Supporting Information

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

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CONTENTS:

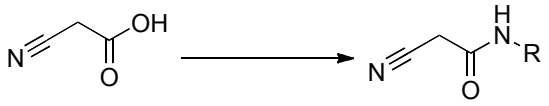
1. Table S1 Starting materials for the synthesis of 5-nitrofurancarboxyl amides **12a-k** and furan amide **18a**

Nitrofuran amides	R^2	R^3	R^4	Thiophenes	Cyanoester amides	Aldehydes
12a[a]	Et	COOEt	NO_2	**13a**	**15a**[g]	**16a**[b]
12b	^{n}Bu	COOEt	NO_2	**13b**	**15a**[g]	**16b**[c]
12c[a]	Et	COOMe	NO_2	**13c**	**15b**[g]	**16a**
12d	Et	COO^{n}Bu	NO_2	**13d**	**15c**[g]	**16a**
12e	Et	CONEt	NO_2	**13e**	**15d**	**16a**
12f	Et	CON^{n}Bu	NO_2	**13f**	**15e**	**16a**
12g	Et	$CONH_2$	NO_2	**13g**	**15f**[g]	**16a**
12h	Et	$CONH(CH_2)_2OH$	NO_2	**13h**[d]	**15g**	**16a**
12i	Et	COOH	NO_2	**13i**[e]	-	-
12j	H	H	NO_2	**13j**[f]	-	-
12k	H	COOEt	NO_2	**13k**[g]	-	-
18a	Et	COOEt	H	**13a**	**15a**	**16a**

[a]Commercially available from Ambinter Stock Screening Collection; [b]**16a** *n*-butyraldehyde is commercially available; [c]**16b** *n*-hexanaldehyde is commercially available; [d]**13h** was protected as the OTBS ester and deprotection occurred during coupling of **13h** to **14a**; [e]**13i** was prepared from hydrolysis of **13a**; [f]**13j** was prepared from 2-iodo-thipohene; [g]commercially available.

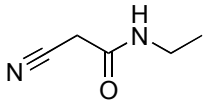
2. Synthesis and Characterization of Intermediates, Known and Unknown analogs

General procedure S1 for the synthesis of 2-cyanoacetamides 15d, 15e and 15g



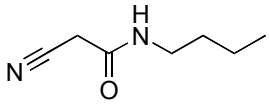
2-Cyanoacetic acid (510 mg, 6.00 mmol, 1.00 eq.) was dissolved in DCM (15 mL). A catalytic amount of DMF (0.03 mL) was added at 0 ^{o}C, following by oxalyl chloride (0.51 mL, 6.00 mmol, 1.00 eq.). The reaction mixture was stirred at 0 ^{o}C for another 5 minutes and then at room temperature for 2 hours. 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 ^{o}C. The mixture was stirred at 0 ^{o}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)[1]



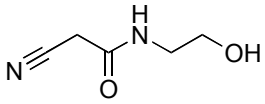
General procedure S1 was followed using ethylamine THF solution (2 M, 3.00 mL) to afford the product as a white solid, (350 mg, 3.12 mmol, 52%). Mp: 73-74 ^{o}C (Lit. [1] 74 ^{o}C); ^{1}H NMR (400 MHz, d_6-Acetone): δ 7.33 (br s, 1H), 3.40 (s, 2H), 3.11 (dq, $^{3}J_1$= 7.4 Hz, $^{3}J_2$= 5.6 Hz, 2H), 0.97 (t, ^{3}J= 7.4 Hz, 3H).

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



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 ^{o}C (Lit. [2] 72-73 ^{o}C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (br s, 1H), 3.35 (s, 2H), 3.21 (dt, $^{3}J_1$= 7.5 Hz, $^{3}J_2$= 5.8 Hz, 2H,), 1.51-1.41 (m, 2H), 1.35-1.23 (m, 2H), 0.87 (t, ^{3}J= 7.3 Hz, 3H).

2-Cyano-*N*-(2-hydroxyethyl)acetamide (15g)[3]



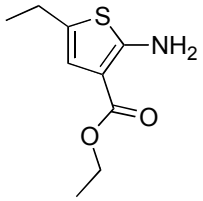
General procedure S1 was followed using 2-aminoethanol (0.36 mL) to afford the product as colourless oil (286 mg, 2.23 mmol, 37%). ^{1}H NMR (400 MHz, d_6-DMSO):

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

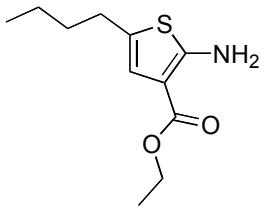
Diethylamine (0.52 mL, 5.00 mmol, 1.00 eq.) was added dropwise to a mixture of α-cyanoester or α-cyanoamide (5.00 mmol, 1.00 eq.), aldehyde (5.00 mmol, 1.00 eq.) and sulfur (162 mg, 5.25 mmol, 1.05 eq.) in DMF (5 mL). The reaction mixture was stirred at room temperature and followed by TLC. After completion 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 (Na_2SO_4) 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)[4]



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 ^oC (Lit. [4] 73 ^oC); ^1H NMR (300 MHz, $CDCl_3$): 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).

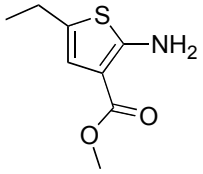
Ethyl 2-amino-5-butylthiophene-3-carboxylate (13b)



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) ν_{max} = 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, $CDCl_3$): δ 6.55 (t, ^4J= 1.1 Hz, 1H), 4.18 (q, ^3J= 7.1 Hz, 2H), 2.50 (dt, ^3J= 7.5

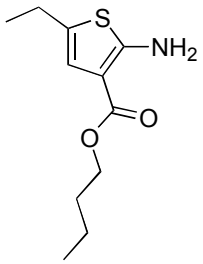
Hz, ^4J= 1.1 Hz, 2H), 1.54-1.44 (m, 2H), 1.35-1.28 (m, 2H), 1.26 (t, ^3J= 7.1 Hz, 3H), 0.85 (t, ^3J= 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4 (C), 161.4 (C), 126.8 (C), 121.4 (CH), 106.1 (C), 59.6 (CH_2), 33.2 (CH_2), 29.4 (CH_2), 22.0 (CH_2), 14.5 (CH_3), 13.8 (CH_3). LRMS (CI^+): m/z (%) 228.11 (75) $[M+H]^+$; HRMS (CI^+): m/z calcd for $C_{11}H_{18}NO_2S$ $[M+H]^+$: 228.1057; found 228.1053.

Methyl 2-amino-5-ethylthiophene-3-carboxylate (13c)[5]



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 ^oC (no Lit. Mp); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.54 (t, ^4J= 1.2 Hz, 1H), 3.71 (s, 3H), 2.53 (dq, ^3J= 7.5 Hz, ^4J= 1.2 Hz, 2H), 1.15 (t, ^3J= 7.5 Hz, 3H).

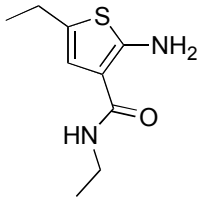
Butyl 2-amino-5-ethylthiophene-3-carboxylate (13d)



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) ν_{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, ^4J= 1.2 Hz, 1H), 4.13 (t, ^3J= 6.6 Hz, 2H), 2.54 (dq, ^3J= 7.5 Hz, ^4J= 1.2 Hz, 2H), 1.66-1.57 (m, 2H), 1.43-1.31 (m, 2H), 1.15 (t, ^3J= 7.5 Hz, 3H), 0.89 (t, ^3J= 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5 (C), 161.2 (C), 128.4

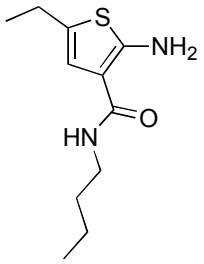
(C), 120.6 (CH), 106.2 (C), 63.5 (CH_2), 31.0 (CH_2), 23.1 (CH_2), 19.3 (CH_2), 15.4 (CH_3), 13.8 (CH_3). LRMS (CI^+): m/z (%) 228.11 (38) $[M+H]^+$; HRMS (CI^+): m/z calcd for $C_{11}H_{18}NO_2S$ $[M+H]^+$: 228.1058; found 228.1052.

2-Amino-*N*,5-diethylthiophene-3-carboxamide (13e) [6]



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 ^oC; IR (KBr) ν_{max} = 3321 (br, s), 2973 (s) (C-H), 1652 (s) (C=O), 1610 (s), 1532 (s), 1265 (s), 739 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 165.8 (C), 158.8(C), 129.2 (C), 117.7 (CH), 108.3 (C), 34.0 (CH_2), 23.1 (CH_2), 15.5 (CH_3), 15.2 (CH_3). LRMS (ES^+): m/z (%) 220.99 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_9H_{14}N_2ONaS$ $[M+Na]^+$: 221.0725; found 221.0731.

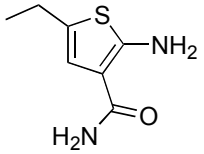
2-Amino-*N*-butyl-5-ethylthiophene-3-carboxamide (13f)



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 ^oC; IR (KBr) ν_{max} = 3310 (br, s), 3084 (m), 2926 (s) (C-H), 1667 (s) (C=O), 1533 (s), 1459 (s), 1253 (s) cm^{-1}. ^1H NMR (400 MHz, d_6-Acetone): δ 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, $CDCl_3$): δ 165.9 (C),

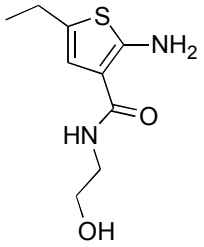
158.7 (C), 129.2 (C), 117.7 (CH), 108.3 (C), 38.9 (CH_2), 32.1 (CH_2), 23.1 (CH_2), 20.2 (CH_2), 15.5 (CH_3), 13.8 (CH_3). LRMS (ES^+): m/z (%) 249.01 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_{11}H_{18}N_2ONaS$ $[M+Na]^+$: 249.1038; found 249.1038.

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 ^oC; IR (KBr) ν_{max} = 3404 (s), 3327 (m), 3207 (m), 2966 (m) (C-H), 1638 (s) (C=O), 1527 (s), 1496 (s), 1422 (s), 783 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.30 (t, ^4J= 1.2 Hz, 1H), 5.71 (br. s, 2H), 5.57 (br. s, 2H), 2.54 (dq, ^3J= 7.5 Hz, ^4J= 1.2 Hz, 2H), 1.15 (t, ^3J= 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0 (C), 159.3 (C), 128.0 (C), 117.4 (CH), 106.1 (C), 22.1 (CH_2), 14.4 (CH_3). LRMS (ES^+): m/z (%) 192.94 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_7H_{10}N_2ONaS$ $[M+Na]^+$: 193.0412; found 193.0407.

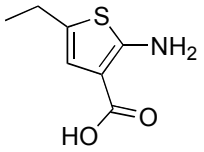
2-Amino-5-ethyl-*N*-(2-hydroxyethyl)thiophene-3-carboxamide (13h)



General procedure S2 was followed using *n*-butyraldehyde **16a** (1.17 mL), 2-cyano-*N*-(2-hydroxyethyl)acetamide **15h** (1.68 mg) to afford the product as a dark yellow solid (1.00 g, 4.67 mmol, 46%). Mp: 120-121 ^oC; IR (KBr) ν_{max} = 3426 (m), 3370 (m), 3292 (m), 1579 (s) (C=O), 1533 (s), 1299 (s), 1068 (s) (C-O) cm^{-1}. ^1H NMR (400 MHz, d_6-Acetone): δ 6.94 (br. s, 1H), 6.67 (br. s, 2H), 6.57 (t, ^4J= 1.1 Hz, 1H), 3.49 (t, ^3J= 5.6 Hz, 2H) 3.29-3.24 (m, 2H), 2.44 (dq, ^3J= 7.5 Hz, ^4J= 1.1 Hz, 2H), 1.04 (t, ^3J= 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4 (C), 160.9 (C), 127.8 (C),

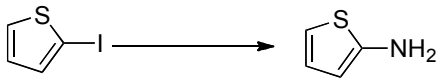
119.8 (CH), 108.1 (C), 62.6 (CH_2), 42.9 (CH_2), 23.6 (CH_2), 15.9 (CH_3). LRMS (ES^+): m/z (%) 237.00 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_9H_{14}N_2O_2NaS$ $[M+Na]^+$: 237.0680; found 237.0678.

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



13a (1.00g, 5mmol, 1.00 eq.) and sodium hydroxide (800mg, 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 ^oC; IR (KBr) ν_{max} = 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, $CDCl_3$): δ 6.58 (s, 1H), 5.81 (br. s, 2H), 2.54 (dq, ^3J= 7.5 Hz, ^4J= 1.0 Hz, 2H), 1.16 (t, ^3J= 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3 (C), 163.1 (C), 128.7 (C), 120.8 (CH), 105.3 (C), 23.0 (CH_2), 15.2 (CH_3). LRMS (CI^+): m/z (%) 172.04 (20) $[M+H]^+$; HRMS (CI^+): m/z calcd for $C_7H_{10}NO_2S$ $[M+H]^+$: 172.0432; found 172.0428.

Thiophen-2-amine (13j)[7]



S1 **13j**

2-iodothiophene **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.), K_2CO_3 (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 ^oC under N_2 atmosphere for 12 hours. Water (100 mL) was added and the mixture was exacted with DCM (100 mL). The organic layer was dried (Na_2SO_4) 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, $CDCl_3$): δ 6.61

(dd, $^{3}J_{1}$= 5.6 Hz, $^{3}J_{2}$= 3.6 Hz, 1H), 6.44 (dd, ^{3}J= 5.6 Hz, ^{4}J= 1.4 Hz, 1H), 6.13 (dd, ^{3}J= 3.6 Hz, ^{4}J= 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 ^{o}C; IR (KBr) ν_{max} = 3134 (m) (NH), 2930 (s) (C-H), 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, $CDCl_3$): δ 11.74 (br. s, 1H), 7.59 (d, ^{3}J= 3.9 Hz, 1H), 7.42 (d, ^{3}J= 3.9 Hz, 1H), 6.85 (s, 1H), 4.28 (q, ^{3}J= 7.2 Hz, 2H), 2.65 (t, ^{3}J= 7.5 Hz, 2H), 1.56-1.50 (m, 2H), 1.31-1.24 (m, 5H), 0.82 (t, ^{3}J= 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 (CH_2), 34.6 (CH_2), 30.0 (CH_2), 23.1 (CH_2), 15.0 (CH_3), 14.4 (CH_3). LRMS (ES^+): m/z (%) 388.94 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_{16}H_{18}N_2O_6NaS$ $[M+Na]^+$: 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 ^oC; IR (KBr) ν_{max} = 3398 (s) (NH), 3127 (m) (CH), 1701 (s) (C=O), 1618 (s) (C=O), 1560 (s), 1522 (s) (NO_2), 1352 (s) (NO_2), 1286 (s), 1131 (s) (C-O), 1111 (s) (C-O) cm^{-1}. ^1H NMR (400 MHz, d_6-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). ^{13}C NMR (100 MHz, d_6-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 (CH_3), 23.4 (CH_2), 15.9 (CH_3). LRMS (ES^+): m/z (%) 346.86 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_{13}H_{12}N_2O_6NaS$ $[M+Na]^+$: 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 ^oC; IR (KBr) ν_{max} = 3120 (m) (NH), 2958 (s) (C-H), 1661 (s) (C=O), 1563 (s), 1535 (s) (NO_2), 1351 (s) (NO_2), 1239 (s) (C-O), 1216 (s) (C-O) cm^{-1}. ^1H NMR (500 MHz, d_6-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),

1.68-1.63 (m, 2H), 1.40-1.33 (m, 2H), 1.17 (t, ^{3}J= 7.6 Hz, 3H), 0.85 (t, ^{3}J= 7.4 Hz, 3H). ^{13}C NMR (100 MHz, d_6-Acetone): δ 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 $C_{16}H_{18}N_2O_6NaS$ $[M+Na]^+$: 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 ^{o}C; IR (KBr) ν_{max} = 3434 (m) (NH), 2913 (m) (C-H), 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): δ 7.62 (br. s, 1H), 7.57 (d, ^{3}J= 3.9 Hz, 1H), 7.36 (d, ^{3}J= 3.9 Hz, 1H), 7.00 (s, 1H), 3.35-3.31 (m, 2H), 2.65 (q, ^{3}J= 7.6 Hz, 2H), 1.15 (t, ^{3}J= 7.6 Hz, 3H), 1.07 (t, ^{3}J= 7.2 Hz, 3H). ^{13}C NMR (100 MHz, d_6-Acetone): δ 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 $C_{14}H_{15}N_3O_5NaS$ $[M+Na]^+$: 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 ^{o}C; IR (KBr) ν_{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): δ 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): δ 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 calcd for $C_{16}H_{19}N_3O_5NaS$ $[M+Na]^+$: 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 ^oC; IR (KBr) ν_{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): δ 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): δ 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 calcd for $C_{14}H_{15}N_3O_6NaS$ $[M+Na]^+$: 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 ^{o}C; IR (KBr) ν_{max} = 3146 (m) (OH), 3108 (m) (NH), 1665 (s) (C=O), 1562 (s), 1540 (s) (NO_2), 1346 (s) (NO_2), 1347 (s), 1252 (s) (C-O), 1202 (s) cm^{-1}. ^{1}H NMR (400 MHz, d_6-Acetone): δ 11.96 (br. s, 1H), 7.57 (d, ^{3}J= 3.9 Hz, 1H), 7.41 (d, ^{3}J= 3.9 Hz, 1H), 6.89 (t, ^{4}J= 1.1 Hz, 1H), 2.69 (dq, ^{3}J= 7.5 Hz, ^{4}J= 1.1 Hz, 2H), 1.18 (t, $^{3}J_1$= 7.5 Hz, 3H). ^{13}C NMR (100 MHz, d_6-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 (CH_2), 15.9 (CH_3). LRMS (ES^{+}): m/z (%) 332.84 (100) [M+Na]$^{+}$; HRMS (ES^{+}): m/z calcd for $C_{12}H_{10}N_2O_6NaS$ [M+Na]$^{+}$: 333.0157; found 333.0167.

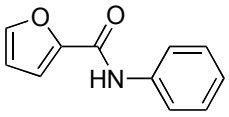
5-nitro-*N*-(thiophen-2-yl)furan-2-carboxamide (12j): The general procedure was followed using thiophen-2-amine **13j** (400 mg, 4.03 mmol). The crude reaction mixture was purified by column chromatography on silica gel (1:1, hexane/ethyl acetate) to afford the product as a brown solid (392 mg, 1.66 mmol, 41%). Mp: 123-124 ^{o}C; IR (KBr) ν_{max} = 3245 (m) (NH), 3121 (w), 1648 (s) (C=O), 1573 (s), 1537 (s) (NO_2), 1349 (s) (NO_2), 1302 (s), 1013 (s), 810 (s) cm^{-1}. ^{1}H NMR (300 MHz, d_6-Acetone): δ 11.44 (br. s, 1H), 7.65 (d, ^{3}J= 3.9 Hz, 1H), 7.51 (d, ^{3}J= 3.9 Hz, 1H), 7.06 (dd, ^{3}J= 5.5 Hz, ^{4}J= 1.4 Hz, 1H), 7.01 (dd, ^{3}J= 3.8 Hz, ^{4}J= 1.4 Hz, 1H), 6.92 (dd, $^{3}J_1$= 5.5 Hz, $^{3}J_2$= 3.8 Hz, 1H). ^{13}C NMR (100 MHz, d_6-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 $C_9H_6N_2O_4NaS$ [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 ^{o}C; IR (KBr) ν_{max} = 3142 (m) (NH), 1670 (s) (C=O), 1662 (s) (C=O), 1532 (s) (NO_2), 1351 (s) (NO_2), 1266 (s) (C-O), 1225 (s) (C-O), 1025 (s), 843 (s) cm^{-1}. ^{1}H NMR (300 MHz, d_6-Acetone): δ 11.83 (br. s, 1H), 7.60 (d, ^{3}J= 3.9 Hz, 1H), 7.45 (d, ^{3}J= 3.9 Hz, 1H), 7.18 (d, ^{3}J= 5.8 Hz, 1H), 6.97 (d, ^{3}J= 5.8 Hz, 1H), 4.31 (q, ^{3}J= 7.1 Hz, 2H), 1.29 (t, ^{3}J= 7.1 Hz, 3H). ^{13}C NMR (100 MHz, d_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_2), 14.6 (CH_3). LRMS (ES^+): m/z (%) 332.89 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_{12}H_{10}N_2O_6NaS$ $[M+Na]^+$: 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 ^{o}C; IR (KBr) ν_{max} = 3411 (m) (NH), 2969 (m) (C-H), 1658 (s) (C=O), 1558 (s), 1275 (s) (C-O), 1225 (s) (C-O), 738 (s) cm^{-1}. ^{1}H NMR (400 MHz, d_6-Acetone): δ 11.60 (br. s, 1H), 7.76 (dd, ^{3}J= 1.8 Hz, ^{4}J= 0.7 Hz, 1H), 7.18 (dd, ^{3}J= 3.6 Hz, ^{4}J= 0.7 Hz, 1H), 6.80 (t, ^{4}J= 1.1 Hz, 1H), 6.61 (dd, $^{3}J_1$= 3.6 Hz, $^{3}J_2$= 1.8 Hz, 1H), 4.24 (q, ^{3}J= 7.1 Hz, 2H), 2.64 (dq, ^{3}J= 7.5 Hz, ^{4}J= 1.1 Hz, 2H), 1.25 (t, ^{3}J= 7.1 Hz, 3H), 1.15 (t, ^{3}J= 7.5 Hz, 3H). ^{13}C NMR (100 MHz, d_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_2), 23.2 (CH_2), 16.0 (CH_3), 14.6 (CH_3). LRMS (ES^+): m/z (%) 315.90 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_{14}H_{15}NO_4NaS$ $[M+Na]^+$: 316.0619; found 316.0613.

***N*-phenylfuran-2-carboxamide (18b)** [8]

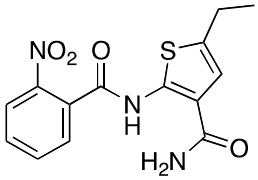


The general procedure in the paper was followed using aniline (0.219 mL, 2.40 mmol). The crude reaction mixture was purified by column chromatography on silica gel (3:1, hexane/ethyl acetate) to afford the product as a white solid (330 mg, 1.76 mmol, 73%). Mp: 126-127 ^{o}C (no Lit. Mp); ^{1}H NMR (300 MHz, $CDCl_3$): δ 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, $^{3}J_{1}$= 8.1 Hz, $^{3}J_{2}$= 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, $^{3}J_{1}$= 3.5 Hz, $^{3}J_{2}$= 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.

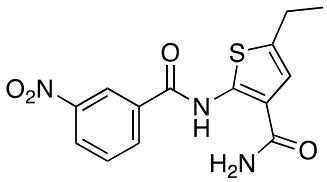
5-Ethyl-2-(2-nitrobenzamido) thiophene-3-carboxamide (20a)



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) ν_{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): δ 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): δ 168.2 (C) 161.5 (C) 148.0 (C),

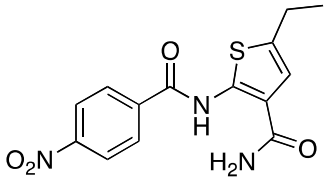
144.2 (C), 137.3 (C), 133.5 (CH), 131.6 (CH), 130.6 (C), 128.4 (CH), 124.5 (CH), 118.1 (CH), 115.2 (C), 22.5 (CH_2), 15.0 (CH_3); LRMS (ES^+): m/z (%) 341.83 (100) $[M+Na]^+$; HRMS (ES^-): m/z calcd for $C_{14}H_{12}N_3O_4S$ $[M-H]^-$: 318.0549; found 318.0551.

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) ν_{max} = 3436 (s) (NH), 1647 (s) (C=O), 1591 (s) (C=C), 1569 (s) (C=C), 1530 (s) (NO_2), 1347 (s) (NO_2) cm^{-1}. ^1H NMR (300 MHz, d_6-acetone): δ 8.68 (dd, $^4J_1$=1.9 Hz, $^4J_2$=1.9 Hz, 1H), 8.38 (ddd, $^4J_1$=0.9 Hz, $^4J_2$=1.9 Hz, ^3J=8.1 Hz, 1H), 8.24 (ddd, $^4J_1$=0.9 Hz, $^4J_2$=1.9 Hz, ^3J=8.1 Hz, 1H), 7.83 (dd, $^3J_1$=8.1 Hz, $^3J_2$=8.1 Hz, 1H), 7.38 (br s, 1H), 7.05 (t, ^4J=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); ^{13}C NMR (100 MHz, d_6-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 (CH_2), 15.0 (CH_3); LRMS (ES^-): m/z (%) 317.80 (100) $[M-H]^-$; HRMS (ES^-): m/z calcd for $C_{14}H_{12}N_3O_4S$ $[M-H]^-$: 318.0549; found 318.0551.

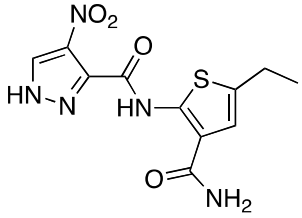
5-Ethyl-2-(4-nitrobenzamido) thiophene-3-carboxamide (20c)



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,

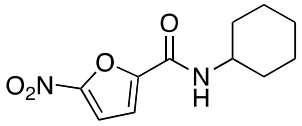
0.2 mmol, 11%). Mp: 266-268 °C; IR (KBr) ν_{max} = 3440 (s) (NH), 3177 (m) (NH_2), 1663 (s) (C=O), 1597 (s) (C=C), 1562 (s) (C=C), 1527 (s) (NO_2), 1343 (s) (NO_2), 705 (s) (CH) cm^{-1}. ^1H NMR (300 MHz, d_6-DMSO): δ 8.49 (d, ^3J=8.7 Hz, 2H), 8.18 (d, ^3J=8.7 Hz, 2H), 8.07 (br s, 1H), 7.72 (br s, 1H), 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): δ 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 $C_{14}H_{12}N_3O_4S$ $[M-H]^-$: 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) ν_{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}. ^1H NMR (300 MHz, d_6-DMSO): δ 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): δ 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 $C_{11}H_{10}N_5O_4S$ $[M-H]^-$: 308.0454; found 308.0450.

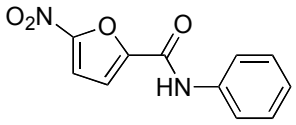
_N_-cyclohexyl-5-nitrofuran-2-carboxamide (22a)[9]



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

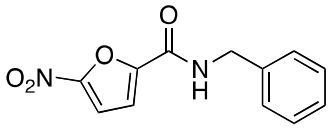
silica gel (3:1, hexane/ethyl acetate) to afford the product as a yellow crystalline solid (440 mg, 1.85 mmol, 65 %). Mp: 149 ^{o}C (no Lit. Mp); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, ^{3}J = 3.8 Hz, 1H), 7.27 (d, ^{3}J = 3.8 Hz, 1H), 6.41 (br s, 1H), 4.11 – 3.76 (m, 1H), 2.09 – 1.18 (m, 10H). LRMS (ES^{+}): m/z (%) 261.01 (100) $[M+Na]^{+}$.

5-Nitro-*N*-phenylfuran-2-carboxamide (22b)[8]



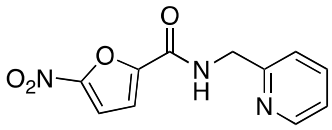
The general procedure in the paper was followed using aniline (186 mg, 2.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (3:1, hexane/ethyl acetate) to afford the product as a yellow solid (283 mg, 1.22 mmol, 61%). Mp: 174-175 ^{o}C (Lit [8] 174-175 ^{o}C); ^{1}H 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]



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 ^{o}C (Lit [10] 91 ^{o}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) $[M+Na]^{+}$.

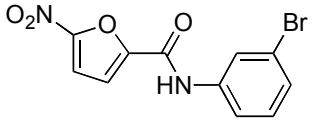
5-Nitro-*N*-(pyridin-2-ylmethyl)furan-2-carboxamide (22d)[9]



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

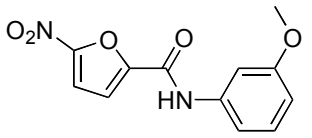
(476 mg, 1.93 mmol, 67 %). Mp: 130-131 ^{o}C (no Lit. Mp); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, ^{3}J = 5.0 Hz, 1H), 8.02 (br s, 1H), 7.80 (d, ^{3}J = 7.7 Hz, 1H), 7.46 – 7.30 (m, 4H), 4.81 (d, ^{3}J = 5.2 Hz, 2H); LRMS (ES^{+}): m/z (%) 270.05 (100) $[M+Na]^{+}$.

***N*-(3-bromophenyl)-5-nitrofuran-2-carboxamide (22f)** [8]



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 ^{o}C (no Lit. Mp); ^{1}H NMR (300 MHz, $CDCl_3$): δ 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]



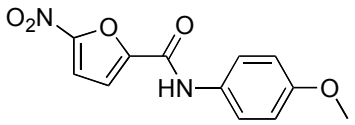
The general procedure in the paper was followed using 3-methoxyaniline (615 mg, 5.00 mmol). The crude reaction mixture was purified by column chromatography on silica gel (2:1, hexane/ethyl acetate) to afford the product as a yellow solid (587 mg, 2.24 mmol, 45%). Mp: 121-122 ^{o}C (no Lit. Mp); ^{1}H NMR (400 MHz, d_6-Acetone): δ 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 ^{o}C; IR (KBr)

ν_{max} = 3347 (m) (NH), 2924 (m), 1686 (s) (C=O), 1494 (s) (NO_2), 1312 (s) (NO_2), 1256 (s), 822 (s), 749 (m) (C-Cl) cm^{-1}. ^1H NMR (400 MHz, d_6-Acetone): δ 10.09 (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}C NMR (100 MHz, d_6-Acetone): δ 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). LRMS (ES^+): m/z (%) 288.94 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_{11}H_7N_2O_4NaCl$ $[M+Na]^+$: 288.9992; found 288.9996.

Methyl 4-(5-nitrofuran-2-carboxamido)benzoate (22j): The general procedure was followed using methyl 4-aminobenzoate (431 mg, 2.85 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 after recrystallization (320 mg, 1.1 mmol, 39 %). Mp: 245-246 °C; IR (KBr) ν_{max} = 3304 (s) (NH), 3141 (m) (NH), 1683 (s) (C=O), 1602 (s) (C-C), 1548 (s) (NO_2), 1484 (m) (C=C), 1401 (m) (C=C), 1355 (s) (NO_2), 1282 (s) (C-O), 1106 (s) (C-O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (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}C NMR (75 MHz, CDCl3) δ 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); LRMS (ES^-): m/z (%) 288.96 (100) $[M-H]^-$;

N-(4-methoxyphenyl)-5-nitrofuran-2-carboxamide (22k) [8]



The general procedure in the paper was followed using 4-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 a yellow solid (670 mg, 2.56 mmol, 51%). Mp: 184-185 °C (Lit [10] 183 °C); ^1H NMR (400 MHz, d_6-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) ν_{max} = 3298 (s) (NH), 3119 (m) (NH), 1658 (s) (C=O), 1583 (s) (C=C), 1521(s) (NO_2), 1356 (s) (NO_2), 1168 (s) (CF_3), 1119 (s) (CF_3), 811 (s) (CH), 699 (s) (CH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 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 (CH_2). LRMS (ES^+): m/z (%) 336.94 (100) $[M+Na]^+$; HRMS (ES^-): m/z calcd for $C_{13}H_8N_2O_4F_3$ $[M-H]^-$: 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 ^{o}C; IR (KBr) ν_{max} = 3423 (m) (NH), 1664 (s) (C=O), 1566 (s), 1536 (s) (NO_2), 1347 (s) (NO_2), 1267 (s) (CH_3), 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 (CH_3).

LRMS (ES^+): m/z (%) 352.87 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_{13}H_9N_2O_5F_3Na$ $[M+Na]^+$: 353.0361; found 353.0358.

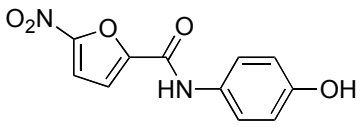
***N*-(3,5-bis(trifluoromethyl)phenyl)-5-nitrofuran-2-carboxamide (22n):** The general procedure was followed using 3-5-bis(trifluoromethyl)aniline (653 mg, 2.85 mmol, 0.95 eq). The crude reaction mixture was purified by column chromatography on silica gel (2:1, hexane/ethyl acetate) to afford the product as an off white crystalline solid after recrystallization (715 mg, 1.9 mmol, 68 %). Mp: 181-182 °C; IR (KBr) ν_{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}. ^1H NMR (300 MHz, $CDCl_3$): 8.44 (br s, 1H), 8.15 (d, ^4J = 1.4 Hz, 2H), 7.69-7.62 (br s, 1H), 7.39 (br s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{13}H_5N_2O_4F_6$ $[M-H]^-$: 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 ^oC; IR (KBr) ν_{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}. ^1H NMR (400 MHz, d_6-acetone): δ 10.10 (br s, 1H), 8.02 (d, ^4J= 2.5 Hz, 1H), 7.92 (dd, ^3J= 9.0 Hz, ^4J= 2.5 Hz, 1H), 7.51 (d, ^3J= 3.9 Hz, 1H), 7.39 (d, ^3J= 3.9 Hz, 1H), 7.13 (d, ^3J= 9.0 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, d_6-Acetone): δ 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 $C_{13}H_9N_2O_5F_3Na$ $[M+Na]^+$: 353.0361; found 353.0367.

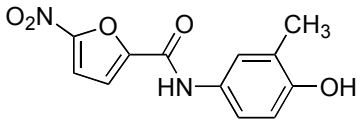
***N*-(4-hydroxy-3-(trifluoromethyl)phenyl)-5-nitrofuran-2- carboxamide (22r):** Pyridine (0.16 mL, 2.00 mmol, 10.0 eq.) was added dropwise to a 2M solution of HCl in Et_2O (1.00 mL, 1.00 mmol, 10.0 eq.), the pyridine salt precipitated immediately and the reaction mixture was stirred at room temperature 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 ^{0}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 (Na_2SO_4) 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 ^{o}C; IR (KBr) ν_{max} = 3361 (s) (NH), 3092 (m) (OH), 1649 (s) (C=O), 1509 (s) (NO_2), 1448 (s), 1354 (s) (NO_2), 1274 (s), 1122 (s) (CF_3), 1101 (s) (CF_3) cm^{-1}. ^{1}H NMR (400 MHz, d_6-Acetone): δ 10.00 (br. s, 1H), 9.23 (s, 1H), 7.96 (d, ^4J= 2.6 Hz, 1H), 7.74 (dd, ^3J= 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). ^{13}C NMR (100 MHz, d_6-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 $C_{12}H_7N_2O_5NaF_3$ $[M+Na]^+$: 339.0205; found 339.0203.

***N*-(4-hydroxyphenyl)-5-nitrofuran-2-carboxamide (22p)** [10]



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 (1.37g, 5.52 mmol, 69%). Mp: (Dec.> 262 ^{o}C); ^{1}H NMR (400 MHz, d_6-Acetone): δ 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) $[M-H]^{-}$.

***N*-(4-hydroxy-3-methylphenyl)-5-nitrofuran-2-carboxamide (22q)**



The general procedure in the paper was followed using 4-amino-2-methylphenol (295 mg, 2.40 mmol). The crude reaction mixture was purified by column chromatography on silica gel (3:2, hexane/ethyl acetate) to afford the product as a yellow solid (301 mg, 1.21 mmol, 48%). Mp: 220-221 ^{o}C; IR (KBr) ν_{max} = 3356 (s) (OH), 3043 (m) (NH), 1650 (s) (C=O), 1524 (s) (NO_2), 1351 (s) (NO_2), 1267 (s) (CH_3) cm^{-1}. ^{1}H NMR (400 MHz, d_6-Acetone): δ 9.68 (br. s, 1H), 8.08 (br. s, 1H), 7.49 (d, ^{3}J= 3.9 Hz, 1H), 7.40 (s, 1H), 7.33 (dd, ^{3}J= 8.8 Hz, ^{4}J= 2.0 Hz, 1H), 7.28 (d, ^{3}J= 3.9 Hz, 1H), 6.67 (d, ^{3}J= 8.8 Hz, 1H), 2.07 (s, 3H). ^{13}C NMR (100 MHz, d_6-Acetone): δ 155.0 (C), 153.5 (C), 153.4 (C), 149.8 (C), 130.8 (C), 125.3 (C), 124.4 (CH), 120.4 (CH), 116.7 (CH), 115.4 (CH), 113.7 (CH), 16.4 (CH_3). LRMS (ES^{+}): m/z (%) 284.94 (100) $[M+Na]^{+}$; HRMS (ES^{+}): m/z calcd for $C_{12}H_{10}N_2O_5Na$ $[M+Na]^{+}$: 285.0487; found 285.0494.

***N*-Allyl-*N*-(4-(allyloxy)-3-(trifluoromethyl)phenyl)-5-nitrofuran-2-carboxamide (22t):** A mixture of **22r** (20 mg, 0.063 mmol, 1.00 eq.), K_2CO_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_2SO_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 ^{o}C. IR (KBr) ν_{max} = 2928 (m) (C-H), 1654 (s) (C=O), 1533

(s), 1504 (s) (NO_2), 1351 (s) (NO_2), 1322 (s), 1276 (s), 1137(br) (CF_3) cm^{-1}. ^1H NMR (400 MHz, d_6-Acetone): δ 7.55 (d, ^4J= 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). ^{13}C NMR (100 MHz, d_6-Acetone): δ 157.4 (C), 157.1 (C), 148.2 (C), 134.8 (CH), 134.6 (C), 133.5 (CH), 133.4 (CH), 127.9 (CH), 125.3 (C), 122.9 (C), 120.0 (C), 119.2 (CH_2), 118.8 (CH), 117.7 (CH_2), 115.5 (CH), 112.5 (CH), 70.2 (CH_2), 53.8 (CH_2). LRMS (ES^+): m/z (%) 419.06 (100) $[M+Na]^+$; HRMS (ES^+): m/z calcd for $C_{18}H_{15}N_2O_5NaF_3$ $[M+Na]^+$: 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.), K_2CO_3 (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 (Na_2SO_4), 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 ^oC; IR (KBr) ν_{max} = 3316 (m) (NH), 3081 (m) (C-H), 1663 (s) (C=O), 1541 (s), 1513 (s) (NO_2), 1348 (s) (NO_2), 1255 (s) (C-O), 811 (m) cm^{-1}. ^1H NMR (400 MHz, d_6-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). ^{13}C NMR (100 MHz, d_6-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 (CH_2), 117.4 (CH), 116.0 (2CH), 114.1 (CH), 69.9 (CH_2). LRMS (ES^-):

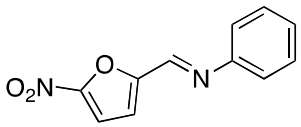
m/z (%) 287.04 (100) $[M-H]^-$; HRMS (ES^-): m/z calcd for $C_{14}H_{11}N_2O_5$ $[M-H]^-$: 287.0668; found 287.0662.

***N*-(4-methoxy-3-methylphenyl)-5-nitrofuran-2-carboxamide (22v):** A mixture of **22q** (52 mg, 0.20 mmol, 1.00 eq.), K_2CO_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_2SO_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 ^oC. IR (KBr) ν_{max} = 3371 (s) (OH), 3126 (m) (NH), 1674 (s) (C=O), 1523 (s) (NO_2), 1505 (s), 1354 (s) (NO_2), 1261 (s) (CH_3), 1236 (s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 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). ^{13}C NMR (100 MHz, d_6-Acetone): δ 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_3), 16.5 (CH_3). LRMS (ES^-): m/z (%) 275.04 (100) $[M-H]^-$; HRMS (ES^-): m/z calcd for $C_{13}H_{11}N_2O_5Na$ $[M-H]^-$: 275.0668; found 275.0672.

General procedure S4 synthesis of imines 24a and 24b

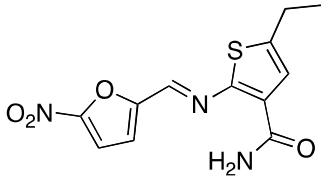
5-nitro-2-furaldehyde **23** (1 eq) in DCM was added dropwise to a stirring solution of amine (1 eq) in DCM. The resulting solution was stirred overnight at room temperature and then concentrated under reduced pressure to afford the crude title compounds.

***N*-((5-nitrofuran-2-yl)methylene) aniline (24a)[11]**



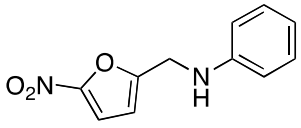
General procedure S4 was followed using aniline (91 µL, 1.0 mmol) in DCM (20 mL). The crude reaction mixture was purified by column chromatography on silica gel (9:1, hexane/ethyl acetate) to afford the product as a brown solid (192 mg, 0.89 mmol, 89%). Mp: 127-128 °C (Lit[11] 124 °C); ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.63 (s, 1H), 7.82 (d, ^3J=3.8 Hz, 1H), 7.50-7.28 (m, 6H).

5-Ethyl-2-(((5-nitrofuran-2-yl)methylene)amino)thiophene-3-carboxamide (24b)



General procedure S4 was followed using **13g** (340 mg, 2.0 mmol, 1 eq). 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 (368 mg, 1.3 mmol, 63%); Mp: 195-196 °C; IR (KBr) ν_{max} = 3402 (s) (NH_2), 3092 (m) (NH), 1634 (s) (C=O), 1523 (s) (NO_2), 1446 (m) (C=C), 1393 (m) (C=C), 1347 (s) (NO_2) cm^{-1}; ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.48 (s, 1H), 8.08 (br d, ^2J=2.7 Hz, 1H), 7.83 (d, ^3J=3.9 Hz, 1H), 7.73 (br d, ^2J=2.7 Hz, 1H), 7.53 (d, ^3J=3.9 Hz, 1H), 7.16 (t, ^4J=1.0 Hz, 1H), 2.80 (dq, ^4J=1.0 Hz, ^3J=7.5 Hz, 2H), 1.24 (t, ^3J=7.5 Hz, 3H); ^{13}C NMR (100 MHz, 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_2), 15.11 (CH_3); LRMS (ES$^+$): m/z (%) 315.9 (100) [M+Na]$^+$; HRMS (ES$^+$): m/z calcd for $C_{12}H_{11}N_3O_4SNa$ [M+Na]$^+$: 316.0362; found 316.0366.

***N*-((5-nitrofuran-2-yl)methyl) aniline (25a)[12]**



25a was synthesised from $NaBH_4$ (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): δ 7.19 (d, ^{3}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 × 2) and dried over Na_2SO_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) ν_{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): δ 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): δ 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 $C_{12}H_{12}N_3O_4S$ $[M-H]^{-}$: 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)	$\%H_2O$[a]	$\%\ CH_3CN$
0	80	20
10	20	80
15	20	80
17	80	20
20	80	20

[a]With 0.1% TFA

Table S3: HPLC analysis method B

Time (min)	$\%H_2O$[a]	$\%\ CH_3CN$
0	98	2
10	2	98
12	2	98
12.5	98	2
15	98	2

[a]With 0.1% TFA

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

Compound	t_r (mins)[method]	Purity
12a	7.71[A]	99.4%
12b	8.95 [A]	99.7%
12c	8.61 [A]	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%

22q	4.80 [A]	99.5%
22r	1.80 [A]	98.0%
22s	0.98 [A]	99.2%
22t	8.67 [B]	99.4%
22u	6.96 [A]	99.8%
22v	4.75 [A]	99.5%
25a	7.27 [B]	95.8%
25b	6.90 [B]	99.7%

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[a]	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

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
22r	316.1	1.906	2.54	0.3163	no	high
22p	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
22t	412.2	0.8319	3.508	0.4495	yes	high
22v	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 EC_{50} 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 P_{450} 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 P_{450}s as the potent trypanocidal analogs **22b** and **22c** with EC_{50} values around 28 nM and 27 nM respectively against *T. brucei* were predicted to have low affinity for this class of metabolizing enzymes.

5. Supplementary References

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