Supplementary Materials for

Repurposing Synthetic Congeners of a Natural Product Aurone Unveils a Lead Antitumor Agent Inhibiting Folded P-Loop Conformation of MET Receptor Tyrosine Kinase

Ahmed H.E. Hassan [1,2,†], Cai Yi Wang [3,†], Cheol Jung Lee [4], Hye Rim Jeon [4], Yeonwoo Choi [4], Suyeon Moon [4], Chae Hyeon Lee [4], Yeon Ju Kim [4], Soo Bin Cho [4], Kazem Mahmoud [5], Selwan M. El-Sayed [1], Sang Kook Lee [3,*] and Yong Sup Lee [2,4,*]

[1] Department of Medicinal Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt

[2] Medicinal Chemistry Laboratory, Department of Pharmacy, College of Pharmacy, Kyung Hee University, 26 Kyungheedae-ro, Seoul 02447, Republic of Korea

[3] Natural Products Research Institute, College of Pharmacy, Seoul National University, Seoul 08826, Republic of Korea

[4] Department of Fundamental Pharmaceutical Sciences, Kyung Hee University, Seoul 02447, Republic of Korea

[5] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Egyptian Russian University, Badr City, Cairo, 11829, Egypt

*·Correspondence: kyslee@khu.ac.kr (Y.S.L.); sklee61@snu.ac.kr (S.K.L.)

† These authors contributed equally to this work.

1. Chemistry

1.1. Preparation of 6-methoxy-3-coumaranone [1]

Prepared as reported previously [1]. Yield = 58%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.0 Hz, 1H), 6.66 (dd, J = 8.0, 2.0 Hz, 1H), 6.55 (d, J = 2.0 Hz, 1H), 4.63 (s, 2H), 3.88 (s, 3H, OCH_3).

1.2. Preparation of 4-(methoxymethoxy)benzaldehyde [1]

Prepared as reported previously [1]. Yield = 78%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 7.89 (tt, J = 5.2, 2.6, 1.8 Hz, 2H), 7.22 (tt, J = 6.8, 2.8, 1.6 Hz, 2H), 5.78 (s, 2H), 3.42 (s, 3H).

1.3. Preparation of sulfuretin analogs [1]

Targeted compounds were prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation or base-catalyzed cross-aldol condensation.

(*Z*)-6-Hydroxy-2-(2-hydroxybenzylidene)benzofuran-3(2*H*)-one (1a) [2]

Compound **1a** was prepared as reported previously [2] employing acid-catalyzed cross-aldol condensation. Yield = 75%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.2 (brs, 1H), 10.3 (brs, 1H), 8.09 (dd, J = 6.4, 1.4 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.23 (dd, J = 6.8, 1.5 Hz, 1H), 7.09 (s, 1H), 6.94 (m, 2H), 6.71 (dd, J = 6.5, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.8, 186.2, 166.8, 157.6, 147.3, 131.8, 131.4, 126.3, 120.0, 119.3, 116.1, 113.4, 105.1, 99.0.

(*Z*)-6-Hydroxy-2-(3-hydroxybenzylidene)benzofuran-3(2*H*)-one (1b)

Compound **1b** was prepared as reported previously [2] employing acid-catalyzed cross-aldol condensation. Yield = 74%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.67 (d, J = 8.4 Hz, 1H), 7.43 (d, J =1.82 Hz, 1H), 7.38 (dd, J = 7.7, 7.3 Hz, 1H), 7.32 (dd, J = 7.9, 7.8 Hz, 1H), 6.88 (m, 1H), 6.81 (d, J = 1.8 Hz, 1H), 6.76 (dd, J =6.6, 1.9 Hz, 1H), 6.72 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.9, 168.3, 167.0, 158.0, 147.7, 133.6, 130.6, 126.4, 122.8, 117.7,

117.5, 113.5, 113.2, 11.1, 98.9, 98.2.

(*Z*)-6-Hydroxy-2-(4-hydroxybenzylidene)benzofuran-3(2*H*)-one (1c) [3]

Compound **1c** was prepared as reported previously [3] employing acid-catalyzed cross-aldol condensation. Yield = 78%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.1 (s, 1H), 10.1 (s, 1H), 7.83 (d, J = 8.6 Hz, 2H), 7.61 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 1.6 Hz, 1H), 6.73 (s, 1H), 6.72 (dd, J = 8.4, 1.6 Hz, 1H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 181.7, 168.0, 166.6, 159.7, 146.2, 133.7, 126.2, 123.5, 116.5, 113.6, 113.3, 111.9, 99.0

(*Z*)-2-(2,4-Dihydroxybenzylidene)-6-hydroxybenzofuran-3(2*H*)-one (1d) [2]

Compound **1d** was prepared as reported previously [2] employing base-catalyzed cross-aldol condensation. Yield = 7% yield.

^{1}H NMR (400 MHz, MeOD-d_4): δ 10.26 (brs, 1H), 10.00 (brs, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.10 (s, 1H), 6.75 (d, J = 1.8 Hz, 1H), 6.68 (dd, J = 6.4, 1.9 Hz, 1H), 6.38 (m, 2H); ^{13}C NMR (100 MHz, MeOD-d_4): δ 180.9, 167.1, 165.8, 160.8, 159.0, 145.0, 132.3, 125.4, 113.3, 112.6, 110.4, 108.2, 105.8, 102.2, 98.4.

(*Z*)-2-(2,5-Dihydroxybenzylidene)-6-hydroxybenzofuran-3(2*H*)-one (1e) [2]

Compound **1e** was prepared as reported previously [2] employing acid-catalyzed cross-aldol condensation. Yield = 7% yield).

^{1}H NMR (400 MHz, MeOD-d_4): δ 7.68 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 6.72-6.69 (m, 4H); ^{13}C NMR (400 MHz, MeOD-d_4): δ 182.5, 167.8, 166.1, 150.2, 149.1, 146.6, 124.8, 118.8, 118.0, 115.7, 115.1, 112.7, 111.9, 106.0, 97.2.

(*Z*)-2-(3,5-Dihydroxybenzylidene)-6-hydroxybenzofuran-3(2*H*)-one (1f) [1]

Compound **1f** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 7% yield.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.2 (brs, 1H), 9.47 (s, 2H), 7.59 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 2.0 Hz, 2H), 6.68 (m, 2H), 6.52 (s, 1H), 6.27 (t, J = 2.2 Hz, 1H'); ^{13}C NMR (125 MHz, DMSO-d_6): δ 182.0, 168.4, 167.1, 159.1, 147.7, 133.8, 126.6, 113.6, 113.3, 111.6, 109.8, 105.0, 98.9; HRMS calcd for C15H11O5 [M+H]+ 271.0607, found 271.0623.

(*Z*)-6-Hydroxy-2-(3,4,5-trihydroxybenzylidene)benzofuran-3(2*H*)-one (1g) [1]

Compound **1g** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 72%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.15 (brs, 1H), 9.18 (brm, 2H), 7.60 (d, J = 8.4 Hz, 1H), 6.95 (s, 2H), 6.73-6.69 (m, 2H), 6.54 (s, 1H); 13C NMR (100 MHz, DMSO-d_6): δ 181.5, 167.8, 166.5, 146.5, 146.1, 136.7, 126.2, 122.6, 113.6, 113.3, 111.3, 98.7.

(*Z*)-6-Hydroxy-2-(2-methoxybenzylidene)benzofuran-3(2*H*)-one (1h) [1]

Compound **1h** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 78% yield.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.19 (brs, 1H), 8.15 (dd, J = 6.3, 1.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.43 (m, 1H), 7.10 (m, 2H), 7.06 (s, 1H), 6.79 (d, J = 1.84 Hz, 1H), 6.72 (dd, J = 6.5, 1.8 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.3, 167.8, 166.4, 158.0, 147.3, 131.4, 130.9, 125.9, 120.8, 120.2, 113.0, 112.7, 111.4, 103.6, 98.6, 55.7.

(*Z*)-6-Hydroxy-2-(3-methoxybenzylidene)benzofuran-3(2*H*)-one (1i) [1]

Compound **1i** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 92% yield.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ 11.16 (brs, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.47 (d, J = 2.1 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 6.99 (dd, J = 5.6, 2.5, 1.9 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.74 (s, 1H), 6.71 (dd, J = 6.4, 1.9 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 181.9, 168.4, 167.1, 159.8, 147.9, 133.7, 130.4, 126.4, 123.9, 116.7, 115.8, 113.6, 113.1, 110.7, 99.1, 55.6.

(*Z*)-6-Hydroxy-2-(4-methoxybenzylidene)benzofuran-3(2*H*)-one (1j) [1]

Compound **1j** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 87% yield.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.17 (brs, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 1.8 Hz, 1H), 6.84 (s, 1H), 6.79 (dd, J = 6.5, 1.9 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, DMSO-*d*6): δ 181.7, 168.1, 166.7, 160.9, 146.6, 133.4, 126.2, 125.0, 115.0, 113.5, 113.3, 111.2, 99.0, 55.7.

(*Z*)-2-(2,3-Dimethoxybenzylidene)-6-hydroxybenzofuran-3(2*H*)-one (1k) [1]

Compound **1k** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 97% yield.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.12 (brs, 1H), 7.80 (dd, J = 8.0, 1.6 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.0, 1.6 Hz, 1H), 6.98 (s, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.74 (dd, J = 8.4, 1.8 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, DMSOd_6): δ 182.0, 168.5, 167.2, 153.1, 152.7, 148.7, 148.5, 126.6, 125.1, 122.9, 115.1, 113.7, 113.2, 104.2, 99.2, 61.6, 56.3.

(*Z*)-2-(2,5-Dimethoxybenzylidene)-6-hydroxybenzofuran-3(2*H*)-one (1l) [1]

Compound **1l** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 93% yield.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.2 (brs, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.05-7.02 (m, 3H), 6.82 (d, J = 1.8 Hz, 1H), 6.74 (dd, J = 8.4, 1.8 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.9, 168.4, 167.1, 153.6, 153.1, 148.0, 126.5, 121.4, 117.0, 116.7, 113.6, 113.3, 113.0, 104.1, 99.3, 56.7, 56.0.

(*Z*)-2-(3,4-Dimethoxybenzylidene)-6-hydroxybenzofuran-3(2*H*)-one (1m) [1]

Compound **1m** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 50%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 11.1 (brs, 1H), 7.62-7.54 (m, 3H), 7.06 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 15.0

Hz, 1H), 6.77 (s, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 3.82 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.6, 168.0, 166.7, 150.8, 149.1, 146.6, 126.2, 125.5, 125.2, 114.6, 113.4, 113.0, 112.3, 111.6, 99.0, 55.9 (2C).

(*Z*)-2-(3,5-Dimethoxybenzylidene)-6-hydroxybenzofuran-3(2*H*)-one (1n) [1]

Compound **1n** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 67%.

^{1}H NMR (400 MHz, Pyridine-d_5): δ 7.82 (d, *J* = 8.4 Hz, 1H), 7.29 (d, *J* = 2.1 Hz, 2H), 7.19 (s, 1H), 7.02 (dd, *J* = 5.2, 1.8 Hz, 1H), 6.93 (dd, *J* = 6.5, 1.8 Hz, 1H), 6.70 (dd, *J* = 2.1 Hz, 1H), 3.72 (s, 6H).

(*Z*)-6-Hydroxy-2-(2,3,4-trimethoxybenzylidene)benzofuran-3(2*H*)-one (1o) [1]

Compound **1o** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 95%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 11.16 (brs, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 6.9 Hz, 1H), 6.86 (s, 1H), 6.73 (d, *J* = 1.9 Hz, 1H), 6.67 (dd, *J* = 8.1, 1.9 Hz, 1H), 3.84 (s, 6H), 3.74 (s, 3H); 13C NMR (125 MHz, DMSO-*d*6): δ 181.6, 168.2, 166.9, 155.7, 153.5, 147.4, 142.2, 126.9, 126.5, 118.8, 113.5 (2C), 109.2, 104.6, 99.1, 62.2, 61.0, 56.6.

(*Z*)-6-Hydroxy-2-(4-(methoxymethoxy)benzylidene)benzofuran-3(2*H*)-one (1p) [1]

Compound **1p** was prepared as reported previously [1] employing base-catalyzed cross-aldol condensation. Yield = 86%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (brs, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 1.8 Hz, 2H), 6.71 (dd, *J* = 8.4, 1.8 Hz, 1H), 5.27 (s, 2H), 3.37 (s, 3H) ; ^{13}C NMR (125 MHz, DMSO-d_6): δ 181.9, 168.3, 166.9, 158.4, 146.9, 133.4, 133.2, 126.4, 126.1, 117.0, 116.3, 113.5, 111.1, 99.1, 98.3, 94.2, 56.3.

(*Z*)-2-(2-Hydroxybenzylidene)-6-methoxybenzofuran-3(2*H*)-one (1q) [1]

Compound **1q** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 76%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.4 (s, 1H), 8.15 (dd, J = 8.0, 1.2 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.31 (td, J = 8.0, 1.2 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.16 (s, 1H), 6.98−6.93 (m, 2H), 6.87 (dd, J = 8.4, 2.0 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.6, 167.8, 167.2, 157.2, 146.8, 131.5, 131.0, 125.4, 119.6, 118.7, 115.8, 114.0, 112.6, 105.2, 97.1, 56.4.

(*Z*)-2-(3-Hydroxybenzylidene)-6-methoxybenzofuran-3(2*H*)-one (1r) [1]

Compound **1r** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 27%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.41−7.40 (m, 2H) 7.32 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 2.0, 1H), 6.88−6.86 (m, 2H), 6.76 (s, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 182.2, 168.5, 167.9, 158.1, 147.6, 133.5, 130.4, 126.0, 122.9, 118.0, 117.7, 114.3, 113.2, 111.7, 97.6, 56.9.

(*Z*)-2-(4-Hydroxybenzylidene)-6-methoxybenzofuran-3(2*H*)-one (1s) [1]

Compound **1s** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 39%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.2 (brs, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.87 (dd, J = 8.4, 2.0 Hz, 1H), 6.80 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.4, 167.5, 167.0, 159.4, 145.6, 133.4 (2C), 125.2, 122.9, 116.0 (2C), 114.2, 112.4, 112.0, 97.0, 56.3.

(*Z*)-2-(2,3-Dihydroxybenzylidene)-6-methoxybenzofuran-3(2*H*)-one (1t) [1]

Compound **1t** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 26%.

^{1}H NMR (500 MHz, DMSO-d_6): δ 7.64 (d, J = 8.6 Hz, 1H), 7.57 (dd, J = 8.0, 1.5 Hz, 1H), 7.14 (s, 1H), 7.11 (d, J = 2.2 Hz, 1H), 6.82−6.79 (m, 2H), 6.71 (t, J = 7.9 Hz, 1H), 3.88 (s, 3H) , 3.12 (s, 1H), , 2.49 (s, 1H); ^{13}C NMR (125 MHz, DMSO-*d*6): δ 182.1, 168.3, 167.7, 147.2, 146.8, 146.1, 125.9, 121.8, 119.9, 119.8, 117.4, 114.6, 113.1, 106.5, 97.7, 40.9; HRMS calcd for C16H13O5 $[M+H]^+$ 285.0763, found 285.0764.

(*Z*)-2-(2,4-Dihydroxybenzylidene)-6-methoxybenzofuran-3(2*H*)-one (1u) [1]

Compound **1u** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 12%.

^{1}H NMR (400 MHz, DMSO-d_6): δ 10.40 (s, 1H), 10.10 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 2.4 Hz, 1H), 7.10 (s, 1H), 6.86 (dd, J = 8.8, 2.4 Hz, 1H), 6.42−6.38 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 181.1, 167.2, 166.7, 161.0, 159.3, 145.0, 132.5, 125.0, 114.5, 112.3, 110.5, 108.3, 106.5, 102.3, 97.0, 56.3.

(*Z*)-2-(3,4-Dihydroxybenzylidene)-6-methoxybenzofuran-3(2*H*)-one (1v) [1]

Compound **1v** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 58%.

^{1}H NMR (400 MHz, methanol-d_4) δ 7.68 (dd, J = 8.8, 4.4 Hz, 1H), 7.52 (s, 1H), 7.29 (dd, J = 8.4, 2.4 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.86−6.82 (m, 2H), 6.73 (d, J = 4.4 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 181.3, 167.4, 166.9 (2C), 148.2, 145.5, 125.2, 124.6, 123.3, 118.2, 116.0, 114.3, 112.5, 112.4, 96.9, 56.3.

(*Z*)-6-Methoxy-2-(2-methoxybenzylidene)benzofuran-3(2*H*)-one (1w) [1]

Compound **1w** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 69%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, J = 8.0, 2.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 7.38 (td, J = 8.0, 2.0 Hz, 1H), 7.07 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.77−6.73 (m, 2H), 3.92 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 168.4, 167.2, 158.7, 147.9, 131.8, 131.1, 125.8, 121.5, 120.8, 115.1, 112.0, 110.8, 106.1, 96.6, 56.0, 55.6.

(*Z*)-6-Methoxy-2-(3-methoxybenzylidene)benzofuran-3(2*H*)-one (1x) [1]

Compound **1x** was prepared as reported previously [1] employing acid-catalyzed cross-aldol condensation. Yield = 36%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.0 Hz, 1H), 7.48−7.46 (m, 2H), 7.38 (t, J = 8.0 Hz, 1H), 6.96 (m, J =

8.0, 2.0 Hz, 1H), 6.79–6.75 (m, 3H), 3.93 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 168.6, 167.5, 159.8, 148.0, 133.7, 129.8, 125.9, 124.1, 116.5, 115.4, 114.9, 112.2, 111.7, 96.7, 56.1, 55.4.

2. *In vitro* evaluation of antiproliferative mechanisms

General Experimental Procedures. General Experimental Procedures. Roswell Park Memorial Institute (RPMI) 1640 medium, Dulbecco Modified Eagle Medium (DMEM) High glucose, Eagle Minimum Essential Medium (EMEM), fetal bovine serum (FBS), antibiotic−antimycotic solution (100×), trypsin−EDTA solution (1×), and phosphate-buffered saline (PBS; 1×) were purchased from HyClone Laboratories, Inc. (South Logan, UT, USA). Laemmli sample buffer (2×) and 2-mercaptomethanol were purchased from Bio-Rad Laboratories, Inc. (Hercules, CA, USA). Dimethyl sulfoxide (DMSO), bicinchoninic acid (BCA), copper(II) sulfate solution, bovine serum albumin (BSA), trichloroacetic acid (TCA), SRB, ribonuclease A (RNase A), and paclitaxel were purchased from Sigma-Aldrich (St. Louis, MO, USA). Anti-Cleaved PARP, anti-Caspas 8, anti-Cleaved Caspas 8, anti-Caspas 9, anti-Cleaved Caspas 9, anti-CDK4, anti-CDK6 and anti-Cdc25C were purchased from Cell Signaling Technology (Danvers, MA, USA). Anti-PARP, anti-Cyclin D1, anti-Cyclin E was purchased from BD Biosciences (Franklin Lakes, NJ, USA). Anti-β-actin were purchased from Santa Cruz Technology (Santa Cruz, CA, USA).

Cell Culture. HCT116 cells (Human colon cancer), MDA-MB-231 cells (Human breast cancer) and A549 cells (Human lung cancer) were purchased from ATCC (Manassas, VA, USA). HCT116 cells were cultured in RPMI medium, which added with 10% FBS and 1% antibiotics−antimycotics (AA). Cells were Suspended in DMEM medium which added with 10% FBS and 1% antibiotics−antimycotics (AA) (PSF; 100 units/mL penicillin G sodium, 100 μg/mL streptomycin, and 250 ng/mL amphotericin B). Cells were cultured at 37 °C in 96 well plates under a humidified atmosphere containing 5% CO_2.

Cell Viability Assay. After 72 h of sample treatment, the cell viability was measured by using the sulforhodamine B (SRB) assay as described previously [4]. Briefly, after incubated with different concentrations of compounds for 72 h, the cells were fixed with 10% trichloroacetic acid (TCA) and stained with SRB solution in 0.1% acetic acids. The stained proteins precipitate was dissolved in 10 mM Tris solution at pH 10 and measured by a Versamax ELISA machine at 515 nm.

Western blotting. HCT116 cells (1×10^5 cells/mL in a 60 mm dish) were cultured with the various concentrations of compounds for 24h, 48h. The cells were collected and lysed in 2×sample loading buffer (250 mM Tris-HCl pH 6.8, 4% SDS, 10% glycerol, 0.006% bromophenol blue, 2% β-mercaptoethanol, 50 mM sodium fluoride, and 5 mM sodium orthovanadate). Run the protein samples with the marker on 6–12% SDS-PAGE gel and transferred onto PVDF membranes (Millipore, Bedford, MA, USA). The membranes were blocked with 5% BSA in Tris-buffered saline containing 0.1% Tween-20 (TBST) for 30 min at room temperature, and then incubated with primary antibodies in 2.5% BSA in TBST overnight at 4 °C on a shaker. After the membranes were washed three times with TBST, they were incubated with the secondary antibodies (HRP) (Younginfrontier, Seoul, Korea) diluted in TBST for 2 h at room temperature. And the membranes were further exposed to enhanced chemiluminescence (ECL) solution (Intron, Daejon, Korea) after washing with TBST. The chemiluminescence signals were measured by using LAS-4000 (Fuji Film Corp., Tokyo, Japan).

Cell Cycle Analysis. The above cultured cells were starved in serum-free medium for 8h before the compound sample treatment. After treatment, cells were collected using trypsin, washed with PBS, and fixed with 70% ethanol. The cell lines were dyed with propidium iodide (PI) mixed with RNase, and flow cytometry analysis was performed as described previously [5].

Annexin V-FITC/PI Staining. After the cell lines were treated with compounds for 48 h, they were collected, washed with cold PBS, and resuspended in 1× binding buffer. Then each set of them were dyed with annexin V-FITC and PI and incubated at ambient temperature for 15 min. the analysis cell apoptosis was performed after Flow cytometry assay.

References

[1] A.H.E. Hassan, T.N. Phan, Y. Choi, S. Moon, J.H. No, Y.S. Lee, Design, Rational Repurposing, Synthesis, In Vitro Evaluation, Homology Modeling and In Silico Study of Sulfuretin Analogs as Potential Antileishmanial Hit Compounds, Pharmaceuticals, 15 (2022) 1058.

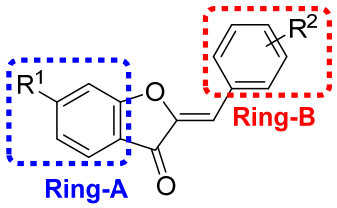
[2] A.H.E. Hassan, H.J. Kim, M.S. Gee, J.-H. Park, H.R. Jeon, C.J. Lee, Y. Choi, S. Moon, D. Lee, J.K. Lee, K.D. Park, Y.S. Lee, Positional scanning of natural product hispidol's ring-B: discovery of highly selective human monoamine oxidase-B inhibitor analogues downregulating neuroinflammation for management of neurodegenerative diseases, J. Enzyme Inhib. Med. Chem., 37 (2022) 768-780.

[3] S.Y. Shin, M.C. Shin, J.-S. Shin, K.-T. Lee, Y.S. Lee, Synthesis of aurones and their inhibitory effects on nitric oxide and PGE2 productions in LPS-induced RAW 264.7 cells, Bioorg. Med. Chem. Lett., 21 (2011) 4520-4523.

[4] W.S. Byun, M. Jin, J. Yu, W.K. Kim, J. Song, H.-J. Chung, L.S. Jeong, S.K. Lee, A novel selenonucleoside suppresses tumor growth by targeting Skp2 degradation in paclitaxel-resistant prostate cancer, Biochem. Pharmacol., 158 (2018) 84-94.

[5] C. Jung, J.-Y. Hong, S.Y. Bae, S.S. Kang, H.J. Park, S.K. Lee, Antitumor Activity of Americanin A Isolated from the Seeds of Phytolacca americana by Regulating the ATM/ATR Signaling Pathway and the Skp2–p27 Axis in Human Colon Cancer Cells, J. Nat. Prod., 78 (2015) 2983-2993.

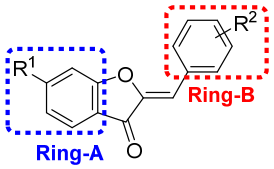
Table S1. % Growth inhibition of diverse blood cancer cell lines triggered by 10 μM concentrations of sulfuretin and its prepared analogs (**1a**–**x**).



1a–x

Comp	R^1	R^2	CCRFCEM	MOLT4	HL60(TB)	K562	RPMI8226
1a	6-Hydoxy	2'-Hydoxy	0.34	4.13	NI	2.64	NI
1b	6-Hydoxy	3'-Hydoxy	1.34	NI	NI	5.19	NI
1c	6-Hydoxy	4'-Hydoxy	3.08	NI	NI	3.43	NI
1d	6-Hydoxy	2',4'-Dihydoxy	NI	NI	NI	NI	NI
1e	6-Hydoxy	2',5'-Dihydoxy	NI	NI	0.99	1.02	NI
1f	6-Hydoxy	3',5'-Dihydoxy	3.81	NI	5.88	10.38	NI
1g	6-Hydoxy	3',4',5'-Trihydoxy	NI	NI	NI	0.65	NI
1h	6-Hydoxy	2'-Methoxy	NI	NI	NI	1.41	NI
1i	6-Hydoxy	3'-Methoxy	NI	NI	0.53	1.15	NI
1j	6-Hydoxy	4'-Methoxy	NI	NI	1.40	3.23	NI
1k	6-Hydoxy	2',3'-Dimethoxy	NI	NI	2.89	4.56	NI
1l	6-Hydoxy	2',5'-Dimethoxy	3.86	NI	4.32	6.78	7.77
1m	6-Hydoxy	3',4'-Dimethoxy	3.92	11.07	30.69	9.71	1.05
1n	6-Hydoxy	3',5'-Dimethoxy	26.19	15.78	54.49	30.19	12.37
1o	6-Hydoxy	2',3',4'-Trimethoxy	NI	1.92	30.27	0.77	0.35
1p	6-Hydoxy	4'-Methoxymethoxy	NI	1.12	0.76	1.71	NI
1q	6-Methoxy	2'-Hydoxy	NI	3.36	6.14	6.88	NI
1r	6-Methoxy	3'-Hydoxy	4.88	NI	2.22	3.50	7.88
1s	6-Methoxy	4'-Hydoxy	32.35	NI	9.18	10.69	NI
1t	6-Methoxy	2',3'-Dihydoxy	72.84	57.69	37.53	14.63	32.70
1u	6-Methoxy	2',4'-Dihydoxy	NI	NI	NI	0.68	NI
1v	6-Methoxy	3',4'-Dihydoxy	47.35	35.26	34.04	7.29	22.21
1w	6-Methoxy	2'-Methoxy	NI	0.96	8.51	13.64	NI
1x	6-Methoxy	3'-Methoxy	NI	NI	NI	NI	NI
Sulfuretin	6-Hydoxy	3',4'-Dihydoxy	17.34	11.66	NI	6.33	2.04

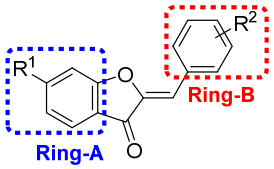
Table S2. % Growth inhibition of diverse non-small cell lung cancer cell lines triggered by 10 μM concentrations of sulfuretin and its prepared analogs (**1a**−**x**).



1a–x

Comp	R^1	R^2	A549	EKVX	HOP62	H23	H322M	HOP92	H460
1a	6-Hydoxy	2'-Hydoxy	NI	2.51	NI	NI	2.14	NI	NI
1b	6-Hydoxy	3'-Hydoxy	NI	5.76	NI	NI	1.06	9.70	NI
1c	6-Hydoxy	4'-Hydoxy	0.70	NI	NI	NI	6.56	NI	NI
1d	6-Hydoxy	2',4'-Dihydoxy	NI	2.99	0.03	NI	NI	4.19	NI
1e	6-Hydoxy	2',5'-Dihydoxy	NI	3.27	NI	NI	NI	NI	NI
1f	6-Hydoxy	3',5'-Dihydoxy	NI	NI	NI	NI	NI	NI	NI
1g	6-Hydoxy	3',4',5'-Trihydoxy	0.35	4.54	NI	NI	NI	NI	NI
1h	6-Hydoxy	2'-Methoxy	NI	4.15	NI	NI	NI	NI	NI
1i	6-Hydoxy	3'-Methoxy	5.92	7.66	1.44	1.30	NI	NI	NI
1j	6-Hydoxy	4'-Methoxy	0.07	6.51	NI	NI	NI	NI	NI
1k	6-Hydoxy	2',3'-Dimethoxy	NI	0.61	NI	NI	NI	NI	NI
1l	6-Hydoxy	2',5'-Dimethoxy	1.23	8.62	NI	3.91	7.43	1.80	8.36
1m	6-Hydoxy	3',4'-Dimethoxy	NI	NI	NI	NI	NI	NI	NI
1n	6-Hydoxy	3',5'-Dimethoxy	27.03	8.86	4.18	9.81	29.10	2.70	37.75
1o	6-Hydoxy	2',3',4'-Trimethoxy	NI	NI	NI	NI	NI	NI	NI
1p	6-Hydoxy	4'-Methoxymethoxy	NI	4.42	NI	2.46	4.35	NI	NI
1q	6-Methoxy	2'-Hydoxy	NI	3.96	3.92	7.64	2.05	7.15	NI
1r	6-Methoxy	3'-Hydoxy	NI	7.71	2.41	2.32	4.52	5.90	NI
1s	6-Methoxy	4'-Hydoxy	6.55	4.62	NI	0.06	5.50	NI	0.21
1t	6-Methoxy	2',3'-Dihydoxy	33.72	17.87	10.96	29.89	27.62	4.63	38.23
1u	6-Methoxy	2',4'-Dihydoxy	2.89	NI	NI	NI	9.05	NI	NI
1v	6-Methoxy	3',4'-Dihydoxy	8.48	NI	NI	NI	10.51	NI	5.90
1w	6-Methoxy	2'-Methoxy	8.95	NI	NI	NI	4.57	8.80	NI
1x	6-Methoxy	3'-Methoxy	NI	NI	NI	NI	NI	NI	NI
Sulfuretin	6-Hydoxy	3',4'-Dihydoxy	NI	NI	NI	NI	0.93	NI	NI

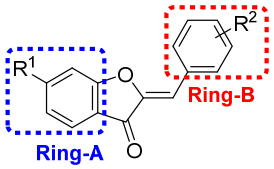
Table S3. % Growth inhibition of diverse colorectal cancer cell lines triggered by 10 μM concentrations of sulfuretin and its prepared analogs (**1a**–**x**).



1a–x

Comp	R^1	R^2	HCC2998	HCT116	HCT15	KM12	SW620
1a	6-Hydoxy	2'-Hydoxy	NI	NI	NI	NI	NI
1b	6-Hydoxy	3'-Hydoxy	NI	NI	7.28	NI	NI
1c	6-Hydoxy	4'-Hydoxy	NI	NI	6.80	NI	NI
1d	6-Hydoxy	2',4'-Dihydoxy	NI	NI	NI	NI	NI
1e	6-Hydoxy	2',5'-Dihydoxy	NI	3.67	NI	NI	NI
1f	6-Hydoxy	3',5'-Dihydoxy	NI	15.40	NI	NI	NI
1g	6-Hydoxy	3',4',5'-Trihydoxy	NI	16.80	NI	NI	NI
1h	6-Hydoxy	2'-Methoxy	NI	NI	1.10	NI	NI
1i	6-Hydoxy	3'-Methoxy	NI	1.04	6.73	NI	NI
1j	6-Hydoxy	4'-Methoxy	NI	15.48	0.83	NI	NI
1k	6-Hydoxy	2',3'-Dimethoxy	NI	0.76	NI	NI	NI
1l	6-Hydoxy	2',5'-Dimethoxy	0.70	20.85	24.96	NI	7.80
1m	6-Hydoxy	3',4'-Dimethoxy	NI	NI	NI	3.15	NI
1n	6-Hydoxy	3',5'-Dimethoxy	NI	40.81	51.76	6.80	25.32
1o	6-Hydoxy	2',3',4'-Trimethoxy	NI	NI	NI	NI	NI
1p	6-Hydoxy	4'-Methoxymethoxy	NI	NI	1.66	NI	NI
1q	6-Methoxy	2'-Hydoxy	NI	6.96	0.36	NI	NI
1r	6-Methoxy	3'-Hydoxy	NI	1.35	5.01	NI	2.27
1s	6-Methoxy	4'-Hydoxy	0.55	NI	3.12	NI	NI
1t	6-Methoxy	2',3'-Dihydoxy	21.28	45.53	69.49	33.70	39.95
1u	6-Methoxy	2',4'-Dihydoxy	NI	2.93	4.59	9.47	NI
1v	6-Methoxy	3',4'-Dihydoxy	NI	11.03	24.00	22.08	4.78
1w	6-Methoxy	2'-Methoxy	NI	9.66	8.51	13.52	10.61
1x	6-Methoxy	3'-Methoxy	NI	NI	0.22	NI	NI
Sulfuretin	6-Hydoxy	3',4'-Dihydoxy	NI	NI	10.67	9.49	NI

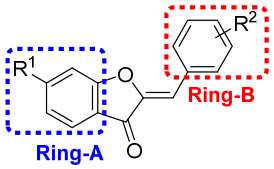
Table S4. % Growth inhibition of diverse brain cancer cell lines triggered by 10 μM concentrations of sulfuretin and its prepared analogs (**1a**−**x**).



1a–x

Comp	R^1	R^2	SF268	SNB75	SF295	SF539	SNB19	U251
1a	6-Hydoxy	2'-Hydoxy	NI	15.81	3.54	NI	2.81	NI
1b	6-Hydoxy	3'-Hydoxy	NI	24.83	5.38	4.56	3.50	NI
1c	6-Hydoxy	4'-Hydoxy	NI	15.49	1.53	11.94	12.88	3.02
1d	6-Hydoxy	2',4'-Dihydoxy	NI	1.32	NI	NI	NI	NI
1e	6-Hydoxy	2',5'-Dihydoxy	NI	NI	NI	NI	NI	NI
1f	6-Hydoxy	3',5'-Dihydoxy	3.63	1.99	NI	NI	NI	1.71
1g	6-Hydoxy	3',4',5'-Trihydoxy	NI	1.20	NI	NI	NI	NI
1h	6-Hydoxy	2'-Methoxy	NI	NI	NI	NI	NI	NI
1i	6-Hydoxy	3'-Methoxy	0.75	NI	1.02	NI	NI	5.99
1j	6-Hydoxy	4'-Methoxy	NI	NI	1.62	2.33	1.24	3.16
1k	6-Hydoxy	2',3'-Dimethoxy	NI	NI	NI	NI	NI	NI
1l	6-Hydoxy	2',5'-Dimethoxy	12.68	11.38	1.43	4.57	4.47	10.54
1m	6-Hydoxy	3',4'-Dimethoxy	11.64	13.83	1.67	3.87	9.83	2.40
1n	6-Hydoxy	3',5'-Dimethoxy	30.13	45.46	10.11	16.36	11.29	35.13
1o	6-Hydoxy	2',3',4'-Trimethoxy	NI	NI	NI	NI	4.52	NI
1p	6-Hydoxy	4'-Methoxymethoxy	2.23	7.33	7.70	NI	19.12	14.28
1q	6-Methoxy	2'-Hydoxy	3.91	0.43	NI	NI	5.45	NI
1r	6-Methoxy	3'-Hydoxy	4.36	8.09	1.95	4.93	2.87	0.84
1s	6-Methoxy	4'-Hydoxy	12.38	15.19	NI	7.49	5.00	6.65
1t	6-Methoxy	2',3'-Dihydoxy	47.38	37.49	6.23	41.46	15.10	39.65
1u	6-Methoxy	2',4'-Dihydoxy	10.53	16.25	NI	NI	4.53	3.01
1v	6-Methoxy	3',4'-Dihydoxy	30.38	29.82	NI	20.95	8.36	16.06
1w	6-Methoxy	2'-Methoxy	7.56	17.41	6.27	2.43	0.84	17.67
1x	6-Methoxy	3'-Methoxy	4.80	15.83	2.88	NI	0.30	NI
Sulfuretin	6-Hydoxy	3',4'-Dihydoxy	5.36	19.89	NI	21.03	5.68	4.36

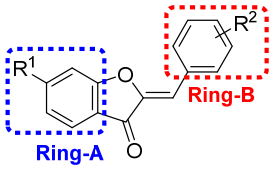
Table S5. % Growth inhibition of diverse melanoma cancer cell lines triggered by 10 μM concentrations of sulfuretin and its prepared analogs (**1a**–**x**).



1a–x

Comp	R^1	R^2	LOXIMVI	M14	MDAMB435	MALME3M	SKMEL28	SKMEL5	UACC257	UACC62
1a	6-Hydoxy	2'-Hydoxy	NI	NI	NI	NI	NI	1.25	NI	5.05
1b	6-Hydoxy	3'-Hydoxy	NI	NI	NI	3.19	NI	5.14	NI	3.09
1c	6-Hydoxy	4'-Hydoxy	NI	NI	1.98	NI	NI	0.62	NI	6.68
1d	6-Hydoxy	2',4'-Dihydoxy	NI	NI	NI	3.51	NI	0.93	0.00	0.65
1e	6-Hydoxy	2',5'-Dihydoxy	4.67	NI	0.90	NI	NI	2.47	NI	NI
1f	6-Hydoxy	3',5'-Dihydoxy	6.28	6.94	NI	6.27	NI	1.66	NI	NI
1g	6-Hydoxy	3',4',5'-Trihydoxy	10.36	4.35	NI	NI	NI	3.91	NI	NI
1h	6-Hydoxy	2'-Methoxy	NI	NI	0.11	5.85	NI	1.62	NI	NI
1i	6-Hydoxy	3'-Methoxy	4.26	4.25	4.70	5.34	NI	0.52	NI	NI
1j	6-Hydoxy	4'-Methoxy	NI	12.89	1.64	5.96	NI	0.31	NI	0.84
1k	6-Hydoxy	2',3'-Dimethoxy	NI	5.56	NI	5.19	NI	2.41	NI	NI
1l	6-Hydoxy	2',5'-Dimethoxy	11.44	26.80	17.29	23.96	11.49	7.61	NI	11.00
1m	6-Hydoxy	3',4'-Dimethoxy	NI	NI	2.36	NI	NI	3.20	NI	1.84
1n	6-Hydoxy	3',5'-Dimethoxy	37.54	46.55	26.59	36.44	13.35	26.94	20.47	30.02
1o	6-Hydoxy	2',3',4'-Trimethoxy	NI	NI	2.43	3.63	NI	5.81	NI	NI
1p	6-Hydoxy	4'-Methoxymethoxy	NI	NI	NI	2.55	15.00	8.18	NI	9.37
1q	6-Methoxy	2'-Hydoxy	2.15	3.96	NI	4.22	NI	1.18	NI	6.57
1r	6-Methoxy	3'-Hydoxy	2.35	NI	1.66	NI	NI	0.32	NI	7.73
1s	6-Methoxy	4'-Hydoxy	4.35	NI	12.63	2.65	NI	NI	1.83	0.66
1t	6-Methoxy	2',3'-Dihydoxy	53.65	9.56	25.87	25.35	17.81	28.60	0.23	27.84
1u	6-Methoxy	2',4'-Dihydoxy	NI	3.53	29.88	7.72	NI	NI	NI	6.57
1v	6-Methoxy	3',4'-Dihydoxy	12.50	NI	8.54	4.17	4.00	0.36	NI	7.38
1w	6-Methoxy	2'-Methoxy	NI	4.48	27.82	8.71	0.45	3.19	3.82	15.46
1x	6-Methoxy	3'-Methoxy	NI	NI	3.09	NI	0.46	NI	NI	8.83
Sulfuretin	6-Hydoxy	3',4'-Dihydoxy	NI	NI	4.57	NI	NI	7.52	NI	5.21

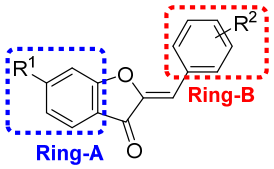
Table S6. % Growth inhibition of diverse ovarian cancer cell lines triggered by 10 μM concentrations of sulfuretin and its prepared analogs (**1a**–**x**).



1a–x

Comp	R^1	R^2	IGROV1	OVCAR3	OVCAR4	OVCAR5	OVCAR8	ADRRES
1a	6-Hydoxy	2'-Hydoxy	NI	NI	NI	NI	NI	NI
1b	6-Hydoxy	3'-Hydoxy	NI	NI	1.81	NI	NI	NI
1c	6-Hydoxy	4'-Hydoxy	NI	NI	NI	NI	NI	NI
1d	6-Hydoxy	2',4'-Dihydoxy	NI	NI	NI	NI	NI	NI
1e	6-Hydoxy	2',5'-Dihydoxy	NI	NI	NI	NI	NI	NI
1f	6-Hydoxy	3',5'-Dihydoxy	NI	NI	NI	NI	1.12	NI
1g	6-Hydoxy	3',4',5'-Trihydoxy	NI	NI	NI	NI	NI	NI
1h	6-Hydoxy	2'-Methoxy	NI	NI	NI	NI	NI	NI
1i	6-Hydoxy	3'-Methoxy	2.99	NI	6.04	NI	NI	1.15
1j	6-Hydoxy	4'-Methoxy	NI	NI	NI	NI	NI	-6.12
1k	6-Hydoxy	2',3'-Dimethoxy	NI	NI	NI	NI	NI	NI
1l	6-Hydoxy	2',5'-Dimethoxy	10.73	4.23	13.31	NI	14.42	7.10
1m	6-Hydoxy	3',4'-Dimethoxy	NI	NI	NI	NI	2.79	NI
1n	6-Hydoxy	3',5'-Dimethoxy	43.54	19.41	28.79	5.35	25.20	6.80
1o	6-Hydoxy	2',3',4'-Trimethoxy	NI	NI	NI	NI	NI	NI
1p	6-Hydoxy	4'-Methoxymethoxy	0.72	NI	NI	NI	NI	1.50
1q	6-Methoxy	2'-Hydoxy	NI	NI	11.58	NI	1.34	3.75
1r	6-Methoxy	3'-Hydoxy	2.45	NI	14.94	NI	3.53	NI
1s	6-Methoxy	4'-Hydoxy	0.27	NI	5.24	NI	8.97	NI
1t	6-Methoxy	2',3'-Dihydoxy	62.54	76.89	46.14	21.03	27.81	39.87
1u	6-Methoxy	2',4'-Dihydoxy	8.62	7.99	0.82	NI	0.73	1.54
1v	6-Methoxy	3',4'-Dihydoxy	23.35	16.75	18.63	5.13	3.57	5.72
1w	6-Methoxy	2'-Methoxy	4.40	3.12	4.53	3.20	1.78	NI
1x	6-Methoxy	3'-Methoxy	NI	NI	4.65	NI	NI	0.79
Sulfuretin	6-Hydoxy	3',4'-Dihydoxy	NI	0.96	4.46	NI	NI	NI

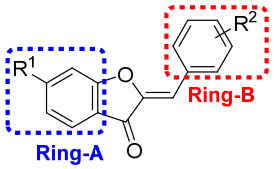
Table S7. % Growth inhibition of diverse renal cancer cell lines triggered by 10 μM concentrations of sulfuretin and its prepared analogs (**1a**−**x**).



1a–x

Comp	R^1	R^2	786O	CAKI1	ACHN	RXF393	SN12C	UO31
1a	6-Hydoxy	2'-Hydoxy	6.35	4.77	NI	NI	NI	NI
1b	6-Hydoxy	3'-Hydoxy	18.19	4.38	NI	NI	1.16	NI
1c	6-Hydoxy	4'-Hydoxy	9.49	NI	NI	NI	3.56	NI
1d	6-Hydoxy	2',4'-Dihydoxy	3.42	3.75	1.79	NI	1.01	13.36
1e	6-Hydoxy	2',5'-Dihydoxy	0.31	0.59	NI	NI	NI	1.35
1f	6-Hydoxy	3',5'-Dihydoxy	0.28	0.99	NI	NI	0.53	3.98
1g	6-Hydoxy	3',4',5'-Trihydoxy	0.93	NI	NI	NI	NI	7.89
1h	6-Hydoxy	2'-Methoxy	0.02	5.72	NI	NI	1.80	10.71
1i	6-Hydoxy	3'-Methoxy	12.66	23.69	NI	NI	NI	18.70
1j	6-Hydoxy	4'-Methoxy	3.59	9.11	NI	NI	NI	14.45
1k	6-Hydoxy	2',3'-Dimethoxy	NI	NI	NI	NI	NI	4.43
1l	6-Hydoxy	2',5'-Dimethoxy	10.54	6.33	31.67	19.47	14.21	39.71
1m	6-Hydoxy	3',4'-Dimethoxy	NI	12.69	NI	NI	5.60	8.55
1n	6-Hydoxy	3',5'-Dimethoxy	23.64	65.63	45.39	38.87	23.38	53.08
1o	6-Hydoxy	2',3',4'-Trimethoxy	NI	3.71	NI	NI	NI	11.33
1p	6-Hydoxy	4'-Methoxymethoxy	10.90	1.41	NI	NI	11.54	0.32
1q	6-Methoxy	2'-Hydoxy	11.33	1.80	NI	NI	5.74	21.90
1r	6-Methoxy	3'-Hydoxy	5.73	7.23	NI	NI	3.58	21.38
1s	6-Methoxy	4'-Hydoxy	8.21	9.26	NI	NI	2.02	23.43
1t	6-Methoxy	2',3'-Dihydoxy	19.63	56.79	33.79	27.15	42.29	69.47
1u	6-Methoxy	2',4'-Dihydoxy	5.14	5.78	NI	NI	6.70	11.41
1v	6-Methoxy	3',4'-Dihydoxy	1.07	27.20	NI	NI	22.35	50.03
1w	6-Methoxy	2'-Methoxy	10.71	17.04	3.39	NI	5.58	13.05
1x	6-Methoxy	3'-Methoxy	8.72	9.79	NI	NI	0.09	0.98
Sulfuretin	6-Hydoxy	3',4'-Dihydoxy	6.04	3.30	NI	NI	8.36	6.56

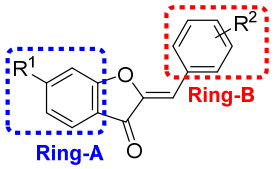
Table S8. % Growth inhibition of diverse prostate cancer cell lines triggered by 10 μM concentrations of sulfuretin and its prepared analogs (**1a**–**x**).



1a–x

Comp	R^1	R^2	PC3	DU145
1a	6-Hydoxy	2'-Hydoxy	NI	NI
1b	6-Hydoxy	3'-Hydoxy	NI	NI
1c	6-Hydoxy	4'-Hydoxy	NI	NI
1d	6-Hydoxy	2',4'-Dihydoxy	1.60	NI
1e	6-Hydoxy	2',5'-Dihydoxy	NI	NI
1f	6-Hydoxy	3',5'-Dihydoxy	0.38	NI
1g	6-Hydoxy	3',4',5'-Trihydoxy	3.49	NI
1h	6-Hydoxy	2'-Methoxy	NI	NI
1i	6-Hydoxy	3'-Methoxy	NI	6.41
1j	6-Hydoxy	4'-Methoxy	NI	NI
1k	6-Hydoxy	2',3'-Dimethoxy	NI	NI
1l	6-Hydoxy	2',5'-Dimethoxy	4.50	22.55
1m	6-Hydoxy	3',4'-Dimethoxy	0.51	NI
1n	6-Hydoxy	3',5'-Dimethoxy	9.19	37.22
1o	6-Hydoxy	2',3',4'-Trimethoxy	NI	NI
1p	6-Hydoxy	4'-Methoxymethoxy	1.55	NI
1q	6-Methoxy	2'-Hydoxy	NI	NI
1r	6-Methoxy	3'-Hydoxy	NI	NI
1s	6-Methoxy	4'-Hydoxy	NI	NI
1t	6-Methoxy	2',3'-Dihydoxy	10.05	32.09
1u	6-Methoxy	2',4'-Dihydoxy	NI	NI
1v	6-Methoxy	3',4'-Dihydoxy	5.56	7.73
1w	6-Methoxy	2'-Methoxy	0.44	1.50
1x	6-Methoxy	3'-Methoxy	NI	NI
Sulfuretin	6-Hydoxy	3',4'-Dihydoxy	NI	NI

Table S9. % Growth inhibition of diverse breast cancer cell lines triggered by 10 μM concentrations of sulfuretin and its prepared analogs (**1a**–**x**).



1a–x

Comp	R^1	R^2	MCF7	BT549	MDAMB231	MDAMB468
1a	6-Hydoxy	2'-Hydoxy	NI	NI	NI	NI
1b	6-Hydoxy	3'-Hydoxy	NI	NI	NI	NI
1c	6-Hydoxy	4'-Hydoxy	NI	NI	NI	1.05
1d	6-Hydoxy	2',4'-Dihydoxy	NI	NI	NI	1.93
1e	6-Hydoxy	2',5'-Dihydoxy	NI	NI	NI	NI
1f	6-Hydoxy	3',5'-Dihydoxy	NI	NI	NI	NI
1g	6-Hydoxy	3',4',5'-Trihydoxy	2.60	5.91	NI	NI
1h	6-Hydoxy	2'-Methoxy	0.99	NI	NI	NI
1i	6-Hydoxy	3'-Methoxy	NI	20.43	NI	NI
1j	6-Hydoxy	4'-Methoxy	NI	7.25	NI	NI
1k	6-Hydoxy	2',3'-Dimethoxy	NI	NI	6.87	NI
1l	6-Hydoxy	2',5'-Dimethoxy	5.77	20.23	NI	NI
1m	6-Hydoxy	3',4'-Dimethoxy	NI	NI	NI	NI
1n	6-Hydoxy	3',5'-Dimethoxy	22.80	45.64	7.24	13.57
1o	6-Hydoxy	2',3',4'-Trimethoxy	NI	NI	NI	NI
1p	6-Hydoxy	4'-Methoxymethoxy	NI	NI	1.70	NI
1q	6-Methoxy	2'-Hydoxy	17.10	9.74	2.51	NI
1r	6-Methoxy	3'-Hydoxy	26.79	4.51	3.89	0.43
1s	6-Methoxy	4'-Hydoxy	NI	21.09	NI	NI
1t	6-Methoxy	2',3'-Dihydoxy	48.96	37.85	37.51	19.42
1u	6-Methoxy	2',4'-Dihydoxy	NI	7.28	NI	3.77
1v	6-Methoxy	3',4'-Dihydoxy	NI	16.70	16.52	5.96
1w	6-Methoxy	2'-Methoxy	6.52	9.03	NI	24.09
1x	6-Methoxy	3'-Methoxy	NI	NI	NI	1.90
Sulfuretin	6-Hydoxy	3',4'-Dihydoxy	NI	NI	3.89	1.16