Supporting Information

SYNTHESIS AND ANTIOXIDANT ACTIVITY OF NEW THIAZOLE ANALOGUES

POSSESSING UREA, THIOUREA AND SELENOUREA FUNCTIONALITY

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Compounds Characterization

1-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)-3-(4-methoxyphenyl)urea (3b):

IR ($\nu_{\max}$, cm^{-1}): 3289 (N-H, stretch), 1719 (C=O, stretch), 1644 (C=O, stretch, urea), 1438 (C=N, stretch), 721 (C-Cl, stretch). ¹H NMR (400 MHz, CDCl₃): δ 3.74 (s, 3H, OCH₃), 5.68 (br s, 1H, NH), 7.26 (br s, 1H, NH), 6.77 – 7.68 (m, 12H, ArH). ¹³C NMR (100.6 MHz, CDCl₃, δ ppm): 56.0 (OCH₃), 113.5, 117.8, 121.5, 122.4, 124.1, 125.9, 126.5, 126.6, 126.9, 127.8, 128.3, 129.8, 130.1, 130.6, 132.5, 134.3, 135.3, 135.6, 138.0, 146.8, 153.9, 156.8 (CO (NH)₂), 160.8, 192.0 (CO). EI-MS (m/z , 70 eV): 498 (M+H)⁺. Anal. Calcd for C₂₄H₁₇Cl₂N₃O₂S: C 57.84; H 3.44; N 8.43. Found: C 57.76; H 3.43; N 8.45.

1-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)-3-(4-fluorophenyl)urea (3c):

IR ($\nu_{\max}$, cm^{-1}): 3369 (N-H, stretch), 1724 (C=O, stretch), 1654 (C=O, stretch, urea), 1436 (C=N, stretch), 718 (C-Cl, stretch). ¹H NMR (400 MHz, CDCl₃): δ 5.70 (br s, 1H, NH), 9.27 (br s, 1H, NH), 6.80 – 7.69 (m, 12H, ArH). ¹³C NMR (100.6 MHz, CDCl₃, δ ppm): 114.2, 115.3, 120.9, 122.8, 123.6, 124.8, 125.4, 126.5, 126.9, 127.9, 129.5, 130.3, 130.9, 132.6, 134.6, 135.5, 135.9,

138.1, 146.4, 153.5, 156.9 (CO (NH)₂), 161.8, 191.6 (CO). EI-MS (m/z, 70 eV): 486 (M+H)⁺.
Anal. Calcd for C₂₃H₁₄Cl₂FN₃O₂S: C 56.80; H 2.90; N 8.64. Found: C 56.76; H 2.93; N 8.72.

1-(4-bromophenyl)-3-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)urea (3d):

IR ($\nu_{\max}$, cm⁻¹): 3299 (N-H, stretch), 1709 (C=O, stretch), 1687 (C=O, stretch, urea), 1425 (C=N, stretch), 735 (C-Cl, stretch). ¹H NMR (400 MHz, CDCl₃): δ 5.51 (br s, 1H, NH), 9.21 (br s, 1H, NH), 6.90 – 7.72 (m, 12H, ArH). ¹³C NMR (100.6 MHz, CDCl₃, δ ppm): 114.2, 116.2, 120.1, 122.5, 123.6, 124.8, 125.4, 126.3, 126.9, 127.2, 128.3, 130.5, 130.8, 132.3, 135.3, 135.7, 135.9, 138.3, 146.4, 152.5, 160.8 (CO (NH)₂), 161.8, 192.3 (CO). EI-MS (m/z, 70 eV): 546 (M+H)⁺.
Anal. Calcd for C₂₃H₁₄BrCl₂N₃O₂S: C 50.48; H 2.58; N 7.68. Found: C 50.76; H 2.62; N 7.71.

1-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)-3-p-tolylthiourea (3e):

IR ($\nu_{\max}$, cm⁻¹): 3299 (N-H, stretch), 1707 (C=O, stretch), 1610 (C=O, stretch, thiourea), 1435 (C=N, stretch), 738 (C-Cl, stretch). ¹H NMR (400 MHz, CDCl₃): δ 2.22 (s, 3H, CH₃), 7.00 (br s, 1H, NH), 8.31 (br s, 1H, NH), 7.06 – 7.68 (m, 12H, ArH). ¹³C NMR (100.6 MHz, CDCl₃, δ ppm): 21.1 (CH₃), 117.8, 119.3, 120.9, 122.4, 125.7, 126.5, 126.6, 126.9, 127.8, 129.8, 130.1, 130.2, 130.6, 132.5, 132.7, 134.3, 135.6, 137.6, 138.0, 146.8, 179.3 (CS (NH)₂), 179.7, 192.0 (CO). EI-MS (m/z, 70 eV): 498 (M+H)⁺. Anal. Calcd for C₂₄H₁₇Cl₂N₃OS₂: C 57.83; H 3.44; N 8.43. Found: C 57.82; H 3.42; N 8.45.

1-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)-3-(4-methoxyphenyl)thiourea (3f):

IR ($\nu_{\max}$, cm⁻¹): 3289 (N-H, stretch), 1719 (C=O, stretch), 1590 (C=O, stretch, thiourea), 1455 (C=N, stretch), 722 (C-Cl, stretch). ¹H NMR (400 MHz, CDCl₃): δ 3.76 (s, 3H, OCH₃), 6.87 (br s, 1H, NH), 8.60 (br s, 1H, NH), 7.10 – 7.71 (m, 12H, ArH). ¹³C NMR (100.6 MHz, CDCl₃, δ ppm): 56.0 (OCH₃), 114.0, 117.8, 119.8, 122.2, 124.6, 126.5, 126.6, 126.9, 127.8, 129.8, 130.1,

130.6, 132.5, 133.0, 134.3, 135.3, 135.6, 138.0, 146.8, 151.9, 153.9, 179.7 (CS (NH)₂), 192.0 (CO). EI-MS (m/z, 70 eV): 514 (M+H)⁺. Anal. Calcd for C₂₄H₁₇Cl₂N₃O₂S₂: C 56.03; H 3.33; N 8.17. Found: C 56.02; H 3.32; N 8.16.

1-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)-3-(4-fluorophenyl)thiourea (3g):

IR ($\nu_{\max}$, cm⁻¹): 3249 (N-H, stretch), 1720 (C=O, stretch), 1590 (C=O, stretch, thiourea), 1443 (C=N, stretch), 778 (C-Cl, stretch). ¹H NMR (400 MHz, CDCl₃): δ 6.82 (br s, 1H, NH), 9.21 (br s, 1H, NH), 7.11 – 7.82 (m, 12H, ArH). ¹³C NMR (100.6 MHz, CDCl₃, δ ppm): 115.1, 118.2, 122.2, 123.5, 124.3, 125.4, 125.8, 126.4, 127.3, 129.4, 130.1, 130.5, 132.3, 133.4, 134.8, 135.4, 135.9, 138.4, 146.9, 150.9, 152.9, 181.4 (CS (NH)₂), 192.3 (CO). EI-MS (m/z, 70 eV): 502 (M+H)⁺. Anal. Calcd for C₂₃H₁₄Cl₂FN₃OS₂: C 54.98; H 2.81; N 8.36. Found: C 54.99; H 2.84; N 8.46.

1-(4-bromophenyl)-3-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)thiourea (3h):

IR ($\nu_{\max}$, cm⁻¹): 3324 (N-H, stretch), 1716 (C=O, stretch), 1580 (C=O, stretch, thiourea), 1453 (C=N, stretch), 744 (C-Cl, stretch). ¹H NMR (400 MHz, CDCl₃): δ 5.12 (br s, 1H, NH), 9.08 (br s, 1H, NH), 6.97 – 7.81 (m, 12H, ArH). ¹³C NMR (100.6 MHz, CDCl₃, δ ppm): 115.3, 117.4, 122.5, 124.8, 125.2, 126.2, 126.6, 126.9, 127.2, 129.4, 130.2, 130.9, 132.8, 133.3, 134.7, 135.1, 135.9, 138.2, 146.6, 151.5, 153.6, 180.7 (CS (NH)₂), 190.6 (CO). EI-MS (m/z, 70 eV): 562 (M+H)⁺. Anal. Calcd for C₂₃H₁₄BrCl₂N₃O₂S₂: C 49.04; H 2.51; N 7.46. Found: C 49.14; H 2.63; N 7.52.

1-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)-3-p-tolylselenourea (3i):

IR ($\nu_{\max}$, cm⁻¹): 3298 (N-H, stretch), 1743 (C=O, stretch), 1510 (C=O, stretch, selenourea), 1434 (C=N, stretch), 753 (C-Cl, stretch). ¹H NMR (400 MHz, CDCl₃): δ 2.23 (s, 3H, CH₃), 7.04 (br s,

1H, NH), 9.31 (br s, 1H, NH), 6.92 – 7.87 (m, 12H, ArH). ¹³C NMR (100.6 MHz, CDCl₃, δ ppm): 22.3(CH₃), 116.3, 121.4, 123.8, 124.1, 125.1, 126.2, 126.9, 127.6, 129.4, 130.1, 130.4, 130.9, 131.8, 132.3, 134.6, 135.4, 137.3, 138.4, 146.4, 179.9, 190.9 (CSe (NH)₂), 191.3 (CO). ⁷⁷Se NMR (76.3 MHz, CDCl₃): δ 260.95. EI-MS (m/z, 70 eV): 546 (M+H)⁺. Anal. Calcd for C₂₄H₁₇Cl₂N₃OSSe: C 52.86; H 3.14; N 7.71. Found: C 52.92; H 3.53; N 7.82.

1-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)-3-(4-methoxyphenyl)selenourea (3j):

IR (ν_{max}, cm⁻¹): 3285 (N-H, stretch), 1721 (C=O, stretch), 1534 (C=O, stretch, selenourea), 1434 (C=N, stretch), 754 (C-Cl, stretch). ¹H NMR (400 MHz, CDCl₃): δ 3.68 (s, 3H, OCH₃), 7.12 (s, 1H, NH), 9.63 (s, 1H, NH), 7.15 – 7.76 (m, 12H, ArH). ¹³C NMR (100.6 MHz, CDCl₃, δ ppm): 56.1 (OCH₃), 115.1, 117.3, 122.4, 123.6, 124.9, 126.2, 126.6, 126.9, 127.9, 129.4, 130.1, 130.7, 132.4, 133.5, 134.8, 135.1, 135.5, 138.4, 146.4, 151.5, 153.4, 191.1 (CSe (NH)₂), 191.4 (CO). ⁷⁷Se NMR (76.3 MHz, CDCl₃): δ 261.82. EI-MS (m/z, 70 eV): 561 (M+H)⁺. Anal. Calcd for C₂₄H₁₇Cl₂N₃O₂SSe: C 51.35; H 3.05; N 7.49. Found: C 51.42; H 3.14; N 7.82.

1-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)-3-(4-fluorophenyl)selenourea (3k):

IR (ν_{max}, cm⁻¹): 3302 (N-H, stretch), 1724 (C=O, stretch), 1587 (C=O, stretch, selenourea), 1434 (C=N, stretch), 753 (C-Cl, stretch). ¹H NMR (400 MHz, CDCl₃): δ 7.12 (br s, 1H, NH), 9.13 (br s, 1H, NH), 7.10 – 7.89 (m, 12H, ArH). ¹³C NMR (100.6 MHz, CDCl₃, δ ppm): 113.9, 117.5, 122.5, 123.1, 124.1, 125.3, 126.3, 127.1, 128.2, 129.7, 130.1, 130.8, 132.6, 133.6, 134.9, 135.6, 135.9, 138.1, 146.5, 151.2, 152.9, 191.2 (CSe (NH)₂), 192.3 (CO). EI-MS (m/z, 70 eV): 550 (M+H)⁺. Anal. Calcd for C₂₃H₁₄BrCl₂N₃OSSe: C 45.27; H 2.31; N 6.89. Found: C 45.92; H 2.34; N 6.93.

1-(4-bromophenyl)-3-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)selenourea (3l):

IR (ν_{max} , cm^{-1}): 3282 (N-H, stretch), 1730 (C=O, stretch), 1515 (C=O, stretch, selenourea), 1435 (C=N, stretch), 774 (C-Cl, stretch). ^1H NMR (400 MHz, CDCl_3): δ 7.05 (br s, 1H, NH), 9.04 (br s, 1H, NH), 7.12 – 7.89 (m, 12H, ArH). ^{13}C NMR (100.6 MHz, CDCl_3 , δ ppm): 114.8, 116.2, 199.3, 122.2, 123.8, 125.6, 126.1, 126.9, 127.3, 129.7, 130.2, 130.8, 132.9, 133.2, 134.4, 135.3, 135.9, 138.7, 146.8, 151.7, 153.7, 191.6 (CO), 192.7 (CSe (NH)₂). EI-MS (m/z , 70 eV): 610 ($\text{M}+\text{H}$)⁺. Anal. Calcd for $\text{C}_{23}\text{H}_{14}\text{BrCl}_2\text{N}_3\text{OSSe}$: C 45.27; H 2.31; N 6.89. Found: C 45.37; H 2.43; N 6.93.

^1H NMR Spectrum of compound **3d**

^{13}C NMR Spectrum of compound **3d**

Date Acquired : 4/01/2014 3:33:46 PM
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Sample ID : BVR-VBR-5
Data File : 26-41-448-BVR-VBR-5.lcd
Method File : FCL-+@-.lcm

Sample Information

ESI-MS Spectrum
VHR 26-41-448-BVR-VBR-5.lcd

Mass Spectrum of compound 3d

IR Spectrum of compound **3d**

⁷⁷Se NMR Spectrum of compound **31**

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Method filename: E:\Program Files\Thermo Finnigan\Eager 300 for EA1112\DATA\Sys_data_ex
Sample ID: VBR-1-Urea-CH3 (#3)
Analysis type: Unknown
Chromatogram filename: UNK-03849045-4.dat
Sample weight: 1.426

Element Name	Element %	Ret. Time
Nitrogen	8.73	0.88
Carbon	59.78	1.36
Hydrogen	3.57	4.82

CHN Spectrum of compound 3a

Table 2. *In vitro* antioxidant activity of **3a-l** by DPPH method

Compound	Concentration ($\mu\text{g/mL}$)				
	25	50	75	100	IC ₅₀
3a	37.26 $\pm$ 0.23	42.85 $\pm$ 1.23	47.27 $\pm$ 1.32	58.95 $\pm$ 0.82	22.95 $\pm$ 0.43
3b	42.23 $\pm$ 0.22	47.25 $\pm$ 0.21	51.21 $\pm$ 0.92	55.25 $\pm$ 0.52	21.43 $\pm$ 0.22
3c	44.84 $\pm$ 0.59	46.35 $\pm$ 1.13	49.89 $\pm$ 1.02	53.99 $\pm$ 0.12	20.33 $\pm$ 0.11
3d	39.06 $\pm$ 0.73	43.45 $\pm$ 0.13	46.17 $\pm$ 0.62	50.45 $\pm$ 0.92	19.89 $\pm$ 0.43
3e	40.37 $\pm$ 0.20	44.25 $\pm$ 0.83	49.87 $\pm$ 0.95	61.57 $\pm$ 0.91	17.95 $\pm$ 0.39
3f	44.73 $\pm$ 0.62	49.14 $\pm$ 1.87	54.82 $\pm$ 1.11	60.11 $\pm$ 0.44	18.17 $\pm$ 0.25
3g	47.28 $\pm$ 0.97	51.33 $\pm$ 0.34	55.23 $\pm$ 0.98	58.11 $\pm$ 0.85	18.32 $\pm$ 0.99
3h	45.24 $\pm$ 0.57	49.29 $\pm$ 1.33	52.36 $\pm$ 1.77	59.87 $\pm$ 0.84	17.36 $\pm$ 0.47
3i	61.88 $\pm$ 0.21	65.81 $\pm$ 1.55	69.11 $\pm$ 1.50	72.33 $\pm$ 0.94	16.47 $\pm$ 0.46
3j	64.38 $\pm$ 1.13	68.36 $\pm$ 0.23	71.08 $\pm$ 1.63	74.78 $\pm$ 0.81	15.17 $\pm$ 0.45
3k	73.22 $\pm$ 0.47	76.55 $\pm$ 1.22	79.22 $\pm$ 1.11	82.85 $\pm$ 0.19	16.98 $\pm$ 0.12
3l	75.48 $\pm$ 0.03	78.32 $\pm$ 1.09	81.47 $\pm$ 1.13	83.21 $\pm$ 0.32	15.89 $\pm$ 0.74
Ascorbic acid	76.28 $\pm$ 1.02	79.29 $\pm$ 0.85	82.74 $\pm$ 0.36	84.28 $\pm$ 0.85	14.33 $\pm$ 0.33
Vitamin E	77.17 $\pm$ 0.30	80.27 $\pm$ 0.37	81.36 $\pm$ 0.23	84.27 $\pm$ 0.42	13.91 $\pm$ 0.42
Blank	-	-	-	-	-

(-) showed no scavenging activity. Values were the means of three replicates $\pm$ SD

Table 3. *In vitro* antioxidant activity of **3a-l** by nitric oxide (NO) method

Compound	Concentration (µg/mL)				
	25	50	75	100	IC ₅₀
3a	38.21 ± 0.45	43.12 ± 0.24	47.43 ± 1.11	55.23 ± 0.44	22.65 ± 0.46
3b	40.49 ± 0.11	44.29 ± 1.22	50.49 ± 0.43	54.22 ± 0.54	21.46 ± 0.28
3c	43.22 ± 0.56	46.31 ± 1.11	51.11 ± 1.01	55.33 ± 0.92	20.31 ± 0.15
3d	45.06 ± 0.55	49.55 ± 0.97	53.86 ± 0.53	58.04 ± 0.33	20.15 ± 0.49
3e	46.11 ± 0.95	50.22 ± 0.94	56.83 ± 0.11	64.02 ± 0.38	21.94 ± 0.96
3f	50.72 ± 0.94	56.38 ± 1.29	61.72 ± 1.14	67.13 ± 0.67	20.19 ± 1.25
3g	55.95 ± 0.34	58.34 ± 0.32	62.99 ± 0.92	69.22 ± 0.92	19.82 ± 1.99
3h	58.66 ± 0.93	62.39 ± 1.32	67.94 ± 1.22	70.73 ± 0.43	18.63 ± 0.82
3i	67.33 ± 0.29	72.81 ± 1.32	75.12 ± 1.22	79.11 ± 0.22	17.65 ± 0.81
3j	70.38 ± 1.11	72.44 ± 0.22	75.22 ± 1.17	78.11 ± 0.45	16.19 ± 0.26
3k	77.49 ± 0.33	80.22 ± 1.76	84.34 ± 1.12	85.74 ± 0.33	15.36 ± 0.12
3l	79.43 ± 0.23	81.33 ± 1.19	84.23 ± 1.17	86.21 ± 0.74	14.43 ± 0.63
Ascorbic acid	82.11 ± 1.52	84.21 ± 0.66	86.22 ± 0.94	87.28 ± 0.23	13.34 ± 0.23
Vitamin E	76.13 ± 0.40	78.24 ± 0.34	81.34 ± 0.21	84.23 ± 0.44	13.94 ± 0.45
Blank	-	-	-	-	-

(-) showed no scavenging activity. Values were the means of three replicates ± SD

Table 4. *In vitro* antioxidant activity of **3a-l** by hydrogen peroxide (H₂O₂) method

Compound	Concentration (µg/mL)				
	25	50	75	100	IC ₅₀
3a	38.48 ± 0.11	43.65 ± 1.32	48.34 ± 1.23	57.43 ± 0.64	23.01 ± 0.54
3b	40.13 ± 0.26	46.95 ± 0.28	52.42 ± 0.53	56.34 ± 0.97	21.98 ± 0.75
3c	43.89 ± 0.89	47.38 ± 1.72	51.33 ± 1.97	55.32 ± 0.68	21.08 ± 0.44
3d	41.34 ± 0.63	45.43 ± 0.17	53.14 ± 0.35	57.34 ± 0.34	20.09 ± 0.54
3e	42.45 ± 0.23	46.23 ± 0.34	53.45 ± 0.23	62.54 ± 0.32	19.54 ± 0.46
3f	45.33 ± 0.65	51.43 ± 1.63	56.33 ± 1.16	66.12 ± 0.64	18.17 ± 0.25
3g	48.64 ± 0.47	54.34 ± 0.77	58.45 ± 0.34	67.13 ± 0.84	18.46 ± 0.64
3h	47.23 ± 0.65	53.54 ± 1.23	57.43 ± 1.43	60.45 ± 0.34	17.75 ± 0.35
3i	67.78 ± 0.97	71.81 ± 1.64	74.23 ± 1.43	77.33 ± 0.44	16.45 ± 0.45
3j	65.43 ± 1.17	71.33 ± 0.96	75.53 ± 1.32	79.34 ± 0.78	16.45 ± 0.78
3k	74.63 ± 0.35	78.34 ± 1.45	83.53 ± 1.34	85.34 ± 0.53	15.56 ± 0.53
3l	76.43 ± 0.86	79.46 ± 1.34	85.34 ± 1.55	87.45 ± 0.54	15.09 ± 0.36
Ascorbic acid	82.21 ± 1.01	84.23 ± 0.84	86.23 ± 0.67	89.12 ± 0.43	14.32 ± 0.30
Vitamin E	79.13 ± 0.34	81.34 ± 0.62	83.24 ± 0.25	85.26 ± 0.42	12.92 ± 0.42
Blank	-	-	-	-	-

(-) showed no scavenging activity. Values were the means of three replicates ± SD