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SUPPLEMENTARY MATERIAL TO

Synthesis and biological activity of novel zingerone–thiohydantoin hybrids

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SPECTRAL AND ANALYTICAL DATA

*4-(3-methoxy-4-propoxyphenyl)butan-2-one (**1c**)*

Yield: 0.947 g (80 %). IR (KBr): 2963m, 2877m, 1714s, 1589w, 1514s, 1465m, 1419m, 1363m, 1258s, 1231s, 1158m, 1138s, 1036m, 978m, 800m cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, δ / ppm): 6.74 (d, 1H, J = 8.0, H-9), 6.71 (s, 1H, H-6), 6.69 (d, 1H, J = 8.2 Hz, H-10), 3.94 (t, 2H, J = 6.8 Hz, CH_2-12), 3.84 (s, 3H, CH_3-11), 2.68-2.88 (m, 4H, CH_2-3, CH_2-4), 2.13 (s, 3H, CH_3-1), 1.84 (sext, 2H, J = 7.2 Hz, CH_2-13), 1.02 (t, 3H, J = 7.5 Hz, CH_3-14). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 208.01 (C2), 149.14 (C7), 146.71 (C8), 133.44 (C5), 119.94 (C10), 112.99 (C9), 112.02 (C6), 70.42 (C12), 55.78 (C11), 45.24 (C4), 29.94 (C3), 29.20 (C1), 22.34 (C13), 10.28 (C14).

*4-(4-isopropoxy-3-methoxyphenyl)butan-2-one (**1d**)*

Yield: 0.926 g (78 %). IR (KBr): 2975m, 2933m, 1714s, 1587w, 1510s, 1465m, 1451m, 1419m, 1369m, 1259s, 1229m, 1157m, 1138m, 1110m, 1035m, 955w, 806w cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, δ / ppm): 6.65-6.83 (m, 3H, H-6, H-9, H-10), 4.46 (sept, 1H, J = 6.0 Hz, CH-12), 3.83 (s, 3H, CH_3-11), 2.68-2.90 (m, 4H, CH_2-3, CH_2-4), 2.14 (s, 3H, CH_3-1), 1.33 (d, 6H, J = 6.2 Hz, CH_3-13, CH_3-14). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 208.24 (C2), 150.24 (C7), 145.44 (C8), 134.02 (C5), 119.98 (C10), 116.01 (C9), 112.28 (C6), 71.45 (C12), 55.8 (C11), 45.31 (C4), 30.04 (C3), 29.30 (C1), 22.02 (C13, C14).

*4-(4-butoxy-3-methoxyphenyl)butan-2-one (**1e**)*

Yield: 1.088 g (87 %). IR (KBr): 2957m, 2935m, 2872w, 1715s, 1589m, 1514s, 1465m, 1419m, 1362m, 1257s, 1233s, 1158s, 1139s, 1034s, 972, 800m cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, δ / ppm): 6.79 (d, 1H, J = 7.8 Hz, H-9), 6.71 (s, 1H, H-6), 6.69 (d, 1H, J = 8.0 Hz, H-10), 3.98 (t, 2H, J = 6.8 Hz, CH_2-12), 3.84 (s, 3H, CH_3-11), 2.68-2.88 (m, 4H, CH_2-3, CH_2-4), 2.13 (s, 3H, CH_3-1), 1.81 (quint, 2H, J = 3.6 Hz, CH_2-13), 1.48 (sext, 2H, J = 3.7 Hz, CH_2-14), 0.96 (t, 3H, J = 7.3 Hz, CH_3-15). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 208.03 (C2),

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149.17 (C7), 146.78 (C8), 133.44 (C5), 119.96 (C10), 112.97 (C9), 112.04 (C6), 68.65 (C12), 55.81 (C11), 45.28 (C4), 31.14 (C3), 29.98 (C1), 29.24 (C13), 19.07 (C14), 13.74 (C15).

*4-(3-methoxy-4-((2-methylallyl)oxy)phenyl)butan-2-one (**1g**)*

Yield: 0.942 g (76 %). IR (KBr): 2938w, 1714s, 1603w, 1515s, 1452m, 1430m, 1364m, 1268s, 1235m, 1158m, 1140m, 1035m, 906w, 860w, 809w, 630w cm^{-1}.^{1}H NMR (200 MHz, $CDCl_3$, δ / ppm): 6,83 (d, 1H, J = 7.8 Hz, H-9) 6.77 (s, 1H, H-6) 6.67 (d, 1H, J = 7.2 Hz, H-10), 5.07 (m, 1H, H-14), 4.96 (m, 1H, H-14), 3.86 (s, 3H, CH_3-11), 2.67-2.90 (m, 4H, CH_2-3, CH_2-4), 2.14 (s, 3H, CH_3-1), 1.82 (s, 3H, CH_3-15). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 207.85 (C2), 148.99 (C7), 146.63 (C8), 143.89 (C13), 133.99 (C5), 120.03 (C10), 114.02 (C9), 112.46 (C14), 111.04 (C6), 72.95 (C12), 56.04 (C11), 45.52 (C4), 30.08 (C3), 29.44 (C1), 19.32 (C15).

*3-((4-(3,4-dimethoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2a**)*

Yield: 0.439 g (68 %). IR (KBr): 3152w, 3079w, 2935m, 1722s, 1638s, 1604s, 1515s, 1452m, 1418m, 1346m, 1257s, 1158m, 1138m, 1035m, 897w, 844w, 799w, 702w, 632w, 516w cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, δ / ppm): 9.98 (bs, NH, exchangeable with D_2O), 6.95 (d, 1H, J = 11.6 Hz, H-14), 6.86 (d, 1H, J = 8.4 Hz, H-15), 6.79 (s, 1H, H-11), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.75 (s, 2H, CH_2-5), 2.57-2.96 (m, 4H, CH_2-8, CH_2-9), 2.03 (s, 3H, CH_3-6). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 173.02 (C2), 167.29 (C4), 160.76 (C7), 149.26 (C12), 148.90 (C13), 135.70 (C10), 127.11 (C15), 120.16 (C14), 111.49 (C11), 55.96 (C16, C17), 40.55 (C9), 33.04 (C5), 31.91 (C8), 13.34 (C6). (+)LC-HRMS (*m*/*z*): calculated for $[C_{15}H_{19}O_3N_3S + H]^+$ 320.1074, observed 320.1220. Combustion analysis for $C_{15}H_{19}O_3N_3S$: Calculated. C 56.06, H 5.96, N 13.07; found C 56.10, H 5.98, N 13.04.

*3-((4-(4-ethoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2b**)*

Yield: 0.465 g (69 %). IR (KBr): 3148m, 2983m, 1724s, 1694s, 1636s, 1602s, 1515s, 1449w, 1418w, 1344m, 1255m, 1233m, 1197m, 1154m, 1137m, 1032m, 896w, 792w, 701w, 516w cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, δ / ppm): 9.68 (bs, NH, exchangeable with D_2O), 6.70-6.86 (m, 3H, H-11, H-14, H-15), 3.87 (s, 3H, CH_3-16), 3.75 (s, 2H, CH_2-5), 2.55-2.93 (m, 4H, CH_2-8, CH_2-9), 2.02 (s, 3H, CH_3-6), 1.45 (t, 3H, J = 7.0 Hz, CH_3-18). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 172.95 (C2), 167.35 (C4), 160.40 (C7), 149.32 (C12), 143.84 (C13), 134.17 (C10), 120.94 (C15), 114.30 (C14), 111.11 (C11), 64.55 (C17), 56.01 (C16), 40.58 (C9), 32.99 (C5), 32.00 (C8), 17.86 (C6), 14.94 (C18). (+)LC-HRMS (*m*/*z*): calculated for $[C_{16}H_{21}O_3N_3S + H]^+$ 336.1376, observed 336.1378. Combustion analysis for $C_{16}H_{21}O_3N_3S$: Calculated. C 57.29, H 6.31, N 12.53; found C 57.33, H 6.33, N 14.49.

*3-((4-(3-methoxy-4-propoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2c**)*

Yield: 0.504 g (72 %). IR (KBr): 3142m, 2965m, 2933m, 2876m, 1709s, 1633s, 1598s, 1516s, 1470m, 1454m, 1418m, 1347m, 1256s, 1230s, 1160m, 1135m, 1034m, 1019m, 978w, 897w, 796m, 702w, 516w, 500w cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, δ / ppm): 9.33 (bs, NH, exchangeable with D_2O), 6.65-6.85 (m, 3H, H-11, H-14, H-15), 3.95 (t, 2H, J = 6.8 Hz, CH_2-17), 3.86 (s, 3H, CH_3-16), 3.75 (s, 2H, CH_2-5), 2.56-2.94 (m, 4H, CH_2-8, CH_2-9), 2.02 (s, 3H, CH_3-6), 1.86 (sext, 2H, J = 7.2 Hz, CH_2-18), 1.03 (t, 3H, J = 7.4 Hz, CH_3-19). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 172.66 (C2), 167.40 (C4), 159.90 (C7), 149.44 (C12), 146.94 (C13), 134.17 (C10), 120.28 (C15), 113.53 (C14), 112.59 (C11), 70.85 (C17), 56.13 (C16), 40.52 (C9), 32.93 (C5), 31.67 (C8), 22.64 (C18), 17.83 (C6), 10.48 (C19). (+)LC-HRMS (*m*/*z*): calculated for $[C_{17}H_{23}O_3N_3S + H]^+$ 350.1533, observed 350.1532. Combustion

analysis for $C_{17}H_{23}O_3N_3S$: Calculated. C 58.43, H 6.63, N 12.02; found C 58.40, H 6.30, N 12.06.

3-((4-(4-isopropoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one ***(2d)***

Yield: 0.228 g (33 %). IR (KBr): 2973m, 2931m, 2857w, 1717s, 1639s, 1610s, 1511s, 1465m, 1334m, 1262s, 1157w, 1139m, 1111m, 1037w, 956w, 850w, 809w, 736w, 710w, 514w cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, δ / ppm): 9.39 (bs, NH, exchangeable with D_2O), 6.66-6.87 (m, 3H, H-11, H-14, H-15), 4.47 (sept, 1H, J = 6.2 Hz, CH-17), 3.85 (s, 3H, CH_3-16), 3.75 (s, 2H, CH_2-5), 2.56-2.94 (m, 4H, CH_2-8, CH_2-9), 2.02 (s, 3H, CH_3-6), 1.35 (d, 6H, J = 6.0 Hz, CH_3-18, CH_3-19). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 172.82 (C2), 167.33 (C4), 160.97 (C7), 150.54 (C12), 145.63 (C13), 134.76 (C10), 120.28 (C15), 116.75 (C14), 112.81 (C11), 71.83 (C17), 56.08 (C16), 40.49 (C9), 32.97 (C5), 32.02 (C8), 22.24 (C18, C19), 17.84 (C6). (+)LC-HRMS (m/z): calculated for $[C_{17}H_{23}O_3N_3S + H]^+$ 350.1533, observed 350.1533. Combustion analysis for $C_{17}H_{23}O_3N_3S$: Calculated. C 58.43, H 6.63, N 12.02; found C 58.45, H 6.36, N 11.98.

3-((4-(4-butoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one ***(2e)***

Yield: 0.637 g (88 %). IR (KBr): 3145m, 2958m, 2935m, 2871m, 1709s, 1636s, 1604s, 1517s, 1467m, 1419m, 1346m, 1257s, 1234s, 1161m, 1138m, 1034m, 1009w, 972w, 897w, 844w, 795w, 701w, 516w cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, δ / ppm): 9.27 (bs, NH, exchangeable with D_2O), 6.65-6.85 (m, 3H, H-11, H-14, H-15), 3.99 (t, 2H, J = 6.8 Hz, CH_2-17), 3.86 (s, 3H, CH_3-16), 3.75 (s, 2H, CH_2-5), 2.56-2.94 (m, 4H, CH_2-8, CH_2-9), 2.02 (s, 3H, CH_3-6), 1.82 (quint, 2H, J = 7.3 Hz, CH_2-18), 1.48 (sext, 2H, J = 7.4 Hz, CH_2-19), 0.97 (t, 3H, J = 7.2 Hz, CH_3-20). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 172.73 (C2), 167.37 (C4), 159.97 (C7), 149.46 (C12), 147.00 (C13), 134.15 (C10), 120.28 (C15), 113.50 (C14), 112.60 (C11), 69.03 (C17), 56.13 (C16), 40.51 (C9), 32.94 (C5), 31.96 (C8), 31.41 (C18), 19.27 (C19), 17.82 (C6), 13.88 (C20). (+)LC-HRMS (m/z): calculated for $[C_{18}H_{25}O_3N_3S + H]^+$ 364.1689, observed 364.1689. Combustion analysis for $C_{18}H_{25}O_3N_3S$: Calculated. C 59.48, H 6.93, N 11.56; found C 59.44, H 6.95, N 11.51.

3-((4-(4-(benzyloxy)-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one ***(2f)***

Yield: 0.686 g (86 %). IR (KBr): 3152w, 3035w, 3954w, 2870w, 1710s, 1639s, 1605s, 1515s, 1455w, 1418w, 1345m, 1256s, 1227s, 1161m, 1136m, 1034w, 1011w, 857w 806w, 745m, 698m, 515w cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, δ / ppm): 8.97 (bs, NH, exchangeable with D_2O), 7.25-7.50 (m, 5H, H-19, H-20, H-21, H22, H-23), 6.65-6.85 (m, 3H, H-11, H-14, H-15), 5.13 (s, 2H, CH_2-17), 3.88 (s, 3H, CH_3-16), 3.74 (s, 2H, CH_2-5), 2.55-2.93 (m, 4H, CH_2-8, CH_2-9), 2.00 (s, 3H, CH_3-6). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 172.52 (C2), 167.34 (C4), 160.12 (C7), 149.71 (C12), 146.58 (C13), 137.46 (C18), 134.86 (C10), 128.43 (C19, C23), 127.69 (C21), 127.26 (C20, C22), 120.28 (C15), 114.65 (C14), 112.65 (C11), 71.41 (C17), 56.13 (C16), 40.45 (C9), 32.90 (C5), 31.97 (C8), 17.83 (C6). (+)LC-HRMS (m/z): calculated for $[C_{21}H_{23}O_3N_3S + H]^+$ 398.1533, observed 398.1532. Combustion analysis for $C_{21}H_{23}O_3N_3S$: Calculated. C 63.45, H 5.83, N 10.57; found C 63.50, H 5.81, N 10.62.

*3-((4-(3-methoxy-4-((2-methylallyl)oxy)phenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2g**)*

Yield: 0.441 g (61 %). IR (KBr): 3150m, 3079m, 2934m, 2852w, 1709s, 1634s, 1601s, 1514s, 1452m, 1418m, 1346m, 1256s, 1158m, 1137m, 1034m, 896w, 834w, 798w, 701w, 516w cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, δ / ppm): 9.79 (bs, NH, exchangeable with D_2O), 6.65-6.85 (m, 3H, H-11, H-14, H-15), 5.08 (m, 1H, H-19), 4.97 (m, 1H, H-19), 4.49 (s, 2H, CH_2-17), 3.87 (s, 3H, CH_3-16), 3.75 (s, 2H, CH_2-5), 2.55-2.94 (m, 4H, CH_2-8, CH_2-9), 2.02 (s, 3H, CH_3-6), 1.82 (s, 3H, CH_3-20). ^{13}C NMR (50 MHz, $CDCl_3$, δ / ppm): 173.02 (C2), 167.27 (C4), 160.53 (C7), 149.50 (C12), 146.63 (C13), 141.06 (C18), 134.54 (C10), 120.21 (C15), 114.13 (C14), 112.64 (C11), 112.42 (C19), 73.05 (C17), 56.11 (C16), 40.47 (C9), 32.99 (C5), 31.94 (C8), 19.34 (C20), 17.84 (C6). (+)LC-HRMS (*m*/*z*): calculated for $[C_{18}H_{23}O_3N_3S + H]^+$ 362.1533, observed 362.1533. Combustion analysis for $C_{18}H_{23}O_3N_3S$: Calculated. C 59.81, H 6.41, N 11.63; found C 59.86, H 6.44, N 11.58.

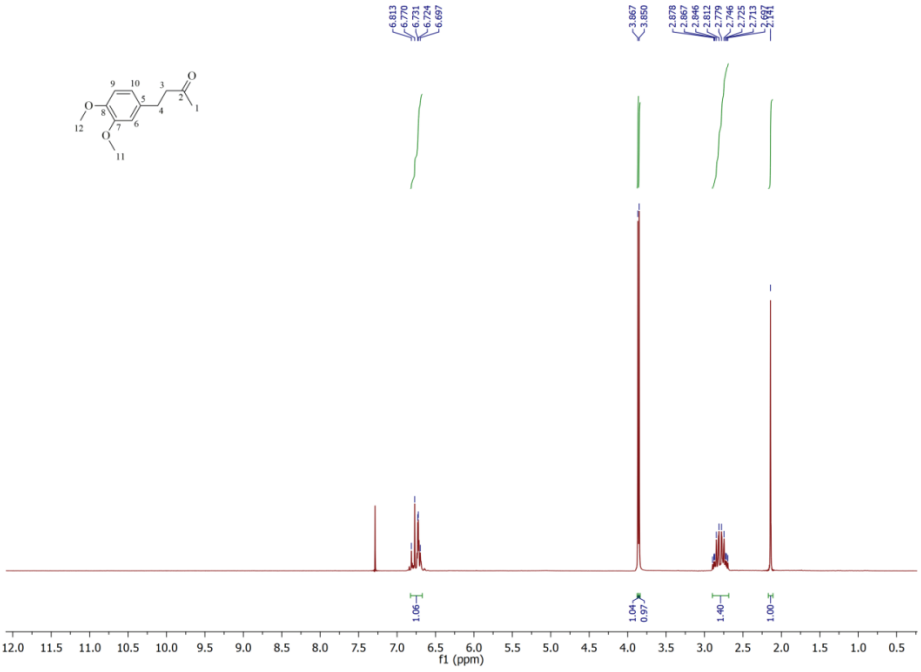


Fig. S-1. ^1H-NMR spectra of 4-(3,4-dimethoxyphenyl)butan-2-one (**1a**)

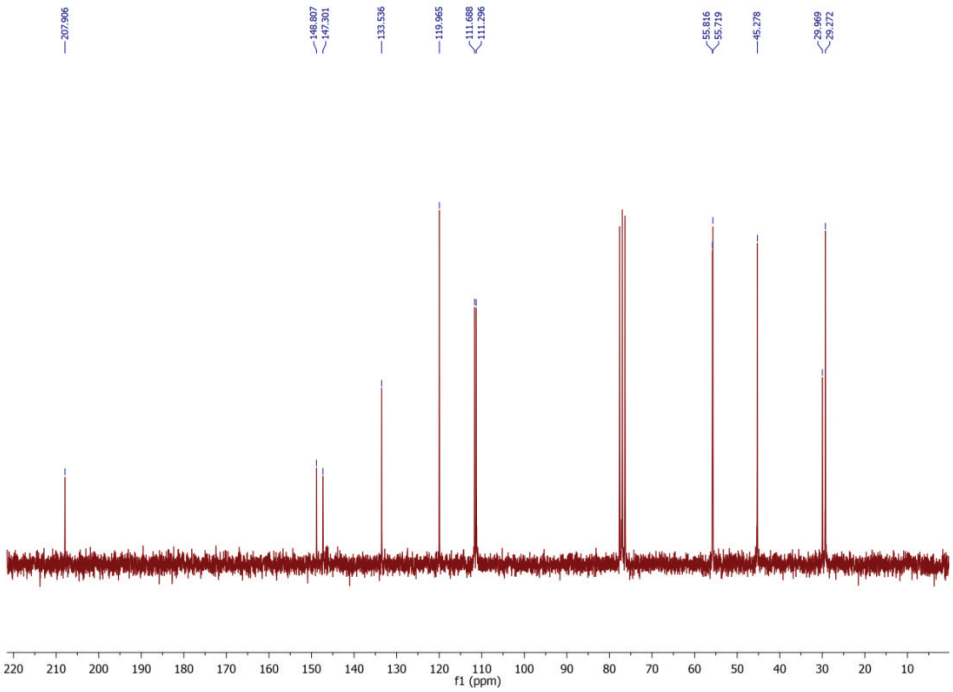


Fig. S-2. ^{13}C-NMR spectra of4-(3,4-dimethoxyphenyl)butan-2-one (**1a**)

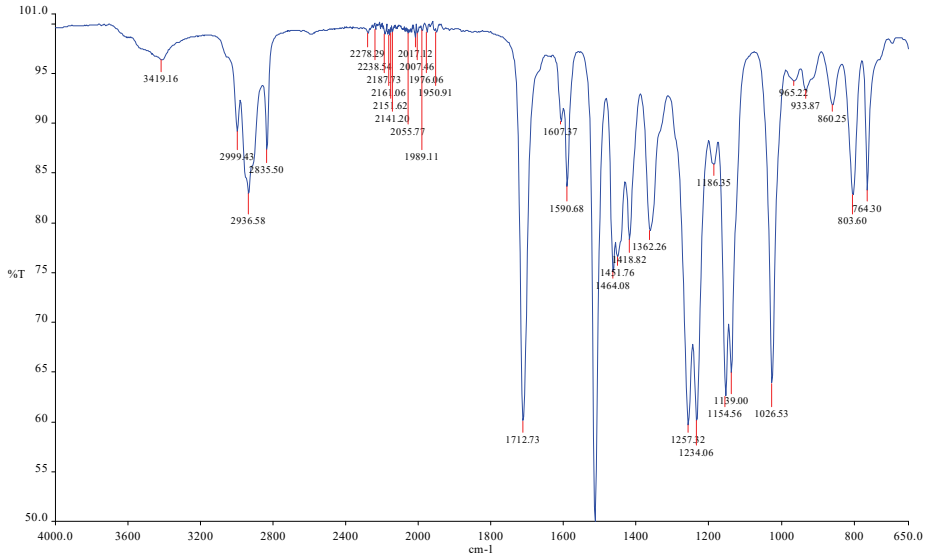


Fig. S-3. IR spectra of4-(3,4-dimethoxyphenyl)butan-2-one (**1a**)

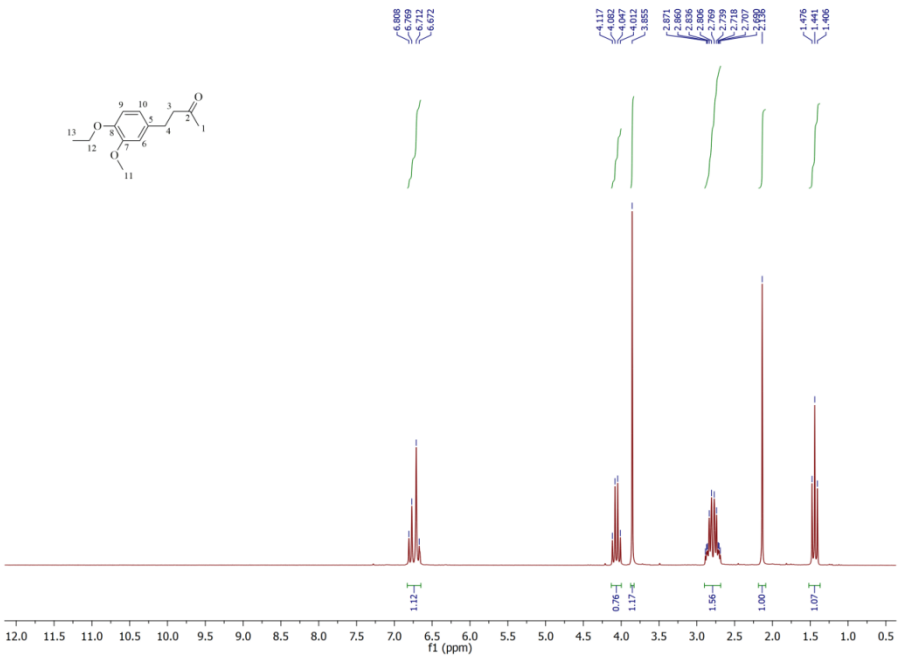


Fig. S-4. ^{1}H-NMR spectra of4-(4-ethoxy-3-methoxyphenyl)butan-2-one (**1b**)

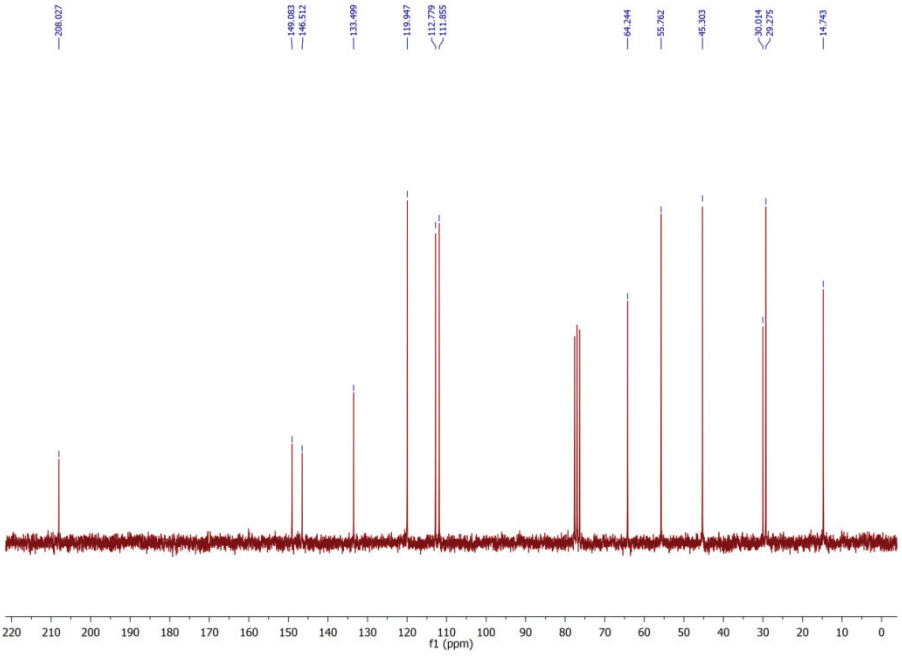


Fig. S-5. ^{13}C-NMR spectra of4-(4-ethoxy-3-methoxyphenyl)butan-2-one (**1b**)

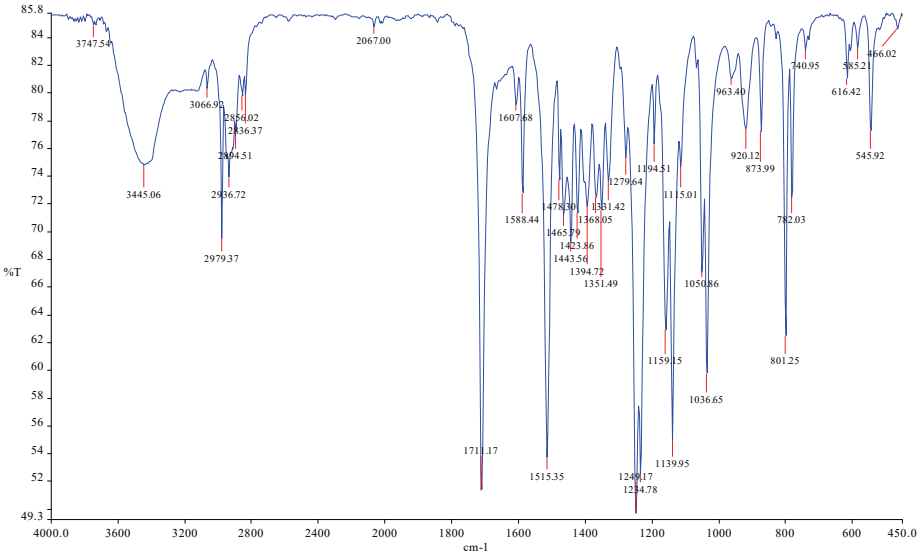


Fig. S-6. IR spectra of4-(4-ethoxy-3-methoxyphenyl)butan-2-one (**1b**)

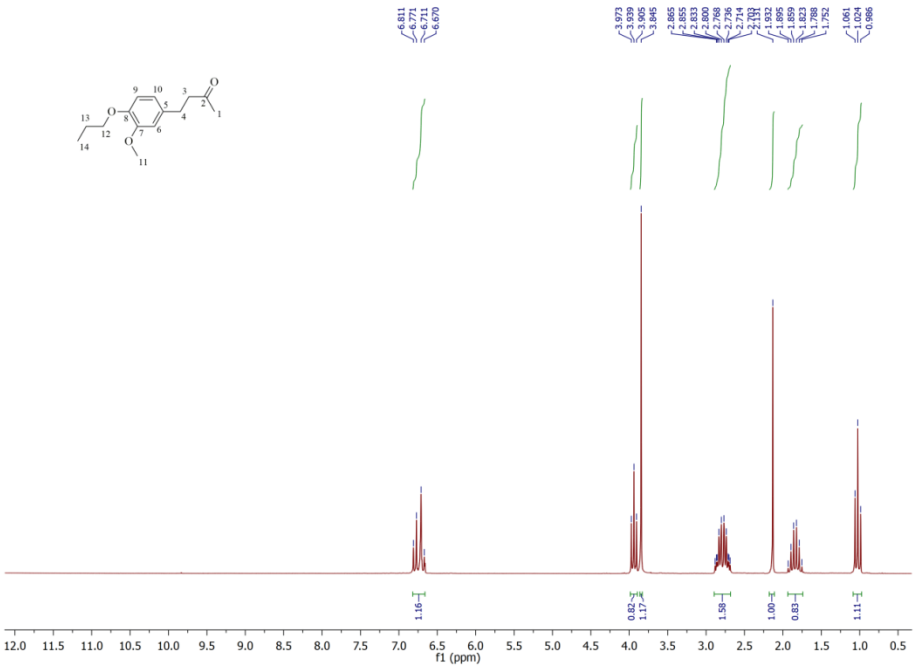


Fig. S-7. ^{1}H-NMR spectra of 4-(3-methoxy-4-propoxyphenyl)butan-2-one (**1c**)

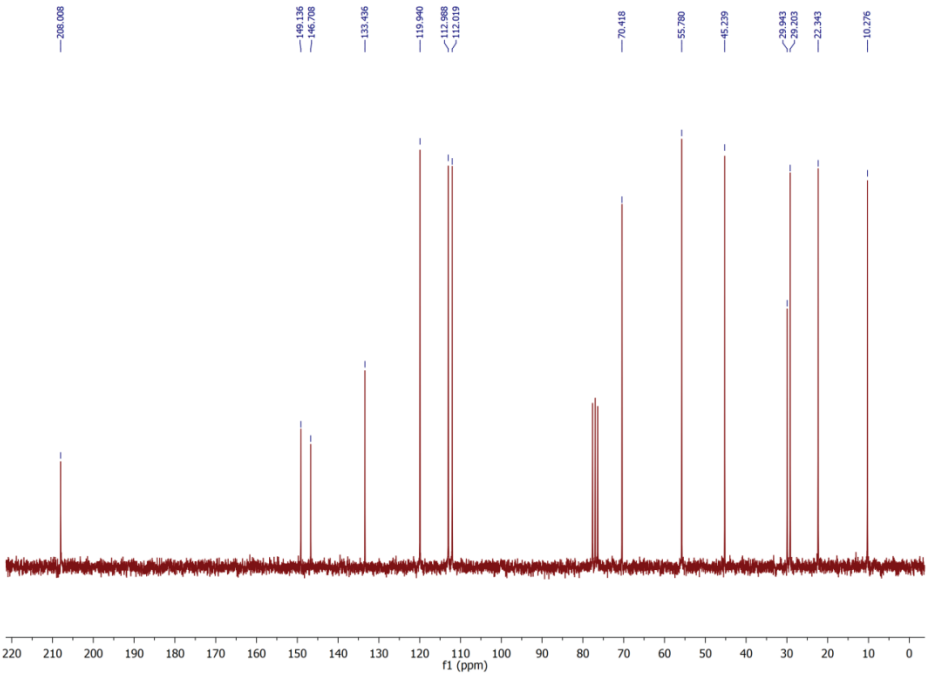


Fig. S-8. ^{13}C-NMR spectra of4-(3-methoxy-4-propoxyphenyl)butan-2-one (**1c**)

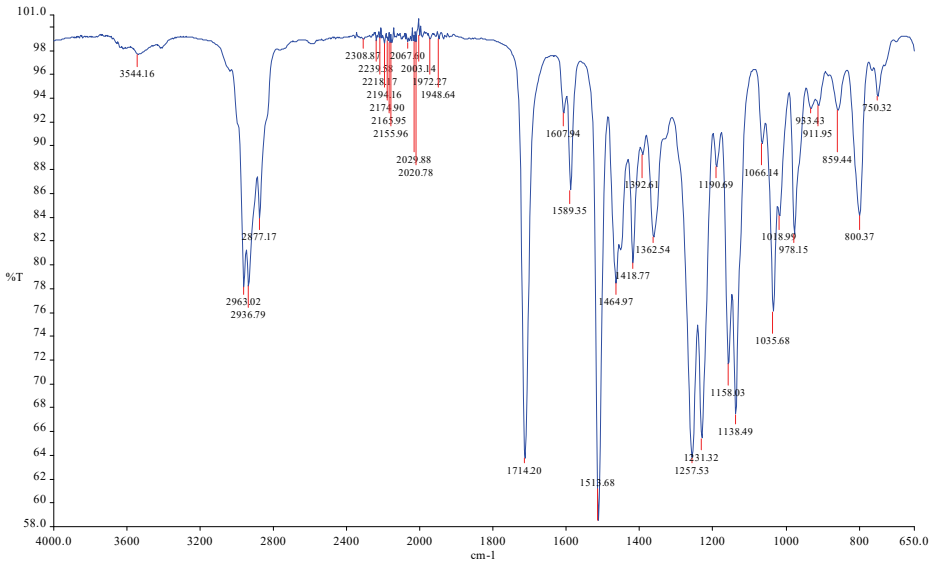


Fig. S-9. IR spectra of4-(3-methoxy-4-propoxyphenyl)butan-2-one (**1c**)

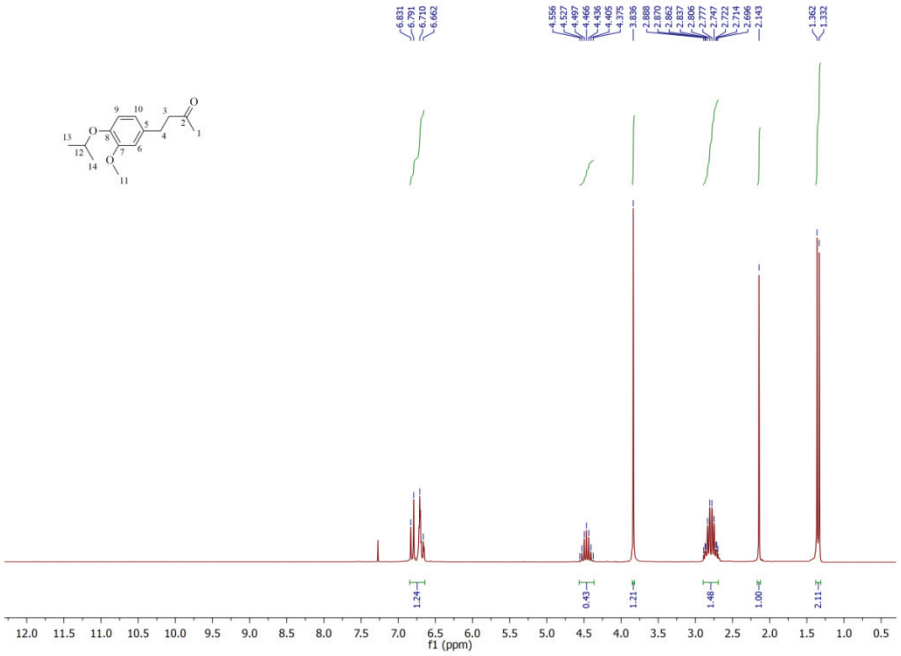


Fig. S-10. ^{1}H-NMR spectra of 4-(4-isopropoxy-3-methoxyphenyl)butan-2-one (**1d**)

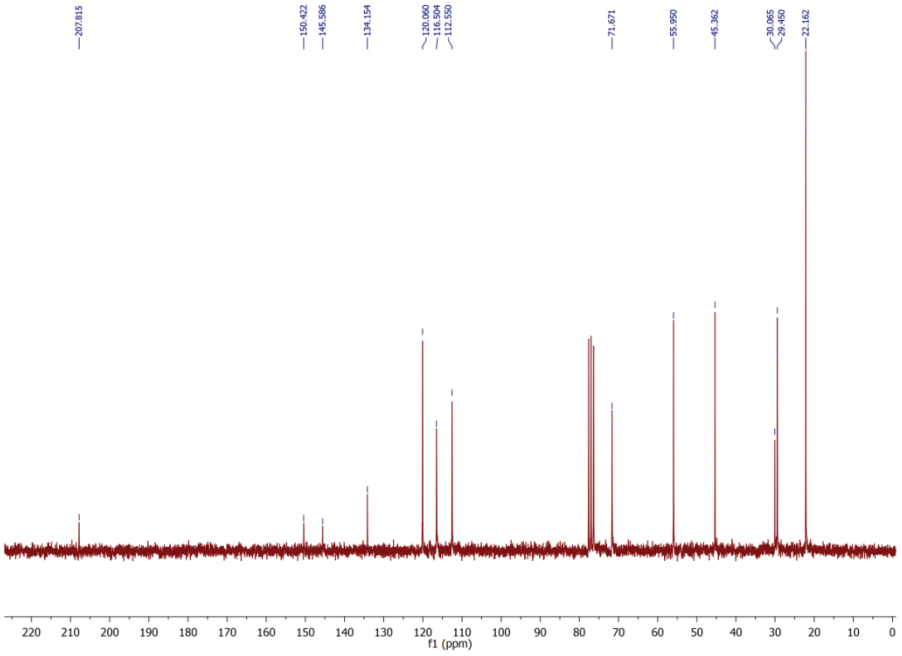


Fig. S-11. ^{13}C-NMR spectra of4-(4-isopropoxy-3-methoxyphenyl)butan-2-one (**1d**)

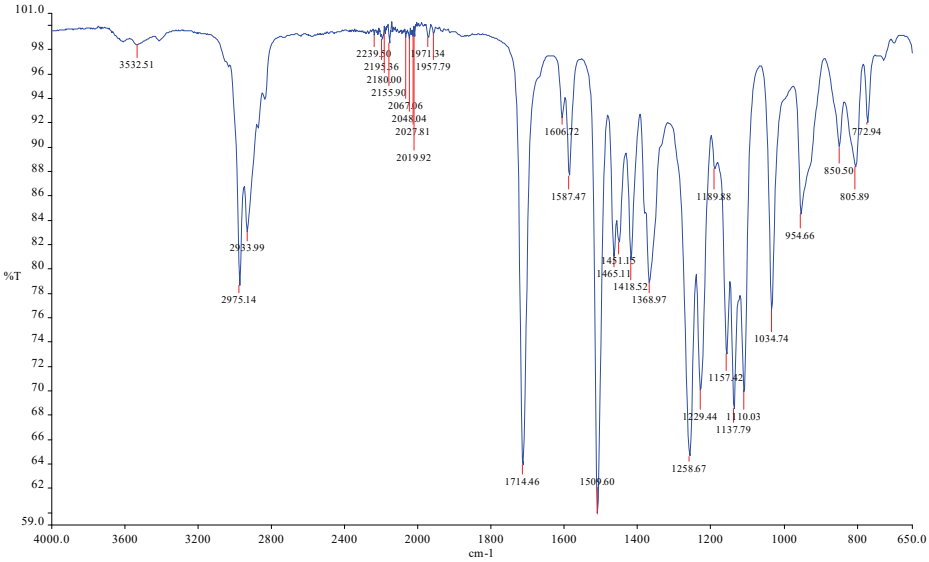


Fig. S-12. IR spectra of4-(4-isopropoxy-3-methoxyphenyl)butan-2-one (**1d**)

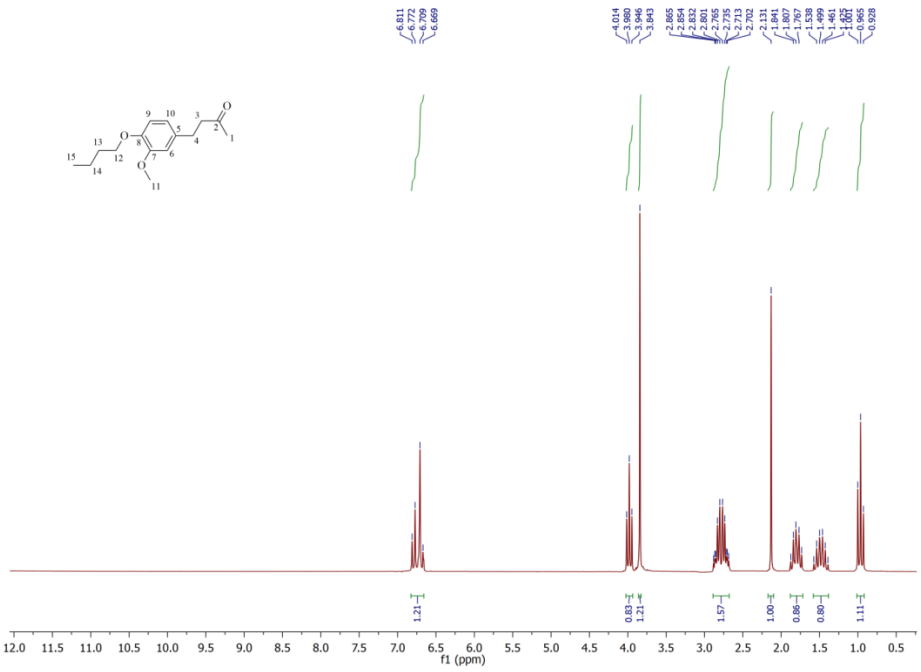


Fig. S-13. ^{1}H-NMR spectra of 4-(4-butoxy-3-methoxyphenyl)butan-2-one (**1e**)

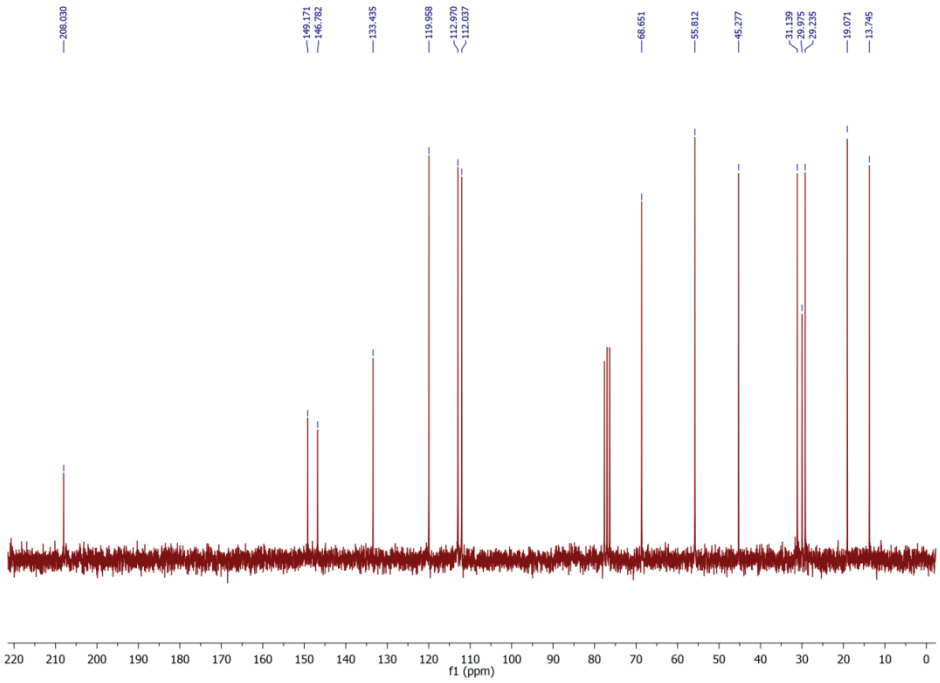


Fig. S-14. ^{13}C-NMR spectra of4-(4-butoxy-3-methoxyphenyl)butan-2-one (**1e**)

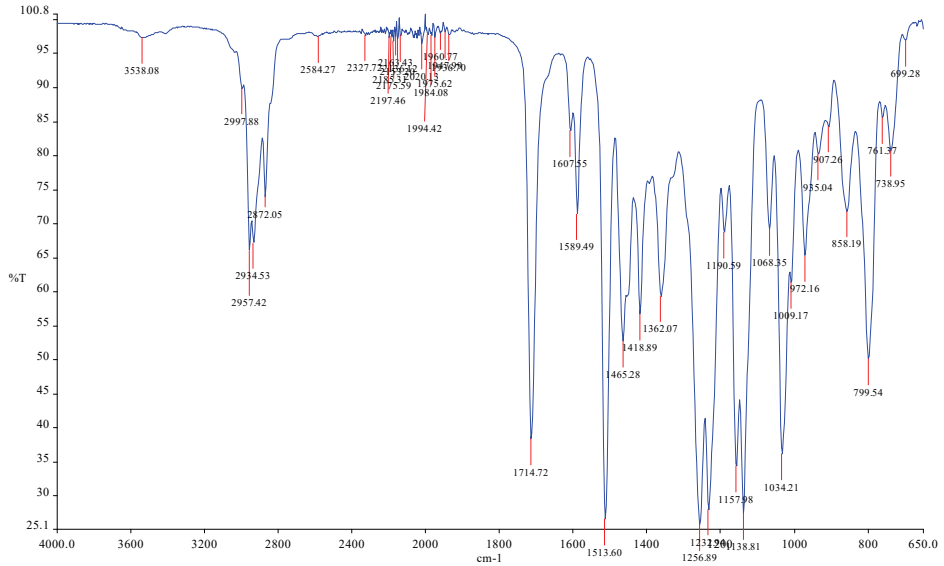


Fig. S-15. IR spectra of4-(4-butoxy-3-methoxyphenyl)butan-2-one (**1e**)

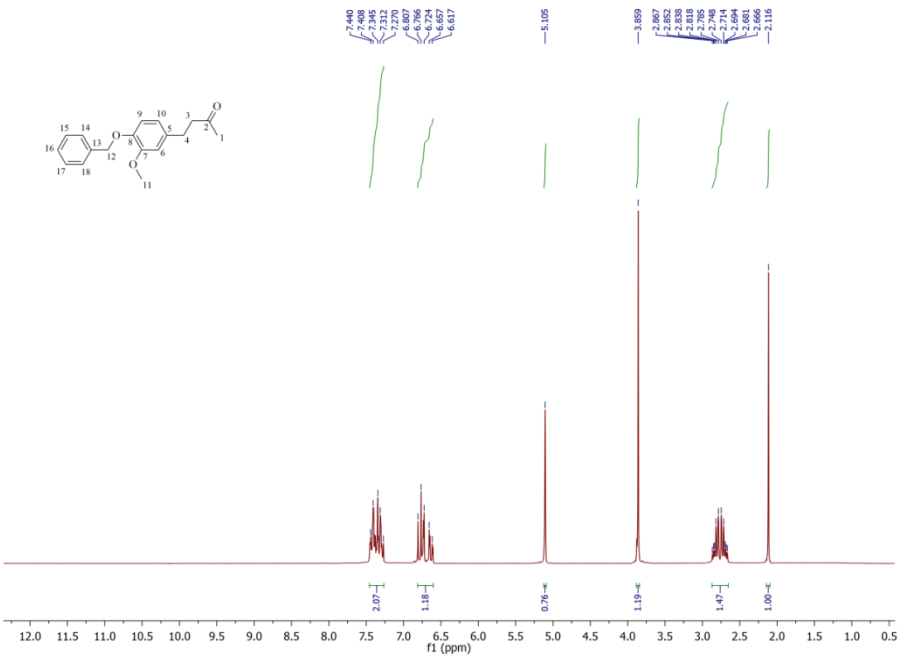


Fig. S-16. ^{1}H-NMR spectra of 4-(4-(benzyloxy)-3-methoxyphenyl)butan-2-one (**1f**)

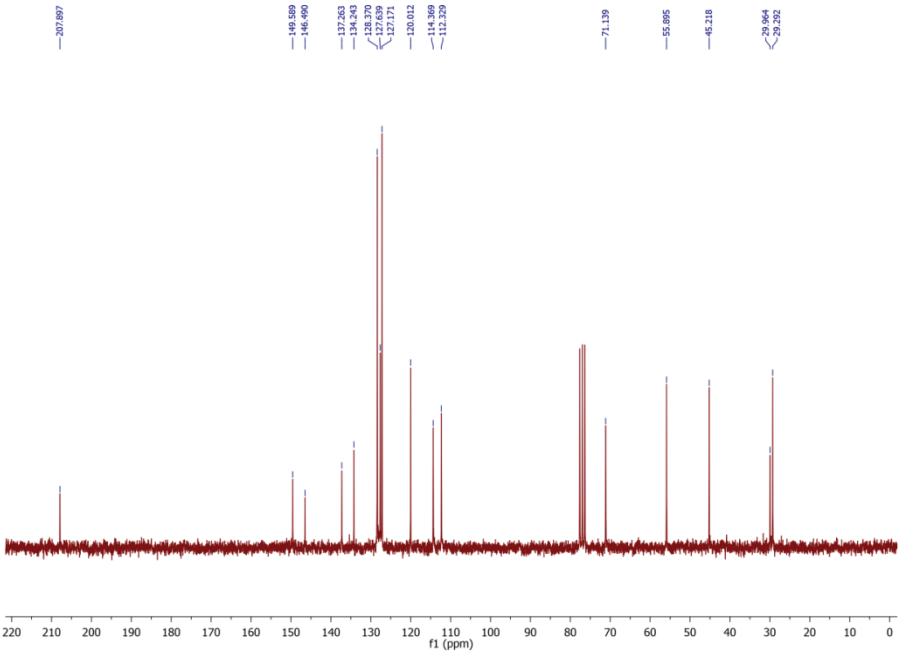


Fig. S-17. ^{13}C-NMR spectra of4-(4-(benzyloxy)-3-methoxyphenyl)butan-2-one (**1f**)

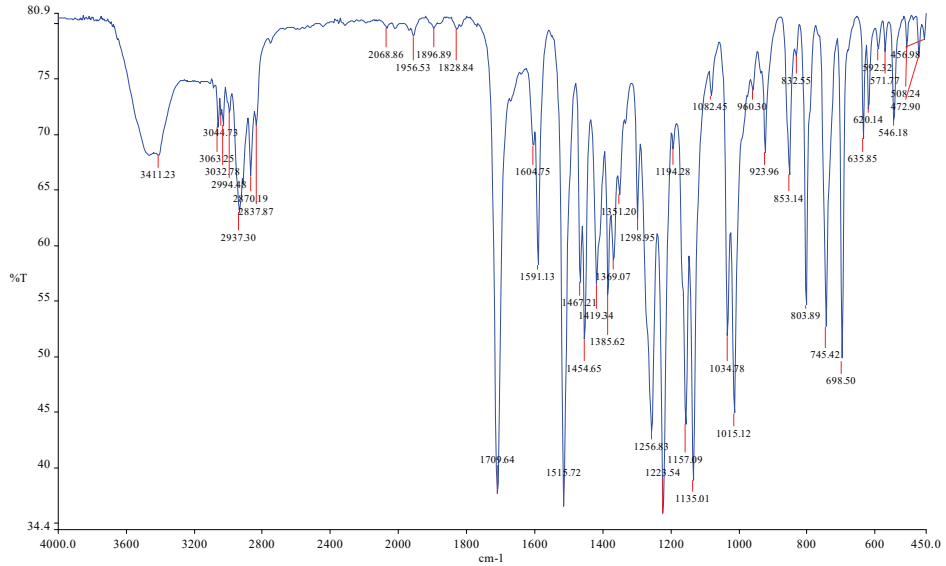


Fig. S-18. IR spectra of4-(4-(benzyloxy)-3-methoxyphenyl)butan-2-one (**1f**)

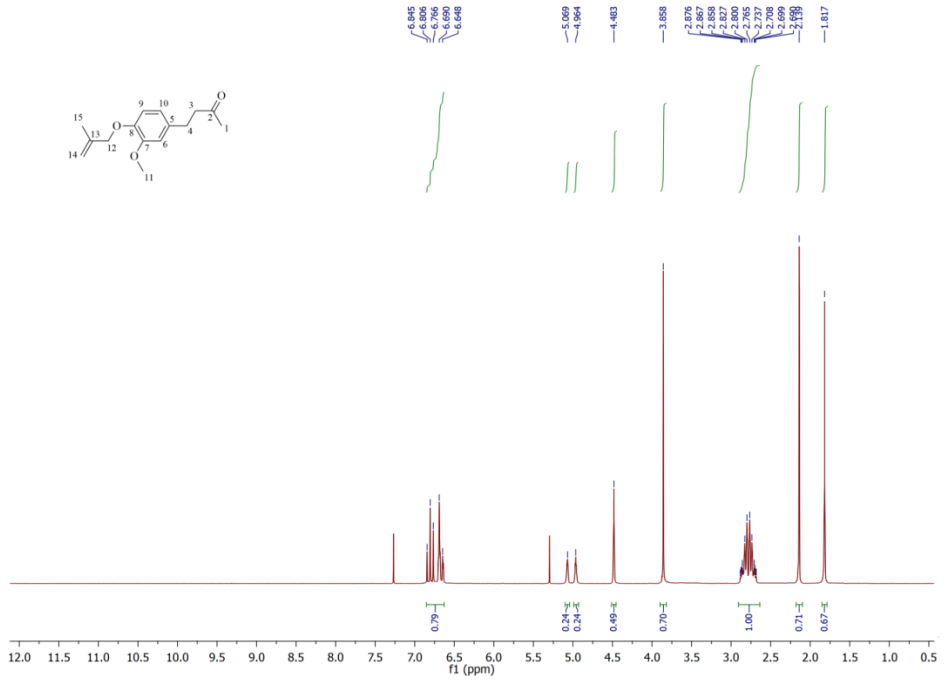


Fig. S-19. ^{1}H-NMR spectra of 4-(3-methoxy-4-((2-methylallyl)oxy)phenyl)butan-2-one (**1g**)

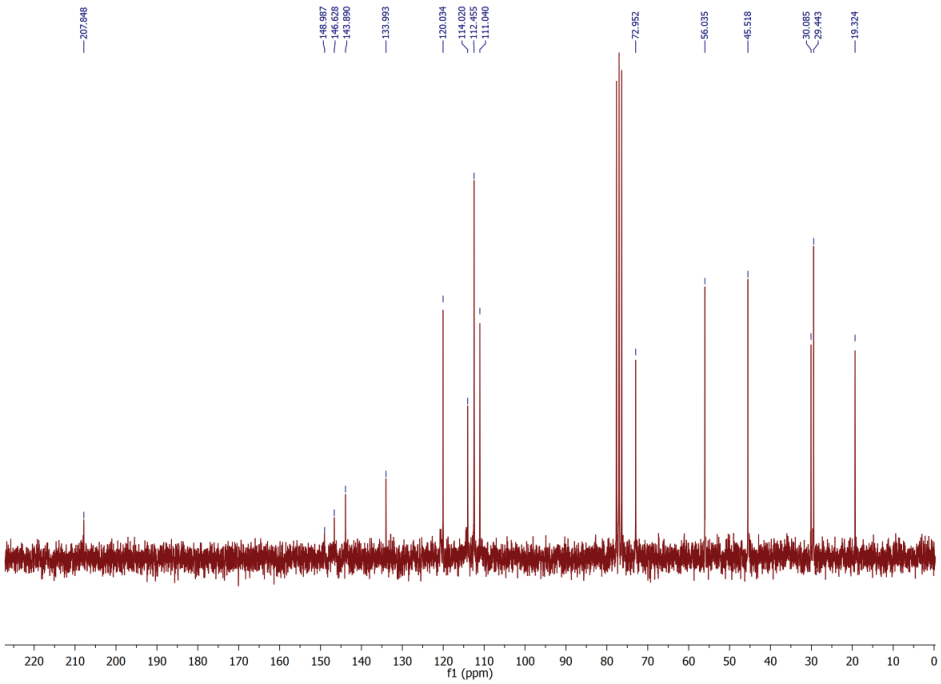


Fig. S-20. ^{13}C-NMR spectra of4-(3-methoxy-4-((2-methylallyl)oxy)phenyl)butan-2-one (**1g**)

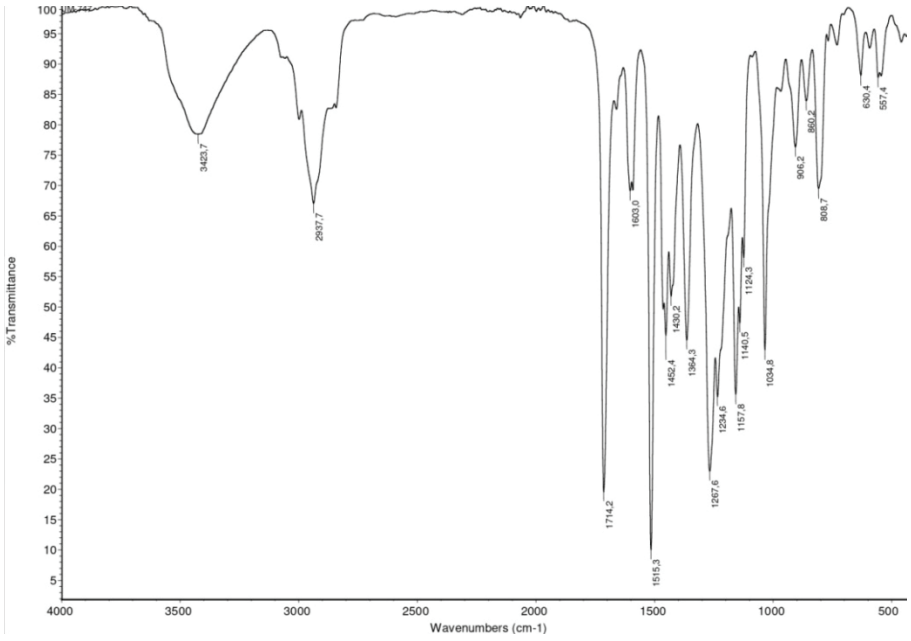


Fig. S-21. IR spectra of4-(3-methoxy-4-((2-methylallyl)oxy)phenyl)butan-2-one (**1g**)

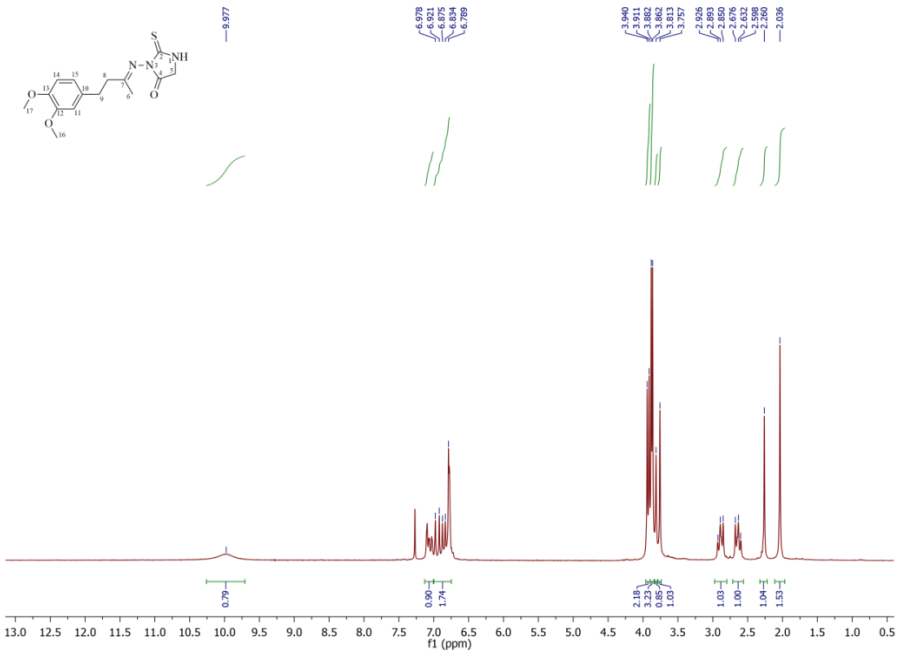


Fig. S-22. ^{1}H-NMR spectra of 3-((4-(3,4-dimethoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2a**)

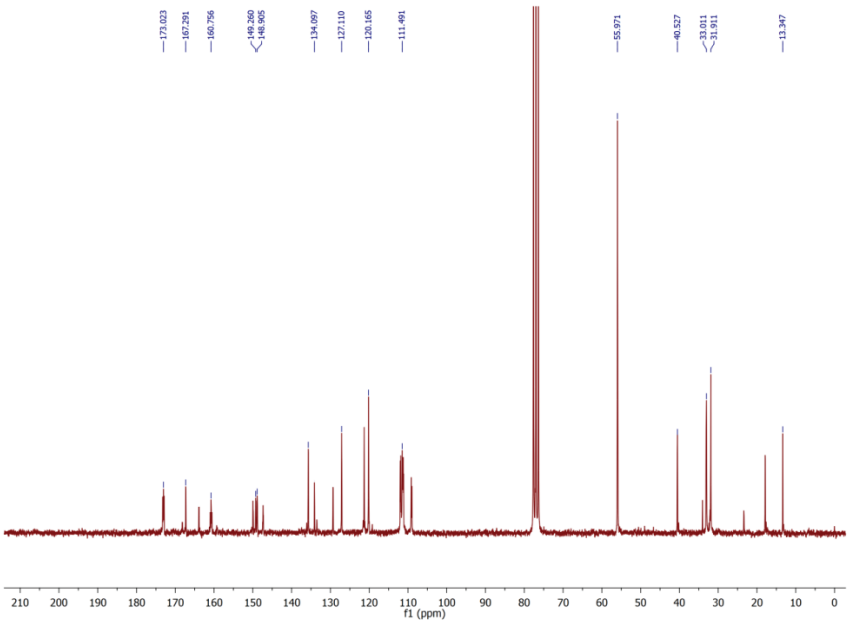


Fig. S-23. ^{13}C-NMR spectra of 3-((4-(3,4-dimethoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2a**)

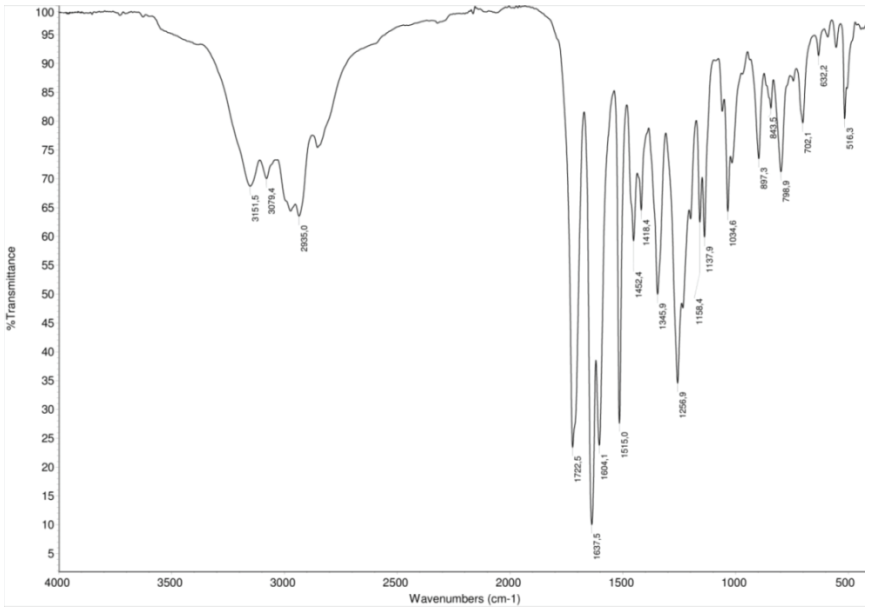


Fig. S-24. IR spectra of3-((4-(3,4-dimethoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2a**)

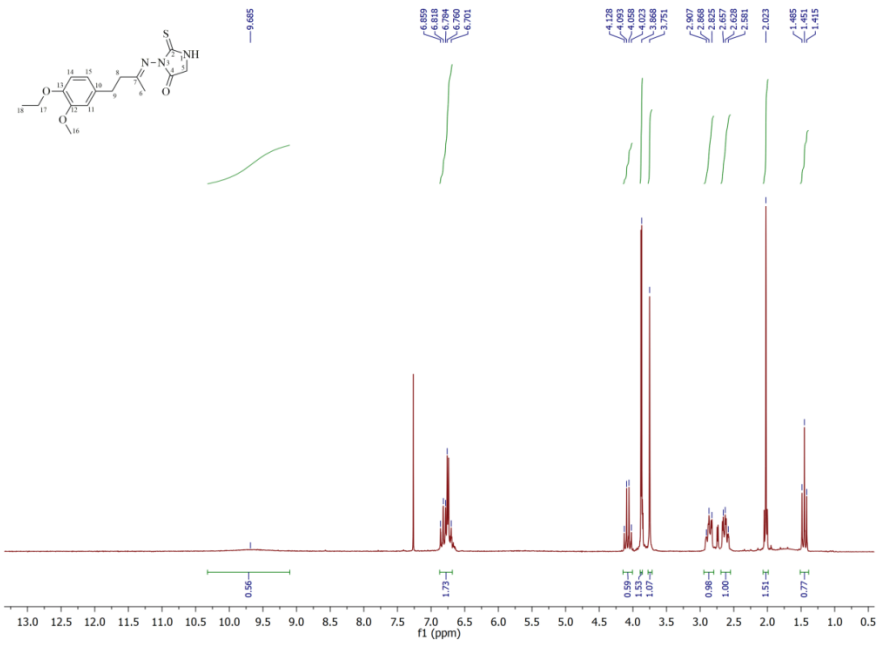


Fig. S-25. ^{1}H-NMR spectra of *3*-((4-(4-ethoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2b**)

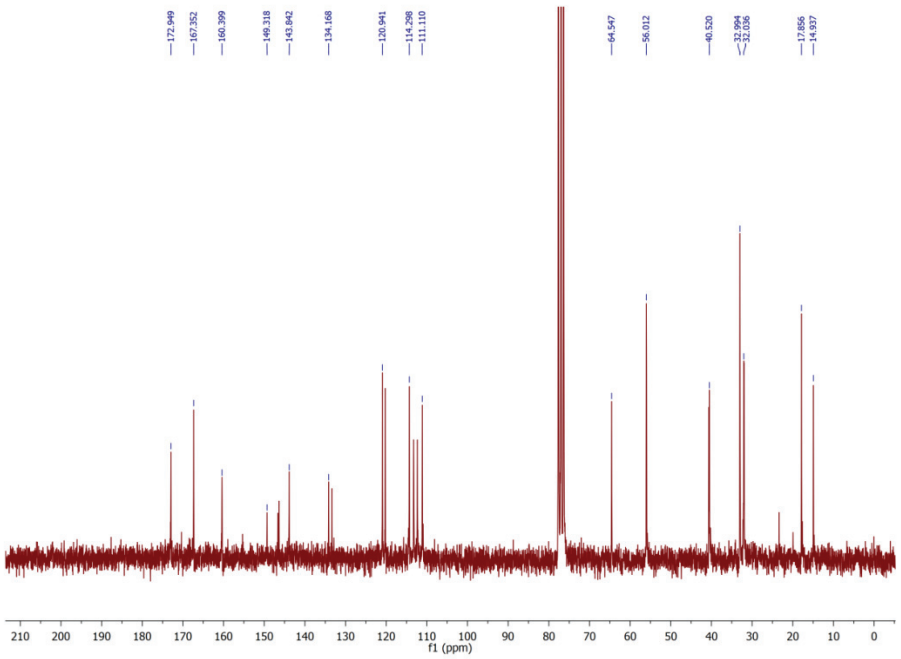


Fig. S-26. ^{13}C-NMR spectra of *3*-((4-(4-ethoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2b**)

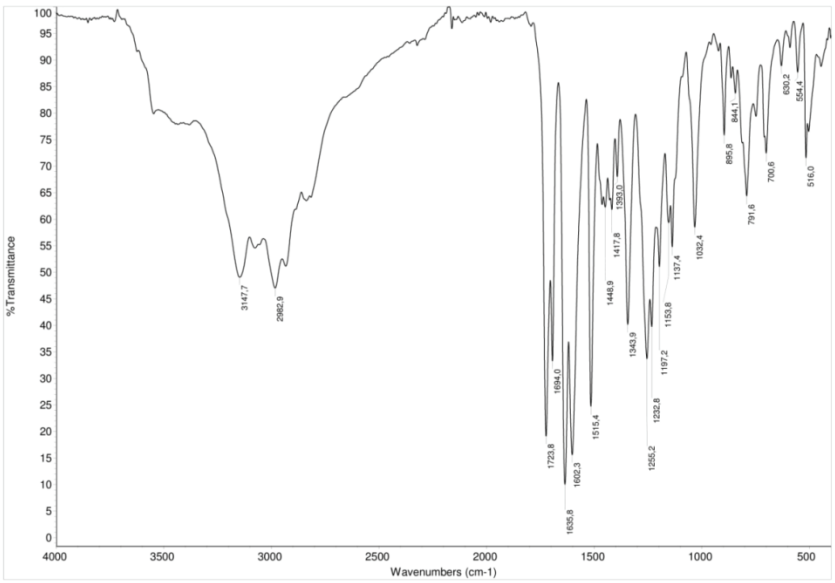


Fig. S-27. IR spectra of *3*-((4-(4-ethoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2b**)

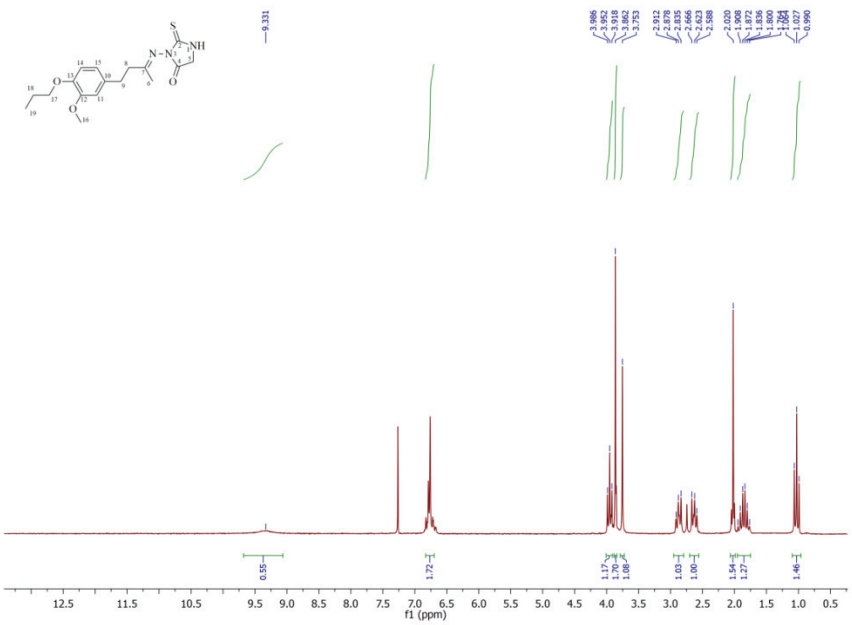


Fig. S-28. ^{1}H-NMR spectra of
3-((4-(3-methoxy-4-propoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2c**)

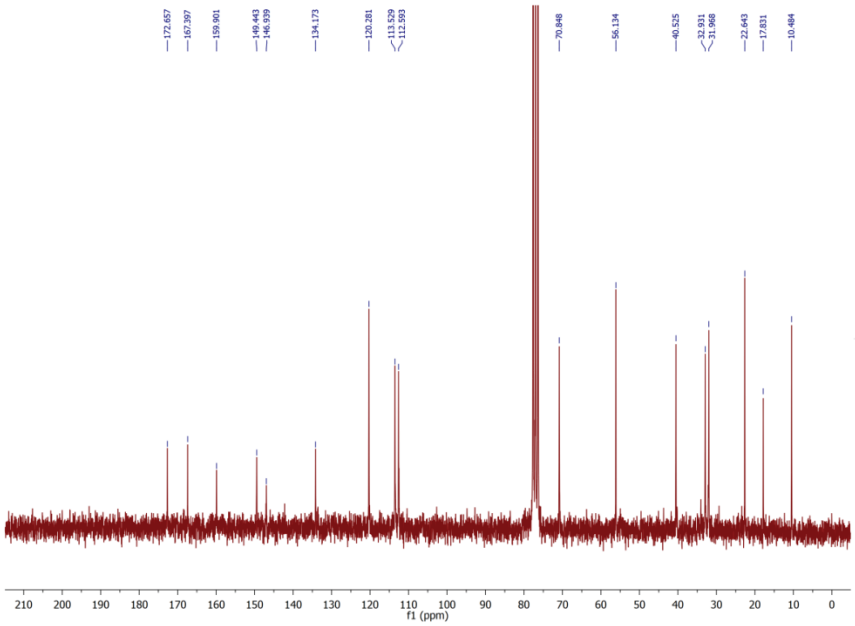


Fig. S-29. ^{13}C -NMR spectra of
3-((4-(3-methoxy-4-propoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2c**)

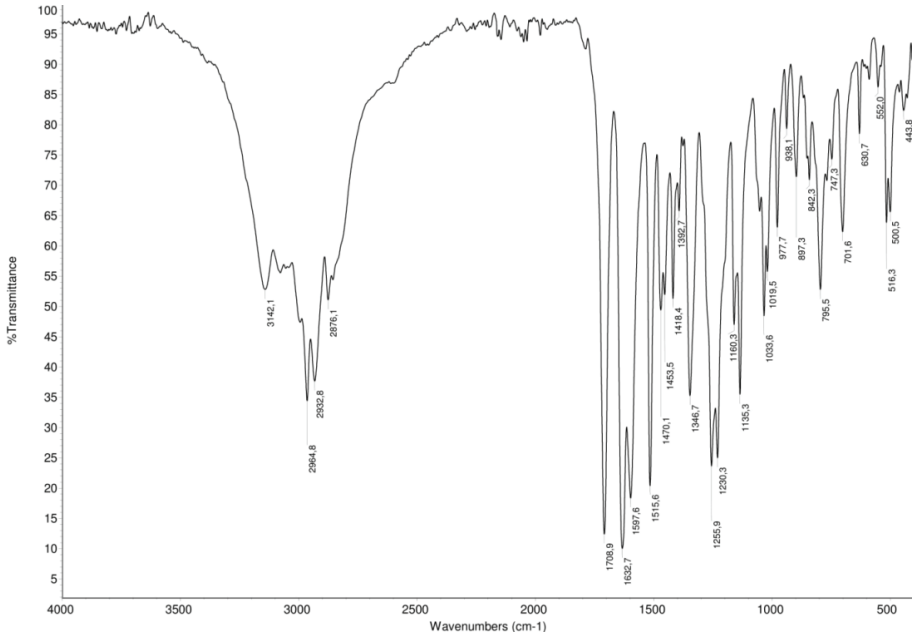


Fig. S-30. IR spectra of 3-((4-(3-methoxy-4-propoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2c**)

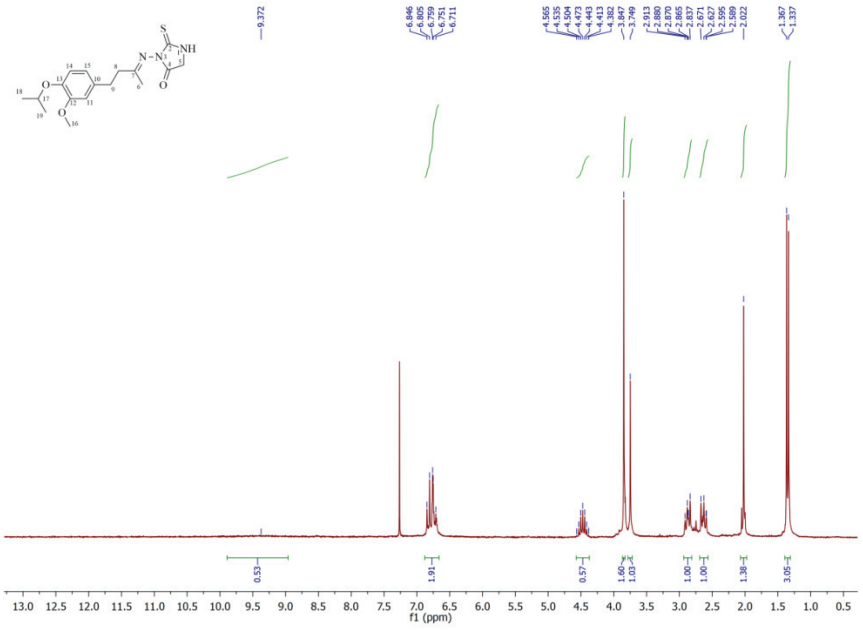


Fig. S-31. ^{1}H-NMR spectra of3-((4-(4-isopropoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2d**)

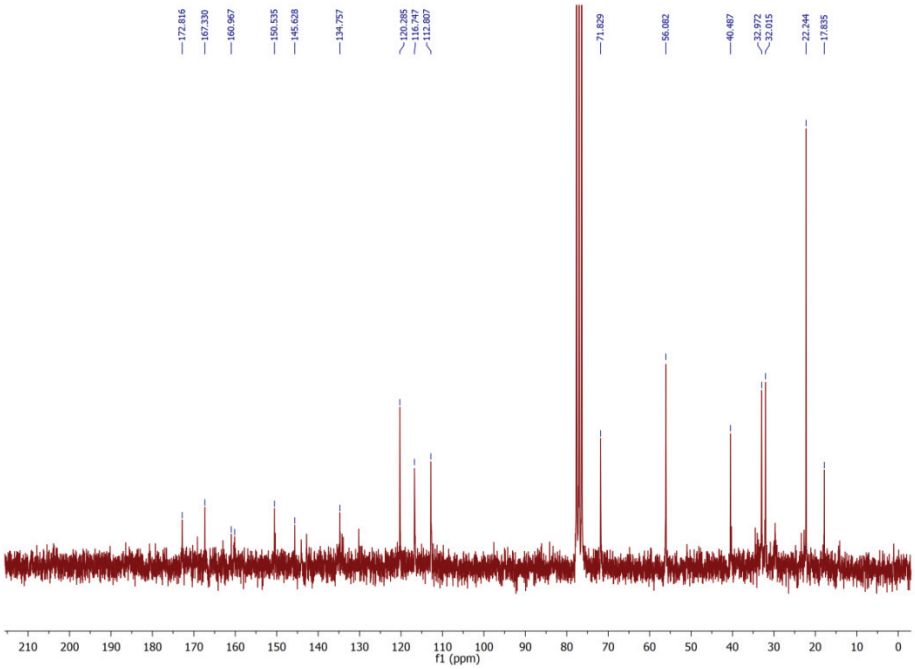


Fig. S-32. ^{13}C -NMR spectra of3-((4-(4-isopropoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2d**)

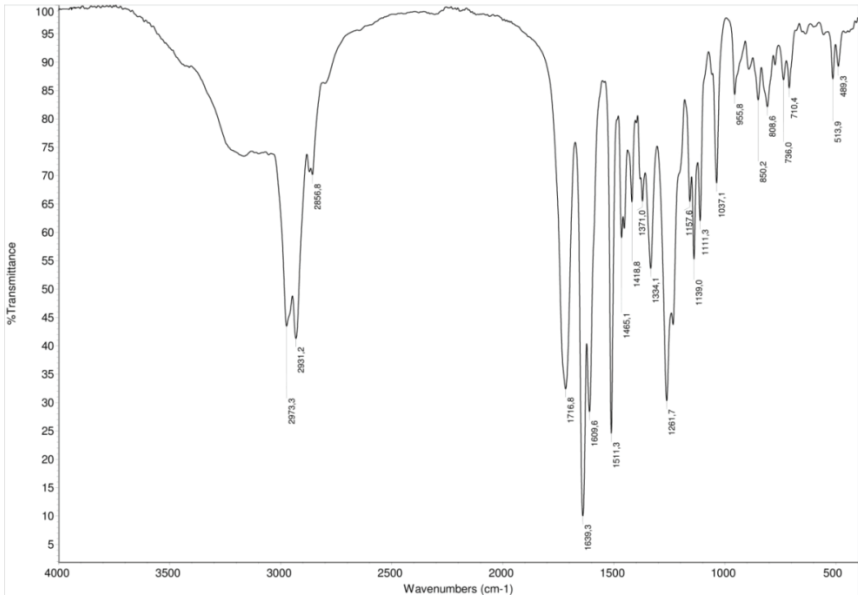


Fig. S-33. IR spectra of3-((4-(4-isopropoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2d**)

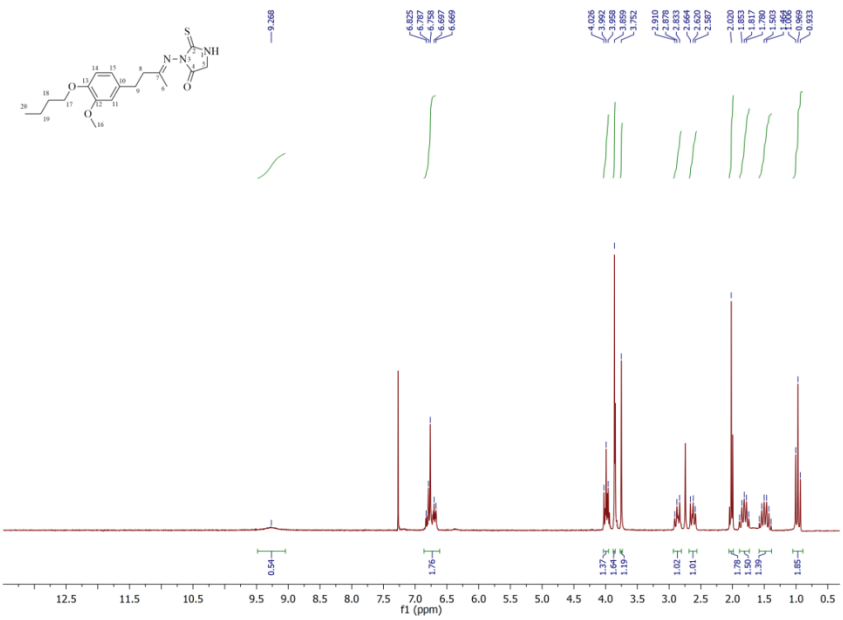


Fig. S-34. ^{1}H-NMR spectra of 3-((4-(4-butoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2e**)

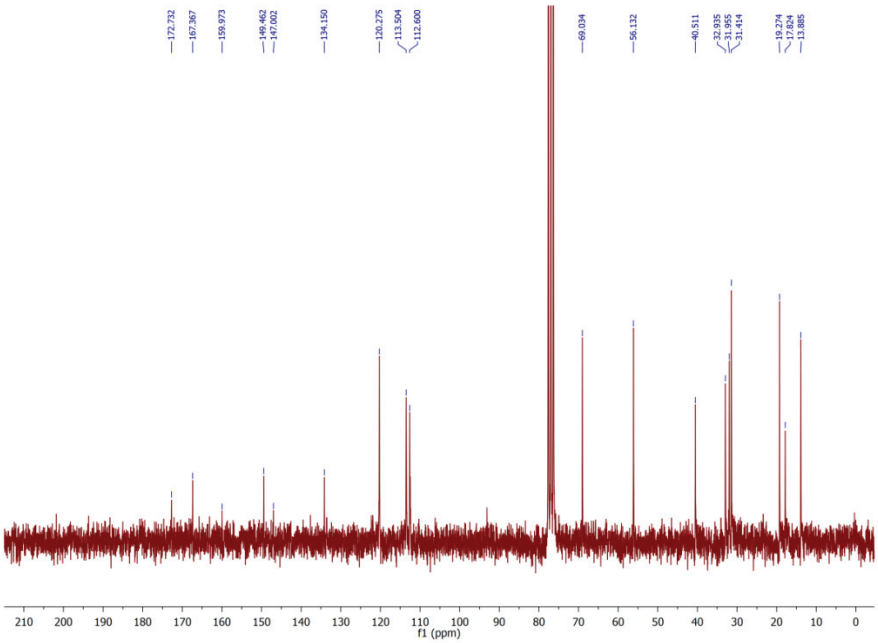


Fig. S-35. ^{13}C -NMR spectra of 3-((4-(4-butoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2e**)

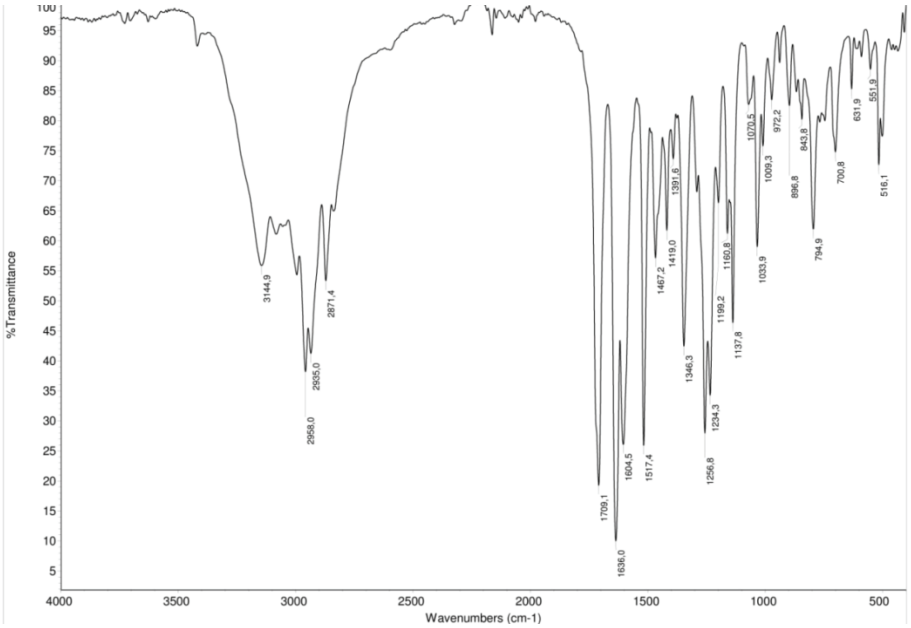


Fig. S-36. IR spectra of 3-((4-(4-butoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2e**)

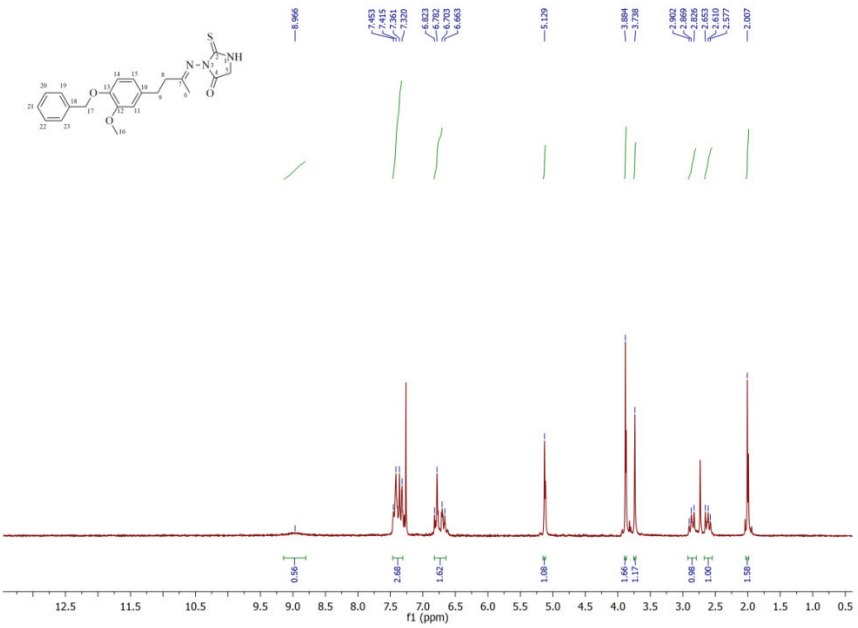


Fig. S-37. ^{1}H-NMR spectra of3-((4-(4-(benzyloxy)-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2f**)

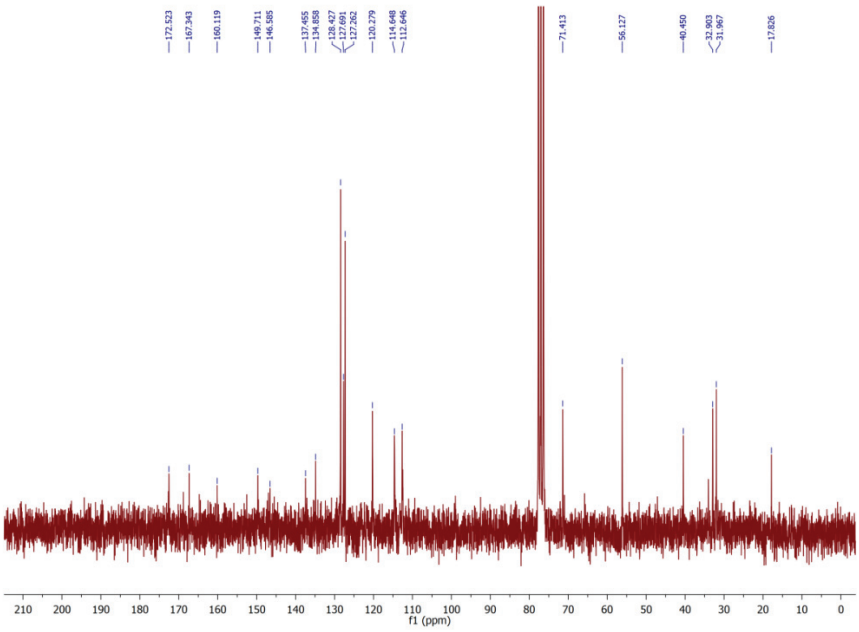


Fig. S-38. ^{13}C -NMR spectra of3-((4-(4-(benzyloxy)-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2f**)

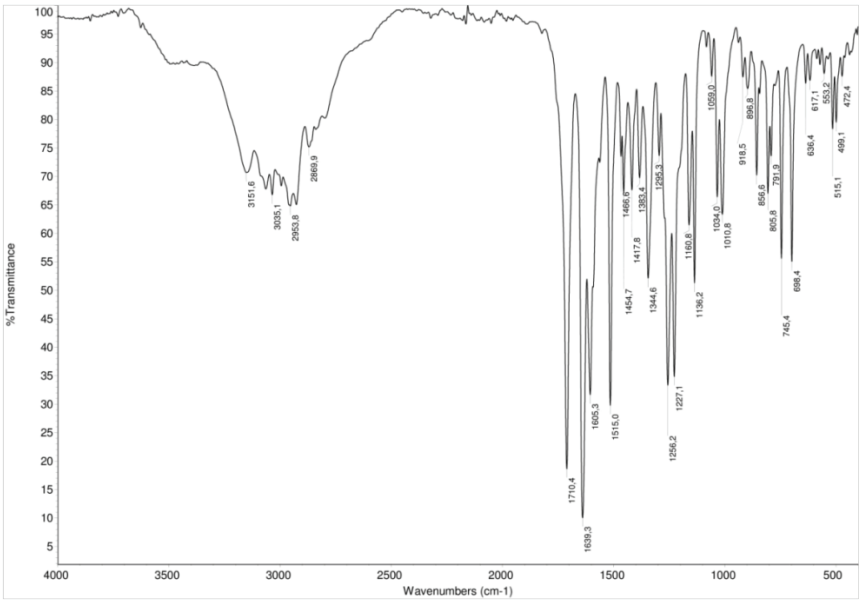


Fig. S-39. IR spectra of3-((4-(4-(benzyloxy)-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2f**)

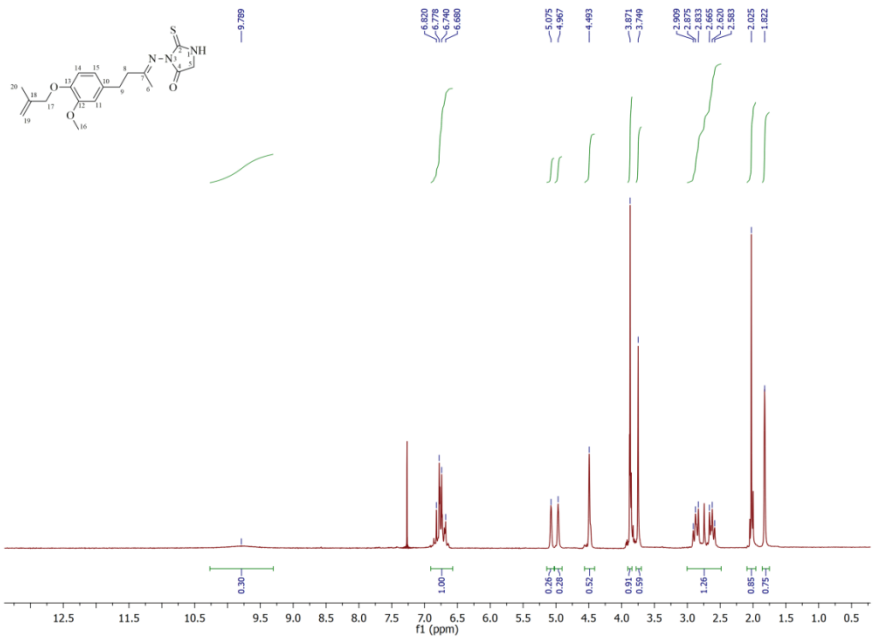


Fig. S-40. ^{1}H-NMR spectra of3-((4-(3-methoxy-4-((2-methylallyl)oxy)phenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2g**)

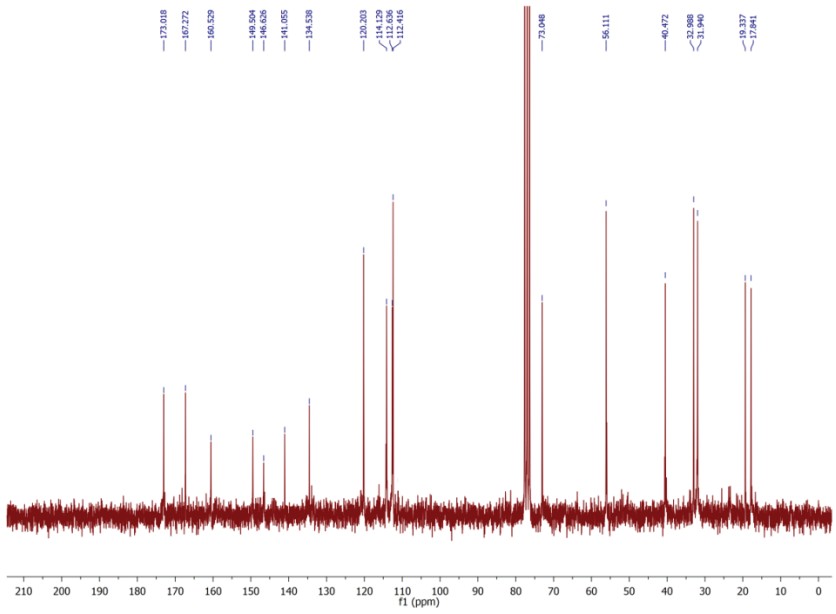


Fig. S-41. ^{13}C-NMR spectra of3-((4-(3-methoxy-4-((2-methylallyl)oxy)phenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2g**)

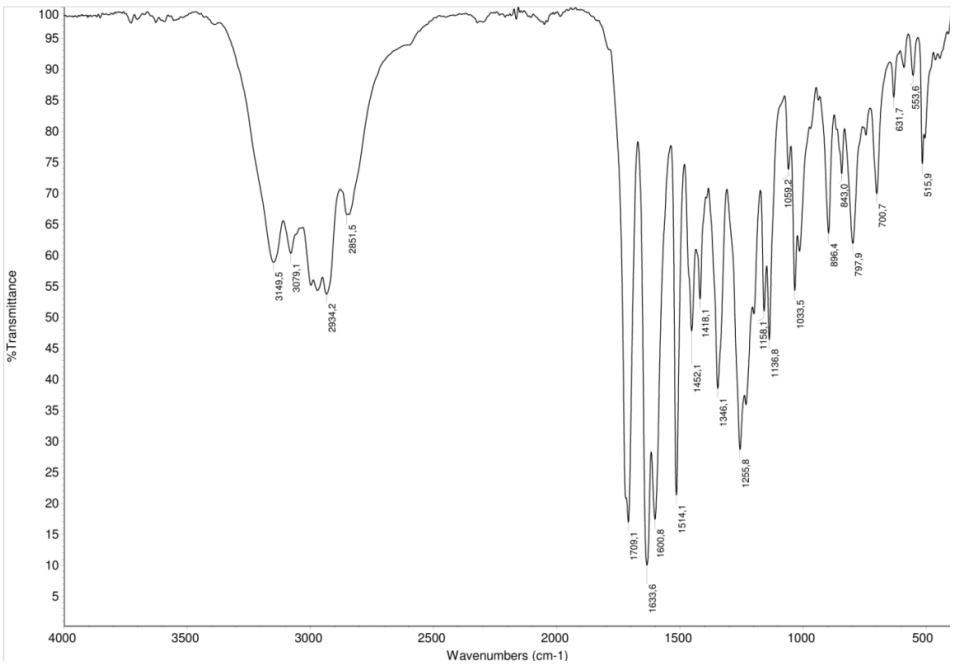


Fig. S-42. IR spectra of3-((4-(3-methoxy-4-((2-methylallyl)oxy)phenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2g**)

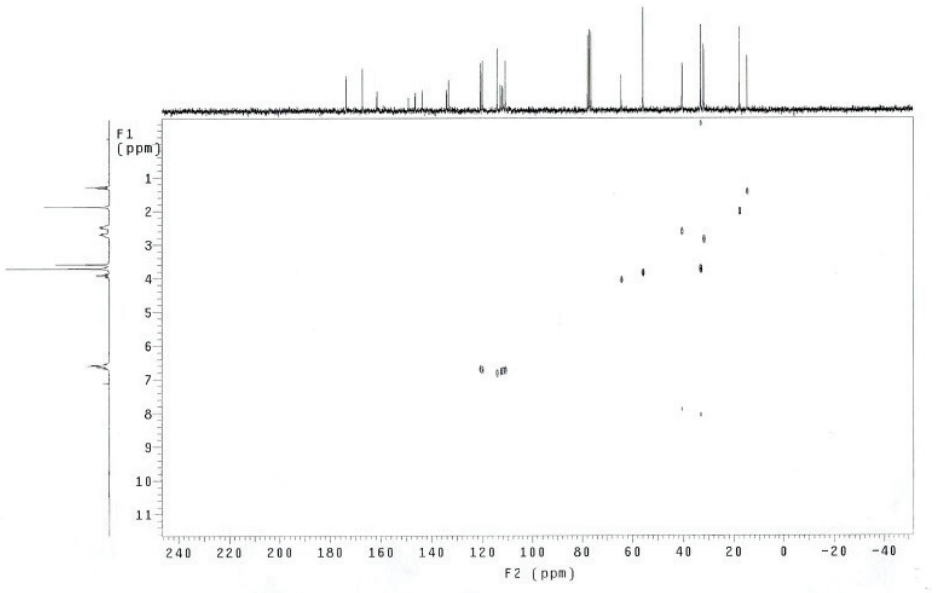


Fig. S-43. 2D HETCOR spectra of *3*-((4-(4-ethoxy-3-methoxyphenyl)butan-2-ylidene)amino)-2-thioxoimidazolidin-4-one (**2b**)

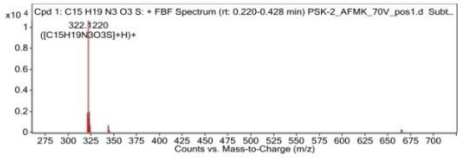
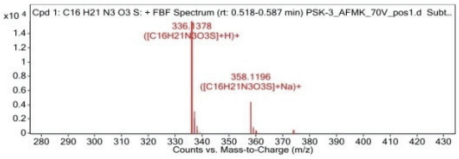
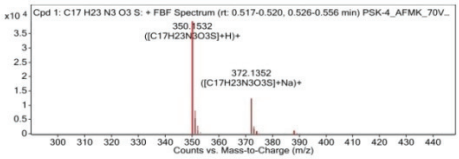
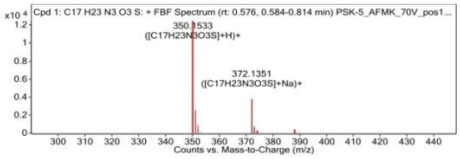
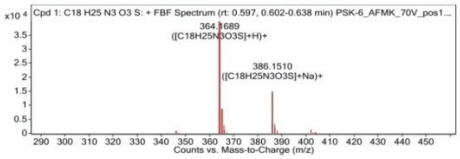
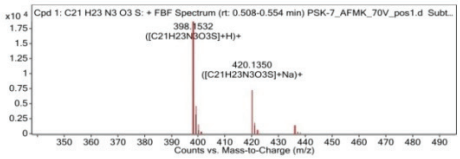
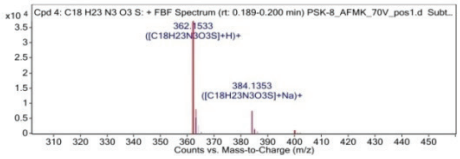
DFT calculation

All calculations were conducted using Gaussian 09[1] with the B3LYP functional[2,3] and the split-valence triple-zeta basis set 6-311+G.[4,5] To attain better description of the delocalization effects which are crucial for the geometry and electronic structure of the investigated molecules, diffuse functions were added to the heavy atoms. The p and d polarization functions were also used. Full geometry optimizations, without any symmetry constraints, and frequency calculations were performed for all species in gas phase. The frequency calculations were performed to confirm that the optimized structures are energetic minima (no imaginary frequencies).

LC-HRMS analysis

Samples dissolved in the methanol (c @ 0.1 mg mL^{-1}) were directly, without separation, injected into analysing system including liquid chromatograph (1290 Infinity LC system; Agilent Technologies, Waldbronn, Germany) with a quarternary pump, a column oven, and an autosampler, connected to the Quadrupole Time-of-Flight mass detector (6550 iFunnel QTOF MS, Agilent Technologies; Santa Clara, CA, USA) equipped with a dual spray Agilent Jet Stream (AJS) electrospray ion source. Mobile phase was composed of a solvents A (water containing both 0.1 % formic acid and 5 mM ammonium formate) and B (ACN containing 0.1 % formic acid), 1:1 (v/v). The mobile phase flow rate was 0.20 mL min^{-1}, the column oven temperature was 25 °C and the injection volumes of samples were 0.2 μL. The compounds were analysed using a mass detector. Positive ion mode was recorded, and the instrument was operated in accurate TOF/MS scanning mode in the *m/z* range of 100 – 1,500, under following conditions: capillary voltage, 3,500 V, fragmentor voltage, 70 V, nozzle voltage, 1,000 V, skimmer 1, 65 V, octupole RF peak, 750 V, desolvation gas (nitrogen) temperature, 200 °C, desolvation gas (nitrogen) flow, 14 L min^{-1}, nebulizer, 241.32 kPa, sheath gas (nitrogen) temperature, 350 °C, sheat gas (nitrogen) flow, 11 L min^{-1}. Ions *m/z* 121.05087300 and 922.00979800 were used as a lock mass for accurate mass measurements. A personal computer system running Agilent MassHunter software (revisions B.06.01 and B.07.00) was used for data acquisition and processing, respectively.

Table S-I. LC-HRMS analysis of **2a-g**

Sample code	Molecular formula	Molecular mass calculated	Molecular mass measured	$[M+H]^+$ *m/z* calculated	$[M+H]^+$ *m/z* measured	Difference (ppm)
2a	$C_{15}H_{19}N_3O_3S$	321.1147	321.1138	320.1074	322.1220	-0.04
						
2b	$C_{16}H_{21}N_3O_3S$	335.1304	335.1305	336.1376	336.1378	-0.48
						
2c	$C_{17}H_{23}N_3O_3S$	349.1460	349.1459	350.1533	350.1532	+0.25
						
2d	$C_{17}H_{23}N_3O_3S$	349.1460	349.1459	350.1533	350.1533	-0.03
						
2e	$C_{18}H_{25}N_3O_3S$	363.1617	363.1616	364.1689	364.1689	+0.11
						
2f	$C_{21}H_{23}N_3O_3S$	397.1460	397.1459	398.1533	398.1532	-0.03
						
2g	$C_{18}H_{23}N_3O_3S$	361.1460	361.1460	362.1533	362.1533	-0.03
						

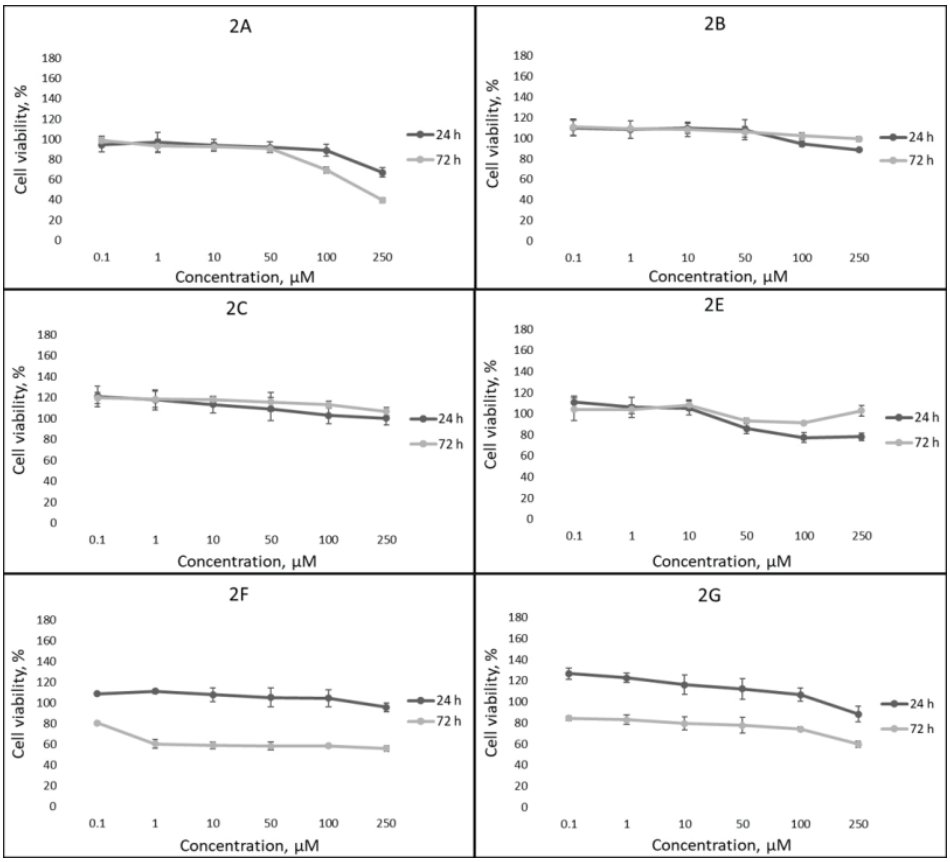


Fig. S-44. The effects of zingerone-thiohydantoin derivatives on MRC-5 cell viability

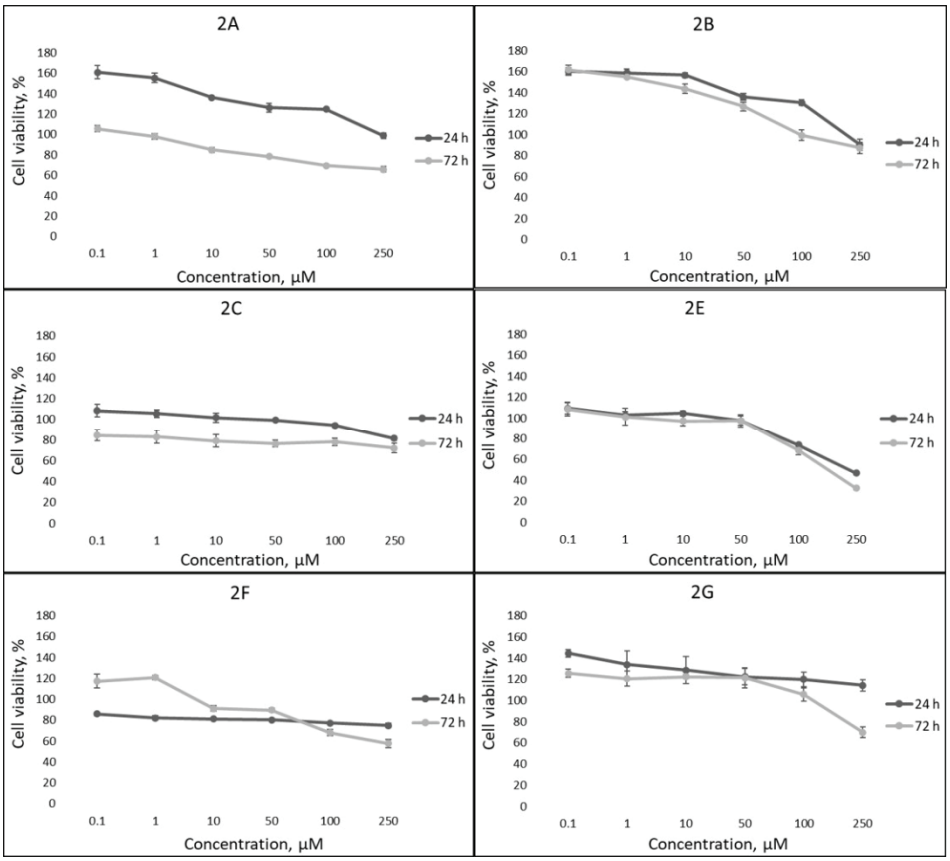


Fig. S-45. The effects of zingerone-thiohydantoin derivatives on HCT-116 cell viability

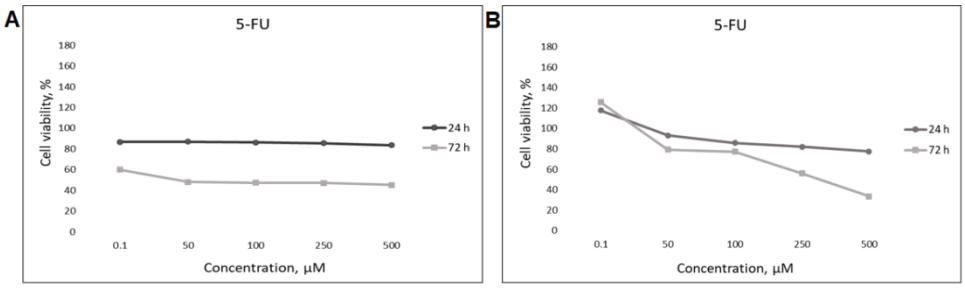


Fig. S-46. The effects of reference control 5-FU on MRC-5 (A) and HCT-116 (B) cell viability

REFERECES

1. Gaussian 09, Revision C.01; Gaussian, Inc.: Wallingford, CT (2009)
2. C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **37** (1988) 785 (https://doi.org/10.1103/PhysRevB.37.785)

3. D. J.Becke, *Chem. Phys.* **98** (1993) 5648 (https://doi.org/10.1063/1.464913)
4. J. H. J. Wachters, *Chem. Phys.* **52** (1970) 1033 (https://doi.org/10.1063/1.1673095)
5. P. J. J. Hay, *Chem. Phys.* **66** (1977) 4377 (https://doi.org/10.1063/1.433731).