Structure-activity relationship and synthesis of potent inhibitors of *P.falciparum* dihydroorotate dehydrogenase for the treatment of malaria; discovery of 5-(4-cyano-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)-*N*-cyclopropyl thiophene-2-carboxamide

*Renato T. Skerlj,[§ *] Cecilia M. Bastos,[§] Michael L. Booker,[§] Martin L. Kramer,[§] Robert H. Barker, Jr.,[§] Cassandra A. Celatka,[§] Thomas J. O'Shea,[§] Benito Munoz,[±] Amar Bir Sidhu,[±] Joseph F. Cortese,[±] Sergio Wittlin,[¶] Petros Papastogiannidis,[¶] Inigo Angulo-Barturen,[Ψ] Maria Belen Jimenez-Diazi,[Ψ] Edmund Sybertz[§]*

[§]Genzyme Corp., 153 Second Ave, Waltham, Massachusetts 02451; [±]Broad Institute of Harvard and MIT, Cambridge, Massachusetts 02141; [¶]Swiss Tropical and Public Health Institute, Socinstrasse 57, CH-4002, Basel, Switzerland and University of Basel, Petersplatz 1, CH-4003, Basel, Switzerland; [Ψ]Medicines Development Campus, Diseases of the Developing World, GlaxoSmithKline, c/Severo Ochoa 2, 28760 Tres Cantos, Spain.

Supporting Information

Experimental procedures and characterization data for the synthesis for compounds **1b-f**, **1i**, **1k**, **1m**, **1o** **2a-n**, **2p-2y**, **3b-d, 4a** and **4q**.

5-(1*H*-Benzo[*d*]imidazol-1-yl)thiophene-2-carboxylic acid (3c). A mixture of benzimidazole (1.2 eq.), Cs_2CO_3 (1.4 eq.), Cu_2O (0.04 eq.), 2-amino-4,6-dihydroxypyrimidine (0.15 eq.), PEG (1.2 eq.) and **3a** (1 eq.) in NMP was heated to 160 °C for 18-20 h. The reaction mixture was cooled to room temperature, followed by the addition of water. The pH was adjusted to ~4.5 to 5 using formic acid, filtered and the solid washed with water. The solid was dissolved in methanol, filtered through Celite and the filtrate was concentrated to dryness. Precipitation with IPA (25 ml) gave 5-(1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxylic acid as an off-white solid (2.47 g, 42% yield). ^{1}H (400 MHz, DMSO d_6) δ 13.46 (br s, 1H), 8.72 (s, 1H), 7.83-7.82 (m, 2H), 7.81 (d, *J* = 3.2 Hz, 1H), 7.55 (d, *J* = 3.2 Hz, 1H), 7.46-7.37 (m, 2H).

General procedure A. A solution of the amine (1.5 eq.) and **3c** (1 eq.) in DCM was stirred for 5 min at 0 °C. HOBt (2.5 eq.) and *N*-methylmorpholine (1.5 eq.) were added, and the mixture stirred for an additional 30 min, followed by the addition of EDC·HCl (2 eq.) and stirred for 3 h at 0 °C, and then at room temperature for 10 h. Water was added, and the layers were separated. The organic layer was washed with saturated sodium bicarbonate solution, brine, dried over Na_2SO_4 and then the solvent was removed to dryness, followed by purification on silica gel column chromatography (eluant; 5% MeOH in dichloromethane).

***N*-Methyl 5-(1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (1b)**. Following general procedure A reaction of **3c** (500 mg, 2.04 mmol) with methyl amine hydrochloride (207 mg, 3.07 mmol) followed by purification gave **1b** (130 mg, 25 % yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.88-7.85 (m, 1H), 7.65-7.63 (m, 1H), 7.46 (d, *J* = 4.4 Hz, 1H), 7.42-7.35 (m, 2H), 7.12 (d, *J* = 4.4 Hz, 1H), 6.07 (m, 1H), 3.05 (d, *J* = 5.2 Hz, 3H); HPLC 99% purity; ES-MS *m/z* 258.4 $[M+H]^+$.

***N*-Ethyl 5-(1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (1c)**. Following general procedure A reaction of **3c** (500 mg, 2.04 mmol) with ethyl amine hydrochloride (250 mg, 3.07 mmol) followed

by purification gave **1c** (400 mg, 72 % yield) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.88-7.84 (m, 1H), 7.65-7.61 (m, 1H), 7.47 (d, *J* = 4.4 Hz, 1H), 7.41-7.35 (m, 2H), 7.12 (d, *J* = 4.4 Hz, 1H), 6.18 (br, 1H), 3.55-3.48 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); HPLC 99% purity; ES-MS *m/z* 272.1 $[M+H]^+$.

***N*-Propyl 5-(1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (1d)**. Following general procedure A reaction of **3c** (200 mg, 0.82 mmol) with n-propyl amine (58 mg, 0.98 mmol) followed by purification gave **1d** (100 mg, 26 % yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO d_6) δ 8.67 (m, 1H), 8.64 (s, 1H), 7.83 (d, *J* = 4.4 Hz, 1H), 7.81-7.74 (m, 2H), 7.48 (d, *J* = 4.4 Hz, 1H), 7.44-7.35 (m, 2H), 3.30-3.25 (m, 2H), 1.56-1.51 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); HPLC 99% purity; ES-MS *m/z* 286.1 $[M+H]^+$.

***N*-isoPropyl 5-(1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (1e)**. Following general procedure A reaction of **3c** (200 mg, 0.82 mmol) with isopropyl amine (58 mg, 0.983 mmol) followed by purification gave **1e** (180 mg, 77 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO d_6) δ 8.62 (s, 1H), 8.43 (d, *J* = 7.6 Hz, 1H), 7.79-7.73 (m, 2H), 7.46 (d, *J* = 4.4 Hz, 1H), 7.42-7.33 (m, 2H), 4.09-4.04 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 6H); HPLC 98% purity; ES-MS *m/z* 286.1 $[M+H]^+$.

***N*-Cyclopropyl 5-(1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (1f)**. Following general procedure A reaction of **3c** (500 mg, 2.04 mmol) with c-propyl amine (175 mg, 3.07 mmol) followed by purification afforded **1f** (160 mg, 27 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.87-7.85 (m, 1H), 7.65-7.62 (m, 1H), 7.43 (d, *J* = 4.4 Hz, 1H), 7.41-7.35 (m, 2H), 7.12 (d, *J* = 4.4 Hz, 1H), 6.15 (m, 1H), 2.93-2.89 (m, 1H), 0.88-0.83 (m, 2H), 0.69-0.65 (m, 2H); HPLC 98% purity; ES-MS *m/z* 284.3 $[M+H]^+$.

***N*-Cyclopentyl 5-(1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (1i)**. Following general procedure A reaction of **3c** (200 mg, 0.82 mmol) and cyclopentyl amine (84 mg, 0.983 mmol) followed by purification gave **1i** (180 mg, 70 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO d_6) δ 8.64 (s, 1H), 8.49 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 4.4 Hz, 1H), 7.46 (d, *J* = 4.4 Hz, 1H), 7.43-7.34 (m,

2H), 4.23-4.18 (m, 1H), 1.91 (m, 1H), 1.71(m, 2H), 1.50 (m, 4H); HPLC 98% purity; ES-MS *m/z* 312.0 $[M+H]^+$.

5-Bromo-*N*-cyclopropylthiophene-2-carboxamide (3b). A mixture of **3a** (2.12 g, 10.2 mmol) and thionyl chloride (5 mL) in 1,2-dichloroethane (2 mL) was heated at 150 °C for 1 h in a microwave reactor. The solution was concentrated, dissolved in DCM (15 mL), placed in an iced bath and c-propyl amine (2.0 mL, 28.6 mmol, 2.6 eq.) was slowly added. The mixture was warmed to room temperature, water (40 mL) was added and the layers separated. The aqueous layer was extracted with DCM (2 x 10 mL), the organic layers were dried ($MgSO_4$) and concentrated to afford **3b** as a yellow solid (2.50 g). ^{1}H NMR (400 MHz, DMSO d_6) δ 8.55 (d, 1H), 7.54 (d, 1H), 7.25 (d, 1H), 2.79-2.73 (m, 1H), 0.72-0.67 (m, 1H), 0.57-0.53 (m, 1H); LC-MS > 98% purity.

General procedure B. A mixture of commercially available substituted benzimidazole (1.3 eq.), **3b** (1 eq.), Cs_2CO_3 (2 eq.), Cu_2O (0.1 eq.), 4,7-dimethoxy-1,10-phenathroline (0.2 eq.), PEG (1.3 eq.) in DMSO was heated at 110-115 °C for 24 h. The reaction mixture was cooled to room temperature, dichloromethane was added and the mixture filtered through Celite. The solvent was removed to dryness and the residue washed with aq. ammonia (10 ml) and then extracted with ethyl acetate. The mixture was purified by SiO_2 column chromatography (eluant; 5% MeOH in dichloromethane).

***N*-Cyclopropyl-5-(2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (1k)**. Following general procedure B reaction of 2-methyl benzimidazole (5.115 mmol) and **3b** (3.938 mmol) followed by purification gave **1 k** (667 mg, 57 % yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO d_6) δ 8.70 (d, *J* = 3.6 Hz, 1H), 7.80 (d, *J* = 4.4 Hz, 1H), 7.64-7.62 (m, 1H), 7.37 (d, *J* = 4.4 Hz, 1H), 7.36-7.25 (m, 3H), 2.84-2.79 (m, 1H), 0.76-0.71 (m, 2H), 0.62-0.58 (m, 2H); HPLC 94% purity; ES-MS *m/z* 298 $[M+H]^+$.

***N*-Cyclopropyl-5-(2-propyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (1m)**. Following general procedure B reaction of **3b** (0.59 g, 2.40 mmol) and 2-propylbenzimidazole (500 mg, 3.12 mmol) followed by purification gave **1m** (11 mg, 1.4 % yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO d_6) δ 8.71 (d, *J* = 3.6 Hz, 1H), 7.81 (t, *J* = 4.4 Hz, 1H), 7.67-7.65 (m, 1H), 7.37 (t, *J* = 4.4

Hz, 1H), 7.28-7.15 (m, 3H), 2.84-2.76 (m, 3H), 1.78-1.69 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.76-0.71 (m, 2H), 0.61-0.58 (m, 2H); HPLC 94% purity; ES-MS *m/z* 326.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(4-chloro-6-fluoro-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2v)**. A mixture of 4-chloro-6-fluoro-1*H*-benzo[*d*]imidazole (0.40 g, 2.64 mmol)[i], **3b** (0.180 g, 0.85 mmol), quinolin-8-ol (24 mg, 0.2 mmol), Cs_2CO_3 (0.40 g, 1.25 mmol), PEG (0.5 g), and Cu_2O (12 mg, 0.1 mmol) in DMSO (4 mL) was heated in a microwave reactor at 150 ºC for 1 h. The mixture was cooled to room temperature, diluted with brine (15 mL) and EtOAc (50 mL) and filtered over Celite. The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated to dryness, and then purified by silica gel column chromatography (1:1 hexane/ EtOAc) to afford **2v** (40 mg, 5% yield) as a light yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.57 (s, 1H), 7.73 (d, *J* = 4.0 Hz, 1H), 7.43 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.39 (d, *J* = 4.0 Hz, 1H), 7.33 (dd, *J* = 2.5, 9.5 Hz, 1H), 2.88-2.85 (m, 1H), 0.86-0.83 (m, 2H), 0.70-0.67 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 164.77, 162.32, 160.38, 146.16, 140.73, 138.82, 138.16, 136.06, 128.90, 126.53, 126.43, 124.35, 113.69, 113.45, 98.18, 97.95, 24.03, 6.612; LC-MS > 93% purity; ES-MS *m/z* 336.0 $[M+H]^+$.

Compounds **2p**, **2r**, **2t**, **2w** were prepared using similar methodology as described for **2v**.

***N*-Cyclopropyl-5-(4-bromo-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2p)**. Light yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 8.78-8.73 (d, *J* = 3.5 Hz, 1H), 7.82 (d, *J* = 4.0 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 3.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 2.82 (m, 1H), 2.51 (s, 3H), 0.75-0.73 (m, 2H), 0.62-0.60 (m, 2H); ^{13}C NMR (125 MHz, DMSO) δ 162.05, 153.84, 140.93, 140.40, 138.75, 137.53, 127.97, 127.70, 126.00, 124.84, 112.02, 110.18, 23.38, 14.30, 6.28; LC-MS > 99% purity; ES-MS *m/z* 376.0 $[M+H]^+$.

***N*-Cyclopropyl-5-(4-(dimethylamino)-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2r)**. Light yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.15-7.12 (t, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 4 Hz, 1H), 6.75 (d , *J* = 7.5 Hz, 1H), 6.61 (s, 1H), 6.22 (s, 1H), 3.26 (s, 3H), 3.21 (s, 3H), 2.94-2.89 (m, 1H), 2.54 (s, 3H), 0.93-0.89 (m, 2H), 0.70-0.67 (m, 2H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 162.38, 138.15, 137.93, 133.62, 133.58, 126.885 125.86, 124.01, 108.09, 108.04, 101.50, 101.39, 42.66, 23.20, 14.20, 12.98, 6.90, 6.74; LC-MS 100% purity; ES-MS *m/z* 341.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(4-fluoro-6-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2t)**. Light yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 8.71 (d, *J* = 3.5 Hz, 1H), 8.59 (s, 1H), 7.80 (d, *J* = 4.0 Hz, 1H), 7.47 (d, *J* = 4.5 Hz, 1H), 7.38 (s, 1H), 7.04 (d, *J* = 12 Hz, 1H), 2.85-2.82 (m, 1H), 2.46 (s, 3H), 0.77-0.73 (m, 2H), 0.62-0.59 (m, 2H); ^{13}C NMR (125 MHz, DMSO) δ 161.65, 153.72, 151.71, 143.68, 139.56, 136.93, 136.09, 136.01, 135.50, 135.44, 129.86, 129.73, 127.28, 122.02, 110.10, 109.97, 106.91, 106.88, 22.87, 21.22, 5.81; LC-MS > 96% purity; ES-MS *m/z* 316.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(7-fluoro-5-methyl-1H-benzo[d]imidazol-1-yl)thiophene-2-carboxamide (2w)**. Light yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ 8.24 (s, 1H), 7.56 (s, 1H), 7.29 (s, 1H), 7.21 (s, 1H), 6.89 (d, *J* = 11.5 Hz, 1H), 2.76 (d, *J* = 3.5 Hz, 1H), 2.39 (s, 3H), 0.74 (s, 2H), 0.59 (s, 2H); ^{13}C NMR (125 MHz, CD_3OD): δ 164.96, 150.74, 148.77, 147.44, 146.35, 146.27, 142.01, 139.07, 136.16, 136.12, 128.20, 126.05, 121.50, 116.64, 116.63, 113.07, 112.93, 23.99, 21.422, 6.60; LC-MS > 95% purity; ES-MS *m/z* 316.1 $[M+H]^+$.

Methyl 5-aminothiophene-2-carboxylate (3d). A solution of 5-nitrothiophene-2-carboxylic acid (8.80 g, 50.9 mmol) in a mixture of 1,2-dichloroethane and thionyl chloride (1:1) (24 mL) was heated in a microwave reactor at 150 °C for 30 min. The mixture was concentrated to dryness, dissolved in DCM (40 mL) and cooled to 0 °C; methanol (16 mL) was slowly added, and the mixture warmed to room temperature. The solvent was removed to give crude methyl 5-nitrothiophene-2-carboxylate (8.60 g, 90% yield) as an off-white solid which was use in the next step. A suspension of methyl 5-nitrothiophene-2-carboxylate (0.45 g, 2.30 mmol) and $Pd(OH)_2$/C (20%, 0.43 g) in EtOH (5 mL), was hydrogenated under atmospheric pressure overnight. The mixture was filtered over Celite, and then concentrated to dryness. Purification by silica gel chromatography (linear gradient from hexane to 30% ethyl acetate/hexane) afforded **3d** (0.30 g, 83% yield) as an off-white solid. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.39 (d, *J* = 3.7 Hz, 1H), 6.03 (d, *J* = 3.1 Hz, 1H), 3.74 (s, 3H); LC-MS > 95% purity; ES-MS *m/z* 158.2 $[M+H]^+$.

1-Bromo-3-(difluoromethoxy)-2-nitrobenzene (4j). A mixture of 3-bromo-2-nitrophenol (8.99 g, 41.4 mmol), K_2CO_3 (29.63 g, 215 mmol), and ethyl chlorodifluoro acetate (15.5 mL, 123 mmol) in a mixture of DMF and water (5:2) (70 mL) was heated at 110 °C for 2.5 h. The mixture was partitioned between EtOAc (3 x 125 mL) and brine (100 mL), separated, and concentrated to dryness. After purification by silica gel column chromatography (linear gradient from hexane to 30% CH_2Cl_2/hexane) **4j** (11.40 g, 93.4% yield) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 1.7, 7.5 Hz, 1H), 7.38 (d, *J* = 20.2 Hz, 2H), 6.45 (d, *J* = 71.7 Hz, 1H); LC-MS > 98% purity.

***N*-Cyclopropyl-5-(4-(difluoromethoxy)-2-methyl-1H-benzo[d]imidazol-1-yl)thiophene-2-carboxamide (2j)**. A mixture of **4j** (1.85 g, 6.93 mmol), **3d** (1.00 g, 6.38 mmol), Xanthphos (192 mg, 0.41 mmol) and Cs_2CO_3 (3.62 g, 11.1 mmol) was suspended in 1,4-dioxane (12 mL) and the mixture was saturated with N_2(g). $Pd_2(dba)_3$ (161 mg. 0.175 mmol) was added and the mixture heated at 80-90 °C for 15 min, cooled to room temperature and concentrated. After purification by silica gel chromatography (linear gradient from hexane to 40% CH_2Cl_2/hexane) methyl 5-(3-(difluoromethoxy)-2-nitrophenylamino) thiophene-2-carboxylate (1.7 g, 77.5% yield) was obtained as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H), 7.66 (d, *J* = 4.0 Hz, 1H), 7.37 (t, *J* = 8.4 Hz, 1H), 7.24 (dd, *J* = 4.5, 16.6 Hz, 2H), 6.83 (dd, *J* = 0.6, 8.1 Hz, 1H), 6.78 (d, *J* = 4.1 Hz, 1H), 3.88 (s, 3H); LC-MS > 98% purity; ES-MS m/z 345.1 $[M+H]^+$.

A mixture of methyl 5-(3-(difluoromethoxy)-2-nitrophenylamino)thiophene-2-carboxylate, (1.70 g, 4.94 mmol) and $Pd(OH)_2$/C (1.83 g, 20%) in EtOH (40 mL) was hydrogenated under atmospheric pressure for 1-2 hours. The mixture was filtered through Celite, and then concentrated to dryness. Triethylortho acetate (12 mL) was added and the mixture heated at 120 °C in a microwave reactor for 1 hour, and then concentrated to dryness. The residue was suspended in 4:1 mixture EtOH and water (15 mL), LiOH (0.526 g, 12.5 mmol) was added and the solution heated at 80 °C for 1 hour. The pH was adjusted to 1 with HCl (12 M, 1.2 mL) and the solution concentrated to dryness. The residue was suspended in a 6:1

mixture of 1,2-dichloroethane and thionyl chloride (35 ml) and heated at 75-80 °C for 2 hours, and the solution concentrated to dryness. The residue was suspended in 1,2-dichloroethane (40 mL), cooled to °C and c-propyl amine (1.8 mL, 9.1 mmol) was slowly added. The mixture was stirred at room temperature for 30 minutes and then partitioned between CH_2Cl_2 (50 mL)/HCl (1M, 30 mL). The layers were separated, concentrated and purified by silica gel column chromatography (linear gradient from CH_2Cl_2 to EtOAc) to afford **2j** (0.44 g, 25% yield) as light yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 8.75 (d, *J* = 3.0 Hz, 1H), 7.82 (d, *J* = 3.5 Hz, 1H), 7.64 (t, *J* = 75.0 Hz, 1H), 7.42 (d, *J* = 3.5 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 2.51 (s, 3H), 2.82 (m, 1H), 0.75 (m, 2H), 0.60 (m, 2H); ^{13}C NMR (125 MHz, DMSO) δ 161.58, 152.72, 141.22, 141.20, 139.88, 138.58, 138.30, 132.84, 127.43, 127.25, 123.73, 118.60, 116.54, 114.50, 112.27, 107.29, 22.88, 13.90, 5.83; HPLC > 99% purity; ES-MS m/z 364.1 $[M+H]^+$; Anal. Calcd. for $C_{17}H_{15}F_2N_3O_2S$: C, 56.16; H, 4.17; N, 11.59; F, 10.71. Found: C, 56.19; H, 4.16; N, 11.56; F, 10.46.

Compounds **2b-c**, **2e-k**, **2m**, **2x**, **1o** were prepared using the methodology described for **2j**.

***N*-Cyclopropyl-5-(2,5-dimethyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2b)**. Light yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 8.67 (d, *J* = 3.8 Hz, 1H), 7.76 (d, *J* = 4.0 Hz, 1H), 7.40 (dt, *J* = 0.7, 1.5 Hz, 1H), 7.37-7.25 (m, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 7.10-6.92 (m, 1H), 2.79 (tq, *J* = 4.0, 7.8 Hz, 1H), 2.49-2.41 (m, 4H), 2.38 (s, 3H), 0.79-0.63 (m, 2H), 0.63-0.48 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 162.39, 152.67, 143.06, 139.92, 139.68, 135.09, 132.56, 128.00, 127.20, 124.94, 119.17, 110.15, 23.57, 21.72, 14.58, 6.49; LC-MS > 98% purity; ES-MS *m/z* 312.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(2,6-dimethyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2c)**. White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 27.3, 31.2 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.09 (dt, *J* = 8.3, 16.7 Hz, 1H), 7.03 (d, *J* = 4.1 Hz, 1H), 2.93-2.76 (m, 1H), 2.51 (s, 3H), 2.42 (s, 3H), 0.85 (q, *J* = 7.0 Hz, 2H), 0.78-0.60 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 165.23, 156.47, 152.67, 141.57, 137.83, 136.36, 123.66, 123.34, 122.78, 118.98, 118.19, 110.73, 110.13, 22.26, 12.71, 5.87; HPLC 98% purity; ES-MS *m/z* 312.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(2-methyl-5-(trifluoromethoxy)-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2e)**. Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.62 (m, 1H), 7.58 (d, *J* = 3.7 Hz, 1H), 7.25-7.16 (m, 1H), 7.14-7.00 (m, 2H), 6.67 (s, 1H), 2.52 (s, 3H), 2.98-2.86 (m, 1H), 0.97-0.79 (m, 2H), 0.76-0.57 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.44, 154.29, 145.57, 145.58, 142.96, 139.74, 139.20, 135.58, 126.98, 126.40, 122.14, 119.59, 117.41, 112.56, 110.56, 23.47, 14.56, 7.10; HPLC > 98% purity; ES-MS *m/z* 382.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(2-methyl-6-(trifluoromethoxy)-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2f)**. Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.54-7.12 (m, 5H), 6.36 (br, 1H), 2.94-2.88 (m, 1H), 2.50 (s, 3H), 0.93-0.88 (m, 2H), 0.70-0.66 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 162.14, 153.72, 145.52, 140.93, 139.28, 139.01, 136.84, 126.78, 126.25, 119.25, 117.00, 116.69, 119.25, 121.80, 103.46, 23.23, 14.28, 6.89; HPLC > 95% purity; ES-MS *m/z* 382.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(2-methyl-5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2g)**. Light yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 8.72 (d, *J* = 3.8 Hz, 1H), 7.97 (s, 1H), 7.79 (d, *J* = 4.0 Hz, 1H), 7.56 (dd, *J* = 1.5, 8.7 Hz, 1H), 7.50-7.42 (m, 1H), 7.40 (d, *J* = 4.0 Hz, 1H), 2.84-2.73 (m, 1H), 2.50 (s, 3H), 0.77-0.67 (m, 2H), 0.61-0.50 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 162.29, 155.62, 142.38, 140.69, 139.39, 138.61, 128.28, 127.95, 124.14, 120.53, 116.59, 111.68, 23.57, 14.63, 6.48; HPLC > 98% purity; ES-MS *m/z* 366.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(2-methyl-6-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2h)**. Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.8 Hz, 1H), 7.55 (dd, *J* = 1.2, 8.8 Hz, 1H), 7.48 (d, *J* = 1.2 Hz, 1H), 7.26 (d, *J* = 4.0 Hz, 1H), 7.10 (d, *J* = 4.0 Hz, 1H), 6.14 (brs, 1H), 2.90-2.93 (m, 1H), 2.59 (s, 3H), 0.90-0.95 (m, 2H), 0.67-0.71 (m, 2H); HPLC > 98% purity; ES-MS *m/z* 366.1. $[M+H]^+$.

***N*-Cyclopropyl-5-(4-methoxy-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2i)**. Light yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 8.69 (d, *J* = 3.7 Hz, 1H), 7.80 (d, *J* = 4.0 Hz, 1H), 7.36 (d, *J* = 4.0 Hz, 1H), 7.16 (t, *J* = 8.1 Hz, 1H), 6.87 (dd, *J* = 0.6, 8.1 Hz, 1H), 6.80 (d, *J* = 7.5 Hz,

1H), 3.96 (s, 3H), 2.82 (tq, *J* = 3.9, 7.6 Hz, 1H), 2.46 (s, 3H), 0.74 (td, *J* = 4.8, 7.0 Hz, 2H), 0.64-0.54 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 161.63, 150.57, 150.35, 139.31, 139.11, 137.90, 131.92, 127.27, 126.82, 123.81, 104.84, 102.70, 55.93, 22.87, 13.84, 5.80; LC-MS > 99 % purity; ES-MS *m/z* 328.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(4-(2-fluoroethoxy)-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2k)**. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.53 (d, *J* = 4.0 Hz, 1H), 7.12-7.16 (dd, *J* = 4.0, 8.0 Hz, 1H), 7.03 (d, *J* = 4.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.55 (brs, 1H), 4.93-4.80 (m, 2H), 4.56-4.48 (m, 2H), 2.93-2.88 (m, 1H), 2.54 (s, 3H), 0.91-0.86 (m, 2H), 0.69-0.66 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 162.40, 150.91, 149.63, 140.07, 138.46, 132.36, 126.89, 125.98, 124.03, 105.95, 103.47, 82.78, 82.81.08, 68.16, 67.95, 23.20, 14.07, 6.79; HPLC > 98% purity; ES-MS *m/z* 359.4 $[M+H]^+$.

***N*-Cyclopropyl-5-(6-fluoro-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2m)**. Ligh yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 4.7, 8.8 Hz, 1H), 7.54-7.47 (m, 1H), 7.07-7.04 (m, 1H), 7.03-6.99 (m, 1H), 6.95-6.89 (m, 1H), 2.97-2.86 (m, 1H), 2.55 (d, *J* = 3.4 Hz, 3H), 0.95-0.87 (m, 2H), 0.72-0.64 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.20, 160.18, 157.78, 151.67, 138.66, 137.70, 136.00, 135.87, 125.80, 124.98, 119.01, 118.91, 110.37, 110.12, 96.20, 95.92, 79.05, 22.24, 13.26, 5.88; HPLC > 98% purity; ES-MS *m/z* 316.1 $[M+H]^+$.

N-Cyclopropyl-5-(5-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2x). Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.17-8.11 (m, 1H), 7.66 (dt, *J* = 5.1, 8.6 Hz, 2H), 7.49 (d, *J* = 3.2 Hz, 1H), 7.15 (t, *J* = 4.3 Hz, 1H), 6.47 (s, 1H), 2.92 (dq, *J* = 3.5, 10.8 Hz, 1H), 0.91 (tt, *J* = 3.5, 6.9 Hz, 2H), 0.76-0.58 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.43, 144.42, 143.46, 140.28, 136.06, 126.93, 126.65, 126.33, 122.05, 121.68, 118.82, 118.78, 111.27, 23.49, 7.11; LC-MS > 98% purity; ES-MS *m/z* 352.4 $[M+H]^+$.

***N*-cyclopropyl-5-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (1o)**. Diisoproylethylamine (0.4 ml, 2.3 mmol) and trifluoroacetic anhydride (280 μL, 2.0 mmol) were added to a cold 0 °C solution of **5** (R=H) (0.15 g, 0.61 mmol), prepared in a similar manner as outlined for **2j**.

The mixture was warmed to room temperature, washed with saturated Na_2CO_3 (5 ml), and concentrated to dryness. A yellow solid was obtained after purification by silica gel chromatography (linear gradient from hexane to 30% EtOAc/hexane) which was dissolved in $POCl_3$ (1 mL) and heated for 10 min at 110 °C in a microwave reactor, and concentrated to dryness. The mixture was partitioned between EtOAc (50 mL) and saturated Na_2CO_3 (20 ml), the layers separated, concentrated to dryness and dried. An off-white solid (0.167 g, 76% overall yield) was obtained after purification by silica gel chromatography (linear gradient from hexane to 20% ethyl acetate in hexane). A mixture of the off-white solid (0.080 g, 0.24 mmol) and c-propyl amine (0.6 mL, 8.4 mmol) in MeOH (0.5 mL) was heated in a microwave reactor at 120 °C for 8 h, concentrated to dryness, and then purified by silica gel chromatography (linear gradient from CH_2Cl_2 to 50% CH_2Cl_2/EtOAc) to give **1o** (43 mg, 50% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO) δ 8.75 (d, *J* = 3.8 Hz, 1H), 8.00-7.85 (m, 1H), 7.79 (d, *J* = 4.0 Hz, 1H), 7.60-7.39 (m, 1H), 7.40-7.27 (m, 1H), 0.83-0.63 (m, 1H), 0.64-0.45 (m, 1H); ^{13}C NMR (101 MHz, DMSO) δ 162.12, 141.98, 140.53, 138.17, 136.61, 129.95, 127.54, 127.48, 125.31, 121.80, 112.11, 23.59, 6.47; LC-MS >98% purity; ES-MS *m/z* 352.4 $[M+H]^+$.

***N*-Cyclopropyl-5-(4-fluoro-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2l)**. To a 0 ^{0}C solution of KOH (0.72 g, 12.8 mmol) and benzyl triethyl ammonium chloride (0.14 g, 0.62 mmol) in DMF (8 mL), was slowly added a solution of 2,6-difluoronitrobenzene (1.05 g, 6.6 mmol) and **3d** (0.92 g, 5.89 mmol) in DMF (4 mL). The mixture was warmed to room temperature, stirred for 2 hours, partitioned between ethyl acetate (50 mL) and brine (30 mL), and concentrated to dryness. The mixture was purified by silica gel chromatography (linear gradient from hexane to CH_2Cl_2) to give methyl 5-(3-fluoro-2-nitrophenylamino)thiophene-2-carboxylate (1.67 g, 96 % yield) as an orange solid. ^{1}H NMR (400 MHz, DMSO) δ 9.46 (s, 1H), 7.61-7.57 (m, 1H), 7.53 (td, *J* = 6.3, 8.5 Hz, 1H), 7.28 (dt, *J* = 1.2, 8.6 Hz, 1H), 7.04 (ddd, *J* = 1.1, 8.4, 10.4 Hz, 1H), 6.74 (d, *J* = 4.1 Hz, 1H), 3.75 (s, 3H); ES-MS *m/z* 297.3 $[M+H]^+$.

A mixture of methyl 5-(3-fluoro-2-nitrophenylamino)thiophene-2-carboxylate, (1.67 g, 5.56 mmol) and $Pd(OH)_2$/C (1.95 g, 20%) in EtOH (60 mL) was hydrogenated under atmospheric pressure for 1-2 hours.

The mixture was filtered through Celite, and then concentrated to dryness. Triethylortho acetate (10 mL) was added, heated at 120 °C in a microwave reactor for 30 min, and then concentrated to dryness. The crude was purified by silica gel chromatography (linear gradient from hexane to a mixture of 10 % EtOAc in CH_2Cl_2) to give methyl 5-(4-fluoro-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxylate (1.67 g, 100% yield) as a light yellow solid ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 0.6, 4.0 Hz, 1H), 7.18 (td, *J* = 4.6, 8.1 Hz, 1H), 7.14-7.11 (m, 1H), 7.07-7.03 (m, 1H), 7.03-6.97 (m, 1H), 3.95 (d, *J* = 0.6 Hz, 3H), 2.59 (s, 3H); ES-MS *m/z* 291.3 $[M+H]^+$.

Methyl 5-(4-fluoro-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxylate (1.67 g, 5.6 mmol) was suspended in 4:1 mixture of EtOH and water (15 mL), LiOH (0.617 g, 14.7 mmol) was added and the mixture was heated in a microwave reactor at 110 °C for 5 min. The pH was adjusted to 1 with HCl (12 M, 1.5 mL) and concentrated to dryness. The residue was suspended in a mixture of 1,2-dichloroethane (30 mL) and thionyl chloride (8 ml) and heated in a microwave reactor at 120 °C for 5 min, and concentrated to dryness. The residue was resuspended in 1,2-dichloroethane (20 mL), cooled to 0 °C and c-propyl amine (1.8 mL, 28.4 mmol) was added slowly. The mixture was stirred at room temperature for 30 minutes and then partitioned between CH_2Cl_2 (50 mL) and HCl (1M, 30 mL). The layers were separated, and the organic layer concentrated to dryness. After purification by silica gel chromatography (linear gradient from CH_2Cl_2 to EtOAc) **2l** (1.43 g, 80% yield) was obtained as a light yellow solid. ^{1}H NMR (400 MHz, DMSO) δ 8.73 (d, *J* = 3.6 Hz, 1H), 7.82 (d, *J* = 4.0 Hz, 1H), 7.41 (d, *J* = 4.0 Hz, 1H), 7.24 (td, *J* = 4.8, 8.1 Hz, 1H), 7.16-7.04 (m, 2H), 2.82 (tq, *J* = 3.9, 7.5 Hz, 1H), 2.50 (s, 3H), 0.79-0.70 (m, 2H), 0.64-0.56 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 161.60, 153.76, 152.96, 151.24, 139.73, 139.35, 138.47, 130.39, 127.38, 127.28, 123.71, 108.37, 106.45, 22.88, 13.86, 5.78; LC-MS > 96 % purity; ES-MS *m/z* 316.3 $[M+H]^+$.

Compounds **2n** and **2y** were prepared using a similar procedure as described for **2l.**

***N*-Cyclopropyl-5-(4-chloro-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2n)**. Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 3.3 Hz, 1H), 7.33-7.24 (m, 1H), 7.21-7.10 (m, 2H), 7.06 (d, *J* = 3.9 Hz, 1H), 6.43 (s, 1H), 3.01-2.76 (m, 1H), 2.59 (s, 3H), 2.71-2.42 (m, 4H),

0.99-0.82 (m, 2H), 0.68 (t, J = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, DMSO) δ 161.63, 153.43, 139.84, 139.04, 138.26, 137.54, 127.43, 127.26, 123.91, 122.57, 122.53, 109.16, 22.88, 13.87, 5.78; LC-MS 99% purity; ES-MS *m/z* 331.8 $[M+H]^+$.

***N*-Cyclopropyl-5-(4-fluoro-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2y)**. Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.66 (d, J = 3.8 Hz, 1H), 7.39 (dd, J = 0.7, 8.3 Hz, 1H), 7.34-7.25 (m, 2H), 7.14 (d, J = 4.0 Hz, 1H), 7.06 (ddd, J = 0.8, 8.0, 10.2 Hz, 1H), 2.96-2.86 (m, 1H), 0.88-0.80 (m, 2H), 0.75-0.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.83, 155.37, 152.84, 142.84, 140.23, 137.42, 136.64, 136.56, 132.17, 132.00, 127.35, 125.59, 125.52, 122.04, 109.72, 109.55, 107.01, 106.97, 23.52, 6.87, 6.68; LC-MS > 98% purity; ES-MS *m/z* 302.3 $[M+H]^+$.

3-Fluoro-2-nitrobenzonitrile (4q). A mixture of 2-bromo-6-fluoronitrobenzene (26.01 g, 0.119 mol) and CuCN (13.06 g, 0.145 mol) in DMF (50 mL) was refluxed for 1 hour under N_2 atmosphere and concentrated to dryness. The product was purified by distillation, suspended in brine (100 mL), filtered and then washed with water (4 x 100 mL). The solution was dried and concentrated to afford **4q** (16.0 g, 81% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.71 (m, 1H), 7.69-7.67 (m, 1H), 7.62-7.58 (m, 1H); ES-MS *m/z* 167 $[M+H]^+$.

***N*-Cyclopropyl-5-(4-cyano-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2q)**.

To an ice cold solution of KOH (2.32 g, 41.43 mmol) and $BnEt_3NCl$ (0.36 g, 1.60 mmol) in DMF (10 mL), was slowly added a solution of **4q** (2.98 g, 17.99 mmol) and **3d** (2.58 g, 16.41 mmol) in DMF (10 mL). The mixture was stirred in the ice bath for another 30 min, and then brine (100 mL) was added. The mixture was filtered, and the solid was washed with water (2 x 20 mL), and dried. The crude was purified by silica gel chromatography (linear gradient from hexane to CH_2Cl_2) to afford methyl 5-(3-cyano-2-nitrophenylamino)thiophene-2-carboxylate (3.81 g, 77% yield) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.72 (d, J = 4.0 Hz, 1H), 7.53-7.49 (m, 2H), 7.34 (dd, J = 2.6, 6.0 Hz, 1H), 6.91 (d, J = 4.0 Hz, 1H), 3.91 (s, 3H), ES-MS *m/z* 304.1 $[M+H]^+$.

A solution of methyl 5-(3-cyano-2-nitrophenylamino)thiophene-2-carboxylate (3.81 g, 12.56 mmol) and $SnCl_2$ (11.23 g, 59.22 mmol) in 1:1 solution of EtOH and conc. HCl (40 mL) was stirred at room

temperature under a N_2 atmosphere overnight. The reaction mixture was cooled to 2-5 °C, and filtered cold. The solid was suspended in water (100 mL), cooled to 0 °C, and KOH (3.5 M, 40 mL) was added slowly keeping the temperature below 15 °C. The mixture was filtered, and the solid was dried to give the crude amine product which was used directly in the next step. The crude was suspended in triethylortho acetate (40 mL) and refluxed for 1.5 hour, and then concentrated to dryness. The crude was purified by silica gel chromatography (linear gradient from hexane to 5% EtOAc in CH_2Cl_2) to give methyl 5-(4-cyano-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxylate (2.42 g, 65% overall yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 4.0 Hz, 1H), 7.63 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.47 (dt, *J* = 2.8, 5.6 Hz, 1H), 7.35-7.29 (m, 1H), 7.14 (d, *J* = 4.0 Hz, 1H), 3.96 (s, 3H), 2.65 (s, 3H); ES-MS *m/z* 298.1 $[M+H]^+$.

A suspension of methyl 5-(4-cyano-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxylate (2.42 g, 8.1 mmol) and LiOH (0.753 g, 17.9 mmol) in a 1:1 solution of methanol and water (30 mL) was stirred at room temperature overnight. The mixture was placed in an ice bath and the pH adjusted with HCl (1M, 18 mL), keeping the temperature below 20 °C, and then filtered cold (0 °C). The solid was washed with HCl (1M, 10 mL), water (10 mL), and then dried to afford the carboxylic acid (1.84 g, 80% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO) δ 7.85 (d, *J* = 4.0 Hz, 1H), 7.78 (dd, *J* = 1.0, 7.6 Hz, 1H), 7.67 (dd, *J* = 1.0, 8.2 Hz, 1H), 7.53-7.50 (m, 1H), 7.41 (dd, *J* = 7.6, 8.1 Hz, 1H), 2.57 (s, 3H); ES-MS *m/z* 284.1 $[M+H]^+$.

HCTU (3.68 g, 8.9 mmol) and N^iPr_2Et (2.2 mL, 12.62 mmol) were added to a solution of the carboxylic acid (1.84 g, 0.64 mmol) in DMF (20 mL), and stirred at room temperature for 30 min. c-Propyl amine (0.88 mL, 12.72 mmol) was added, the reaction mixture stirred for 30 min, and then concentrated to dryness. The mixture was partitioned between DCM (50 mL) and brine (2 x 50 mL), washed with HCl (1M, 4 x 25 mL) and $NaHCO_3$ (saturated solution, 4 x 25 mL), and the organic layer concentrated. The crude was purified by silica gel chromatography (linear gradient from CH_2Cl_2 to EtOAc) to afford **2q** (1.87 g, 90.0% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.50 (br s, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.5, 8.0 Hz, 1H), 7.09 (d, *J* = 3.5 Hz, 1H), 6.96 (br s, 1H),

2.93-2.90 (m, 1H), 2.62 (s, 3H), 0.94-0.88 (m, 2H), 0.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ161.97, 155.01, 143.65, 139.54, 138.67, 137.13, 127.77, 126.67, 126.59, 123.19, 116.48, 114.67, 102.70, 23.27, 14.32, 6.91; LC-MS > 99% purity; ES-MS *m/z* 323.1 $[M+H]^+$; Anal. Calcd. for $C_{17}H_{14}N_4OS$: C, 63.34; H, 4.36; N, 17.63; S, 10.24. Found: C, 63.33; H, 4.38; N, 17.38; F, 9.95.

***N*-(2-Bromo-6-methylphenyl)acetamide (4a)** A mixture of 2-bromo-6-methyl aniline (1.49 g, 8.0 mmol) and acetic anhydride (1.5 mL) was heated at 100 °C in a microwave reactor for 4 min. The mixture was partitioned between EtOAc (20 mL) and water (25 mL), the organic layer was washed with water (2 x 10 mL), and then concentrated to dryness. The mixture was suspended in hexane (25 mL), filtered and the solid washed with hexane (2 x 25 mL) and dried to afford **4a** (1.54 g, 84% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 2.29 (s, 3H), 2.23 (s, 3H); ES-MS *m/z* 228.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(2-methyl-substituted-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2a)**. A mixture of **4a** (1.88 g, 8.22 mmol), **3d** (0.88 g, 5.66 mmol), Ruphos (0.565 g, 1.21 mmol), $K_3PO_4 \cdot H_2O$ (4.71 g, 20.45 mmol), $Pd_2(dba)_3$ (0.233 g, 0.254 mmol) and molecular sieves (5 Å) in ^{t}BuOH (10 g) was heated at 120 °C in a microwave reactor for 2 hours. The mixture was diluted with EtOAc (100 mL), filtered, concentrated and then purified by silica gel chromatography (linear gradient from hexane to 10 % EtOAc in CH_2Cl_2) to give methyl 5-(2,4-dimethyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxylate (0.99 g, 61% yield) as a white solid (ES-MS *m/z* 287.1). This white solid (0.85 g, 3.0 mmol) was suspended in 4:1 mixture of EtOH and water (10 mL), LiOH (0.425 g, 10 mmol) was added, and heated in a microwave reactor at 110 °C for 5 min. The pH was adjusted to 1 with HCl (12 M, 1.5 mL) and concentrated to dryness. The residue was suspended in a mixture of 1,2-dichloroethane (30 mL) and thionyl chloride (8 ml) and heated in a microwave reactor at 120 °C for 10 min, and concentrated to dryness. The residue was suspended in 1,2-dichloroethane (20 mL), cooled to 0 °C and c-propyl amine (0.70 mL, 3.54 mmol) was slowly added. The mixture was stirred at room temperature for 30 minutes and then partitioned between CH_2Cl_2 (50 mL) and HCl (1M, 30 mL). The layers were separated, dried, concentrated to dryness and the crude purified by silica gel

chromatography (linear gradient from CH_2Cl_2 to EtOAc) to afford **2l** (0.56 g, 60 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.48 (m, 1H), 7.17-7.04 (m, 3H), 7.03 (d, *J* = 3.9 Hz, 1H), 6.45 (s, 1H), 2.90 (dq, *J* = 3.5, 10.9 Hz, 1H), 2.67 (s, 3H), 2.57 (s, 3H), 1.01-0.80 (m, 3H), 0.77-0.60 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.63, 151.41, 141.77, 140.70, 138.43, 136.70, 129.50, 127.12, 126.03, 123.87, 123.44, 107.67, 23.45, 16.86, 14.49, 7.08; LC-MS > 98% purity; ES-MS *m/z* 312.1 $[M+H]^+$.

Compounds **2d** and **2s** were prepared used the same methodology described for **2a**

***N*-Cyclopropyl-5-(2,7-dimethyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2d)**. Off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 3.7, 4.3 Hz, 1H), 7.46 (d, *J* = 3.1 Hz, 1H), 7.20-7.13 (m, 1H), 7.07 (d, *J* = 3.9 Hz, 1H), 6.99-6.94 (m, 1H), 2.95-2.83 (m, 1H), 2.43 (s, 3H), 2.10 (s, 3H), 0.93-0.85 (m, 2H), 0.72-0.65 (m, 2H); ^{13}C NMR (101 MHz, DMSO) δ 162.46, 153.39, 143.03, 141.55, 141.11, 135.41, 130.47, 127.42, 125.72, 123.00, 121.63, 117.43, 23.58, 23.45, 17.07, 14.23, 6.46; LC-MS > 98% purity; ES-MS *m/z* 312.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(4-fluoro-2,6-dimethyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2s)**. Light yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ 7.75-7.75 (d, *J* = 4.0 Hz, 1H), 7.28-7.27 (d, *J* = 3.5 Hz, 1H), 6.92-6.87 (m, 2H), 2.88-2.85 (m, 1H), 2.53 (s, 3H), 2.42(s, 3H), 0.86-0.83 (m, 2H), 0.70-0.67 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 163.35, 153.24, 152.80, 151.24, 139.37, 139.34, 139.27, 139.06, 135.17, 135.12, 127.87, 127.73, 127.35, 127.14, 109.84, 109.70, 105.95, 105.92, 22.58, 20.23, 12.40, 5.17; LC-MS > 95% purity; ES-MS *m/z* 330.1 $[M+H]^+$.

***N*-Cyclopropyl-5-(4-chloro-6-fluoro-2-methyl-1*H*-benzo[*d*]imidazol-1-yl)thiophene-2-carboxamide (2u)**. A mixture of 5-nitrothiophene-2-carboxylic acid (9.91 g, 57.3 mmol) and thionyl chloride (15 mL, 20.6 mmol, 3.6 eq.) in 1,2-dichloroethane (30 mL) was refluxed for 6 h. The mixture was cooled to room temperature, and concentrated to dryness. The mixture was dissolved in 1,2-dichloroethane (50 mL), cooled to 0 °C and c-propyl amine (11 mL, 157 mmol, 3 eq.) was slowly added, allowed to warm to room temperature, and then concentrated to dryness. After purification by

silica gel chromatography (linear gradient from DCM to 5% EtOAc in CH_2Cl_2) *N*-cyclopropyl-5-nitrothiophene-2-carboxamide (10.3 g, 84% yield) was obtained as a yellow solid. The carboxamide (10.3 g, 48.5 mmol) and $Pd(OH)_2/C$ (20%, 10.3 g) in EtOH (250 mL) was hydrogenated under atmospheric pressure overnight. The solution was filtered through Celite and concentrated to dryness to give 5-amino *N*-cyclopropylthiophene-2-carboxamide (8.51 g, 96% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO) δ 7.86 (d, *J* = 3.7 Hz, 1H), 7.24 (t, *J* = 3.1 Hz, 1H), 6.17 (s, 2H), 5.78 (d, *J* = 4.0 Hz, 1H), 2.76-2.60 (m, 1H), 0.69-0.54 (m, 2H), 0.53-0.35 (m, 2H); LC-MS > 97% purity.

A mixture of *N*-(2-bromo-6-chloro-4-fluorophenyl)acetamide (0.24 g, 0.80 mmol) and 5-amino-*N*-cyclopropylthiophene-2-carboxamide (0.11 g, 0.60 mmol), Ruphos (0.052 mg, 0.11 mmol), $K_3PO_4 \cdot H_2O$ (0.44 g, 1.90 mmol), $Pd_2(dba)_3$ (37 mg, 0.04 mmol), molecular sieves (5 Å) in ^{t}BuOH (2 g) was heated at 120 °C in a microwave reactor for 4 hours. The mixture was diluted with EtOAc (30 mL), filtered, dried and purified by silica gel chromatography (linear from hexane to 50% EtOAc in hexane) to afford **2u** (17 mg, 8% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.12 (dt, *J* = 4.7, 9.3 Hz, 1H), 7.08 (d, *J* = 3.9 Hz, 1H), 6.85 (dd, *J* = 2.3, 7.9 Hz, 1H), 6.45 (s, 1H), 2.91 (dq, *J* = 3.5, 10.7 Hz, 1H), 2.59 (s, 3H), 0.97-0.81 (m, 2H), 0.77-0.54 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.28, 160.88, 158.45, 153.92, 138.68, 137.38, 137.24, 135.69, 126.88, 124.62, 124.50, 112.64, 112.36, 96.60, 96.32, 23.51, 14.20, 7.11; LC-MS > 99% purity; ES-MS *m/z* 350.8 $[M+H]^+$.

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