous MeOH (10 mL) was added BTZ core compound D (0.3 mmol) and Et_3N (0.6 mmol) at room temperature. The mixture was stirred overnight at 40 °C, and concentrated. The residue was purified by column chromatography over silica gel (DCM : MeOH = 20 : 1) to yield the yellow solids, which were further treated by n-hexane to give 37-43. (The data and NMR copies of compounds 37-43 were listed in the supporting information.)
8-nitro-6-(trifluoromethyl)-2-(5-(4-(trifluoromethyl)phenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-4H-benzo[e][1,3]thiazin-4-one (37). According to above general procedure, employing 1-(4-(trifluoromethyl)phenyl)ethan-1-one afforded compound 37 as a yellow solid, mp: 169-170 °C; 1H NMR (500 Mz, CDCl3) δ 9.16 (s, 1H), 8.77 (s, 1H), 7.55-7.54 (m, 2H), 7.41-7.39 (m, 2H), 4.24-4.14 (m, 1H), 4.02-3.92 (m, 1.5H), 3.82-3.68 (m, 0.5 H), 3.53-3.49 (m, 0.5 H), 3.31 (t, J = 6.5 Hz, 1H), 3.12 (brs, 0.5 H), 3.06 (brs, 0.5 H), 2.99 (brs, 0.5 H), 2.92 (brs, 0.5 H), 2.87 (d, J = 9.5 Hz, 1H), 2.64-2.53 (m, 1H), 2.49-2.42 (m, 2H), 1.35 (d, J = 6.0 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 166.08, 159.98, 149.28 (d, J = 16.83 Hz), 143.71, 134.66, 133.88, 129.69 (q, J = 35.2 Hz), 129.56(q, J = 32.1 Hz), 127.29, 126.94, 126.02 (q, J = 3.0 Hz), 125.64 (q, J = 3.0 Hz), 123.91, 122.44 (q, J = 271.0 Hz), 64.24, 58.84, 58.35 (d, J = 8.10 Hz), 56.53 (d, J = 33.49 Hz), 53.59 (d, J = 22.59 Hz), 41.76, 39.90, 23.23; ESI-MS: 559 (M + H)+; HRMS-ESI (m/z): Calcd. For C24H21F6N4O3S(M+H)+: 559.1233; Found: 559.1236.

8-nitro-2-(5-(4-(trifluoromethoxy)phenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (38). According to above general procedure, employing 1-(4-(trifluoromethoxy)phenyl)ethan-1-one afforded compound 38 as a yellow solid. mp: 150-151 °C; 1H NMR (500 Mz, CDCl3) δ 9.18 (s, 1H), 8.78 (s, 1H), 7.30 (brs, 2H), 7.15 (brs, 2H), 4.24-4.15 (m, 1H), 4.02-3.94 (m, 1.5H), 3.82-3.79 (m, 0.5 H), 3.68-3.66 (m, 0.5 H), 3.52 (brs, 0.5 H), 3.26 (brs, 1H), 3.12 (brs, 0.5 H), 3.06 (brs, 0.5H), 2.99 (brs, 0.5 H), 2.93 (brs, 0.5 H), 2.85 (d, J = 9.5 Hz, 1H), 2.58-2.54 (m, 1H), 2.48-2.45 (m, 2H), 1.33 (d, J = 4.2 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 166.09, 159.99, 148.29, 143.97, 143.84, 143.73, 134.69, 133.93, 129.78 (q, J = 35.0 Hz), 128.25, 126.99, 126.04 (q, J = 3.0 Hz), 122.50 (q, J = 255.3 Hz), 121.17, 120.60 (q, J = 255.3 Hz), 63.89, 58.63, 56.60, 53.64, 41.78, 39.95, 23.34; ESI-MS: 575 (M + H)+; HRMS-ESI (m/z): Calcd. For C24H21F6N4O3S(M+H)+: 575.1182; Found: 575.1185.

2-(5-(3,4-difluorophenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (39). According to above general procedure, employing 1-(3,4-difluorophenyl)ethan-1-one afforded compound 39 as a yellow solid. mp: 75-80 °C; 1H NMR (500 Mz, CDCl3) δ 9.17 (s, 1H), 8.78 (s, 1H), 8.77-7.06 (m, 2H), 6.99 (brs, 1H), 4.22-4.16 (m, 1H), 4.02-3.92 (m, 1.5H), 3.82-3.80 (d,
J=11.78Hz, 0.5H), 3.74 (s, 0.5H), 3.73 (s, 0.5H), 3.71 (s, 0.5H), 3.70 (s, 0.5H), 3.66-3.65 (d, J=7.64Hz, 0.5H), 3.53-3.52 (d, J=7.48Hz, 0.5H), 3.22 (brs, 1H), 3.11 (brs, 0.5H), 3.06 (brs, 1H), 2.98 (brs, 1H), 2.93 (brs, 1H), 2.83-2.82 (d, J=8.67Hz, 1H), 2.58-2.54 (m, 1H), 2.46 (brs, 1H), 1.32 (brs, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 143.77, 133.93, 126.05, 122.71, 117.37, 63.61, 58.82, 58.63, 58.17, 56.64, 53.64, 53.52, 41.74, 39.94, 23.20, 18.59; ESI-MS: 527 (M + H); HRMS-ESI (m/z): Calcd. For C\(_{23}\)H\(_{20}\)F\(_5\)N\(_4\)O\(_3\)S (M+H): 527.1171; Found: 527.1173.

2-(5-(4-chloro-3-fluorophenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (40). According to above general procedure, employing 1-(4-chloro-3-fluorophenyl)ethan-1-one afforded compound 40 as a yellow solid. mp: 138-139 °C; \(^1\)H NMR (500 Mz, CDCl\(_3\)): δ 9.18 (s, 1H), 8.78 (s, 1H), 7.31 (t, J = 8.0 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 4.23-4.16 (m, 1H), 4.02-3.92 (m, 1.5H), 3.82-3.80 (m, 0.5 H), 3.66-3.65 (m, 0.5 H), 3.53-3.52 (m, 0.5 H), 3.24 (brs, 1H), 3.12 (brs, 0.5 H), 3.06 (brs, 0.5H), 2.98 (brs, 0.5 H), 2.95 (brs, 0.5 H), 2.83 (brs, 1H), 2.60-2.45 (m, 3H), 1.32 (d, J = 5.5 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 166.13, 160.04, 159.56, 157.09, 146.47, 146.41, 146.26, 146.21, 143.73, 134.66, 133.92, 130.74, 129.97 (q, J = 70.75Hz), 129.61 (q, J = 70.75Hz), 126.97, 126.62, 126.03 (q, J = 3.50Hz), 123.90 (q, J = 275.61Hz), 123.29 (q, J = 275.07Hz), 119.36, 118.48, 115.17, 114.93, 63.65, 58.85, 58.75, 58.28, 58.16, 56.65, 56.33, 53.63, 53.51, 51.04, 41.73, 39.92, 29.84, 23.16; ESI-MS: 543 (M + H); HRMS-ESI (m/z): Calcd. For C\(_{23}\)H\(_{19}\)ClF\(_4\)N\(_4\)O\(_3\)S (M+H): 543.0875; Found: 543.0877.

2-(5-(3-chloro-4-fluorophenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (41). According to above general procedure, employing 1-(3-chloro-4-fluorophenyl)ethan-1-one afforded compound 41 as a yellow solid. mp: 168-169 °C; \(^1\)H NMR (500 Mz, CDCl\(_3\)): δ 9.17 (s, 1H), 8.78 (s, 1H), 7.31 (t, J = 5.9 Hz, 1H), 7.14 (brs, 1H), 7.08-7.05 (m, 1H), 4.21-4.15 (m, 1H), 4.01-3.91 (m, 1.5H), 3.82-3.80 (m, 0.5 H), 3.66-3.64 (m, 0.5 H), 3.53 (brs, 0.5 H), 3.22 (brs, 1H), 3.11 (brs, 0.5 H), 3.06 (brs, 0.5H), 2.98 (brs, 0.5 H), 2.93 (brs, 0.5 H), 2.81 (d, J = 6.5 Hz, 1H), 2.59-2.51 (m, 1H), 2.48-2.46 (m, 2H), 1.32 (brs, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 143.87, 134.04, 129.15, 126.16, 63.59, 58.74, 53.63, 40.06, 18.69; ESI-MS: 543 (M + H); HRMS-ESI (m/z): Calcd. For C\(_{23}\)H\(_{19}\)ClF\(_4\)N\(_4\)O\(_3\)S (M+H): 543.0875; Found: 543.0877.
2-(5-(3,5-difluorophenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one (42). According to above general procedure, employing 1-(3,5-difluorophenyl)ethan-1-one afforded compound 42 as a yellow solid. mp: 168-169 °C; ¹H NMR (500 Mz, CDCl₃): δ 9.16 (s,1H), 8.79 (s, 1H), 7.38 (brs, 1H), 6.84 (t, = 8.6 Hz,1H), 6.75 (t, = 10.0 Hz,1H), 4.22-4.14 (m, 1H), 4.02-3.95 (m, 1.5H), 3.82-3.79 (m, 0.5 H), 3.71-3.64 (m, 1.5 H), 3.53-3.49 (m, 0.5 H), 3.11 (brs, 0.5 H), 3.05 (brs, 0.5H), 2.98 (brs, 0.5 H), 2.92 (brs, 0.5 H), 2.87-2.82 (m, 1H), 2.60-2.44 (m, 3H), 1.32 (brs, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 166.0, 160.0, 143.7, 129.7 (q, J = 36.0 Hz), 129.33 (t, J = 7.5 Hz), 127.00, 126.0 (q, J = 3.0 Hz), 122.5 (q, J = 271.5 Hz), 111.7 (d, J = 22.5 Hz), 103.7 (t, J = 27.0 Hz), 60.51, 58.33, 58.22, 56.68, 56.46, 55.31, 53.80, 53.52, 41.70, 39.91, 22.06, 21.17, 14.32; ESI-MS: 527 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C₂₃H₂₀F₅N₄O₃S (M+H)⁺: 527.1171; Found: 527.1173.

8-nitro-6-(trifluoromethyl)-2-(5-(3,4,5-trifluorophenyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)-4H-benzo[e][1,3]thiazin-4-one (43). According to above general procedure, employing 1-(3,4,5-trifluorophenyl)ethan-1-one afforded compound 43 as a yellow solid. mp: 158-161 °C; ¹H NMR (500 Mz, CDCl₃): δ 9.16 (s,1H), 8.77 (s, 1H), 6.92 (brs, 2H), 4.22-4.15 (m, 1H), 4.02-3.92 (m, 1.5H), 3.84-3.80 (m, 0.5 H), 3.67-3.63 (m, 0.5 H), 3.55-3.53 (m, 0.5 H), 3.20 (brs, 1H), 3.13 (brs, 0.5H), 3.08 (brs, 0.5 H), 2.99 (brs, 1H), 2.82 (brs, 1H), 2.59-2.48 (m, 3H), 1.31 (brs, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 166.07, 160.11, 151.40 (ddd, J₁ = 3.6 Hz, J₁ = 9.9 Hz, J₁ = 248.8 Hz ), 143.75, 134.60, 133.89, 129.81 (q, J = 34.5 Hz), 126.97, 126.03 (q, J = 3.0 Hz), 122.50 (q, J = 276.0 Hz), 110.73 (d, J = 16.5 Hz), 63.59, 60.52, 58.39 (d, J = 106.19 Hz), 56.35, 53.51, 41.72, 39.90, 23.12, 22.98, 21.17, 14.33; ESI-MS: 545 (M + H)⁺; HRMS-ESI (m/z): Calcd. For C₂₃H₁₉F₆N₄O₃S (M+H)⁺: 545.1077; Found: 545.1080.
NMR copies of target compounds.