JOTCS A
Journal of the Turkish Chemical Society
Section: A
Chemistry
TURKISH CHEMICAL SOCIETY

Supplementary Document to

Synthesis of Thiazole Derivatives as Antimicrobial Agents by Green Chemistry Techniques

By

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MATERIALS AND METHODS

All the chemicals were purchased from *Fluka Chemie AG Buchs* (Switzerland) and used without further purification. Melting points of the synthesised compounds were determined in open capillaries on a Büchi B-540 melting point apparatus and are uncorrected. Reactions were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 aluminium sheets. The mobile phase was ethyl acetate: diethyl ether (1:1), and detection was made using UV light. FT-IR spectra were recorded using a *Perkin Elmer* 1600 series FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were registered in DMSO-d_6 on a *BRUKER AVENE II* 400 MHz NMR Spectrometer (400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C). The chemical shifts are given in ppm relative to Me_4Si as an internal reference, *J* values are given in Hz. Microwave and ultrasound mediated syntheses were carried out using monomode CEM-Discover microwave apparatus and Bandelin Sonorex Super RK102H ultrasonic bath, respectively. The elemental analysis was performed on *a Costech Elemental Combustion System* CHNS-O elemental analyser. All the compounds gave C, H and N analysis within ±0.4% of the theoretical values. The Mass spectra were obtained on a *Quattro LC-MS* (70 eV) Instrument.

General method for the preparation of compounds 2, 26

(2-Fluoro-4-nitrophenyl)-[3-(1*H*-imidazol-1-yl)propyl] amine (2).

Recrystallised from ethyl acetate; Yield: 62% (Method 1), 81% (Method 2), 83% (Method 3), mp. 135-136 °C; FT-IR (υ_{max}, cm^{-1}): 3400 (NH), 3072 (ar-H), 1483, 1330 (NO_2); ^{1}H NMR (DMSO-d_6,δ ppm): 1.98-2.07 (m, 2H, CH_2), 3.19 (t, 2H, CH_2, *J*=8.0 Hz), 4.05 (t, 2H, CH_2, *J*=4.0 Hz), 6.77 (d, 1H, ar-H, *J*=8.0), 6.90 (bs, 2H, ar-H), 7.20 (bs, 1H, ar-H), 7.65 (bs, 1H, ar-H), 7.89-7.97 (m, 1H, ar-H); ^{13}C-NMR (400 MHz, DMSO-d_6) δppm: 30.10 (CH_2), 44.15 ($2CH_2$), 109.93 (d, CH, *J*=5.0 Hz), 114.24 (CH), 119.78 (CH), 122.80 (CH), 123.10 (CH), 135.12 (C), 137.78 (CH), 143.79 and 147.70 (d, C, $J_{C\text{-}F}$=391.0 Hz), 150.11 (C); EI-MS: 266.23 ([M+2]$^{+}$, 20), 265.28 ([M+1]$^{+}$, 100); Elemental

Analysis for $C_{12}H_{13}FN_4O_2$; Calculated (%): C, 54.54; H, 4.96; N, 21.20; Found (%): C, 54.24; H, 4.92; N, 21.24.

2-Fluoro-*N*-(2-morpholinoethyl)-4-nitroaniline (26).

Recrystallised from ethanol; Yield: 60% (Method 1), 92% (Method 2), 90% (Method 3); mp. 88-89 °C; FT-IR ($\upsilon_{max,}$ cm^{-1}): 3272 (NH), 2946 (ar-CH), 15313, 1329 (NO_2); ^{1}H NMR (DMSO-d_6, δ ppm): 2.51-2.54 (m, 4H, $2CH_2$), 3.57 (t, 4H, $2CH_2$, *J*=4.4 Hz), 3.57 (t, 4H, $2CH_2$, *J*=8.3 Hz), 6.81-6.90 (m, 2H, ar-H), 7.23 (d, 1H, ar-H, *J*=8.3 Hz), 7.35 (bs, 1H, ar-H), 8.52 (s, 1H, NH, D_2O exch.), 9.33 (s, 1H, OH, D_2O exch.); ^{13}C NMR (DMSO-d_6, δ ppm): 45.31 (CH_2), 53.71 ($2CH_2$), 56.85 (CH_2), 66.65 ($2CH_2$), arC: [110.17 and 110.22 (d, CH, J_{C-F}=5.0 Hz), 111.05 (CH), 123.12 (CH), 135.93 (C), 143.87 (C), 147.59 and 150.00 (d, C, J_{C-F}=241.0 Hz); LC-MS: 270.12 ($[M+1]^+$, 45), 201.26 (100); Elemental Analysis for $C_{12}H_{16}FN_3O_3$; Calculated (%): C, 53.53; H, 5.99; N, 15.61; Found (%): C, 53.43; H, 9.99; N, 15.67.

General method for the preparation of compounds 3, 27

2-Fluoro-N^1-[3-(1*H*-imidazol-1-yl)propyl]benzene-1,4-diamine(3).

Yield: Yellow liquid, 84% (Method 1), 94% (Method 2), 98% (Method 3); FT-IR (υ_{max}, cm^{-1}): 3330 (NH_2), 3215 (NH), 3032 (ar-H); ^{1}H NMR (400 MHz, DMSO-d_6,δ ppm): 1.94 (d, 2H, CH_2 *J*=4.0 Hz), 2.89 (t, 2H, CH_2, *J*=4.8 Hz), 4.04 (t, 2H, CH_2,*J*=8.0 Hz), 4.49 (bs, 2H, NH_2 D_2O exch.), 6.27 (dd, 1H, ar-H, *J*=8.9, 4,0 Hz), 6.36 (dd, 1H, ar-H, *J*=9.2, 4,0 Hz), 6.42 (d, 1H, ar-H, *J*=8.9 Hz), 6.89 (bs, 1H, ar-H), 7.19 (bs, 1H, ar-H), 7.63 (bs, 1H, ar-H), 8.99 (bs, 1H, NH, D_2O exch.); ^{13}C-NMR (400 MHz, DMSO-d_6,δppm): 30.96 (CH_2), 41.71 (CH_2), 44.38 (CH_2), 102.48 and 102.64 (d, CH, *J*=16.0 Hz), 110.68 (CH), 114.00 (CH), 116.00 (CH), 119.78 (CH), 127.22 (C), 128.10 (CH), 151.48 and 153.83 (d, C, J_{C-F}=235.0 Hz), 169.13 (C); EI-MS: 235.17 ($[M+1]^+$, 25), 139.05 (100); Elemental Analysis for $C_{12}H_{15}FN_4$: Calculated (%): C, 61.52; H, 6.45; N, 23.92; Found (%): C, 61.52; H, 6.44; N, 23.98.

2-Fluoro-N^1-(2-morpholinoethyl)benzene-1,4-diamine (27).

Yield: Brown liquid, 75% (Method 1), 95% (Method 2), 98% (Method 3); FT-IR ($\upsilon_{max,}$ cm^{-1}): 3336 (NH_2), 3223 (NH), 2955 (ar-CH); ^{1}H NMR (DMSO-d_6, δ ppm): 2.49 (t, 4H, $2CH_2$, *J*=6.5 Hz), 3.03 (t, 4H, $2CH_2$, *J*=6.4 Hz), 3.50-3.53 (m, 4H, $2CH_2$), 4.54 (bs, 2H, NH_2, D_2O exch.), 6.25-6.30 (m, 1H, ar-H), 6.35 (dd, 1H, ar-H, *J*=13.8, 2.4 Hz), 6.52 (dd, 1H, ar-H, *J*=10.0, 8.5 Hz), 8.99 (bs, 1H, NH, D_2O exch.); ^{13}C NMR (DMSO-d_6, δ ppm): 49.01 (CH_2), 53.72 ($2CH_2$), 57.56 (CH_2), 66.72 ($2CH_2$), arC: [102.27 and 102.48 (d, CH, J_{C-F}=21.0 Hz), 110.71 (CH), 114.97 (CH), 127.63 (C), 140.75 (C), 151.38 and 153.72 (d, C, J_{C-F}=234.0 Hz), LC-MS: 239.21 ($[M]^+$, 15), 129.26 (100); Elemental Analysis for

$C_{12}H_{16}FN_3O_3$; Calculated (%): C, 60.23; H, 7.58; N, 17.56; Found (%): C, 60.43; H, 7.59; N, 17.57.

General method for the preparation of compounds 4, 9a, 9b, 14, 21

1-{4-[(3-(1*H*-Imidazol-1-yl)propyl)amino]-3-fluorophenyl}-3-phenylthiourea (4).

Recrystallised from butyl acetate-diethylether (1:1, v:v); Yield: 81% (Method 1), 97% (Method 2), 94% (Method 3); mp. 65 °C; FT-IR (υ_{max}, cm^{-1}): 3304 (3NH), 3110 (ar-CH), 1687 (C=N), 1227 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6,δ ppm): 1.94-2.17 (m, 2H, CH_2), 3.47 (bs, 2H, CH_2), 4.06 (bs, 2H, CH_2), 6.56 (bs, 1H, ar-H), 6.94 (t, 1H, ar-H, *J*=14.1 Hz), 7.19-7.05 (m, 2H, ar-H), 7.34 (m, 3H, ar-H), 7.51 (d, 4H, ar-H, *J*=8.0 Hz), 9.89 (bs, 3H, 3NH, D_2O exch.); ^{13}C-NMR (400 MHz, DMSO-d_6,δ ppm): 27.30 (CH_2), 42.23 (CH_2), 47.35 (CH_2), arC: [106.48 and 106.64 (d, CH, *J*=16.0 Hz), 108.08 (CH), 108.18 (CH), 116.00 (CH), 120.48 (CH), 125.02 (2CH), 126.45 (CH), 128.21 (C), 130.01 (2CH), 133.51 (C), 133.42 (CH), 136.51 (C), 149.48 and 155.83 (d, C, $J_{C\text{-}F}$=635.0 Hz)], 179.13 (C=S); LC-MS: 369.47 ($[M]^+$, 25), 260.35 (100); Elemental Analysis for $C_{19}H_{20}FN_5S$; Calculated (%): C, 61.77; H, 5.46; N, 18.96; Found (%): C, 61.75; H, 5.56; N, 18.66.

2-{2-[(3-(1*H*-Imidazol-1-yl)propyl)amino]acetyl}-*N*-benzylhydrazinecarbothioamide (9a).

Recrystallised from methanol, Yield: 46% (Method 1), 79% (Method 2), 77% (Method 3); mp. 221-222 °C; FT-IR (υ_{max}, cm^{-1}): 3329, 3289 (4NH), 3087 (ar-CH), 1531 (C=N), 1614 (C=O), 1531 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6,δ ppm):3.39 (s, 2H, CH_2+DMSO-d_6), 4.52 (s, 4H, $2CH_2$), 4.71 (s, 2H, CH_2), 4.72 (s, 2H, OCH_2), 7.23 (m, 2H, ar-H), 7.30 (d, 3H, ar-H, *J*=4.2 Hz), 7.31 (d, 3H, ar-H, *J*=5.7 Hz), 8.31 (s, 2H, NH, D_2O exch.), 8.76 (s, 2H, 2NH, D_2O exch.); ^{13}C-NMR (400 MHz, DMSO-d_6,δ ppm): 25.93 (CH_2), 46.30 (CH_2), 47.41 ($2CH_2$), 47.90 (CH_2), arC: [127.04 (2CH), 127.72 (3CH), 128.44 (3CH), 139.53 (C), 168.21 (C=O), 183.14 (C=S); LC-MS: 346.13 ($[M]^+$, 15), 274.40 (100); Elemental Analysis for $C_{16}H_{22}N_6OS$; Calculated (%): C, 55.47; H, 6.40; N, 24.26; Found (%): C, 55.47; H, 6.42; N, 24.25.

2-{2-[(3-(1*H*-Imidazol-1-yl)propyl)amino]acetyl}-*N*-phenylhydrazinecarbothioamide (9b).

Recrystallised from ethanol; Yield: 83% (Method 1), 96% (Method 2), 96% (Method 3); mp. 201-202 °C; FT-IR (υ_{max}, cm^{-1}): 3348, 3136 (4NH), 3063 (ar-CH), 1750 (C=O), 1519 (C=N), 1287 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6,δ ppm):4.52 (s, 4H, $2CH_2$), 4.71 (s, 2H, CH_2), 4.72 (s, 2H, CH_2), 7.23-7.24 (m, 2H, arH), 7.30 (d, 3H, ar-H, *J*=4.7 Hz), 7.31 (s, 2H, ar-H), 8.30 (bs, 2H, NH, D_2O exch.), 8.93 (s, 2H, 2NH, D_2O exch.); ^{13}C-NMR

(400 MHz, DMSO-d_6,δ ppm):26.27 (CH_2), 46.23 (CH_2), 47.01 ($2CH_2$), arC: [125.27 (2CH), 128.63 (3CH), 129.20 (3CH), 139.64 (C), 167.30 (C=O), 172.10 (C=S); LC-MS:333.40 ($[M+1]^+$, 10), 309.37 (100); Elemental Analysis for $C_{15}H_{20}N_6OS$; Calculated (%): C, 54.20; H, 6.06; N, 25.28; Found (%): C, 54.20; H, 6.02; N, 25.25.

2-{2-[(4-[(3-(1*H*-Imidazol-1-yl)propyl)amino]-3-fluorophenyl)amino]acetyl}-*N*-benzylhydrazinecarbothioamide (14).

Recrystallised from Ethanol; Yield: 60% (Method 1), 92% (Method 2); 89% (Method 3); mp. 104-105 °C; FT-IR (u_{max}, cm^{-1}): 3250, 3199 (5NH), 3031 (ar-CH), 1699 (C=O), 1242 (C=S); ^{1}H NMR (DMSO-d_6, δ ppm): 2.50 41 (s, 2H, CH_2), 2.51 (s, 2H, CH_2), 3.47 (bs, 2H, CH_2), 4.72 (d, 4H, $2CH_2$, *J*=4.0 Hz), 7.20 (bs, 1H, arH), 7.22 (bs, 1H, arH), 7.23 (bs, 1H, arH), 7.26 (bs, 1H, arH), 7.28 (bs, 1H, arH), 7.30 (bs, 2H, arH), 7.32 (bs, 1H, arH), 7.34 (bs, 1H, arH); ^{13}C NMR (DMSO-d_6, δ ppm): 29.20 (CH_2), 47.60 (CH_2), 49.88 (CH_2), 51.77 ($2CH_2$), arC: [104.92 and 105.35 (d, CH, *J*=43.0 Hz), 110.56 (CH), 114.79 (CH), 122.53 (CH), 127.51 (CH), 127.73 (2CH), 128.43 (2CH), 130.06 (C), 131.50 (CH), 133.37 (C), 136.69 (CH), 139.74 (C), 149.41 and 153.63 (d, C, J_{C-F}=422 Hz), 162.58 (C=O), 183.29 (C=S); LC-MS: 384.38 (50), 358.23 (100); Elemental Analysis for $C_{22}H_{26}FN_7OS$; Calculated (%): C, 58.00; H, 5.75; N, 21.52; Found: C, 58.00; H, 5.72; N, 21.52.

2-{2-[(2-Morpholinoethyl)amino]acetyl}-*N*-phenylhydrazinecarbothioamide (21).

Recrystallised from ethanol, Yield: 46% (Method 1), 89% (Method 2), 87% (Method 3); mp. 121-122 °C; FT-IR (u_{max}, cm^{-1}): 3290, 3215 (4NH), 3092 (ar-CH), 1667 (C=O), 1241 (C=S); ^{1}H-NMR (400 MHz, DMSO-d_6,δ ppm):2.00 (d, 6H, $3CH_2$, *J*=10.8 Hz), 2.50 (t, 2H, CH_2, *J*=2.0 Hz), 3.37 (bs, 8H, $4CH_2$), 7.18 (t, 1H, ar-H, *J*=7.6 Hz), 7.33 (dd, 2H, ar-H, *J*=8.0 Hz), 7.58 (d, 2H, ar-H, *J*=8.0 Hz), 9.83 (s, 2H, 2NH, D_2O exch.), 10.35 (s, 2H, 2NH, D_2O exch.); ^{13}C-NMR (400 MHz, DMSO-d_6,δ ppm): 43.79 (CH_2), 50.11 (CH_2), 51.99 (CH_2), 56.30 ($2CH_2$), 58.30 ($2CH_2$), 59.52 (CH_2), arC: [124.96 (2CH), 128.19 (2CH), 130.37 (CH), 139.25 (C), 153.22 (C=O), 176.88 (C=S); LC-MS: 357.34 ($[M+2+H_2O]^+$, 15), 339.45 ($[M+2]^+$, 10), 215.31 (100); Elemental Analysis for $C_{16}H_{25}N_5O_2S$; Calculated (%): C, 53.39; H, 6.87; N, 20.75; Found (%): C, 53.37; H, 6.82; N, 20.75.

General method for the synthesis of compounds 6, 11 and **16**

2-{[4-([3-(1*H*-Imidazol-1-yl)propyl]amino)-3-fluorophenyl]imino}-3-phenylthiazolidin-5-on (6).

Recrystallised from ethyl acetate; Yield: 60% (Method 1), 88% (Method 2), 30% (Method 3); mp: 225-226 °C; FT IR (υ_{max}, cm^{-1}): 2958 (ar-CH), 1701 (C=O), 1431 (C=N); ^{1}H-NMR (DMSO-d_6, δ ppm): 1.95-2.05 (m, 2H, CH_2), 3.39 (m, 2H, CH_2), 3.99-4.05 (m, 2H, CH_2), 4.06-4.13 (m, 2H, CH_2), 6.63 (bs, 1H, ar-H), 6.88 (d, 1H, ar-H, *J*=5.4 Hz), 6.89 (d, 1H, ar-H, *J*=6.1 Hz), 6.98 (s, 1H, ar-H), 7.27 6.88 (d, 2H, ar-H, *J*=5.5 Hz), 7.33 (dd, 2H, ar-H, *J*=11.0, 4.6 Hz), 7.36 (s, 1H, ar-H), 7.43 (dd, 1H, ar-H, *J*=8.2, 1.8 Hz), 7.50 (d, 1H, arH, *J*=7.3 Hz); ^{13}C-NMR (DMSO-d_6, δ ppm): 30.38 (CH_2), 33.23 (thiazole C-4), 40.04 (CH_2), 44.62 (CH_2), arC: [111.19 (CH), 117.56 (CH), 120.91 (CH), 121.10 (CH), 121.45 (CH), 124.35 (2CH), 128.63 (2CH), 128.74 (C), 133.79 (CH), 136.81 (CH), 141.34 (C), 146.74 (C), 159.78 (C), 153.21 and 158,30 (d, C, $J_{C\text{-}F}$=509.0 Hz)], 181.75 (thiazole C-5); LC-MS: 432.51 ($[M+Na]^+$, 10), 409.23 ($[M]^+$, 100); Elemental Analysis for $C_{21}H_{20}FN_5OS$: Calculated (%): C, 61.60; H, 4.92; N, 17.10; Found (%): C, 61.61; H, 4.93; N, 17.09

2-{[3-(1*H*-Imidazol-1-yl)propyl]amino}-*N*′-(4-oxo-3-phenylthiazolidin-2-ylidene) acetohydrazide (11).

Recrystallised from ethylacetate:*n*-hexane (1:1), Yield: 75% (Method 1), 85% (Method 2), 30% (Method 3); mp. 225-226 °C; FT-IR (υ_{max}, cm^{-1}): 3231, 3187 (NH), 3029 (ar-CH), 1748, 1731 (2C=O), 1584 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6, δppm: 2.21 (s, 2H, CH_2), 2.50 (s, 2H, CH_2), 3.50 (s, 2H, CH_2), 3.78 (s, 2H, CH_2), 4.61 (s, 2H, CH_2), 6.98 (s, 2H, ar-H), 7.37 (s, 3H, arH), 7.53 (s, 3H, ar-H), 8.21 (s, 1H, NH, D_2O exch.), 9.81 (s, 1H, NH, D_2O exch.); ^{13}C-NMR (400 MHz, DMSO-d_6, δppm: 26.27 (CH_2), 32.03 (thiazole C-4), 47.27 (CH_2), 47.30 (CH_2), 48.51 (CH_2), arC: [120.46 (CH), 127.32 (2CH), 128.26 (CH), 129.50 (2CH), 130.93 (CH), 132.40 (C), 134.43 (CH), 150.86 (thiazole C-2), 164.07 (C=O), 167.41 (thiazole C-5). LC-MS: 372.01 ($[M]^+$, 45), 247.67 (100); Elemental Analysis for $C_{17}H_{20}N_6O_2S$; Calculated (%): C, 54.82; H, 5.41; N, 22.56; Found (%): C, 54.82; H, 5.41; N, 22.56.

2-{[4-([3-(1*H*-Imidazol-1-yl)propyl]amino)-3-fluorophenyl]amino}-*N*′-(3-benzyl-4-oxothiazolidin-2-ylidene)aceto hydrazide (16).

Recrystallised from ethyl acetate; Yield: 69% (Method 1), 97% (Method 2), 96% (Method 3); mp. 170-171 °C; FT-IR (υ_{max}, cm^{-1}): 3328 (3NH), 3067 (ar-CH), 1710 (2C=O), 1512 (N=C); ^{1}H-NMR (DMSO-d_6, δ ppm): 2.50 (bs, 4H, $2CH_2$), 3.38 (bs, 4H, $2CH_2$), 4.02 (s, 2H, CH_2), 4.79 (s, 2H, CH_2), 7.24 (d, 1H, ar-H, *J*=7.2 Hz), 7.26 (bs, 1H, ar-H), 7.27 (bs, 1H, ar-H), 7.28 (d, 2H, ar-H, *J*=7.4 Hz), 7.30 (s, 1H, ar-H), 7.33 (bs,

2H, ar-H), 7.35 (d, 2H, ar-H, *J*=7.6 Hz), 7.38 (bs, 1H, ar-H), 8.16 (s, 2H, 2NH, D_2O exch.), 8.30 (bs, 1H, NH, D_2O exch.); ^{13}C-NMR (DMSO-d_6, δ ppm): 29.60 (CH_2), 32.72 (thiazole C-4), 45.67 (CH_2), 46.29 (CH_2), 47.09 (CH_2), 47.79 (CH_2), arC: [104.02 and 104.47 (d, CH, *J*=45 Hz), 127.57 (CH), 127.93 (CH), 128.10 (CH), 128.34 (2CH), 128.41 (CH), 128.65 (2CH), 128.73 (CH), 128.82 (CH), 136.34 (C), 136.71 (C), 139.52 (C), 148.6 and 153.25 (d, C, $J_{C\text{-}F}$=457 Hz), 160.07 (thiazole C-2), 171.50 (thiazole C-5), 172.30 (C=O); LC-MS: 553.31 ($[M+1+K]^+$, 20), 477.10 ($[M\text{-}H_2O]^+$, 10), 384.30 (100); Elemental Analysis for $C_{24}H_{26}FN_7O_2S$: Calculated (%): C, 58.17; H, 5.29; N, 19.78; Found (%): C, 58.11; H, 5.23; N, 19.79.

General Method for the Synthesis of Compounds 5, 10, 15 and 22

***N*^{1}-[3-(1*H*-Imidazol-1-yl)propyl]-*N*^{4}-[5-(4-chlorophenyl)-3-phenylthiazol-2(3*H*)-yliden]-2-fluorobenzen-1,4-diamine (5).**

Recrystallised from acetone; Yield: 85% (Method 1), 97% (Method 2), 95% (Method 3); mp. 148-149 °C; FT-IR (υ_{max}, cm^{-1}): 3261 (NH), 3059 (ar-CH), 1674 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6, δppm): 1.98 (bs, 2H, CH_2), 2.99 (bs, 2H, CH_2), 4.05 (bs, 2H, CH_2), 6.50 (s, 1H, ar-H), 6.59 (s, 1H, ar-H), 6.81-6.99 (m, 4H, ar-H), 7.20 (bs, 3H, ar-H), 7.76 (s, 1H, arH), 7.85-7.89 (m, 2H, ar-H), 10.11 (s, 1H, NH, D_2O exch.); ^{13}C-NMR (400 MHz, DMSO-d_6, δppm):30.41 (CH_2), 44.33 (CH_2), 65.37 (CH_2), arC: [112.04 (CH), 117.26 (CH), 121.40 (CH), 126.18 (thiazole C-5), 128.76 (2CH), 129.46 (CH), 129.95 (2CH), 130.41 (thiazole C-4), 131.59 (CH), 132.04 (CH), 133.72 (C), 136.77 (C), 138.72 (C), 148.54 (C), 149.02 (C), 151.91 and 157.38 (d, C, $J_{C\text{-}F}$=547.0 Hz), 160.20 (thiazole C-2); LC-MS: 504.46 ($[M]^+$, 100), 486.43 (50); Elemental Analysis for $C_{27}H_{23}ClFN_5S$; Calculated (%): C, 64.34; H, 4.60; N, 13.89; Found (%): C, 64.30; H, 4.58; N, 13.87;

2-{[3-(1*H*-Imidazol-1-yl)propyl]amino}-*N*′-[5-(4-chlorophenyl)-3-phenylthiazol-2(3*H*)-ylidene]acetohydrazide (10).

Recrystallised from acetone, Yield: 86% (Method 1), 99% (Method 2), 99% (Method 3); mp. 148-150 °C; FT-IR (υ_{max}, cm^{-1}): 3231 (2NH), 3059 (ar-CH), 1672 (C=O), 1599 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6, δppm): 2.57 (s, 2H, CH_2), 3.42 (bs, 4H, $2CH_2$), 4.10 (s, 2H, CH_2), 6.90 (s, 1H, ar-H), 7.26 (d, 2H, ar-H, *J*=8.0 Hz), 7.41 (d, 2H, ar-H, *J*=7.6 Hz), 7.43 (d, 3H, ar-H, *J*=8.3 Hz), 7.59 (d, 3H, ar-H, *J*=7.4 Hz) 7.97 (s, 2H, ar-H); ^{13}C-NMR (400 MHz, DMSO-d_6, δppm): 30.02 (CH_2), 47.03 (CH_2), 48.65 ($2CH_2$), arC: [117.26 (CH), 117.32 (thiazole C-5), 118.26 (thiazole C-4), 121.50 (2CH), 129.30 (2CH), 129.40 (CH), 129.43 (2CH), 130.86 (2CH), 131.07 (CH), 132.63 (CH), 135.40 (C), 136.70 (C), 142.01 (C), 156.17 (thiazole C-2), 163.35 (C=O); LC-MS: 505.39 ($[M+K]^+$, 55), 466.01 ($[M]^+$, 15), 447.45 ($[M\text{-}1+H_2O]^+$, 100); Elemental Analysis for

$C_{23}H_{23}ClN_6OS$; Calculated (%): C, 59.16; H, 4.96; N, 18.00; Found (%): C, 59.20; H, 4.96; N, 18.00.

2-{[4-([3-(1*H*-Imidazol-1-yl)propyl]amino)-3-fluorophenyl]amino}-*N*'-[3-benzyl-5-(4-chlorophenyl)thiazol-2(3*H*)-ylidene]acetohydrazide (15).

Recrystallised from acetone; Yield: 84% (Method 1), 94% (Method 2), 98% (Method 3); mp. 122-123 °C; FT-IR (υ_{max}, cm^{-1}): 3165 (3NH), 3060 (ar-CH), 1719 (C=O), 1493 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6, δppm): 1.98 (s, 2H, CH_2), 2.99 (bs, 2H, CH_2), 3.38 (bs, 2H, CH_2), 4.05 (bs, 2H, CH_2), 4.98 (bs, 2H, CH_2), 6.44-6.39 (m, 2H, ar-H), 6.81-6.99 (m, 3H, ar-H), 7.20-8.00 (m, 11H, ar-H); ^{13}C-NMR (400 MHz, DMSO-d_6, δppm): 30.58 (CH_2), 30.65 (CH_2), 44.37 (CH_2), 63.95 (CH_2), 65.37 (CH_2), arC: [111.05 and 111.10 (d, CH, J=5.0 Hz), 116.02 and 116.22 (d, C, J=20.0 Hz), 117.26 (CH), 121.41 (CH), 124.40 (thiazole C-5), 127.50 (C), 128.67 (CH), 128.76 (CH), 128.98 (2CH), 129 18 (2CH), 129.31 (2CH), 129.46 (CH), 129.83 (2CH), 130.03 (thiazole C-4), 130.42 (C), 136.77 (C), 141.01 and 148.50 (d, C, $J_{C\text{-}F}$=749.0 Hz), 151.91 (C), 157.38 (C), 159.38 (C), 160.02 (C=O); LC-MS: 591.21 ([M+1]$^+$, 15), 297.22 (100); Elemental Analysis for $C_{30}H_{29}ClFN_7OS$; Calculated (%): C, 61.06; H, 4.95; N, 16.61; Found (%): C, 61. 06; H, 4.95; N, 16.67.

***N*'-(5-(4-Chlorophenyl)-3-phenylthiazol-2(3*H*)-ylidene)-2-((2-morpholinoethyl) amino) acetohydrazide (22).**

Recrystallised from butyl acetate:diethyl ether (2:1 v:v); Yield: 65% (Method 1), 89% (Method 2), 88% (Method 3); mp. 148-149; FT-IR ($\upsilon_{max,}$ cm^{-1}): 3293, 3217 (2NH), 3096 (ar-CH), 1743 (C=O), 1539 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.14 (s, 4H, $2CH_2$), 2.50 (s, 4H, $2CH_2$+ DMSO-d_6), 3.42 (bs, 4H, $2CH_2$+H_2O), 5.45 (s, 2H, CH_2), 6.93 (s, 1H, ar-H), 7.25 (d, 2H, ar-H, J=7.2 Hz), 7.48 (d, 2H, ar-H, J=8.0 Hz), 7.64 (d, 2H, ar-H, J=10.8 Hz), 7.96 (t, 1H, ar-H, J=2.4 Hz), 7.98 (d, 2H, ar-H, J=2.0 Hz), 8.79 (s, 2H, NH, D_2O exch); ^{13}C NMR (DMSO-d_6, δ ppm): 43.29 (CH_2), 46.02 (CH_2), 48.84 (CH_2), 57.88 ($2CH_2$), 66.42 ($2CH_2$), arC: [121.11 (thiazole C-5), 124.51 (thiazole C-4), 128.21 (2CH), 128.94 (3CH), 129.92 (2CH), 130.50 (2CH), 133.33 (C), 139.18 (C), 140.29 (C), 156.30 (thiazole C-2)], 170.17 (C=O); LC-MS: 472.47 ([M]$^+$, 40), 214.33 (100). Elemental Analysis for $C_{23}H_{26}ClN_5O_2S$; Calculated (%): C, 58.53; H, 5.55; N, 14.84; Found (%): C, 58.51; H, 5.59; N, 14.82.

General Method for The Synthesis of Compounds 7, 12, 19 and **28**

Ethyl 2-{([3-(1*H*-imidazol-1-yl)propyl]amino}acetate (7).

Yield: 80% (Method 1), 100% (Method 2), 100% (Method 3); FT-IR (υ_{max}, cm^{-1}): 3326 (NH), 3110 (ar-CH), 1732 (C=O), 1260 (N=CH); ^{1}H-NMR (400 MHz, DMSO-d_6, δppm):

1.17 (t, 3H, CH_3, *J*=4.6 Hz), 1.81 (t, 2H, CH_2, *J*=8.0 Hz), 3.28 (bs, 2H, CH_2), 3.30 (s, 2H, CH_2), 4.00 (dd, 2H, CH_2, *J*=4.6 Hz), 4.07 (q, 2H, OCH_2, *J*=8.0 Hz), 6.87 (s, 1H, ar-H), 7.15 (s, 1H, ar-H), 7.59 (s, 1H, ar-H); 9.11 (s, 2H, NH, D_2O exch); ^{13}C-NMR (400 MHz, DMSO-*d*$_6$, δppm): 14.36 (CH_3), 31.27 (CH_2), 44.19 (CH_2), 45.79 (CH_2), 56.46 (CH_2), 60.33 (O<u>C</u>H_2), arC: [119.71 (CH), 128.50 (CH), 137.69 (CH), 171.81 (C=O); LC-MS: 298.17 (100), 212.14 ([M+1]$^+$, 30); Elemental Analysis for $C_{10}H_{17}N_3O_2$; Calculated (%): C, 56.85; H, 8.11; N, 19.89; Found (%): C, 56.80; H, 8.12; N, 19.88.

Ethyl-2-{[4-([3-(1*H*-imidazol-1-yl)propyl]amino)-3-fluorophenyl]amino} acetate (12).

Yield: 89% (Method 1), 94% (Method 2), 100% (Method 3); FT-IR (υ_{max}, cm^{-1}): 3373 (2NH), 2981 (ar-CH), 1738 (C=O); ^{1}H-NMR (400 MHz, DMSO-*d*$_6$, δppm): 1.17 (d, 3H, CH_3, *J*=2.8 Hz), 1.93-1.98 (m, 2H, CH_2), 2.90 (q, 2H, CH_2, *J*=6.9 Hz), 3.80 (s, 2H, CH_2), 4.01-4.08 (m, 2H, CH_2), 4.10 (d, 2H, OCH_2,*J*=7.1 Hz), 6.25 (dd, 1H, ar-H, *J*= 4.0, 2.7 Hz), 6.34 (d, 1H, ar-H, *J*=2.4 Hz), 6.38 (d, 1H, ar-H, *J*=2.6 Hz), 6.90 (bs, 1H, ar-H), 7.18 (bs, 1H, ar-H), 7.65 (bs, 1H, ar-H);8.25 (s, 2H, NH, D_2O exch), 8.49 (s, 2H, NH, D_2O exch); ^{13}C-NMR (400 MHz, DMSO-*d*$_6$, δppm):14.52 (CH_3), 29.46 (CH_2), 44.00 (CH_2), 58.58 (CH_2), 60.30 (CH_2), 70.25 (CH_2), 108.81 and 109.21 (d, CH, *J*=40.0 Hz), 118.51 (CH), 114.00 (CH), 125.30 (CH), 119.69 (CH), 120.01 (C), 124.63 (CH), 128.81 (CH), 140.01 (C), 149.51 and 151.71 (d, C, $J_{C\text{-}F}$=220.0 Hz), 171.10 (C=O); LC-MS:321.17 ([M+1]$^+$, 45), 139.05 (100); Elemental Analysis for $C_{16}H_{21}FN_4O_2$: Calculated (%): C, 59.99; H, 6.61; N, 17.49; Found (%): C, 59.62; H, 6.64; N, 17.48.

Ethyl 2-[(2-Morpholinoethyl)amino]acetate (19).

Yield: Yellow liquid; 65% (Method 1), 100% (Method 2), 100% (Method 3); FT-IR (υ_{max},cm^{-1}): 3398 (NH), 1738 (C=O); ^{1}H NMR (DMSO-*d*$_6$, δ ppm): 1.19 (t, 3H, CH_3, *J*=8.0 Hz), 2.49 (t, 4H, 2CH_2 *J*=4.4 Hz), 3.20 (s, 2H, CH_2), 3.36 (s, 2H, CH_2), 3.57 (t, 4H, 2CH_2, *J*=4.8 Hz), 4.06-4.11 (m, 4H, 2CH_2); 8.12 (s, 1H, NH); ^{13}C NMR (DMSO-*d*$_6$, δ ppm): 14.66 (CH_3), 52.85 (2CH_2), 59.10 (2CH_2), 60.03 (CH_2), 66.56 (2CH_2), 67.65 (CH_2), 170.16 (C=O); LC-MS: 216.01 ([M]$^+$, 16), 188.16 (100); Elemental Analysis for $C_{10}H_{20}N_2O_3$ Calculated (%): C, 55.53; H, 9.32; N, 12.95; Found (%): C, 55.54; H, 9.32; N, 12.93.

Ethyl2-((3-fluoro-4-((2-morpholinoethyl)amino)phenyl) amino)acetate (28).

Yield: Yellow liquid, 79% (Method 1), 97% (Method 2), 100% (Method 3); FT-IR (υ_{max}, cm^{-1}): 3383 (2NH), 2962 (ar-CH), 1737 (C=O); ^{1}H NMR (DMSO-*d*$_6$, δ ppm): 1.27 (t, 3H, CH_3, *J*=4.6 Hz), 2.34-2.39 (m, 4H, 2CH_2), 2.46-2.50 (m, 4H, 2CH_2), 3.54-3.60 (m, 4H, 2CH_2), 3.79 (d, 2H, CH_2, *J*=8.0 Hz), 4.09 (q, 2H, OCH_2, *J*=9.6 Hz), 6.25 (dd, 1H, ar-H,

J=7.6, 3.6), 6.41 (dd, 1H, ar-H, *J*=5.1, 3.6 Hz), 6.58 (t, 1H, ar-H, *J*=12.2 Hz), 8.05 (s, 1H, NH, D_2O exch.), 8.10 (s, 1H, NH, D_2O exch.); ^{13}C NMR (DMSO-d_6, δ ppm): 14.01 (CH_3), 45.12 ($2CH_2$), 52.57 ($2CH_2$), 54.72 (CH_2), 62.31 ($O\underline{C}H_2$), 66.48 ($2CH_2$), arC:[105.27 (CH), 118.61 (2CH), 125.67 (C), 140.23 (C), 149.58 and 151.82 (d, C, J_{C-F}=224.0 Hz)], 172.41 (C=O); LC-MS: 343.65 ([M+H_2O]$^+$, 15), 274.97 (100); Elemental Analysis for $C_{16}H_{24}FN_3O_3$; Calculated (%): C, 59.06; H, 7.43; N, 12.91; Found (%): C, 59.06; H, 7.43; N, 12.97.

General method for the synthesis of compounds 8, 13, 20 and **29**

2-{[3-(1*H*-Imidazol-1-yl)propyl]amino}acetohydrazide (8).

Recrystallised from butyl acetate:diethyl ether (1:2 v:v); Yield: 96 % (Method 1), 100% (Method 2), 100% (Method 3); mp. 45 °C; FT-IR (υ_{max}, cm^{-1}): 3272 (2NH+NH_2), 3112 (ar-CH), 1645 (C=O), 1263 (N=CH); ^1H-NMR (400 MHz, DMSO-d_6, δppm): 2.50 (t, 2H, CH_2, *J*=7.1 Hz), 2.70 (t, 2H, CH_2, *J*=4.9 Hz), 3.57 (d, 2H, CH_2, *J*=8.0 Hz), 4.24 (s, 2H, NH_2, D_2O exch.), 5.90 (s, 1H, NH, D_2O exch.), 6.29 (dd, 1H, arH, *J*=4.0 Hz), 6.35 (dd, 1H, ar-H, *J*=4.0 Hz), 6.86 (dd, 1H, ar-H, *J*=8.0 Hz), 9.09 (s, 1H, NH, D_2O exch.); ^{13}C-NMR (400 MHz, DMSO-d_6, δppm): 28.06 (CH_2), 45.85 (CH_2), 54.31 ($2CH_2$), arC: [100.91 (CH), 108.41 (CH), 122.53 (CH)], 169.70 (C=O); LC-MS: 198.25 ([M+1]$^+$, 15), 170.28 (100); Elemental Analysis for $C_8H_{15}N_5O$; Calculated (%): C, 48.72; H, 7.67; N, 35.51; Found (%): C, 48.72; H, 7.62; N, 35.51.

2-{[4-([3-(1*H*-Imidazol-1-yl)propyl]amino)-3-fluorophenyl]amino}aceto hydrazide (13).

Recrystallised from butyl acetate:diethyl ether (1:2); Yield: 95% (Method 1), 100% (Method 2), 100% (Method 3); mp: 200-201 °C; FT-IR (υ_{max}, cm^{-1}): 3343 (3NH), 3297, 3299 (NH_2), 3036 (ar-CH); ^1H NMR (DMSO-d_6,δ ppm): 1.94 (dd, 2H, CH_2, *J*=8.0, 2.8 Hz), 2.89 (d, 2H, CH_2, *J*=8.0 Hz), 4.02 (d, 2H, CH_2, *J*=7.2 Hz), 4.04 (s, 2H, NH_2 D_2O exch.), 4.06 (s, 2H, CH_2), 6.28 (d, 1H, ar-H, *J*=4.0 Hz), 6.36 (s, 1H, ar-H), 6.39 (d, 1H, ar-H, *J*= 4.0 Hz), 6.90 (s, 1H, ar-H), 7.17 (s, 1H, ar-H), 7.64 (s, 1H, ar-H); ^{13}C NMR (DMSO-d_6, δ ppm): 30.89 (CH_2), 41.68 (CH_2), 44.39 (CH_2), 46.68 (CH_2), arC: [101.36 and 101.14 (d, CH, *J*=22.0 Hz), 110.71 (CH), 110.74 (CH), 114.82 (CH), 119.81 (CH), 127.42 and 127.54 (d, C, *J*=12.0 Hz), 128.78 (CH), 140.77 (C), 151.47 and 153.82 (d, C, J_{C-F}=940 Hz)], 170.12 (C=O); LC-MS: 345.28 ([M+K]$^+$, 30), 148.99 (100); Elemental Analysis for $C_{14}H_{19}FN_6O$; Calculated (%): C, 56.85; H, 8.11; N, 19.89; Found (%): C, 56.80; H, 8.12; N, 19.88.

2-[(2-Morpholinoethyl)amino]acetohydrazide (20).

Recrystallised from butyl ethanol:n-hexane (2:1 v:v); Yield: 99.5% (Method 1), 100% (Method 2), 100% (Method 3); mp. 76 °C; FT-IR ($\upsilon_{max,}$ cm^{-1}): 3314, 3265 (NH, NH_2), 1652 (C=O); ^{1}H NMR (DMSO-d_6, δ ppm): 2.40 (t, 4H, $2CH_2$, *J*=6.2 Hz), 2.89 (s, 2H, CH_2), 3.42 (bs, 4H, $2CH_2$), 3.56 (t, 4H, $2CH_2$, *J*=4.6 Hz), 3.83 (s, 2H, NH_2, D_2O exch.), 8.28 (s, 2H, 2NH, , D_2O exch.); ^{13}C NMR (DMSO-d_6, δ ppm): 53.68 ($2CH_2$), 56.50 (CH_2), 60.60 ($2CH_2$), 66.62 ($2CH_2$), 168.59 (C=O); LC-MS: 220.34 ($[M+H_2O]^+$, 15), 202.11 ($[M]^+$, 10), 114.39 (100); Elemental Analysis for $C_8H_{18}N_4O_2$; Calculated (%): C, 47.51; H, 8.97; N, 27.70; Found (%): C, 47.51; H, 8.99; N, 27.72.

2-{(3-Fluoro-4-[(2-morpholinoethyl)amino]phenyl)amino}acetohydrazide (29).

Recrystallised from ethanol:n-hexane (2:1); Yield: 79% (Method 1), 100% (Method 2), 100% (Method 3); mp. 228-229 °C; FT-IR ($\upsilon_{max,}$ cm^{-1}): 3345 (NH), 3304 and 3281 (NH_2), 2963 (ar-CH), 1654 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 2.44-2.53 (m, 4H, $2CH_2$), 2.78 (t, 2H, CH_2, *J*=7.2 Hz), 3.18 (t, 2H, CH_2, *J*=6.9 Hz), 3.94 (s, 2H, CH_2), 5.42 (s, 1H, NH_2, D_2O exch.), 6.23-6.38 (m, 2H, ar-H), 6.57 (t, 1H, ar-H, *J*=12.1 Hz); ^{13}C NMR (DMSO-d_6, δ ppm): 41.02 (CH_2), 45.17 (CH_2), 52.82 ($2CH_2$), 54.31 (CH_2), 66.78 ($2CH_2$), arC: [105.21 (CH), 118.71 (2CH), 125.78 (C), 141.20 (C), 149.55 and 155.72 (d, C, J_{C-F}=617.0 Hz)], 171.45 (C=O); LC-MS: 312.39 ($[M+2]^+$, 15), 149.18 (100); Elemental Analysis for $C_{14}H_{22}FN_5O_2$; Calculated (%): C, 54.01; H, 7.12; N, 22.49; Found (%): C, 54.06; H, 7.13; N, 22.47.

General method for the synthesis of compounds 17a-d and 25a-b

2-{[(4-[(3-(1*H*-Imidazol-1-yl)propyl)amino]-3-fluorophenyl)imino]methyl} phenol (17a).

Recrystallised from butyl acetate:diethyl ether (1:2); Yield: 73% (Method 1), 98% (Method 2), 100% (Method 3); mp. 178-179 °C; FT-IR (υ_{max}, cm^{-1}): 3184 (OH), 3057 (ar-CH), 1671 (N=CH); ^{1}H-NMR (400 MHz, DMSO-d_6) δppm: 1.94 (s, 2H, CH_2), 2.51 (s, 2H, CH_2), 3.41 (s, 2H, CH_2), 6.86 (d, 2H, ar-H, *J*=8.0 Hz), 6.90 (d, 2H, ar-H, *J*=8.0 Hz), 6.99 (t, 1H, ar-H, *J*=8.0 Hz), 7.22 (d, 1H, ar-H, *J*=8.0 Hz), 7.26 (d, 1H, ar-H, *J*=4.0 Hz), 7.48 (d, 1H, ar-H, *J*=4.0 Hz), 7.61 (d, 1H, ar-H, *J*=8.0 Hz), 7.68 (d, 1H, ar-H, *J*=8.0 Hz), 8.26 (s, 1H, N=C<u>H</u>), 10.16 (s, 1H, NH, D_2O exch.), 11.19 and 11.24 (s, 1H, OH, D_2O exch.); ^{13}C-NMR (400 MHz, DMSO-d_6, δppm):24.23 (CH_2), 30.61 (CH_2), 44.46 (CH_2), arC: [106.36 and 107.35 (d, CH, *J*= 99.0 Hz), 114.11 (CH), 116.45 (CH), 119.53 (C), 119.77 (CH), 120.42 (C), 123.22 (CH), 127.52 (CH), 129.62 (CH), 131.04 (CH), 136.70 (CH), 141.41 (CH), 144.46 (C), 147.01 (C), 156.72 and 158.08 (d, C, J_{C-F}=136.0 Hz), 159.23 (N=<u>C</u>H); LC-MS: 339.26 ($[M+1]^+$, 70), 243.16 (100); Elemental Analysis for

$C_{19}H_{19}FN_4O$; Calculated (%): C, 67.44; H, 5.66; N, 16.56; Found (%): C, 67.24; H, 5.62; N, 16.54.

N^1-[3-(1*H*-Imidazol-1-yl)propyl)-2-fluoro-N^4-(4-methoxybenzylidene)benzene-1,4-diamine (17b).

Recrystallised from ethyl acetate:diethylether (1:2); Yield: 55.5 % (Method 1), 76% (Method 2), 99% (Method 3); mp:128-129 °C; FT-IR (υ_{max}, cm^{-1}): 3234 (NH), 3009 (ar-CH), 1665, 1248 (N=CH). ^{1}H-NMR (400 MHz, DMSO-*d*$_6$, δppm): 1.96-2.04 (m, 2H, CH_2), 3.06 (t, 2H, CH_2, *J*=6.4 Hz), 3.82 (s, 3H, OCH_3), 4.07 (t, 2H, CH_2, *J*=6.8 Hz), 6.91 (s, 1H, ar-H), 6.99-7.06 (m, 3H, ar-H), 7.13 (dd, 1H, arH, *J*=2.4 Hz), 7.18 (dd, 2H, ar-H, *J*=2.4 Hz), 7.66 (s, 1H, ar-H), 7.82 (d, 2H, ar-H, *J*=8.8 Hz), 7.51 (s, 1H, N=C<u>H</u>); ^{13}C-NMR (400 MHz, DMSO-*d*$_6$, δppm): 30.55 (CH_2), 44.23 ($2CH_2$), 55.31 (OCH_3), arC: [107.48 and 107.76 (d, CH, *J*=28.4 Hz), 112.24 and 112.45 (d, CH, *J*=21.0 Hz), 114.60 (2CH), 119.28 and 119.52 (d, CH, *J*=24.1 Hz), 122.82 (CH), 129.16 (CH), 130.07 (C), 130.60 (2CH), 135.49 (C), 137.88 (CH), 140.45 (C), 150.30 and 152.64 (d, C, J_{C-F}=234.8 Hz)], 155.96 (N=<u>C</u>H); LC-MS: 352.47 ($[M]^+$, 60), 266.37 (100); Elemental Analysis for $C_{20}H_{21}FN_4O$; Calculated (%): C, 68.16; H, 6.01; N, 15.90; Found (%): C, 68.14; H, 6.02; N, 15.90.

N^1-[3-(1*H*-Imidazol-1-yl)propyl]-N^4-[(1*H*-indol-3-yl)methylene]-2-fluorobenzene-1,4-diamine (17c).

Recrystallised from ethyl acetate:diethylether (1:2); Yield: 99.9 % (Method 1), 100% (Method 2), 100% (Method 3); mp:118-120 °C; FT-IR (υ_{max}, cm^{-1}): 3174 (2NH), 3059 (ar-CH), 1672 (N=CH); ^{1}H-NMR (400 MHz, DMSO-*d*$_6$, δppm): 2.01 (d, 2H, CH_2, *J*=6.8 Hz), 3.05 (d, 2H, CH_2, *J*=5.6 Hz), 4.07 (d, 2H, CH_2, *J*=6.4 Hz), 6.65 (dd, 1H, ar-H, *J*=8.4 Hz), 6.92-6.99 (m, 1H, ar-H), 7.12-7.21 (m, 3H, ar-H), 7.45 (bs, 2H, ar-H), 7.76 (d, 1H, ar-H, *J*=8.8 Hz), 7.91 (d, 1H, ar-H, *J*=10.0 Hz), 8.16-8.18 (m, 1H, ar-H), 8.35 (dd, 1H, ar-H, *J*=6.8 Hz), 8.72 (bs, 2H, 2NH, D_2O exch.), 10.95 (s, 1H, N=C<u>H</u>); ^{13}C-NMR (400 MHz, DMSO-*d*$_6$, δppm): 30.73 (CH_2), 40.19 (CH_2), 44.37 (CH_2), arC: [102.15 and 102.80 (d, CH, *J*=65.0 Hz), 107.26 (2CH), 117.78 (C), 112.43 (CH), 112.70 (CH), 115.02 (CH), 115.76 (C), 118.32 (CH), 120.14 (CH), 121.10 (CH), 122.23 (CH), 123.13 (CH), 124.46 (C), 125.27 (C), 134.39 and 134.59 (d, C, J_{C-F}= 20.0 Hz), 146.93 and 150.57 (d, C, J_{C-F}=364 Hz)], 152.68 (N=<u>C</u>H); LC-MS: 367.47 ($[M+1]^+$, 70), 266.37 (100); Elemental Analysis for $C_{21}H_{20}FN_5$; Calculated (%): C, 69.79; H, 5.58; N, 19.38; Found (%): C, 69.74; H, 5.52; N, 19.34.

5-{[(4-[(3-(1*H*-Imidazol-1-yl)propyl]amino)-3-fluorophenyl)imino]methyl}-2-methoxyphenol (17d).

Recrystallised from ethyl acetate:diethyl ether (1:2); Yield: 58% (Method 1), 90% (Method 2), 100% (Method 3); mp: 138-139 °C; FT-IR (υ_{max}, cm^{-1}): 3356 (OH), 3228 (NH), 3082 (ar-CH), 1627 (N=C), 1260 (N=CH); ^{1}H-NMR (400 MHz, DMSO-d_6, δppm): 1.91 (bs, 2H, CH_2), 3.36 (bs, 4H, $2CH_2$), 3.78 (bs, 3H, OCH_3), 6.91-6.99 (m, 4H, ar-H), 7.13-7.20 (m, 3H, ar-H), 7.65 (s, 1H, ar-H), 7.82 (s, 1H, ar-H), 8.41 (s, 1H, NH, D_2O exch.), 9.26 (s, 1H, OH, D_2O exch.), 11.07 (s, 1H, N=C<u>H</u>); ^{13}C-NMR (400 MHz, DMSO-d_6, δppm: 30.31 (CH_2), 41.63 (CH_2), 44.23 (CH_2), 56.20 (OCH_3), arC: [102.32 and 102.69 (d, CH, *J*=36.3 Hz), 107.55 and 107.82 (d, CH, *J*=27.0 Hz), 112.15 (CH), 113.66 (CH), 120.13 (CH), 122.12 (CH), 122.78 (CH), 127.81 (C), 130.08 (C), 135.79 (C), 143.05 (CH), 145.73 (CH), 147.01 (C), 149.70 (C), 165.99 and 171.92 (d, C, $J_{C\text{-}F}$=592.5 Hz)], 156.94 (N=<u>C</u>H); LC-MS: 369.48 ($[M+1]^+$, 50), 273.38 (100); Elemental Analysis for $C_{20}H_{21}FN_4O_2$; Calculated (%): C, 65.20; H, 5.75; N, 15.21; Found (%): C, 65.20; H, 5.72; N, 15.20.

***N*'-[(1*H*-Indol-3-yl)methylene]-2-[(2-morpholinoethyl)amino]acetohydrazide (25a).**

Recrystallised from ethanol; Yield: 75% (Method 1), 90% (Method 2), 100% (Method 3); mp. 145-146 °C; FT-IR ($\upsilon_{max,}$ cm^{-1}): 3180 (2NH), 3059 (ar-CH), 1670 (C=O), 1577 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.50 (bs, 8H, $4CH_2$+ DMSO-d_6), 3.48 (bs, 6H, $3CH_2$+H_2O), 7.16-7.24 (m, 2H, ar-H), 7.46-7.48 (m, 1H, ar-H), 7.92 (bs, 1H, ar-H), 8.35 (d, 1H, ar-H, *J*=7.5 Hz), 8.91 (s, 1H, N=C<u>H</u>), 11.69 (s, 1H, NH, D_2O exch.); ^{13}C NMR (DMSO-d_6, δ ppm): 46.23 (CH_2), 46.82 (CH_2), 47.86 (CH_2), 53.51 ($2CH_2$), 66.12 ($2CH_2$), arC: [111.81 (CH), 120.51 (CH), 122.26 (CH), 122.93 (CH), 124.62 (C), 128.51 (C), 129.33 (CH), 136.24 (C)], 141.229 (N=<u>C</u>H), 170.47 (C=O); LC-MS: 329.47 ($[M]^+$, 25), 124.31 (100); Elemental Analysis for $C_{17}H_{23}N_5O_2$; Calculated (%): C, 61.99; H, 7.04; N, 21.26; Found (%): C, 61.99; H, 7.09; N, 21.27.

***N*'-(3-Hydroxy-4-methoxybenzylidene)-2-[(2-morpholinoethyl)amino]aceto hydrazide (25b).**

Recrystallised from ethanol; Yield: 98% (Method 1), 90% (Method 2), 100% (Method 3); mp. 151-152 °C; FT-IR ($\upsilon_{max,}cm^{-1}$): 3189 (2NH), 3051 (ar-CH), 1671 (C=O), 1549 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 2.49 (bs, 8H, $4CH_2$+ DMSO-d_6), 3.46 (bs, 6H, $3CH_2$+H_2O), 3.81 (s, 3H, OCH_3), 7.02 (d, 1H, ar-H, *J*=8.3 Hz), 7.23 (d, 1H, ar-H, *J*=8.3 Hz), 7.35 (bs, 1H, ar-H), 8.52 (s, 1H, N=C<u>H</u>), 9.33 (s, 3H, 2NH+OH, D_2O exch.); ^{13}C NMR (DMSO-d_6, δ ppm): 46.01 (CH_2), 46.67 (CH_2), 47.56 (CH_2), 52.91 ($2CH_2$), 56.32 (O<u>C</u>H_3), 66.71 ($2CH_2$), arC: [107.81 (CH), 114.51 (CH), 122.25 (CH), 128.93 (C), 147.23

(C), 148.91 (C)], 153.29 (N=CH), 170.37 (C=O); LC-MS: 337.42 ($[M+1]^+$, 30, 301.26 (100); Elemental Analysis for $C_{16}H_{24}N_4O_4$; Calculated (%): C, 57.13; H, 7.19; N, 16.66; Found (%): C, 57.13; H, 7.19; N, 16.67.

3-{[(2-Morpholinoethyl)amino]methyl}-4-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thione (23).

Recrystallised from butyl acetate:diethyl ether (2:1); Yield: 79% (Method 1), 89% (Method 2), 80% (Method 3); mp. 176-177 °C; FT-IR ($\upsilon_{max,}$ cm^{-1}): 3244 (2NH), 3035 (ar-CH), 2811 (SH), 1644 (C=N); ^{1}H NMR (DMSO-d_6, δ ppm): 1.97 (bs, 4H, $2CH_2$), 2.01 (bs, 4H, $2CH_2$), 3.33 (s, 2H, CH_2), 3.35 (bs, 4H, $2CH_2$), 7.18 (t, 1H, ar-H, *J*=9.6 Hz) 7.33 (t, 2H, ar-H, *J*=10.4 Hz), 7.59 (d, 2H, ar-H, *J*=10.4 Hz), 9.82 (s, 1H, NH, D_2O exch), 10.33 (s, 1H, NH, D_2O exch); ^{13}C NMR (DMSO-d_6, δ ppm): 42.128 (CH_2), 52.45 (CH_2), 55.09 (CH_2), 57.19 ($2CH_2$), 66.37 ($2CH_2$), arC:[124.19 (2CH), 125.63 (2CH), 128.49 (CH), 139.48 (C), 148.57 (triazole C-5)], 176.90 (triazole C-3); LC-MS: 301.47 ($[M-H_2O]^+$, 10), 114.33 (100); Elemental Analysis for $C_{15}H_{21}N_5OS$; Calculated (%): C, 56.40; H, 6.63; N, 21.92; Found (%): C, 56.41; H, 6.69; N, 21.92.

3,3-Dimethyl-6-{[(3-{[(2-morpholinoethyl)amino]methyl}-4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)methyl]amino}-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylic acid (24).

Recrystallised from butyl acetate: diethyl ether (2:1); Yield: 65% (Method 1), 80% (Method 2), 82% (Method 3); mp. 118-119 °C; FT-IR ($\upsilon_{max,}$ cm^{-1}): 3500 (OH), 3259 (2NH), 3032 (ar-CH), 1769 (C=O), 1660 (C=N), 1235 (C=S); ^{1}H NMR (DMSO-d_6, δ ppm): 1.45 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.73 (bs, 4H, $2CH_2$), 2.89 (bs, 4H, $2CH_2$), 3.09-3.64 (bs, 6H, $3CH_2+H_2O$), 4.28 (s, 1H, CH), 4.35 (s, 1H, CH), 5.07 (s, 1H, CH), 5.40 (s, 2H, CH_2), 7.30 (d, 2H, ar-H, *J*=12.0 Hz), 7.47 (d, 2H, ar-H, *J*=8.4 Hz), 7.58 (t, 2H, ar-H, *J*=7.6 Hz), 7.95 (s, 2H, 2NH, D_2O exch.), 10.07 (s, 1H, OH, D_2O exch). ^{13}C NMR (DMSO-d_6, δ ppm): Due to the slight solubility in NMR solvents, ^{13}C NMR could not be obtained; LC-MS: 548.47 ($[M+1]^+$, 30), 124.33 (100); Elemental Analysis for $C_{24}H_{33}N_7O_4S_2$; Calculated (%): C, 52.63; H, 6.07; N, 17.90; Found (%): C, 52.61; H, 6.09; N,