Supporting Information

A class of 5-nitro-2-furancarboxylamides with potent trypanocidal activity against *Trypanosoma brucei*

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CONTENTS:

1. Table S1 .................................................................................................................. S2

2. Synthesis and Characterization of Intermediates, Known and Unknown compounds .................................................................................................................. S2

3. HPLC Analysis of Purity ......................................................................................... S29

4. Calculated Chemical Properties .......................................................................... S31

5. Supplementary References ..................................................................................... S34
1. Table S1 Starting materials for the synthesis of 5-nitrofurancarboxyl amides 12a-k and furan amide 18a

| Nitrofuran amides | R²    | R³    | R⁴    | Thiophenes | Cyanoester amides | Aldehydes |
|-------------------|-------|-------|-------|------------|------------------|-----------|
| 12a**             | Et    | COOEt | NO₂   | 13a        | 15a³           | 16a⁶      |
| 12b               | nBu   | COOEt | NO₂   | 13b        | 15a³           | 16b⁵      |
| 12c**             | Et    | COOMe | NO₂   | 13c        | 15b³           | 16a       |
| 12d               | Et    | COO”Bu| NO₂   | 13d        | 15c³           | 16a       |
| 12e               | Et    | CONEt | NO₂   | 13e        | 15d             | 16a       |
| 12f               | Et    | CON”Bu| NO₂   | 13f        | 15e             | 16a       |
| 12g               | Et    | CONH₂ | NO₂   | 13g        | 15f³           | 16a       |
| 12h               | Et    | CONH(CH₂)₂OH | NO₂ | 13h        | 15g             | 16a       |
| 12i               | Et    | COOH  | NO₂   | 13i        | -              | -         |
| 12j               | H     | H     | NO₂   | 13j        | -              | -         |
| 12k               | H     | COOEt | NO₂   | 13k        | -              | -         |
| 18a               | Et    | COOEt | H     | 13a        | 15a             | 16a       |

**Commercially available from Ambinter Stock Screening Collection; ¹6a n-butyraldehyde is commercially available; ²16b n-hexanaldehyde is commercially available; ³13h was protected as the OTBS ester and deprotection occurred during coupling of 13h to 14a; ⁴13i was prepared from hydrolysis of 13a; ⁵13j was prepared from 2-iodo-thiophene; ⁶commercially available.

2. Synthesis and Characterization of Intermediates, Known and Unknown analogs

General procedure S1 for the synthesis of 2-cyanoacetamides 15d, 15e and 15g
2-Cyanoacetic acid (510 mg, 6.00 mmol, 1.00 eq.) was dissolved in DCM (15 mL). A catalytic amount of DMF (0.03 mL) was added at 0 °C, following by oxalyl chloride (0.51 mL, 6.00 mmol, 1.00 eq.). The reaction mixture was stirred at 0 °C for another 5 minutes and then at room temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to about 8 mL, diluted with 10 mL DCM, and added to another flask containing the corresponding amine (6.00 mmol, 1.00 eq.) and triethylamine (1.67 mL, 12.0 mmol, 2.00 eq.) in DCM (30 mL) at 0 °C. The mixture was stirred at 0 °C for 5 minutes and then at room temperature for 3 hours. The solvent was removed in vacuo and the crude residue was purified by column chromatography over silica gel with hexane and ethyl acetate.

**2-Cyano-N-ethylacetamide (15d)**

![2-Cyano-N-ethylacetamide (15d)](image)

General procedure S1 was followed using ethylamine THF solution (2 M, 3.00 mL) to afford the product as a white solid, (350 mg, 3.12 mmol, 52%). Mp: 73-74 °C (Lit. 1 74 °C); ¹H NMR (400 MHz, d₆-Acetone): δ 7.33 (br s, 1H), 3.40 (s, 2H), 3.11 (d q, ³J₁= 7.4 Hz, ³J₂= 5.6 Hz, 2H), 0.97 (t, ³J= 7.4 Hz, 3H).

**N-butyl-2-cyanoacetamide (15e)**

![N-butyl-2-cyanoacetamide (15e)](image)

General procedure S1 was followed using n-butylamine (0.50 mL) to afford the product as a white solid (413 mg, 2.95 mmol, 49%). Mp: 70-71 °C (Lit. 2 72-73 °C); ¹H NMR (300 MHz, CDCl₃): δ 6.56 (br s, 1H), 3.35 (s, 2H), 3.21 (dt, ³J₁= 7.5 Hz, ³J₂= 5.8 Hz, 2H), 1.51-1.41 (m, 2H), 1.35-1.23 (m, 2H), 0.87 (t, ³J= 7.3 Hz, 3H).

**2-Cyano-N-(2-hydroxyethyl)acetamide (15g)**

![2-Cyano-N-(2-hydroxyethyl)acetamide (15g)](image)

General procedure S1 was followed using 2-aminoethanol (0.36 mL) to afford the product as colourless oil (286 mg, 2.23 mmol, 37%). ¹H NMR (400 MHz, d₆-DMSO):
δ 8.23 (br s, 1H), 4.73 (t, 3J= 5.4 Hz, 1H), 3.60 (s, 2H), 3.42-3.38 (m, 2H), 3.14-3.10 (m, 2H).

**General procedure S2 for the synthesis of 2-aminothiophenes 13a-j**

Diethylamine (0.52 mL, 5.00 mmol, 1.00 eq.) was added dropwise to a mixture of α-cyanoester or α-cyanoamide (5.00 mmol, 1.00 eq.), aldehyde (5.00 mmol, 1.00 eq.) and sulfur (162 mg, 5.25 mmol, 1.05 eq.) in DMF (5 mL). The reaction mixture was stirred at room temperature and followed by TLC. After completion of the starting material, the reaction mixture was diluted with ethyl acetate (30 mL) and washed with water (3×10 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane and ethyl acetate).

**Ethyl 2-amino-5-ethylthiophene-3-carboxylate (13a)**

General procedure S2 was followed using n-butyraldehyde 16a (0.45 mL, 5.00 mmol) and ethyl 2-cyanoacetate 15a (0.53 mL, 5.00 mmol) to afford the product as a light orange solid (655 mg, 3.20 mmol, 66%). Mp: 70-71 °C (Lit. 473 °C); ¹H NMR (300 MHz, CDCl₃): δ 6.56 (t, 4J= 1.2 Hz, 1H), 4.18 (q, 3J= 7.1 Hz, 2H), 2.54 (dq, 3J= 7.5 Hz, 4J= 1.2 Hz, 2H), 1.26 (t, 3J= 7.1 Hz, 3H), 1.15 (t, 3J= 7.5 Hz, 3H).

**Ethyl 2-amino-5-butylthiophene-3-carboxylate (13b)**

General procedure S2 was followed using n-hexanaldehyde 16b (0.60 mL, 5.00 mmol) and ethyl 2-cyanoacetate 15a (0.53 mL, 5.00 mmol) to afford the product as an off white liquid (670 mg, 2.95 mmol, 59%). IR (Nujol) νₐₖₔ = 3443 (m) (NH), 3336 (m), 1679 (s) (C=O), 1583 (s), 1265 (s) (C-O), 1153 (m) (C-O) cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 6.55 (t, 4J= 1.1 Hz, 1H), 4.18 (q, 3J= 7.1 Hz, 2H), 2.50 (dt, 3J= 7.5
Methyl 2-amino-5-ethylthiophene-3-carboxylate (13c)

General procedure S2 was followed using n-butyraldehyde 16a (0.45 mL, 5.00 mmol) and methyl 2-cyanoacetate 15b (0.44 mL, 5.00 mmol) to afford the product as an orange solid (751 mg, 4.05 mmol, 76%). Mp: 59-60 °C (no Lit. Mp); $^1$H NMR (300 MHz, CDCl$_3$): δ 6.54 (t, $^4$J= 1.2 Hz, 1H), 3.71 (s, 3H), 2.53 (dq, $^3$J= 7.5 Hz, $^4$J= 1.2 Hz, 2H), 1.15 (t, $^3$J= 7.5 Hz, 3H).

Butyl 2-amino-5-ethylthiophene-3-carboxylate (13d)

General procedure S2 was followed using n-butyraldehyde 16a (0.45 mL, 5.00 mmol) and butyl 2-cyanoacetate 15c (0.71 mL, 5.00 mmol) to afford the product as a colourless liquid (605 mg, 2.66 mmol, 53%). IR (Nujol) $v_{\text{max}}$ = 3444 (m) (NH), 3337 (m), 1677 (s) (C=O), 1584 (s), 1266 (s) (C-O), 1155 (m) (C-O) cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$): δ 6.55 (t, $^4$J= 1.2 Hz, 1H), 4.13 (t, $^3$J= 6.6 Hz, 2H), 2.54 (dq, $^3$J= 7.5 Hz, $^4$J= 1.2 Hz, 2H), 1.66-1.57 (m, 2H), 1.43-1.31 (m, 2H), 1.15 (t, $^3$J= 7.5 Hz, 3H), 0.89 (t, $^3$J= 7.3 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 165.5 (C), 161.2 (C), 128.4
(C), 120.6 (CH), 106.2 (C), 63.5 (CH2), 31.0 (CH2), 19.3 (CH2), 15.4 (CH3), 13.8 (CH3). LRMS (CI⁺): m/z (%) 228.11 (38) [M+H]⁺; HRMS (CI⁺): m/z calcd for C11H18NO2S [M+H]⁺: 228.1058; found 228.1052.

2-Amino-N,5-diethylthiophene-3-carboxamide (13e)

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{S} & \quad \text{NH}_2 \\
\end{align*}
\]

General procedure S2 was followed using n-butyraldehyde 16a (0.20 mL, 2.20 mmol) and 2-cyano-N-ethylacetamide 15d (250 mg, 2.20 mmol). The product was obtained as a off white solid (214 mg, 1.08 mmol, 49%). Mp: 91-92 °C; IR (KBr) \( \nu_{\text{max}} = 3321 \) (br, s), 2973 (s) (C-H), 1652 (s) (C=O), 1610 (s), 1532 (s), 1265 (s), 739 (s) cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 6.86 (br s, 1H), 6.67 (br s, 2H), 6.56 (t, \( ^4J = 1.1 \) Hz, 1H), 3.22-3.13 (m, 2H), 2.43 (dq, \( ^3J = 7.5 \) Hz, \( ^4J = 1.1 \) Hz, 2H), 1.03 (t, \( ^3J = 7.5 \) Hz, 3H), 0.99 (t, \( ^3J = 7.3 \) Hz, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 165.8 (C), 158.8 (C), 129.2 (C), 117.7 (CH), 108.3 (C), 34.0 (CH2), 23.1 (CH2), 15.5 (CH3), 15.2 (CH3). LRMS (ES⁺): m/z (%) 220.99 (100) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C9H14N2ONaS [M+Na]⁺: 221.0725; found 221.0731.

2-Amino-N-butyl-5-ethylthiophene-3-carboxamide (13f)

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
\text{S} & \quad \text{NH}_2 \\
\end{align*}
\]

General procedure S2 was followed using n-butyraldehyde 16a (1.02 mL, 11.43 mmol), N-butyl-2-cyanoacetamide 15e (200 mg, 11.43 mmol) to afford the product as an off white solid (140 mg, 5.23 mmol, 46%). Mp: 83-84 °C; IR (KBr) \( \nu_{\text{max}} = 3310 \) (br, s), 3084 (m), 2926 (s) (C-H), 1667 (s) (C=O), 1533 (s), 1459 (s), 1253 (s) cm\(^{-1}\). \(^1\)H NMR (400 MHz, \( d_6 \)-Acetone): \( \delta \) 6.28 (t, \( ^4J = 1.1 \) Hz, 1H), 3.31-3.25 (m, 2H), 2.55 (dq, \( ^3J = 7.5 \) Hz, \( ^4J = 1.1 \) Hz, 2H), 1.51-1.44 (m, 2H), 1.35-1.26 (m, 2H), 1.18 (t, \( ^3J = 7.5 \) Hz, 3H), 0.87 (t, \( ^3J = 7.3 \) Hz, 3H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 165.9 (C),
158.7 (C), 129.2 (C), 117.7 (CH), 108.3 (CH<sub>2</sub>), 32.1 (CH<sub>2</sub>), 23.1 (CH<sub>2</sub>), 20.2 (CH<sub>2</sub>), 15.5 (CH<sub>3</sub>), 13.8 (CH<sub>3</sub>). LRMS (ES<sup>+</sup>): m/z (%) 249.01 (100) [M+Na]<sup>+</sup>; HRMS (ES<sup>+</sup>): m/z calcd for C<sub>11</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S [M+Na]<sup>+</sup>: 249.1038; found 249.1038.

2-Amino-5-ethylthiophene-3-carboxamide (13g)

General procedure S2 was followed using n-butyraldehyde 16a (0.45 mL, 5.00 mmol) and 2-cyanoacetamide 15f (420 mg, 5.00 mmol) to afford the product as an off white solid (410 mg, 2.41 mmol, 48%). Mp: 116-117 °C; IR (KBr) ν<sub>max</sub> = 3404 (s), 3327 (m), 3207 (m), 2966 (m) (C-H), 1638 (s) (C=O), 1527 (s), 1496 (s), 1422 (s), 783 (m) cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.30 (t, <sup>4</sup>J = 1.2 Hz, 1H), 5.71 (br. s, 2H), 5.57 (br. s, 2H), 2.54 (dq, <sup>3</sup>J = 7.5 Hz, <sup>4</sup>J = 1.2 Hz, 2H), 1.15 (t, <sup>3</sup>J = 7.5 Hz, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 167.0 (C), 159.3 (C), 128.0 (C), 117.4 (CH), 106.1 (C), 22.1 (CH<sub>2</sub>), 14.4 (CH<sub>3</sub>). LRMS (ES<sup>+</sup>): m/z (%) 192.94 (100) [M+Na]<sup>+</sup>; HRMS (ES<sup>+</sup>): m/z calcd for C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S [M+Na]<sup>+</sup>: 193.0412; found 193.0407.

2-Amino-5-ethyl-N-(2-hydroxyethyl)thiophene-3-carboxamide (13h)

General procedure S2 was followed using n-butyraldehyde 16a (1.17 mL), 2-cyanoacetamide 15h (1.68 mg) to afford the product as a dark yellow solid (1.00 g, 4.67 mmol, 46%). Mp: 120-121 °C; IR (KBr) ν<sub>max</sub> = 3426 (m), 3370 (m), 3292 (m), 1579 (s) (C=O), 1533 (s), 1299 (s), 1068 (s) (C-O) cm<sup>-1</sup>. <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-Acetone): δ 6.94 (br. s, 1H), 6.67 (br. s, 2H), 6.57 (t, <sup>4</sup>J = 1.1 Hz, 1H), 3.49 (t, <sup>3</sup>J = 5.6 Hz, 2H) 3.29-3.24 (m, 2H), 2.44 (dq, <sup>3</sup>J = 7.5 Hz, <sup>4</sup>J = 1.1 Hz, 2H), 1.04 (t, <sup>3</sup>J = 7.5 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 167.4 (C), 160.9 (C), 127.8 (C),
119.8 (CH), 108.1 (C), 62.6 (CH₂), 42.9 (CH₂), 23.6 (CH₂), 15.9 (CH₃). LRMS (ES⁺): m/z (%) 237.00 (100) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₉H₁₄N₂O₂NaS [M+Na]⁺: 237.0680; found 237.0678.

2-Amino-5-ethylthiophene-3-carboxylic acid (13i)

[Chemical structure image]

13a (1.00g, 5mmol, 1.00 eq.) and sodium hydroxide (800 mg, 20mmol, 4.00 eq.) was dissolved in 50mL methanol/water (1:1) and refluxed for 4 hours. After cooling down the reaction mixture was acidified to pH 2-3. The mixture was extracted with ethyl acetate and the organic layer was concentrated. The crude reaction mixture was purified by flash chromatography (hexane/ethyl acetate: from 3:1 to 1:1) to afford the product as a light yellow solid (630 mg, 3.68 mmol, 74%). Mp: 91-92 °C; IR (KBr) νmax = 3451 (s), 3331 (s), 2971 (s) (C=H), 1638 (s) (C=O), 1600 (s), 1495 (s), 1252 (s) (C-O), 939 (m) cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 6.58 (s, 1H), 5.81 (br. s, 2H), 2.54 (dq, J= 7.5 Hz, J= 1.0 Hz, 2H), 1.16 (t, J= 7.5 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 170.3 (C), 163.1 (C), 128.7 (C), 120.8 (CH), 105.3 (C), 23.0 (CH₂), 15.2 (CH₃). LRMS (Cl⁺): m/z (%) 172.04 (20) [M+H]⁺; HRMS (Cl⁺): m/z calcd for C₇H₁₀NO₂S [M+H]⁺: 172.0432; found 172.0428.

Thiophen-2-amine (13j)

2-iiodothiophene S1 (2.2 mL, 20.0 mmol, 1.00 eq.), CuI (760 mg, 4.00 mmol, 0.20 eq.), L-proline (920 mg, 8.00 mmol, 0.40 eq.), K₂CO₃ (8.29 g, 60.0 mmol, 3.00 eq.) and ammonia solution (35% aqueous, 16.6 mL, 300 mmol) in 40 mL DMSO were stirred at 60 °C under N₂ atmosphere for 12 hours. Water (100 mL) was added and the mixture was exacted with DCM (100 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/ethyl acetate: from 10:1 to 3:1). The product was obtained as an off white liquid (400 mg, 4.03 mmol, 20%). ¹H NMR (300 MHz, CDCl₃): δ 6.61
(dd, $^3J_1= 5.6$ Hz, $^3J_2= 3.6$ Hz, 1H), 6.44 (dd, $^3J= 5.6$ Hz, $^4J= 1.4$ Hz, 1H), 6.13 (dd, $^3J= 3.6$ Hz, $^4J= 1.4$ Hz, 1H), 3.67 (br, s, 1H).

For the synthesis of furancarboxyl amide-containing intermediates 22q, 24a, 24b, or the known analogs 18b, 22a-d, 22f, 22g, 22k, 22p and 25a general procedure provided in the paper was used.

**General Procedure for the synthesis of furancarboxyl amides 12a-k, 18a-b and 22a-q**

The furoic acid chlorides 14a and 14b were prepared *in situ*: thionyl chloride (1.10 eq.) was added dropwise to a mixture of 5-nitrofuran-2-carboxylic acid or 2-furoic acid (1.10 eq.), triethylamine (1.50 eq.) in DCM (0.4 M) under a N$_2$ atmosphere. The reaction mixture was stirred at room temperature for 5 hours. Then crude 14a or 14b was added to another flask containing the corresponding amine or aniline (1.00 eq.) and triethylamine (2.00 eq.) in DCM (0.4 M). The reaction mixture was stirred at room temperature for 5 hours. The solvent was then removed under reduced pressure and the crude reaction mixture was purified by column chromatography.

**Ethyl 5-butyl-2-(5-nitrofuran-2-carboxamido)thiophene-3-carboxylate (12b):** The general procedure was followed using 2-amiothiophene 13b (454 mg, 2.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (7:1, hexane/ethyl acetate) to afford the product as an orange solid (455 mg, 1.24 mmol, 62%). Mp: 104-105 °C; IR (KBr) $\nu_{\text{max}} = 3134$ (m) (NH), 2930 (s) (CH), 1685 (s) (C=O), 1656 (s) (C=O), 1567 (s), 1541 (s) (NO$_2$), 1348 (s) (NO$_2$), 1267 (s) (C-O), 1240 (s) (C-O) cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 11.74 (br. s, 1H), 7.59 (d, $^3J= 3.9$ Hz, 1H), 7.42 (d, $^3J= 3.9$ Hz, 1H), 6.85 (s, 1H), 4.28 (q, $^3J= 7.2$ Hz, 2H), 2.65 (t, $^3J= 7.5$ Hz, 2H), 1.56-1.50 (m, 2H), 1.31-1.24 (m, 5H), 0.82 (t, $^3J= 7.4$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.2 (C), 153.9 (C), 153.5 (C), 147.8 (C), 146.0 (C),
138.0 (C), 121.7 (CH), 119.0 (CH), 115.4 (C), 114.3 (CH), 62.1 (CH₂), 34.6 (CH₂), 30.0 (CH₂), 23.1 (CH₂), 15.0 (CH₃), 14.4 (CH₃). LRMS (ES⁺): m/z (%) 388.94 (100) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₁₆H₁₈N₂O₆NaS [M+Na]⁺: 389.0783; found 389.0793.

**Methyl 5-ethyl-2-(5-nitrofuran-2-carboxamido)thiophene-3-carboxylate (12c):**

The general procedure was followed using 2-amiothiophene 13c (370 mg, 2.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (5:1, hexane/ethyl acetate) to afford the product as an orange solid (420 mg, 1.30 mmol, 65%). Mp: 155-156 °C; IR (KBr) ν_max = 3398 (s) (NH), 3127 (m) (CH), 1701 (s) (C=O), 1618 (s) (C=O), 1560 (s), 1522 (s) (NO₂), 1352 (s) (NO₂), 1286 (s), 1131 (s) (C=O), 1111 (s) (C-O) cm⁻¹. ¹H NMR (400 MHz, d₆-Acetone): δ 11.74 (br s, 1H), 7.58 (d, ³J= 3.9 Hz, 1H), 7.42 (d, ³J= 3.9 Hz, 1H), 6.83 (t, ⁴J= 1.1 Hz, 1H), 3.80 (s, 3H), 2.67 (dq, ³J= 7.5 Hz, ⁴J= 1.1 Hz, 2H), 1.16 (t, ³J= 7.5 Hz, 3H). ¹³C NMR (100 MHz, d₆-Acetone): δ 166.2 (C), 153.6 (C), 153.0 (C), 147.3 (C), 145.7 (C), 139.2 (C), 120.5 (CH), 118.6 (CH), 114.6 (C), 113.8 (CH), 52.4 (CH₃), 23.4 (CH₂), 15.9 (CH₃). LRMS (ES⁺): m/z (%) 346.86 (100) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₁₃H₁₂N₂O₆NaS [M+Na]⁺: 347.0312; found 347.0314.

**Butyl 5-ethyl-2-(5-nitrofuran-2-carboxamido)thiophene-3-carboxylate (12d):**

The general procedure was followed using 2-amiothiophene 13d (454 mg, 2.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (7:1, hexane/ethyl acetate) to afford the product as an orange solid (425 mg, 1.16 mmol, 58%). Mp: 108-109 °C; IR (KBr) ν_max = 3120 (m) (NH), 2958 (s) (C-H), 1661 (s) (C=O), 1563 (s), 1535 (s) (NO₂), 1351 (s) (NO₂), 1239 (s) (C-O), 1216 (s) (C-O) cm⁻¹. ¹H NMR (500 MHz, d₆-Acetone): δ 11.78 (br s, 1H), 7.59 (d, ³J= 3.9 Hz, 1H), 7.43 (d, ³J= 3.9 Hz, 1H), 6.88 (s, 1H), 4.24 (t, ³J= 6.6 Hz, 2H), 2.68 (q, ³J= 7.6 Hz, 2H),

S10
1.68-1.63 (m, 2H), 1.40-1.33 (m, 2H), 1.17 (t, \( ^3J = 7.6 \) Hz, 3H), 0.85 (t, \( ^3J = 7.4 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, \( d_6 \)-Acetone): \( \delta 166.3 \) (C), 154.0 (C), 153.2 (C), 147.8 (C), 146.0 (C), 139.6 (C), 120.9 (CH), 119.0 (CH), 115.3 (C), 114.3 (CH), 65.9 (CH\(_2\)), 31.9 (CH\(_2\)), 23.7 (CH\(_2\)), 20.3 (CH\(_2\)), 16.4 (CH\(_3\)), 14.4 (CH\(_3\)). LRMS (ES\(^+\)): m/z (%) 388.93 (100) [M+Na]\(^+\); HRMS (ES\(^+\)): m/z calcd for C\(_{16}\)H\(_{15}\)N\(_3\)O\(_6\)NaS [M+Na]\(^+\): 389.0783; found 389.0772.

**N-(5-ethyl-3-(ethylcarbamoyl)thiophen-2-yl)-5-nitrofuran-2-carboxamide** (12e):

The general procedure was followed using 2-amiothiophene 13e (60 mg, 0.30 mmol). The crude reaction mixture was purified by column chromatography on silica gel (2:1, hexane/ethyl acetate) to afford the product as a yellow solid (57 mg, 0.16 mmol, 57%). Mp: 142-143 \(^\circ\)C; IR (KBr)  \( \nu_{\text{max}} = 3434 \) (m) (NH), 2913 (m) (CH\(_\text{N}\)), 2851 (m), 1664 (s) (C=O), 1558 (s) (C=O), 1532 (s) (NO\(_2\)), 1351 (s) (NO\(_2\)), 1276 (s) cm\(^{-1}\). \(^1\)H NMR (400 MHz, \( d_6 \)-Acetone): \( \delta 7.62 \) (br. s, 1H), 7.57 (d, \( ^3J = 3.9 \) Hz, 1H), 7.36 (d, \( ^3J = 3.9 \) Hz, 1H), 7.00 (s, 1H), 3.35-3.31 (m, 2H), 2.65 (q, \( ^3J = 7.6 \) Hz, 2H), 1.15 (t, \( ^3J = 7.6 \) Hz, 3H), 1.07 (t, \( ^3J = 7.2 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, \( d_6 \)-Acetone): \( \delta 166.0 \) (C), 153.4 (C), 152.9 (C), 148.0 (C), 143.4 (C), 139.0 (C), 118.7 (CH), 117.9 (CH), 117.4 (C), 113.8 (CH), 34.8 (CH\(_2\)), 23.4 (CH\(_2\)), 15.8 (CH\(_3\)), 15.2 (CH\(_3\)). LRMS (ES\(^+\)): m/z (%) 359.95 (100) [M+Na]\(^+\); HRMS (ES\(^+\)): m/z calcd for C\(_{14}\)H\(_{15}\)N\(_3\)O\(_5\)NaS [M+Na]\(^+\): 360.0630; found 360.0632.

**N-(3-(butylcarbamoyl)-5-ethylthiophen-2-yl)-5-nitrofuran-2-carboxamide** (12f):

The general procedure was followed using 2-amiothiophene 13f (120 mg, 0.53 mmol). The crude reaction mixture was purified by column chromatography on silica gel (4:1, hexane/ethyl acetate) to afford the product as a yellow solid (114 mg, 0.31 mmol, 59%). Mp: 107-108 \(^\circ\)C; IR (KBr)  \( \nu_{\text{max}} = 3337 \) (m) (NH), 2963 (m) (C-H), 1670 (s) (C=O), 1565 (s), 1536 (s) (NO\(_2\)), 1350 (s) (NO\(_2\)), 1272 (s) cm\(^{-1}\). \(^1\)H NMR (400
MHz, $d_6$-Acetone): $\delta$ 7.59 (br. s, 1H), 7.56 (d, $^3J = 3.9$ Hz, 1H), 7.36 (d, $^3J = 3.9$ Hz, 1H), 7.01 (t, $^4J = 1.1$ Hz, 1H), 3.29 (dt, $^3J_1 = 7.3$ Hz, $^3J_2 = 5.8$ Hz, 2H), 2.65 (dq, $^3J = 7.5$ Hz, $^4J = 1.1$ Hz, 2H), 1.50-1.43 (m, 2H), 1.32-1.22 (m, 2H), 1.15 (t, $^3J = 7.5$ Hz, 3H), 0.81 (t, $^3J = 7.3$ Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-Acetone): $\delta$ 166.1 (C), 153.4 (C), 153.0 (C), 148.0 (C), 143.4 (C), 139.0 (C), 118.7 (CH), 117.9 (CH), 117.4 (C), 113.8 (CH), 39.7 (CH$_2$), 32.5 (CH$_2$), 23.4 (CH$_2$), 20.8 (CH$_2$), 15.8 (CH$_3$), 14.1 (CH$_3$).

LRMS (ES$^+$): m/z (%) 387.96 (100) [M+Na]$^+$; HRMS (ES$^+$): m/z calcld for C$_{16}$H$_{19}$N$_{3}$O$_{5}$NaS [M+Na]$^+$: 388.0943; found 388.0941.

$N$-(5-ethyl-3-(2-hydroxyethylcarbamoyl)thiophen-2-yl)-5-nitrofuran-2-carboxamide (12h): The general procedure was followed using 2-amiothiophene 13h (75 mg, 0.20 mmol). The crude reaction mixture was purified by column chromatography on silica gel (1:2, hexane/ethyl acetate) to afford the product as a yellow solid (33 mg, 0.093 mmol, 47%). Mp: 165-166 $^\circ$C; IR (KBr) $\nu_{\text{max}}$ = 3327 (m) (OH), 3120 (m) (NH), 2969 (m) (C-H), 1669 (s) (C=O), 1566 (s), 1536 (s) (NO$_2$), 1412 (s), 1348 (s) (NO$_2$) cm$^{-1}$. $^1$H NMR (300 MHz, $d_6$-Acetone): $\delta$ 7.63 (br. s, 1H), 7.56 (d, $^3J = 3.9$ Hz, 1H), 7.36 (d, $^3J = 3.9$ Hz, 1H), 7.04 (s, $^4J = 1.0$ Hz, 1H), 3.85 (br. s, 1H), 3.59 (t, $^3J = 5.7$ Hz, 2H), 3.40 (t, $^3J = 5.7$ Hz, 2H), 2.65 (dq, $^3J_1 = 7.5$ Hz, $^3J_2 = 7.5$ Hz, 2H), 1.15 (t, $^3J = 7.5$ Hz, 3H). $^{13}$C NMR (100 MHz, $d_6$-Acetone): $\delta$ 166.4 (C), 153.4 (C), 152.9 (C), 148.0 (C), 143.6 (C), 139.0 (C), 118.8 (CH), 118.0 (CH), 117.3 (C), 113.8 (CH), 61.5 (CH$_2$), 42.9 (CH$_2$), 23.4 (CH$_2$), 15.8 (CH$_3$). LRMS (ES$^+$): m/z (%) 375.94 (100) [M+Na]$^+$; HRMS (ES$^+$): m/z calcld for C$_{14}$H$_{18}$N$_{3}$O$_{6}$NaS [M+Na]$^+$: 376.0579; found 376.0576.

5-Ethyl-2-(5-nitrofuran-2-carboxamido)thiophene-3-carboxylic acid (12i): The general procedure was followed using thiophen-2-amine 13i (600 mg, 3.50 mmol). The crude reaction mixture was purified by column chromatography on silica gel (1:2,
hexane/ethyl acetate) to afford the product as a yellow solid (267 mg, 0.86 mmol, 25%). Mp: 231-232 °C; IR (KBr) ν<sub>max</sub> = 3146 (m) (OH), 3108 (m) (NH), 1665 (s) (C=O), 1562 (s), 1540 (s) (NO₂), 1346 (s) (NO₂), 1347 (s), 1252 (s) (C-O), 1202 (s) cm⁻¹. "H NMR (400 MHz, d₆-Acetone): δ 11.96 (br. s, 1H), 7.57 (d, J=3.9 Hz, 1H), 7.41 (d, J=3.9 Hz, 1H), 6.89 (t, 4J=1.1 Hz, 1H), 2.69 (dq, J=7.5 Hz, J=1.1 Hz, 2H), 1.18 (t, J=7.5 Hz, 3H). "C NMR (100 MHz, d₆-Acetone): δ 166.9 (C), 153.5 (C), 152.9 (C), 147.4 (C), 145.9 (C), 139.0 (CH), 121.0 (CH), 118.5 (CH), 115.0 (C), 113.8 (CH), 23.3 (CH₂), 15.9 (CH₃). LRMS (ES⁺): m/z (%) 332.84 (100) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₁₂H₁₀N₂O₆NaS [M+Na]⁺: 333.0157; found 333.0167.

5-nitro-N-(thiophen-2-yl)furan-2-carboxamide (12j): The general procedure was followed using thiophen-2-amine 13j (400 mg, 4.03 mmol). The crude reaction mixture was purified by column chromatography on silica gel (1:1, hexane/ethyl acetate) to afford the product as a brown solid (392 mg, 1.66 mmol, 41%). Mp: 123-124 °C; IR (KBr) ν<sub>max</sub> = 3245 (m) (NH), 3121 (w), 1648 (s) (C=O), 1573 (s), 1537 (s) (NO₂), 1349 (s) (NO₂), 1302 (s), 1013 (s), 810 (s) cm⁻¹. "H NMR (300 MHz, d₆-Acetone): δ 11.44 (br. s, 1H), 7.65 (d, J=3.9 Hz, 1H), 7.51 (d, J=3.9 Hz, 1H), 7.06 (dd, J=5.5 Hz, J=1.4 Hz, 1H), 7.01 (dd, J=3.8 Hz, J=1.4 Hz, 1H), 6.92 (dd, J=5.5 Hz, J₂=3.8 Hz, 1H). "C NMR (100 MHz, d₆-Acetone): δ 154.0 (C), 153.3 (C), 148.8 (C), 140.0 (C), 125.5 (CH), 119.7 (CH), 118.1 (CH), 114.7 (CH), 114.2 (CH). LRMS (ES⁺): m/z (%) 260.96 (100) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₉H₆N₂O₄NaS [M+Na]⁺: 260.9946; found 260.9947.

Ethyl 2-(5-nitrofuran-2-carboxamido)thiophene-3-carboxylate (12k): The general procedure was followed using 2-amiothiophene 13k (1.00 g, 5.84 mmol). The crude reaction mixture was purified by column chromatography on silica gel (4:1, hexane/ethyl acetate) to afford the product as a yellow solid (0.92 g, 2.96 mmol,
51%). Mp: 186-187 °C; IR (KBr) ν\textsubscript{max} = 3142 (m) (NH), 1670 (s) (C=O), 1662 (s) (C=O), 1532 (s) (NO\textsubscript{2}), 1351 (s) (NO\textsubscript{2}), 1266 (s) (C-O), 1225 (s) (C-O), 1025 (s), 843 (s) cm\textsuperscript{-1}. \textsuperscript{1}H NMR (300 MHz, d\textsubscript{6}-Acetone): δ 11.83 (br. s, 1H), 7.60 (d, \textsuperscript{3}J= 3.9 Hz, 1H), 7.45 (d, \textsuperscript{3}J= 3.9 Hz, 1H), 7.18 (d, \textsuperscript{3}J= 5.8 Hz, 1H), 6.97 (d, \textsuperscript{3}J= 5.8 Hz, 1H), 4.31 (q, \textsuperscript{3}J= 7.1 Hz, 2H), 1.29 (t, \textsuperscript{3}J= 7.1 Hz, 3H). \textsuperscript{13}C NMR (100 MHz, d\textsubscript{6}-Acetone): δ 165.8 (C), 153.9 (C), 152.9 (C), 147.6 (C), 147.3 (C), 125.0 (CH), 118.8 (CH), 118.5 (CH), 115.6 (C), 113.8 (CH), 61.9 (CH\textsubscript{2}), 14.6 (CH\textsubscript{3}). LRMS (ES\textsuperscript{+}): m/z (%) 332.89 (100) [M+Na]\textsuperscript{+}; HRMS (ES\textsuperscript{+}): m/z calcd for C\textsubscript{11}H\textsubscript{8}N\textsubscript{2}O\textsubscript{4}NaS [M+Na]\textsuperscript{+}: 330.0157; found 333.0149.

Ethyl 5-ethyl-2-(furan-2-carboxamido)thiophene-3-carboxylate (18a): The general procedure was followed using 2-amiothiophene 12a (199 mg, 1.00 mmol, 1.00 eq.). The crude reaction mixture was purified by column chromatography on silica gel (7:1, hexane/ethyl acetate) to afford the product as a yellow solid (164 mg, 0.56 mmol, 56%). Mp: 100-101 °C; IR (KBr) ν\textsubscript{max} = 3411 (m) (NH), 2969 (m) (CH\textsubscript{3}), 1658 (s) (C=O), 1558 (s), 1275 (s) (C-O), 1225 (s) (C-O), 738 (s) cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, d\textsubscript{6}-Acetone): δ 11.60 (br. s, 1H), 7.76 (dd, \textsuperscript{3}J= 1.8 Hz, \textsuperscript{4}J= 0.7 Hz, 1H), 7.18 (dd, \textsuperscript{3}J= 3.6 Hz, \textsuperscript{4}J= 0.7 Hz, 1H), 6.80 (t, \textsuperscript{4}J= 1.1 Hz, 1H), 6.61 (dd, \textsuperscript{3}J= 3.6 Hz, \textsuperscript{4}J= 1.8 Hz, 1H), 4.24 (q, \textsuperscript{3}J= 7.1 Hz, 2H), 2.64 (dq, \textsuperscript{4}J= 7.5 Hz, \textsuperscript{4}J= 1.1 Hz, 2H), 1.25 (t, \textsuperscript{3}J= 7.1 Hz, 3H), 1.15 (t, \textsuperscript{3}J= 7.5 Hz, 3H). \textsuperscript{13}C NMR (100 MHz, d\textsubscript{6}-Acetone): δ 166.0 (C), 154.9 (C), 147.5 (C), 147.0 (CH), 146.8 (C), 138.1 (C), 137.8 (C), 120.2 (CH), 117.1 (CH), 113.7 (CH), 61.4 (CH\textsubscript{2}), 23.2 (CH\textsubscript{2}), 16.0 (CH\textsubscript{3}), 14.6 (CH\textsubscript{3}). LRMS (ES\textsuperscript{+}): m/z (%) 315.90 (100) [M+Na]\textsuperscript{+}; HRMS (ES\textsuperscript{+}): m/z calcd for C\textsubscript{12}H\textsubscript{10}N\textsubscript{2}O\textsubscript{4}NaS [M+Na]\textsuperscript{+}: 316.0619; found 316.0613.

N-phenylfuran-2-carboxamide (18b)

\textsuperscript{8}
The general procedure in the paper was followed using aniline (0.219 mL, 2.40 mmol). The crude reaction mixture was purified by column chromatography on silica gel (3:1, hexane/ethyl acetate) to afford the product as a white solid (330 mg, 1.76 mmol, 73%). Mp: 126-127 °C (no Lit. Mp); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.01 (br. s, 1H), 7.58 (d, $^3$J = 8.1 Hz, 2H), 7.44 (dd, $^3$J = 1.8 Hz, $^4$J = 0.8 Hz, 1H), 7.30 (dd, $^3$J = 8.1 Hz, $^3$J = 7.4 Hz, 2H), 7.18 (t, $^3$J = 3.2 Hz, 1H), 7.08 (t, $^3$J = 7.4 Hz, 1H), 6.49 (dd, $^3$J = 3.5 Hz, $^3$J = 1.8 Hz, 1H). LRMS (ES$^+$): m/z (%) 187.98 (100) [M+Na]$^+$. 

**General procedure S3 Synthesis of analogues 20a-c and 21**

A solution of the carboxylic acid (1.00 eq) in thionyl chloride was stirred under reflux (~80 °C) for 3-6 h under an inert atmosphere and then concentrated under reduced pressure. Triethylamine (3.00 eq) was added to a solution of 13g (0.95 eq) in anhydrous DCM. The freshly prepared acid chloride was dissolved in anhydrous DCM and added dropwise to the solution of 13g. The resulting reaction mixture was stirred overnight at room temperature and then concentrated under reduced pressure to afford the crude title compounds which were purified as detailed below.

**5-Ethyl-2-(2-nitrobenzamido) thiophene-3-carboxamide (20a)**

General procedure S3 was followed using 2-nitrobenzoic acid (334 mg, 2.0 mmol, 1.00 eq) and 13g (323 mg, 1.9 mmol, 0.95 eq). The crude reaction mixture was purified by column chromatography on silica gel (from 2:1 to 1:1, hexane/ethyl acetate) and the product was recrystallized from EtOAc to afford the product as a yellow solid (38 mg, 0.1 mmol, 6%) Mp: 93-94 °C; IR (KBr) $\nu_{max}$ = 3425 (s) (NH), 1658 (s) (C=O), 1590 (s) (C=C), 1566 (s) (C=C), 1528 (s) (NO$_2$), 1346 (s) (NO$_2$) cm$^{-1}$. $^1$H NMR (300 MHz, $d_6$-acetone): $\delta$ 8.13 (d, $^3$J = 7.9 Hz, 1H), 8.01-7.81 (m, 3H), 7.44 (br s, 1H), 7.17 (s, 1H), 6.89 (br s, 1H), 2.81 (q, $^3$J = 7.6 Hz, 2H), 1.31, (t, $^3$J = 7.6 Hz, 3H); $^{13}$C NMR (100 MHz, $d_6$-acetone): $\delta$ 168.2 (C) 161.5 (C) 148.0 (C),
144.2 (C), 137.3 (C), 133.5 (CH), 131.6 (CH), 130.6 (C), 128.4 (CH), 124.5 (CH), 118.1 (CH), 115.2 (C), 22.5 (CH₂), 15.0 (CH₃); LRMS (ES⁺): m/z (%) 341.83 (100) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₁₄H₁₂N₃O₄S [M+H]⁺: 318.0549; found 318.0551.

5-Ethyl-2-(3-nitrobenzamido) thiophene-3-carboxamide (20b)

General procedure S3 was followed using 3-nitrobenzoic acid (334 mg, 2.0 mmol, 1.00 eq) and 13g (323 mg, 1.9 mmol, 0.95 eq). The crude reaction mixture was purified by column chromatography on silica gel (from 2:1 to 3:2, hexane/ethyl acetate) and the product was recrystallized from EtOAc to afford the product as a yellow solid (84 mg, 0.3 mmol, 14%). Mp: 176-178 °C; IR (KBr) νmax = 3436 (s) (NH), 1647 (s) (C=O), 1591 (s) (C=C), 1569 (s) (C=C), 1530 (s) (NO₂), 1347 (s) (NO₂) cm⁻¹. ¹H NMR (300 MHz, d₆-acetone): δ 8.68 (dd, 4J₁=1.9 Hz, 4J₂=1.9 Hz, 1H), 8.38 (ddd, 4J₁=0.9 Hz, 4J₂=1.9 Hz, 3J=8.1 Hz, 1H), 8.24 (ddd, 4J₁=0.9 Hz, 4J₂=1.9 Hz, 3J=8.1 Hz, 1H), 7.83 (dd, 3J₁=8.1 Hz, 3J₂=8.1 Hz, 1H), 7.38 (br s, 1H), 7.05 (t, 3J=1.0 Hz, 1H), 6.84 (br s, 1H), 2.67 (dq, 4J=1.0 Hz, 3J=7.4 Hz, 2H), 1.18 (t, 3J=7.4 Hz, 3H); ¹³C NMR (100 MHz, d₆-acetone): δ 167.8 (C), 160.4 (C), 148.7 (C), 144.9 (C), 137.5 (C), 134.5 (C), 132.8 (CH), 130.8 (CH), 126.7 (CH), 122.2 (CH), 118.4 (CH), 115.4 (C), 22.5 (CH₂), 15.0 (CH₃); LRMS (ES⁺): m/z (%) 317.80 (100) [M-H⁺]; HRMS (ES⁺): m/z calcd for C₁₄H₁₂N₃O₄S [M-H⁺]: 318.0549; found 318.0551.

5-Ethyl-2-(4-nitrobenzamido) thiophene-3-carboxamide (20c)

General procedure S3 was followed using 4-nitrobenzoic acid (334 mg, 2.0 mmol, 1.00 eq) and 13g (323 mg, 1.9 mmol, 0.95 eq). The crude reaction mixture was purified by column chromatography on silica gel (3:2, hexane/ethyl acetate) and the product was recrystallized in EtOAc to afford the product as a dark red solid (68 mg,
0.2 mmol, 11%). Mp: 266-268 °C; IR (KBr) $\nu_{\text{max}} = 3440$ (s) (NH), 3177 (m) (NH$_2$), 1663 (s) (C=O), 1597 (s) (C=C), 1562 (s) (C=C), 1527 (s) (NO$_2$), 1343 (s) (NO$_2$), 705 (s) (CH) cm$^{-1}$. $^1$H NMR (300 MHz, $d_6$-DMSO): $\delta$ 8.49 (d, $^3J$=8.7 Hz, 2H), 8.18 (d, $^3J$=8.7 Hz, 2H), 8.07 (br s, 1H), 7.72 (br s, 1H), 7.30 (s, 1H), 2.80 (q, $^3J$=7.4 Hz, 2H), 1.31 (t, $^3J$=7.4 Hz, 3H); $^{13}$C NMR (75 MHz, $d_6$-DMSO): $\delta$ 167.7 (C), 160.9 (C), 150.0 (C), 143.8 (C), 138.1 (C), 137.1 (C), 128.9 (2CH), 124.7 (2CH), 119.5 (CH), 116.2 (C), 22.6 (CH$_2$), 15.78 (CH$_3$); LRMS (ES$^-$): m/z (%) 317.8 (100) [M-H]$^-$; HRMS (ES$^-$): m/z calcd for C$_{14}$H$_{12}$N$_3$O$_4$S [M-H]$^-$: 318.0549; found 318.0551.

$N$-(3-carbamoyl-5-ethylthiophen-2-yl)-4-nitro-1H-pyrazole-3-carboxamide (21)

General procedure S3 was followed using 4-nitro-1H-pyrazole-3-carboxylic acid (314 mg, 2.0 mmol, 1.00 eq) and 13g (323 mg, 1.9 mmol, 0.95 eq). The crude reaction mixture was purified by column chromatography on silica gel (ethyl acetate) to afford the product as a yellow solid (232 mg, 0.8 mmol, 42%). Mp: 297 °C; IR (KBr) $\nu_{\text{max}} = 3430$ (s) (NH), 3333 (m) (NH$_2$), 3149 (m) (NH), 1640 (s) (C=O), 1589 (s) (C=C), 1566 (s) (C=C), 1510 (s) (NO$_2$), 1339 (s) (NO$_2$), 741 (s) (CH) cm$^{-1}$. $^1$H NMR (300 MHz, $d_6$-DMSO): $\delta$ 14.46 (br s, 1H), 12.99 (s, 1H), 8.99 (br s, 1H), 7.89 (br s, 1H), 7.51 (br s, 1H), 7.22 (s, 1H), 2.74 (q, $^3J$=7.6 Hz, 2H), 1.26 (t, $^3J$=7.6 Hz, 3H). $^{13}$C NMR (75 MHz, $d_6$-DMSO): $\delta$ 166.7 (C), 155.3 (C), 142.3 (C), 138.9 (C), 136.5 (C), 133.5 (C), 132.4 (CH), 119.2 (CH), 115.9 (C), 22.2 (CH$_2$), 15.4 (CH$_3$); LRMS (ES$^-$): m/z (%) 308.03 (100) [M-H]$^-$; HRMS (ES$^-$): m/z calcd for C$_{11}$H$_{10}$N$_2$O$_4$S [M-H]$^-$: 308.0454; found 308.0450.

$N$-cyclohexyl-5-nitrofuran-2-carboxamide (22a)

The general procedure in the paper was followed using cyclohexylamine (283 mg, 2.85 mmol). The crude reaction mixture was purified by column chromatography on...
silica gel (3:1, hexane/ethyl acetate) to afford the product as a yellow crystalline solid (440 mg, 1.85 mmol, 65%). Mp: 149 °C (no Lit. Mp); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39 (d, $^3$J = 3.8 Hz, 1H), 7.27 (d, $^3$J = 3.8 Hz, 1H), 6.41 (br s, 1H), 4.11 – 3.76 (m, 1H), 2.09 – 1.18 (m, 10H). LRMS (ES$^+$): m/z (%) 261.01 (100) [M+Na]$^+$.  

5-Nitro-N-phenylfuran-2-carboxamide (22b)$^8$  

![5-Nitro-N-phenylfuran-2-carboxamide (22b)](image)

The general procedure in the paper was followed using aniline (186 mg, 2.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (3:1, hexane/ethyl acetate) to afford the product as a yellow solid (283 mg, 1.22 mmol, 61%). Mp: 174-175 °C (Lit $^8$ 174-175 °C); $^1$H NMR (400 MHz, CDCl$_3$): δ 8.15 (br. s, 1H, NH), 7.61 (d, $^3$J= 8.6 Hz, 2H, ArH), 7.36-7.31 (m, 4H, ArH), 7.15 (t, $^3$J= 7.4 Hz, 1H); LRMS (ES$^+$): m/z (%) 231.06 (100) [M-H]$^-$.

N-benzyl-5-nitrofuran-2-carboxamide (22c)$^10$  

![N-benzyl-5-nitrofuran-2-carboxamide (22c)](image)

The general procedure in the paper was followed using 1-phenylmethanamine (409 mg, 2.85 mmol). The crude reaction mixture was purified by column chromatography on silica gel (3:1, hexane/ethyl acetate) to afford the product as a white crystalline (508 mg, 2.06 mmol, 72 %). Mp: 91-92 °C (Lit $^10$ 91 °C); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.45-7.33 (m, 6H), 7.32 (d, $^3$J = 3.8 Hz, 1H), 6.88 (br s, 1H), 4.67 (d, $^3$J = 6.0 Hz, 2H); LRMS (ES$^+$): m/z (%) 268.96 (100) [M+Na]$^+$.  

5-Nitro-N-(pyridin-2-ylmethyl)furan-2-carboxamide (22d)$^9$  

![5-Nitro-N-(pyridin-2-ylmethyl)furan-2-carboxamide (22d)](image)

The general procedure in the paper was followed using pyridin-2-ylmethanamine (308 mg, 2.85 mmol). The crude reaction mixture was purified by column chromatography on silica gel (3:1, hexane/ethyl acetate) to afford the product as a pale yellow solid
(476 mg, 1.93 mmol, 67 %). Mp: 130-131 °C (no Lit. Mp); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 8.65 (d, \(^3\)J = 5.0 Hz, 1H), 8.02 (br s, 1H), 7.80 (d, \(^3\)J = 7.7 Hz, 1H), 7.46 – 7.30 (m, 4H), 4.81 (d, \(^3\)J = 5.2 Hz, 2H); LRMS (ES\(^+\)): m/z (%) 270.05 (100) [M+Na]\(^+\].

\(N\)-(3-bromophenyl)-5-nitrofuran-2-carboxamide (22f) \(^8\)

\[ \text{O}_2\text{N}\]
\[ \text{O} \]
\[ \text{H} \]
\[ \text{N} \]
\[ \text{Br} \]

The general procedure in the paper was followed using 3-bromoaniline (544 µL, 5.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (4:1, hexane/ethyl acetate) to afford the product as a dark yellow solid (780 mg, 2.48 mmol, 50%). Mp: 187-188 °C (no Lit. Mp); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 8.17 (br. s, 1H), 7.89 (t, \(^4\)J = 2.0 Hz, 1H,), 7.51 (ddd, \(^3\)J = 8.0 Hz, \(^4\)J\(_1\) = 2.0 Hz, \(^4\)J\(_2\) = 1.3 Hz, 1H), 7.36 (d, \(^3\)J = 3.8 Hz, 1H,), 7.33 (d, \(^3\)J = 3.8 Hz, 1H), 7.29 (ddd, \(^3\)J = 8.0 Hz, \(^4\)J\(_1\) = 2.0 Hz, \(^4\)J\(_2\) = 1.3 Hz, 1H,), 7.20 (t, \(^3\)J = 8.0 Hz, 1H). LRMS (ES\(^+\)): m/z (%) 310.75 (100), 312.74 (98) [M+H]\(^+\].

\(N\)-(3-methoxyphenyl)-5-nitrofuran-2-carboxamide (22g) \(^8\)

\[ \text{O}_2\text{N}\]
\[ \text{O} \]
\[ \text{H} \]
\[ \text{N} \]
\[ \text{O} \]

The general procedure in the paper was followed using 3-methoxyaniline (615 mg, 5.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (2:1, hexane/ethyl acetate) to afford the product as a yellow solid (587 mg, 2.24 mmol, 45%). Mp: 121-122 °C (no Lit. Mp); \(^1\)H NMR (400 MHz, d\(_6\)-Acetone): \(\delta\) 9.93 (br s, 1H), 7.52 (d, \(^3\)J = 3.9 Hz, 1H), 7.41 (d, \(^4\)J = 2.2 Hz, 1H), 7.34 (d, \(^3\)J = 3.9 Hz, 1H), 7.26 (d, \(^3\)J = 8.0 Hz, 1H), 7.15 (t, \(^3\)J = 8.0 Hz, 1H), 6.6 (d, \(^3\)J = 8.0 Hz, 1H,), 3.67 (s, 3H). LRMS (ES\(^+\)): m/z (%) 260.85 (100) [M-H]\(^-\].

\(N\)-(4-chlorophenyl)-5-nitrofuran-2-carboxamide (22i): The general procedure was followed using 4-chloroaniline (306 µL, 2.40 mmol). The crude reaction mixture was purified by column chromatography on silica gel (3:1, hexane/ethyl acetate) to afford the product as a brown solid (420 mg, 1.58 mmol, 66%). Mp: 184-185 °C; IR (KBr)
$\nu_{\text{max}} = 3347 \text{ (m)} \ (\text{NH}), \ 2924 \text{ (m)}, \ 1686 \text{ (s)} \ (\text{C=O}), \ 1494 \text{ (s)} \ (\text{NO}_2), \ 1312 \text{ (s)} \ (\text{NO}_2)$, 1256 (s), 822 (s), 749 (m) \ (\text{Cl-}) \ cm^{-1}. \ ^1\text{H} \ \text{NMR} \ (400 \ MHz, \ d_6-\text{Acetone}) \ : \ \delta \ 10.09 \ (\text{br. s}, \ 1H), \ 7.73 \ (d, \ ^3J=9.0 \ Hz, \ 2H), \ 7.52 \ (d, \ ^3J=3.9 \ Hz, \ 1H), \ 7.36 \ (d, \ ^3J=3.9 \ Hz, \ 1H), \ 7.28 \ (d, \ ^3J=9.0 \ Hz, \ 2H). \ ^13\text{C} \ \text{NMR} \ (100 \ MHz, \ d_6-\text{Acetone}) \ : \ \delta \ 155.5 \ (C), \ 152.7 \ (C), \ 149.1 \ (C), \ 137.9 \ (C), \ 129.9 \ (C), \ 129.7 \ (2CH), \ 122.9 \ (2CH), \ 117.6 \ (CH), \ 113.7 \ (CH). \ \text{LRMS (ES}^+\text{)}: \ m/z \ (%) \ 288.94 \ (100) \ [\text{M}+\text{Na}]^+; \ \text{HRMS (ES}^+\text{)}: \ m/z \ \text{calcd for} \ C_{11}H_7N_2O_4NaCl \ [\text{M}+\text{Na}]^+: \ 288.9992; \ \text{found} \ 288.9996. \\

\textbf{Methyl 4-(5-nitrofuran-2-carboxamido)benzoate (22j):} \ The \ \text{general} \ \text{procedure} \ \text{was} \ \text{followed} \ \text{using} \ \text{methyl} \ 4\text{-aminobenzoate} \ (431 \ mg, 2.85 \ mmol). \ The \ \text{crude} \ \text{reaction} \ \text{mixture} \ \text{was} \ \text{purified} \ \text{by} \ \text{column} \ \text{chromatography} \ \text{on} \ \text{silica} \ \text{gel} \ (2:1, \ \text{hexane/ethyl} \ \text{acetate}) \ \text{to} \ \text{afford} \ \text{the} \ \text{product} \ \text{as} \ \text{a} \ \text{yellow} \ \text{solid} \ \text{after} \ \text{recrystallization} \ (320 \ mg, 1.1 \ mmol, 39 \%). \ \text{Mp:} \ 245-246 \ ^\circ C; \ \text{IR} \ (\text{KBr}) \ \nu_{\text{max}} = 3304 \ (\text{s}) \ (\text{NH}), \ 3141 \ (\text{m}) \ (\text{NH}), \ 1683 \ (s) \ (\text{C=O}), \ 1602 \ (s) \ (\text{C=C}), \ 1548 \ (s) \ (\text{NO}_2), \ 1484 \ (m) \ (\text{C=C}), \ 1401 \ (m) \ (\text{C=C}), \ 1355 \ (s) \ (\text{NO}_2), \ 1282 \ (s) \ (\text{C-O}), \ 1106 \ (s) \ (\text{C-O}) \ \text{cm}^{-1}; \ ^1\text{H} \ \text{NMR} \ (400 \ MHz, \ \text{CDCl}_3) \ \delta \ 8.50 \ (\text{br s}, \ 1H), \ 8.13 \ (d, \ ^3J=8.8 \ Hz, \ 2H), \ 7.84 \ (d, \ ^3J=8.8 \ Hz, \ 2H), \ 7.49 \ (d, \ ^3J=3.8 \ Hz, \ 1H), \ 7.47 \ (d, \ ^3J=3.8 \ Hz, \ 1H), \ 3.97 \ (s, \ 3H). \ ^13\text{C} \ \text{NMR} \ (75 \ MHz, \ \text{CDCl}_3) \ \delta \ 165.2 \ (C), \ 154.6 \ (C), \ 151.7 \ (C), \ 143.4 \ (C), \ 141.3 \ (C), \ 130.5 \ (2CH), \ 127.0 \ (C), \ 119.32 \ (2CH), \ 116.14 \ (CH), \ 112.67 \ (CH), \ 52.61 \ (CH_3); \ \text{LRMS (ES}^+\text{)}: \ m/z \ (%) \ 288.96 \ (100) \ [\text{M-H}]^+; \\

\textbf{N-(4-methoxyphenyl)-5-nitrofuran-2-carboxamide (22k)}^8 \\

The \ \text{general} \ \text{procedure} \ \text{in} \ \text{the} \ \text{paper} \ \text{was} \ \text{followed} \ \text{using} \ 4\text{-methoxyaniline} \ (615 \ mg, 5.00 \ mmol). \ The \ \text{crude} \ \text{reaction} \ \text{mixture} \ \text{was} \ \text{purified} \ \text{by} \ \text{column} \ \text{chromatography} \ \text{on} \ \text{silica} \ \text{gel} \ (2:1, \ \text{hexane/ethyl} \ \text{acetate}) \ \text{to} \ \text{afford} \ \text{the} \ \text{product} \ \text{a} \ \text{yellow} \ \text{solid} \ (670 \ mg, 2.56 \ mmol, 51\%). \ \text{Mp:} \ 184-185 \ ^\circ C \ (\text{Lit} \ 183 \ ^\circ C); \ ^1\text{H} \ \text{NMR} \ (400 \ MHz, \ d_6-\text{Acetone}):
δ 10.00 (br s, 1H), 7.75 (d, 3J= 9.1 Hz, 2H), 7.65 (d, 3J= 3.9 Hz, 1H), 7.45 (d, 3J= 3.9 Hz, 1H), 6.96 (d, 3J= 9.1 Hz, 2H), 3.81 (s, 3H); LRMS (ES⁺): m/z (%) 261.01 (100) [M-H].

**5-Nitro-N-(3-(trifluoromethyl)benzyl)furan-2-carboxamide (22l):** The general procedure was followed using (3-(trifluoromethyl)phenyl) methanamine (499 mg, 2.85 mmol). The crude reaction mixture was purified by column chromatography on silica gel (1:1, hexane/ethyl acetate) to afford the product as a pale yellow crystalline solid after recrystallization (657 mg, 2.1 mmol, 73%). Mp: 108-109 °C; IR (KBr) \( \nu_{\text{max}} = 3298 \) (s) (NH), 3119 (m) (NH), 1658 (s) (C=O), 1583 (s) (C=C), 1521(s) (NO₂), 1356 (s) (NO₂), 1168 (s) (CF₃), 1119 (s) (CF₃), 811 (s) (CH), 699 (s) (CH) cm⁻¹. \(^1\)H NMR (300 MHz, CDCl₃): 7.56 - 7.37 (m, 4H), 7.31 (d, 3J = 3.8 Hz, 1H), 7.25 (d, 3J = 3.8 Hz, 1H), 6.91 (s, 1H), 4.64 (d, 3J = 6.1 Hz, 2H). \(^{13}\)C NMR (75 MHz, \( d_6 \) DMSO) δ 156.6 (C), 151.9 (C), 148.3 (C), 140.6 (C), 132.0 (C), 129.8 (CH), 124.4 (CH), 124.4 (C), 124.2 (CH), 122.8 (CH), 116.3 (CH), 113.8 (CH), 42.3 (CH₂).

LRMS (ES⁺): m/z (%) 336.94 (100) [M+Na]⁺; HRMS (ES) m/z calcd for C₁₃H₈N₂O₄F₃ [M-H]: 313.0427; found 313.0436.

**N-(3-methoxy-5-(trifluoromethyl)phenyl)-5-nitrofuran-2-carboxamide (22m):**

The general procedure was followed using 3-methoxy-5-(trifluoromethyl)aniline (335 mg, 2.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (3:1, hexane/ethyl acetate) to afford the product as a yellow solid (335 mg, 1.01 mmol, 51%). Mp: 170-171 °C; IR (KBr) \( \nu_{\text{max}} = 3423 \) (m) (NH), 1664 (s) (C=O), 1566 (s), 1536 (s) (NO₂), 1347 (s) (NO₂), 1267 (s) (CH₃), 738 (s) cm⁻¹. \(^1\)H NMR (400 MHz, \( d_6 \) Acetone): δ 10.28 (br s, 1H), 7.71 (s, 1H), 7.60 (s, 1H), 7.53 (d, 3J = 3.9 Hz, 1H), 7.39 (d, 3J = 3.9 Hz, 1H), 6.90 (s, 1H), 3.77 (s, 3H). \(^{13}\)C NMR (100 MHz, \( d_6 \) Acetone): δ 161.5 (C), 155.8 (C), 153.0 (C), 148.7 (C), 140.9 (C), 132.5 (C), 132.2 (C), 117.9 (CH), 113.7 (CH), 110.1 (CH), 110.0 (CH), 107.4 (CH), 56.2 (CH₃).
LRMS (ES\(^+\)): m/z (%) 352.87 (100) [M+Na]\(^+\); HRMS (ES\(^+\)): m/z calcd for C\(_{13}\)H\(_9\)N\(_2\)O\(_5\)F\(_3\)Na [M+Na]\(^+\): 353.0361; found 353.0358.

**N-(3,5-bis(trifluoromethyl)phenyl)-5-nitrofuran-2-carboxamide (22n):** The general procedure was followed using 3-5-bis(trifluoromethyl)aniline (653 mg, 2.85 mmol, 0.95 eq). The crude reaction mixture was purified by column chromatography on silica gel (2:1, hexane/ethyl acetate) to afford the product as an off white crystalline solid after recrystallization (715 mg, 1.9 mmol, 68 %). Mp: 181-182 °C; IR (KBr) \(\nu_{\text{max}}\) = 3358 (s) (NH), 1690 (s) (C=O), 1564 (s) (C=C), 1518 (s) (NO\(_2\)), 1384 (s) (NO\(_2\)), 1175 (s) (CF\(_3\)), 1131 (s) (CF\(_3\)), 889 (s) (CH) cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): 8.44 (br s, 1H), 8.15 (d, \(^4\)J = 1.4 Hz, 2H), 7.69-7.62 (br s, 1H), 7.39 (br s, 2H). \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 154.6 (C), 151.7 (C), 143.4 (C), 138.3 (C), 133.4 (2C), 132.5 (2CH), 120.5 (2C), 119.3 (CH), 118.3 (CH), 113.1 (CH). LRMS (ES\(^+\)): m/z (%) 366.88 (100) [M-H]\(^-\); HRMS (ES\(^+\)): m/z calcd for C\(_{13}\)H\(_9\)N\(_2\)O\(_4\)F\(_6\) [M-H]\(^-\): 367.0154; found 367.0157.

**N-(4-methoxy-3-(trifluoromethyl)phenyl)-5-nitrofuran-2-carboxamide (22o):** The general procedure was followed using 4-methoxy-3-(trifluoromethyl)aniline (382 mg, 2.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (3:1, hexane/ethyl acetate) to afford the product as a yellow solid (444 mg, 1.34 mmol, 67%). Mp: 207-208 °C; IR (KBr) \(\nu_{\text{max}}\) = 3283 (m) (NH), 1667 (s) (C=O), 1563 (s), 1510 (s) (NO\(_2\)), 1323 (s) (NO\(_2\)), 1261 (s) (CH\(_3\)), 1146 (s) (CF\(_3\)), 1133 (s) (CF\(_3\)) cm\(^{-1}\). \(^1\)H NMR (400 MHz, d\(_6\)-acetone): \(\delta\) 10.10 (br s, 1H), 8.02 (d, \(^4\)J = 2.5 Hz, 1H), 7.92 (dd, \(^3\)J = 9.0 Hz, \(^4\)J = 2.5 Hz, 1H), 7.51 (d, \(^3\)J = 3.9 Hz, 1H), 7.39 (d, \(^3\)J = 3.9 Hz, 1H), 7.13 (d, \(^3\)J = 9.0 Hz, 1H), 3.81 (s, 3H). \(^13\)C NMR (100 MHz, d\(_6\)-Acetone): \(\delta\) 155.4 (C), 155.2 (C), 149.1 (C), 131.6 (C), 126.8 (CH), 125.9 (C), 123.2 (C), 120.4 (CH), 118.5 (C), 117.4 (CH), 113.9 (CH), 113.7 (CH), 56.7 (CH\(_3\)). LRMS (ES\(^+\)): m/z
(%): 352.88 (100) [M+Na]+; HRMS (ES⁺): m/z calcd for C₁₃H₉N₂O₅F₃Na [M+Na]+: 353.0361; found 353.0367.

**N-(4-hydroxy-3-(trifluoromethyl)phenyl)-5-nitrofuran-2-carboxamide (22r):**
Pyridine (0.16 mL, 2.00 mmol, 10.0 eq.) was added dropwise to a 2M solution of HCl in Et₂O (1.00 mL, 1.00 mmol, 10.0 eq.), the pyridine salt precipitated immediately and the reaction mixture was stirred at room temperature for 10 minutes. The solvent was removed under reduced pressure and transferred to a 10 mL microwave tube. 22o (33 mg, 0.10 mmol) was added and the mixture was irradiated by microwave at 160 °C for 5 minutes. After cooling, ethyl acetate (20 mL) was added and the reaction mixture was washed with water (2×8 mL). The organic layer was dried (Na₂SO₄) and concentrated under vacuum. The crude reaction mixture was purified by column chromatography (from 1:1 to 1:2, hexane/ethyl acetate) to afford the product as a yellow solid (16 mg, 0.05 mmol, 52%). Mp: 267-268 °C; IR (KBr) ν max = 3361 (s) (NH), 3092 (m) (OH), 1649 (s) (C=O), 1509 (s) (NO₂), 1448 (s), 1354 (s) (NO₂), 1274 (s), 1122 (s) (CF₃), 1101 (s) (CF₃) cm⁻¹. ¹H NMR (400 MHz, d₆-Acetone): δ 10.00 (br. s, 1H), 9.23 (s, 1H), 7.96 (d, ³J= 2.6 Hz, 1H), 7.74 (dd, ⁴J= 9.0 Hz, ⁴J= 2.6 Hz, 1H), 7.51 (d, ³J= 3.9 Hz, 1H), 7.33 (d, ³J= 3.9 Hz, 1H), 6.96 (d, ³J= 9.0 Hz, 1H). ¹³C NMR (100 MHz, d₆-Acetone): δ 155.4 (C), 153.3 (C), 149.2 (C), 130.9 (C), 126.9 (CH), 126.1 (C), 123.4 (C), 120.2 (CH), 118.2 (CH), 117.3 (CH), 117.0 (C), 113.7 (CH). LRMS (ES⁺): m/z (%) 338.97 (100) [M+Na]+; HRMS (ES⁺): m/z calcd for C₁₂H₇N₂O₅F₃Na [M+Na]+: 339.0205; found 339.0203.

**N-(4-hydroxyphenyl)-5-nitrofuran-2-carboxamide (22p)**

\[\text{O}_2\text{N} \overset{\text{N}}{\text{O}} \overset{\text{O}}{\text{O}} \overset{\text{OH}}{\text{N}} \overset{\text{H}}{\text{N}} \text{OH}\]
The general procedure in the paper was followed using 4-amino-phenol (959 mg, 8.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (1:1, hexane/ethyl acetate) to afford the product as an orange solid (1.37 g, 5.52 mmol, 69%). Mp: (Dec. > 262 °C); \(^1\)H NMR (400 MHz, \(d_6\)-Acetone): \(\delta\) 9.79 (br. s, 1H), 8.20 (s, 1H), 7.53-7.49 (m, 3H), 7.29 (d, \(^3\)J = 3.9 Hz, 1H), 6.71 (d, \(^3\)J = 9.0 Hz, 2H); LRMS (ES\(^{+}\)): m/z (%) 247.05 (100) [M-H].

\(\text{N-(4-hydroxy-3-methylphenyl)-5-nitrofuran-2-carboxamide (22q)}\)

\(\text{N-(4-allyloxy)-3-(trifluoromethyl)phenyl)-5-nitrofuran-2-carboxamide (22t):} \)

A mixture of 22r (20 mg, 0.063 mmol, 1.00 eq.), K\(_2\)CO\(_3\) (87 mg, 0.63 mmol, 10.0 eq.) and allyl bromide (0.052 mL, 0.63 mmol, 10 eq.) in acetone (5 mL) was stirred at room temperature for 24 hours. The reaction mixture was then diluted in ethyl acetate (20 mL), washed with water (10 mL), dried (Na\(_2\)SO\(_4\)) and concentrated under vacuum. The crude reaction mixture was purified by column chromatography (3:1, hexane/ethyl acetate) to afford the product as a light yellow solid (14 mg, 0.034 mmol, 55%). Mp: 73-74 °C. IR (KBr) \(\nu_{\text{max}}\) = 2928 (m) (C-H), 1654 (s) (C=O), 1533
(s), 1504 (s) (NO₂), 1351 (s) (NO₂), 1322 (s), 1276 (s), 1137(br) (CF₃) cm⁻¹. ¹H NMR (400 MHz, d₆-Acetone): δ 7.55 (d, ²J= 2.6 Hz, 1H), 7.45 (dd, ³J= 8.8 Hz, ⁴J= 2.6 Hz, 1H), 7.23 (br, 1H), 7.16 (d, ³J= 8.8 Hz, 1H), 6.35 (br, 1H), 5.99-5.91 (m, 1H), 5.88-5.80 (m, 1H), 5.35 (d, ³J= 17.3 Hz, 1H), 5.16 (d, ³J= 10.6 Hz, 1H), 5.06 (d, ³J= 17.3 Hz, 1H), 5.04 (d, ³J= 10.6 Hz, 1H), 4.64 (dt, ³J= 4.8 Hz, ³J= 1.5 Hz, 2H), 4.36 (d, ³J= 6.0 Hz, 2H). ¹³C NMR (100 MHz, d₆-Acetone): δ 157.4 (C), 157.1 (C), 148.2 (C), 134.8 (CH), 133.5 (CH), 133.4 (CH), 127.9 (CH), 125.3 (C), 122.9 (C), 120.0 (C), 119.2 (CH₂), 118.8 (CH), 117.7 (CH₂), 115.5 (CH), 112.5 (CH), 70.2 (CH₂), 53.8 (CH₂). LRMS (ES⁺): m/z (%) 419.06 (100) [M+Na]⁺; HRMS (ES⁺): m/z calcd for C₁₈H₁₅N₂O₅NaF₃ [M+Na]⁺: 419.0831; found 419.0835.

N-(4-(allyloxy)phenyl)-5-nitrofuran-2-carboxamide (22u): A mixture of 22p (80 mg, 0.32 mmol, 1.00 eq.), K₂CO₃ (88 mg, 0.64 mmol, 2.00 eq.) and allyl bromide (0.060 mL, 0.64 mmol, 2.00 eq.) in acetone (5 mL) was stirred at room temperature for 24 hours. The reaction mixture was diluted in ethyl acetate (20 mL), washed with water (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (4:1, hexane/ethyl acetate) to afford the product as an orange solid (66 mg, 0.23 mmol, 72%). Mp: 152-153 °C; IR (KBr) ν_max = 3316 (m) (NH), 3081 (m) (C-H), 1663 (s) (C=O), 1541 (s), 1513 (s) (NO₂), 1348 (s) (NO₂), 1255 (s) (C-O), 811 (m) cm⁻¹. ¹H NMR (400 MHz, d₆-Acetone): δ 9.88 (br s, 1H), 7.61 (dd, ³J= 6.5 Hz, ⁴J= 2.2 Hz, 2H), 7.51 (d, ³J= 3.8 Hz, 1H), 7.31 (d, ³J= 3.8 Hz, 1H), 6.83 (d, ³J= 6.5 Hz, 2H), 5.93 (m, 1H), 5.29 (d, ³J= 18.0 Hz, 1H), 5.11 (d, ³J= 10.5 Hz, 1H), 4.67 (m, 2H). ¹³C NMR (100 MHz, d₆-Acetone): δ 156.0 (C), 155.5 (C), 152.1 (C), 148.9 (C), 135.1 (CH), 132.5 (C), 123.3 (2CH), 117.8 (CH₂), 117.4 (CH), 116.0 (2CH), 114.1 (CH), 69.9 (CH₂). LRMS (ES⁺):
m/z (%) 287.04 (100) [M-H]; HRMS (ES): m/z calcd for C_{14}H_{11}N_{2}O_{5} [M-H]: 287.0668; found 287.0662.

\( N-(4\text{-methoxy-3-methylphenyl})-5\text{-nitrofuran-2-carboxamide (22v):} \) A mixture of 22q (52 mg, 0.20 mmol, 1.00 eq.), K\textsubscript{2}CO\textsubscript{3} (55 mg, 0.40 mmol, 2.00 eq.) and iodomethane (0.03 mL, 0.40 mmol, 2.00 eq.) in acetone (5 mL) was stirred at room temperature for 3 hours. The reaction mixture was then diluted in ethyl acetate (20 mL), washed with water (10 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated under vacuum. The crude reaction mixture was purified by column chromatography on silica gel (3:1 hexane:ethyl acetate). The product was obtained as a yellow solid (28 mg, 0.10 mmol, 51%). Mp: 200-201 °C. IR (KBr) \( \nu_{\text{max}} = 3371 \) (s) (OH), 3126 (m) (NH), 1674 (s) (C=O), 1523 (s) (NO\textsubscript{2}), 1505 (s), 1354 (s) (NO\textsubscript{2}), 1261 (s) (CH\textsubscript{3}), 1236 (s) cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta 8.04 \) (br s, 1H), 7.42 (dd, \( ^3J= 8.8 \) Hz, \( ^4J= 2.6 \) Hz, 1H), 7.34 (d, \( ^3J= 3.8 \) Hz, 1H), 7.33 (s, 1H), 7.28 (d, \( ^3J= 3.8 \) Hz, 1H), 6.76 (d, \( ^3J= 8.8 \) Hz, 1H), 3.77 (s, 3H), 2.18 (s, 3H). \textsuperscript{13}C NMR (100 MHz, d\textsubscript{6}-Acetone): \( \delta 155.8 \) (C), 155.0 (C), 152.5 (C), 149.7 (C), 131.5 (C), 127.2 (C), 124.2 (CH), 120.2 (CH), 116.9 (CH), 113.7 (CH), 110.9 (CH), 55.8 (CH\textsubscript{3}), 16.5 (CH\textsubscript{3}). LRMS (ES\textsuperscript{+}): m/z (%) 275.04 (100) [M-H]; HRMS (ES\textsuperscript{+}): m/z calcd for C\textsubscript{13}H\textsubscript{11}N\textsubscript{2}O\textsubscript{5}Na [M-H]: 275.0668; found 275.0672.

**General procedure S4 synthesis of imines 24a and 24b**

5-nitro-2-furaldehyde 23 (1 eq) in DCM was added dropwise to a stirring solution of amine (1 eq) in DCM. The resulting solution was stirred overnight at room temperature and then concentrated under reduced pressure to afford the crude title compounds.

\( N-((5\text{-nitrofuran-2-yl})\text{methylene}) \text{aniline (24a)} \)
General procedure S4 was followed using aniline (91 μL, 1.0 mmol) in DCM (20 mL). The crude reaction mixture was purified by column chromatography on silica gel (9:1, hexane/ethyl acetate) to afford the product as a brown solid (192 mg, 0.89 mmol, 89%). Mp: 127-128 °C (Lit\textsuperscript{11} 124 °C); \textsuperscript{1}H NMR (300 MHz, \textit{d}_6-DMSO): δ 8.63 (s, 1H), 7.82 (d, \textit{J}=3.8 Hz, 1H), 7.50-7.28 (m, 6H).

\textit{5-Ethyl-2-(((5-nitrofuran-2-yl)methylene)amino)thiophene-3-carboxamide (24b)}

\textsuperscript{13}C NMR (100 MHz, \textit{d}_6-DMSO): δ 162.8 (C), 152.7 (C), 151.6 (C), 149.4 (C), 144.2 (CH), 144.0 (C), 132.9 (C), 125.7 (CH), 120.2 (CH), 114.3 (CH), 23.34 (CH\textsubscript{2}), 15.11 (CH\textsubscript{3}); LRMS (ES\textsuperscript{+}): m/z (%) 315.9 (100) [M+Na]\textsuperscript{+}; HRMS (ES\textsuperscript{+}): m/z calcd for C\textsubscript{12}H\textsubscript{11}N\textsubscript{3}O\textsubscript{4}SNa [M+Na]\textsuperscript{+}: 316.0362; found 316.0366.

\textit{N-((5-nitrofuran-2-yl)methyl) aniline (25a)}\textsuperscript{12}

\textbf{25a} was synthesised from NaBH\textsubscript{4} (49 mg, 1.3 mmol, 1.3 eq) and imine 24a in DCM (15 mL) following the procedure provided for 25b in the paper. The crude reaction
mixture was purified by column chromatography on silica gel (9:1, hexane/ethyl acetate) to afford the product as a brown oil (172 mg, 0.79 mmol, 79%). \[^1\]H NMR (300 MHz, d\(_6\)-acetone): \(\delta 7.19 \) (d, \(^{1}J=3.8 \) Hz, 1H), 6.88 (t, \(^{3}J=7.4 \) Hz, 2H), 6.48 (d, \(^{3}J=7.4 \) Hz, 2H), 6.45-6.35 (m, 2H), 4.27 (d, \(^{4}J=2.6 \) Hz, 2H). LRMS (ES\(^+\)): m/z (%) 219.04 (100) [M+H\(^+\)].

5-Ethyl-2-(((5-nitrofuran-2-yl)methyl)amino)thiophene-3-carboxamide (25b):

NaBH\(_4\) (102 mg, 2.7 mmol, 3 eq) was added to the previously synthesised and purified imine 24b (see ESI for detail, 267 mg, 0.9 mmol, 1 eq) in DCM (20 mL). Acetic acid (25 drops) was slowly added to the solution and left to stir over 45 min. The solution was washed with water (30 mL), extracted in DCM (30 mL \times 2) and dried over Na\(_2\)SO\(_4\). The combined organic layers were concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (7:3, hexane:ethyl acetate) to afford the product as a solid (230 mg, 0.78 mmol, 87%). Mp 105-106 °C; IR (KBr) \(\nu_{\text{max}} = 3458 \) (s) (NH\(_2\)), 3204 (m) (NH), 1634 (s) (C=O), 1598 (s) (C=C), 1545 (s) (NO\(_2\)), 1500 (s) (C=C), 1338 (s) (NO\(_2\)), 806 (s) (CH) cm\(^{-1}\). \[^1\]H NMR (300 MHz, d\(_6\)-DMSO): \(\delta 8.51 \) (br t, \(^{3}J=6.4 \) Hz, 1H), 7.65 (d, \(^{3}J=3.8 \) Hz, 1H), 7.23 (br s, 1H), 6.89 (t, \(^{4}J=1.0 \) Hz, 1H), 6.88 (br s, 1H), 6.73 (d, \(^{3}J=3.8 \) Hz, 1H), 4.52 (d, \(^{3}J=6.4 \) Hz, 2H), 2.57 (dq, \(^{4}J=1.0 \) Hz, \(^{3}J=7.4 \) Hz, 2H), 1.15 (t, \(^{3}J=7.4 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, d\(_6\)-DMSO): \(\delta 167.2 \) (C), 160.0 (C), 156.8 (C), 151.1 (C), 126.5 (C), 121.0 (CH), 114.1 (CH), 111.8 (CH), 107.0 (C), 43.6 (CH\(_2\)), 22.4 (CH\(_2\)), 15.3 (CH\(_3\)); LRMS (ES\(^+\)): m/z (%) 317.8 (100) [M-H\(^-\)]; HRMS (ES\(^-\)): m/z calcd for C\(_{12}\)H\(_{12}\)N\(_3\)O\(_4\)S [M-H\(^-\)]: 294.0553; found 294.0549.

3. HPLC analysis of purity
HPLC analysis was performed using a Gilson UV-VIS 155 HPLC system under the gradient conditions shown in the analysis method below (Table 3) (RP, reverse phase), XTerra RP 18 5 µm column (3.0 x 50 mm, Waters). The concentration of the compounds were ca. 4 mM, injection volumes were 20 µL, flow rate was 1 mL/min and detection was acquired using UV spectroscopy (254 nm)

Table S2: HPLC analysis method A

| Time (min) | %H₂O<sup>a</sup> | % CH₃CN |
|------------|------------------|---------|
| 0          | 80               | 20      |
| 10         | 20               | 80      |
| 15         | 20               | 80      |
| 17         | 80               | 20      |
| 20         | 80               | 20      |

<sup>a</sup>With 0.1% TFA

Table S3: HPLC analysis method B

| Time (min) | %H₂O<sup>a</sup> | % CH₃CN |
|------------|------------------|---------|
| 0          | 98               | 2       |
| 10         | 2                | 98      |
| 12         | 2                | 98      |
| 12.5       | 98               | 2       |
| 15         | 98               | 2       |

<sup>a</sup>With 0.1% TFA

Table S4: Retention times and purities of tested compounds (synthesised)

| Compound | t<sub>r</sub> (mins)<sup>method</sup> | Purity  |
|----------|------------------------------------|---------|
| 12a      | 7.71<sup>a</sup>                   | 99.4%   |
| 12b      | 8.95<sup>a</sup>                   | 99.7%   |
| 12c      | 8.61<sup>a</sup>                   | 95.0%   |
|   |   |   |
|---|---|---|
| 12d | 9.10^A | 99.7% |
| 12e | 6.34^A | 97.2% |
| 12f | 7.88^A | 98.9% |
| 12g | 4.79^A | 96.9% |
| 12h | 4.32^A | 94.7% |
| 12i | 8.10^B | 98.5% |
| 12j | 3.42^A | 99.1% |
| 12k | 6.34^A | 99.8% |
| 13g | 4.73^A | 95.5% |
| 18a | 7.55^A | 98.5% |
| 18b | 2.46^A | 99.4% |
| 19  | 3.88^B | 99.8% |
| 20a | 7.08^B | 95.8% |
| 20b | 7.92^B | NA   |
| 20c | 7.83^B | 99.6% |
| 21  | 6.15^B | 99.3% |
| 22a | 6.25^B | 99.7% |
| 22b | 3.68^A | 99.1% |
| 22c | 6.28^B | 99.8% |
| 22d | 1.08^B | 99.9% |
| 22e | 6.05^A | 99.1% |
| 22f | 5.73^A | 98.3% |
| 22g | 4.16^A | 99.2% |
| 22h | 6.08^A | 99.8% |
| 22i | 5.41^A | 98.5% |
| 22j | 6.82^B | 99.8% |
| 22k | 3.61^A | 99.9% |
| 22l | 7.38^B | 96.6% |
| 22m | 9.28^A | 95.1% |
| 22n | 8.72^B | 99.6% |
| 22o | 5.88^A | 99.8% |
| 22p | 5.22^A | 99.8% |
Table S5: Purchased compound Suppliers and Purity

| Compound | Supplier          | Purity (HPLC) |
|----------|------------------|---------------|
| Nifurtimox(5) | Bayer Argentina | >95%          |
| 13l      | Alfa Aesar       | 98%           |
| 19       | Aldrich          | 98%           |

4. Calculated Chemical and Drug-likeness Properties

Table S6 Calculated chemical and drug-likeness properties of series 12 and 22 analogs.

| Compound | MW    | logS<sup>a</sup> | logP  | Log BBB | P-pg substrate | P450 affinity category |
|----------|-------|------------------|-------|---------|----------------|------------------------|
| NFX 5    | 287.2 | 2.408            | 0.4096| -0.3046 | no             | medium                 |
| 12a      | 338.2 | 1.646            | 3.156 | -0.1129 | no             | high                   |
| 12k      | 324.2 | 1.953            | 2.87  | -0.1312 | no             | high                   |
| 12b      | 366.2 | 1.138            | 3.919 | -0.05358| no             | high                   |
| 12j      | 337.2 | 2.206            | 2.443 | -0.4004 | no             | high                   |
| 12c      | 365.2 | 1.781            | 3.178 | -0.3232 | yes            | high                   |
| 12d      | 309.2 | 2.408            | 2.009 | -0.4912 | no             | high                   |
|    | Mw  | X   | Y   | Z   | T  | S  |
|----|-----|-----|-----|-----|----|----|
| 12e| 353.2| 2.793| 1.536| -0.5585| no | low |
| 12f| 310.2| 2.147| 2.559| -0.6875| no | high |
| 12h| 238.2| 2.813| 2.018| -0.04278| no | high |
| 12i| 310.2| 2.123| 2.429| -0.04044| no | high |
| 12g| 293.2| 2.024| 3.358| 0.0755| no | medium |
| 22a| 238.1| 2.785| 1.922| 0.02955| no | high |
| 22c| 246.1| 2.719| 1.558| -0.2923| no | low |
| 22d| 247.1| 2.966| 0.4538| -0.4664| no | low |
| 22b| 232.1| 2.547| 1.862| -0.07048| no | low |
| 22e| 300.1| 1.61| 2.82| 0.4742| no | high |
| 22f| 311.0| 2.315| 2.649| 0.08623| no | high |
| 22g| 262.1| 2.63| 1.883| 0.02835| no | low |
| 22h| 300.1| 1.61| 2.82| 0.4623| no | high |
| 22i| 266.6| 2.103| 2.589| 0.4147| no | high |
| 22j| 290.1| 2.577| 1.794| -0.08947| no | low |
| 22k| 262.1| 2.591| 1.886| 0.06418| no | low |
| 22m| 330.1| 1.546| 2.687| 0.4645| no | high |
| 22n| 368.1| 0.9882| 3.622| 0.6396| no | high |
| 22o| 330.1| 1.613| 2.708| 0.4726| no | high |
| 22p| 316.1| 1.906| 2.54| 0.3163| no | high |
| 22q| 248.1| 2.807| 1.64| -0.2478| no | low |
| 22s| 356.1| 1.09| 3.261| 0.5033| no | high |
| 22u| 288.1| 2.052| 2.318| 0.0971| no | high |
| 22v| 412.2| 0.8319| 3.508| 0.4495| yes | high |
| 22w| 276.1| 2.316| 2.241| 0.09782| no | high |

*a predicts aqueous solubility in µM;*

The chemical and drug-likeness properties of the series 12 and 22 analogs were calculated using StarDrop (by Dr Thomas Spangenberg at the World Health Organization). Drug-like molecular weight (<450) and calculated logP (<5) values
were obtained for all analogs (Table S6, columns 2 and 4). Approximately one third of the analogs showed better predicted solubility than nifurtimox (5) (column 2) with 5 analogs (12h, 12b, 22b, 22c, 22k) having improved predicted solubility compared to 5 and double digit nM EC50 values against T.brucei. The majority of the analogs have calculated logS values of above 1 (10 µM). During our in vitro assays, we also observed that the majority of the analogs were soluble at concentrations of above 10 µM in aqueous solution containing 1% DMSO. Considering most of our analogs are 10-1000 fold more potent than nifurtimox (5), the concentrations that need to be achieved may ultimately be considerably lower than is the case for nifurtimox (5) and hence we suspect that the solubility of our analogs may be acceptable. This can only be addressed, of course, through more advanced studies that fall outside the scope of this report.

Excitingly, approximately 50% of the analogs were predicted to have medium to good blood-brain barrier penetration with logBBB values > 0 (Table S6, column 5). 12g and 22s, the most active analogs against T. brucei in vitro, both have relatively good calculated logBBB values of 0.0755 and 0.5033 respectively, which are considerably better than nifurtimox (5). The majority of the analogs were predicted not to be substrates of the p-glycoprotein (P-gp) efflux pump (column 6). Potential affinity for P450 proteins was widely predicted to exist (as exemplified for the D26 isozyme in Table S6, column 7). However, there is still chemical space to explore for the development of novel analogs that are not predicted to bind P450s as the potent trypanocidal analogs 22b and 22c with EC50 values around 28 nM and 27 nM respectively against T. brucei were predicted to have low affinity for this class of metabolizing enzymes.

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