Discovery of aryl aminothiazole γ-secretase modulators with novel effects on amyloid β-peptide production

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Supplemental Information

Experimental Section:

Generation of HEK293 APP-C99 stably transfected cell line

The cDNA of APP-C99 with N-terminal signal peptide was cloned into pCMV6-AC-IRES-GFP-Puro (OriGene). After transfection of pCMV6-APP-C99-IRES-GFP-Puro into HEK293 cells for 48 hours, Puromycin selection was undertaken for 1 week. HEK293 APP-C99 stably transfected cell line were isolated via limiting dilution cloning and confirmed by western blots.

Tissue culture and transfection of adherent cells

Adherent HEK cells were cultured in complete growth media: Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, 10 units/mL penicillin, and 10 mg/mL streptomycin. For transfection, adherent HEK cells were seeded in 24-well plates at a density of $5x10^5$ cells per well. Transfection was carried out with jetPrime reagent (Polyplus Transfection SA, Illkrich, France). Cells were incubated for 24 h and media were changed for conditioning after another 12 h, at which time the conditioned media were harvested for ELISA, and the cells were harvested for western blots.

Aβ ELISA assay

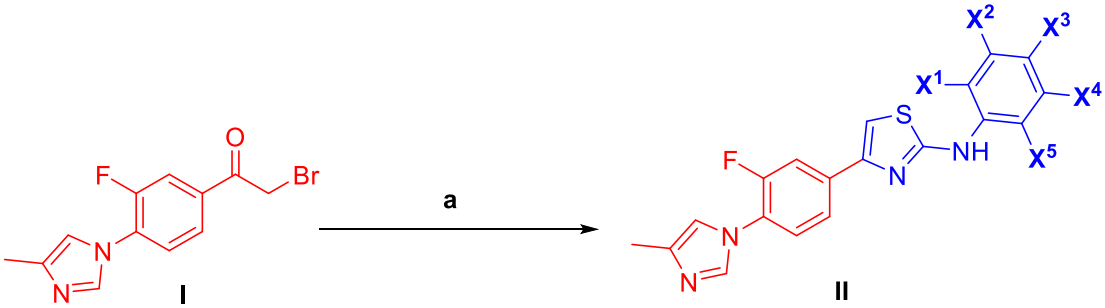
Conditioned media from transfected HEK cells were harvested and diluted with 1% BSA in wash buffer (TBS supplemented with 0.05% Tween). For Aβ 1-x, x-37, x-38, x-40, and x-42 assays, each well of an uncoated 96-well multi-array plate (Meso Scale Discovery, Rockville, MD #L15XA-3) was coated with 30 uL of a PBS solution containing 3 µg/mL of 266 capture antibody (Elan Pharmaceutical, Dublin, Ireland) and incubated at room temperature overnight. A detection antibody solution was prepared with biotinylated monoclonal antibody recognizing the respective C-terminal residue of each Aβ peptide, plus 100 ng/mL Streptavidin Sulfo-TAG (Meso Scale Discovery, Rockville, MD #R32AD-5) and 1% BSA diluted in wash buffer. Following overnight incubation, 50 µL/well of the CM sample plus 25 µL/ well of the detection antibody solution were incubated for 2 hr at room temperature with shaking at >300 rpm, washing wells with wash buffer between incubations. The plate was read and analyzed according to manufacturer's protocol.

General Chemistry

The Chemicals and solvents used for chemical synthesis were obtained from the various commercial vendors (e.g. Fischer, Acros, TCI America, and Sigma-Aldrich). All commercial building blocks and solvents used in the synthesis was used without further purification or drying and their purity was greater than 95%. Chemical reactions were monitored via thin layer chromatography (TLC) using aluminum sheets with silica gel 60 F_{254} (Merck). After the completion of reaction, the solvents was evaporated in rotovapor and then purified by column chromatography using silica gel 0.060-0.200 mm, pore diameter ca. 6 nm. High-resolution mass spectroscopy (HRMS) analysis was recorded on a LCT Premier mass spectrometer (Micromass Ltd., Manchester, UK), a quadrupole and time-of-flight tandem mass analyzer with an electrospray ion source. The purity analysis of synthesized intermediates as well as final target compounds were measured by an LC-MS instrument. For LC/ESI-MS measurement, samples were prepared by dissolving 1 mg/mL of compound in H_2O/MeOH (1:1) containing 2 mM ammonium acetate, 10 µL of which was injected for HPLC analysis, eluting with a gradient of water/methanol (containing 2 mM ammonium acetate) from 90:10 to 0:100 for 15 min at a flow rate of 250 µL/min. LC-MS analysis was performed using a Waters Analytical System-Acquity HPLC with an APCI mass spectrometer; UV absorption was detected using an Acquity diode array detector. ^{1}H and ^{13}C NMR spectra were performed on a Bruker Avance 500 and 400 MHz spectrometer and were recorded at ambient temperature using either DMSO-d_6, or $CDCl_3$ as solvent. Melting points were measured on Mel-Temp Digital apparatus and are reported without correction.

Experimental Methods

Table S1. Convergent synthesis of aminothiazole target compounds, D-ring substitution variants of lead compound **1**.



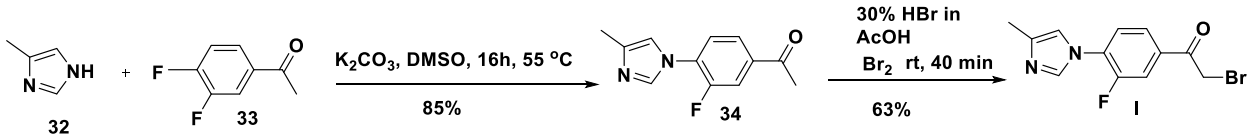
Target compounds **1-31** represented by structure **II** are phenyl-substituted derivatives excepts for **7**, **9** and **10**, which are benzyl, adamantyl- and cyclohexyl-substituted, respectively

Compd	X^1	X^2	X^3	X^4	X^5	Compd	X^1	X^2	X^3	X^4	X^5
1	CH_3	-	CH_3	C_2H_5	-	**17**	Cl	-	Cl	-	-
2	CH_3	-	CH_3	CH_3	-	**18**	F	-	-	F	-
3	F	-	F	F	-	**19**	F	-	-	-	F
4	-	-	OH	-	-	**20**	-	-	F	F	-
5	CH_3	-	CH_3	-	-	**21**	F	-	-	-	-
6	-		-		-	**22**	-	F	-	-	-
7			benzyl			**23**	-	-	F	-	-
8	-	-	nitro	-	-	**24**	F	-	CH_3	CH_3	
9			adamantly			**25**	CH_3	-	F	CH_3	-
10			cyclohexyl			**26**	CH_3	-	CH_3	F	-

11	Cl	-	Cl	Cl	-	**27**	F	-	CH_3	C_2H_5	-
12	Br	-	Br	-	Br	**28**	F	-	CH_3	-	-
13	F	F	F	-	-	**29**	CH_3	-	F	-	-
14	F	-	F	-	F	**30**	F	-	-	CH_3	-
15	F	F	-	-	-	**31**	CH_3	-	-	F	-
16	F	-	F	-	-						

[a]Reagents and conditions: (a) aromatic or alicyclic thiourea 0.9 eq. , 3 mL EtOH, reflux, 4 h (60-97%) . Detail method for the synthesis of intermediate **I** and thioureas needed for the synthesis of target compounds (**1**-**31**) explained below.

2-bromo-1-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)ethan-1-one (I)

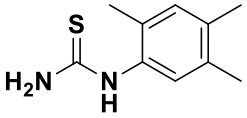
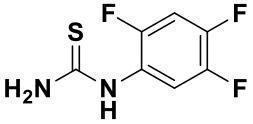
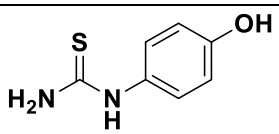
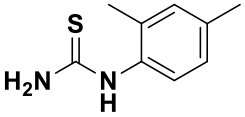
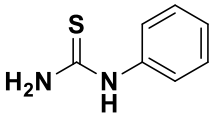
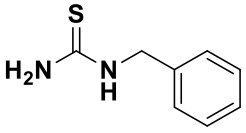
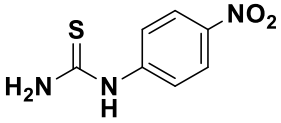
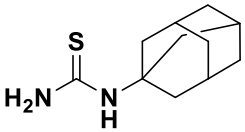
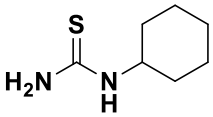
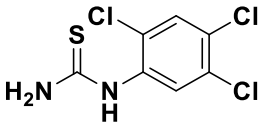


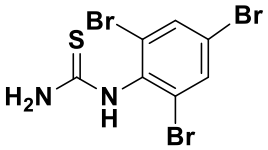
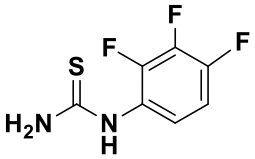
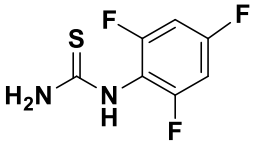
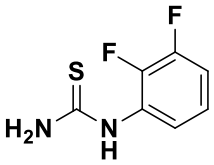
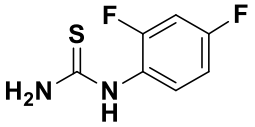
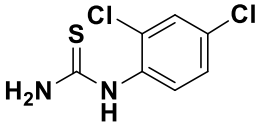
4-Methylimidazole (**32**, 2.0 g, 24.40 mmol) was suspended in DMSO (10 mL) then, potassium carbonate (6.74 g, 48.8 mmol) was added to the suspension. Next, 3,4-Difluoroacetophenone (**33**, 3.38 g, 21.96 mmol) was also added to the suspension and was heated to 60 °C for 4 h. The reaction was cooled to room temperature, then water (10 mL) was added, and the resulting mixture stirred for 1 h at room temperature. Finally, the resulting precipitate collected by filtration was vacuum dried and subjected to the column chromatography (ethyl acetate: hexane: 10: 90) afford compound **34** as an orange solid (yield 85%, 4.51 g). To compound **34** (2.0 g, 9.17 mmol) dissolved in ethyl acetate (10 mL), hydrogen bromide (0.8 mL, 33% solution in acetic acid) was added. To this mixture was added bromine [120 µL, 4.5 mmol, in ethyl acetate (10 mL)] drop-wise over 15 minutes at room temperature and it was stirred for an additional one hour. concentrated to ~1/4 volume under reduced pressure. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated using rota-vapor and subjected to the column chromatography (ethyl acetate: hexane: 10: 90) provided titled compound 2-bromo-1-(3-fluoro-4-(4-methyl-1*H*-imidazol-1-yl)phenyl)ethanone hydrobromide (**I**) as an orange-brown solid (1.196 g, 63%).

Synthesis of thioureas (35-65)

The thioureas needed for the synthesis of target compounds **1-31** are numbered as **35-65** respectively**.** Many of the thioureas are commercial available. The commercial available thoiureas are explained in the table below with CAS number.

Table S2. Structure and CAS number of the commercial available thioureas

Target compounds synthesized	Thioureas used in synthesis	Structure with CAS number
2	**36**	 117174-87-5
3	**37**	 1340519-84-7
4	**38**	 1520-27-0
5	**39**	 16738-20-8
6	**40**	 103-85-5
7	**41**	 621-83-0
8	**42**	 3696-22-8
9	**43**	 25444-82-0
10	**44**	 5055-72-1
11	**45**	 90617-76-8

12	**46**	 5337-47-3
13	**47**	 175205-26-2
14	**48**	 208173-23-3
15	**49**	 572889-25-9
16	**50**	 175277-76-6
17	**51**	 6326-14-3
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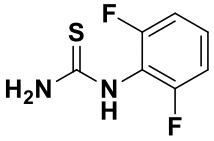
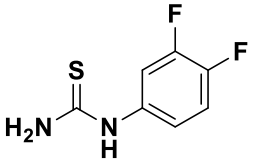
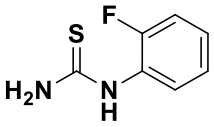
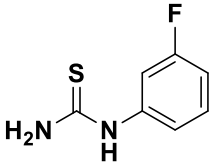
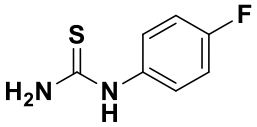
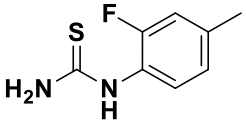
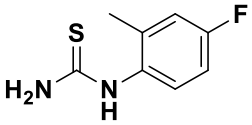
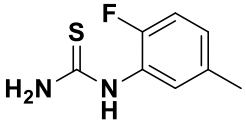
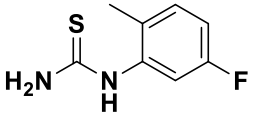
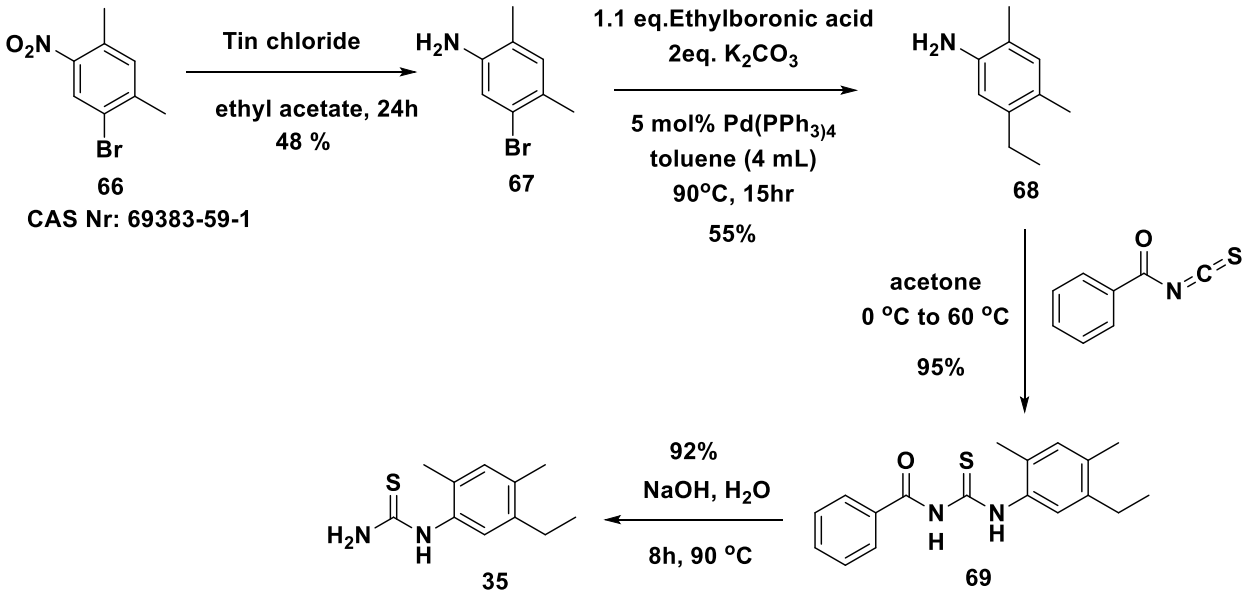
19	**53**	 59772-31-5
20	**54**	 883091-83-6

21	**55**	 656-32-6
22	**56**	 458-05-9
23	**57**	 459-05-2
28	**62**	 930396-09-1
29	**63**	 946612-94-8
30	**64**	 1038356-01-2
31	**65**	 16822-86-9

Synthesis of 1-(5-ethyl-2,4-dimethylphenyl)thiourea (35)



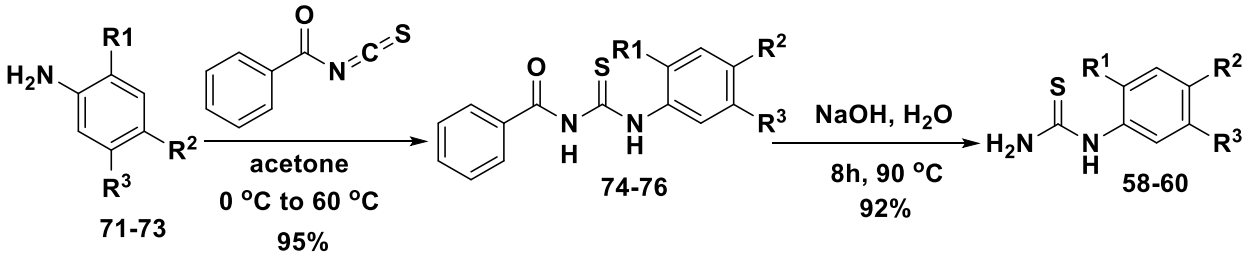
5-Bromo-2,4-dimethylaniline (67). 1-Bromo-2,4-dimethyl-5-nitrobenzene (2.0 g, 8.69 mmol) was suspended in ethyl acetate (10 mL). To the resulting suspension, tin (II) chloride (251 mg, 26.08 mmol) was added then further stirred at room temperature at 24 h. After completion of reaction as indicated by TLC, the reaction mixture was concentrated, and then saturated sodium bicarbonate solution (30 mL) was added, followed by extraction of organic layer with ethyl acetate (2 X 50 mL) and washing with brine (2 X 30 mL). The resulting crude was then subjected to the column chromatography (ethyl acetate: hexane: 5: 95) provided titled compound 5-bromo-2,4-dimethylaniline as an orange-brown solid (834 mg, 48 %).

5-Ethyl-2,4-dimethylaniline (68). To the solution of 5-Bromo-2,4-dimethylaniline **(67**, 800 mg, 3.99 mmol) and ethylboronic acid (443 mg, 6 mmol) in toluene (5 mL) was added K_2CO_3 (707.5 mg, 5.12 mmol), and $Pd(PPh_3)_4$ (138 mg, 0.12 mmol). The reaction mixture was heated at 90°C for 15h. After completion of reaction as indicated in TLC, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated in rota vapor. Thus obtained crude was purified by column chromatography ((ethyl acetate: hexane: 2: 98) to afford the titled compound (327 mg, 55%) as a white solid.

N-((5-ethyl-2,4-dimethylphenyl)carbamothioyl)benzamide (**69**). To a solution of 5-ethyl-2,4-dimethylaniline (**68**, 300 mg, 2.01 mmol) was added benzoyl isothiocyanate (**70**, 360 mg, 2.21 mmol) and acetone (20 mL) at 0°C. After 30 min, resulting mixture was heated 60 °C for 2 h, and the solvent removed under reduced pressure. The resulting white residue was purified by column chromatography (ethyl acetate: hexane: 2: 98) to afford the titled compound (596 mg, 95%) as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.81 – 7.76 (m, 2H), 7.58 – 7.49 (m, 4H), 7.08 (d, J = 1.1 Hz, 1H), 2.51 (qd, J = 8.0, 1.0 Hz, 2H), 2.17 (d, J = 17.8 Hz, 6H), 1.13 (t, J = 8.0 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 180.20, 165.43, 137.84, 136.26, 135.28, 134.87, 131.80, 129.99, 128.33, 128.01, 125.55, 121.66, 20.71, 19.84, 19.81, 18.01. HRMS (ESI) for $C_{18}H_{20}N_2OSNa$: Calculated: 335.1194, found: 335.1188; Purity by HPLC-UV (214 nm)-ESI-MS: 97.20%. mp 186-188 °C.

1-(5-ethyl-2,4-dimethylphenyl)thiourea (35). N-((5-ethyl-2,4-dimethylphenyl)carbamothioyl) benzamide (**69**,500 mg, 1.60 mmol) and sodium hydroxide (128 mg, 3.20 mmol) in water (5 mL) was heated at 90°C for 8 h, and then concentrated in vacuo. Thus obtained crude was dissolved in dichloromethane/water (20 mL each), then washed with brine (30 mL) and extracted with DCM (2 X 50 mL), again concentrated in vacuo and finally purified by column chromatography (ethyl acetate: hexane: 2: 98) to give white solid as titled compound (306 mg, 92%).

Synthesis of 1-(2-fluoro-4,5-dimethylphenyl)thiourea (58), 1-(4-fluoro-2,5-dimethylphenyl) thiourea (59) and 1-(5-fluoro-2,4-dimethylphenyl)thiourea (60)



Compound	R^1	R^2	R^3
71, 74, 58	F	CH_3	CH_3
72, 75, 59	CH_3	F	CH_3
73, 76, 60	CH_3	CH_3	F

General method for the synthesis of phenyl(carbamothioyl)benzamide (74-76)

To a solution of anilines (1 eqv) was added benzoyl isothiocyanate (**70**, 1.10 eqv) and acetone (20 mL) at 0°C. After 30 min, resulting mixture was heated 60 °C for 2 h, and the solvent removed under reduced pressure. The resulting white residue was purified by column chromatography (ethyl acetate: hexane: 2: 98) to afford the titled compounds (95%) as a white solids.

N-((2-fluoro-4,5-dimethylphenyl)carbamothioyl)benzamide (74). It was synthesized using 2-fluoro-4,5-dimethylaniline **(71**, 1.0 g, 7.18 mmol) and benzoyl isothiocyanate (**70**, 1.1 g, 7.90 mmol). Yield (2061 mg, 95%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.81 – 7.76 (m, 2H), 7.62 (d, J = 4.9 Hz, 1H), 7.58 – 7.49 (m, 3H), 6.99 (d, J = 7.9 Hz, 1H), 2.24 (d, J = 0.6 Hz, 3H), 2.20 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 180.23, 180.16, 165.43, 154.07, 152.39, 136.44, 136.42, 135.23, 135.18, 134.87, 131.80, 128.33, 128.01, 126.63, 126.49, 121.87, 121.82, 116.81, 116.67, 21.45, 20.19, 20.16. HRMS (ESI) for $C_{16}H_{15}FN_2OSNa$: Calculated: 325.0787, found: 325.0825; Purity by HPLC-UV (214 nm)-ESI-MS: 98.50%. mp 178-179 °C.

N-((4-fluoro-2,5-dimethylphenyl)carbamothioyl)benzamide (75). It was synthesized using 4-fluoro-2,5-dimethylaniline **(72**, 1.0 g, 7.18 mmol) and benzoyl isothiocyanate (**70**, 1.1 g, 7.90 mmol). Yield (2061 mg, 95%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.81 – 7.76 (m, 2H), 7.62 (d, J = 4.9 Hz, 1H), 7.58 – 7.49 (m, 3H), 6.99 (d, J = 7.9 Hz, 1H), 2.26 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 180.20, 165.43, 160.77, 159.09, 134.87, 133.27, 133.25, 131.80, 128.81, 128.76, 128.33, 128.01, 125.08, 124.95, 123.90, 123.85, 117.56, 117.42, 18.02, 18.00, 15.80, 15.76. HRMS (ESI) for $C_{16}H_{15}FN_2OSNa$: Calculated: 325.0787, found: 325.1281; Purity by HPLC-UV (214 nm)-ESI-MS: 96.00%. mp 177-179 °C.

N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide (76). It was synthesized using 5-fluoro-2,4-dimethylaniline **(73**, 1.0 g, 7.18 mmol) and benzoyl isothiocyanate (**70**, 1.1 g, 7.90

mmol). Yield (2061 mg, 95%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.81 – 7.76 (m, 2H), 7.58 – 7.48 (m, 5H), 7.15 – 7.11 (m, 1H), 2.24 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 180.20, 165.43, 159.73, 158.05, 135.15, 135.10, 134.87, 131.80, 129.93, 129.88, 128.33, 128.01, 125.80, 125.78, 120.55, 120.41, 112.10, 111.97, 18.01, 16.39, 16.35. HRMS (ESI) for $C_{16}H_{15}FN_2OSNa$: Calculated: 325.0787, found: 325.0781; Purity by HPLC-UV (214 nm)-ESI-MS: 97.50%. mp 176-178 °C.

General method for the synthesis of 1-(2-fluoro-4,5-dimethylphenyl)thiourea (58), 1-(4-fluoro-2,5-dimethylphenyl)thiourea (59) and 1-(5-fluoro-2,4-dimethylphenyl)thiourea (60)

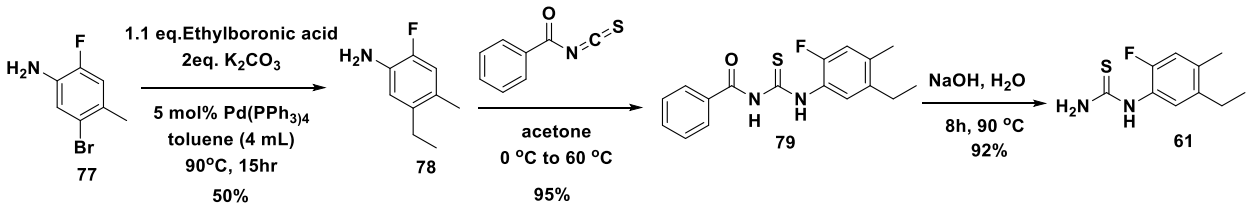
Phenyl(carbamothioyl)benzamide (1 eqv) and sodium hydroxide (2 eqv) in water (5 mL) was heated at 90^{o}C for 8 h, and then concentrated in vacuo. Thus obtained crude was dissolved in dichloromethane/water (20 mL each), then washed with brine (30 mL) and extracted with DCM (2 X 50 mL), again concentrated in vacuo and finally purified by column chromatography (ethyl acetate: hexane: 2: 98) to give white solid as titled compound (92%).

1-(2-Fluoro-4,5-dimethylphenyl)thiourea (58). It was synthesized using N-((2-fluoro-4,5-dimethylphenyl)carbamothioyl)benzamide **(74**, 1.0 g, 3.30 mmol) and sodium hydroxide (264 mg, 6.60 mmol). Yield (603 mg, 92%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.10 (s, 2H), 7.65 (d, J = 5.1 Hz, 1H), 6.99 (d, J = 7.9 Hz, 1H), 2.24 (d, J = 0.7 Hz, 3H), 2.20 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.45, 182.37, 153.00, 151.32, 136.61, 136.59, 135.07, 135.02, 125.79, 125.66, 121.11, 121.05, 116.92, 116.79, 21.45, 20.19, 20.16. HRMS (ESI) for $C_9H_{11}FN_2S$ Na: Calculated: 221.0525, found: 221.0635; Purity by HPLC-UV (214 nm)-ESI-MS: 97.00%. mp 171-172 °C.

1-(4-Fluoro-2,5-dimethylphenyl)thiourea (59). It was synthesized using N-((4-fluoro-2,5-dimethylphenyl)carbamothioyl)benzamide **(75**, 1.0 g, 3.30 mmol) and sodium hydroxide (264 mg, 6.60 mmol). Yield (603 mg, 92%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.10 (s, 2H), 7.65 (d, J = 5.0 Hz, 1H), 6.99 (d, J = 7.9 Hz, 1H), 2.26 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.41, 160.98, 159.30, 133.12, 133.10, 128.90, 128.85, 125.13, 125.00, 123.83, 123.78, 117.55, 117.42, 18.02, 18.00, 15.80, 15.76. HRMS (ESI) for $C_9H_{11}FN_2SNa$: Calculated: 221.0525, found: 221.0781; Purity by HPLC-UV (214 nm)-ESI-MS: 98.50%. mp 171-172 °C.

1-(5-Fluoro-2,4-dimethylphenyl)thiourea (60). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(76**, 1.0 g, 3.30 mmol) and sodium hydroxide (264 mg, 6.60 mmol). Yield (603 mg, 92%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.10 (s, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.15 – 7.11 (m, 1H), 2.24 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.41, 159.84, 158.16, 135.05, 135.00, 129.75, 129.69, 124.81, 124.79, 120.08, 119.95, 112.07, 111.93, 18.01, 16.39, 16.35. HRMS (ESI) for $C_9H_{11}FN_2SNa$: Calculated: 221.0525, found: 221.1127; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 171-172 °C.

Synthesis of 1-(5-ethyl-2-fluoro-4-methylphenyl)thiourea (61)



5-Ethyl-2-flouro-4-dmethylaniline (78). To the solution of 5-Bromo-2-flouro-4-methylaniline **(77**, 1000 mg, 4.90 mmol) and ethylboronic acid (543 mg, 7.35 mmol) in toluene (5 mL) was added K_2CO_3 (880 mg, 6.37 mmol), and $Pd(PPh_3)_4$ (283 mg, 0.24 mmol). The reaction mixture was heated at 90°C for 15h. After completion of reaction as indicated in TLC, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (2 × 30 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated in rota vapor. Thus obtained crude was purified by column chromatography ((ethyl acetate: hexane: 2: 98) to afford the titled compound (412 mg, 50%) as a white solid.

N-((5-Ethyl-2-fluoro-4-methylphenyl)carbamothioyl)benzamide (79). To a solution of 5-ethyl-2-flouro-4-dmethylaniline (**78**, 400 mg, 2.61 mmol) was added benzoyl isothiocyanate (**70**, 468 mg, 2.87 mmol) and acetone (20 mL) at 0°C. After 30 min, resulting mixture was heated 60 °C for 2 h, and the solvent removed under reduced pressure. The resulting white residue was purified by column chromatography (ethyl acetate: hexane: 2: 98) to afford the titled compound (784 mg, 95%) as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.81 – 7.76 (m, 2H), 7.64 (dt, J = 4.9, 1.0 Hz, 1H), 7.58 – 7.49 (m, 3H), 7.03 (d, J = 7.9 Hz, 1H), 2.51 (qd, J = 8.0, 1.0 Hz, 2H), 2.21 (s, 3H), 1.13 (t, J = 8.0 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 180.23, 180.16, 165.43, 153.20, 151.52, 139.57, 139.55, 134.96, 134.90, 134.87, 131.80, 128.33, 128.01, 126.93, 126.80, 120.81, 120.75, 116.89, 116.75, 20.71, 19.84, 19.82, 19.80. HRMS (ESI) for C17H17FN2OSNa: Calculated: 339.0944, found: 339.1020; Purity by HPLC-UV (214 nm)-ESI-MS: 99.0%. mp 191-193 °C.

1-(5-ethyl-2-fluoro-4-methylphenyl)thiourea (61). N-((5-Ethyl-2-fluoro-4-methylphenyl)carbamothioyl)benzamide (**79**, 500 mg, 1.58 mmol) and sodium hydroxide (126 mg, 3.16 mmol) in water (5 mL) was heated at 90°C for 8 h, and then concentrated in vacuo. Thus obtained crude was dissolved in dichloromethane/water (20 mL each), then washed with brine (30 mL) and extracted with DCM (2 X 50 mL), again concentrated in vacuo and finally purified by column chromatography (ethyl acetate: hexane: 2: 98) to give white solid as titled compound (308 mg, 92%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.10 (s, 2H), 7.67 (dt, J = 4.9, 1.0 Hz, 1H), 7.03 (d, J = 7.9 Hz, 1H), 2.51 (qd, J = 8.0, 1.0 Hz, 2H), 2.21 (s, 3H), 1.13 (t, J = 8.0 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 182.45, 182.37, 152.34, 150.66, 139.72, 139.70, 134.90, 134.85, 126.19, 126.06, 118.85, 118.80, 117.00, 116.86, 20.71, 19.84, 19.82, 19.80. HRMS (ESI) for $C_{10}H_{13}FN_2SNa$: Calculated: 235.0681, found: 235.0678; Purity by HPLC-UV (214 nm)-ESI-MS: 98.0%. mp 197-199 °C.

General method for the synthesis of aminothiazole target compounds (1-31). A solution of 2-bromo-1-(3-fluoro-4-(4-methyl-1*H*-imidazol-1-yl)phenyl)ethanone (**I**, 100 mg, 1 eqv.) and corresponding thioureas (**35-65**,1 eqv) was stirred in absolute ethanol (8 mL) and reflux for 4 h. After the completion of reaction as indicated in TLC, the reaction mixture was cooled to room temperature and the solvent removed by rota vapor. The residue was finally purified by column chromatography (DCM: methanol: 2.5: 97.5) to yield solid as titled compound (60-97%).

N-(5-Ethyl-2,4-dimethylphenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (1). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(5-ethyl-2,4-dimethylphenyl)thiourea (**35**, 70.80 mg, 0.34 mmol). Yield (125 mg, 92%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.35 (t, *J* = 1.0 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.01 (d, *J* = 0.9 Hz, 1H), 2.51 (qd, *J* = 8.0, 1.0 Hz, 2H), 2.37 (d, *J* = 0.7 Hz, 3H), 2.16 (d, *J* = 16.0 Hz, 6H), 1.13 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 137.11, 136.79, 135.43, 130.39, 130.33, 129.90, 128.33, 126.97, 126.84, 124.37, 124.32, 122.64, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 110.94, 20.71, 19.84, 19.81, 18.01, 12.89. HRMS (ESI) for $C_{23}H_{23}FN_4SNa$: Calculated: 429.1525, found: 429.1532; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 201-203 °C.

4-(3-Fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(2,4,5-trimethylphenyl)thiazol-2-amine (2). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,4,5-trimethylphenyl)thiourea (**36**, 66.05 mg, 0.34 mmol). Yield (129 mg, 98%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.33 (s, 1H), 7.22 – 7.16 (m, 2H), 6.97 (s, 1H), 2.37 (d, *J* = 0.7 Hz, 3H), 2.23 – 2.16 (m, 9H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 136.00, 134.96, 134.74, 130.39, 130.33, 129.31, 129.25, 126.97, 126.84, 124.37, 124.32, 122.63, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 110.94, 21.45, 20.17, 18.01, 12.89.HRMS (ESI) for $C_{22}H_{21}FN_4SNa$: Calculated: 415.1369, found: 415.1562; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 203-205 °C.

4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(2,4,5-trifluorophenyl)thiazol-2-amine (3). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,4,5-trifluorophenyl)thiourea (**37**, 70.10 mg, 0.34 mmol). Yield (120 mg, 88%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.46 (dt, *J* = 8.0, 5.0 Hz, 1H), 7.45 (s, 1H), 7.22 – 7.16 (m, 2H), 7.03 (td, *J* = 8.0, 5.0 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.16, 154.91, 153.48, 151.16, 151.14, 147.80, 147.29, 140.73, 140.65, 137.19, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 122.63, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 114.00, 110.94, 105.46, 12.89. HRMS (ESI) for $C_{19}H_{12}F_4N_4SNa$: Calculated: 427.0617, found: 427.0781; Purity by HPLC-UV (214 nm)-ESI-MS: 97.00%. mp 195-196 °C.

4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(2,4,5-trifluorophenyl)thiazol-2-amine (4). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(4-hydroxyphenyl)thiourea (**38**, 57.19 mg, 0.34 mmol). Yield (73.93 mg, 62 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.07 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.43 – 7.38 (m, 2H), 7.22 – 7.16 (m, 2H), 6.89 – 6.84 (m, 2H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.75, 157.35, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 135.98, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 124.00, 122.03, 122.01, 116.48, 116.35, 115.75, 115.02, 114.94, 110.94, 12.89. HRMS (ESI) for C19H15FN4OSNa: Calculated: 389.0849, found: 389.0912; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 191-192 °C.

N-(2,4-dimethylphenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (5). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,4-dimethylphenyl)thiourea (**39**, 61.29 mg, 0.34 mmol). Yield (118.70 mg, 95 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.24 – 7.19 (m, 2H), 7.19 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.95 (dq, *J* = 7.4, 0.8 Hz, 1H), 6.91 (t, *J* = 1.2 Hz, 1H), 2.37 (d, *J* = 0.6 Hz, 3H), 2.21 (s, 2H), 2.16 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65,

137.72, 137.19, 133.46, 131.78, 130.39, 130.33, 128.77, 127.00, 126.97, 126.84, 124.37, 124.32, 122.82, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 110.94, 20.97, 18.17, 12.89. HRMS (ESI) for $C_{21}H_{19}FN_4SNa$: Calculated: 401.1212, found: 401.1418; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 203-204 °C.

4-(3-Fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-phenylthiazol-2-amine (6). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-phenylthiourea (**40**, 51.75 mg, 0.34 mmol). Yield (105 mg, 89 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.59 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.45 (s, 1H), 7.30 – 7.23 (m, 2H), 7.22 – 7.16 (m, 2H), 7.00 (tt, *J* = 7.5, 1.5 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.75, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 139.30, 137.19, 130.39, 130.33, 129.19, 126.97, 126.84, 124.37, 124.32, 123.09, 122.03, 122.01, 121.56, 116.48, 116.35, 115.02, 114.94, 110.94, 12.89. HRMS (ESI) for $C_{19}H_{15}FN_4SNa$: Calculated: 373.0899, found: 373.0913; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 204-205 °C.

N-Benzyl-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (7). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-benzylthiourea (**41**, 56.50 mg, 0.34 mmol). Yield (112.70 mg, 92 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.35 – 7.30 (m, 2H), 7.30 – 7.24 (m, 1H), 7.22 – 7.16 (m, 2H), 7.07 (s, 1H), 5.28 (t, *J* = 7.6 Hz, 1H), 4.63 (dt, *J* = 7.5, 1.0 Hz, 2H), 2.37 (d, *J* = 0.6 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.16, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 138.94, 137.19, 130.39, 130.33, 128.81, 127.42, 127.15, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 110.94, 46.47, 12.89. HRMS (ESI) for $C_{20}H_{17}FN_4SNa$: Calculated: 387.1056, found: 387.1120; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 206-207 °C.

4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(4-nitrophenyl)thiazol-2-amine (8). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(4-nitrophenyl)thiourea (**42**, 67 mg, 0.34 mmol). Yield (115.60 mg, 87%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.92 (s, 1H), 8.11 – 8.07 (m, 2H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 7.8, 1.4 Hz, 3H), 7.45 (s, 1H), 7.22 – 7.16 (m, 2H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.75, 155.16, 153.48, 151.16, 151.14, 142.78, 141.23, 140.73, 140.65, 137.19, 130.39, 130.33, 126.97, 126.84, 124.78, 124.37, 124.32, 122.03, 122.01, 120.13, 116.48, 116.35, 115.02, 114.94, 110.94, 12.89. HRMS (ESI) for $C_{19}H_{14}FN_5O_2SNa$: Calculated: 418.0750, found: 418.0812; Purity by HPLC-UV (214 nm)-ESI-MS: 98.00%. mp 203-204 °C.

4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(4-nitrophenyl)thiazol-2-amine (9). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(4-nitrophenyl)thiourea (**43**, 71.40 mg, 0.34 mmol). Yield (89.29 mg, 65%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.07 (s, 1H), 4.40 (s, 1H), 2.37 (d, *J* = 0.6 Hz, 3H), 2.14 – 2.04 (m, 9H), 1.62 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.79, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 110.94, 51.79, 42.08, 36.21, 29.42, 12.89. HRMS (ESI) for $C_{23}H_{25}FN_4SNa$: Calculated: 431.1682, found: 431.1732; Purity by HPLC-UV (214 nm)-ESI-MS: 96.00%. mp 191-192 °C.

N-Cyclohexyl-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (10). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-cyclohexylthiourea (**44**, 53.80 mg, 0.34 mmol). Yield (88.70 mg, 74%). ^{1}H NMR (600

MHz, DMSO-d_6) δ 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.07 (s, 1H), 4.90 (d, *J* = 9.7 Hz, 1H), 3.24 (dp, *J* = 9.7, 7.0 Hz, 1H), 2.37 (d, *J* = 0.6 Hz, 3H), 1.70 – 1.60 (m, 2H), 1.50 – 1.45 (m, 1H), 1.47 – 1.41 (m, 2H), 1.44 – 1.33 (m, 6H). ^{13}C NMR (150 MHz, Common NMR Solvents) δ 164.34, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 110.94, 50.87, 32.62, 25.10, 24.67, 12.89. HRMS (ESI) for $C_{19}H_{21}FN_4SNa$: Calculated: 379.1369, found: 379.1423; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 199-200 °C.

4-(3-Fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(2,4,5-trichlorophenyl)thiazol-2-amine (11). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,4,5-trichlorophenyl)thiourea (**45**, 86.80 mg, 0.34 mmol). Yield (129.80 mg, 85%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.67 (s, 1H), 7.62 – 7.57 (m, 2H), 7.45 (s, 1H), 7.22 – 7.16 (m, 2H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 134.91, 130.90, 130.39, 130.33, 128.54, 127.74, 126.97, 126.84, 125.69, 124.37, 124.32, 122.47, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 110.94, 12.89. HRMS (ESI) for $C_{19}H_{12}Cl_3FN_4SNa$: Calculated: 474.9730, found: 475.9830; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 196-197 °C.

4-(3-Fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(2,4,6-tribromophenyl)thiazol-2-amine (12). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,4,6-tribromophenyl)thiourea (**46**, 131.16 mg, 0.34 mmol). Yield (126.40 mg, 64%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.61 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.70 (s, 2H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.22 – 7.16 (m, 2H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.76, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.83, 137.19, 133.57, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 116.48, 116.35, 115.77, 115.02, 114.94, 114.58, 110.94, 12.89. HRMS (ESI) for $C_{19}H_{12}Br_3FN_4SNa$: Calculated: 606.8215, found: 606.7258; Purity by HPLC-UV (214 nm)-ESI-MS: 98.00%. mp 193-194 °C.

4-(3-Fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(2,3,4-triflourophenyl)thiazol-2-amine (13). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,3,4-trifluorophenyl)thiourea (**47**, 70.10 mg, 0.34 mmol). Yield (120 mg, 88%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.46 (dt, *J* = 8.0, 5.0 Hz, 1H), 7.45 (s, 1H), 7.22 – 7.16 (m, 2H), 7.03 (td, *J* = 8.0, 5.0 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.16, 154.91, 153.48, 151.16, 151.14, 147.80, 147.29, 140.73, 140.65, 137.19, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 122.63, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 114.00, 110.94, 105.46, 12.89. HRMS (ESI) for $C_{19}H_{12}F_4N_4SNa$: Calculated: 427.0617, found: 427.0781; Purity by HPLC-UV (214 nm)-ESI-MS: 97.00%. mp 195-196 °C.

4-(3-Fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(2,4,6-trifluorophenyl)thiazol-2-amine (14). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,4,6-trifluorophenyl)thiourea (**48**, 70.10 mg, 0.34 mmol). Yield (118 mg, 87%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.22 – 7.16 (m, 2H), 6.73 (td, *J* = 7.7, 0.9 Hz, 2H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.76, 157.44, 156.44, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 117.75, 116.48, 116.35, 115.02, 114.94, 110.94, 104.57, 12.89. HRMS (ESI) for $C_{19}H_{12}F_4N_4SNa$: Calculated: 427.0617, found: 427.0824; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 197-199 °C.

N-(2,3-difluorophenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (15). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,3-difluorophenyl)thiourea (**49**, 63.90 mg, 0.34 mmol). Yield (109.80 mg, 85%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.82 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.28 (ddd, *J* = 7.6, 5.0, 1.6 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.06 (td, *J* = 7.5, 4.9 Hz, 1H), 6.90 (tdd, *J* = 7.7, 4.9, 1.4 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.16, 153.48, 152.53, 151.16, 151.14, 149.79, 140.73, 140.65, 137.19, 130.39, 130.33, 128.85, 128.34, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 120.01, 116.48, 116.35, 115.02, 114.94, 112.59, 110.94, 12.89. HRMS (ESI) for $C_{19}H_{13}F_3N_4SNa$: Calculated: 409.0711, found: 409.0825; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 193-194 °C.

N-(2,4-difluorophenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (16). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,4-difluorophenyl)thiourea (**50**, 63.90 mg, 0.34 mmol). Yield (109.80 mg, 85%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.32 (dt, *J* = 7.5, 5.0 Hz, 1H), 7.22 – 7.16 (m, 2H), 6.96 (td, *J* = 8.0, 1.5 Hz, 1H), 6.86 (td, *J* = 7.9, 1.6 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H).^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 159.31, 156.83, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 123.73, 123.16, 122.03, 122.01, 116.48, 116.35, 115.02, 114.99, 114.94, 110.94, 105.50, 12.89. HRMS (ESI) for $C_{19}H_{13}F_3N_4SNa$: Calculated: 409.0711, found: 409.1221; Purity by HPLC-UV (214 nm)-ESI-MS: 98.00%. mp 194-195 °C.

N-(2,4-Dichlorophenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (17). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,4-dichlorophenyl)thiourea (**51**, 75.10 mg, 0.34 mmol). Yield (98.40 mg, 70%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.74 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.31 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.22 – 7.16 (m, 2H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 136.00, 131.15, 130.39, 130.36, 130.33, 129.51, 127.81, 126.97, 126.84, 125.34, 124.37, 124.32, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 110.94, 12.89. HRMS (ESI) for $C_{19}H_{13}Cl_2FN_4SNa$: Calculated: 441.0120, found: 441.1123; Purity by HPLC-UV (214 nm)-ESI-MS: 97.00%. mp 197-198 °C.

N-(2,5-difluorophenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (18). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,5-difluorophenyl)thiourea (**52**, 63.90 mg, 0.34 mmol). Yield (109.80 mg, 85%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.22 – 7.13 (m, 3H), 6.81 (tdd, *J* = 7.7, 4.9, 1.4 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 160.77, 156.09, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 130.39, 130.33, 129.21, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 117.26, 116.48, 116.35, 115.02, 114.94, 113.20, 110.94, 109.99, 12.89. HRMS (ESI) for $C_{19}H_{13}F_3N_4SNa$: Calculated: 409.0711, found: 409.0336; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 194-195 °C.

N-(2,6-difluorophenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (19). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2,6-difluorophenyl)thiourea (**53**, 63.90 mg, 0.34 mmol). Yield (109.80 mg, 85%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.01 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.22 – 7.16 (m, 2H), 7.11 (tt, *J* = 7.5, 5.1 Hz, 1H), 6.88 (td, *J* = 7.5, 1.1 Hz, 2H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.76, 157.19,

155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 130.39, 130.33, 128.95, 126.97, 126.84, 124.37, 124.32, 122.81, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 114.26, 110.94, 12.89. HRMS (ESI) for $C_{19}H_{13}F_3N_4SNa$: Calculated: 409.0711, found: 409.0825; Purity by HPLC-UV (214 nm)-ESI-MS: 98.00%. mp 194-195 °C.

N-(3,4-difluorophenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (20). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(3.4-difluorophenyl)thiourea (**54**, 63.90 mg, 0.34 mmol). Yield (109.80 mg, 85%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.38 (td, *J* = 7.7, 4.9 Hz, 1H), 7.32 (ddd, *J* = 8.0, 5.0, 1.5 Hz, 1H), 7.22 – 7.16 (m, 3H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.75, 155.16, 153.48, 151.16, 151.14, 149.01, 148.09, 140.73, 140.65, 137.19, 135.76, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 119.49, 116.60, 116.48, 116.35, 115.02, 114.94, 110.94, 107.78, 12.89. HRMS (ESI) for $C_{19}H_{13}F_3N_4SNa$: Calculated: 409.0711, found: 409.0721; Purity by HPLC-UV (214 nm)-ESI-MS: 98.00%. mp 192-193 °C.

N-(2-Fluorophenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (21). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(2-fluorophenyl)thiourea (**55**, 57.80 mg, 0.34 mmol). Yield (104.80 mg, 84%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.47 (ddd, *J* = 7.4, 5.0, 1.4 Hz, 1H), 7.45 (s, 1H), 7.22 – 7.16 (m, 2H), 7.15 – 7.07 (m, 2H), 6.96 (tdd, *J* = 7.6, 5.1, 1.5 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 157.52, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 130.39, 130.33, 128.77, 127.49, 126.97, 126.84, 126.75, 124.37, 124.32, 123.36, 122.69, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 110.94, 12.89. HRMS (ESI) for $C_{19}H_{14}F_2N_4SNa$: Calculated: 391.0805, found: 391.0921; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 198-199 °C.

N-(3-Fluorophenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (22). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(3-fluorophenyl)thiourea (**56**, 57.80 mg, 0.34 mmol). Yield (104.80 mg, 84%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.52 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.45 (s, 1H), 7.39 (dt, *J* = 7.4, 1.5 Hz, 1H), 7.27 (td, *J* = 7.5, 4.9 Hz, 1H), 7.22 – 7.16 (m, 2H), 6.66 (tt, *J* = 7.7, 1.5 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.95, 162.75, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 138.38, 137.19, 130.40, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 118.25, 116.48, 116.35, 115.02, 114.94, 110.94, 110.78, 110.31, 12.89. HRMS (ESI) for $C_{19}H_{14}F_2N_4SNa$: Calculated: 391.0805, found: 391.0854; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 197-196 °C.

N-(4-Fluorophenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (23). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide **(I**, 100 mg, 0.34 mmol) and 1-(3-fluorophenyl)thiourea (**57**, 57.80 mg, 0.34 mmol). Yield (104.80 mg, 84%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.09 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.41 – 7.36 (m, 2H), 7.27 – 7.19 (m, 3H), 7.19 (dd, *J* = 7.6, 1.4 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.75, 160.63, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.97, 137.19, 130.39, 130.33, 126.97, 126.84, 125.87, 124.37, 124.32, 122.03, 122.01, 116.47, 116.35, 115.02, 114.94, 110.94, 12.89. HRMS (ESI) for $C_{19}H_{14}F_2N_4SNa$: Calculated: 391.0805, found: 391.0264; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 196-197 °C.

N-(2-Fluoro-4,5-dimethylphenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (24). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide (**I**, 100 mg, 0.34 mmol) and 1-(2-fluoro-4,5-dimethylphenyl)thiourea (**58**, 67.40 mg, 0.34 mmol). Yield (104.80 mg, 84%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.41 (d, *J* = 4.8 Hz, 1H), 7.22 – 7.16 (m, 2H), 6.93 (d, *J* = 7.9 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H), 2.24 (d, *J* = 0.7 Hz, 3H), 2.20 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.20, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 135.86, 134.88, 130.39, 130.33, 128.04, 126.97, 126.84, 124.37, 124.32, 122.15, 122.03, 122.01, 116.48, 116.35, 116.25, 115.02, 114.94, 110.94, 21.45, 20.17, 12.89. HRMS (ESI) for $C_{21}H_{18}F_2N_4SNa$: Calculated: 392.1118, found: 392.1231; Purity by HPLC-UV (214 nm)-ESI-MS: 98.00%. mp 207-208 °C.

N-(4-Fluoro-2,5-dimethylphenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (25). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide (**I**, 100 mg, 0.34 mmol) and 1-(4-fluoro-2,5-dimethylphenyl)thiourea (**59**, 67.40 mg, 0.34 mmol). Yield (104.80 mg, 84%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.41 (d, *J* = 4.8 Hz, 1H), 7.22 – 7.16 (m, 2H), 6.93 (d, *J* = 7.9 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H), 2.26 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 159.40, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 133.69, 130.39, 130.33, 129.24, 126.97, 126.84, 125.10, 124.37, 124.32, 123.76, 122.03, 122.01, 117.66, 116.48, 116.35, 115.02, 114.94, 110.94, 18.01, 15.78, 12.89. HRMS (ESI) for $C_{21}H_{18}F_2N_4SNa$: Calculated: 392.1118, found: 392.1354; Purity by HPLC-UV (214 nm)-ESI-MS: 98.00%. mp 206-207 °C.

N-(5-Fluoro-2,4-dimethylphenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (26). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide (**I**, 100 mg, 0.34 mmol) and 1-(5-fluoro-2,3-dimethylphenyl)thiourea (**60**, 67.40 mg, 0.34 mmol). Yield (104.80 mg, 84%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.41 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.07 – 7.04 (m, 1H), 2.37 (d, *J* = 0.7 Hz, 3H), 2.24 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 158.51, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 135.57, 130.39, 130.33, 130.23, 128.26, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 120.65, 116.48, 116.35, 115.02, 114.94, 113.08, 110.94, 18.01, 16.37, 12.89. HRMS (ESI) for $C_{21}H_{18}F_2N_4SNa$: Calculated: 392.1118, found: 392.1905; Purity by HPLC-UV (214 nm)-ESI-MS: 96.00%. mp 206-207 °C.

N-(5-Ethyl-2-fluoro-4-methylphenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (27). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide (**I**, 100 mg, 0.34 mmol) and 1-(5-ethyl-2-fluoro-4-methylphenyl)thiourea (**61**, 72.0 mg, 0.34 mmol). Yield (192 mg, 72%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.29 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.22 – 7.16 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 1H), 2.51 (qd, *J* = 8.0, 1.0 Hz, 2H), 2.37 (d, *J* = 0.7 Hz, 3H), 2.21 (s, 3H), 1.13 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.16, 154.49, 153.48, 151.16, 151.14, 140.73, 140.65, 138.56, 137.19, 135.11, 130.39, 130.33, 128.36, 126.97, 126.84, 124.37, 124.32, 122.11, 122.03, 122.01, 116.52, 116.48, 116.35, 115.02, 114.94, 110.94, 20.71, 19.84, 19.81, 12.89. HRMS (ESI) for $C_{22}H_{20}F_2N_4SNa$: Calculated: 433.1275, found: 433.1183; Purity by HPLC-UV (214 nm)-ESI-MS: 97.00%. mp 209-210 °C.

4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(2-fluoro-4-methylphenyl)thiazol-2-amine (28). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide (**I**, 100 mg, 0.34 mmol) and 1-(2-fluoro-4-methylphenyl)thiourea (**62**, 62.50 mg, 0.34 mmol). Yield

(113 mg, 88%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.27 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.22 – 7.16 (m, 2H), 6.97 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.89 (dq, *J* = 7.5, 0.8 Hz, 1H), 2.37 (d, *J* = 0.6 Hz, 3H), 2.29 (d, *J* = 1.6 Hz, 1H), 2.29 (s, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 155.16, 154.91, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 134.43, 130.39, 130.33, 126.97, 126.84, 126.43, 125.41, 124.37, 124.32, 122.97, 122.03, 122.01, 118.06, 116.48, 116.35, 115.02, 114.94, 110.94, 20.93, 12.89. HRMS (ESI) for $C_{20}H_{16}F_2N_4SNa$: Calculated: 405.0898, found: 405.0762; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 208-209 °C.

N-(4-fluoro-2-methylphenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (29). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide (**I**, 100 mg, 0.34 mmol) and 1-(4-flouro-2-methylphenyl)thiourea (**63**, 62.50 mg, 0.34 mmol). Yield (113 mg, 88%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.27 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.00 – 6.96 (m, 1H), 6.94 (td, *J* = 7.6, 1.4 Hz, 1H), 2.37 (d, *J* = 0.7 Hz, 3H), 2.20 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 161.12, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 132.48, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 123.09, 122.03, 122.01, 117.26, 116.48, 116.35, 115.56, 115.02, 114.94, 110.94, 18.01, 12.89. HRMS (ESI) for $C_{20}H_{16}F_2N_4SNa$: Calculated: 405.0898, found: 405.1145; Purity by HPLC-UV (214 nm)-ESI-MS: 98.00%. mp 207-208 °C.

4-(3-Fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)-N-(2-fluoro-5-methylphenyl)thiazol-2-amine (30). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide (**I**, 100 mg, 0.34 mmol) and 1-(2-fluoro-5-methylphenyl)thiourea (**64**, 62.50 mg, 0.34 mmol). Yield (113 mg, 88%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.45 (s, 1H), 7.22 – 7.16 (m, 2H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.89 – 6.84 (m, 1H), 2.37 (d, *J* = 0.6 Hz, 3H), 2.29 (d, *J* = 1.5 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.55, 157.31, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 134.49, 130.39, 130.33, 129.82, 127.51, 126.97, 126.84, 124.37, 124.32, 123.66, 122.03, 122.01, 116.82, 116.48, 116.35, 115.02, 114.94, 110.94, 20.65, 12.89. HRMS (ESI) for $C_{20}H_{16}F_2N_4SNa$: Calculated: 405.0898, found: 405.4129; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 206-207 °C.

N-(5-Fluoro-2-methylphenyl)-4-(3-fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl)thiazol-2-amine (31). It was synthesized using N-((5-fluoro-2,4-dimethylphenyl)carbamothioyl)benzamide (**I**, 100 mg, 0.34 mmol) and 1-(5-fluoro-2-methylphenyl)thiourea (**64**, 62.50 mg, 0.34 mmol). Yield (113 mg, 88%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.88 (s, 1H), 7.81 (dd, *J* = 7.5, 5.1 Hz, 1H), 7.59 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (s, 1H), 7.34 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.22 – 7.13 (m, 3H), 6.77 – 6.72 (m, 1H), 2.37 (d, *J* = 0.7 Hz, 3H), 2.32 (d, *J* = 1.1 Hz, 3H). ^{13}C NMR (150 MHz, Common NMR Solvents) δ 162.55, 161.16, 155.16, 153.48, 151.16, 151.14, 140.73, 140.65, 137.19, 136.77, 134.66, 130.88, 130.39, 130.33, 126.97, 126.84, 124.37, 124.32, 122.03, 122.01, 116.48, 116.35, 115.02, 114.94, 110.94, 109.27, 106.04, 17.61, 12.89. HRMS (ESI) for $C_{20}H_{16}F_2N_4SNa$: Calculated: 405.0898, found: 405.1643; Purity by HPLC-UV (214 nm)-ESI-MS: 99.00%. mp 205-206 °C.