

# 2D-QSAR and CoMFA Models for Antitubercular Activity of Marine-Derived Sclerodermanes

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## Spectral data of compounds 13, 15-28

**Scalarafuran (13):** white needles;  $[\alpha]_D^{25}$  -31 (c 0.27 CH<sub>2</sub>Cl<sub>2</sub>); UV (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 232 (3.48) nm; IR (neat)  $\nu_{\max}$  3449, 2930, 2848, 1734, 1463, 1388, 1369, 1243, 1041, 1018, 739 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.50 (1H, d,  $J$  = 1.6 Hz; H-20), 7.24 (1H, dd,  $J$  = 1.6, 1.6 Hz; H-19), 5.73 (1H, ddd,  $J$  = 10.1, 7.3, 1.0 Hz; H-16), 3.57 (1H, dd,  $J$  = 11.4, 4.4 Hz; H-12), 2.12 (1H, m; H-15a), 2.07 (3H, s; 16-OCOCH<sub>3</sub>), 1.81 (1H, m; H-7a), 1.75 (1H, m; H-15b), 1.75 (1H, m; H-11a), 1.64 (1H, m; H-1a), 1.59 (1H, m; H-6a), 1.59 (1H, m; H-2a), 1.48 (1H, m; H-11b), 1.41 (1H, m; H-6b), 1.40 (1H, m; H-2b), 1.33 (1H, m; H-3a), 1.23 (1H, m; H-14), 1.23 (3H, s; H-25), 1.12 (1H, m; H-3b), 1.08 (1H, m; H-9), 0.90 (1H, m; H-1b), 0.87 (1H, m; H-7b), 0.87 (3H, s; H-24), 0.81 (3H, s; H-23), 0.82 (1H, m; H-5), 0.81 (3H, s; H-22), 0.77 (3H, s; H-21); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  171.2, 139.0, 137.3, 134.5, 120.9, 79.7, 68.1, 58.6, 56.6, 54.0, 42.0, 41.6, 40.1, 39.8, 37.4, 37.4, 33.3, 33.2, 27.9, 24.6, 21.4, 21.3, 18.8, 18.6, 18.1, 17.5, 16.2; HREIMS [M<sup>+</sup>]  $m/z$  428.2918 (calcd for C<sub>27</sub>H<sub>40</sub>O<sub>4</sub>, 428.2921). **16-**

**Deacetoxyscalarafuran (15):** white needles;  $[\alpha]_D^{25}$  +2 (c 0.08, CH<sub>2</sub>Cl<sub>2</sub>); UV (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 232 (3.41) nm; IR (neat)  $\nu_{\max}$  3461, 2927, 2847, 1462, 1384, 1038, 787 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.53 (1H, s; H-19), 7.04 (1H, s; H-20), 3.64 (1H, dd,  $J$  = 11.5, 4.0 Hz; H-12), 2.75 (1H, dd,  $J$  = 16.0, 5.5 Hz; H-16a), 2.41 (1H, m; H-16b), 1.85 (1H, m; H-7a), 1.79 (1H, m; H-15a), 1.76 (1H, m; H-11a), 1.68 (1H, m; H-1a), 1.66 (1H, m; H-15b), 1.59 (1H, m; H-2a), 1.57 (1H, m; H-6a), 1.51 (1H, m; H-11b), 1.44 (1H, m; H-2b), 1.44 (1H, m; H-6b), 1.35 (1H, m; H-3a), 1.24 (3H, s; H-25), 1.12 (1H, m; H-14), 1.10 (1H, m; H-3b), 0.93 (3H, s; H-24), 0.92 (1H, m; H-7b), 0.91 (1H, m; H-9), 0.85 (3H, s; H-23), 0.83 (3H, s; H-22), 0.81 (3H, s; H-21), 0.78 (1H, m; H-5), 0.77 (1H, m; H-1b); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  137.4, 136.2, 134.6, 119.9, 80.0, 58.8, 56.7, 55.8, 42.0, 41.7, 40.3, 39.9, 37.5, 37.4, 33.3, 33.3, 28.0, 21.3, 21.0, 19.2, 18.6, 18.2, 17.7, 17.6, 16.2; HREIMS [M<sup>+</sup>]  $m/z$  370.2865 (calcd for C<sub>25</sub>H<sub>38</sub>O<sub>2</sub>, 370.2866).



**Scalarafuran acetate (16).** white solid;  $[\alpha]_{\text{D}}^{25}$  -36 (c 0.53, CH<sub>2</sub>Cl<sub>2</sub>); UV (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 231 nm (3.43); IR (neat)  $\nu_{\text{max}}$  2925, 2851, 1738, 1463, 1387, 1370, 1240, 1024, 971 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.24 (1H, dd,  $J$  = 1.5, 1.0 Hz; H-20), 7.04 (1H, d,  $J$  = 1.5 Hz; H-19), 5.73 (1H, ddd,  $J$  = 10.0, 7.0, 1.0 Hz; H-16), 4.71 (1H, dd,  $J$  = 11.0, 4.0 Hz; H-12), 2.17 (1H, m; H-15a), 2.15 (3H, s; 12-OCOCH<sub>3</sub>), 2.10 (3H, s; 16-OCOCH<sub>3</sub>), 1.95 (1H, ddd,  $J$  = 12.5, 4.0, 2.0 Hz; H-11a), 1.84 (1H, ddd,  $J$  = 12.5, 3.0, 3.0 Hz; H-7a), 1.74 (1H, ddd,  $J$  = 12.5, 12.5, 10.0 Hz; H-15b), 1.63 (1H, m; H-1a), 1.60 (1H, m; H-2a), 1.60 (1H, m; H-6a), 1.48 (1H, ddd,  $J$  = 12.5, 12.5, 11.0 Hz; H-11b), 1.41 (1H, m; H-2b), 1.41 (1H, m; H-6b), 1.34 (1H, m; H-3a), 1.34 (3H, s; H-25), 1.25 (1H, m; H-14), 1.12 (1H, ddd,  $J$  = 13.5, 13.5, 4.0 Hz; H-3b), 1.01 (1H, dd,  $J$  = 12.5, 1.5 Hz; H-9), 0.93 (3H, s; H-24), 0.90 (1H, m; H-1b), 0.87 (1H, m; H-7b), 0.83 (3H, s; H-22), 0.82 (3H, s; H-23), 0.80 (1H, m; H-5), 0.80 (3H, s; H-21); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  171.0, 170.4, 139.3, 135.8, 133.7, 121.0, 82.0, 68.0, 58.2, 56.6, 54.2, 41.9, 41.5, 39.6, 38.8, 37.5, 37.4, 33.2, 33.2, 24.5, 23.3, 21.7, 21.3, 21.2, 20.3, 18.4, 18.07, 17.5, 16.2; HREIMS  $[M^+]$   $m/z$  470.3026 (calcd for C<sub>29</sub>H<sub>42</sub>O<sub>5</sub>, 470.3027).

**16-Deacetoxyscalarafuran acetate (17).** white solid;  $[\alpha]_{\text{D}}^{25}$  -2 (c 0.55, CH<sub>2</sub>Cl<sub>2</sub>); UV (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 232 nm (3.30); IR (neat)  $\nu_{\text{max}}$  2925, 2851, 1739, 1463, 1387, 1236, 1024, 802 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.05 (1H, d,  $J$  = 1.5 Hz; H-19), 7.03 (1H, dd,  $J$  = 3.0, 1.5 Hz; H-20), 4.76 (1H, dd,  $J$  = 12.0, 4.0 Hz; H-12), 2.73 (1H, dd,  $J$  = 16.0, 5.5 Hz; H-16a), 2.39 (1H, m; H-16b), 2.15 (3H, s; 12-OCOCH<sub>3</sub>), 1.94 (1H, ddd,  $J$  = 12.0, 4.0, 2.0 Hz; H-11a), 1.85 (1H, ddd,  $J$  = 12.5, 3.5, 3.5 Hz; H-7a), 1.79 (1H, m; H-15a), 1.62 (1H, m; H-1a), 1.61 (1H, m; H-15b), 1.56 (1H, m; H-2a), 1.56 (1H, m; H-6a), 1.48 (1H, m; H-11b), 1.42 (1H, m; H-2b), 1.42 (1H, m; H-6b), 1.33 (1H, m; H-3a), 1.29 (3H, s; H-25), 1.20 (1H, m; H-14), 1.12 (1H, m; H-3b), 1.02 (1H, dd,  $J$  = 12.5, 2.0 Hz; H-9), 0.94 (1H, m; H-7b), 0.91 (3H, s; H-24), 0.87 (1H, m; H-1b), 0.84 (3H, s; H-22), 0.83 (3H, s; H-23), 0.81 (1H, m; H-5), 0.80 (3H, s; H-21); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  170.5, 136.5, 136.0, 133.7, 119.9, 82.5, 58.3,

56.0, 55.6, 42.0, 41.7, 39.6, 39.0, 37.5, 37.5, 33.3, 33.2, 23.4, 21.8, 21.3, 21.1, 20.7, 18.5, 18.2, 17.7, 17.6, 16.3; HREIMS [ $M^+$ ]  $m/z$  412.2973 (calcd for  $C_{27}H_{40}O_3$ , 412.2972).

**12-Oxoscalarafuran (18).** white solid;  $[\alpha]_D^{25} +47$  ( $c$  0.39,  $CH_2Cl_2$ ); UV ( $CH_2Cl_2$ )  $\lambda_{max}$  (log  $\epsilon$ ) 232 nm (3.54); IR (neat)  $\nu_{max}$  2930, 2850, 1735, 1711, 1461, 1389, 1369, 1240, 1041, 800, 738  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.67 (1H, d,  $J = 1.8$  Hz; H-19), 7.28 (1H, dd,  $J = 1.8, 1.8$  Hz; H-20), 5.76 (1H, ddd,  $J = 9.5, 7.8, 1.4$  Hz; H-16), 2.64 (1H, t,  $J = 14.2$  Hz; H-11a), 2.39 (1H, dd,  $J = 14.2, 2.5$  Hz; H-11b), 2.26 (1H, ddd,  $J = 13.0, 7.8, 1.6$  Hz; H-15a), 2.08 (3H, s; 16- $OCOCH_3$ ), 1.93 (1H, m; H-7a), 1.83 (1H, ddd,  $J = 13.0, 13.0, 9.5$  Hz; H-15b), 1.61 (1H, m; H-1a), 1.60 (1H, m; H-2a), 1.58 (1H, m; H-6a), 1.44 (1H, m; H-6b), 1.43 (3H, s; H-25), 1.40 (1H, m; H-2b), 1.35 (1H, m; H-3a), 1.25 (1H, m; H-14), 1.11 (1H, m; H-3b), 1.08 (3H, s; H-24), 1.00 (1H, m; H-9), 0.86 (3H, s; H-23), 0.85 (1H, m; H-7b), 0.83 (3H, s; H-22), 0.81 (3H, s; H-21), 0.80 (1H, m; H-5), 0.78 (1H, m; H-1b);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$  211.6, 171.0, 139.5, 138.3, 127.8, 120.5, 67.3, 59.0, 56.5, 55.2, 48.7, 41.7, 41.5, 39.2, 37.9, 37.5, 35.0, 33.3, 33.2, 25.9, 24.5, 21.3, 21.3, 18.3, 18.0, 16.7, 15.4; HREIMS [ $M^+$ ]  $m/z$  426.2768 (calcd for  $C_{27}H_{38}O_4$ , 426.2765).

**12,16-Deacetoxy-12-oxo-scalarafuran (19).** white solid;  $[\alpha]_D^{25} +52$  ( $c$  0.27,  $CH_2Cl_2$ ); UV ( $CH_2Cl_2$ )  $\lambda_{max}$  (log  $\epsilon$ ) 232 nm (3.33); IR (neat)  $\nu_{max}$  2924, 2851, 1759, 1708, 1460, 1388, 1261, 1042, 791  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.64 (1H, d,  $J = 1.6$  Hz; H-19), 7.05 (1H, dd,  $J = 2.75, 1.6$  Hz; H-20), 2.75 (1H, brd,  $J = 16.0, 5.9$  Hz; H-16a), 2.65 (1H, dd,  $J = 14.4, 14.3$  Hz; H-11a), 2.41 (1H, m; H-16b), 2.38 (1H, dd,  $J = 14.3, 2.5$  Hz; H-11b), 1.95 (1H, ddd,  $J = 12.6, 3.2, 3.2$  Hz; H-7a), 1.86 (1H, m; H-15a), 1.73 (1H, m; H-15b), 1.69 (1H, m; H-1a), 1.58 (1H, m; H-6a), 1.58 (1H, m; H-2a), 1.45 (1H, m; H-2b), 1.43 (1H, m; H-6b), 1.36 (3H, s; H-25), 1.34 (1H, m; H-3a), 1.10 (1H, m; H-14), 1.10 (1H, m; H-3b), 1.07 (3H, s; H-24), 0.99 (1H, m; H-9), 0.86 (3H, s; H-23), 0.83 (3H, s; H-22), 0.81 (1H, m; H-7b), 0.81

(3H, s; H-21), 0.79 (1H, m; H-5), 0.77 (1H, m; H-1b);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  212.5, 138.5, 136.4, 127.8, 119.6, 59.3, 56.9, 56.6, 49.2, 41.8, 41.6, 39.3, 38.2, 38.1, 35.0, 33.3, 33.2, 26.5, 21.3, 20.5, 18.4, 18.1, 17.6, 16.8, 15.5; HREIMS  $[\text{M}^+]$   $m/z$  368.2711 (calcd for  $\text{C}_{25}\text{H}_{36}\text{O}_2$ , 368.2710).

**12-*E*-Oximoscalarafuran (20).** white solid;  $[\alpha]_{\text{D}}^{25} +0.6$  ( $c$  0.29,  $\text{CH}_2\text{Cl}_2$ ); UV ( $\text{CH}_2\text{Cl}_2$ )  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 231 nm (2.98); IR (neat)  $\nu_{\text{max}}$  3434, 2931, 2861, 1713, 1390, 1369, 1264, 1037, 795  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (1H, d,  $J = 1.5$  Hz; H-19), 7.27 (1H, dd,  $J = 1.5, 1.5$  Hz; H-20), 5.77 (1H, ddd,  $J = 10.0, 7.5, 1.5$  Hz; H-16), 3.52 (1H, dd,  $J = 14.5, 2.5$  Hz; H-11a), 2.23 (1H, ddd,  $J = 12.5, 7.5, 1.5$  Hz; H-15a), 2.11 (3H, s; 16- $\text{OCOCH}_3$ ), 1.90 (1H, ddd,  $J = 13.0, 3.0, 3.0$  Hz; H-7a), 1.83 (1H, m; H-11b), 1.80 (1H, m; H-1a), 1.76 (1H, m; H-15b), 1.60 (1H, m; H-2a), 1.58 (1H, m; H-6a), 1.50 (1H, m; H-14), 1.45 (1H, m; H-2b), 1.44 (3H, s; H-25), 1.40 (1H, m; H-6b), 1.36 (1H, m; H-3a), 1.13 (1H, m; H-3b), 1.01 (3H, s; H-24), 1.00 (1H, m; H-9), 0.99 (1H, m; H-7b), 0.89 (3H, s; H-23), 0.87 (1H, m; H-1b), 0.84 (3H, s; H-22), 0.82 (3H, s; H-21), 0.79 (1H, m; H-5);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 164.0, 139.7, 138.8, 128.8, 121.0, 67.9, 58.9, 56.5, 56.1, 41.9, 41.8, 41.6, 39.5, 38.1, 38.0, 33.3, 33.2, 27.8, 25.0, 21.4, 21.3, 18.5, 18.0, 16.9, 16.8, 15.6; HREIMS  $[\text{M}^+]$   $m/z$  441.2878 (calcd for  $\text{C}_{27}\text{H}_{39}\text{O}_4\text{N}$ , 441.2874).

**12,16-Deacetoxy-12-*E*-oximino-scalarafuran (21).** white solid;  $[\alpha]_{\text{D}}^{25} +105$  ( $c$  0.69,  $\text{CH}_2\text{Cl}_2$ ); UV ( $\text{CH}_2\text{Cl}_2$ )  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 232 nm (3.63); IR (neat)  $\nu_{\text{max}}$  3337, 2924, 2849, 1733, 1678, 1441, 1461, 1387, 1045, 953  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 (1H, d,  $J = 1.5$  Hz; H-19), 7.06 (1H, dd,  $J = 2.5, 1.5$  Hz; H-20), 3.52 (1H, dd,  $J = 14.5, 2.5$  Hz; H-11a), 2.76 (1H, dd,  $J = 15.5, 5.5$  Hz; H-16a), 2.42 (1H, m; H-16b), 1.92 (1H, ddd,  $J = 12.5, 3.5, 3.0$  Hz; H-7a), 1.84 (1H, m; H-11b), 1.83 (1H, m; H-15a), 1.82 (1H, m; H-1a), 1.68 (1H, m; H-15b), 1.63 (1H, m; H-2a), 1.58 (1H, m; H-6a), 1.47 (1H, m; H-14), 1.45 (1H, m; H-2b), 1.44 (1H,

m; H-6b), 1.38 (3H, s; H-25), 1.36 (1H, m; H-3a), 1.13 (1H, ddd,  $J = 13.5, 13.5, 4.5$  Hz; H-3b), 1.02 (1H, m; H-9), 1.01 (3H, s; H-24), 0.96 (1H, m; H-7b), 0.87 (1H, m; H-1b), 0.86 (3H, s; H-23), 0.84 (3H, s; H-22), 0.83 (3H, s; H-21), 0.80 (1H, dd,  $J = 12.5, 2.0$  Hz; H-5);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  164.9, 139.86, 136.2, 127.7, 120.0, 59.3, 58.1, 56.6, 42.3, 41.9, 41.7, 39.6, 38.2, 38.1, 33.3, 33.2, 28.2, 21.4, 21.0, 18.5, 18.1, 18.1, 16.9, 16.9, 15.6; HREIMS  $[\text{M}^+]$   $m/z$  383.2819 (calcd for  $\text{C}_{25}\text{H}_{37}\text{O}_2\text{N}$ , 383.2819).

**12-*E*-*O*-Methyloximino-scalarafuran (22).** white solid;  $[\alpha]_{\text{D}}^{25} +55$  ( $c$  0.43,  $\text{CH}_2\text{Cl}_2$ ); UV ( $\text{CH}_2\text{Cl}_2$ )  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 232 nm (3.50); IR (neat)  $\nu_{\text{max}}$  2930, 1729, 1629, 1463, 1389, 1369, 1251, 1051, 805  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.66 (1H, d,  $J = 1.5$  Hz; H-19), 7.27 (1H, dd,  $J = 1.5, 1.5$  Hz; H-20), 5.78 (1H, ddd,  $J = 10.0, 8.0, 1.5$  Hz; H-16), 3.86 (3H, s; 12- $\text{NOCH}_3$ ), 3.41 (1H, dd,  $J = 14.5, 2.5$  Hz; H-11a), 2.24 (1H, ddd,  $J = 13.0, 8.0, 1.5$  Hz; H-15a), 2.10 (3H, s; 16- $\text{OCOCH}_3$ ), 1.90 (1H, m; H-7a), 1.80 (1H, m; H-11b), 1.78 (1H, m; H-15b), 1.75 (1H, m; H-1a), 1.61 (1H, m; H-2a), 1.56 (1H, m; H-6a), 1.50 (1H, dd,  $J = 13.0, 1.5$  Hz; H-14), 1.46 (1H, m; H-2b), 1.43 (3H, s; H-25), 1.42 (1H, m; H-6b), 1.36 (1H, m; H-3b), 1.1 (1H, ddd,  $J = 13.0, 13.0, 4.0$  Hz; H-3a), 1.00 (1H, m; H-9), 0.99 (3H, s; H-24), 0.97 (1H, m; H-7a), 0.86 (3H, s; H-23), 0.83 (3H, s; H-22), 0.82 (1H, m; H-1b), 0.81 (3H, s; H-21), 0.78 (1H, dd,  $J = 12.5, 2.5$  Hz; H-5);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0, 162.4, 139.8, 138.7, 129.14, 120.9, 67.8, 64.2, 58.5, 56.5, 55.8, 41.9, 41.6, 41.4, 39.5, 37.9, 37.9, 33.3, 33.2, 28.2, 24.9, 21.4, 21.3, 18.5, 18.0, 17.5, 16.7, 15.5; HREIMS  $[\text{M}^+]$   $m/z$  455.3035 (calcd for  $\text{C}_{28}\text{H}_{41}\text{O}_4\text{N}$ , 455.3030).

**12,16-Deacetoxy-12-*E*-*O*-methyloximino-scalarafuran (23).** white solid;  $[\alpha]_{\text{D}}^{25} +62$  ( $c$  0.64,  $\text{CH}_2\text{Cl}_2$ ); UV ( $\text{CH}_2\text{Cl}_2$ )  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 232 nm (3.53); IR (neat)  $\nu_{\text{max}}$  2924, 2854, 1761, 1712, 1463, 1388, 1262, 1050, 802  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (1H, d,  $J = 1.4$  Hz; H-19), 7.05 (1H, brs; H-20), 3.85 (3H, s; 12- $\text{NOCH}_3$ ), 3.39 (1H, dd,  $J = 14.2, 2.7$  Hz; H-

11a), 2.75 (1H, dd,  $J = 16.0, 5.9$  Hz; H-16a), 2.40 (1H, m; H-16b), 1.90 (1H, m; H-7a), 1.83 (1H, m; H-15a), 1.82 (1H, m; H-1a), 1.79 (1H, m; H-11b), 1.66 (1H, m; H-15b), 1.63 (1H, m; H-2a), 1.58 (1H, m; H-6a), 1.53 (1H, m; H-14), 1.43 (1H, m; H-2b), 1.41 (1H, m; H-6b), 1.39 (1H, m; H-3a), 1.35 (3H, s; H-25), 1.10 (1H, m; H-3b), 0.97 (1H, m; H-7b), 0.97 (3H, s; H-24), 0.86 (1H, m; H-9), 0.85 (1H, m; H-1b), 0.85 (3H, s; H-23), 0.82 (3H, s; H-22), 0.81 (1H, m; H-5), 0.80 (3H, s; H-21);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  163.2, 140.0, 136.0, 129.1, 120.0, 61.3, 58.8, 57.7, 56.6, 41.9, 41.9, 41.8, 38.1, 38.0, 35.6, 33.3, 33.2, 28.5, 21.4, 20.8, 18.5, 18.2, 18.1, 16.8, 16.8, 15.6; HREIMS  $[\text{M}^+]$   $m/z$  397.2974 (calcd for  $\text{C}_{26}\text{H}_{39}\text{O}_2\text{N}$ , 397.2975).

**Sesterstatin 5 (24).** white solid;  $[\alpha]_{\text{D}}^{25} +66$  ( $c$  0.31, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 219 nm (3.67); IR (neat)  $\nu_{\text{max}}$  3446, 2929, 1385, 1041, 789  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  7.42 (1H, d,  $J = 1.8$  Hz; H-19), 7.32 (1H, dd,  $J = 1.8, 1.6$  Hz; H-20), 5.03 (1H, d,  $J = 6.2$  Hz; 16-OH), 4.78 (1H, d,  $J = 4.9$  Hz; 12-OH), 4.46 (1H, m; H-16), 3.35 (1H, m; H-12), 1.84 (1H, dd,  $J = 12.1, 6.7$  Hz; H-15a), 1.76 (1H, m; H-7a), 1.61 (1H, m; H-11a), 1.61 (1H, m; H-1a), 1.56 (1H, m; H-2a), 1.49 (1H, m; H-6a), 1.47 (1H, m; H-15b), 1.42 (1H, m; H-11b), 1.37 (1H, m; H-6b), 1.37 (1H, m; H-2b), 1.31 (1H, m; H-3a), 1.10 (3H, s; H-25), 1.08 (1H, m; H-3b), 0.97 (1H, m; H-14), 0.86 (1H, m; H-7b), 0.84 (1H, m; H-9), 0.82 (3H, s; H-24), 0.81 (3H, s; H-22), 0.79 (3H, s; H-23), 0.78 (3H, s; H-21), 0.77 (1H, m; H-5), 0.76 (1H, m; H-1b);  $^{13}\text{C}$  NMR (125 MHz,  $\text{DMSO}-d_6$ )  $\delta$  137.7, 136.6, 134.9, 126.5, 78.1, 65.1, 58.2, 56.1, 54.0, 41.8, 41.2, 40.1, 40.0, 37.1, 37.0, 33.2, 33.1, 28.8, 27.3, 21.3, 20.0, 18.3, 17.9, 17.7, 16.1; HREIMS  $[\text{M}^+]$   $m/z$  386.2816 (calcd for  $\text{C}_{25}\text{H}_{38}\text{O}_3$ , 386.2815).

**12-Deacetyl-12-*epi*-scalaradiol (25).** white solid;  $[\alpha]_{\text{D}}^{25} +0.02$  ( $c$  0.19, MeOH); UV (MeOH)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 206 nm (3.31); IR (neat)  $\nu_{\text{max}}$  3221, 2932, 2844, 1466, 1385, 1064, 797  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  5.65 (1H, brd; 12-OH), 5.48 (1H, d,  $J = 4.0$ ; 20-OH), 5.44

(1H, dd,  $J = 4.5, 4.5$ ; 19-OH), 4.58 (1H, dd,  $J = 5.0, 5.0$  Hz; H-16), 3.90 (1H, dd,  $J = 12.7, 4.9$  Hz; H-20), 3.72 (1H, m; H-20), 3.72 (1H, m; H-19a), 3.69 (1H, m; H-19b), 2.10 (1H, m; H-15a), 1.89 (1H, brs; H-18), 1.89 (1H, brs; H-15b), 1.78 (1H, m; H-7a), 1.63 (1H, m; H-1a), 1.62 (1H, m; H-11a), 1.55 (1H, m; H-11b), 1.55 (1H, m; H-2a), 1.45 (1H, m; H-6a), 1.33 (1H, m; H-6b), 1.33 (1H, m; H-3a), 1.32 (1H, m; H-2b), 0.98 (1H, m; H-3b), 0.97 (1H, m; H-14), 0.86 (1H, m; H-7b), 0.84 (1H, m; H-9), 0.84 (3H, s; H-24), 0.82 (3H, s; H-22), 0.79 (3H, s; H-23), 0.78 (3H, s; H-21), 0.77 (1H, m; H-5), 0.76 (1H, m; H-1b), 0.72 (3H, s; H-25);  $^{13}\text{C}$  NMR (125 MHz, DMSO- $d_6$ )  $\delta$  136.1, 123.6, 79.2, 64.5, 59.1, 57.3, 56.0, 55.1, 54.2, 41.8, 41.8, 41.5, 39.2, 37.4, 36.8, 33.2, 33.0, 27.4, 21.7, 21.3, 18.3, 18.0, 16.7, 16.3, 9.2; HREIMS  $[\text{M}^+]$   $m/z$  390.3130 (calcd for  $\text{C}_{25}\text{H}_{42}\text{O}_3$ , 390.3128).

**12-*O*-Deacetyl-16 $\alpha$ -nitromethyl-16 $\beta$ ,17 $\beta$ -dihydro-19-deoxyscalarin (26):** white solid;  $[\alpha]_{\text{D}}^{25}$  -0.4 ( $c$  0.21,  $\text{CH}_2\text{Cl}_2$ ); UV ( $\text{CH}_2\text{Cl}_2$ )  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 232 (2.99) nm; IR (neat)  $\nu_{\text{max}}$  3468, 2925, 2853, 1773, 1555, 1460, 1388, 1082, 981, 738  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.62 (1H, dd,  $J = 11.8, 4.1$  Hz; 16- $\text{CH}_2\text{NO}_2\text{a}$ ), 4.42 (1H, dd,  $J = 11.8, 11.8$  Hz; 16- $\text{CH}_2\text{NO}_2\text{b}$ ), 4.38 (1H, dd,  $J = 9.8, 7.1$  Hz; H-19a), 4.08 (1H, dd,  $J = 10.8, 9.8$  Hz; H-19b), 3.40 (1H, dd,  $J = 11.2, 4.3$  Hz; H-12), 3.16 (1H, m; H-16), 2.62 (1H, dd,  $J = 14.9, 5.3$  Hz; H-17), 1.90 (1H, ddd,  $J = 14.9, 10.8, 7.1$  Hz; H-18), 1.70 (1H, m; H-11a), 1.62 (1H, m; H-15a), 1.62 (1H, m; H-15b), 1.58 (1H, m; H-7a), 1.57 (1H, m; H-1a), 1.56 (1H, m; H-6a), 1.52 (1H, m; H-6b), 1.42 (1H, m; H-11b), 1.41 (1H, m; H-2a), 1.39 (1H, m; H-3a), 1.37 (1H, m; H-2b), 1.10 (1H, m; H-3b), 0.96 (1H, m; H-14), 0.92 (3H, s; H-25), 0.90 (1H, m; H-9), 0.82 (3H, s; H-22), 0.81 (3H, s; H-23), 0.81 (3H, s; H-24), 0.80 (1H, m; H-1b), 0.80 (1H, m; H-5), 0.78 (1H, m; H-7b), 0.77 (3H, s; H-21);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  174.9, 80.4, 73.5, 69.7, 58.9, 56.4, 51.7, 50.3, 42.2, 42.0, 41.3, 40.2, 40.0, 37.5, 37.1, 33.3, 33.2, 30.3, 27.4, 21.4, 21.2, 18.6, 18.1, 17.2, 16.4, 9.1; HREIMS  $[\text{M}^+]$   $m/z$  447.2978 (calcd for  $\text{C}_{26}\text{H}_{41}\text{O}_5\text{N}$ , 447.2979).

**12-*O*-Deacetyl-16 $\alpha$ -nitromethyl-16 $\beta$ ,17 $\alpha$ -dihydro-19-deoxyscalarin (27):** white solid;

$[\alpha]_D^{25}$  -5 (*c* 0.25, CH<sub>2</sub>Cl<sub>2</sub>); UV (CH<sub>2</sub>Cl<sub>2</sub>)  $\lambda_{\max}$  (log  $\epsilon$ ) 231 (2.85) nm; IR (neat)  $\nu_{\max}$  3467, 2924, 2852, 1766, 1553, 1464, 1378, 1201, 1021, 976, 738 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.95 (1H, d, *J* = 10.1 Hz; H-19a), 4.47 (1H, dd, *J* = 11.9, 8.0 Hz; 16-CH<sub>2</sub>NO<sub>2</sub>a), 4.44 (1H, dd, *J* = 11.9, 8.0 Hz; 16-CH<sub>2</sub>NO<sub>2</sub>b), 4.18 (1H, dd, *J* = 10.1, 5.3 Hz; H-19b), 3.35 (1H, dd, *J* = 11.2, 4.1 Hz; H-12), 3.23 (1H, br dd, *J* = 13.7, 7.6 Hz; H-16), 2.37 (1H, d, *J* = 8.0 Hz; H-17), 2.33 (1H, dd, *J* = 8.0, 5.3 Hz; H-18), 1.70 (1H, m; H-1a), 1.69 (1H, m; H-2a), 1.68 (1H, m; H-7a), 1.65 (1H, m; H-2b), 1.65 (1H, m; H-11a), 1.57 (1H, m; H-6a), 1.42 (1H, m; H-15a), 1.42 (1H, m; H-15b), 1.39 (1H, m; H-11b), 1.38 (1H, m; H-6b), 1.34 (1H, m; H-3a), 1.09 (1H, m; H-3b), 0.89 (3H, s; H-25), 0.85 (1H, m; H-9), 0.83 (3H, s; H-22), 0.79 (3H, s; H-23), 0.79 (3H, s; H-24), 0.78 (1H, m; H-5), 0.77 (3H, s; H-21), 0.75 (1H, m; H-7b), 0.75 (1H, m; H-1b), 0.71 (1H, m; H-14); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  176.8, 83.7, 79.2, 70.0, 58.5, 56.5, 49.9, 48.0, 42.0, 41.6, 41.02, 40.4, 39.9, 37.5, 37.4, 33.3, 33.2, 30.6, 27.8, 21.2, 19.5, 18.5, 18.1, 17.3, 16.4, 9.8; HREIMS [M<sup>+</sup>] *m/z* 447.2979 (calcd for C<sub>26</sub>H<sub>41</sub>O<sub>5</sub>N, 447.2979).

**16-Deacetoxyscalarapyridazine (28).** yellow solid;  $[\alpha]_D^{25}$  -4 (*c* 0.04, CH<sub>2</sub>Cl<sub>2</sub>); UV (CH<sub>2</sub>Cl<sub>2</sub>)

$\lambda_{\max}$  (log  $\epsilon$ ) 327 nm (4.21); IR (neat)  $\nu_{\max}$  3401, 2925, 1628, 1603, 1508, 1250, 1168, 1027, 837 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  10.00 (1H, s; H-19), 8.77 (1H, s; H-20), 3.82 (1H, dd, *J* = 11.0, 4.5 Hz; H-12), 2.86 (1H, dd, *J* = 18.5, 5.5 Hz; H-16a), 2.70 (1H, ddd, *J* = 18.5, 11.0, 8.0 Hz; H-16b), 1.95 (1H, m; H-15a), 1.86 (1H, m; H-11a), 1.85 (1H, m; H-7a), 1.75 (1H, m; H-15b), 1.68 (1H, m; H-1a), 1.63 (1H, m; H-11b), 1.59 (1H, m; H-2a), 1.57 (1H, m; H-6a), 1.44 (1H, m; H-2b), 1.40 (1H, m; H-6b), 1.36 (1H, m; H-3a), 1.24 (3H, s; H-25), 1.12 (1H, m; H-3b), 1.11 (1H, m; H-14), 0.93 (3H, s; H-24), 0.90 (1H, m; H-9), 0.89 (1H, m; H-7b), 0.85 (3H, s; H-23), 0.84 (3H, s; H-22), 0.81 (3H, s; H-21), 0.79 (1H, m; H-1b), 0.76 (1H, m; H-5); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  152.1, 150.9, 148.0, 135.0, 77.3, 57.8, 56.5, 53.7,

42.6, 42.0, 41.4, 39.8, 37.8, 37.2, 33.2, 33.2, 29.0, 27.2, 21.2, 18.6, 18.5, 18.2, 17.2, 16.2, 16.1; HREIMS [M<sup>+</sup>]  $m/z$  382.2973 (calcd for C<sub>25</sub>H<sub>38</sub>ON<sub>2</sub>, 382.2979).



IR, NMR, and mass spectra of **1** (Figures S1-S4)

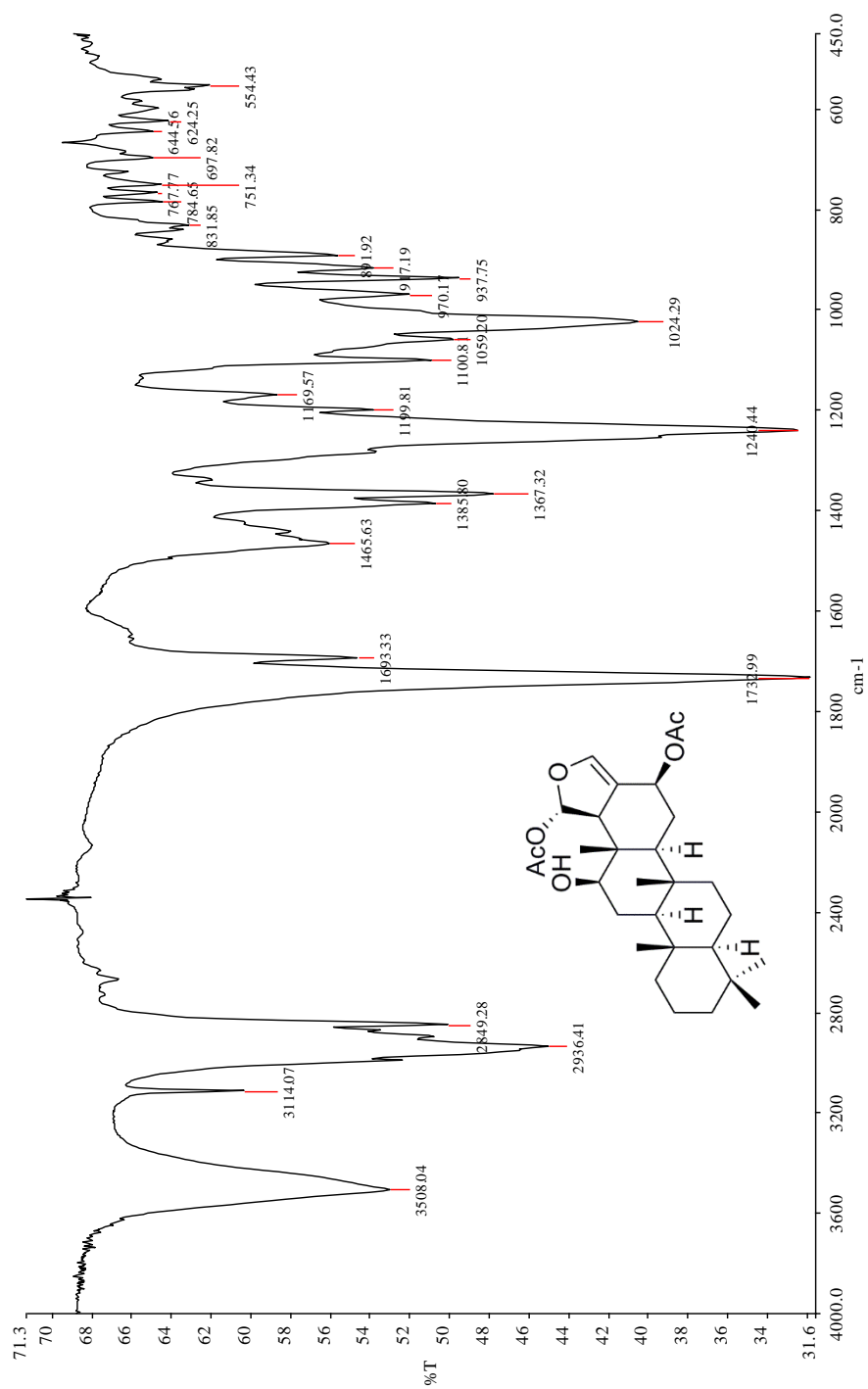
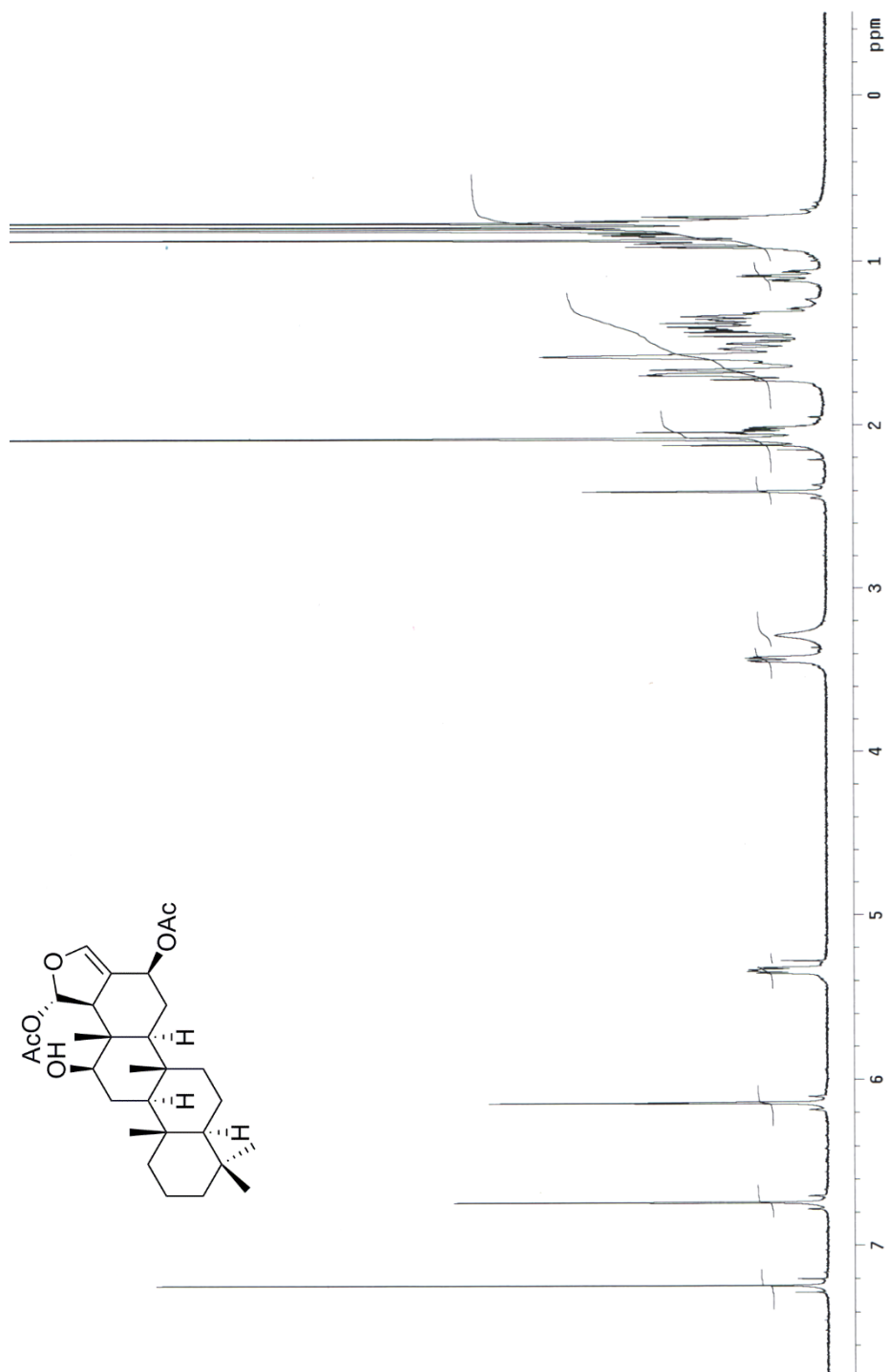
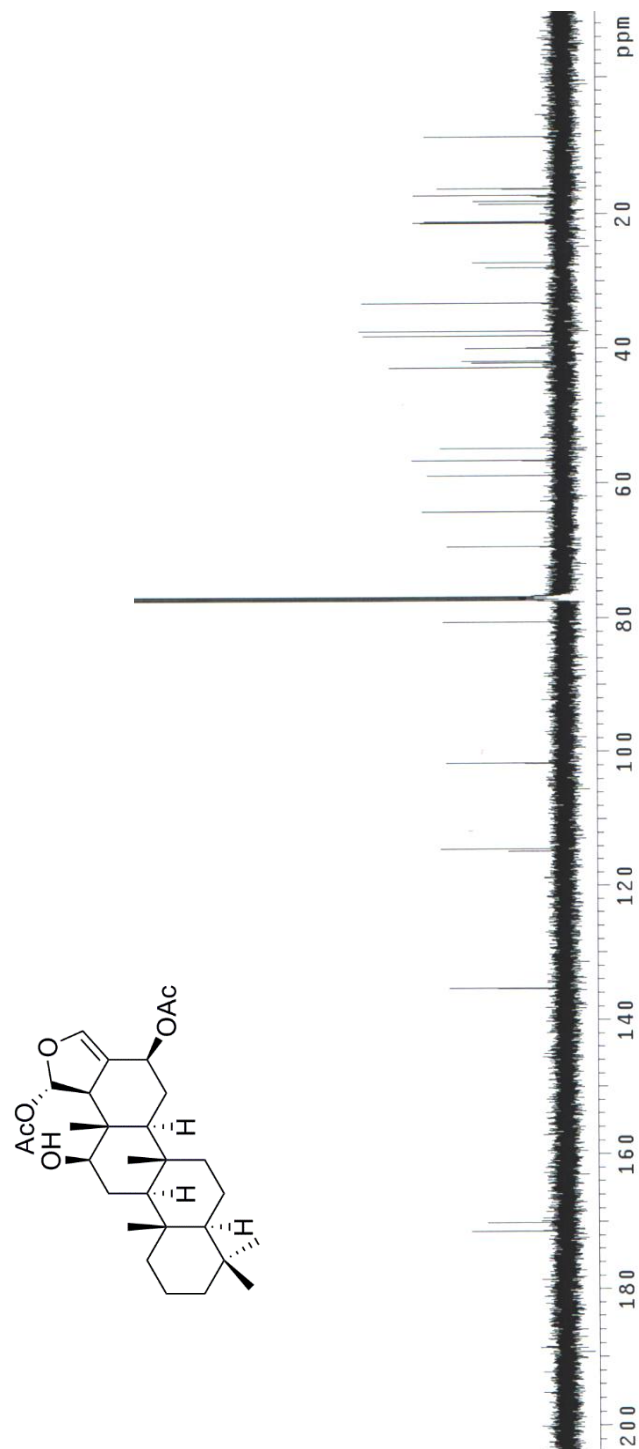


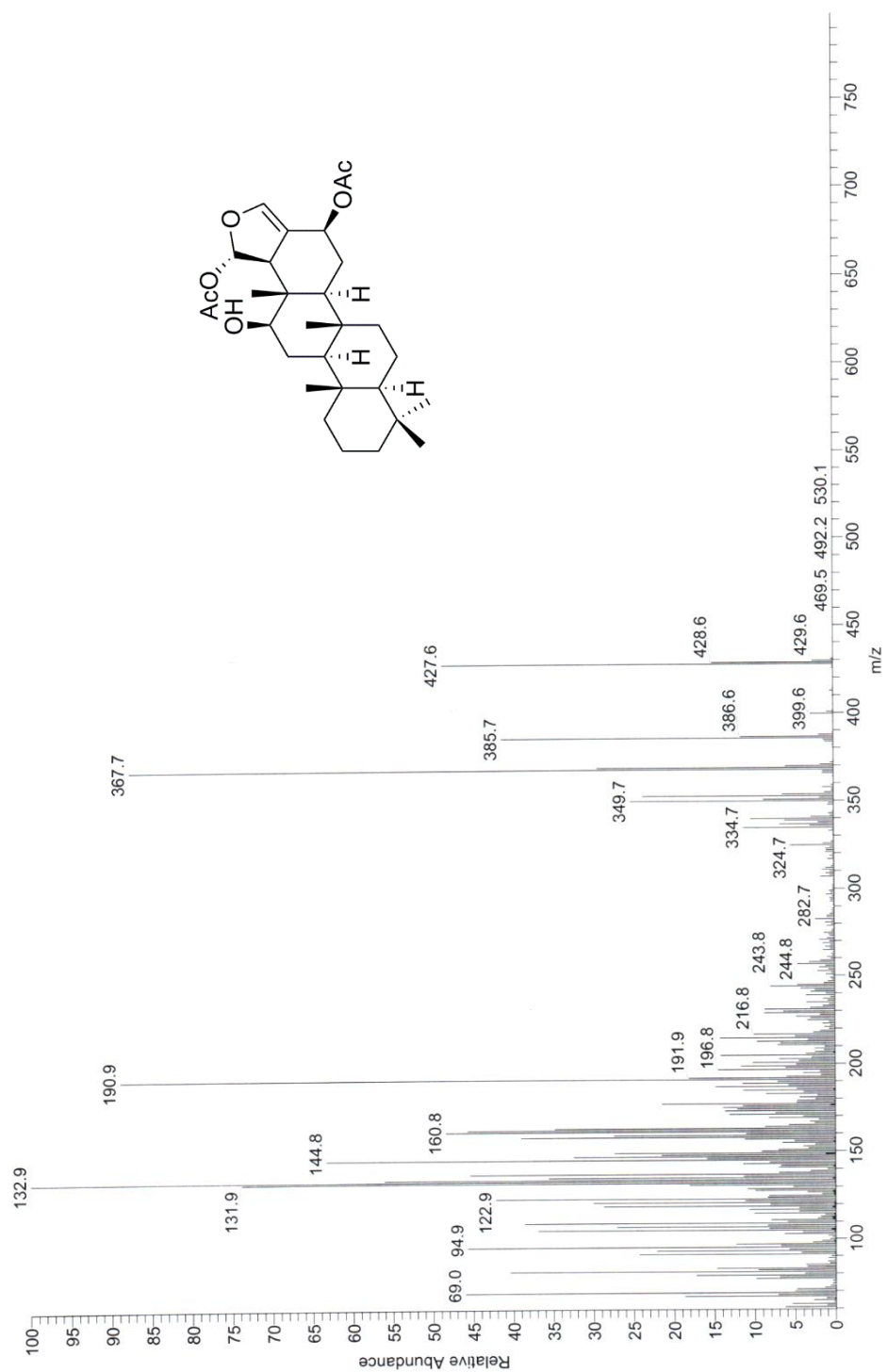
Figure S1 IR spectrum of **1**



**Figure S2**  $^1\text{H}$  NMR spectrum of **1** (500MHz,  $\text{CDCl}_3$ )



**Figure S3**  $^{13}\text{C}$  NMR spectrum of **1** (125MHz, CDCl<sub>3</sub>)



**Figure S4** EI mass spectrum of **1**

IR, NMR, and mass spectra of **4** (Figures S5-S8)

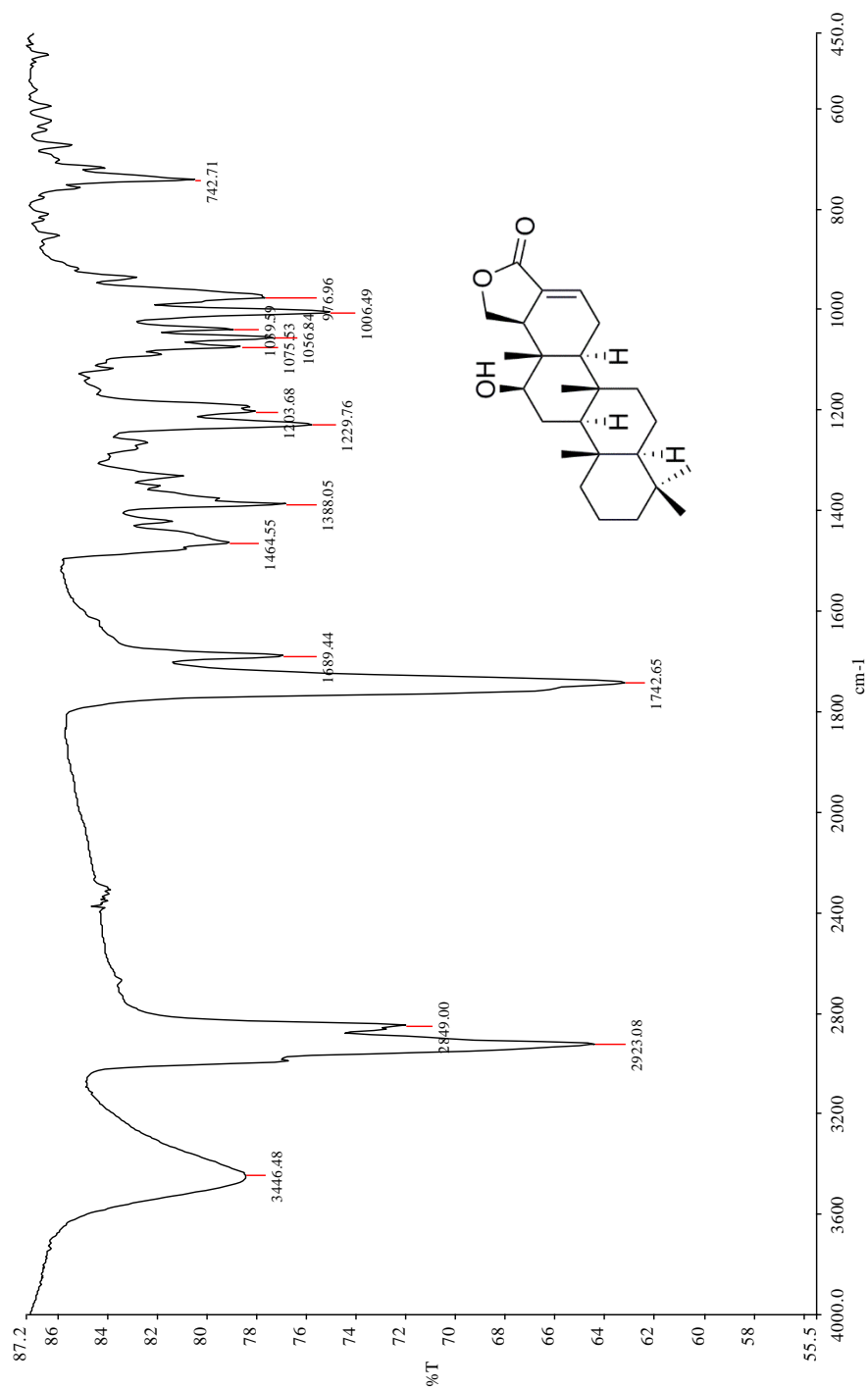
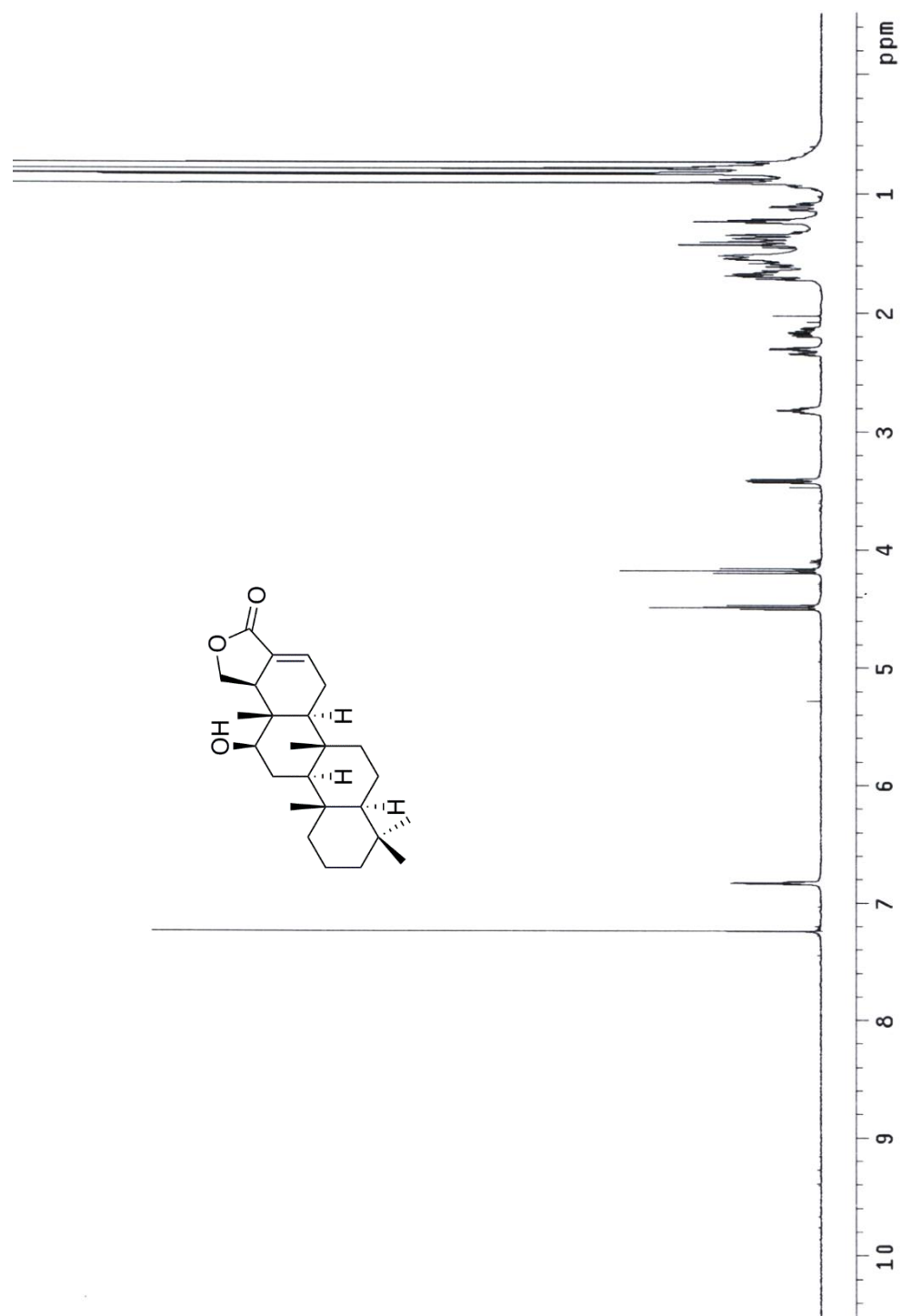
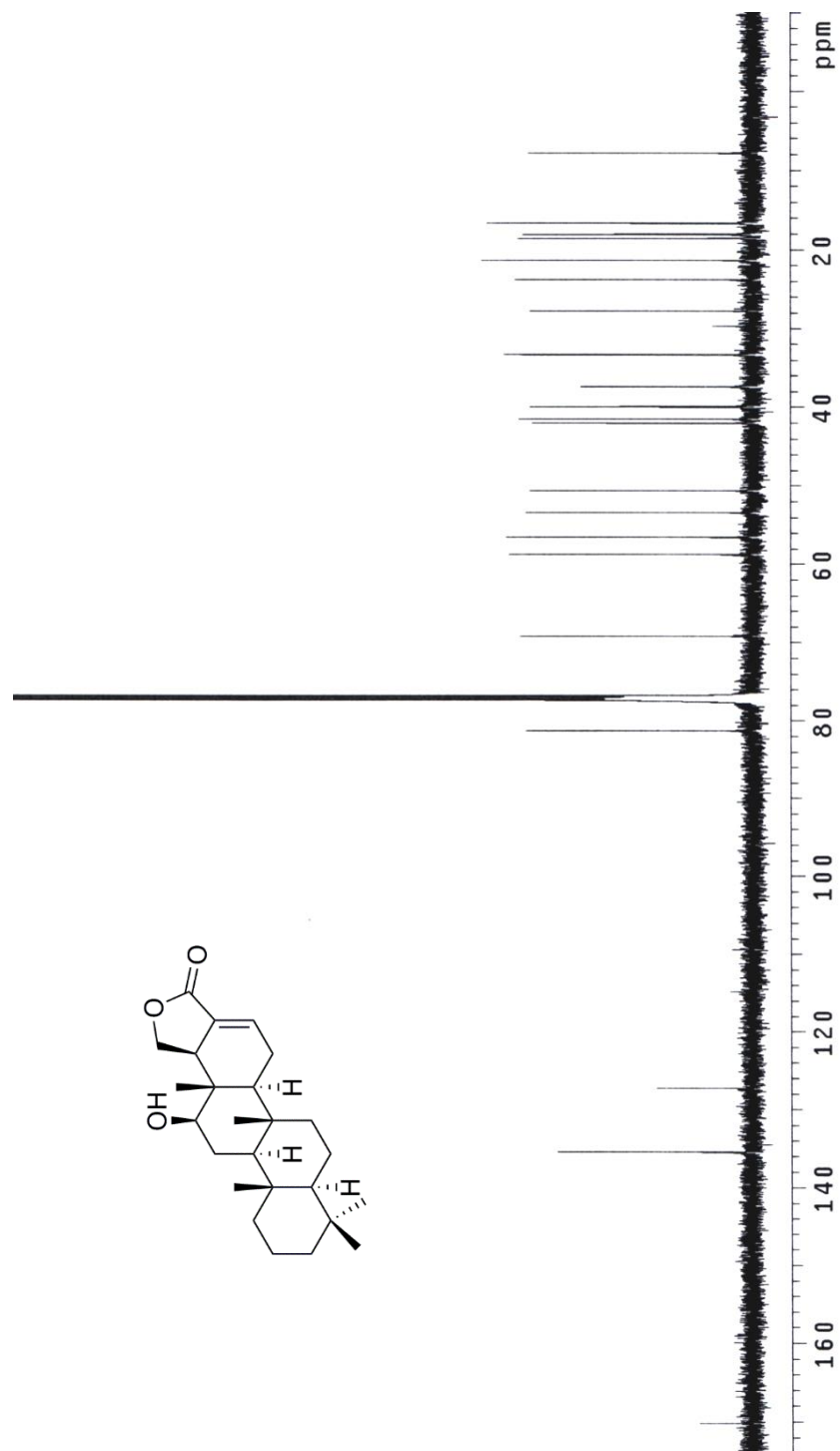


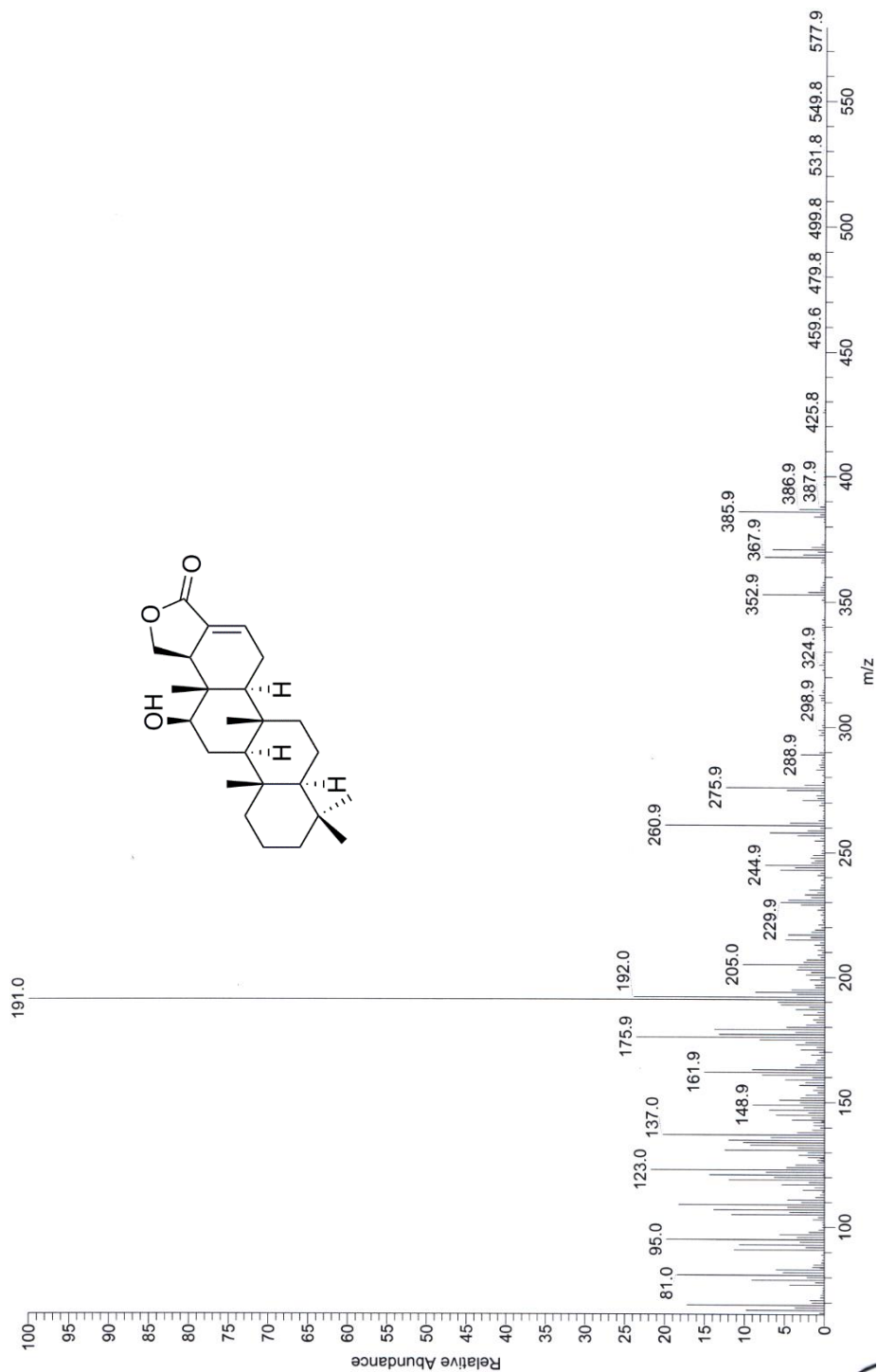
Figure S5 IR spectrum of **4**



**Figure S6**  $^1\text{H}$  NMR spectrum of compound **4** (500MHz,  $\text{CDCl}_3$ )



**Figure S7**  $^{13}\text{C}$  NMR spectrum of compound **4** (125MHz,  $\text{CDCl}_3$ )



**Figure S8** EI mass spectrum of compound **4**



IR, NMR, and mass spectra of 13 (Figures S9-S12)

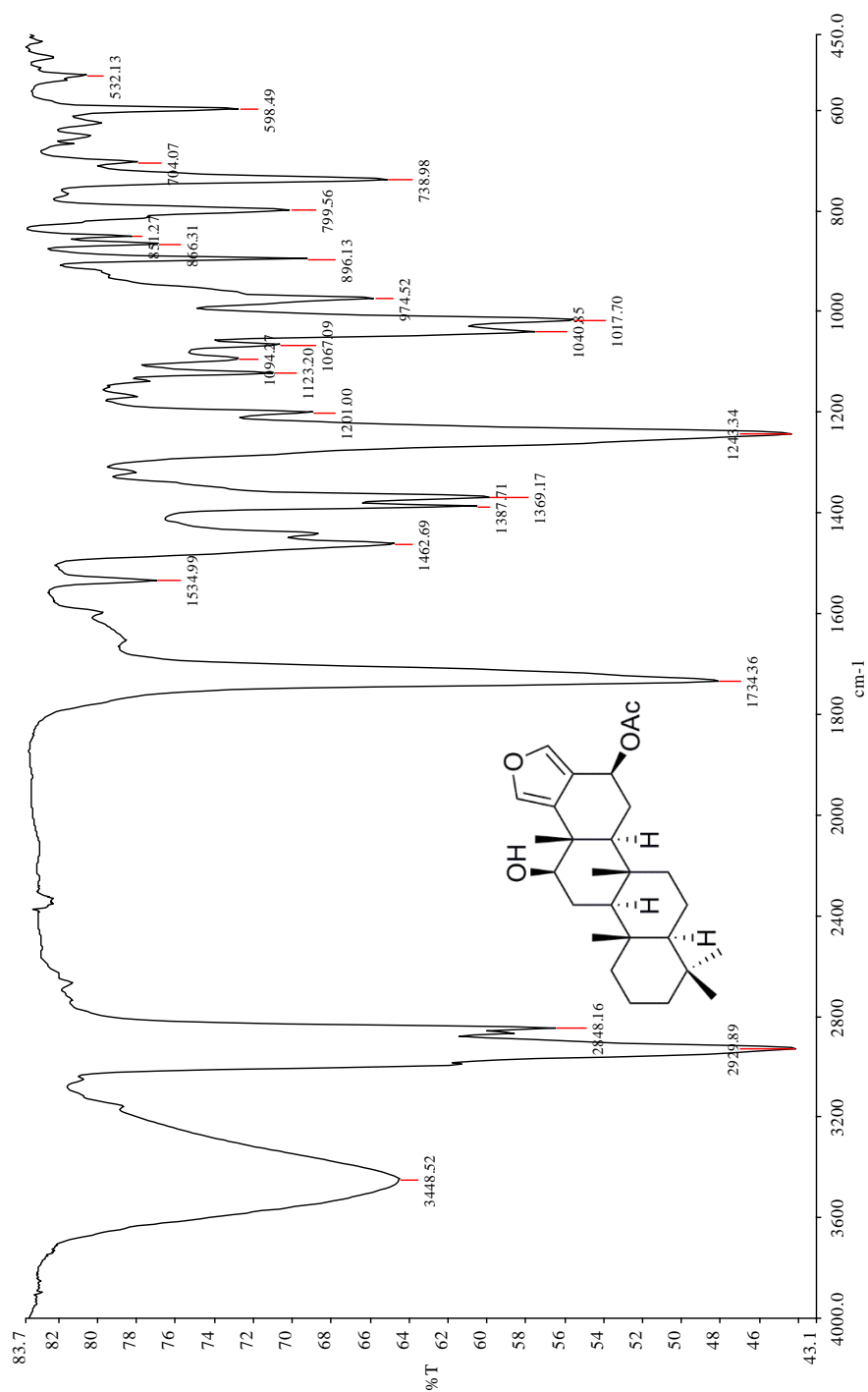
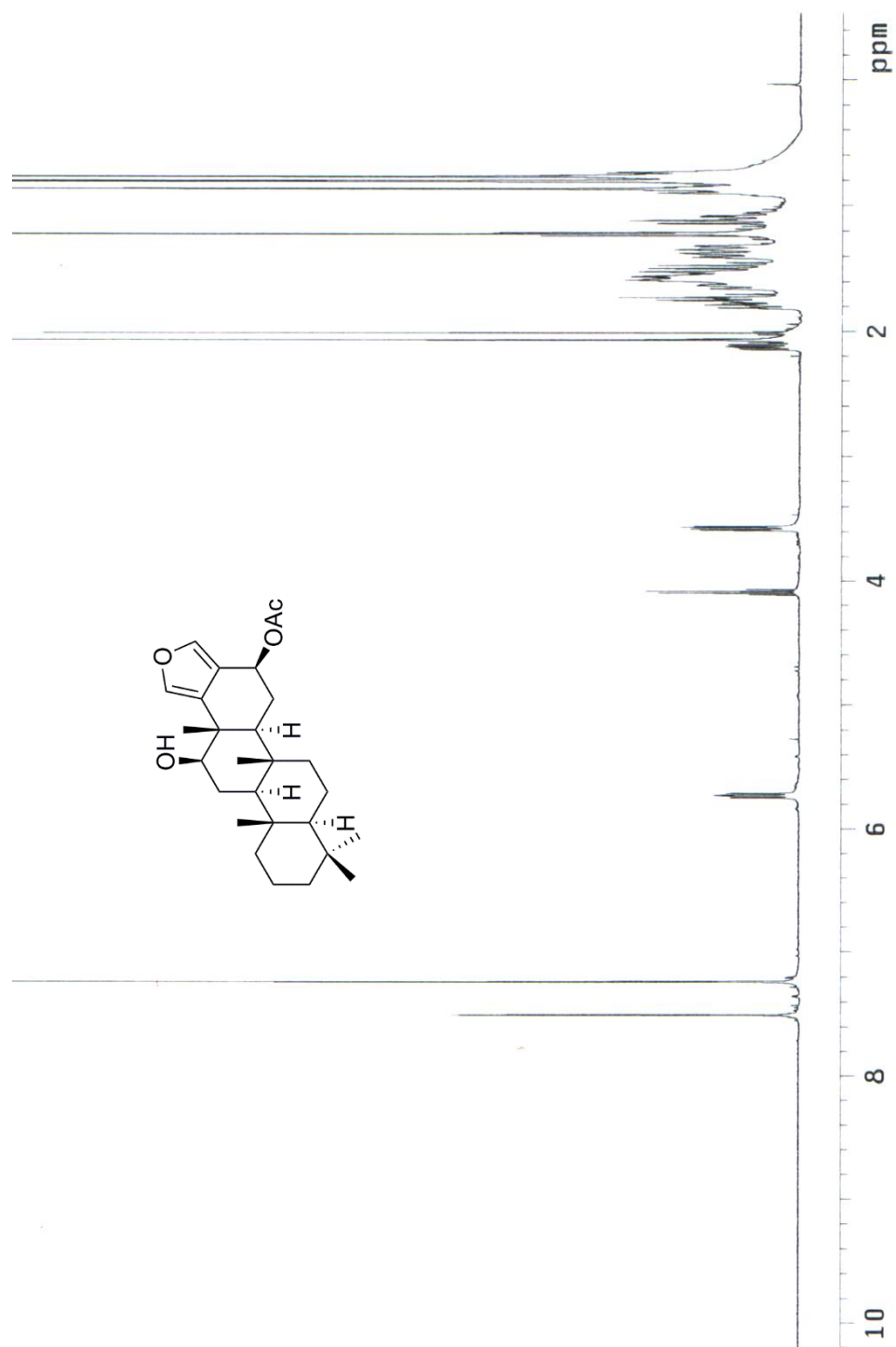
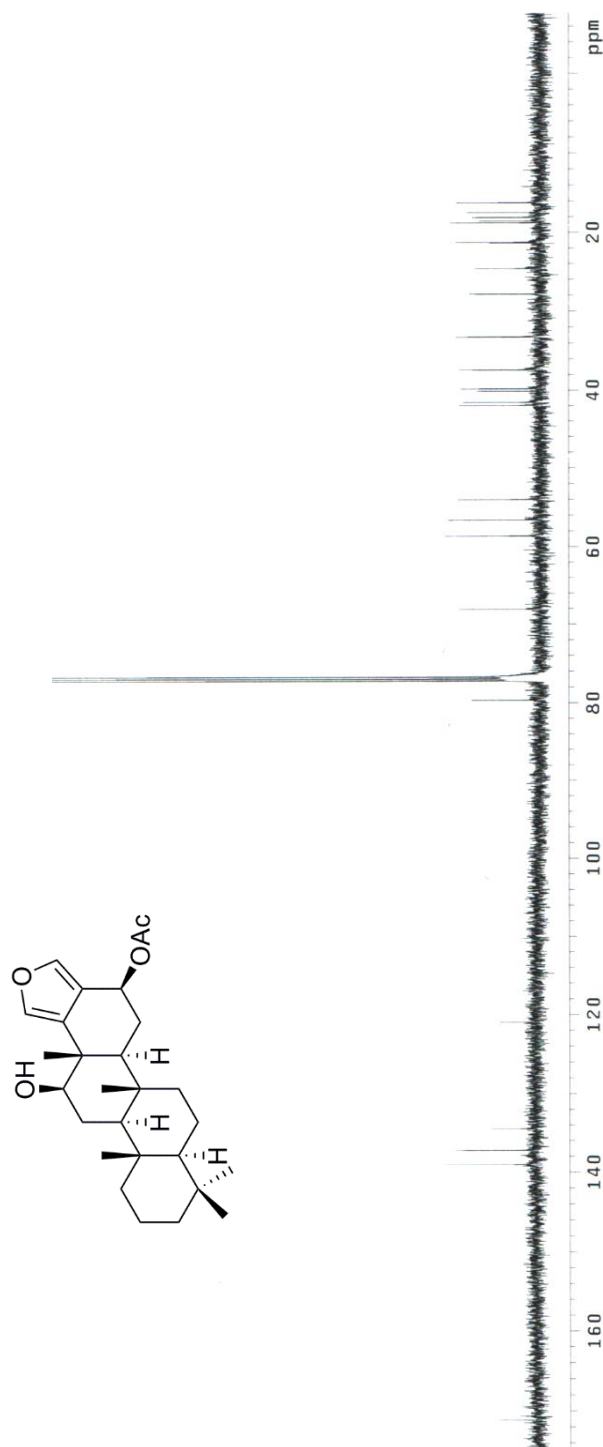


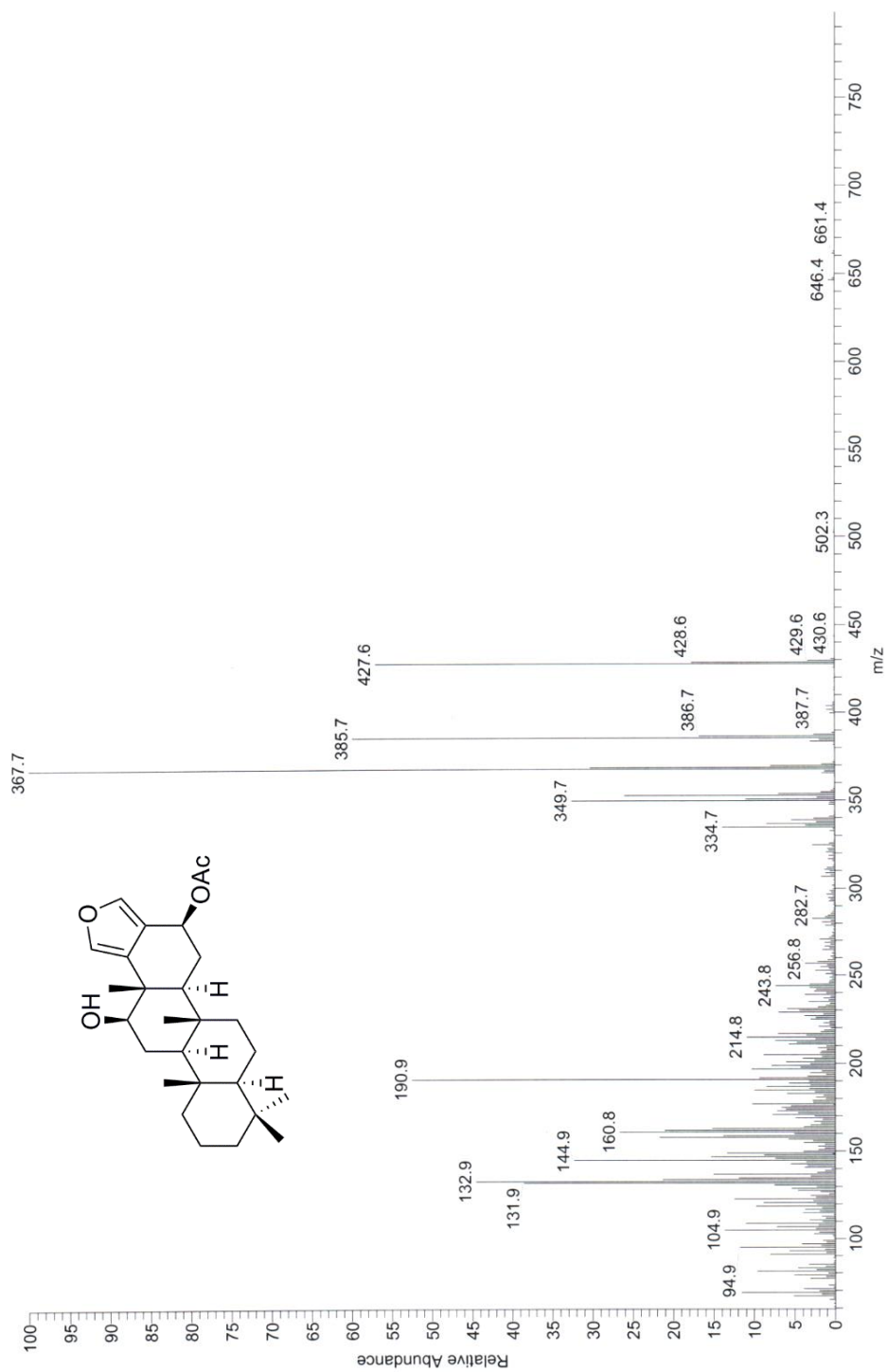
Figure S9 IR spectrum of compound 13



**Figure S10**  $^1\text{H}$  NMR spectrum of compound **13** (500MHz,  $\text{CDCl}_3$ )

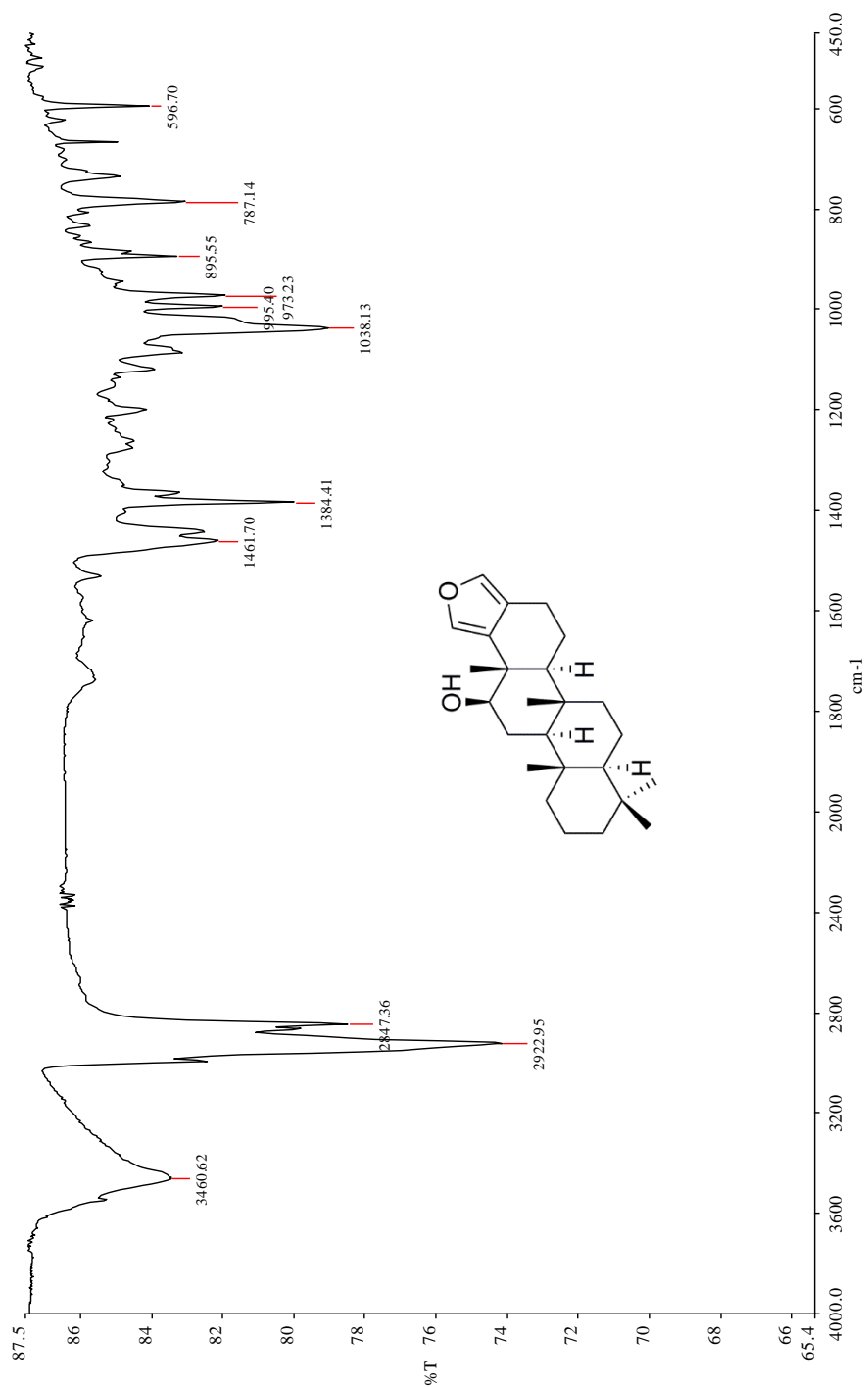


**Figure S11**  $^{13}\text{C}$  NMR spectrum of compound **13** (125MHz,  $\text{CDCl}_3$ )

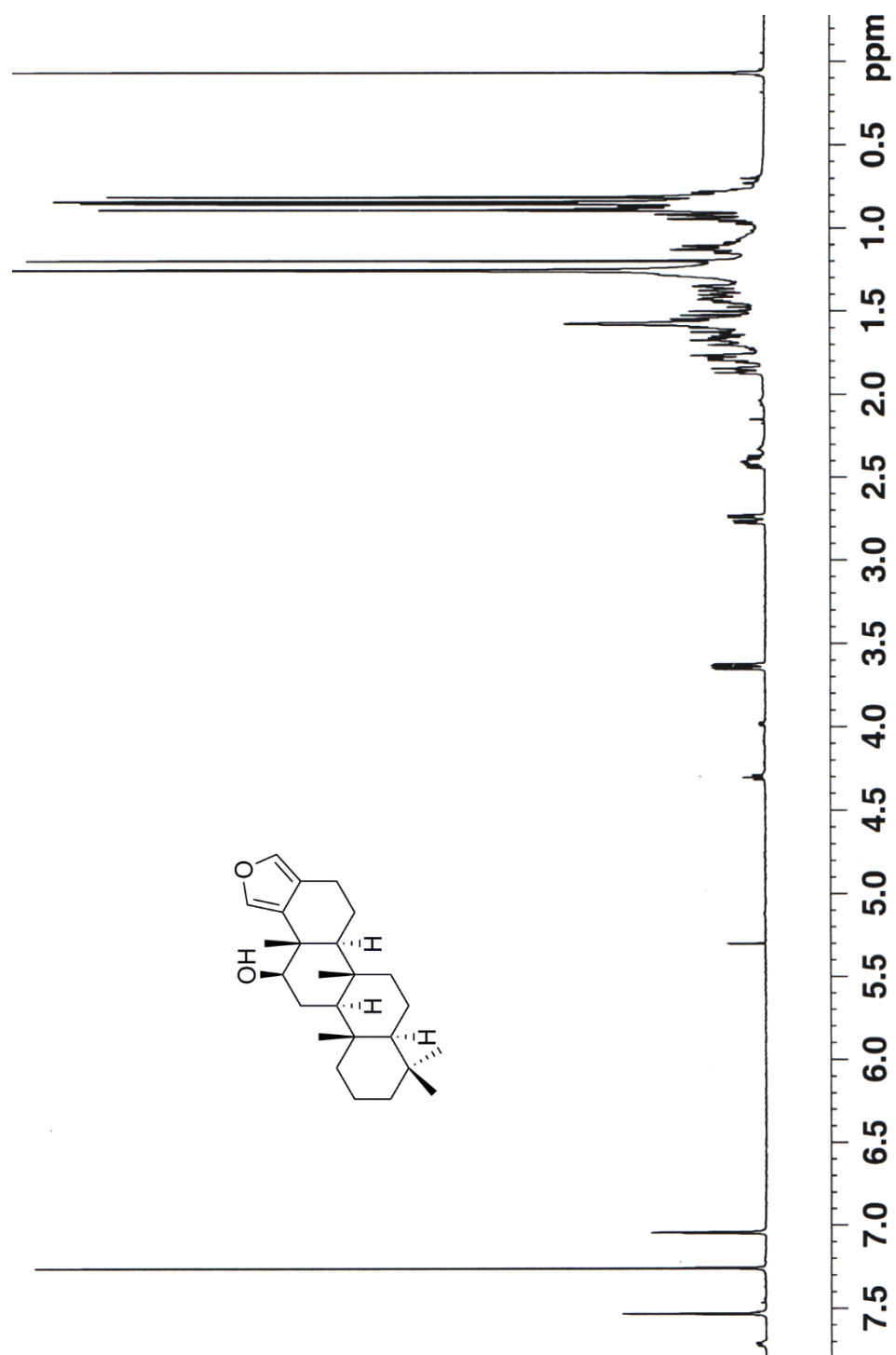


**Figure S12** EI mass spectrum of compound **13**

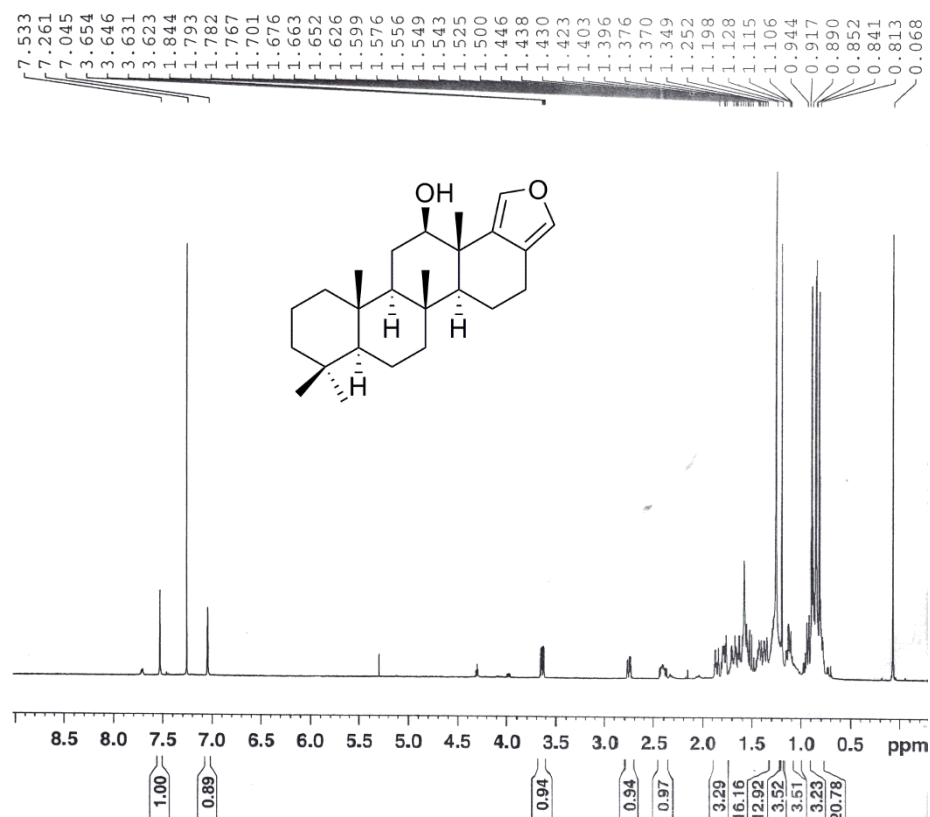
IR, NMR, and mass spectra of 15 (Figures S13-S23)



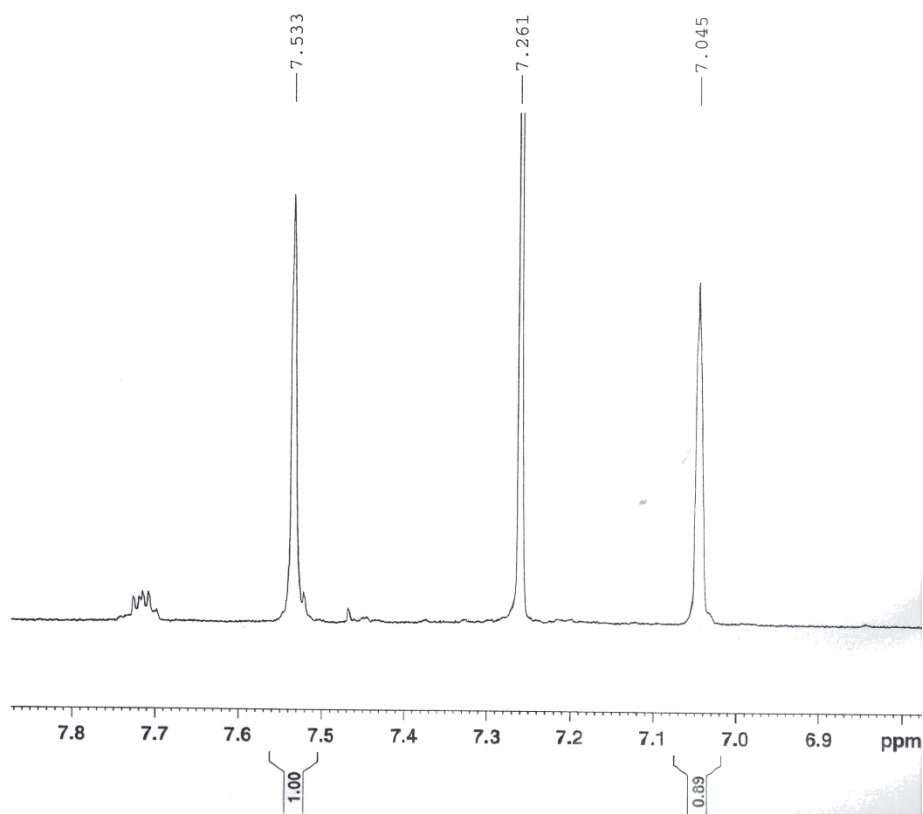
**Figure S13** IR spectrum of compound 15



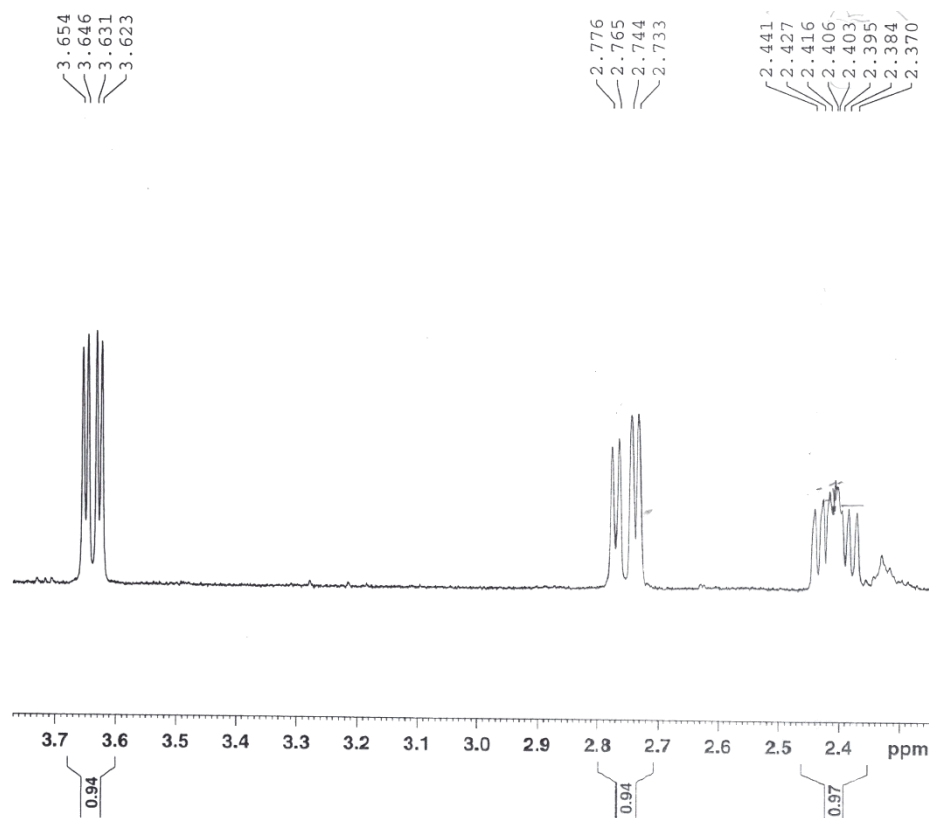
**Figure S14**  $^1\text{H}$  NMR spectrum of compound **15** (500MHz,  $\text{CDCl}_3$ )



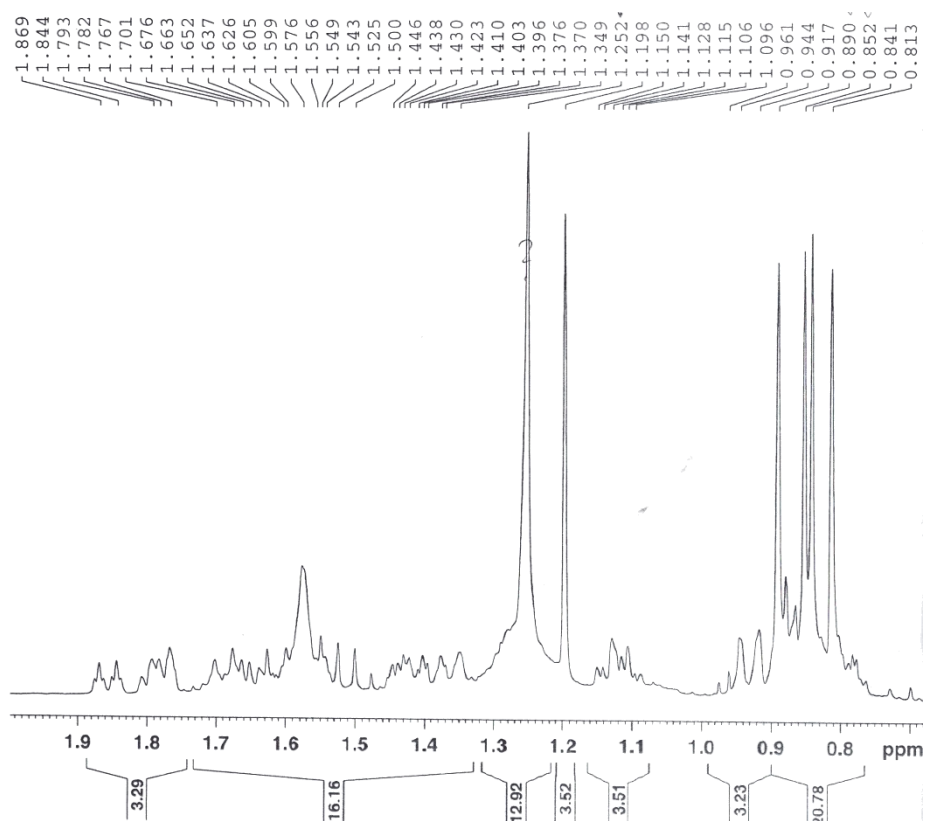
**Figure S16**  $^1\text{H}$  NMR spectrum of **15** (peak-picked and integration tagged; 500 MHz,  $\text{CDCl}_3$ )



**Figure S17**  $^1\text{H}$  NMR spectrum of **15** (expanding 7.8-6.8 ppm; 500 MHz,  $\text{CDCl}_3$ )

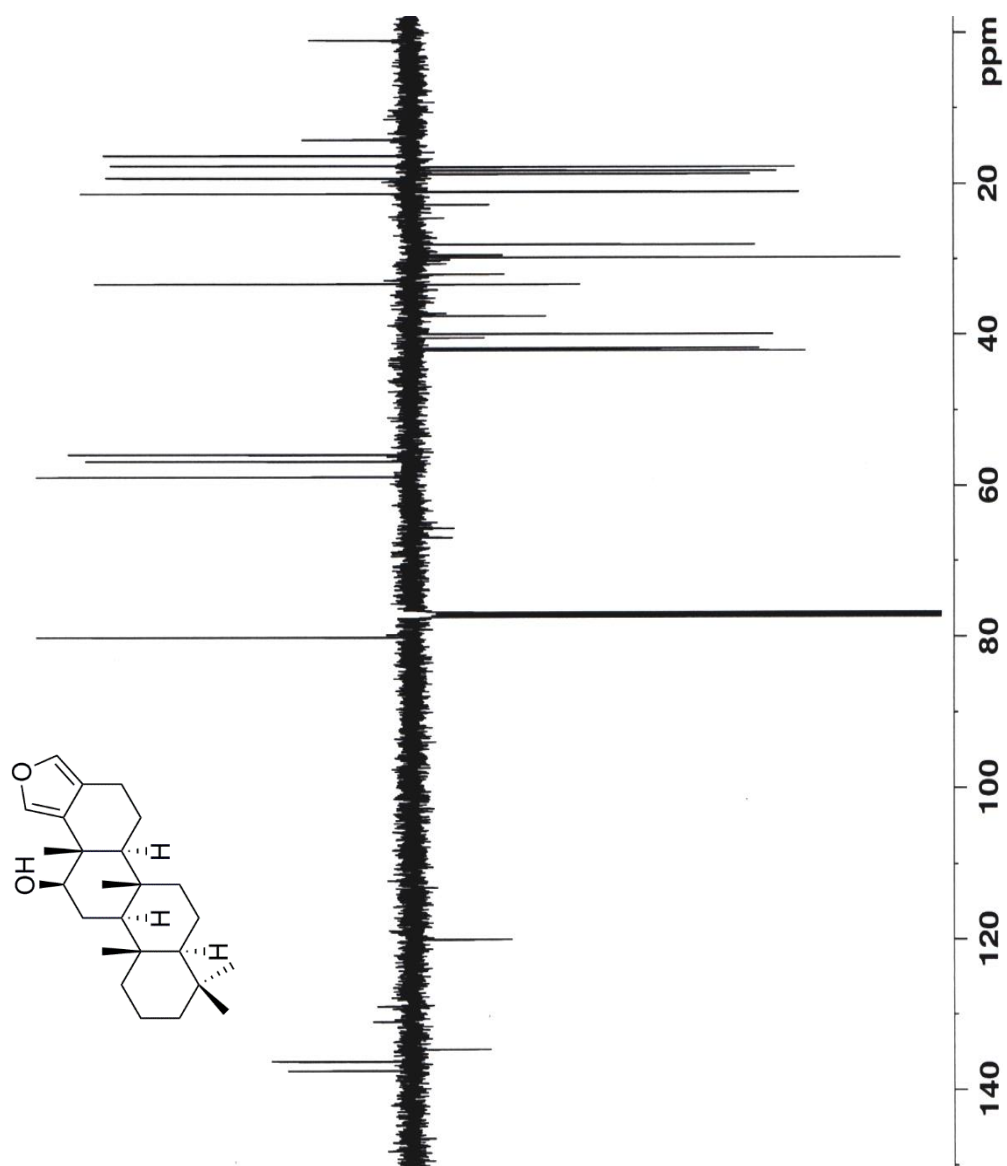


**Figure S18**  $^1\text{H}$  NMR spectrum of **15** (expanding 3.8-2.3 ppm; 500 MHz,  $\text{CDCl}_3$ )

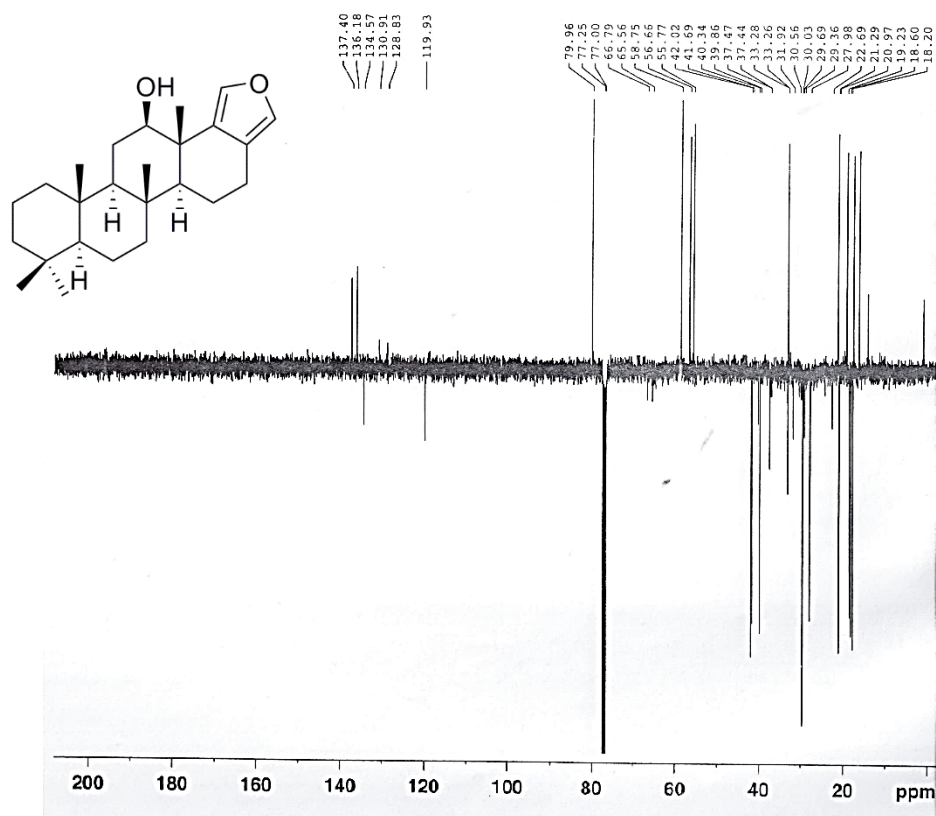


**Figure S19**  $^1\text{H}$  NMR spectrum of **15** (expanding 2.0-0.7 ppm; 500 MHz,  $\text{CDCl}_3$ )

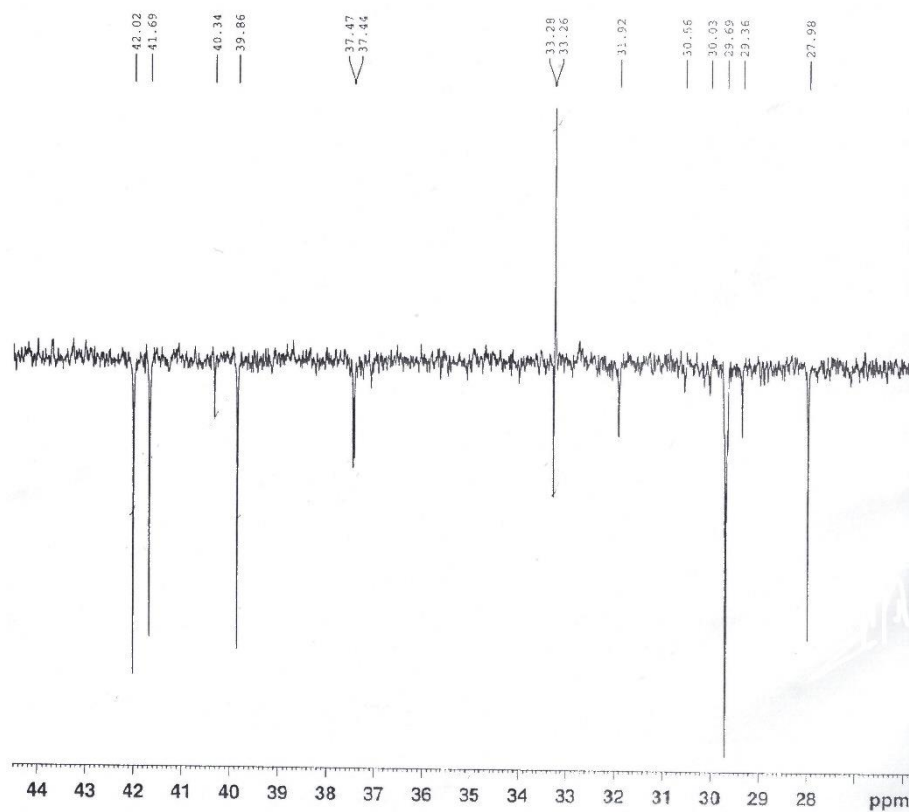




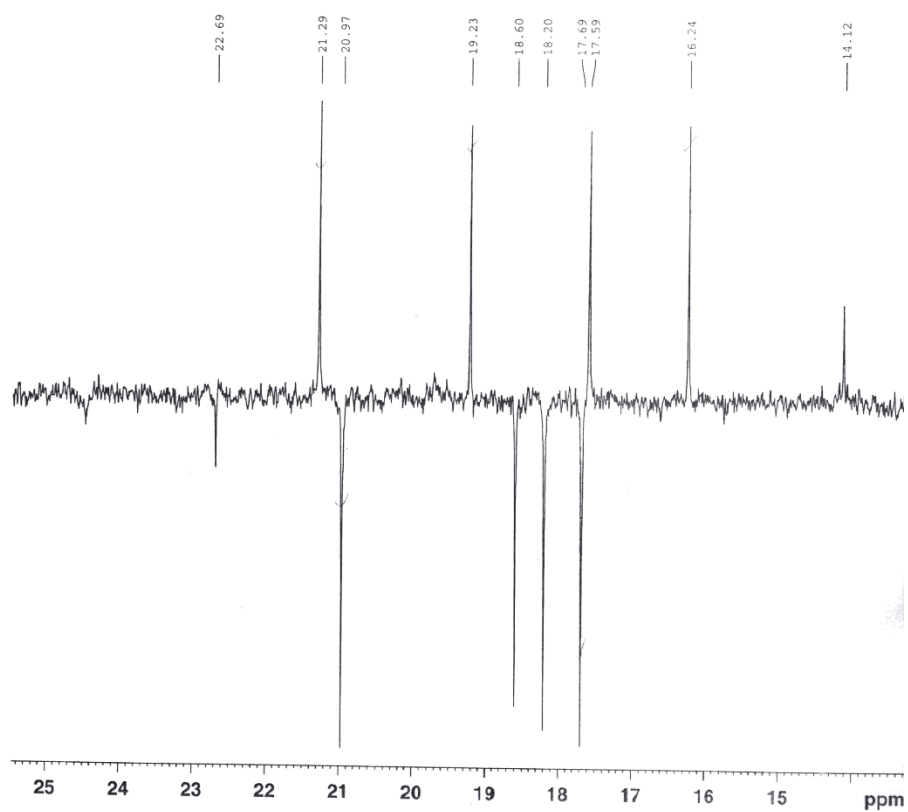
**Figure S20** APT spectrum of compound **15** (125MHz, CDCl<sub>3</sub>)



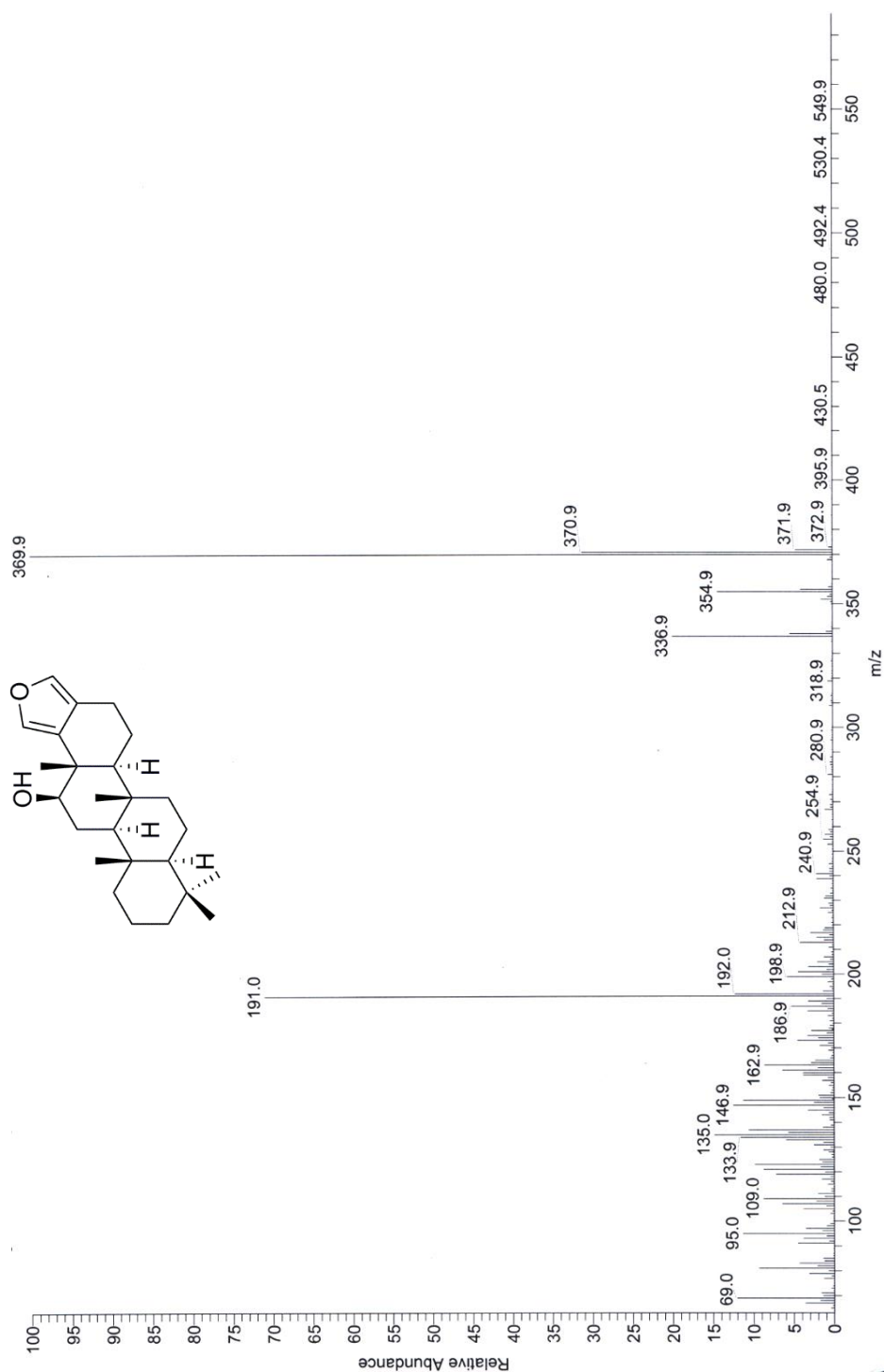
**Figure S21** APT spectrum of **15** (peak picking tagged; 125 MHz, CDCl<sub>3</sub>)



**Figure S22** APT spectrum of **15** (expanding 44-26 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S22** APT spectrum of **15** (expanding 25-14 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S23** EI mass spectrum of compound **15**

IR, NMR, and mass spectra of 16 (Figures S24-S36)

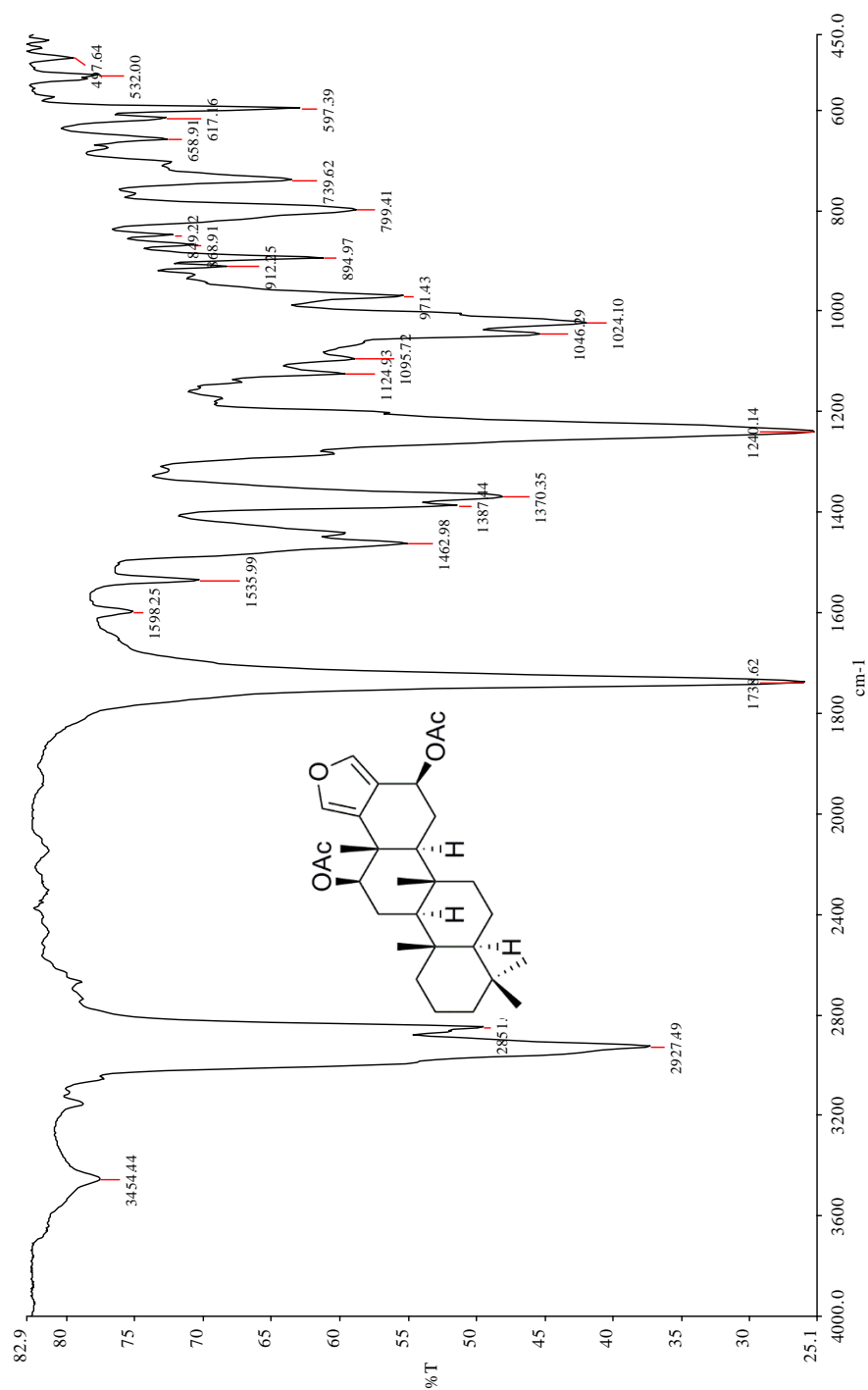
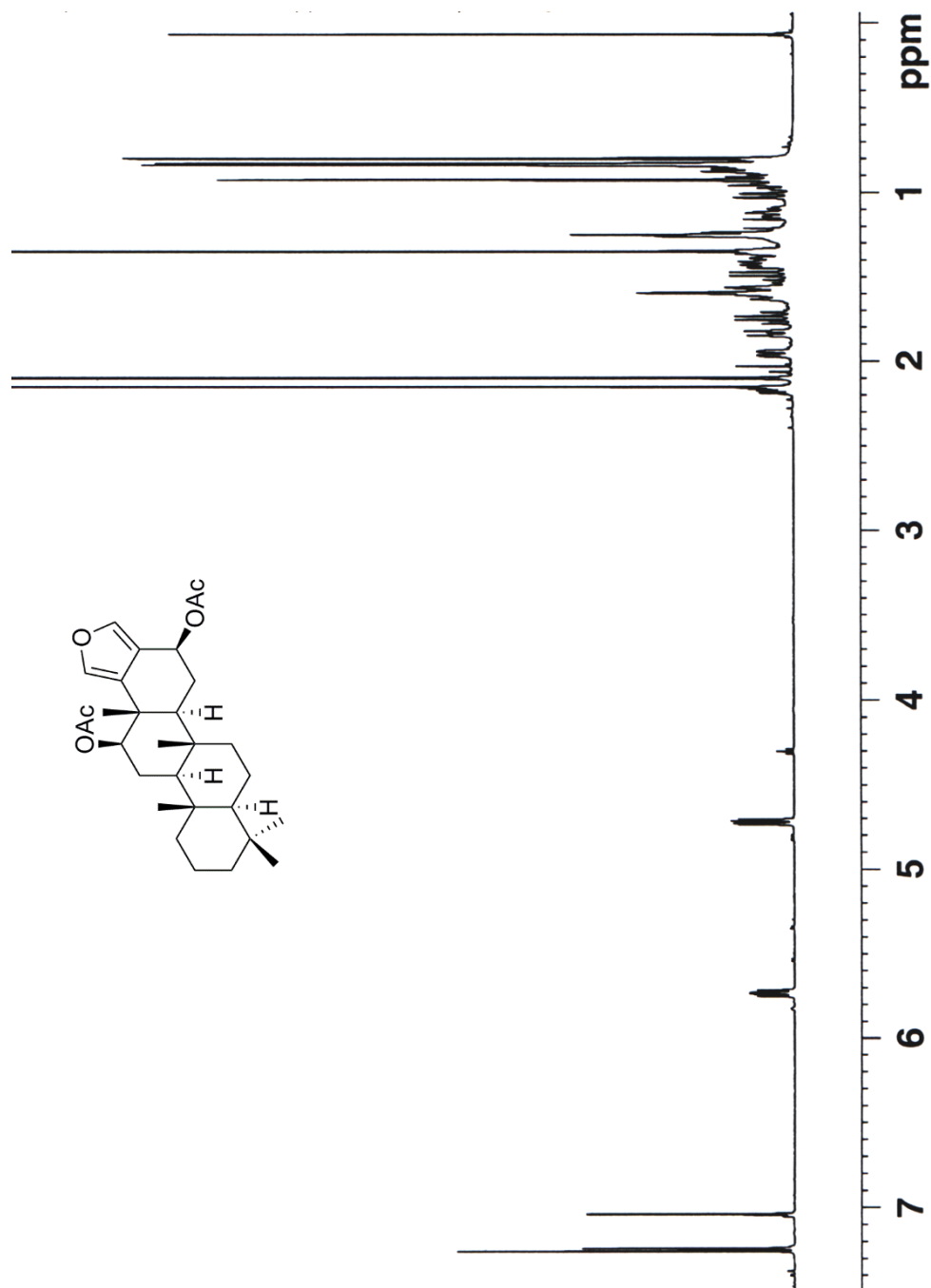
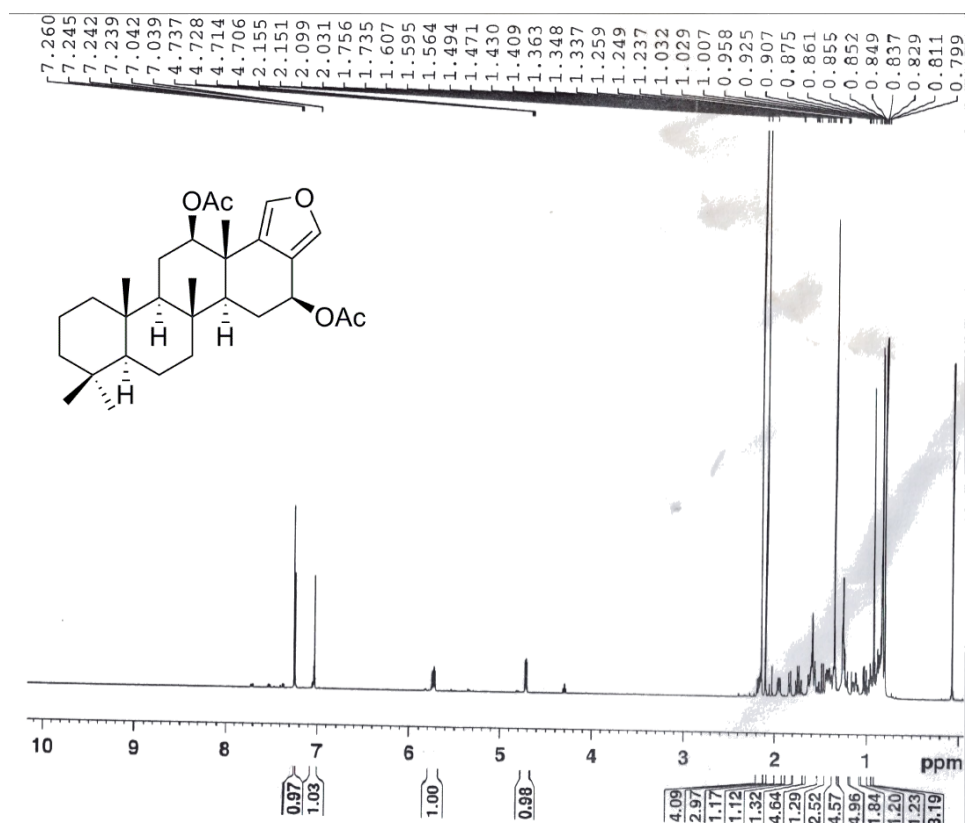


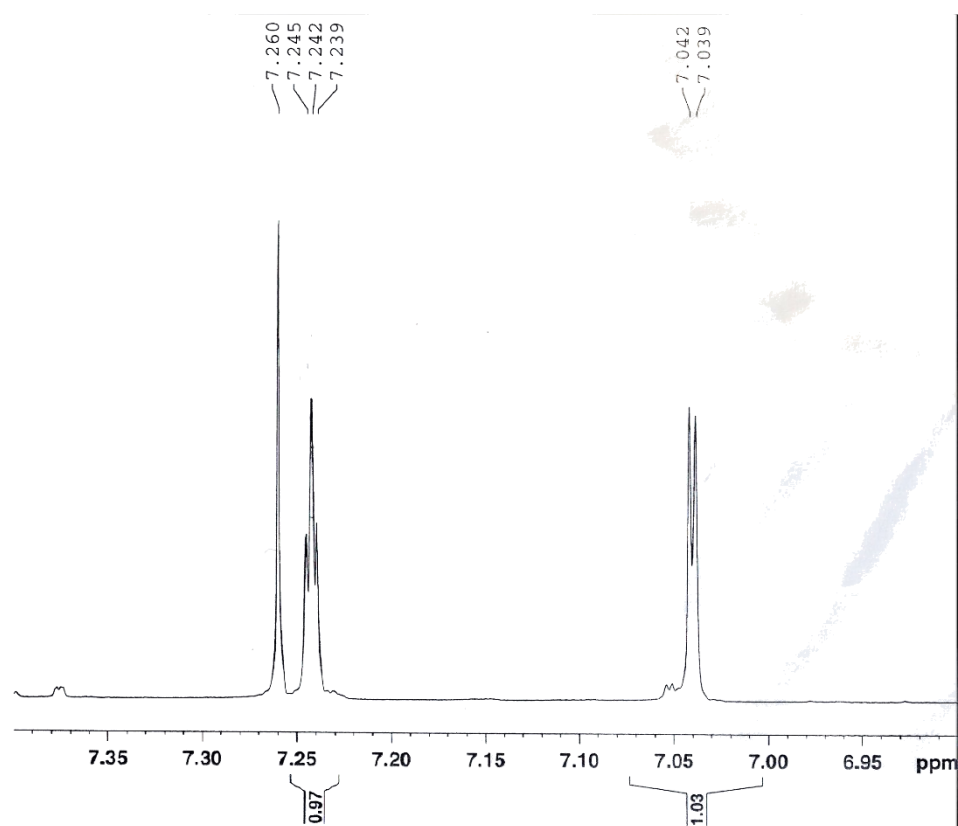
Figure S24 IR spectrum of compound 16



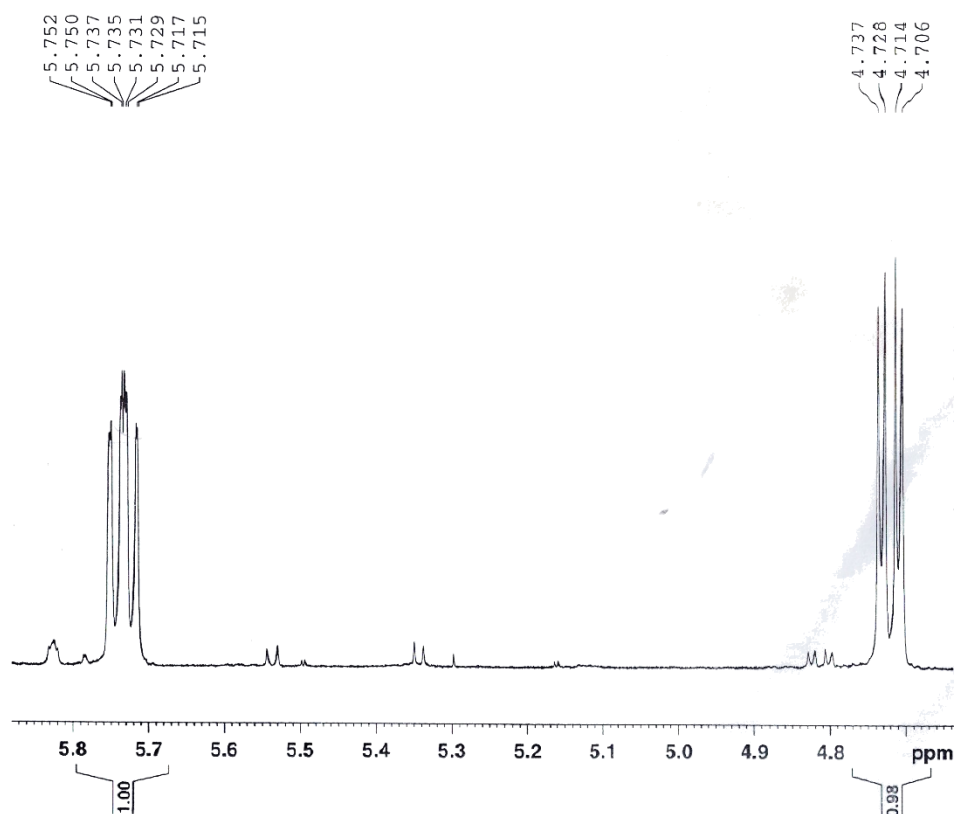
**Figure S25**  $^1\text{H}$  NMR spectrum of compound **16** (500MHz,  $\text{CDCl}_3$ )



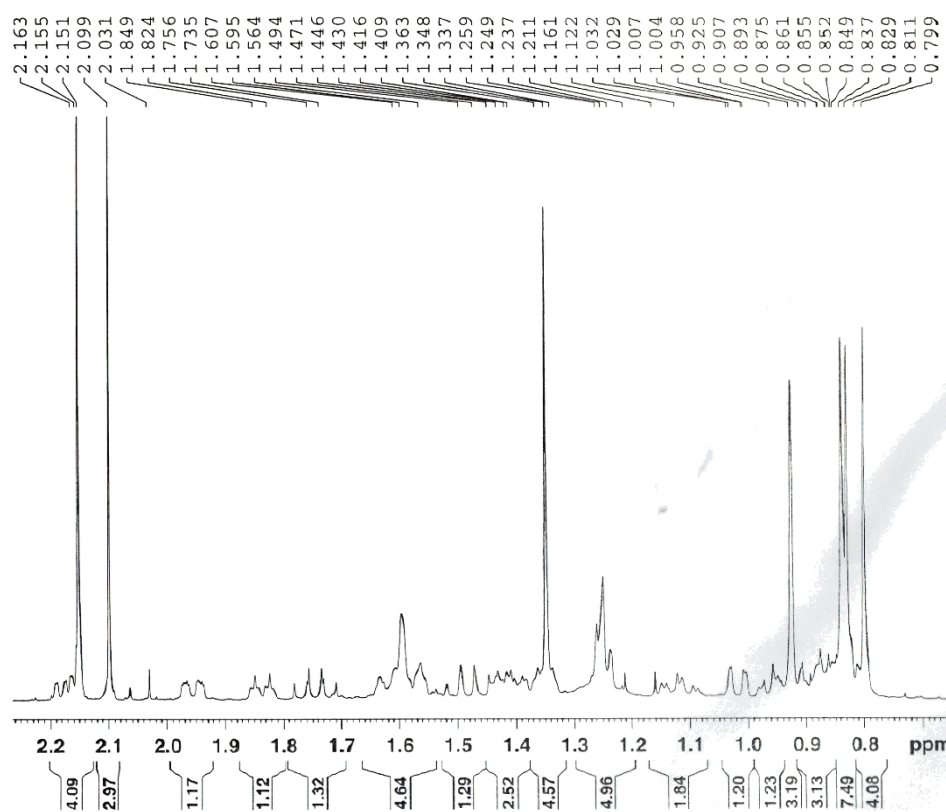
**Figure S26**  $^1\text{H}$  NMR spectrum of **16** (peak-picked and integration tagged; 500 MHz,  $\text{CDCl}_3$ )



**Figure S27**  $^1\text{H}$  NMR spectrum of **16** (expanding 7.35-6.95 ppm; 500 MHz,  $\text{CDCl}_3$ )

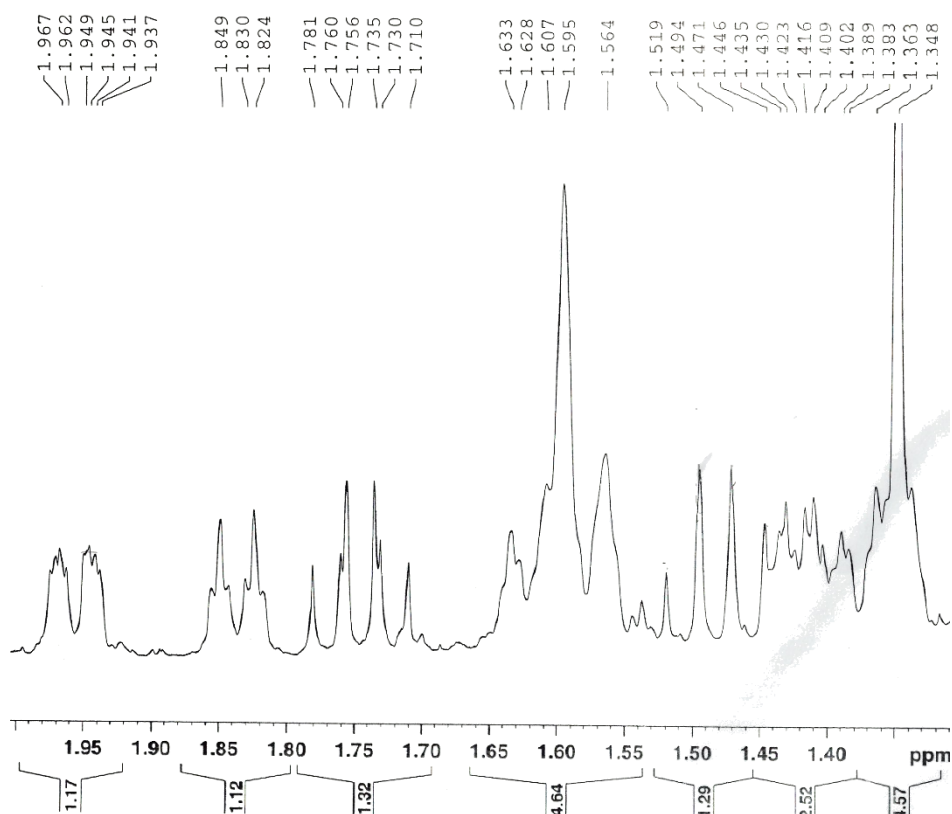


**Figure S28**  $^1\text{H}$  NMR spectrum of **16** (expanding 5.80-4.70 ppm; 500 MHz,  $\text{CDCl}_3$ )

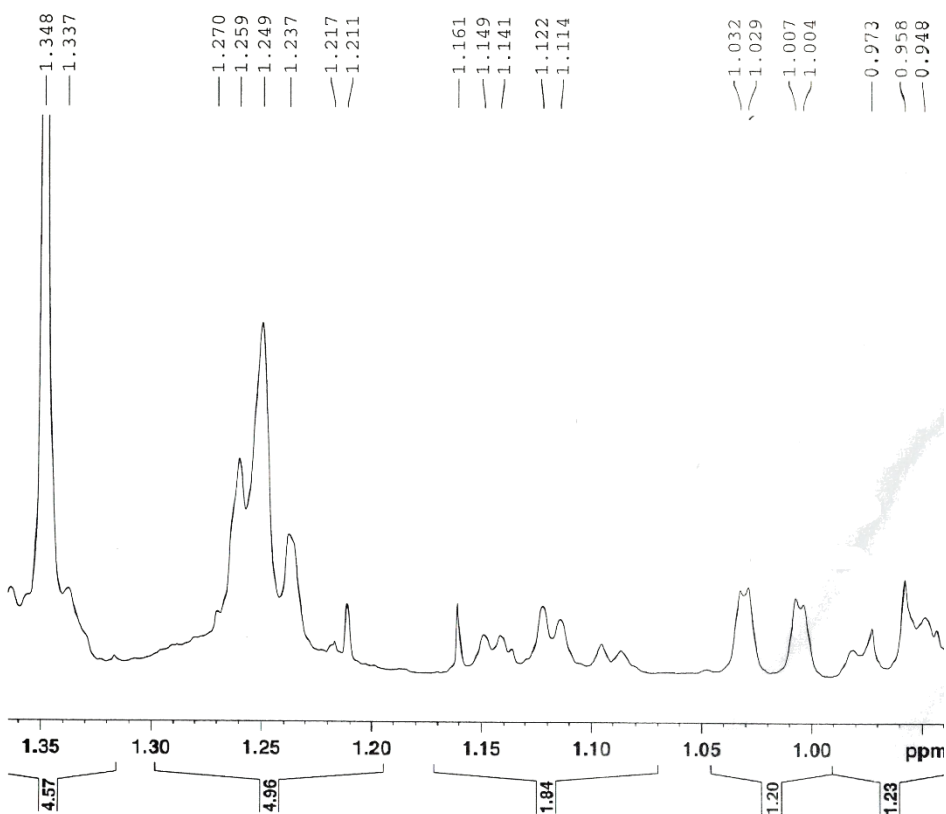


**Figure S29**  $^1\text{H}$  NMR spectrum of **16** (expanding 72.20-0.70 ppm; 500 MHz,  $\text{CDCl}_3$ )

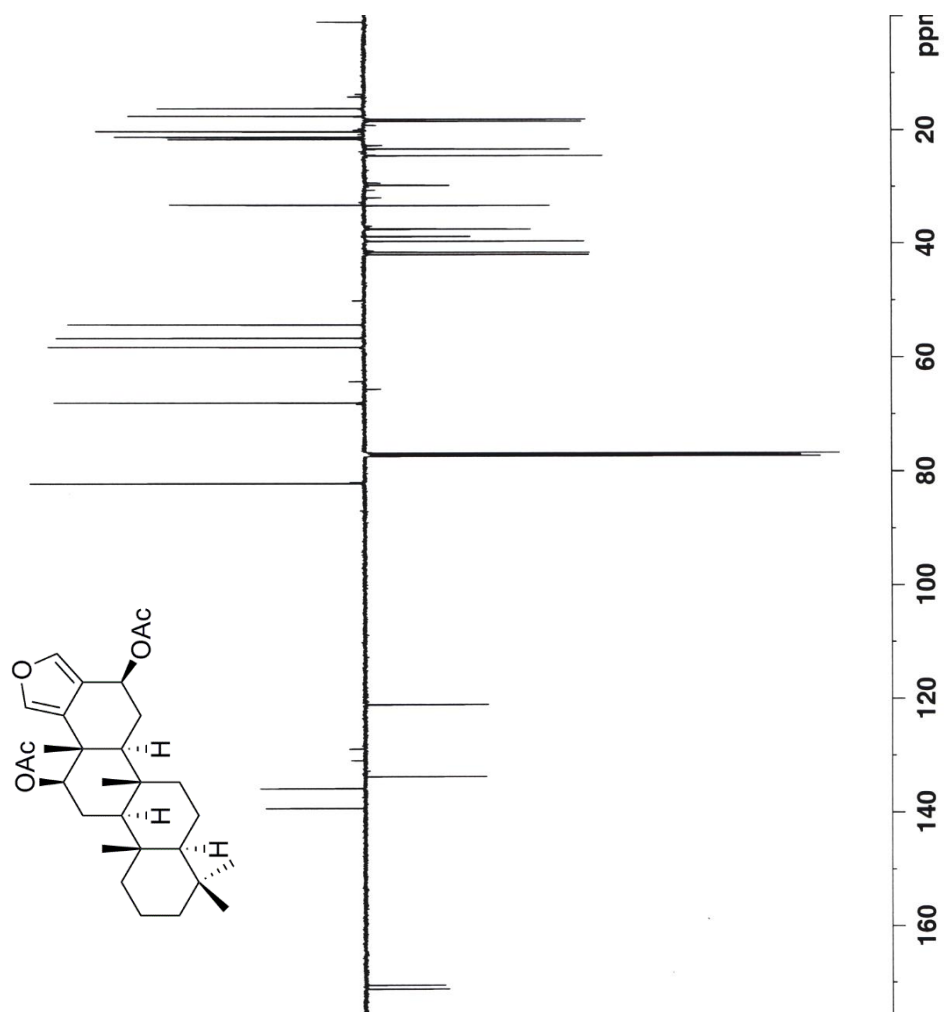




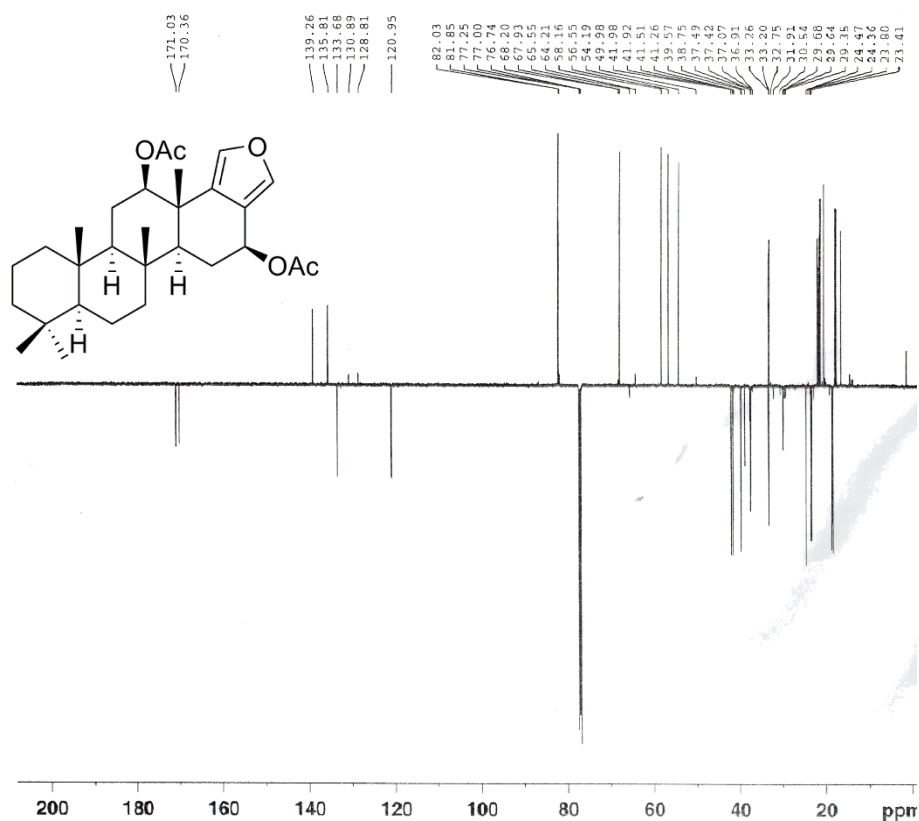
**Figure S30**  $^1\text{H}$  NMR spectrum of **16** (expanding 2.00-1.30 ppm; 500 MHz,  $\text{CDCl}_3$ )



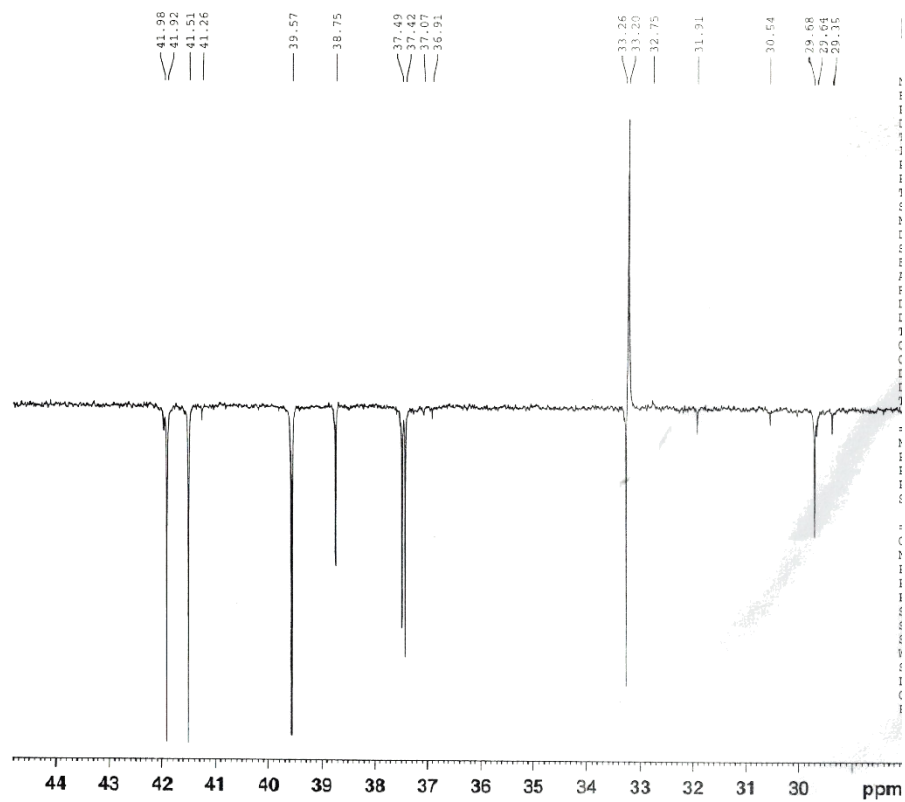
**Figure S31**  $^1\text{H}$  NMR spectrum of **16** (expanding 1.35-0.95 ppm; 500 MHz,  $\text{CDCl}_3$ )



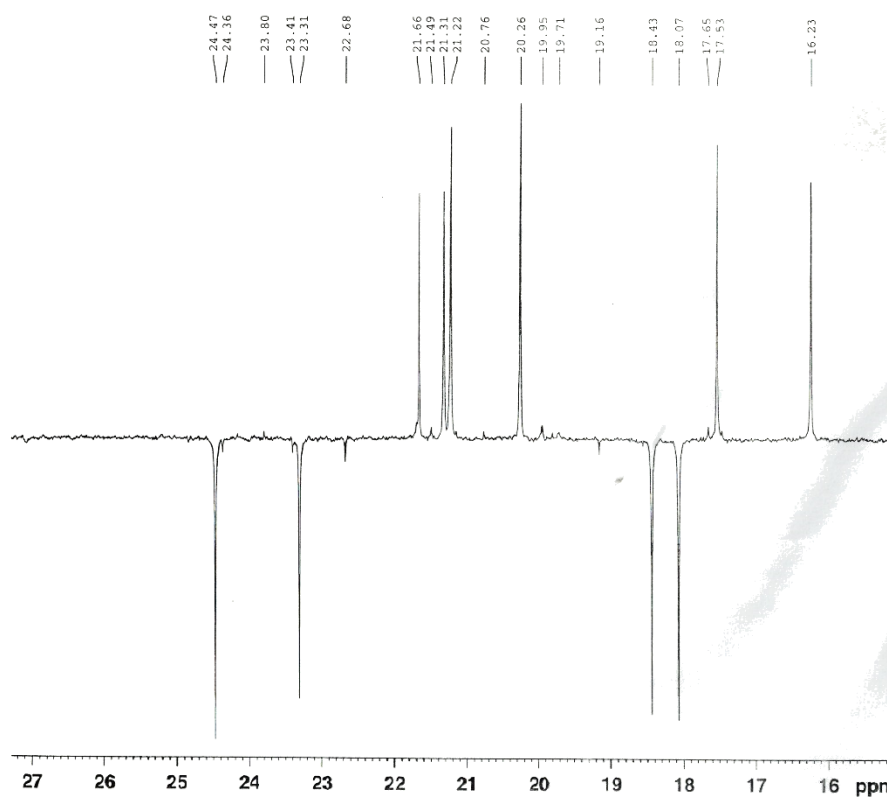
**Figure S32** APT spectrum of compound **16** (125MHz, CDCl<sub>3</sub>)



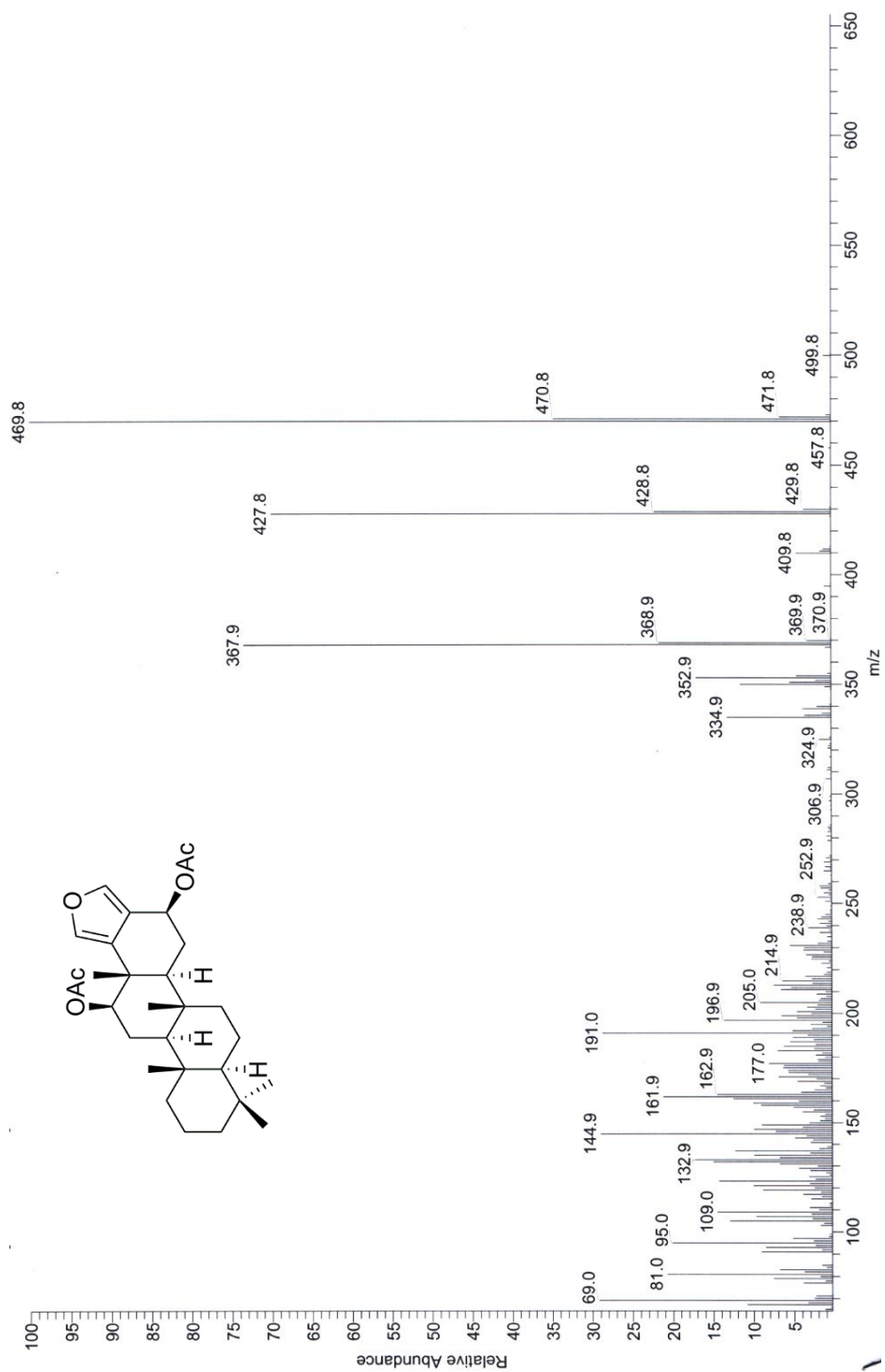
**Figure S33** APT spectrum of **16** (peak picking tagged; 125 MHz, CDCl<sub>3</sub>)



**Figure S34** APT spectrum of **16** (expanding 44-28 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S35** APT spectrum of **16** (expanding 27-16 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S36** EI mass spectrum of compound **16**)

IR, NMR, and mass spectra of 17 (Figures S37-S51)

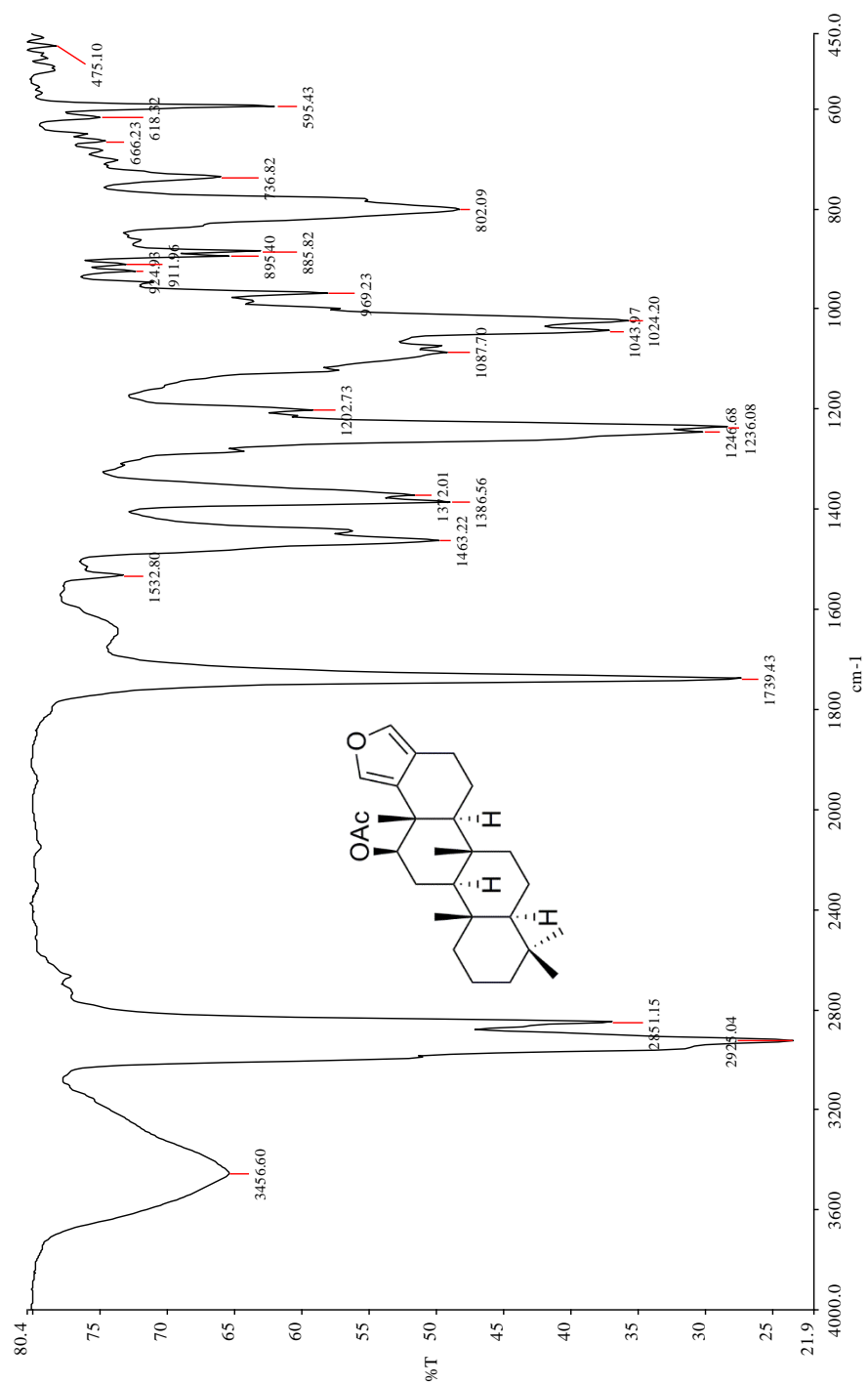
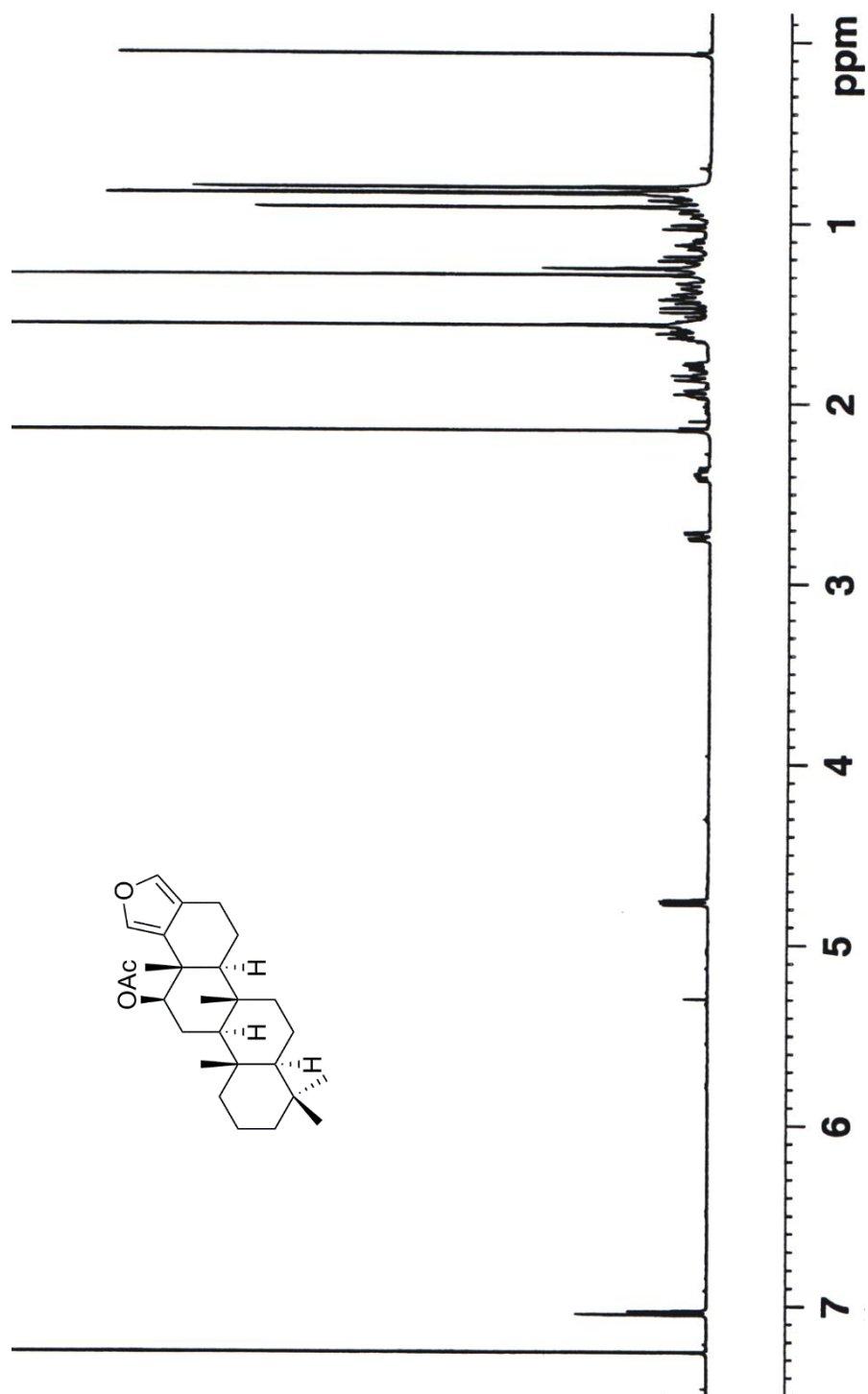
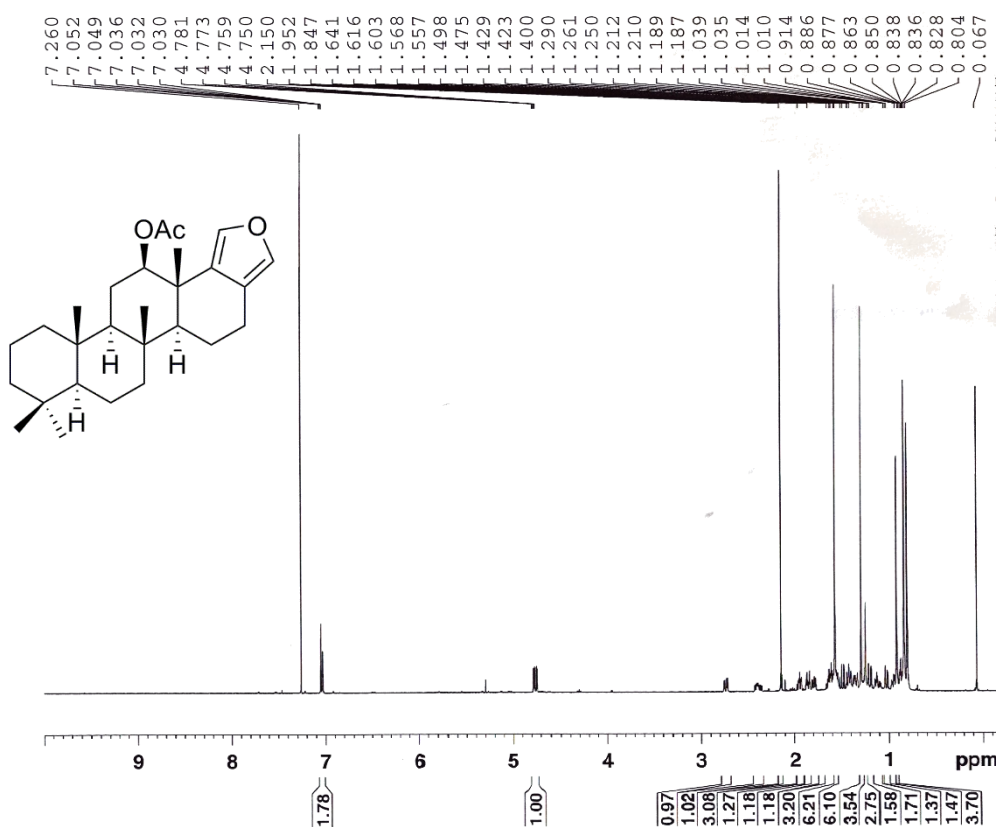


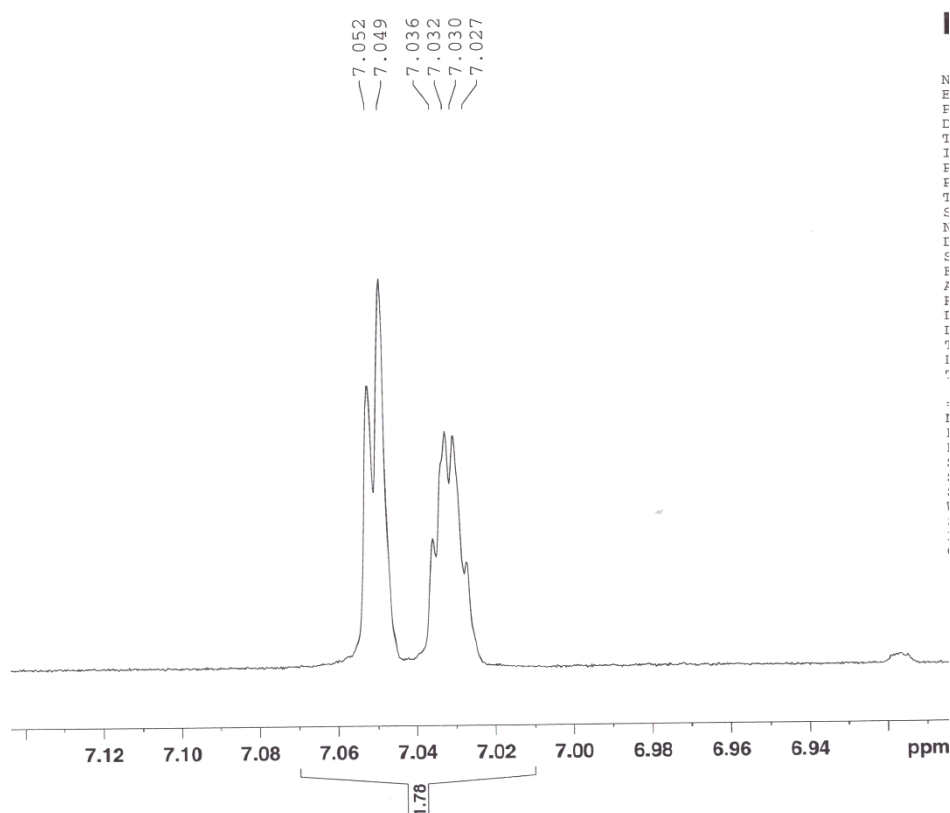
Figure S37 IR spectrum of compound 17



**Figure S38**  $^1\text{H}$  NMR spectrum of compound **17** (500MHz,  $\text{CDCl}_3$ )

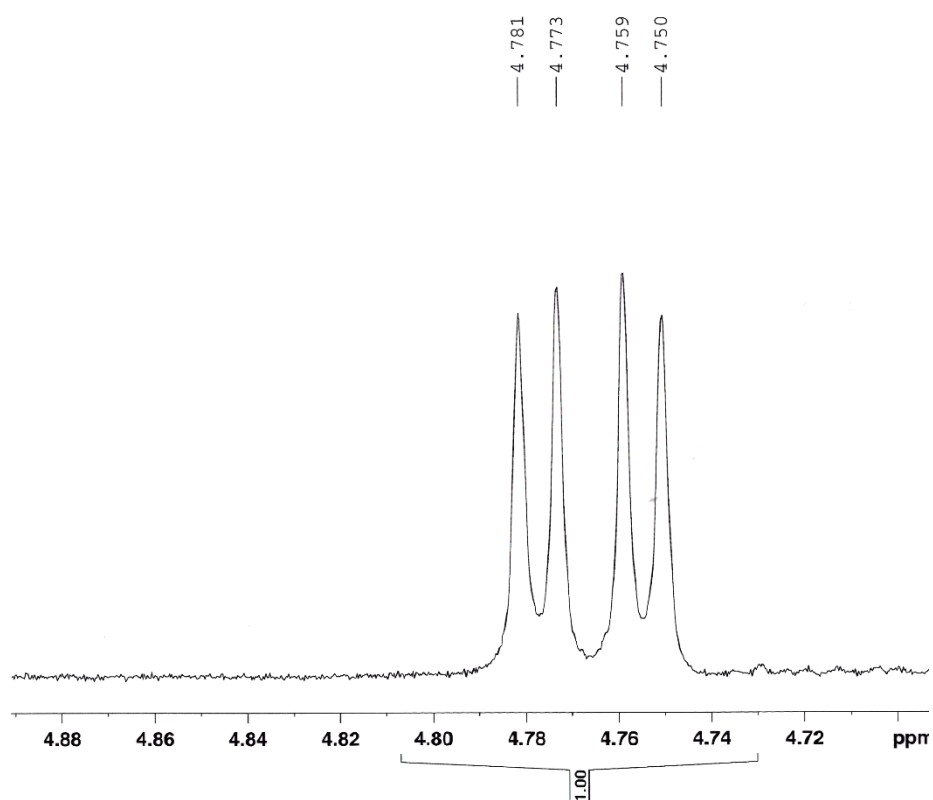


**Figure S39** <sup>1</sup>H NMR spectrum of **17** (peak-picked and integration tagged; 500 MHz, CDCl<sub>3</sub>)

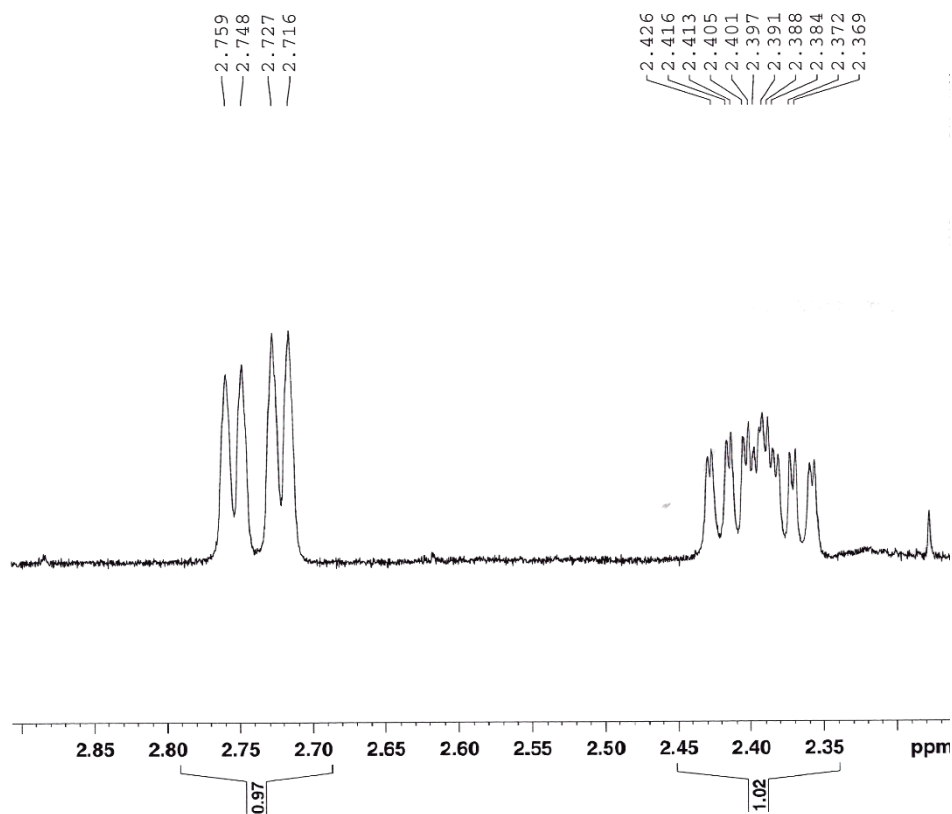


**Figure S40** <sup>1</sup>H NMR spectrum of **17** (expanding 7.12-6.92 ppm; 500 MHz, CDCl<sub>3</sub>)

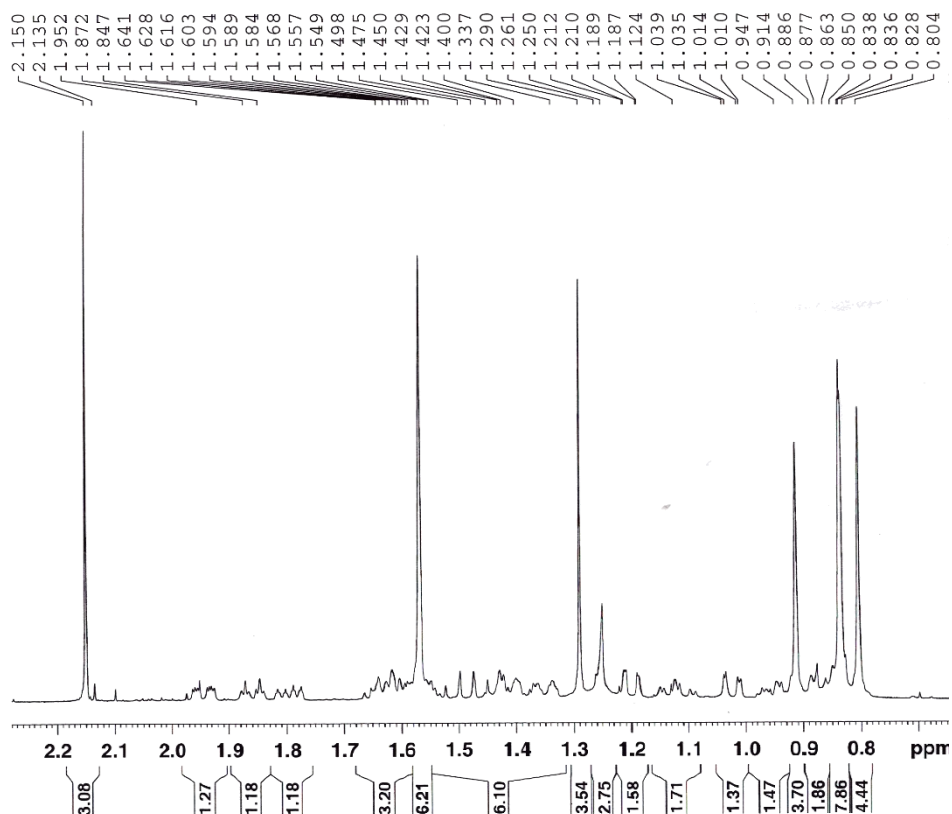




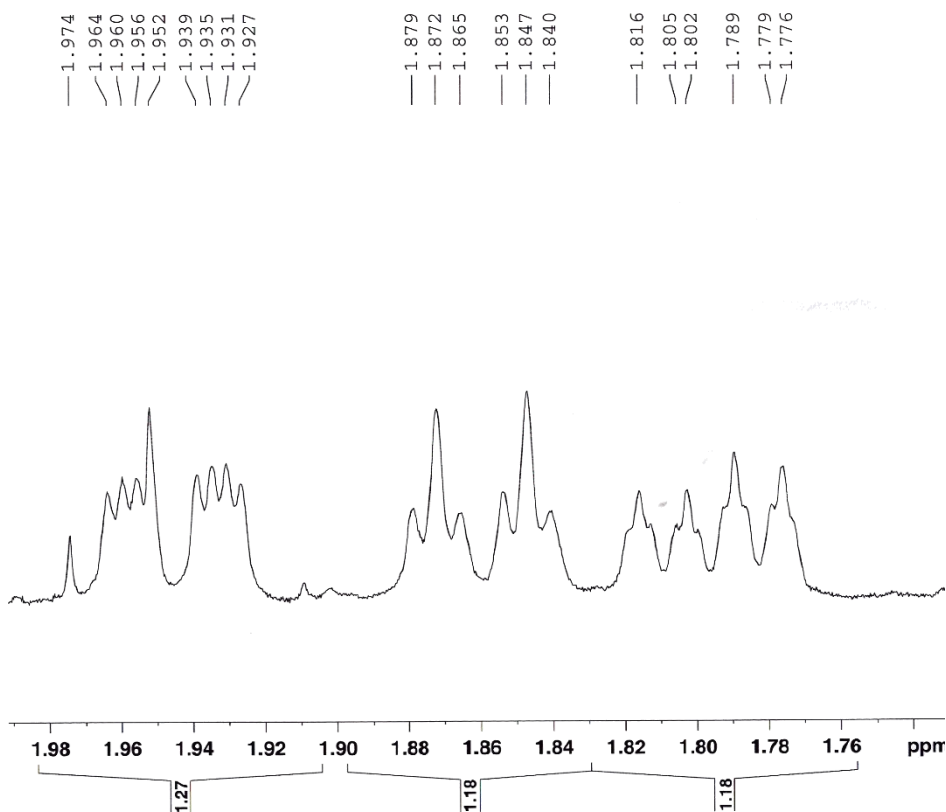
**Figure S41**  $^1\text{H}$  NMR spectrum of **17** (expanding 4.88-4.71 ppm; 500 MHz,  $\text{CDCl}_3$ )



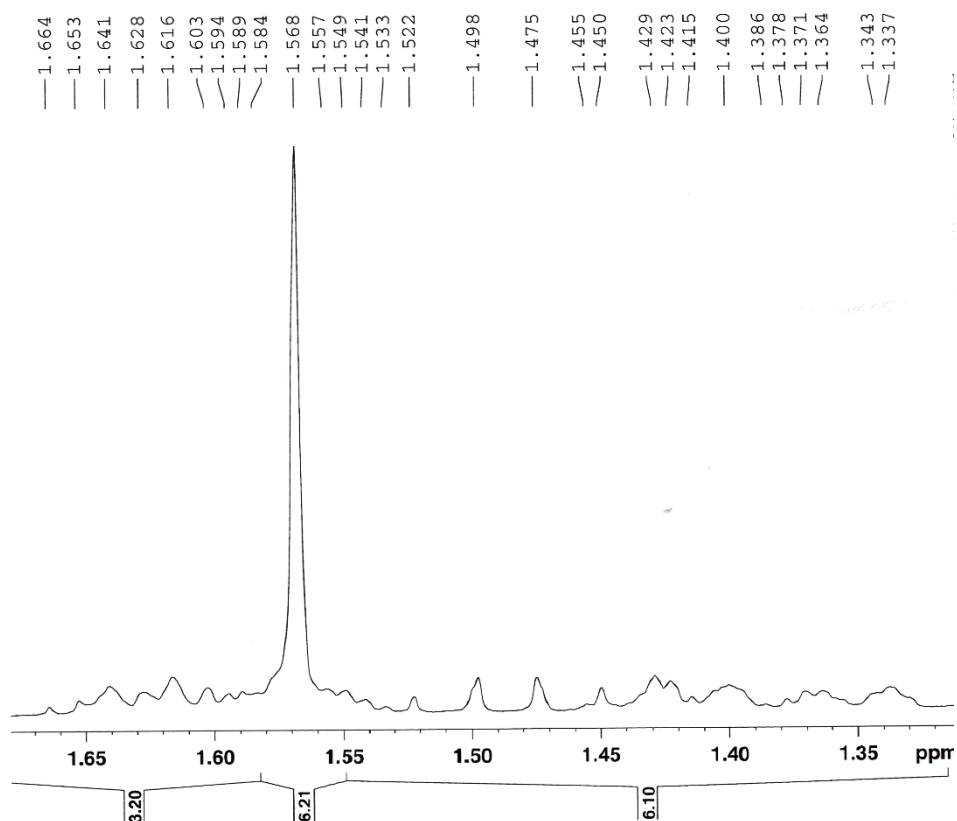
**Figure S42**  $^1\text{H}$  NMR spectrum of **17** (expanding 2.85-2.30 ppm; 500 MHz,  $\text{CDCl}_3$ )



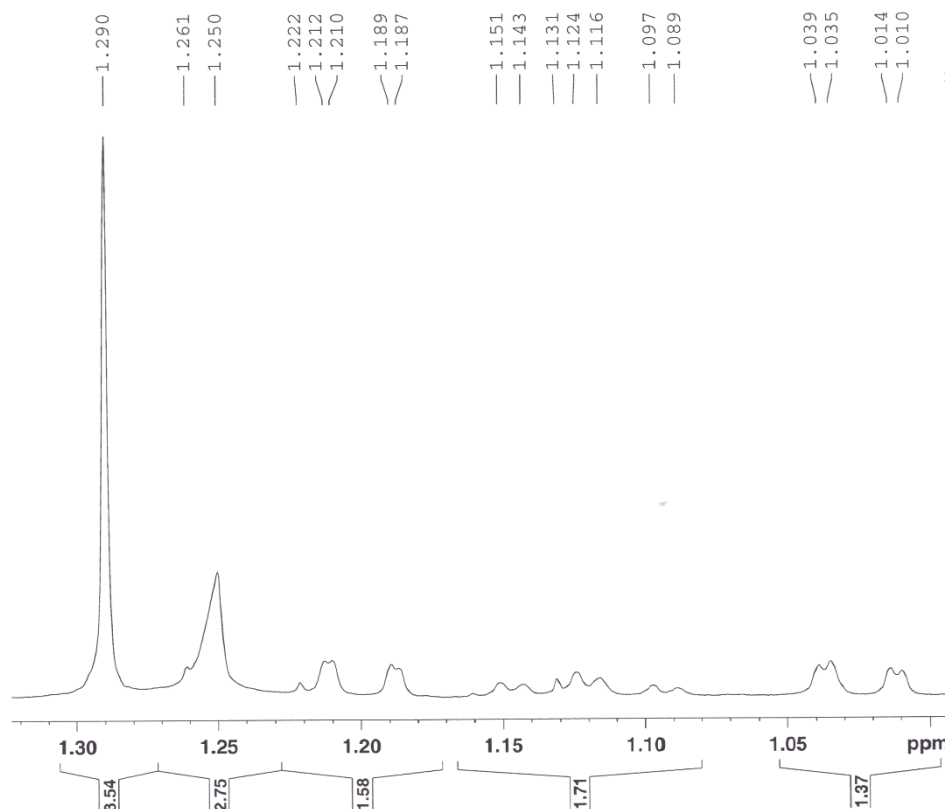
**Figure S43**  $^1\text{H}$  NMR spectrum of **17** (expanding 2.20-0.70 ppm; 500 MHz,  $\text{CDCl}_3$ )



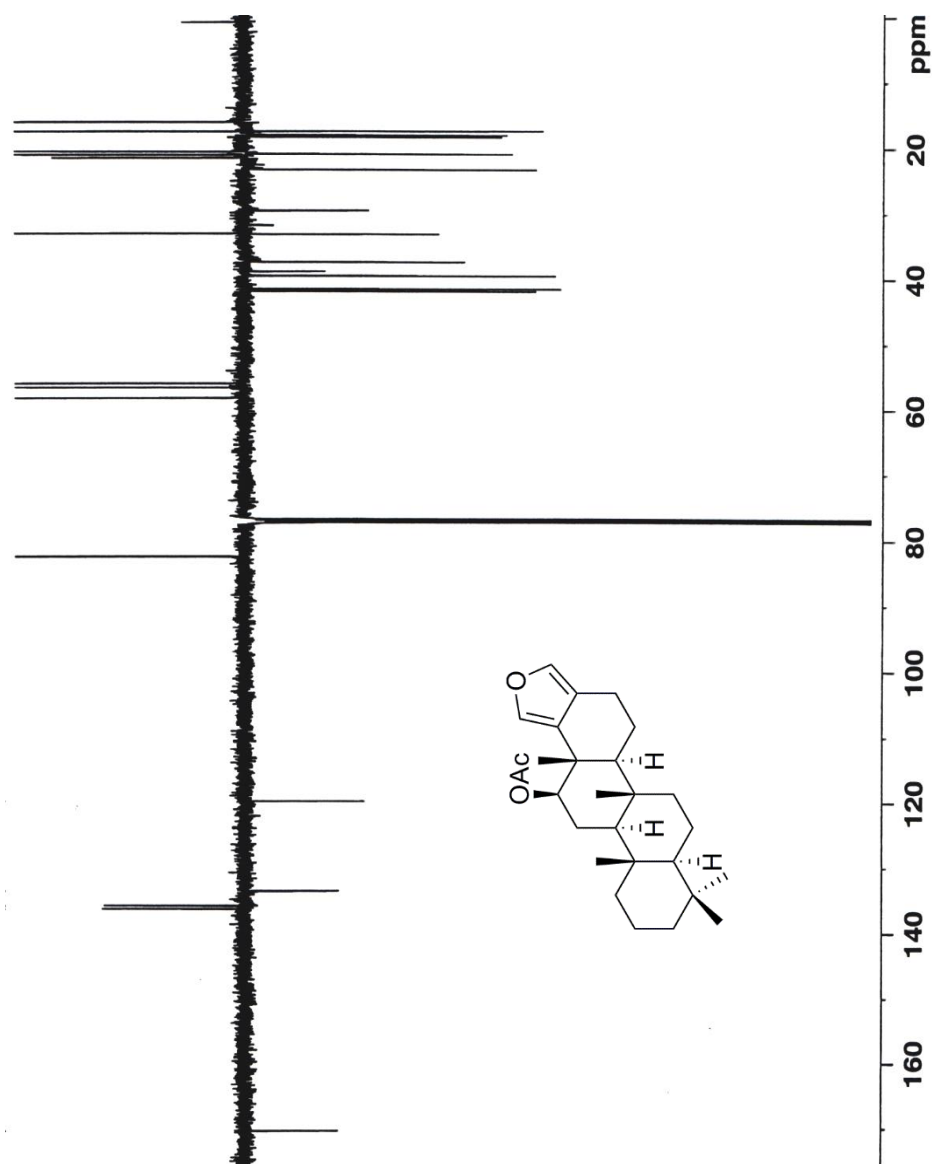
**Figure S44**  $^1\text{H}$  NMR spectrum of **17** (expanding 1.98-1.74 ppm; 500 MHz,  $\text{CDCl}_3$ )



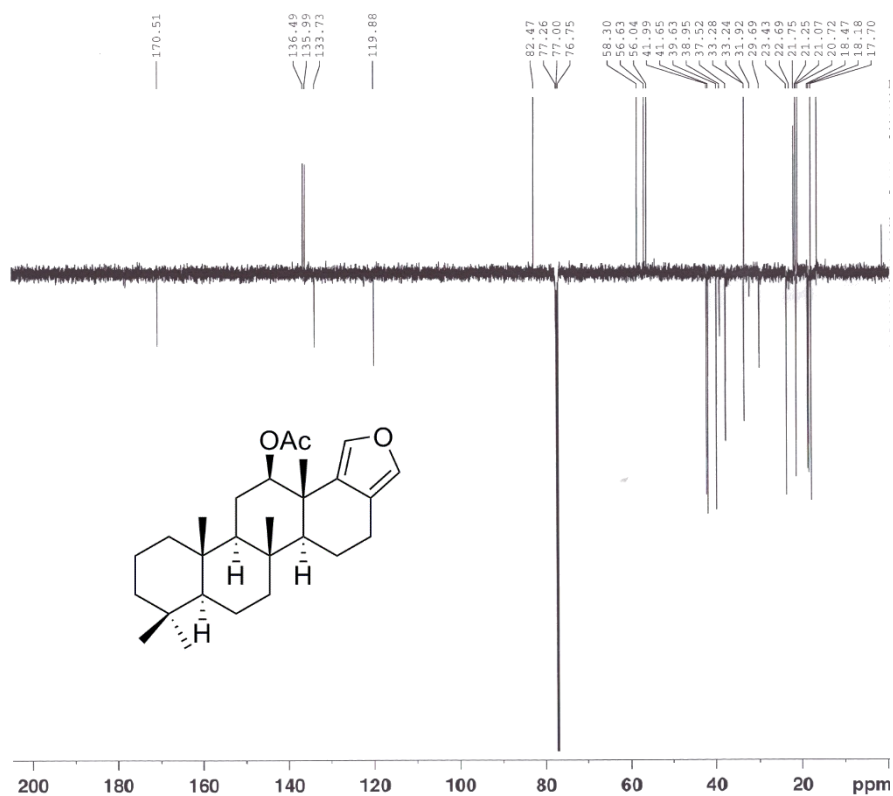
**Figure S45**  $^1\text{H}$  NMR spectrum of **17** (expanding 1.655-1.35 ppm; 500 MHz,  $\text{CDCl}_3$ )



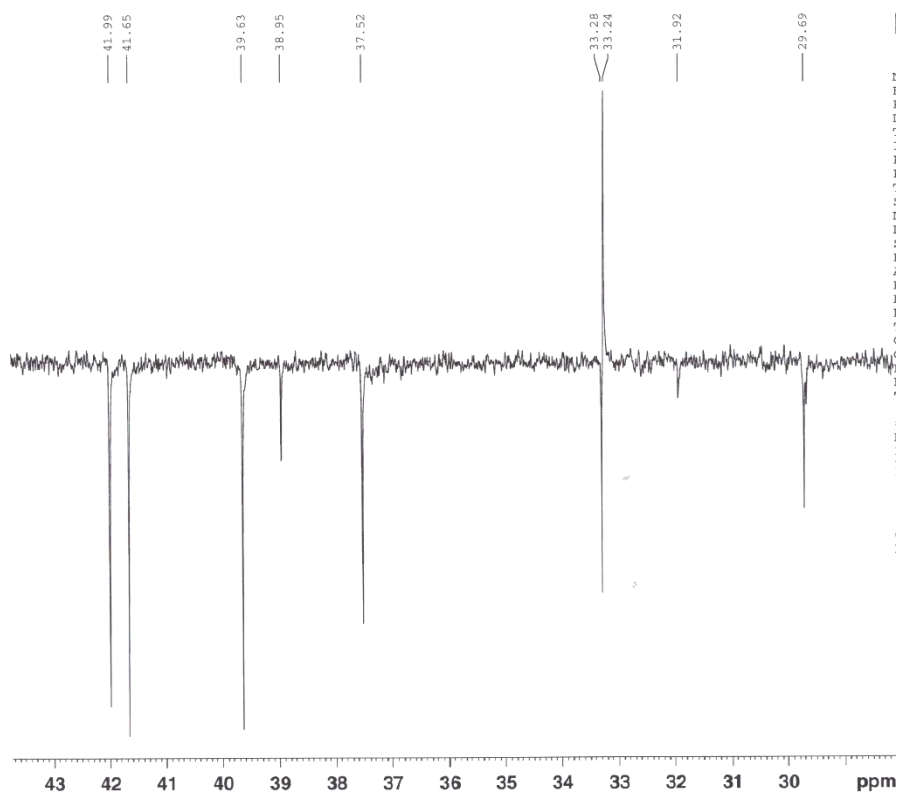
**Figure S46**  $^1\text{H}$  NMR spectrum of **17** (expanding 1.30-1.00 ppm; 500 MHz,  $\text{CDCl}_3$ )



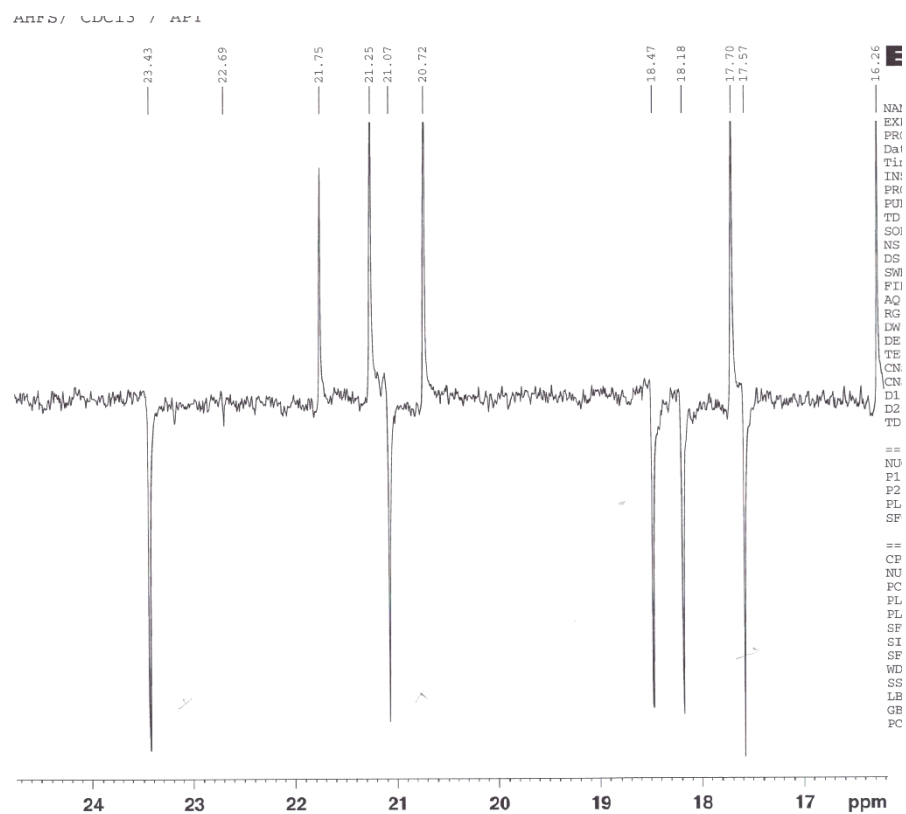
**Figure S47** APT spectrum of compound **17** (125MHz, CDCl<sub>3</sub>)



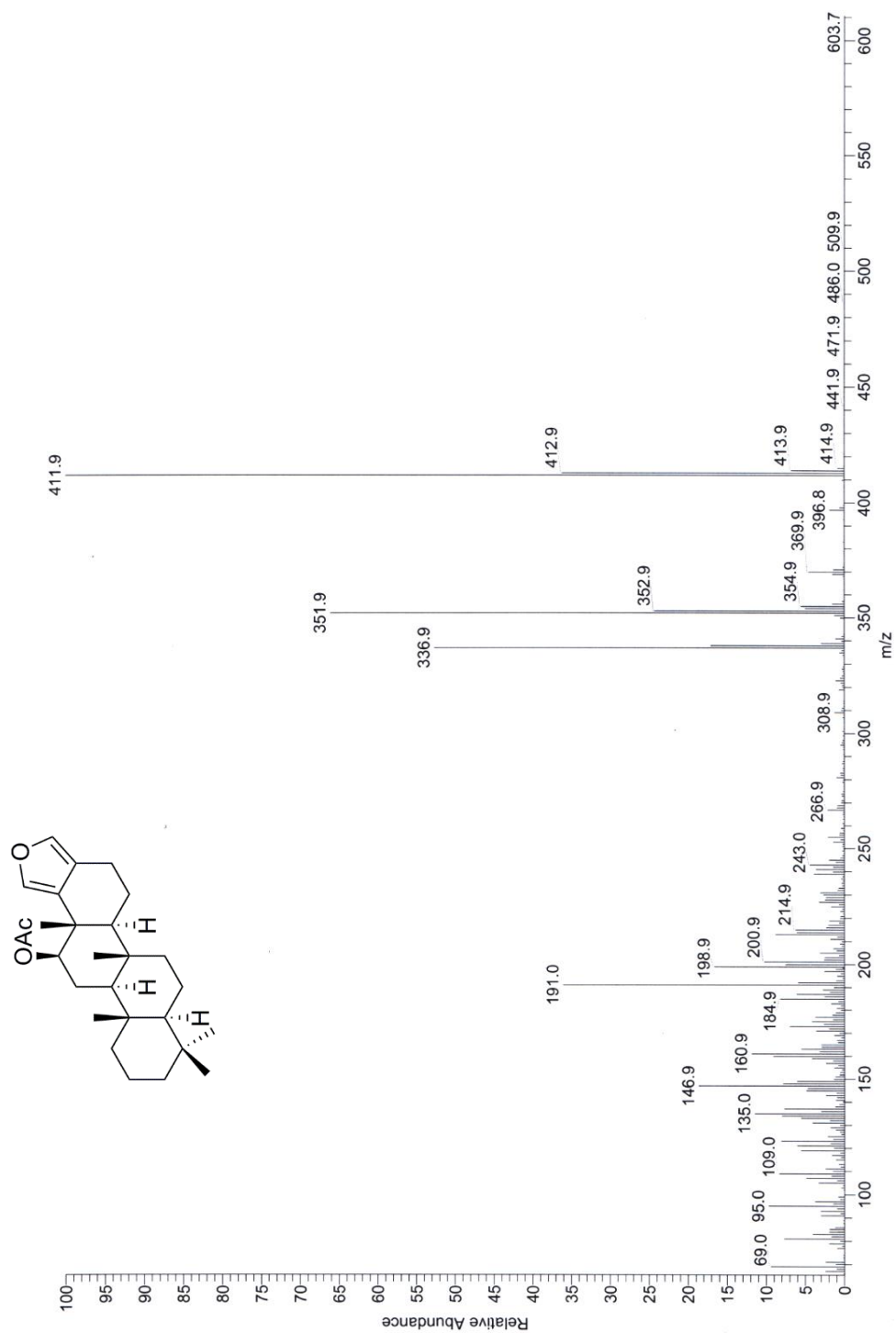
**Figure S48** APT spectrum of **17** (peak picking tagged; 125 MHz,  $\text{CDCl}_3$ )



**Figure S49** APT spectrum of **17** (expanding 43-29 ppm; 125 MHz,  $\text{CDCl}_3$ )



**Figure S50** APT spectrum of **17** (expanding 24-17 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S51** EI mass spectrum of compound **17**

IR, NMR, and mass spectra of 18 (Figures S52-S65)

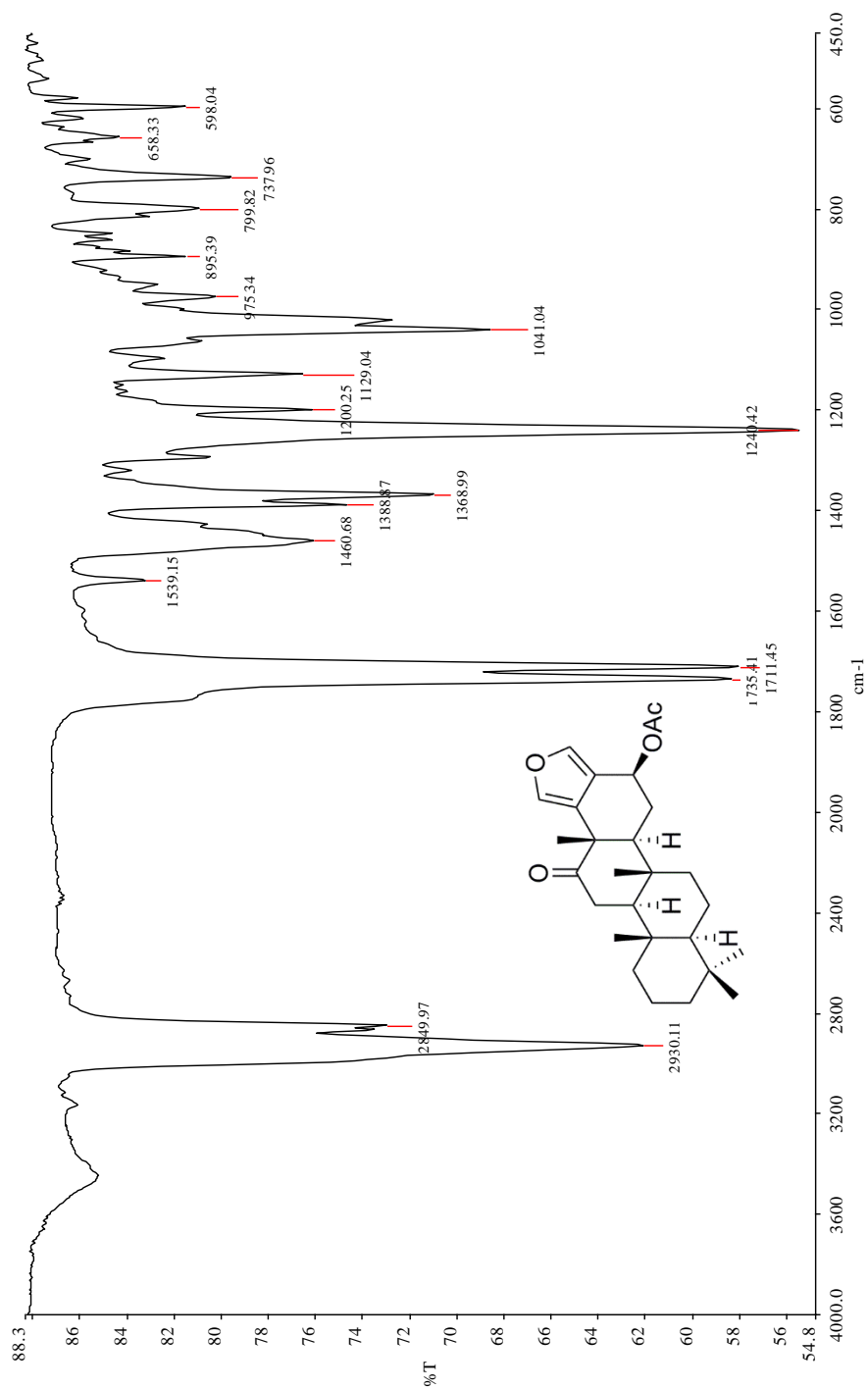
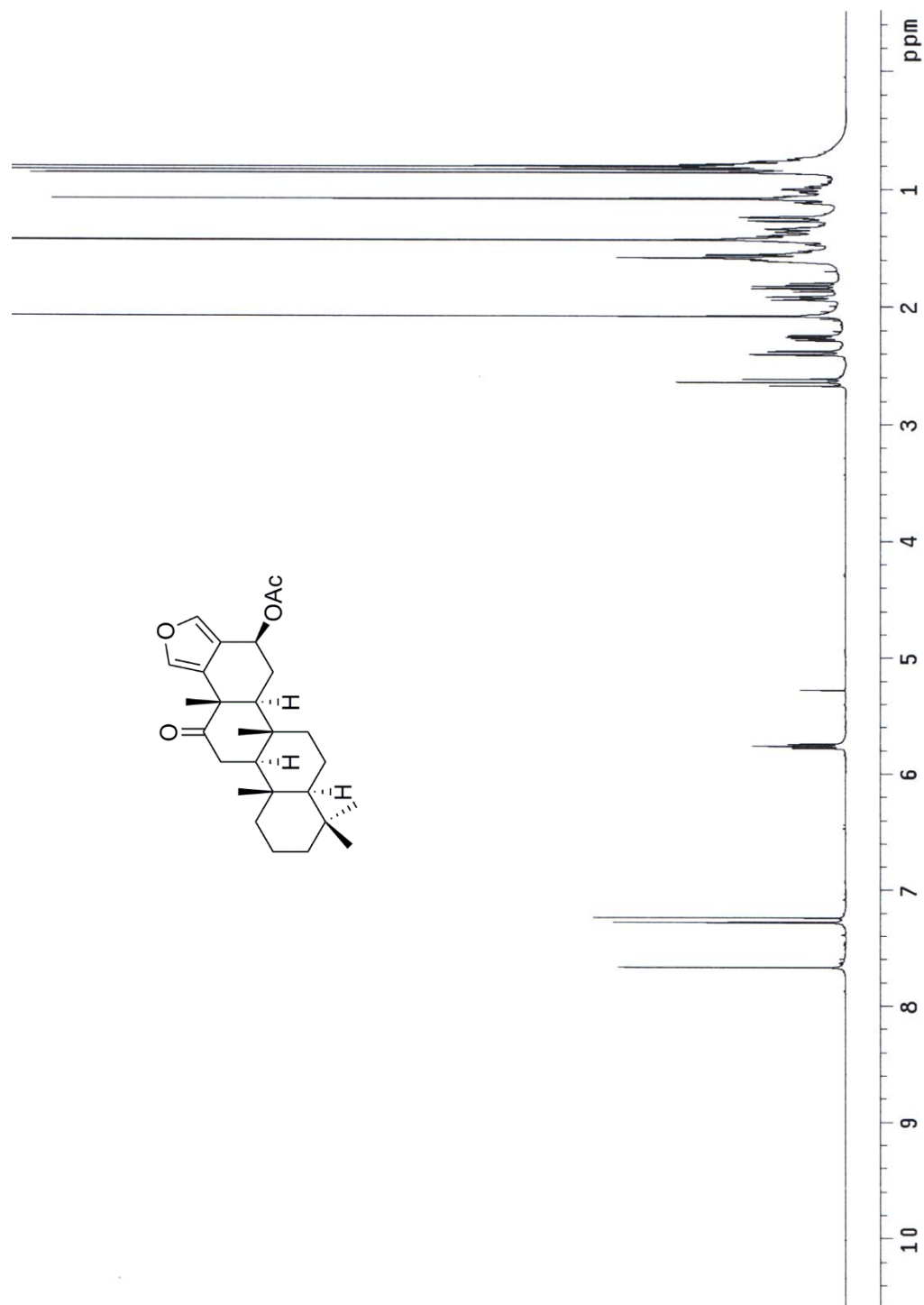


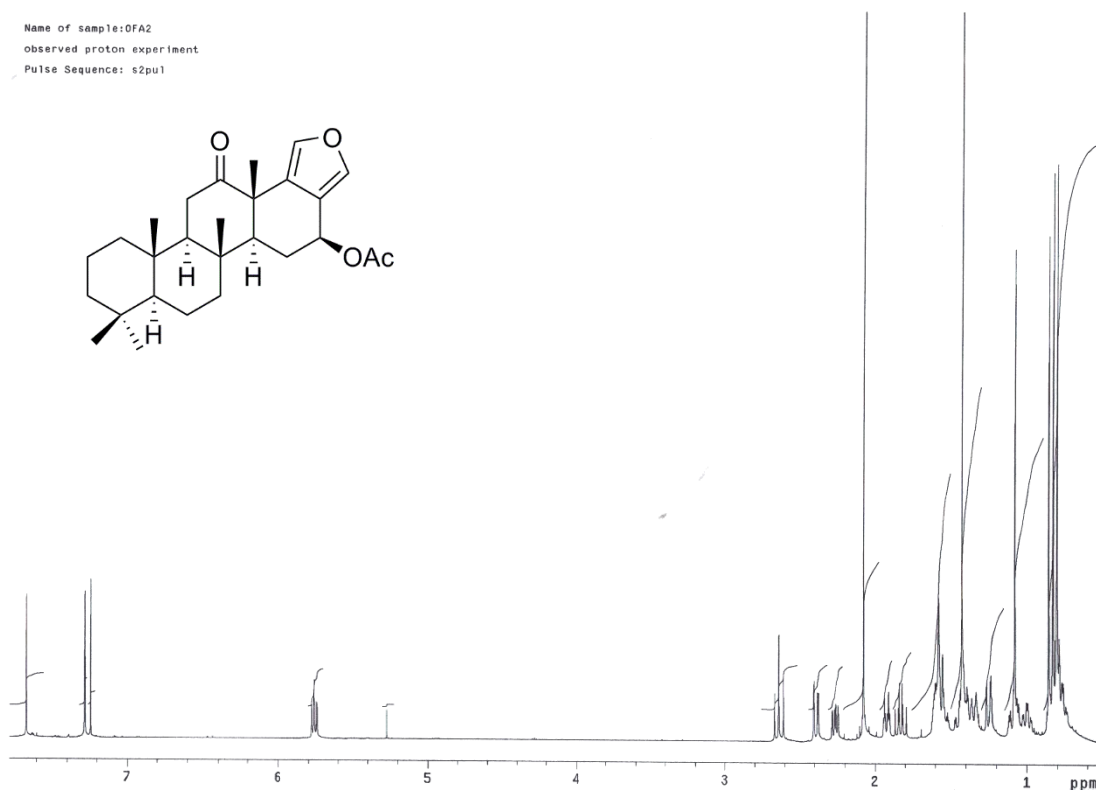
Figure S52 IR spectrum of compound 18



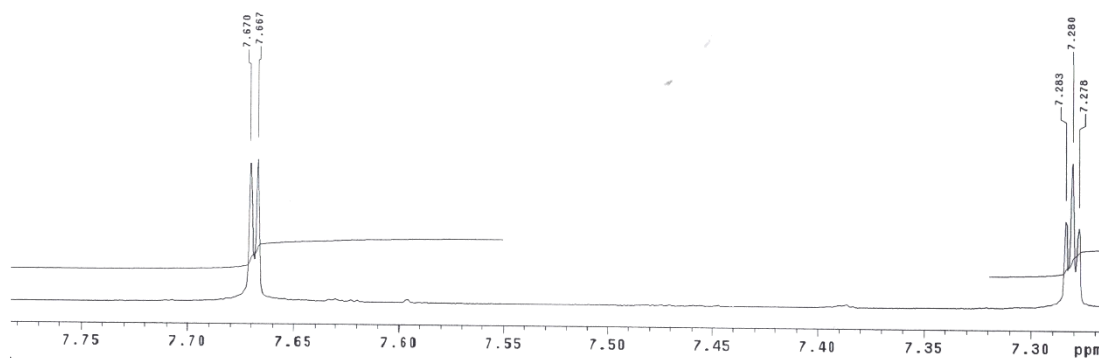


**Figure S53** <sup>1</sup>H NMR spectrum of compound **18** (500MHz, CDCl<sub>3</sub>)

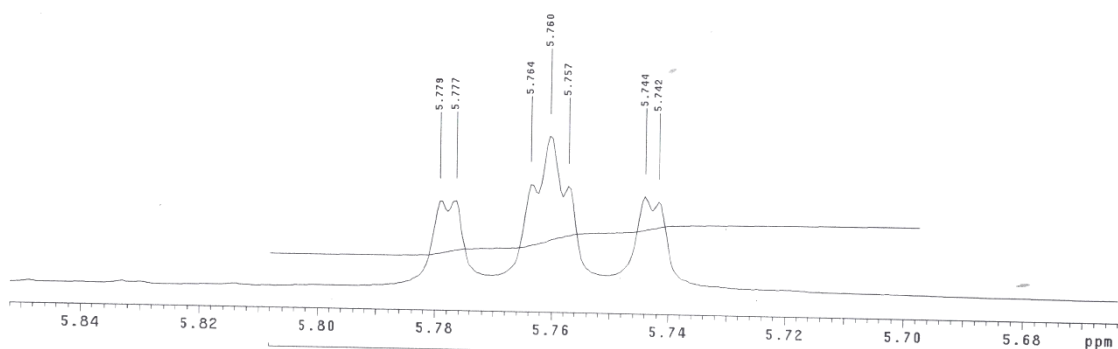
Name of sample: DFA2  
observed proton experiment  
Pulse Sequence: s2pu1



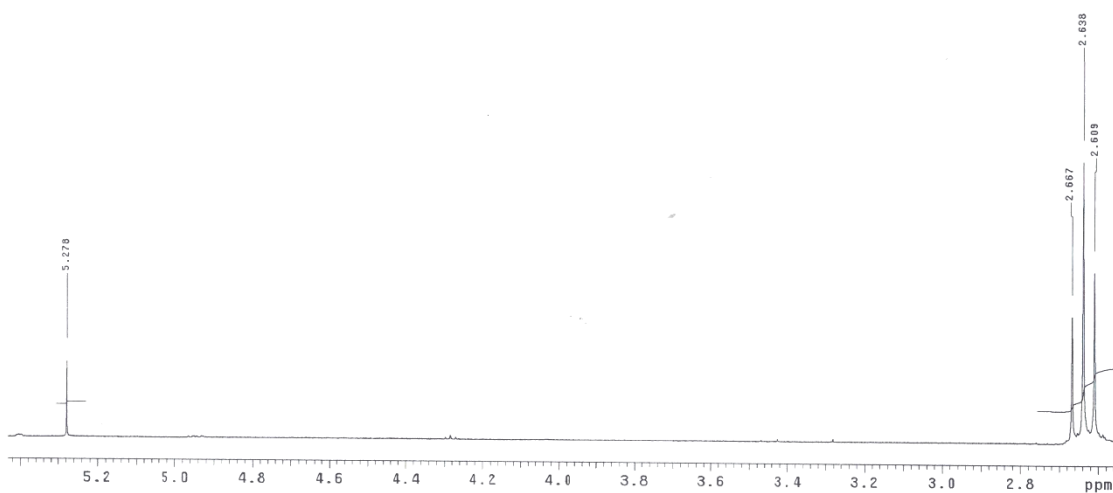
**Figure S54** <sup>1</sup>H NMR spectrum of **18** (integration tagged; 500 MHz, CDCl<sub>3</sub>)



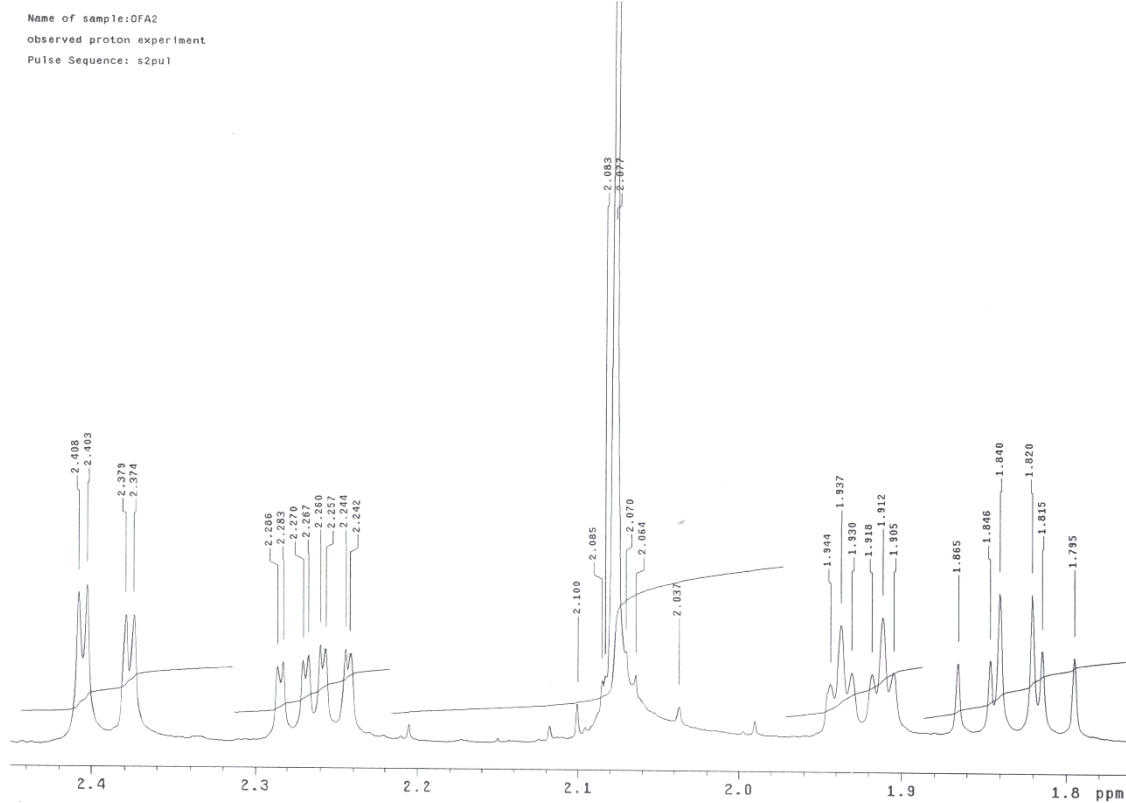
**Figure S55** <sup>1</sup>H NMR spectrum of **18** (expanding 7.75-7.27 ppm; 500 MHz, CDCl<sub>3</sub>)



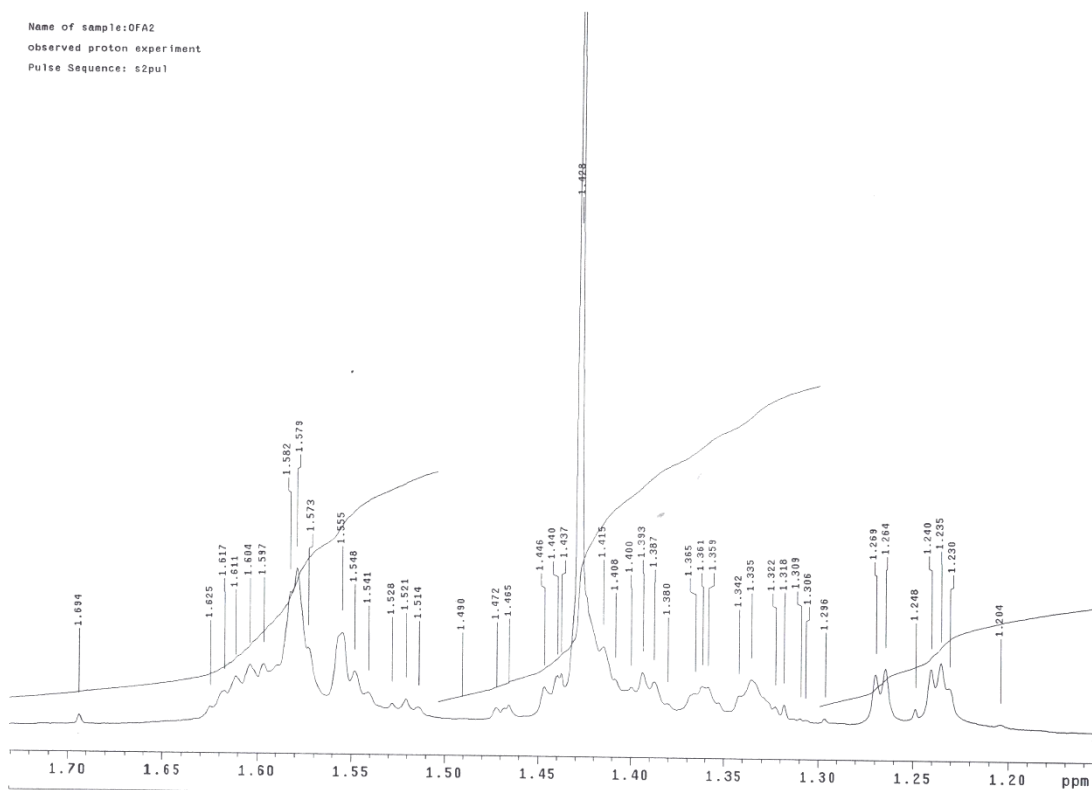
**Figure S56** <sup>1</sup>H NMR spectrum of **18** (expanding 5.84-5.68 ppm; 500 MHz, CDCl<sub>3</sub>)



**Figure S57** <sup>1</sup>H NMR spectrum of **18** (expanding 5.25-2.60 ppm; 500 MHz, CDCl<sub>3</sub>)

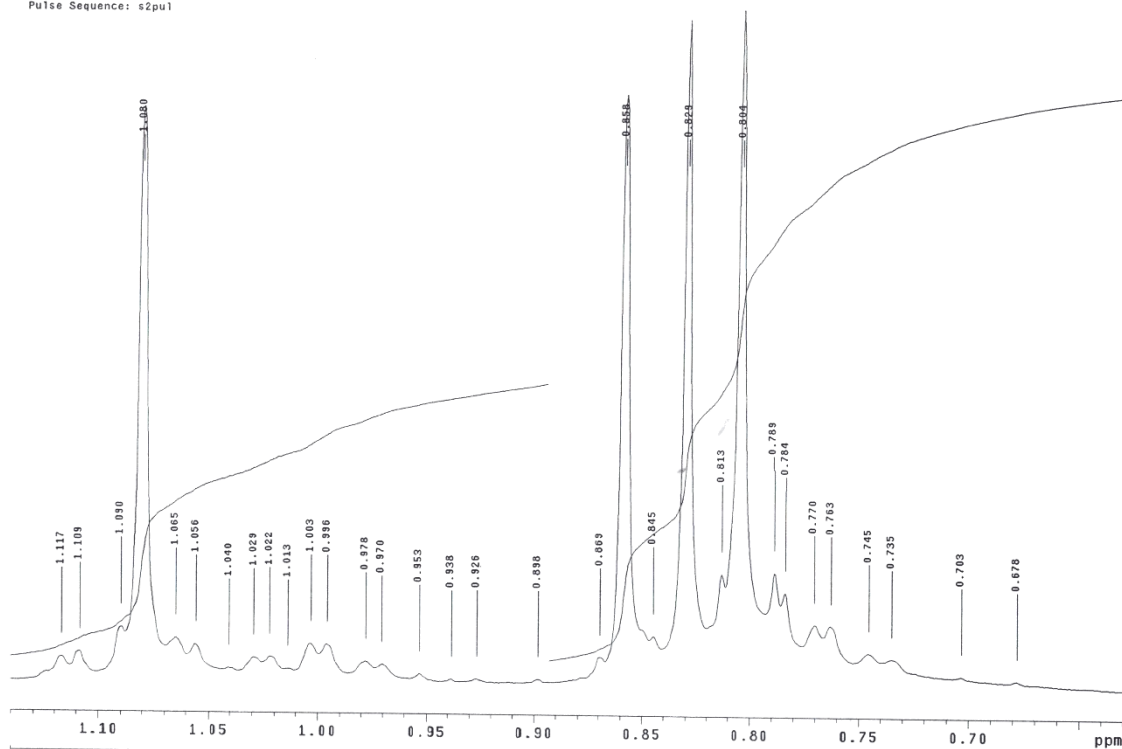


**Figure S58**  $^1\text{H}$  NMR spectrum of **18** (expanding 2.45-1.75 ppm; 500 MHz,  $\text{CDCl}_3$ )

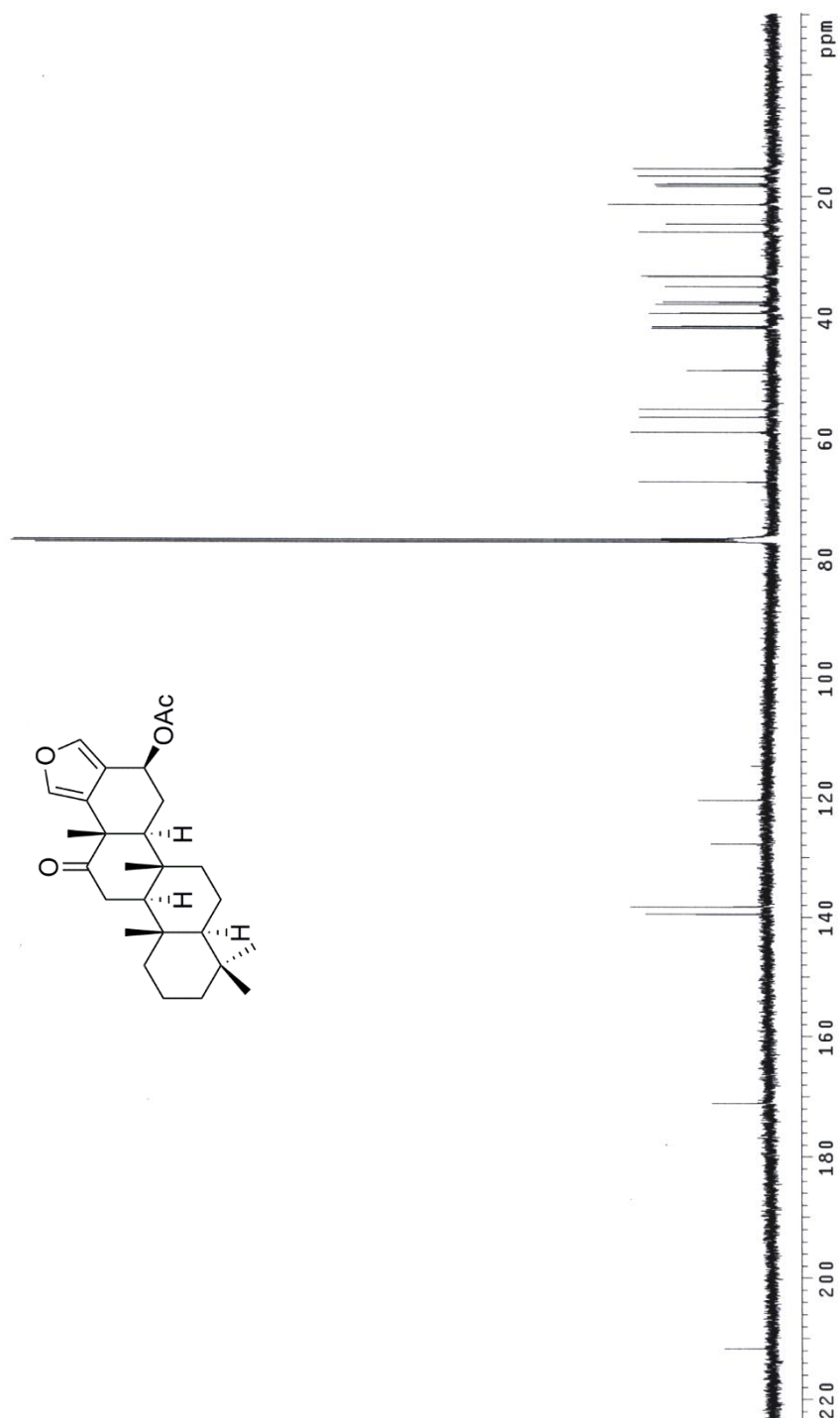


**Figure S59**  $^1\text{H}$  NMR spectrum of **18** (expanding 1.70-1.20 ppm; 500 MHz,  $\text{CDCl}_3$ )

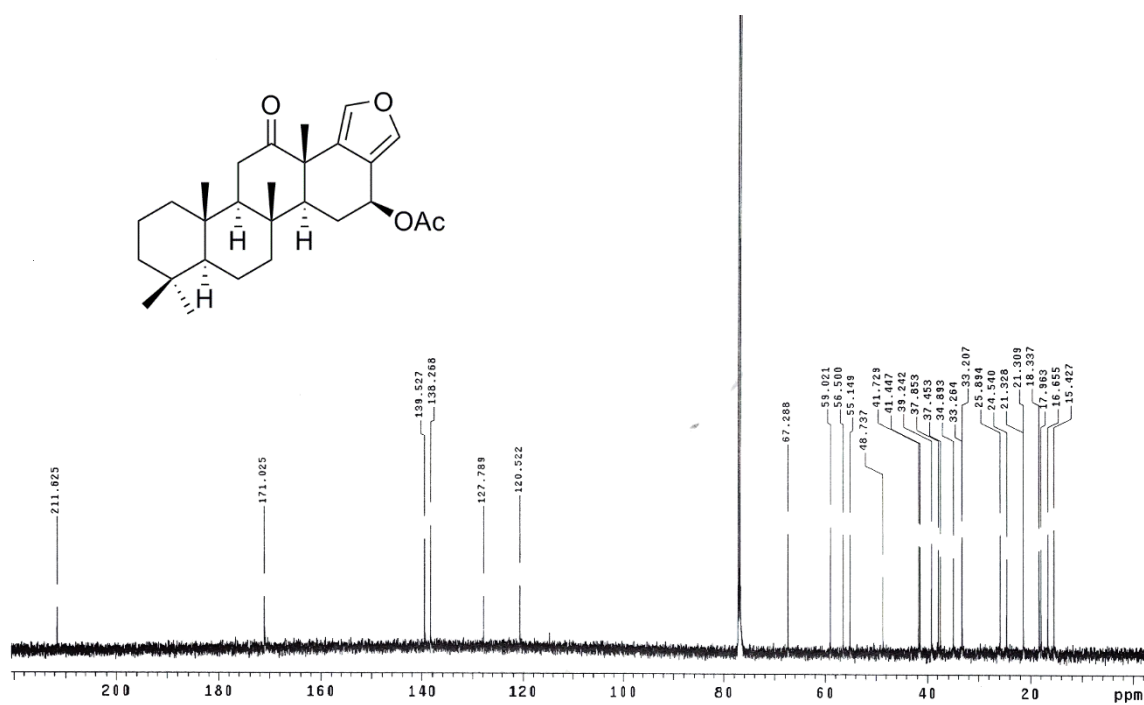
Pulse Sequence: s2pu1



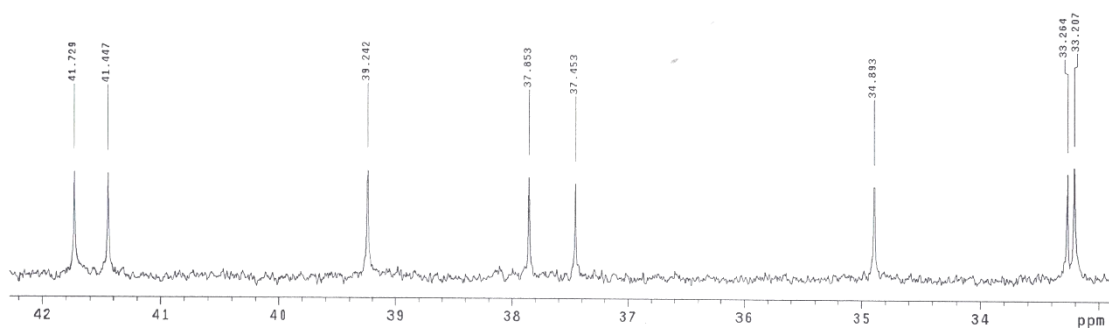
**Figure S60**  $^1\text{H}$  NMR spectrum of **18** (expanding 1.13-0.65 ppm; 500 MHz,  $\text{CDCl}_3$ )



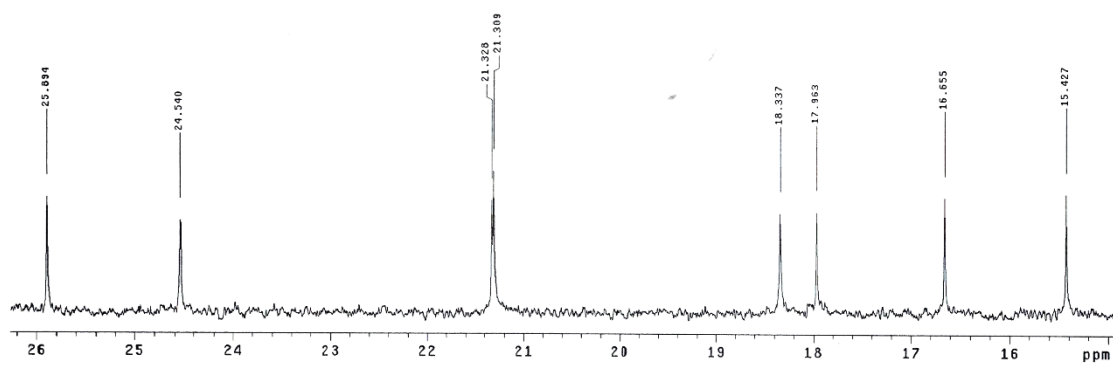
**Figure S61**  $^{13}\text{C}$  NMR spectrum of compound **18** (125MHz,  $\text{CDCl}_3$ )



**Figure S62**  $^{13}\text{C}$  NMR spectrum of **18** (peak picking tagged; 125 MHz,  $\text{CDCl}_3$ )

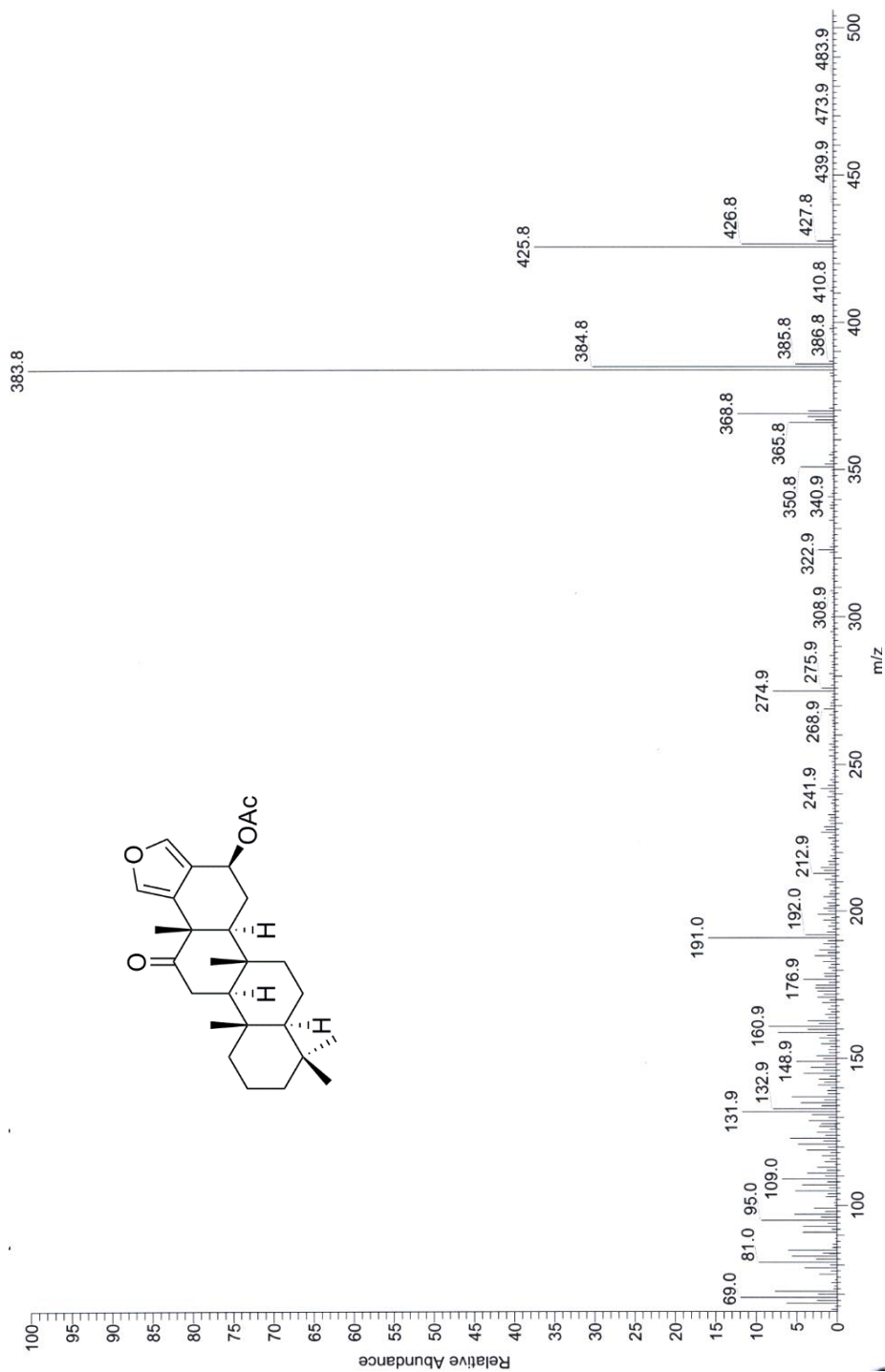


**Figure S63**  $^{13}\text{C}$  NMR spectrum of **18** (expanding 42-33 ppm; 125 MHz,  $\text{CDCl}_3$ )



**Figure S64**  $^{13}\text{C}$  NMR spectrum of **18** (expanding 26-15 ppm; 125 MHz,  $\text{CDCl}_3$ )





**Figure S65** EI mass spectrum of compound **18**

IR, NMR, and mass spectra of 19 (Figures S66-S77)

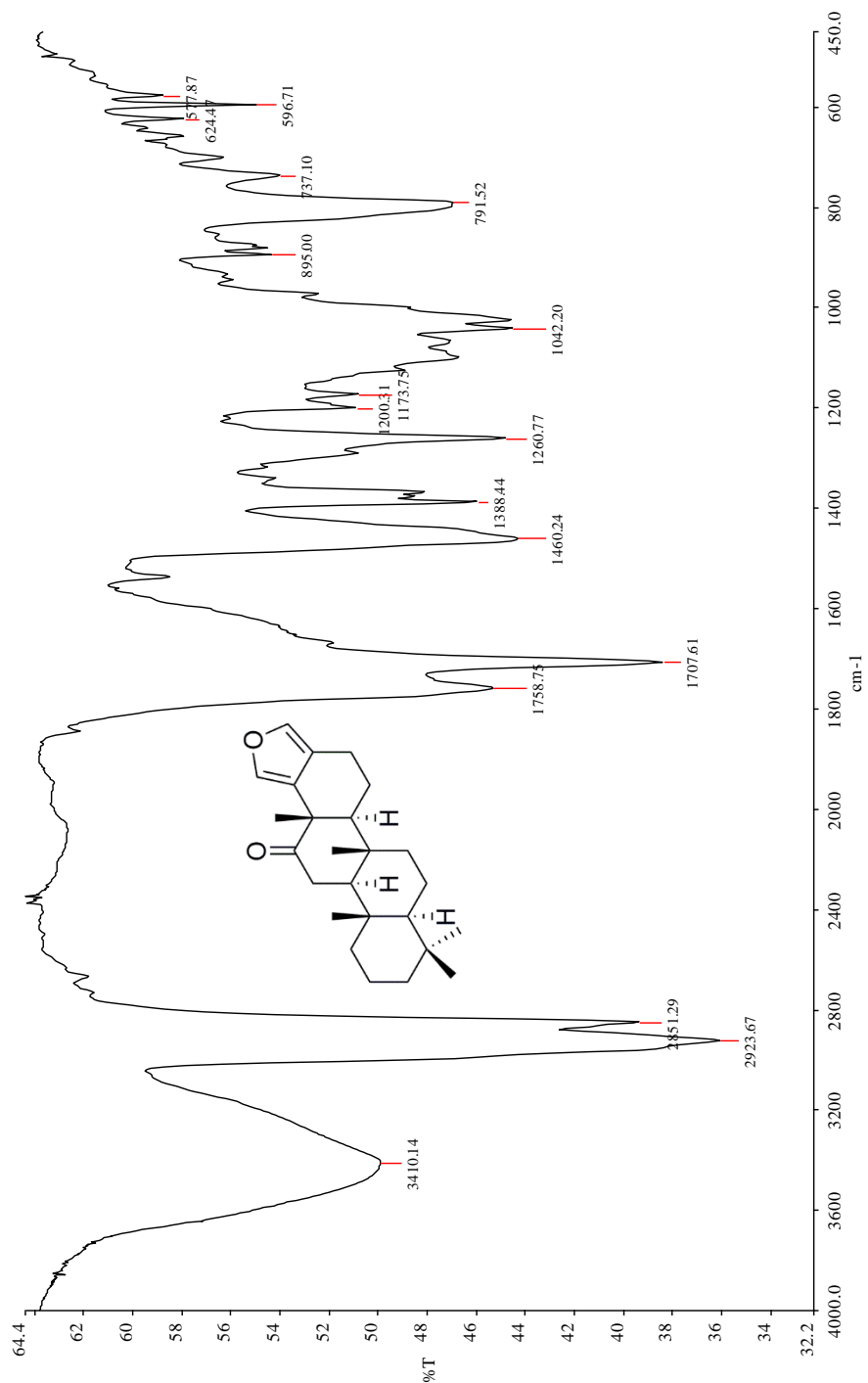
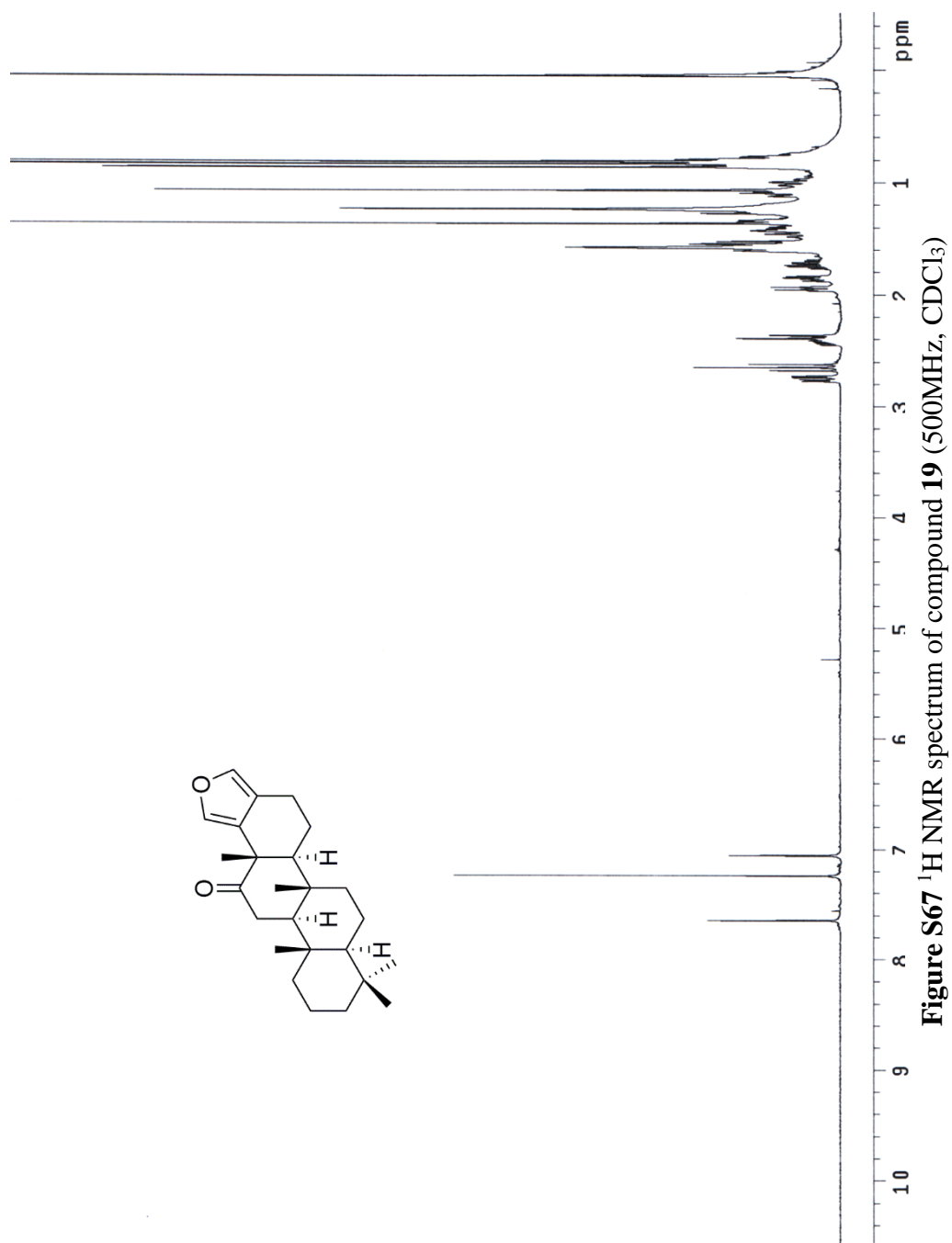
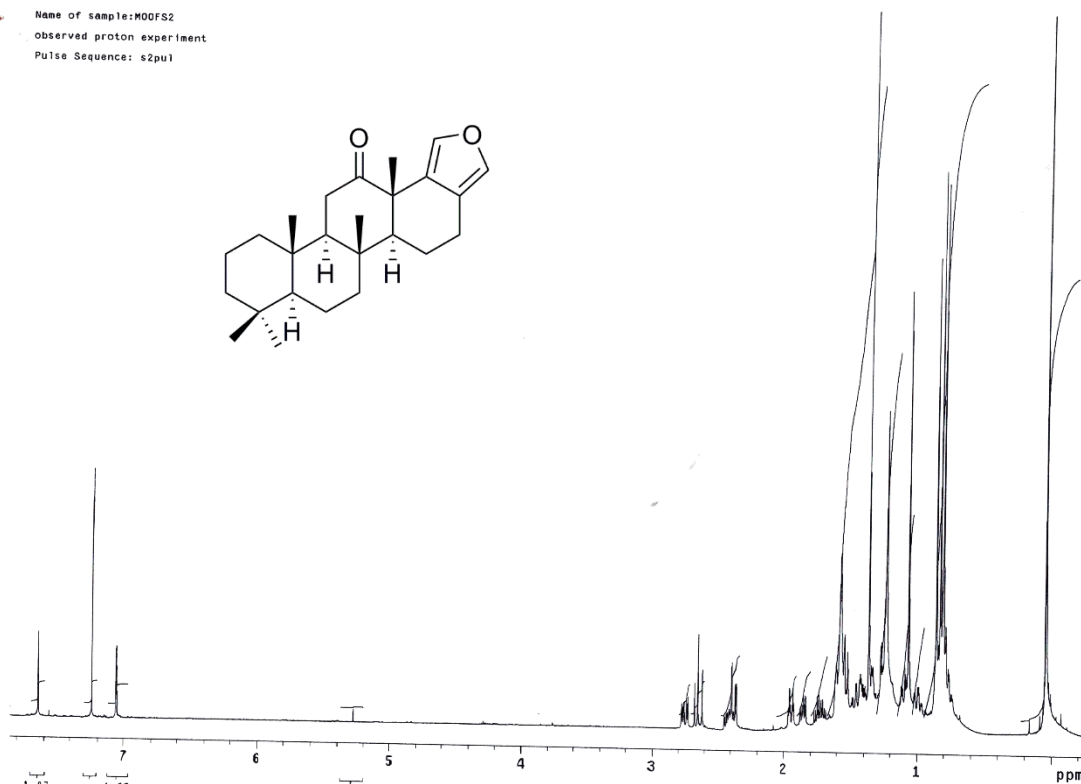


Figure S66 IR spectrum of compound 19

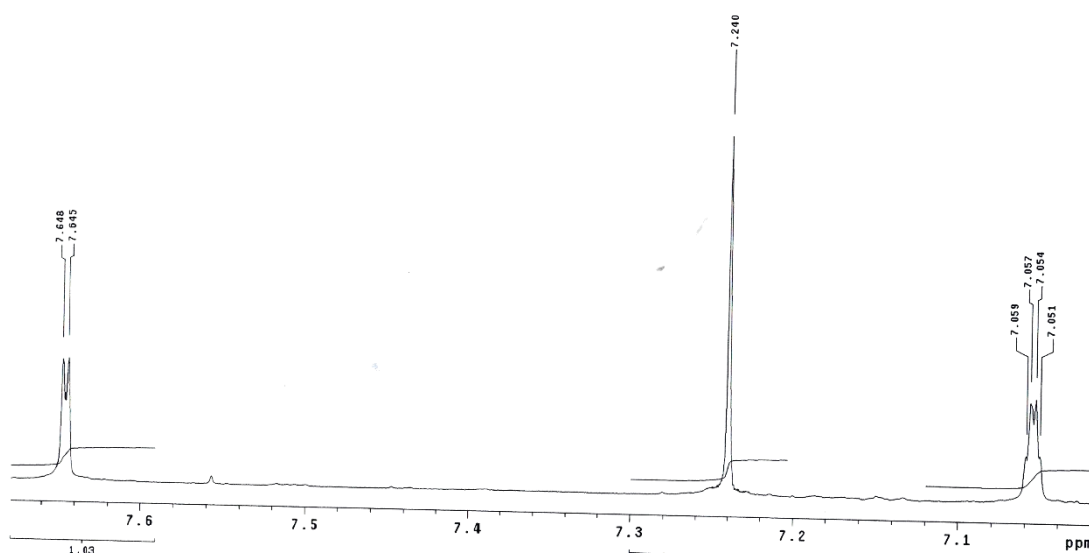


**Figure S67**  $^1\text{H}$  NMR spectrum of compound **19** (500MHz,  $\text{CDCl}_3$ )

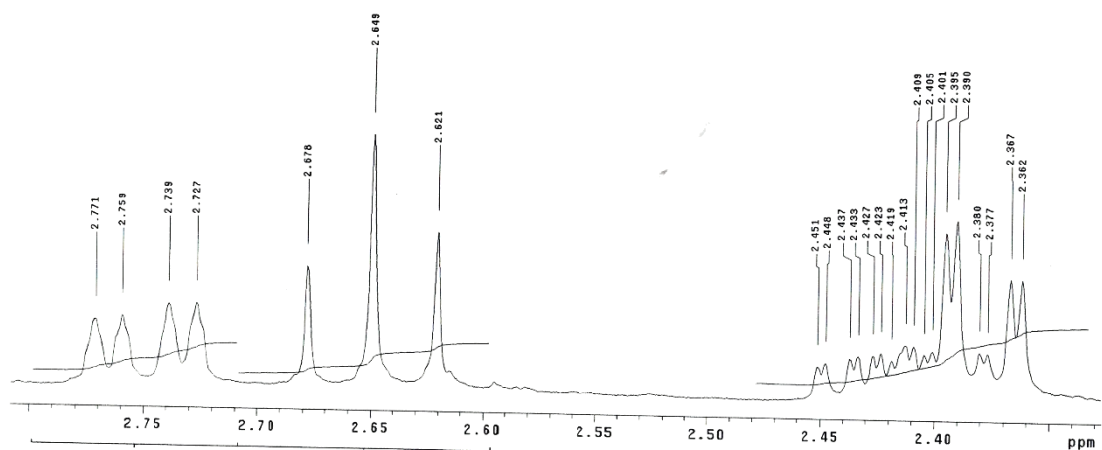
Name of sample: M00FS2  
observed proton experiment  
Pulse Sequence: s2pu1



**Figure S67**  $^1\text{H}$  NMR spectrum of **19** (integration tagged; 500 MHz,  $\text{CDCl}_3$ )

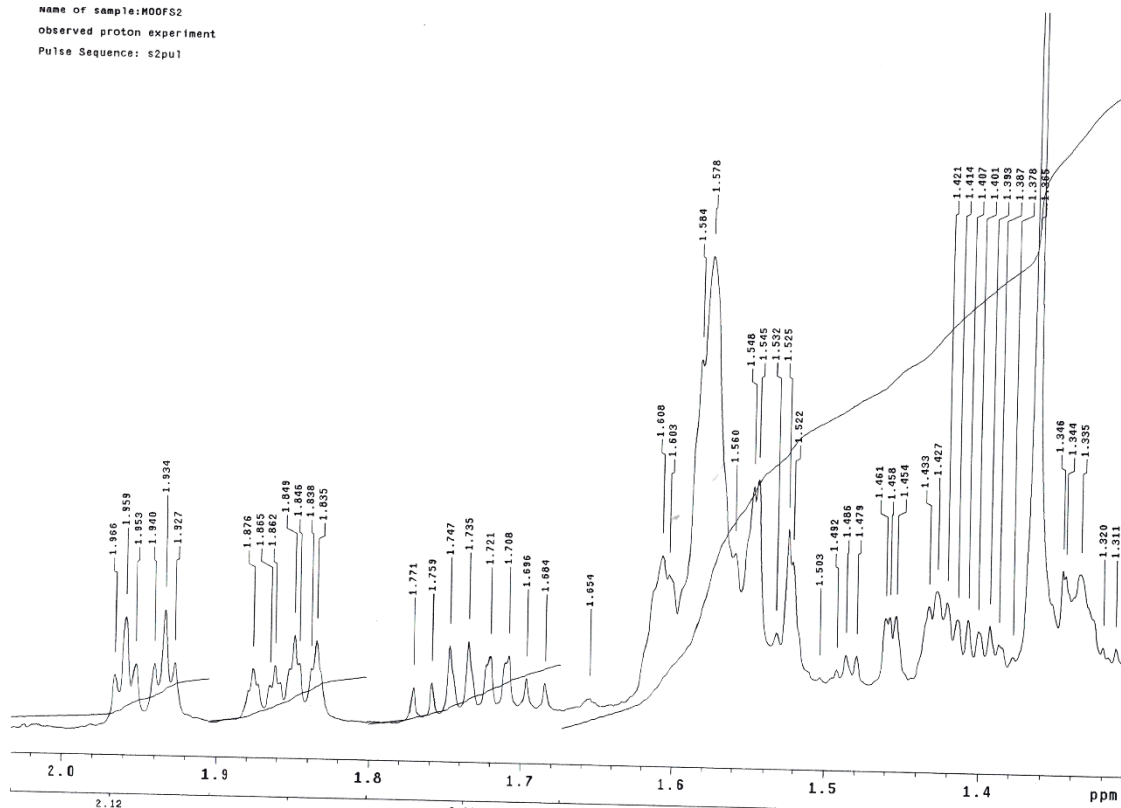


**Figure S68**  $^1\text{H}$  NMR spectrum of **19** (expanding 7.65-7.00 ppm; 500 MHz,  $\text{CDCl}_3$ )

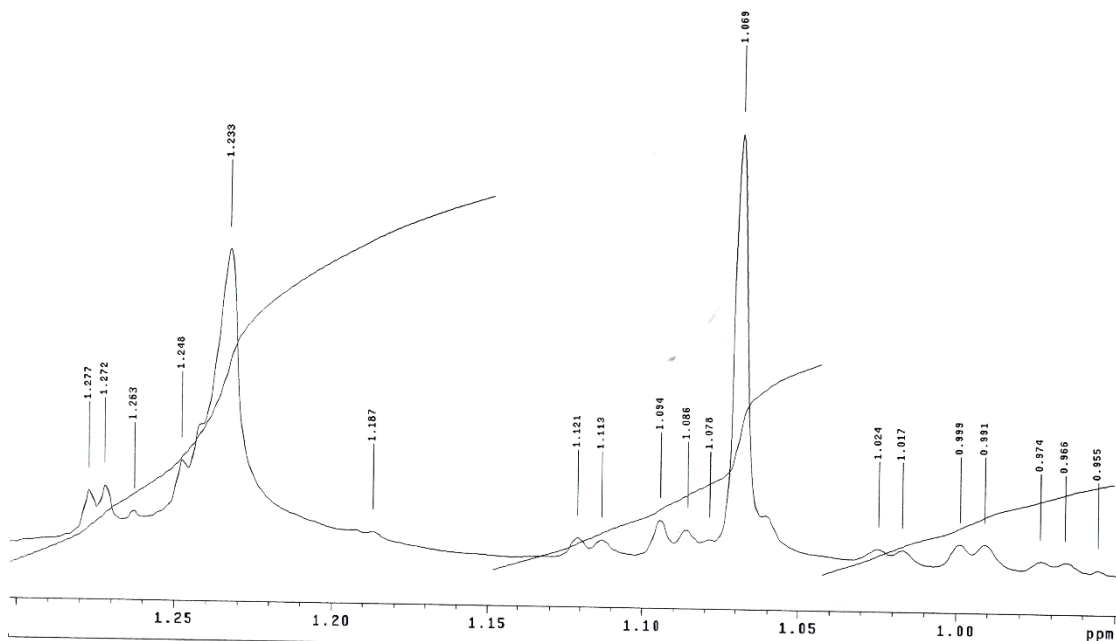


**Figure S69**  $^1\text{H}$  NMR spectrum of **19** (expanding 2.80–2.35 ppm; 500 MHz,  $\text{CDCl}_3$ )

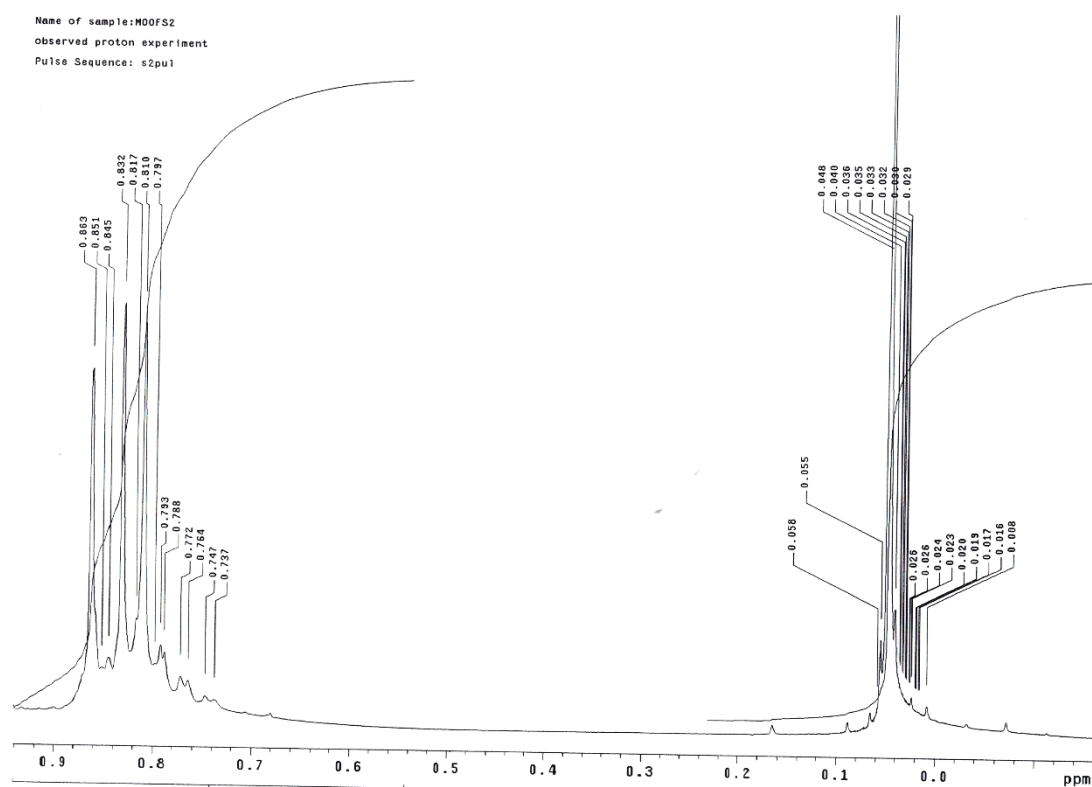
Name of sample: H00FS2  
 Observed proton experiment  
 Pulse Sequence: s2pu1



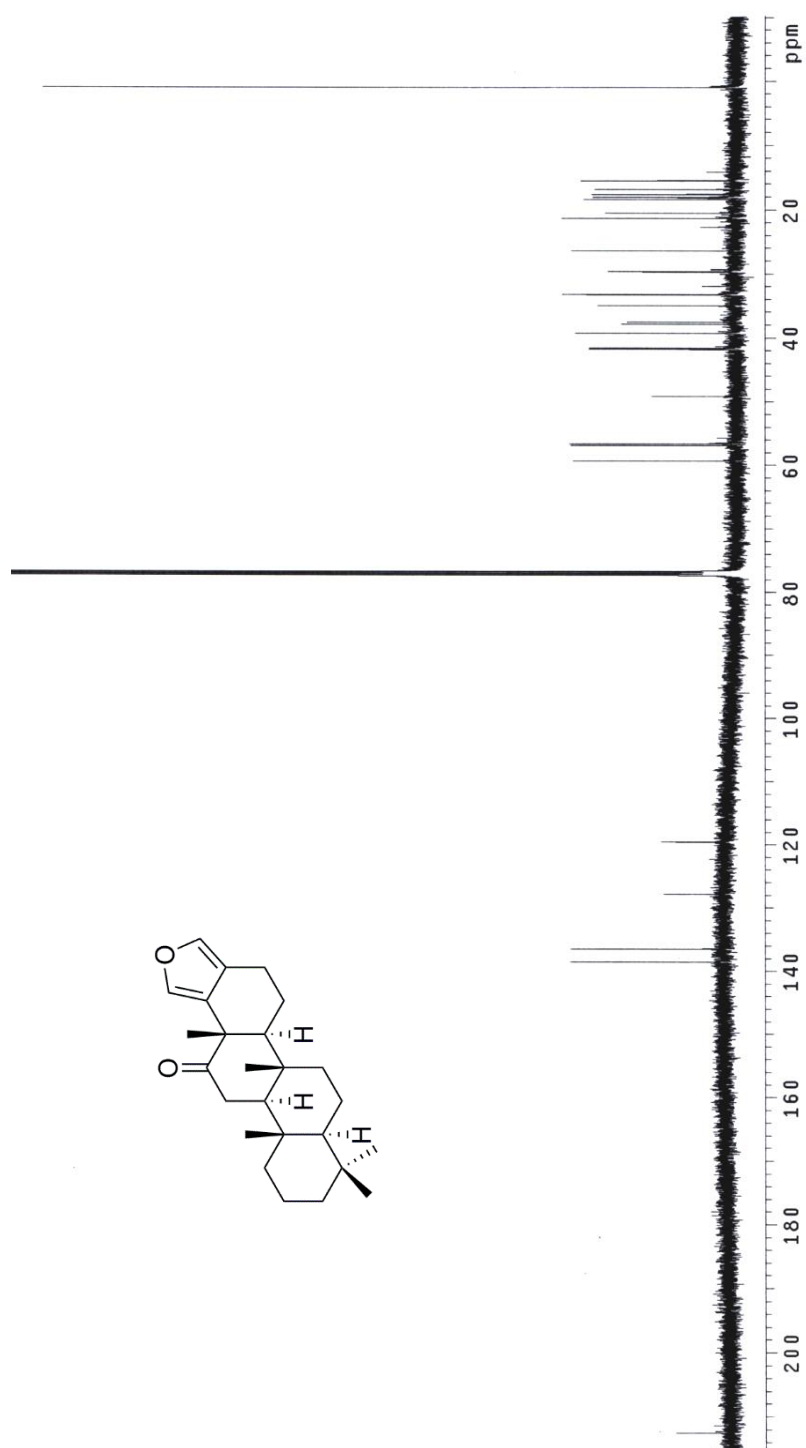
**Figure S70**  $^1\text{H}$  NMR spectrum of **18** (expanding 2.00–1.35 ppm; 500 MHz,  $\text{CDCl}_3$ )



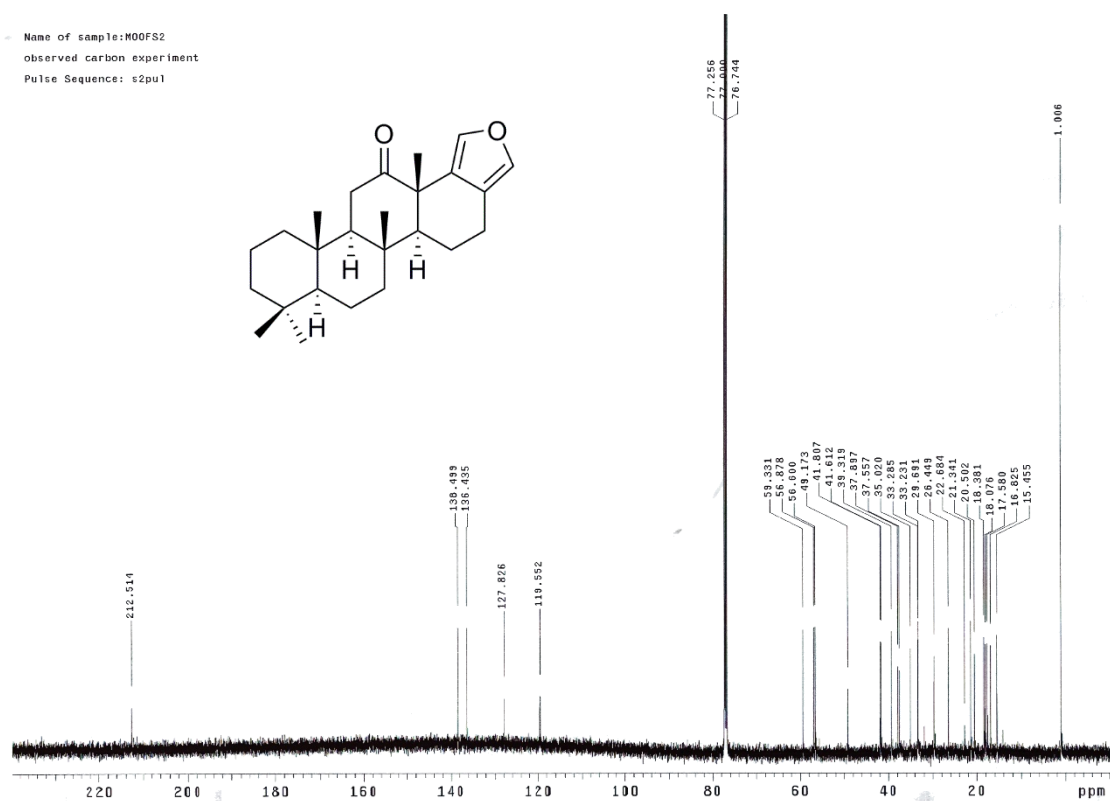
**Figure S71**  $^1\text{H}$  NMR spectrum of **19** (expanding 1.30-0.95 ppm; 500 MHz,  $\text{CDCl}_3$ )



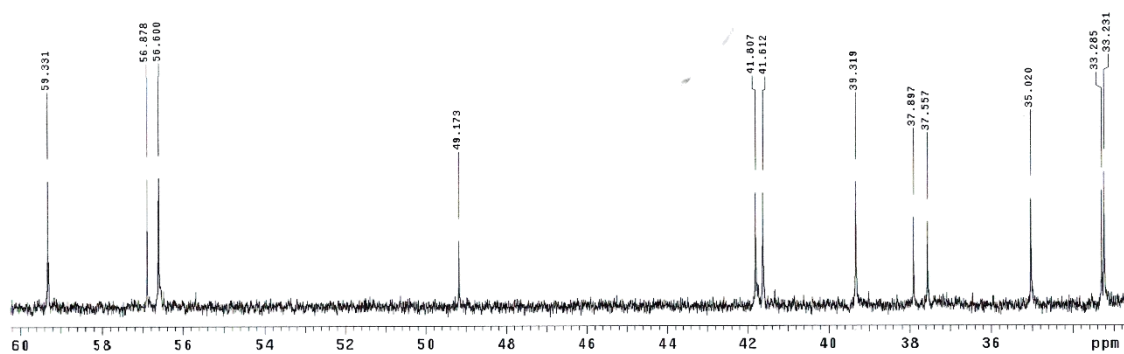
**Figure S72**  $^1\text{H}$  NMR spectrum of **19** (expanding 0.90-0.00 ppm; 500 MHz,  $\text{CDCl}_3$ )



**Figure S73**  $^{13}\text{C}$  NMR spectrum of compound **19** (125MHz,  $\text{CDCl}_3$ )

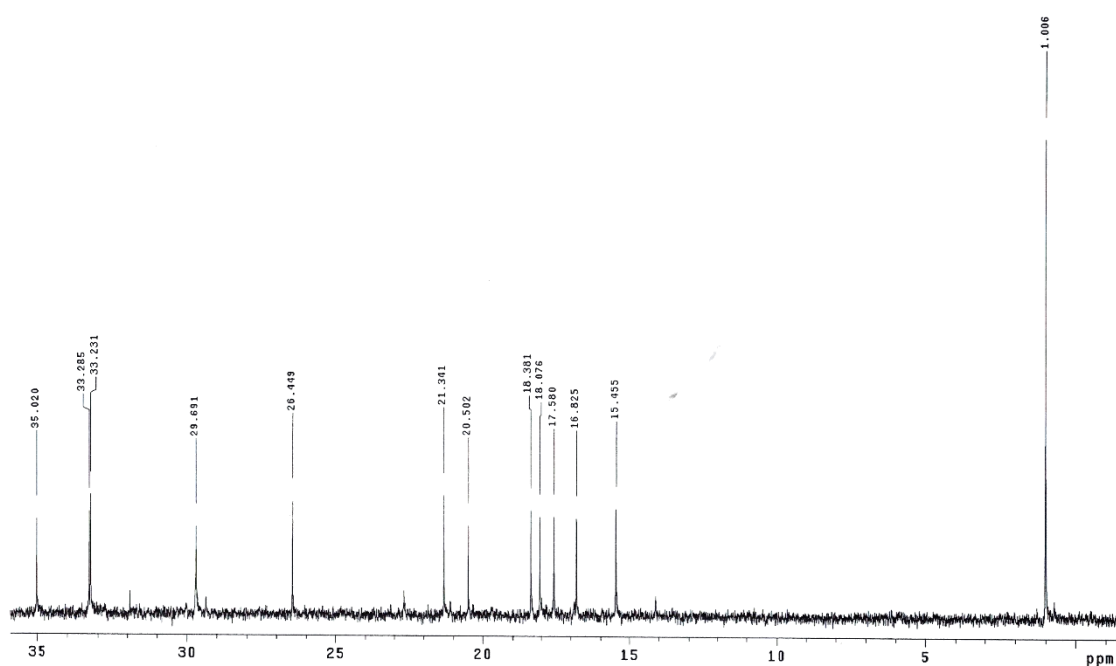


**Figure S74**  $^{13}\text{C}$  NMR spectrum of **19** (peak picking tagged; 125 MHz,  $\text{CDCl}_3$ )

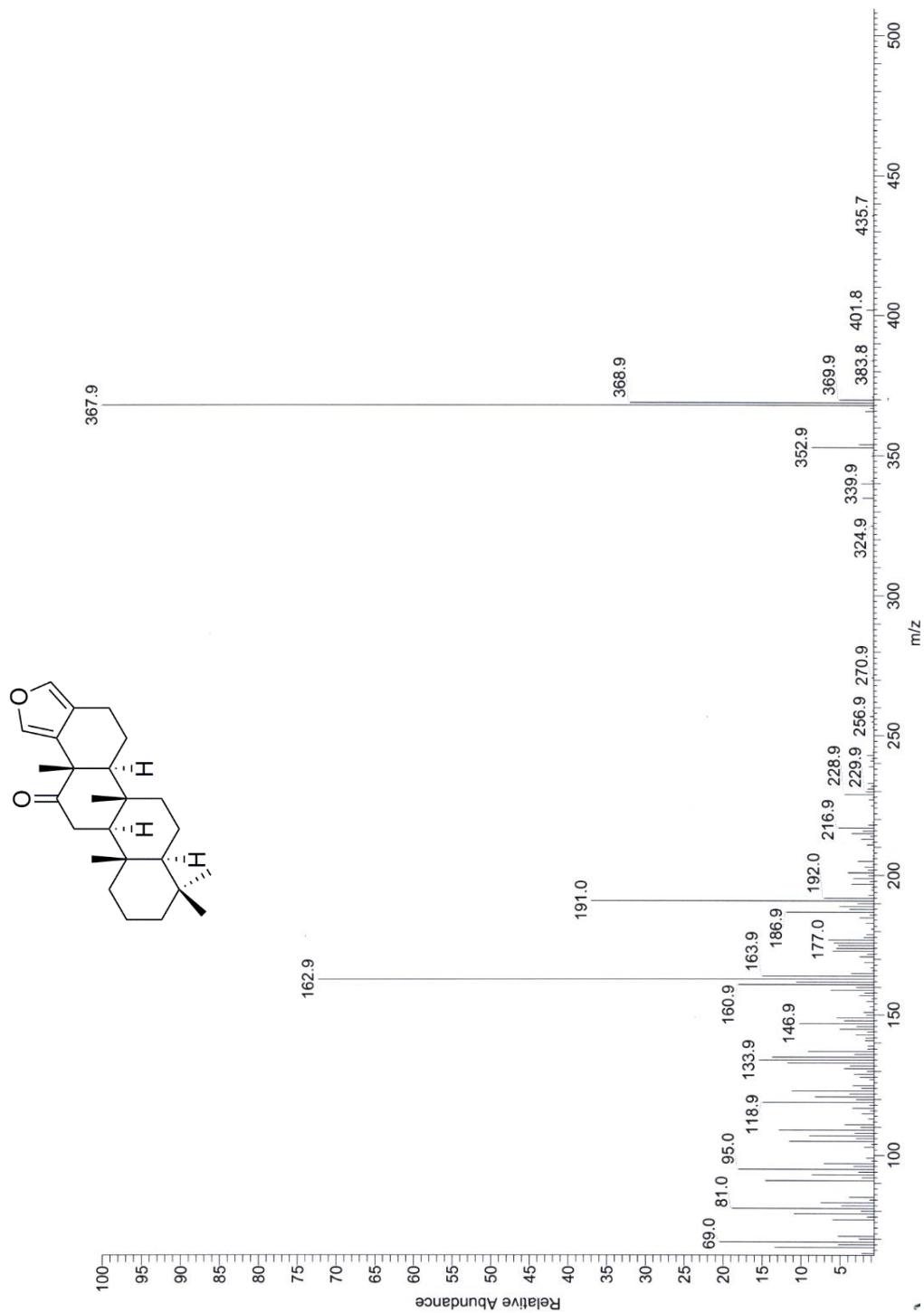


**Figure S75**  $^{13}\text{C}$  NMR spectrum of **19** (expanding 60-33 ppm; 125 MHz,  $\text{CDCl}_3$ )





**Figure S76**  $^{13}\text{C}$  NMR spectrum of **19** (expanding 36-0 ppm; 125 MHz,  $\text{CDCl}_3$ )



**Figure S77** EI mass spectrum of compound **19**

IR, NMR, and mass spectra of 20 (Figures S78-S92)

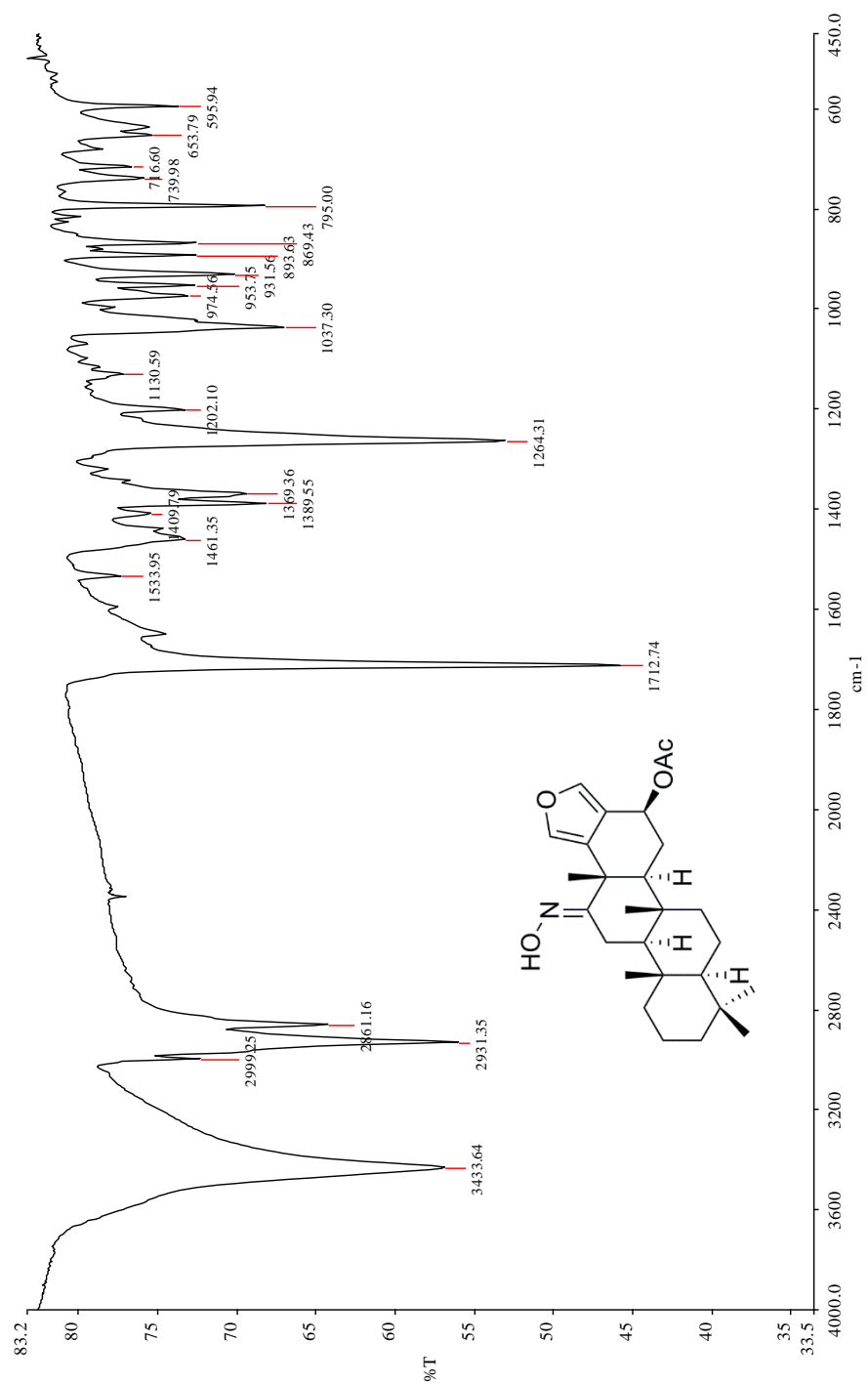
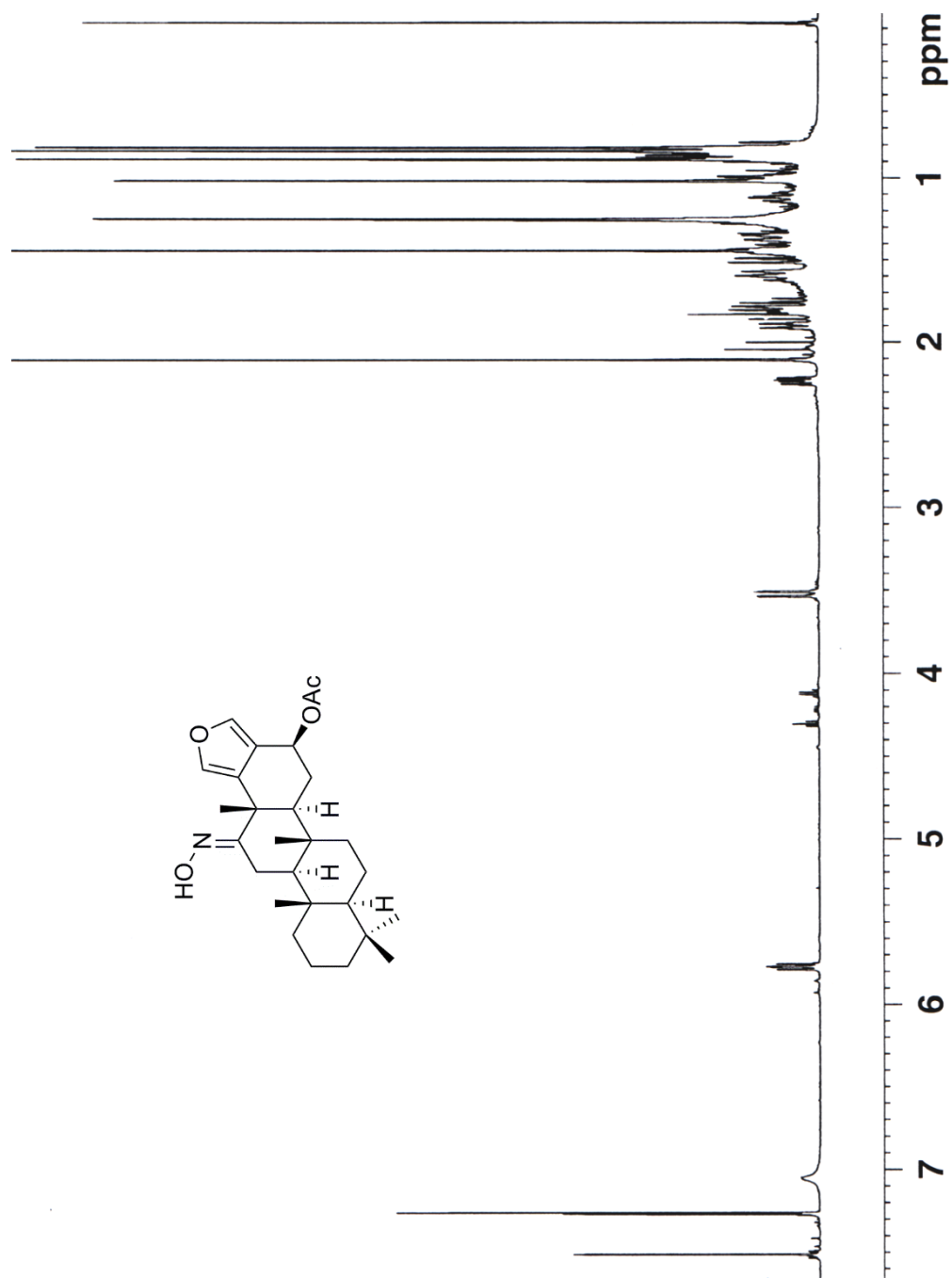
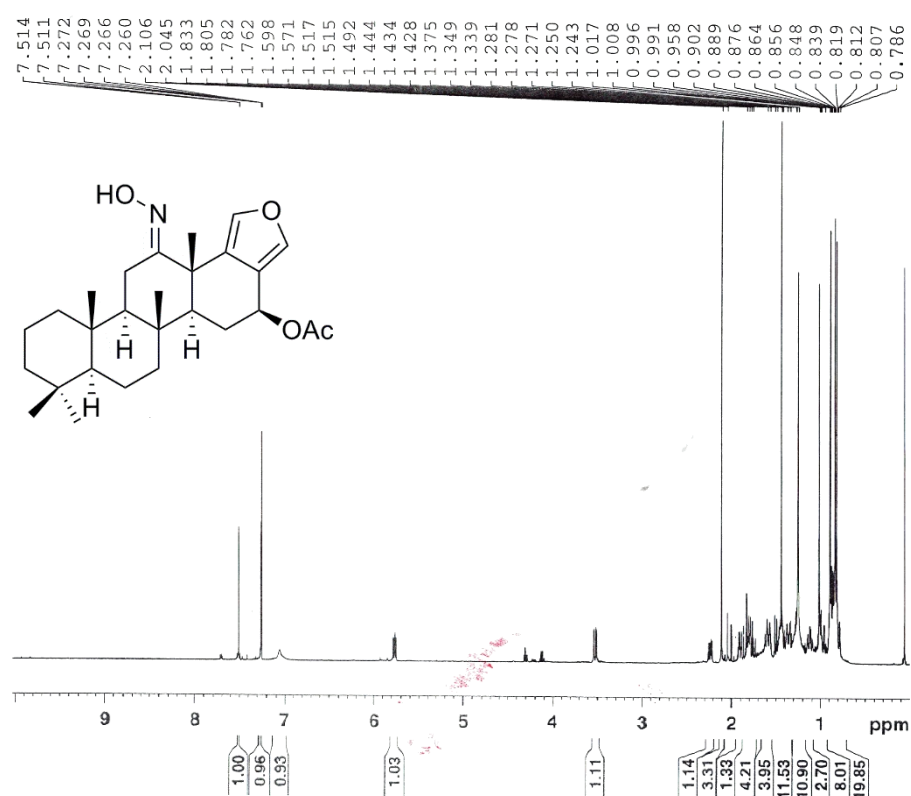


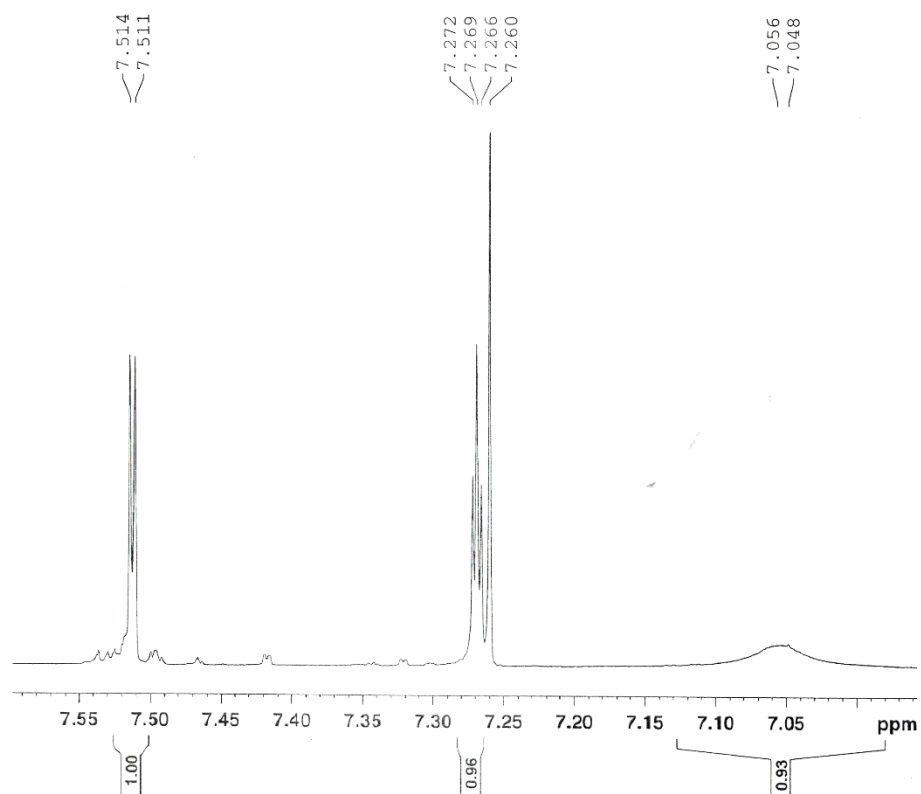
Figure S78 IR spectrum of compound 20



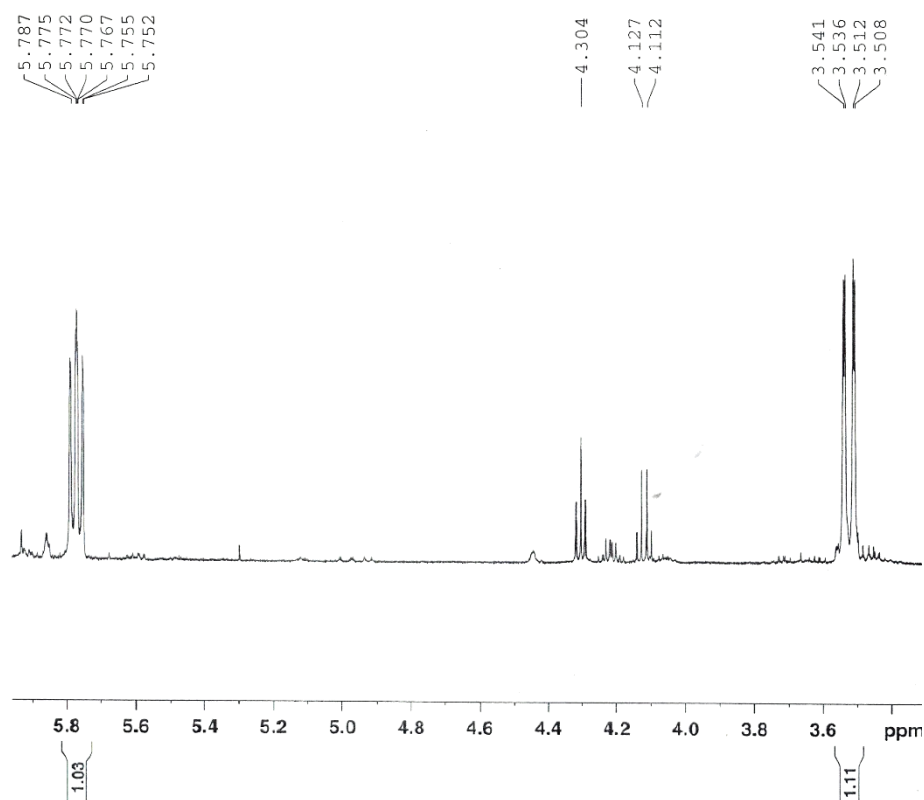
**Figure S79**  $^1\text{H}$  NMR spectrum of compound **20** (500MHz,  $\text{CDCl}_3$ )



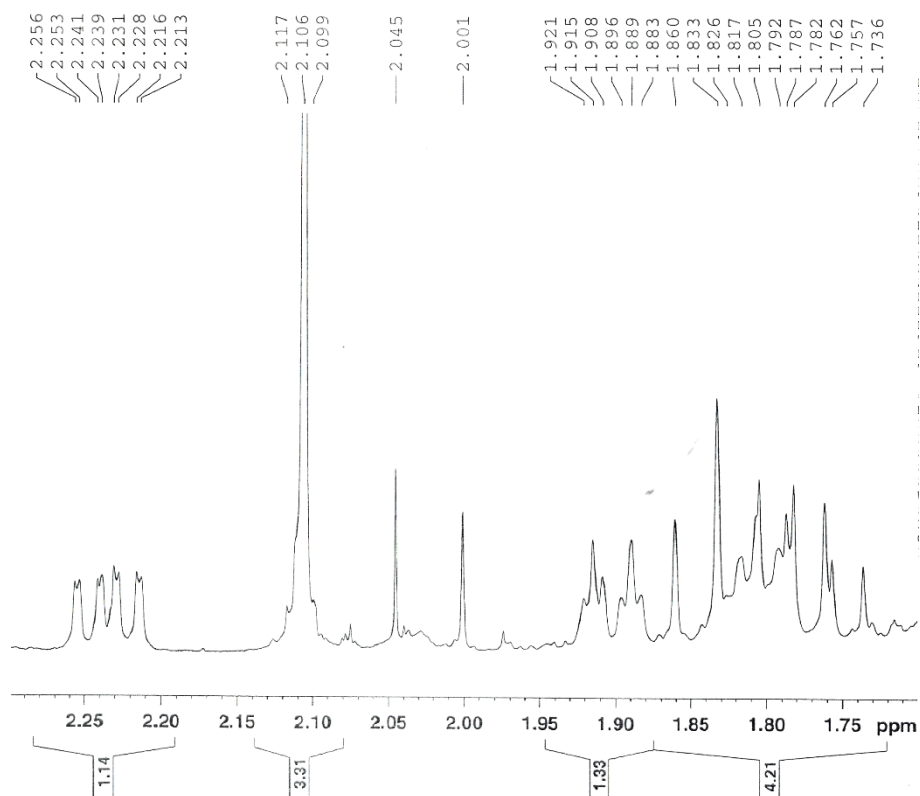
**Figure S80**  $^1\text{H}$  NMR spectrum of **20** (peak-picked and integration tagged; 500 MHz,  $\text{CDCl}_3$ )



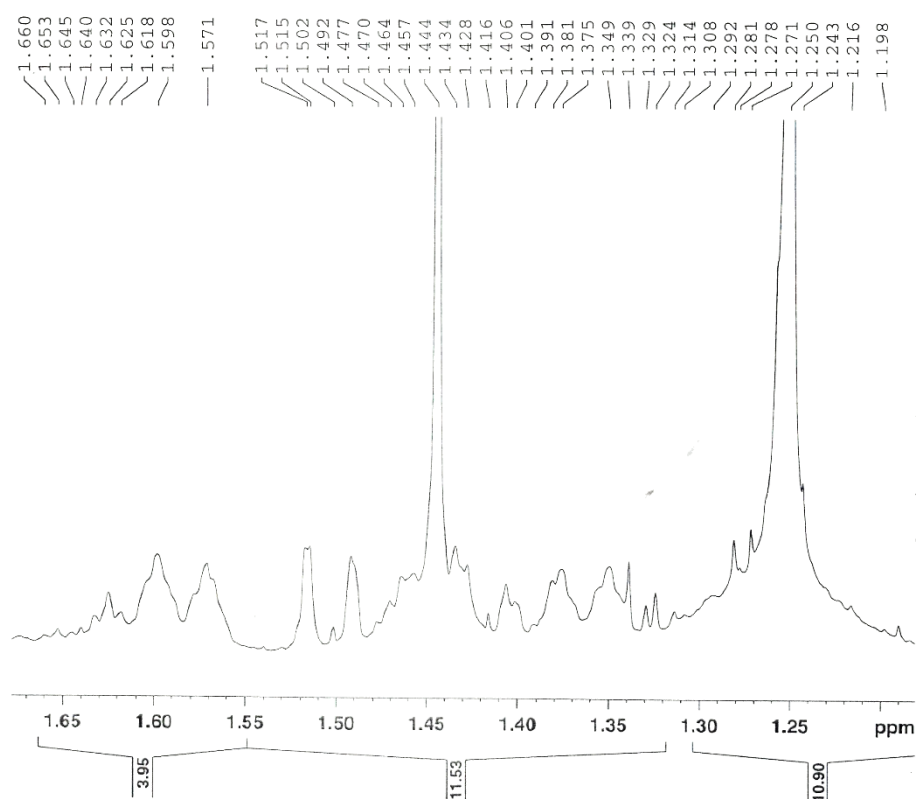
**Figure S81**  $^1\text{H}$  NMR spectrum of **20** (expanding 7.55-7.00 ppm; 500 MHz,  $\text{CDCl}_3$ )



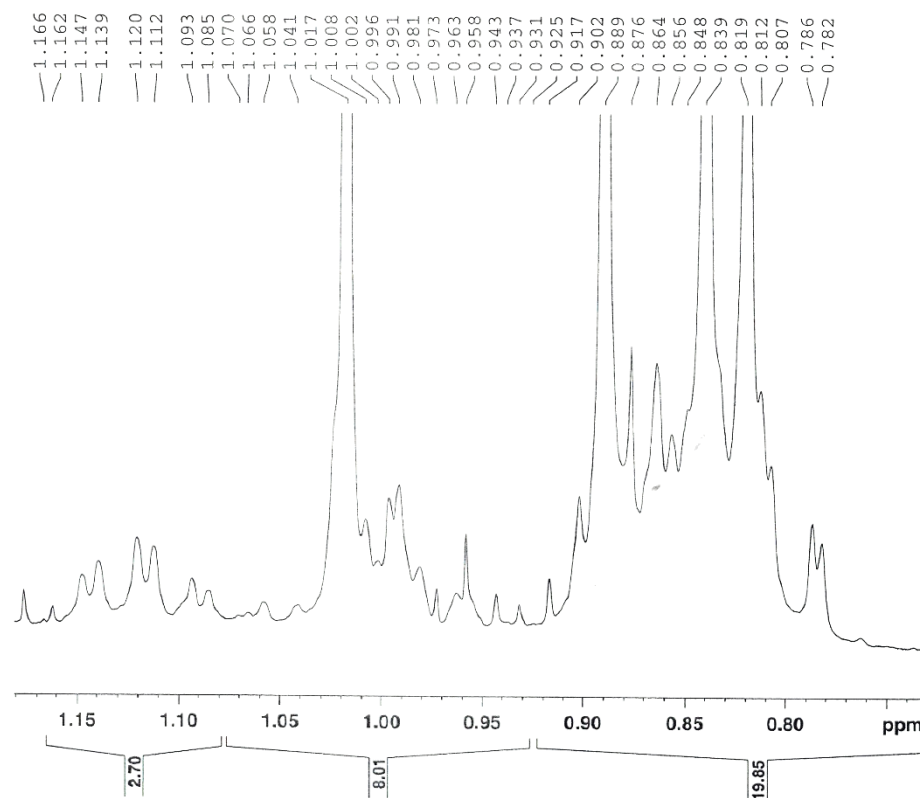
**Figure S82**  $^1\text{H}$  NMR spectrum of **20** (expanding 5.85-3.40 ppm; 500 MHz,  $\text{CDCl}_3$ )



**Figure S83**  $^1\text{H}$  NMR spectrum of **20** (expanding 2.30-1.70 ppm; 500 MHz,  $\text{CDCl}_3$ )



**Figure S84**  $^1\text{H}$  NMR spectrum of **20** (expanding 1.65-1.20 ppm; 500 MHz,  $\text{CDCl}_3$ )



**Figure S85**  $^1\text{H}$  NMR spectrum of **20** (expanding 1.18-0.75 ppm; 500 MHz,  $\text{CDCl}_3$ )

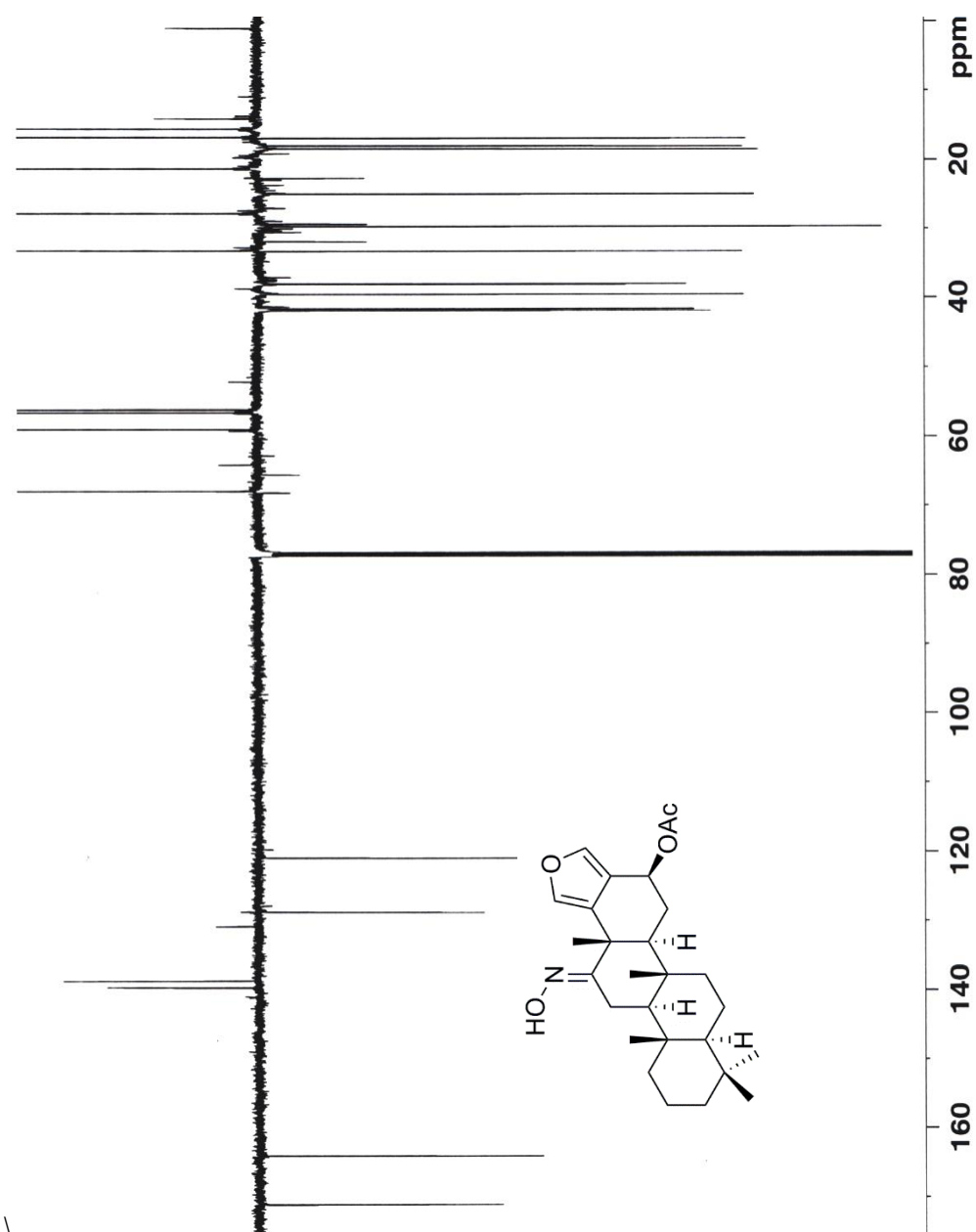
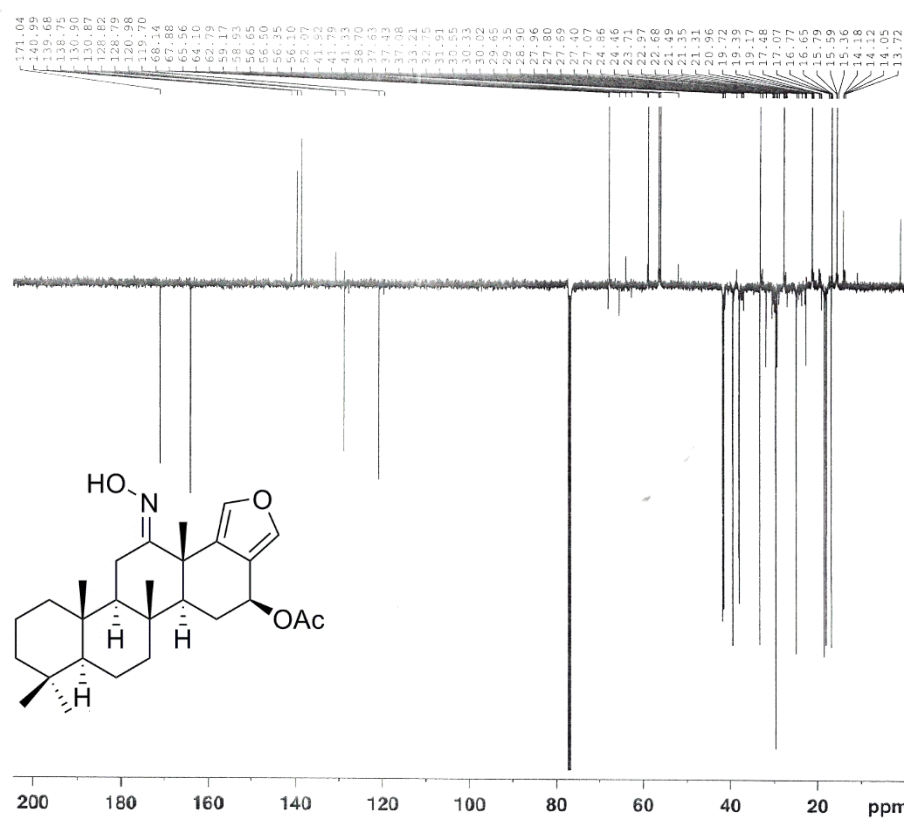
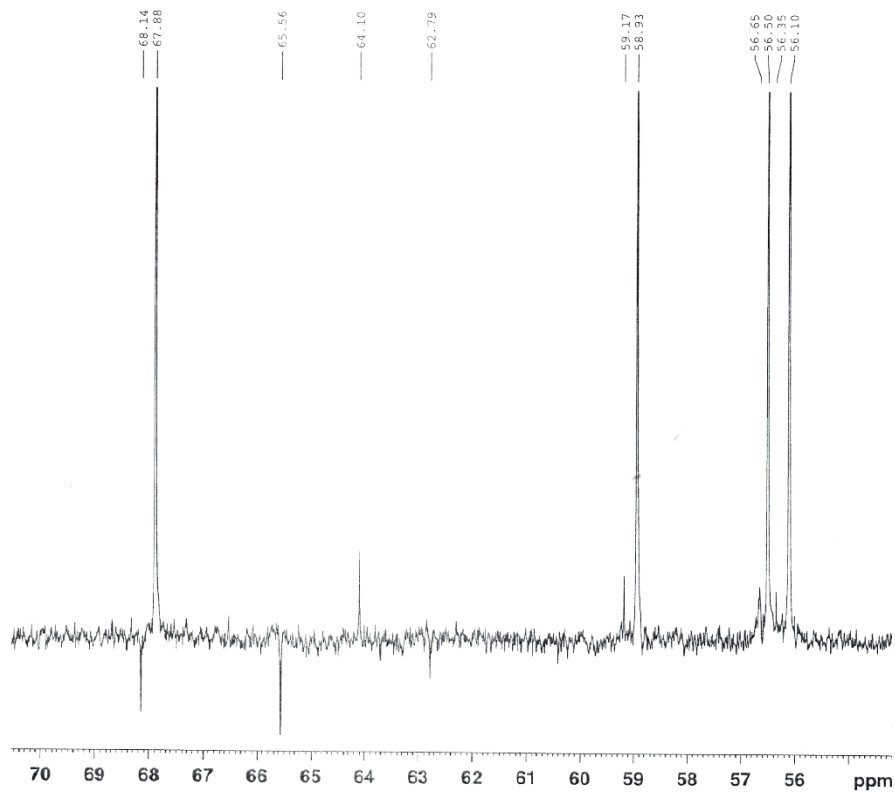


Figure S86 APT spectrum of compound **20** (125MHz, CDCl<sub>3</sub>)

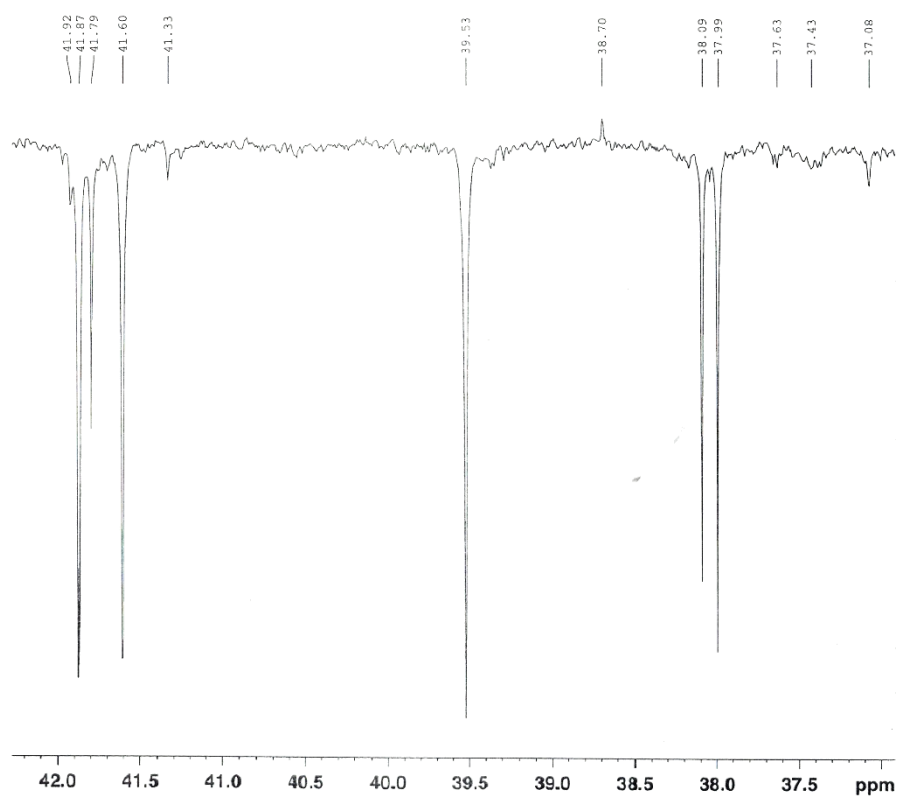




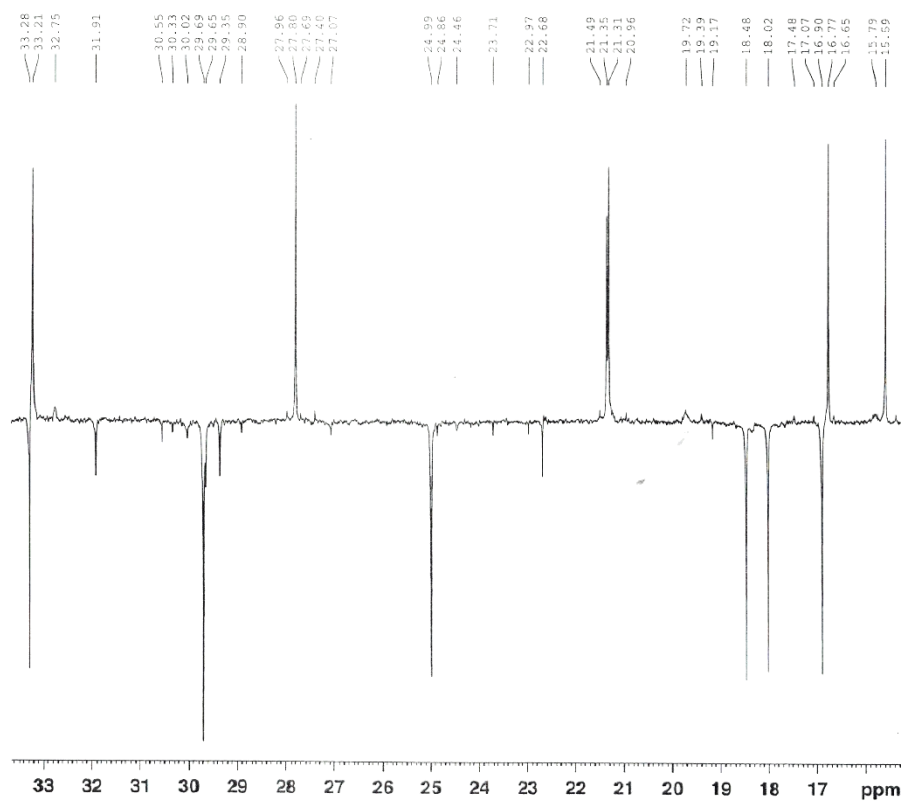
**Figure S87** APT spectrum of **20** (peak picking tagged; 125 MHz, CDCl<sub>3</sub>)



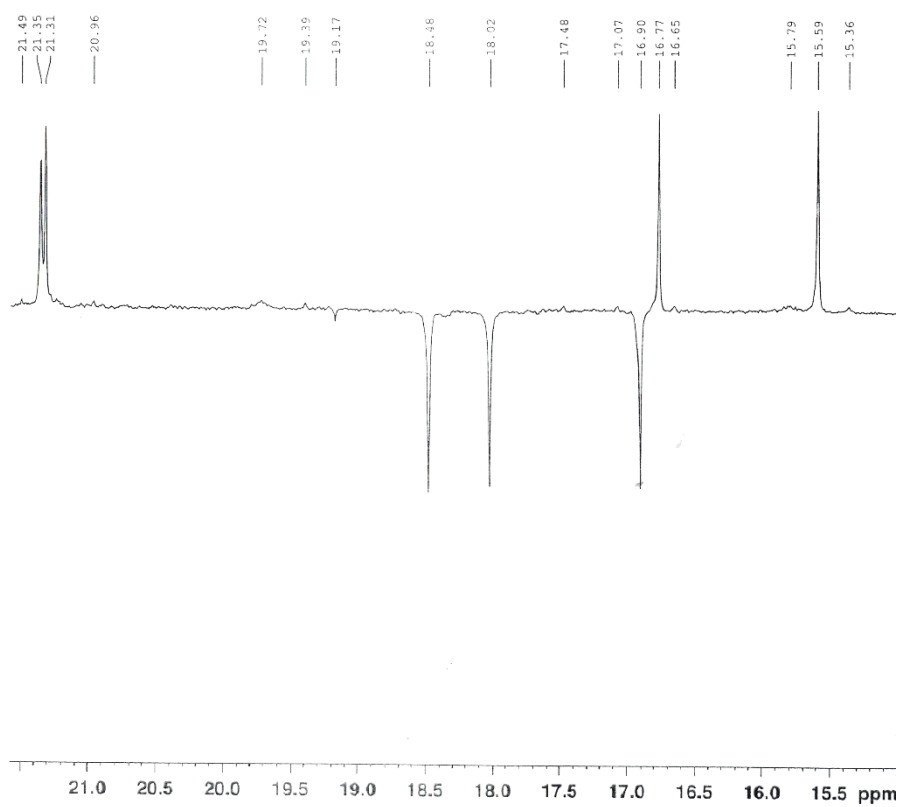
**Figure S88** APT spectrum of **20** (expanding 70-55 ppm; 125 MHz, CDCl<sub>3</sub>)



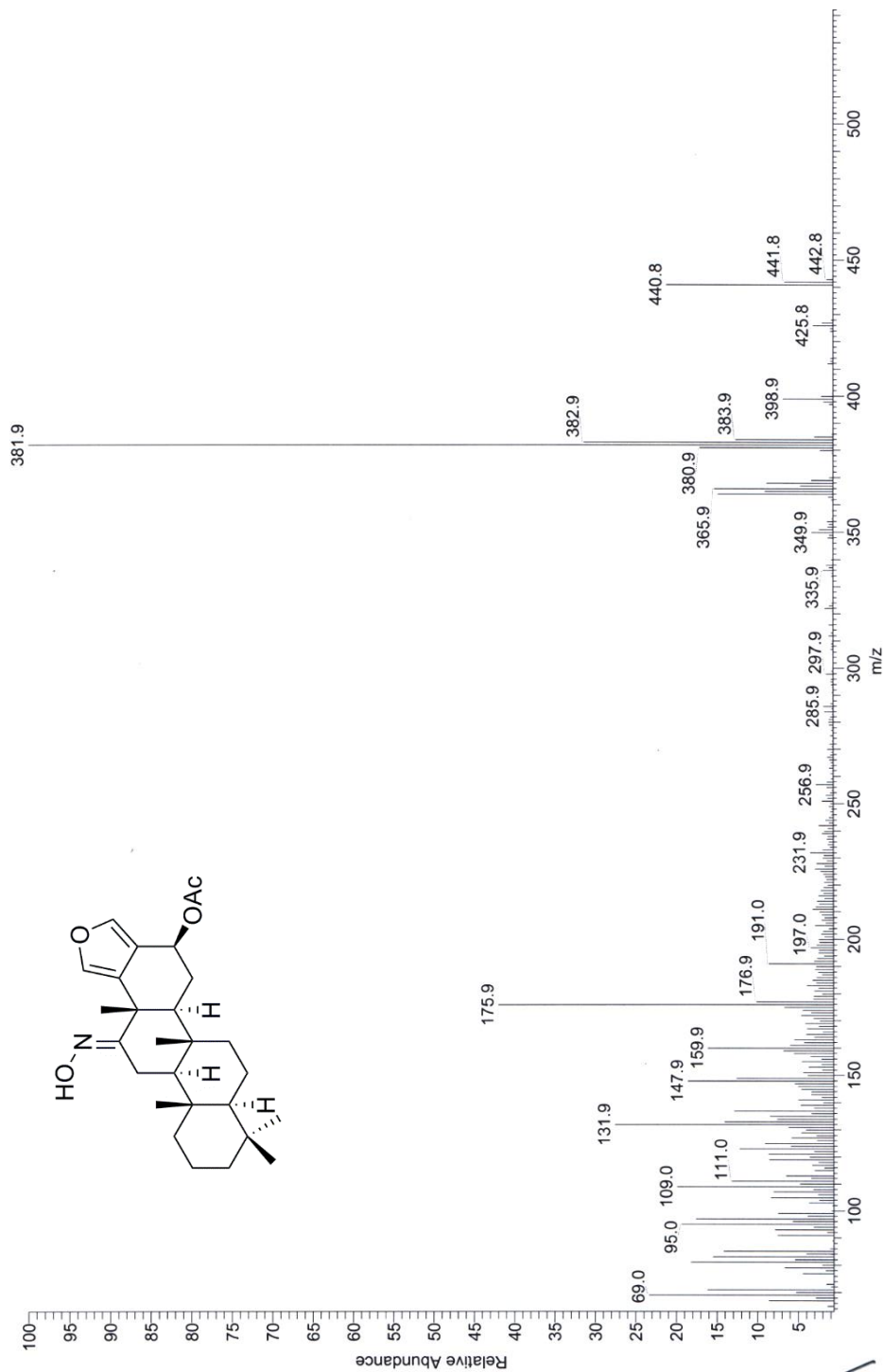
**Figure S89** APT spectrum of **20** (expanding 42-37 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S90** APT spectrum of **20** (expanding 33-15 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S91** APT spectrum of **20** (expanding 21.5-15.0 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S92** EI mass spectrum of compound **20**

IR, NMR, and mass spectra of 21 (Figures S93-S105)

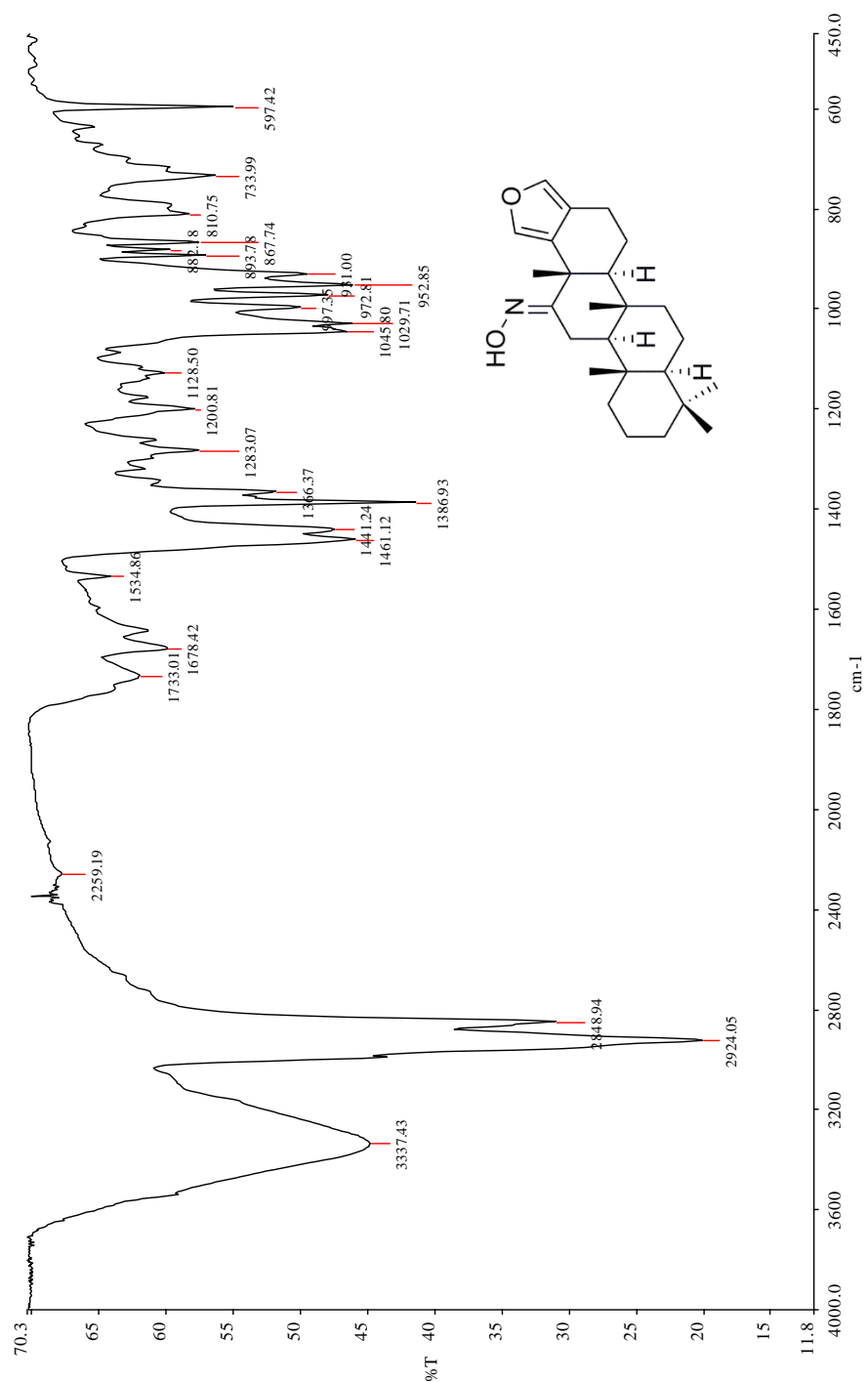
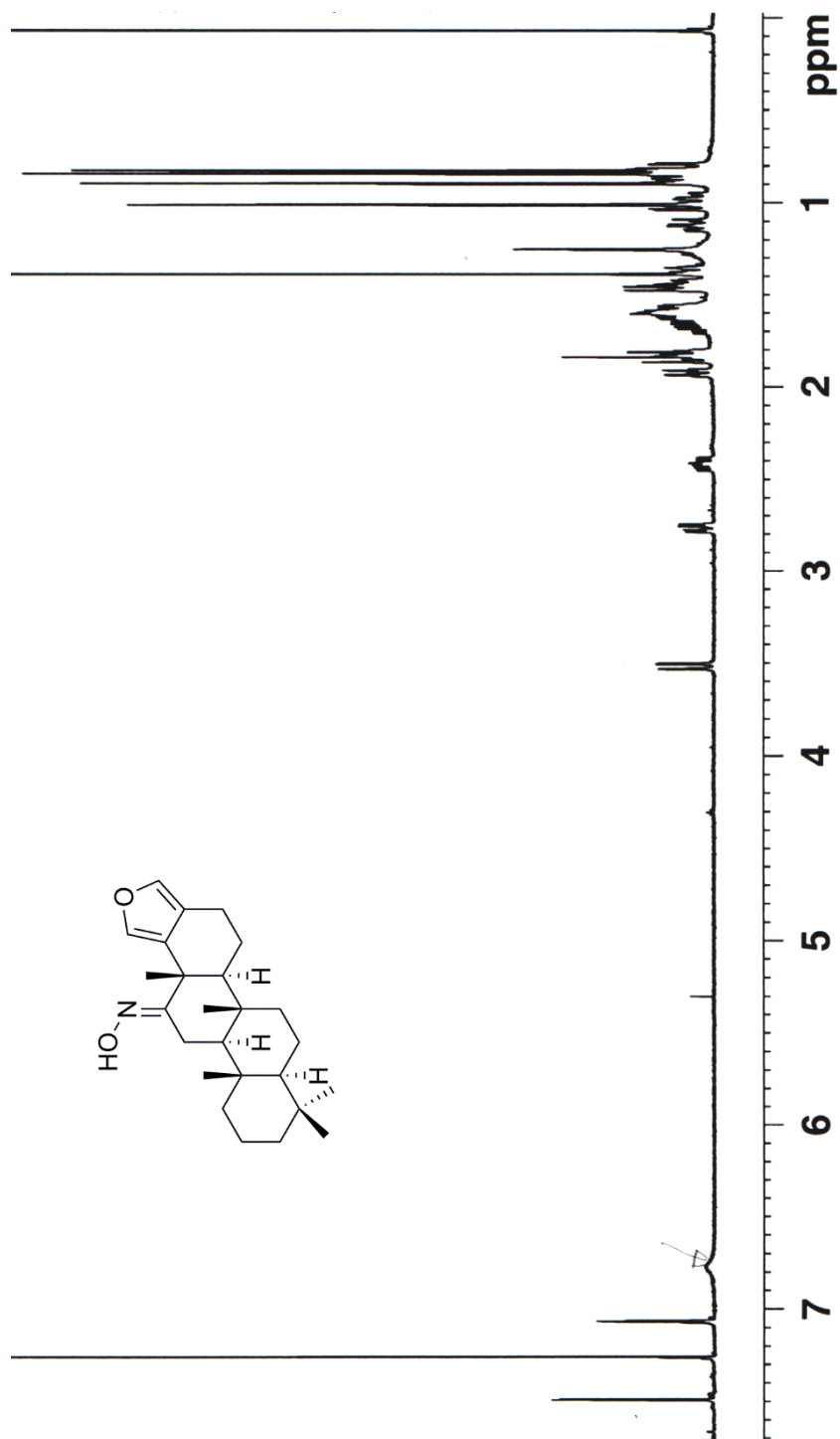
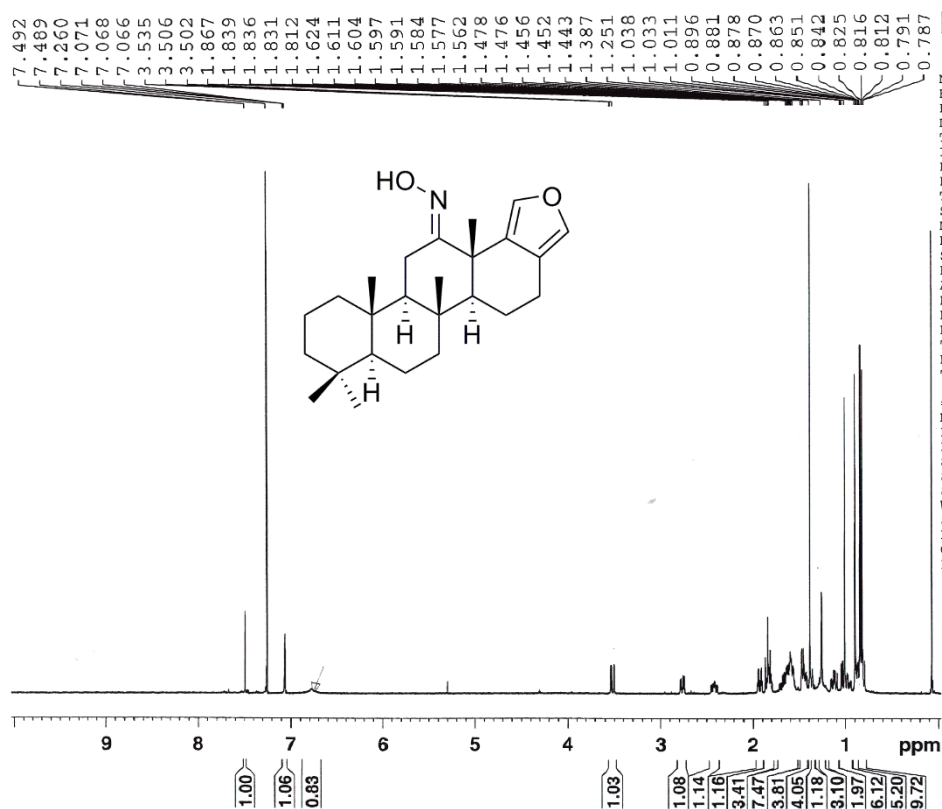


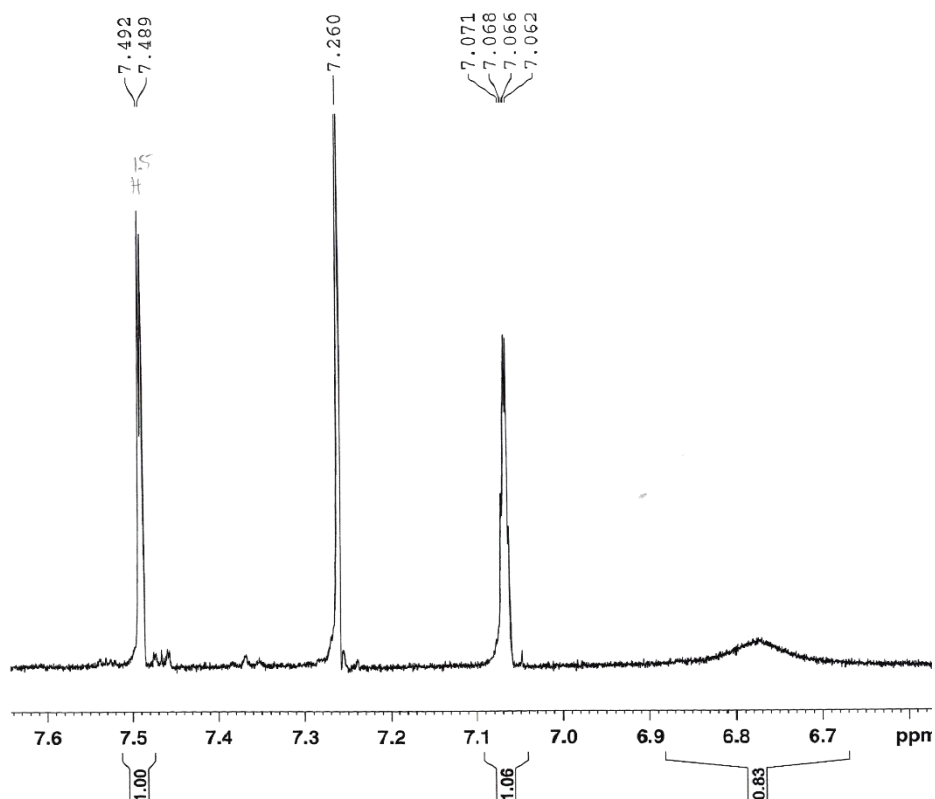
Figure S93 IR spectrum of compound 21



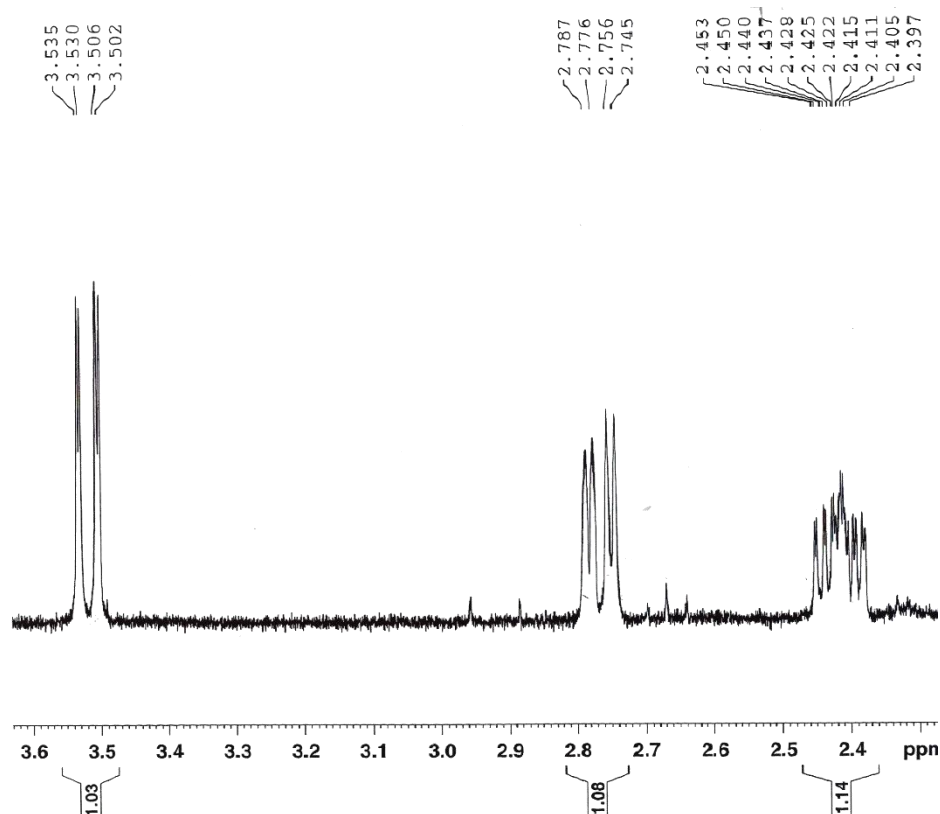
**Figure S94**  $^1\text{H}$  NMR spectrum of compound **21** (500MHz,  $\text{CDCl}_3$ )



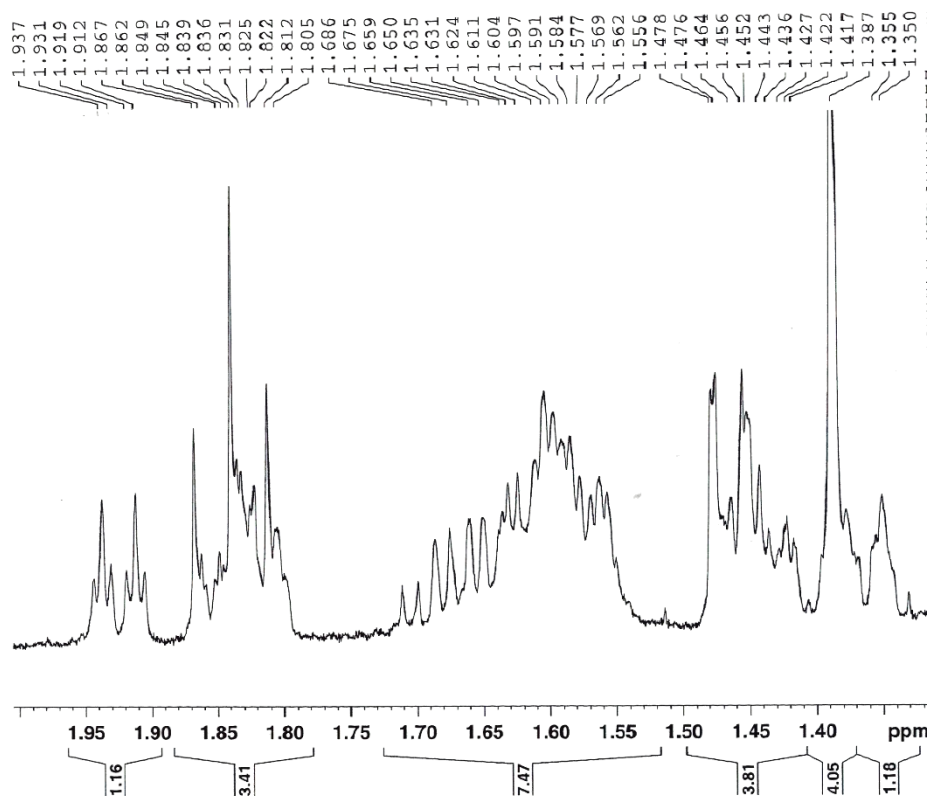
**Figure S95**  $^1\text{H}$  NMR spectrum of **21** (peak-picked and integration tagged; 500 MHz,  $\text{CDCl}_3$ )



**Figure S96**  $^1\text{H}$  NMR spectrum of **21** (expanding 7.60-6.70 ppm; 500 MHz,  $\text{CDCl}_3$ )

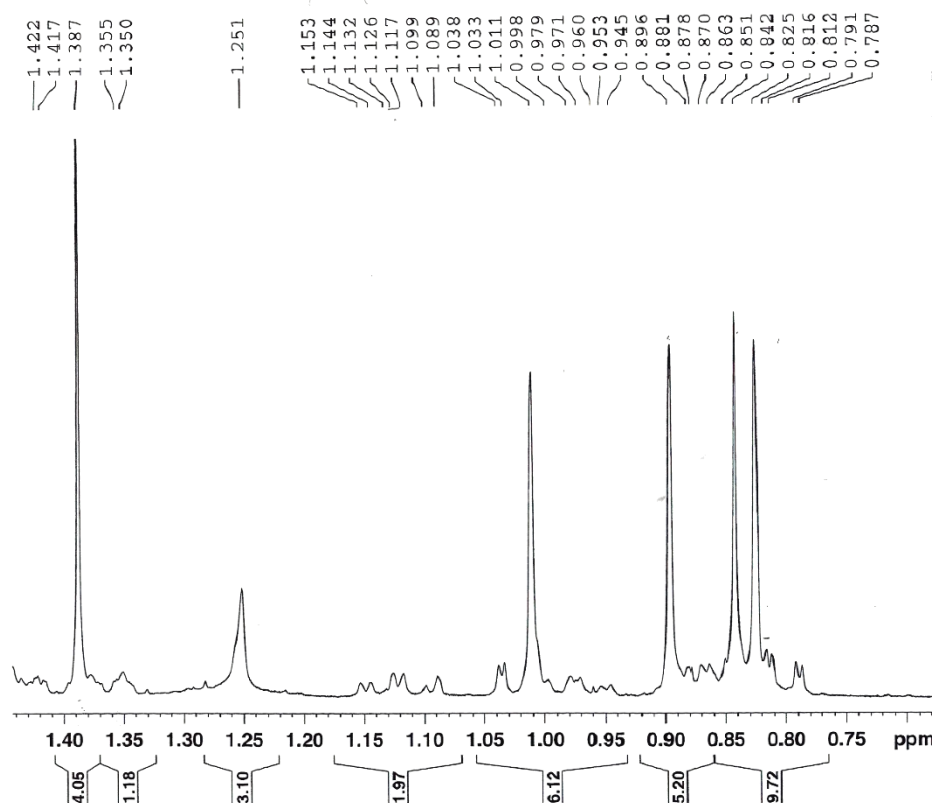


**Figure S97**  $^1\text{H}$  NMR spectrum of **21** (expanding 3.60-2.30 ppm; 500 MHz,  $\text{CDCl}_3$ )

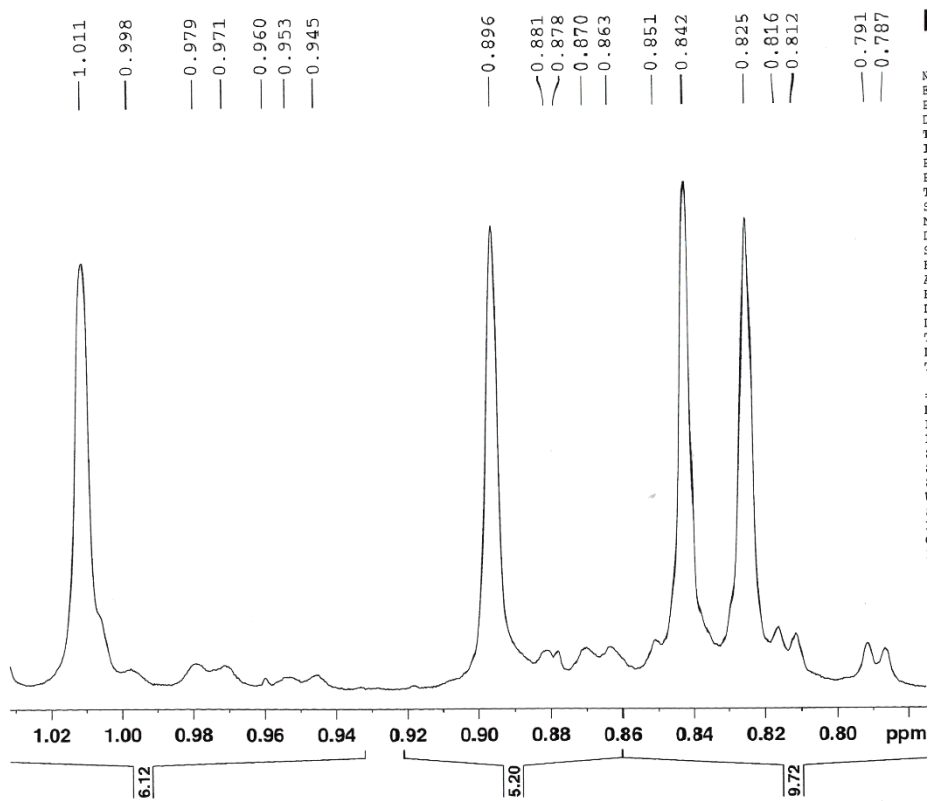


**Figure S98**  $^1\text{H}$  NMR spectrum of **21** (expanding 1.95-1.35 ppm; 500 MHz,  $\text{CDCl}_3$ )

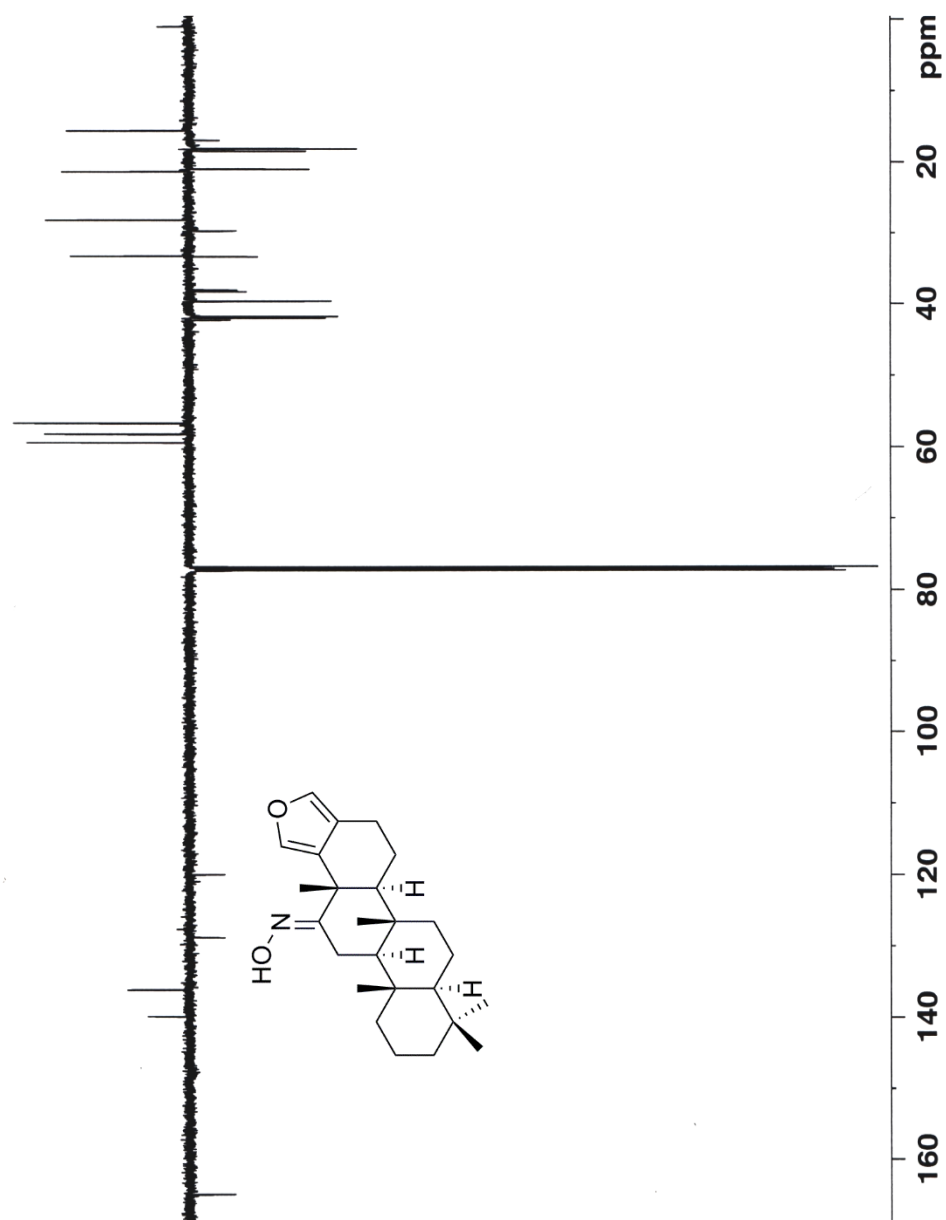




**Figure S99**  $^1\text{H}$  NMR spectrum of **21** (expanding 1.45-0.70 ppm; 500 MHz,  $\text{CDCl}_3$ )



**Figure S100**  $^1\text{H}$  NMR spectrum of **21** (expanding 1.02-0.78 ppm; 500 MHz,  $\text{CDCl}_3$ )



**Figure S101** APT spectrum of compound **21**(125MHz, CDCl<sub>3</sub>)

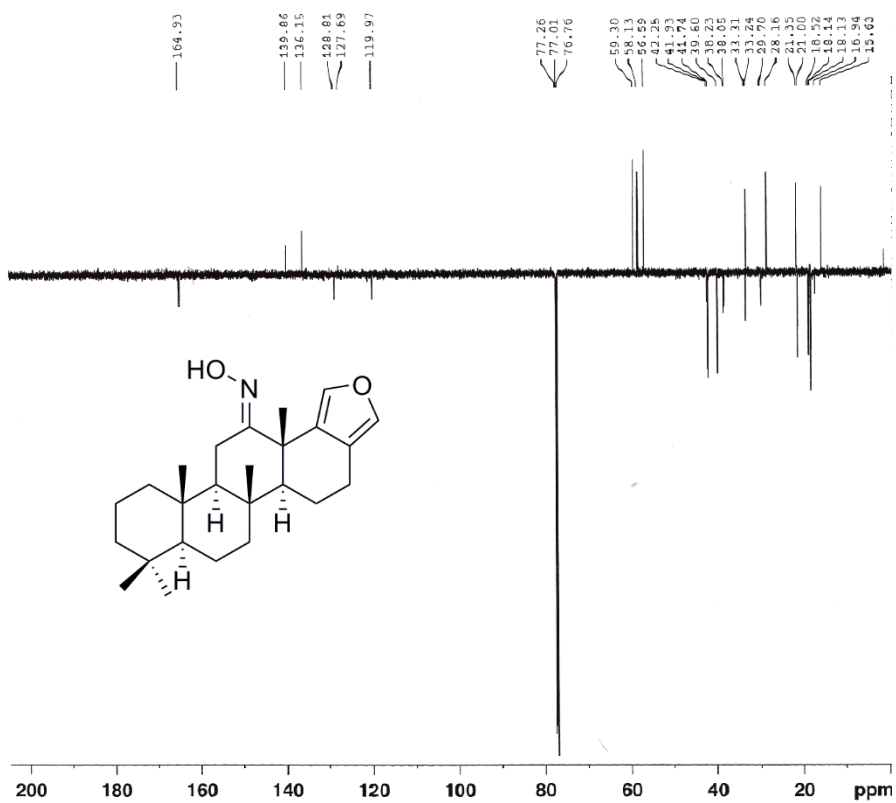


Figure S102 APT spectrum of **21** (125 MHz, CDCl<sub>3</sub>)

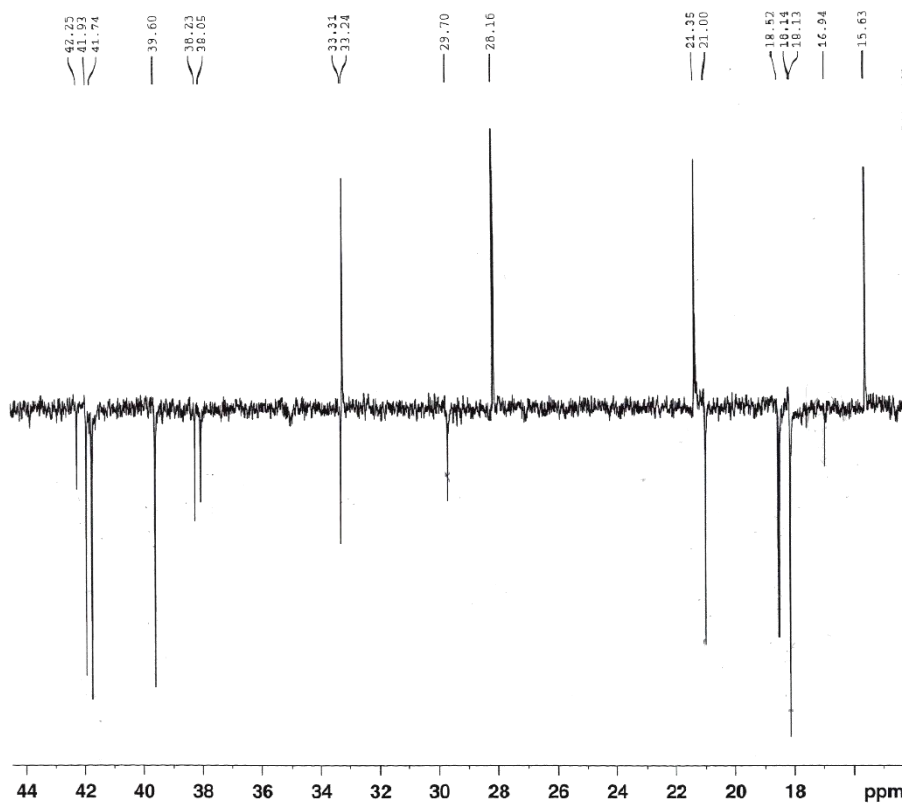
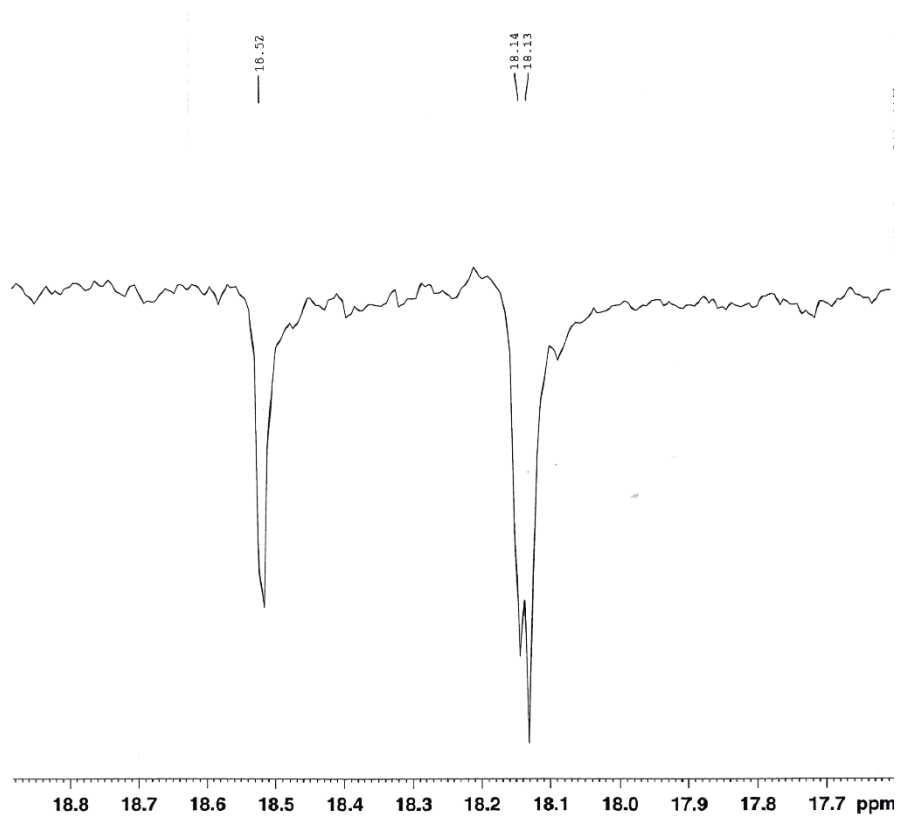
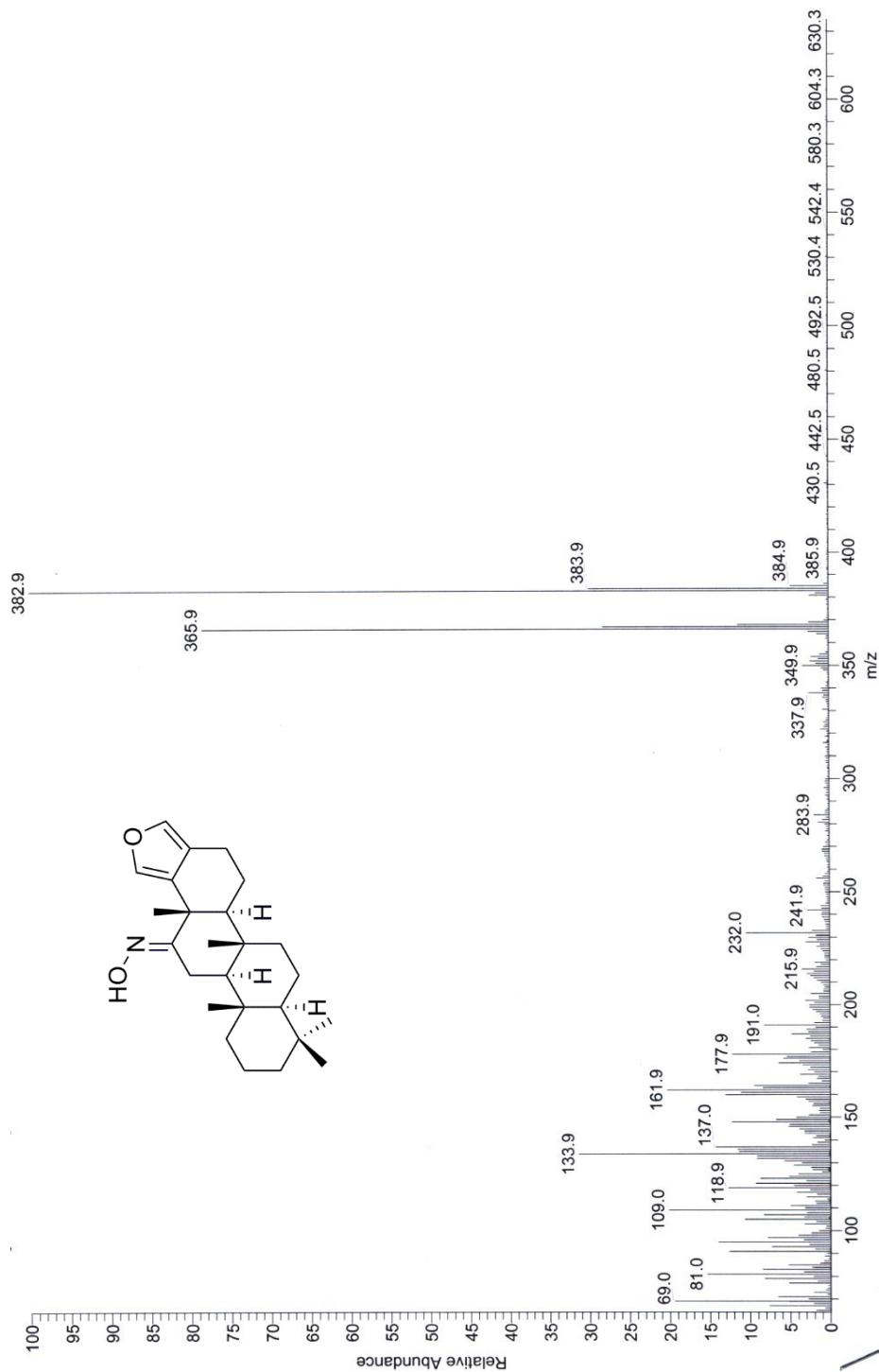


Figure S103 APT spectrum of **21** (expanding 44-16 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S104** APT spectrum of **21** (expanding 18.8-17.7 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S105** EI mass spectrum of compound **21**

IR, NMR, and mass spectra of 22 (Figures S106-S118)

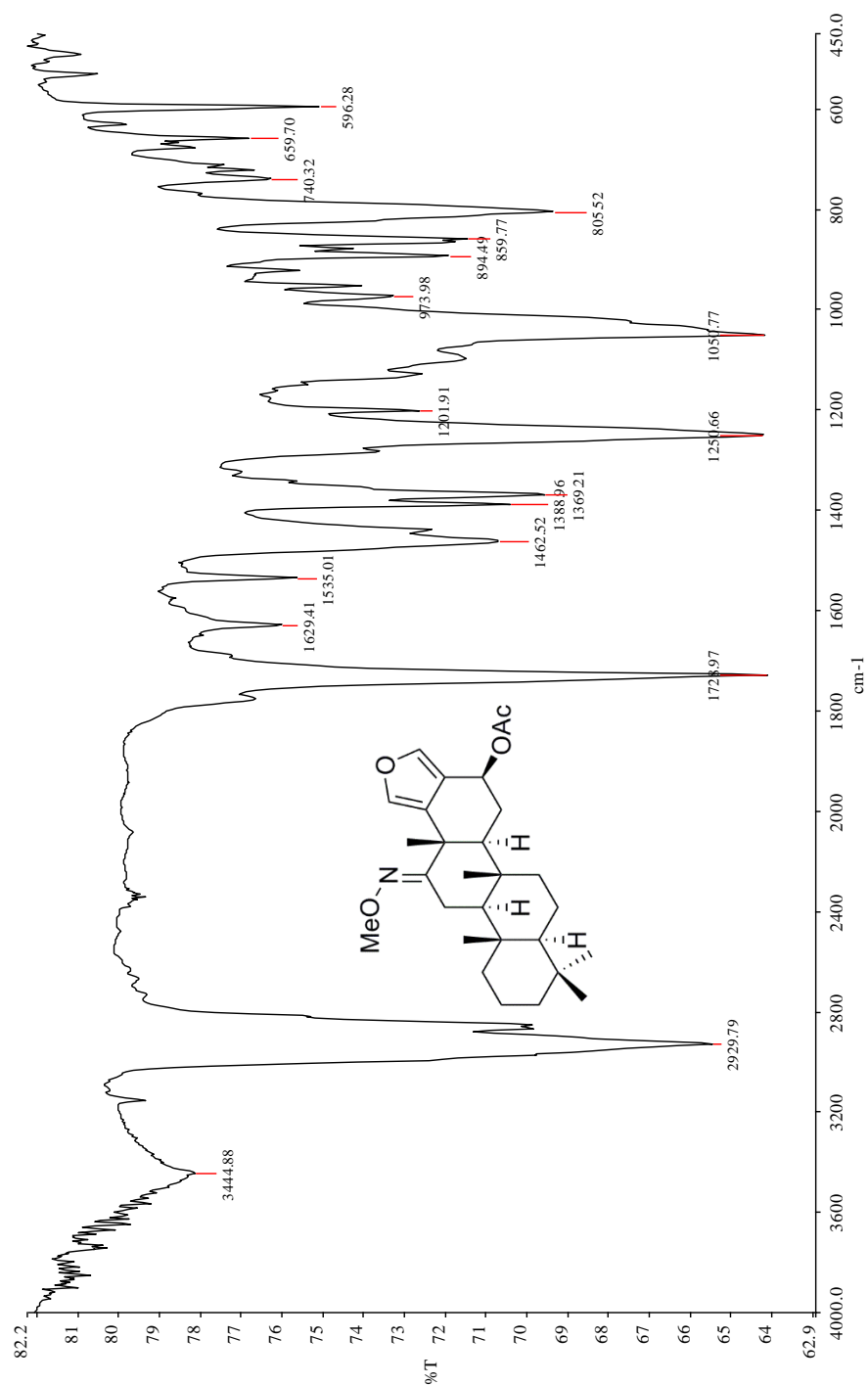
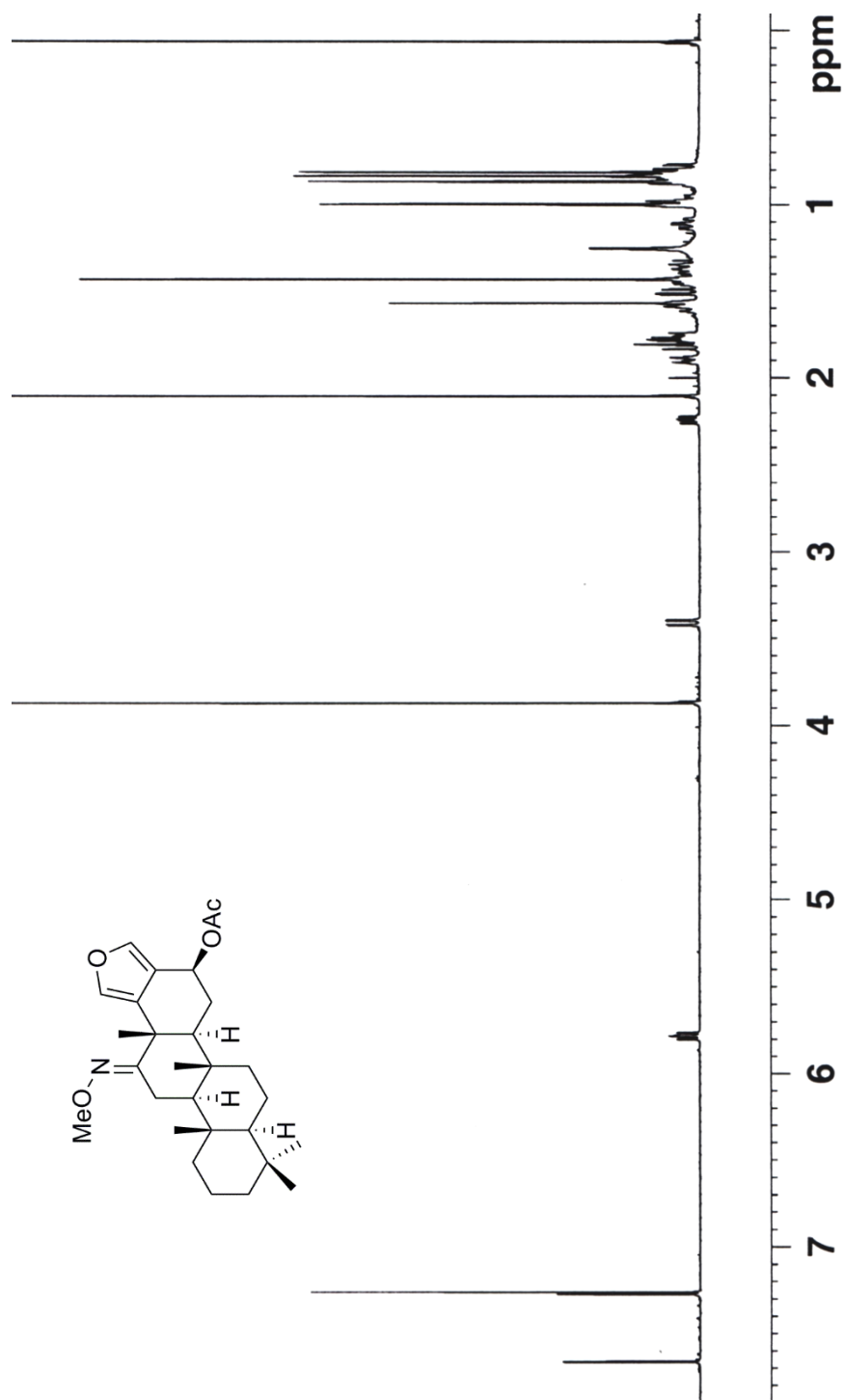
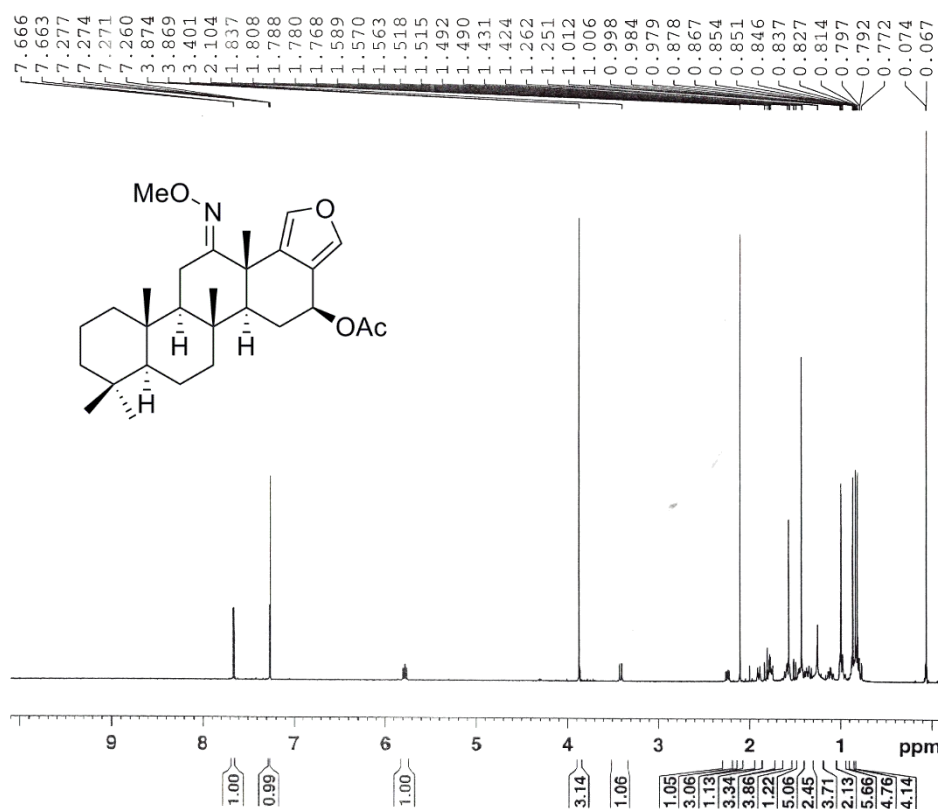


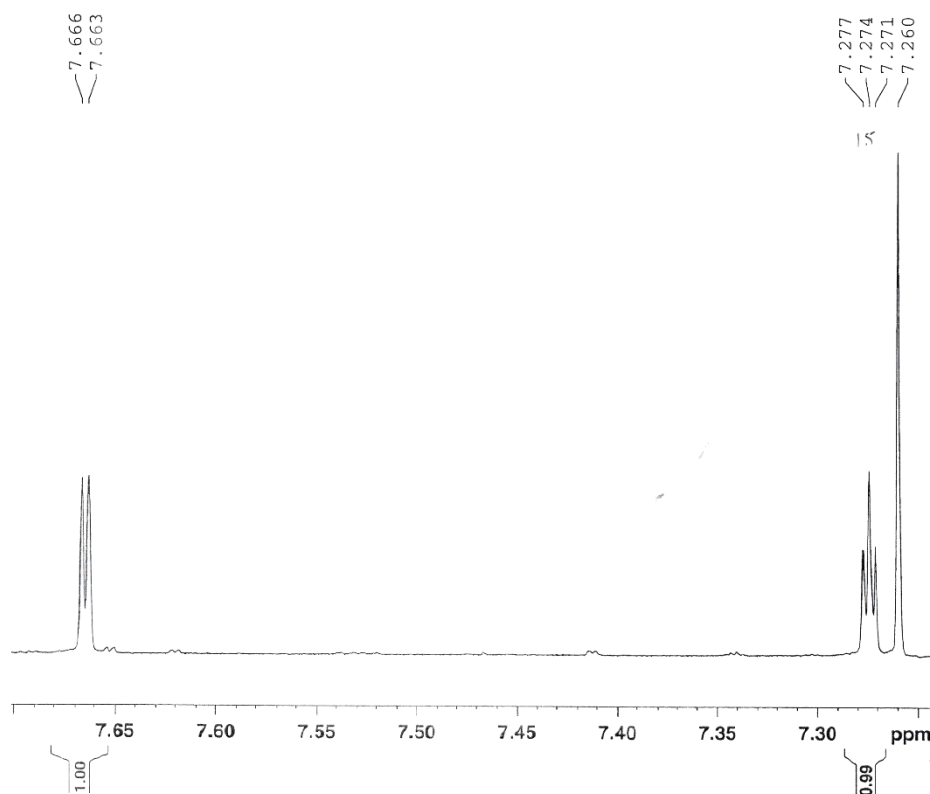
Figure S106 IR spectrum of compound 22



**Figure S107** <sup>1</sup>H NMR spectrum of compound **22** (500MHz, CDCl<sub>3</sub>)

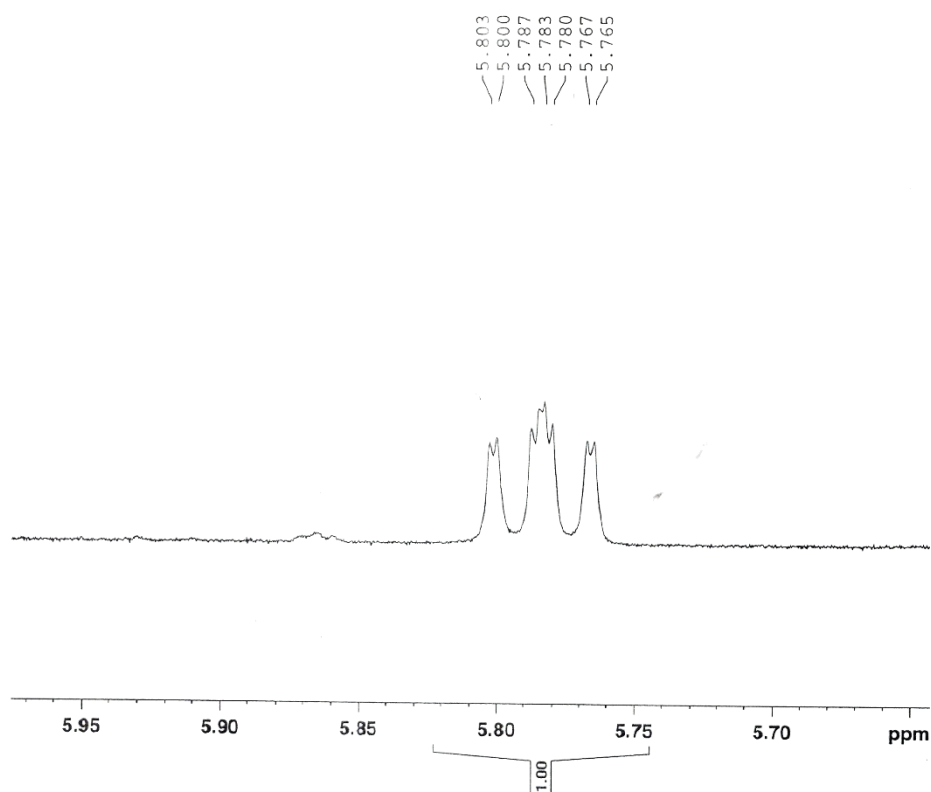


**Figure S108** <sup>1</sup>H NMR spectrum of **22**  
(peak-picked and integration tagged; 500 MHz, CDCl<sub>3</sub>)

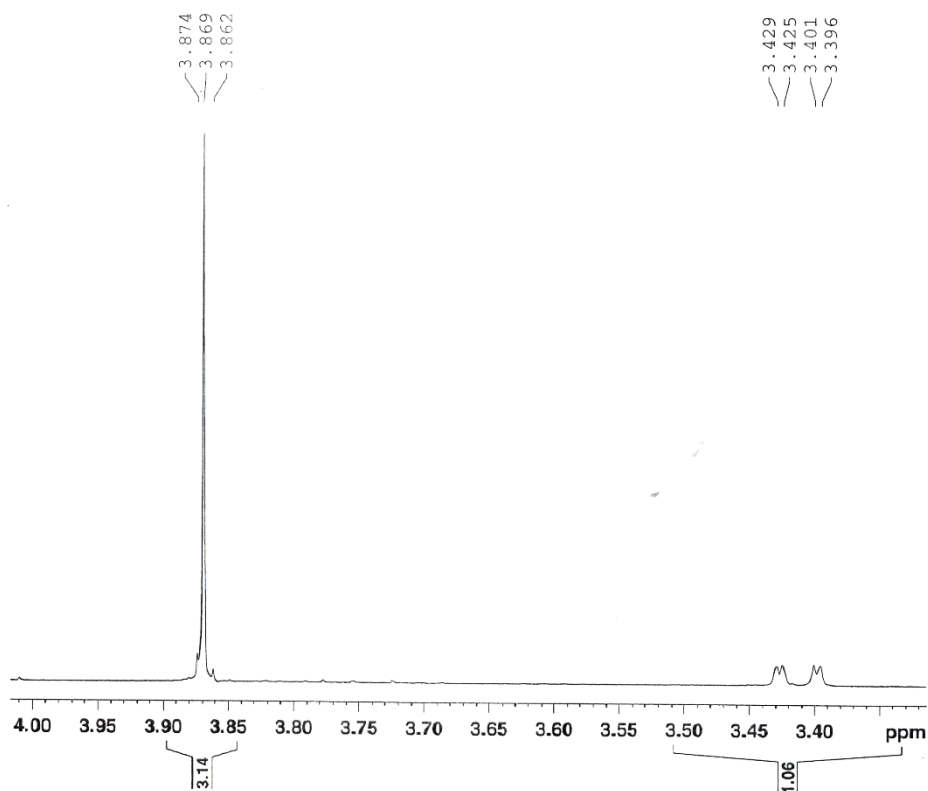


**Figure S109** <sup>1</sup>H NMR spectrum of **22** (expanding 7.70-7.25 ppm; 500 MHz, CDCl<sub>3</sub>)

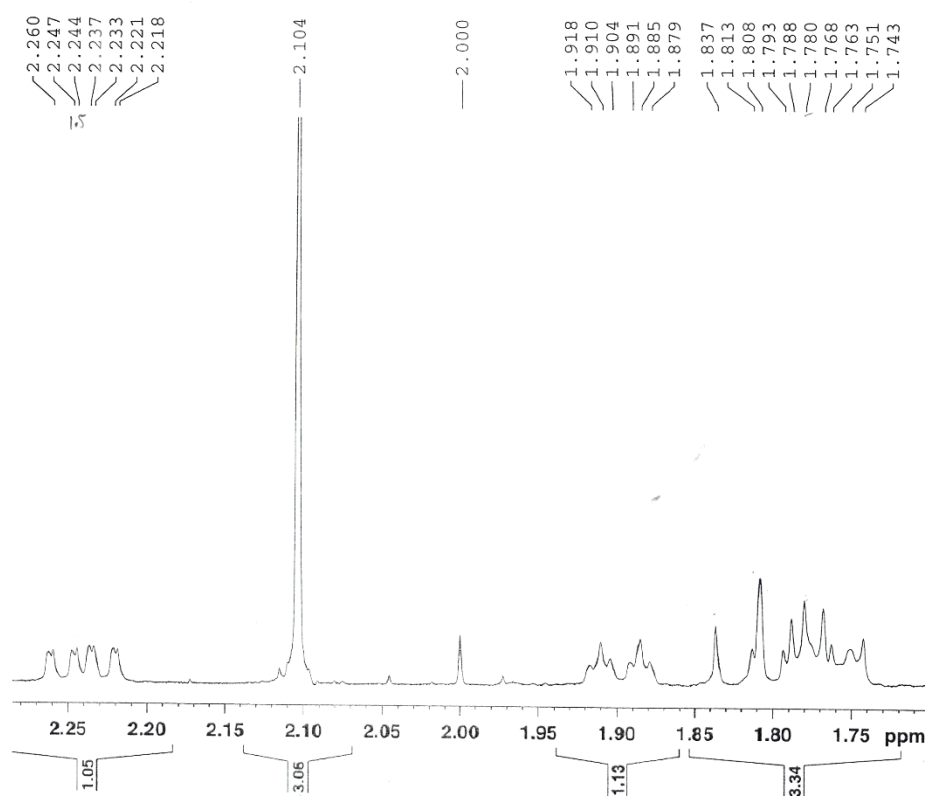




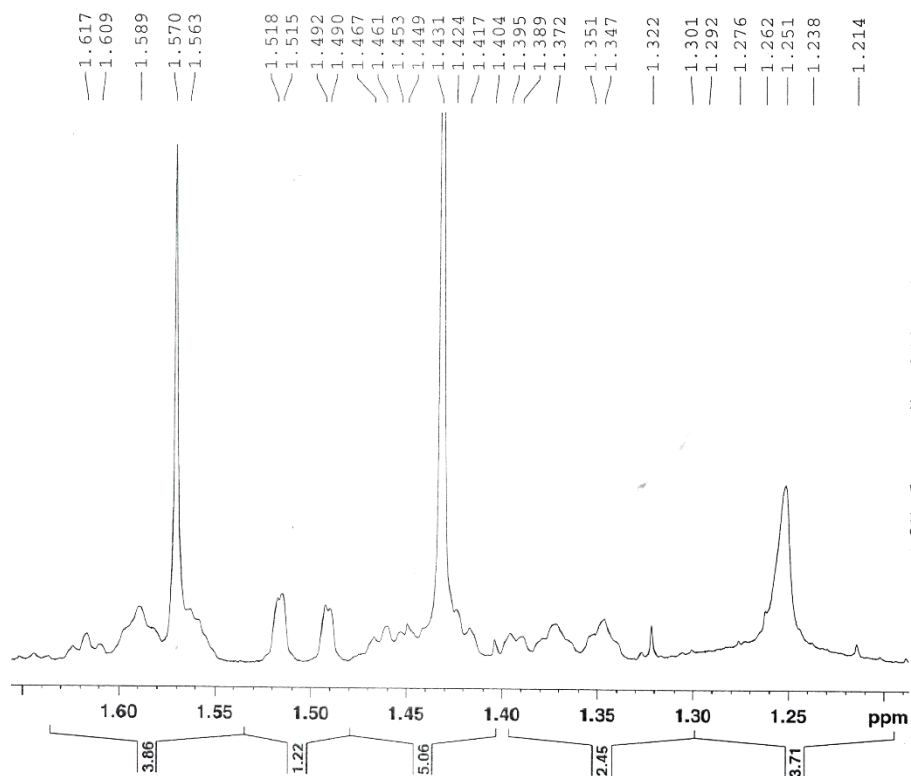
**Figure S110**  $^1\text{H}$  NMR spectrum of **22** (expanding 5.95-5.65 ppm; 500 MHz,  $\text{CDCl}_3$ )



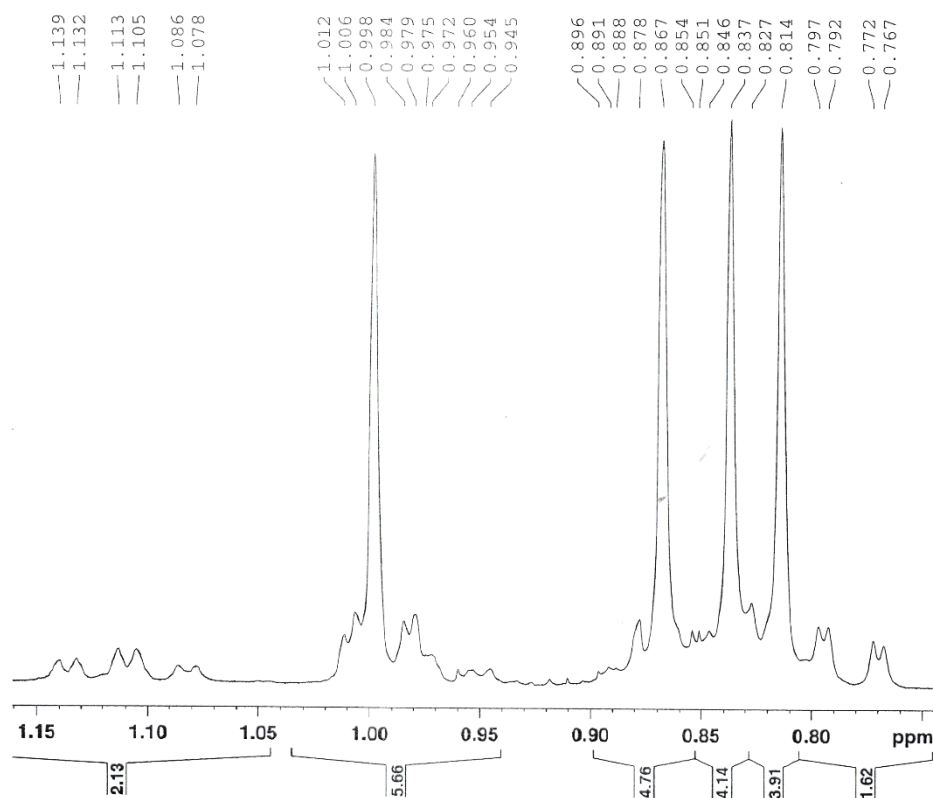
**Figure S111**  $^1\text{H}$  NMR spectrum of **22** (expanding 4.00-3.35 ppm; 500 MHz,  $\text{CDCl}_3$ )



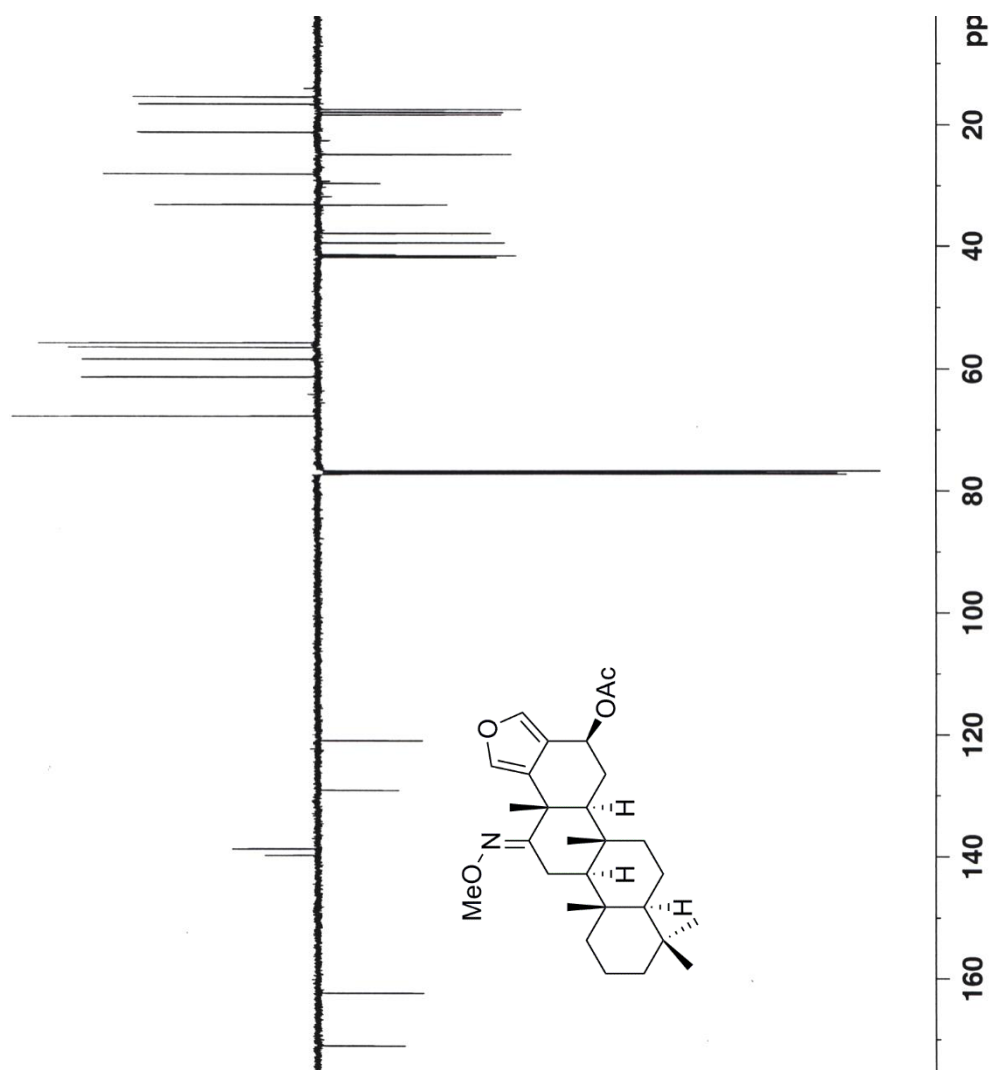
**Figure S112** <sup>1</sup>H NMR spectrum of **22** (expanding 2.25-1.75 ppm; 500 MHz, CDCl<sub>3</sub>)



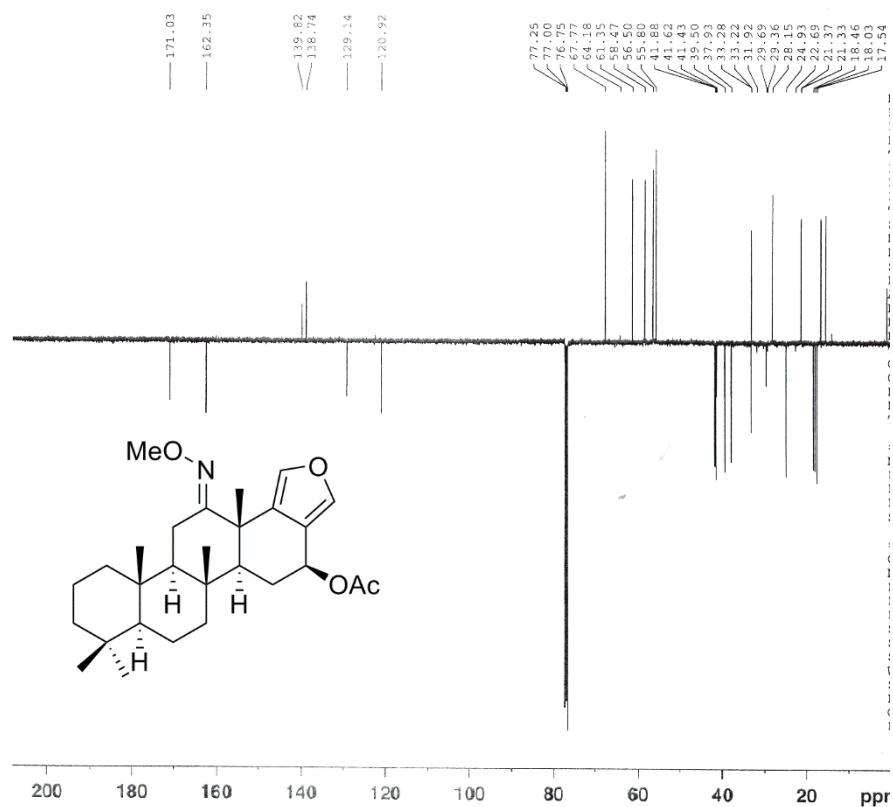
**Figure S113** <sup>1</sup>H NMR spectrum of **22** (expanding 1.65-1.20 ppm; 500 MHz, CDCl<sub>3</sub>)



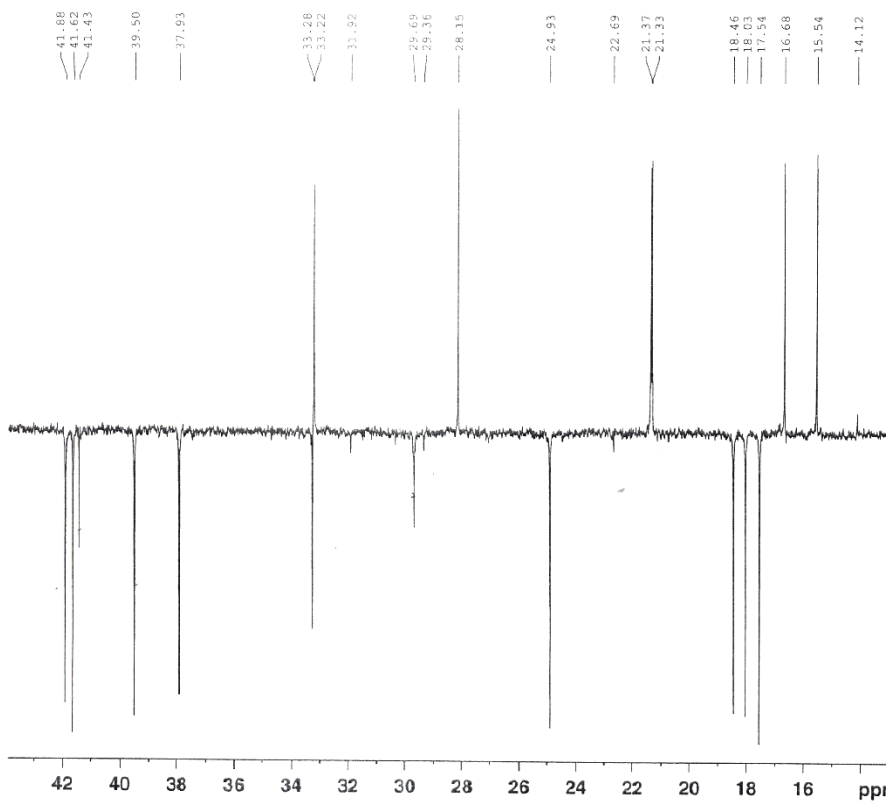
**Figure S114**  $^1\text{H}$  NMR spectrum of **22** (expanding 1.15-0.75 ppm; 500 MHz,  $\text{CDCl}_3$ )



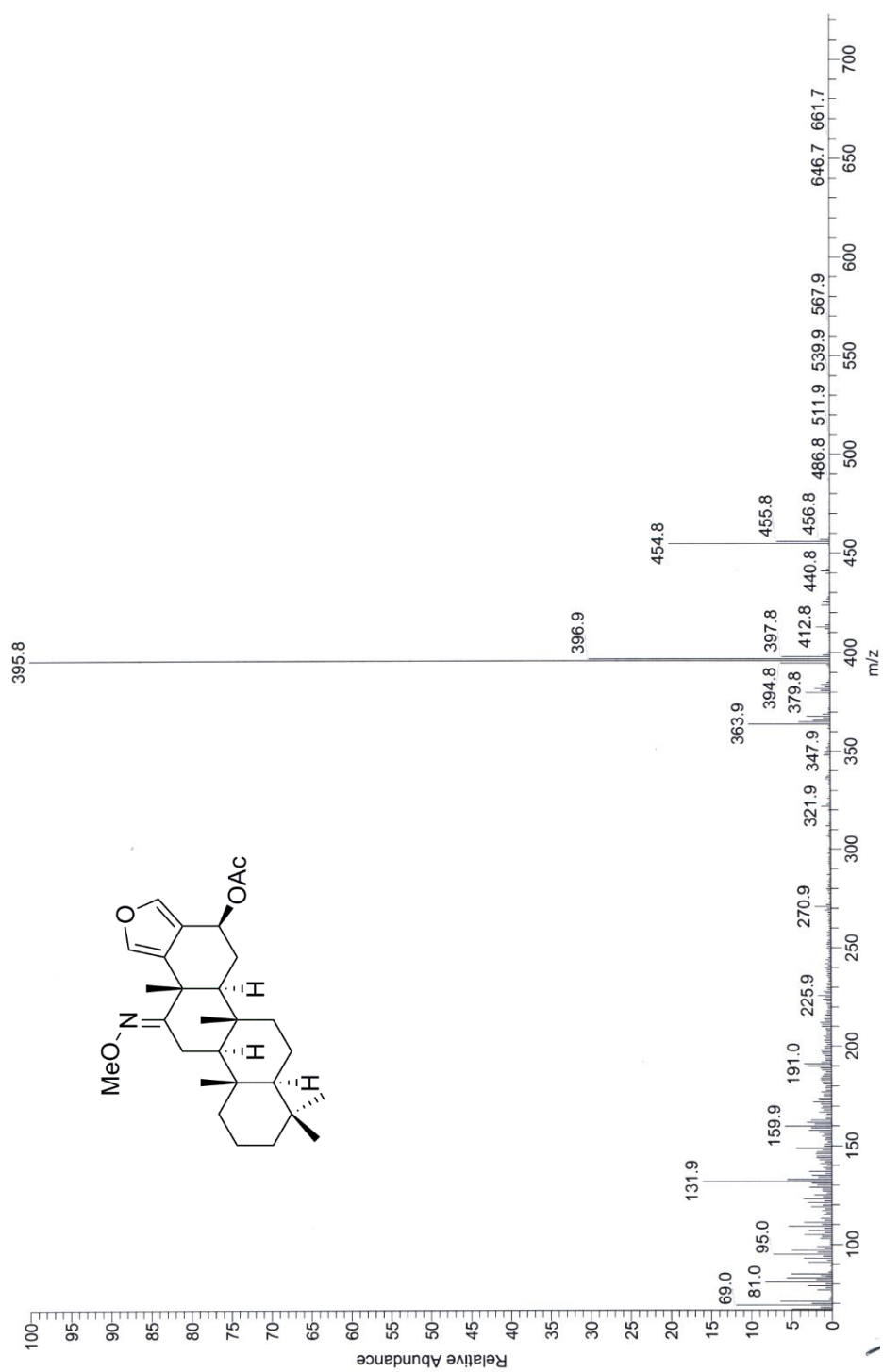
**Figure S115** APT spectrum of compound **22** (125MHz, CDCl<sub>3</sub>)



**Figure S116** APT spectrum of **22** (peak picking tagged; 125 MHz, CDCl<sub>3</sub>)



**Figure S117** APT spectrum of **22** (expanding 44-14 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S118** EI mass spectrum of compound **22**

IR, NMR, and mass spectra of 23 (Figures S119-S133)

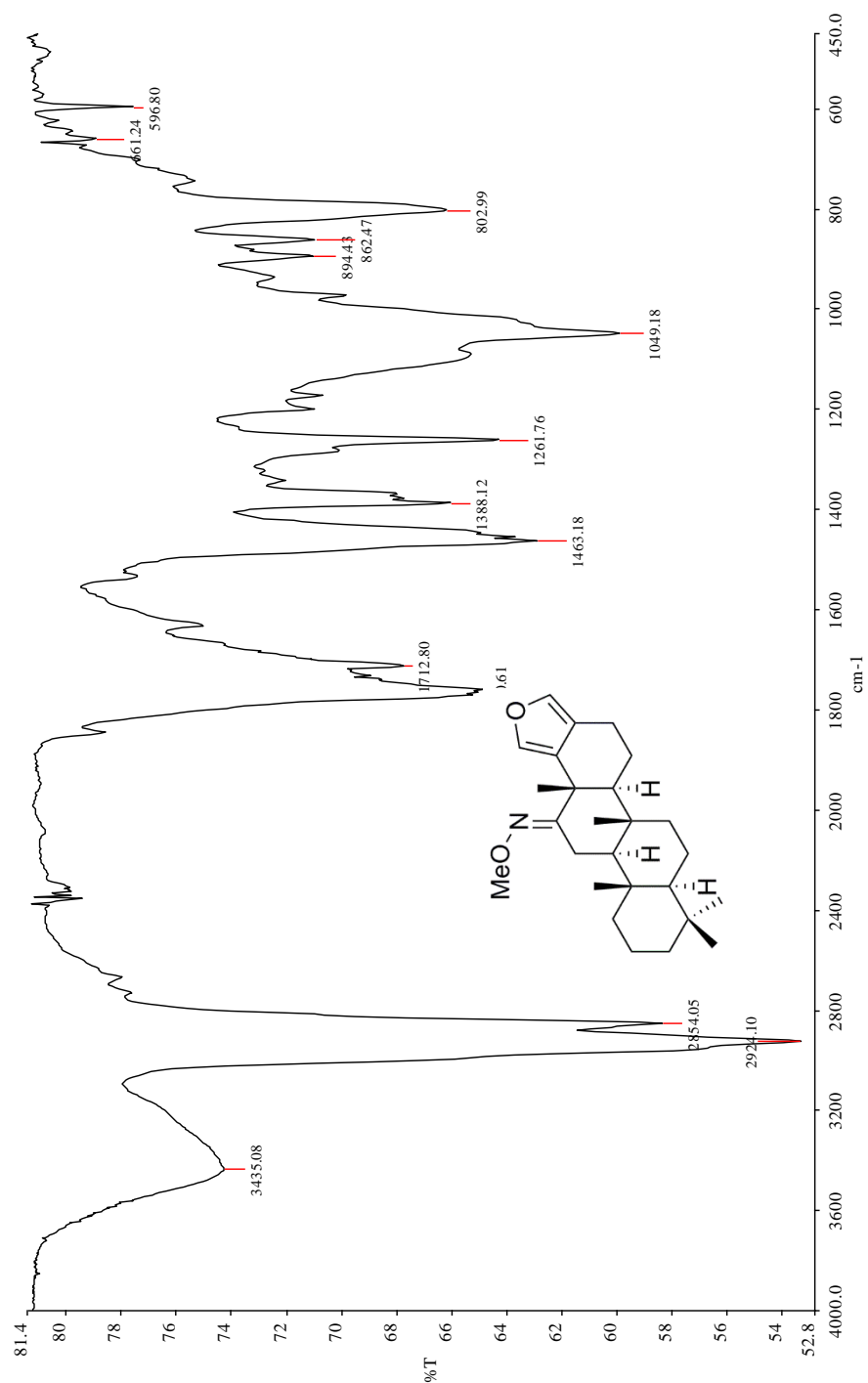
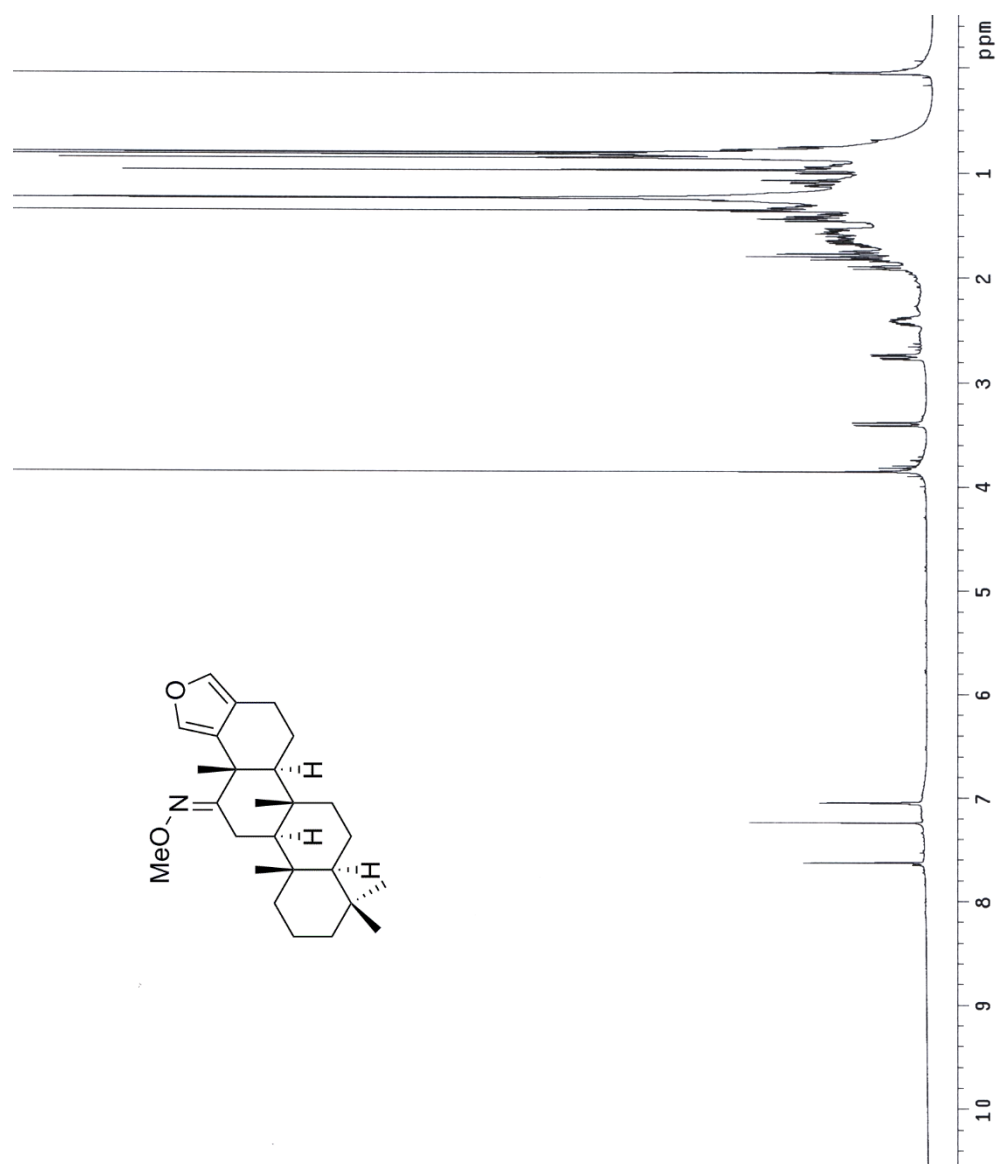
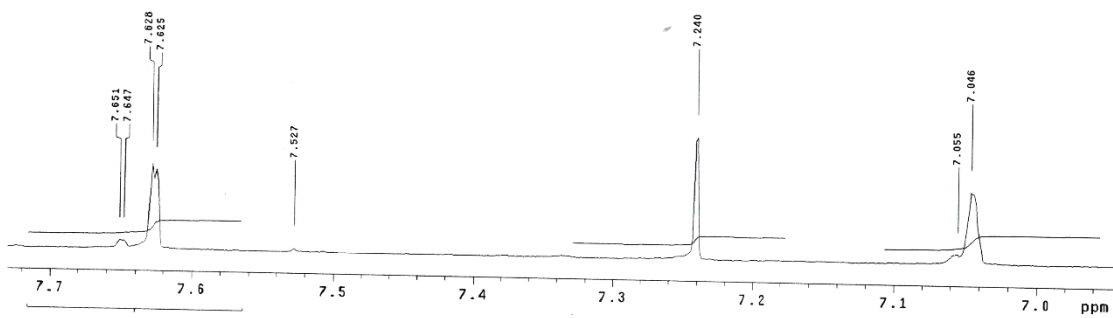
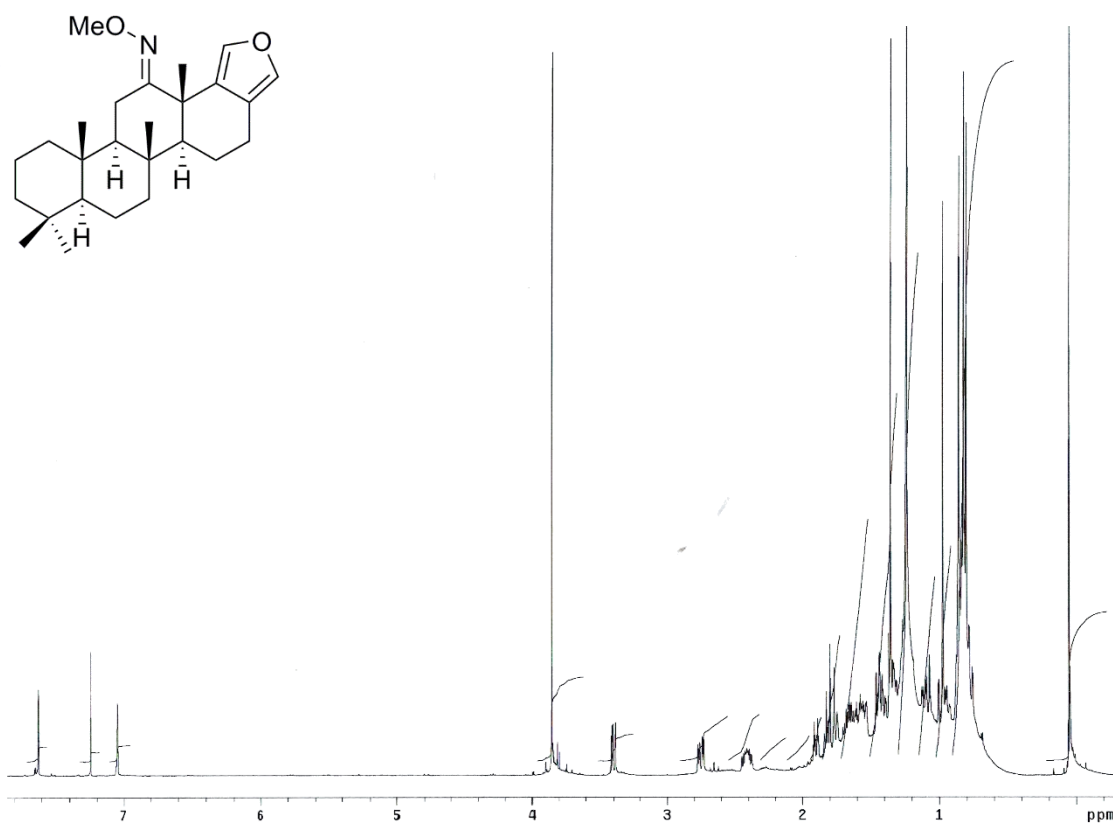


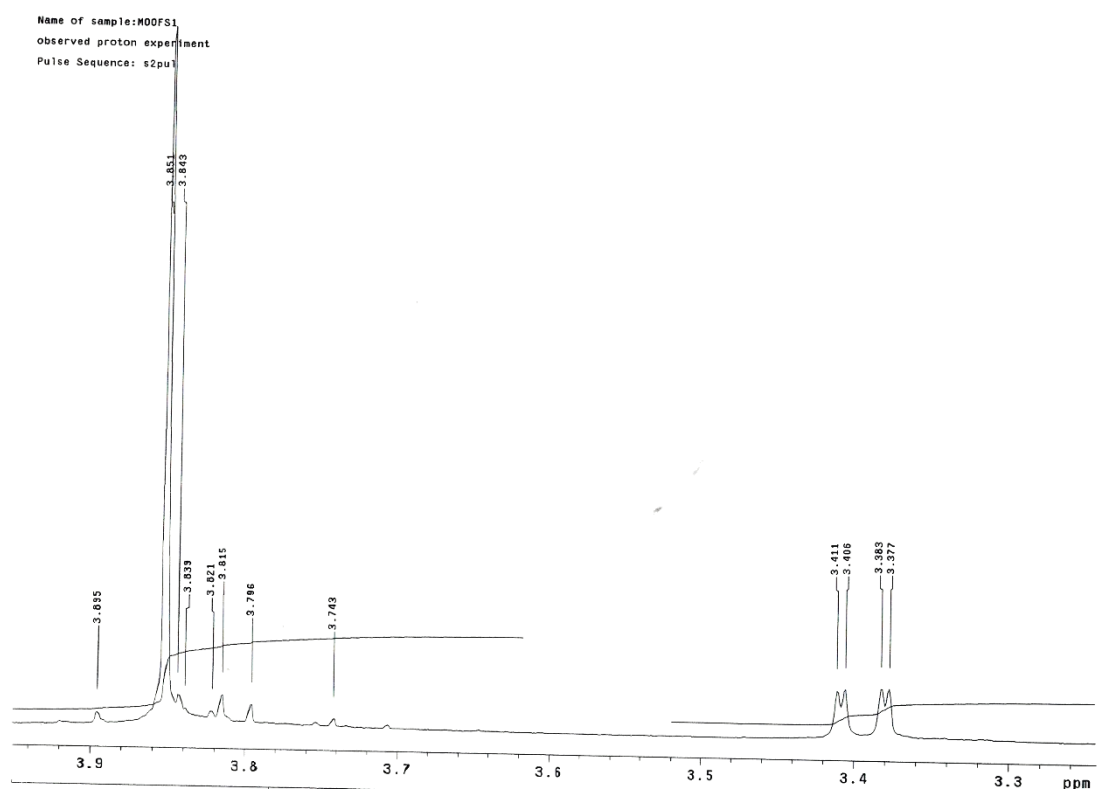
Figure S119 IR spectrum of compound 23



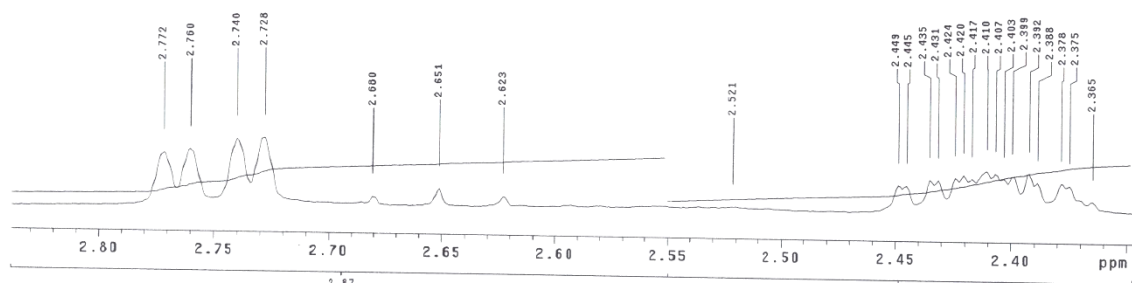
**Figure S120**  $^1\text{H}$  NMR spectrum of compound **23** (500MHz,  $\text{CDCl}_3$ )



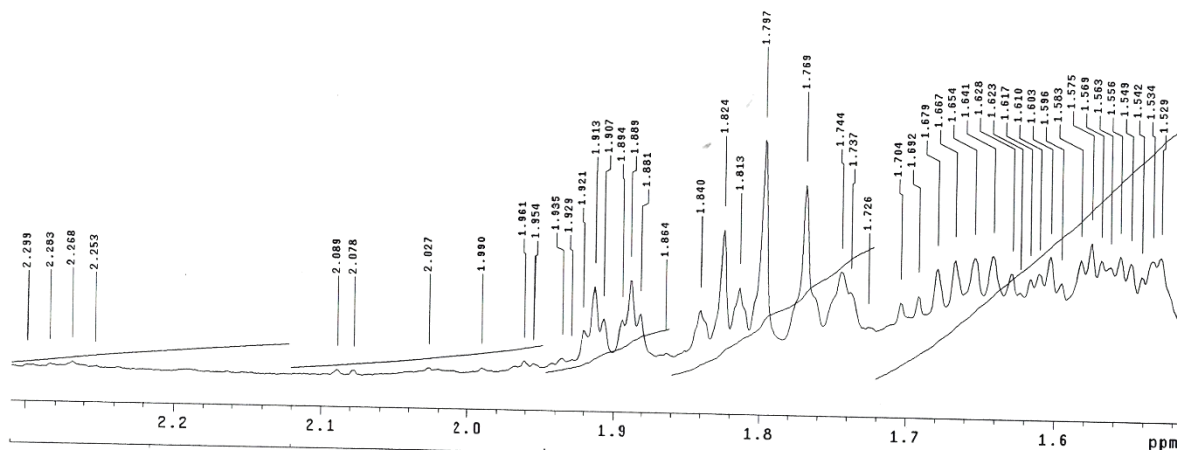




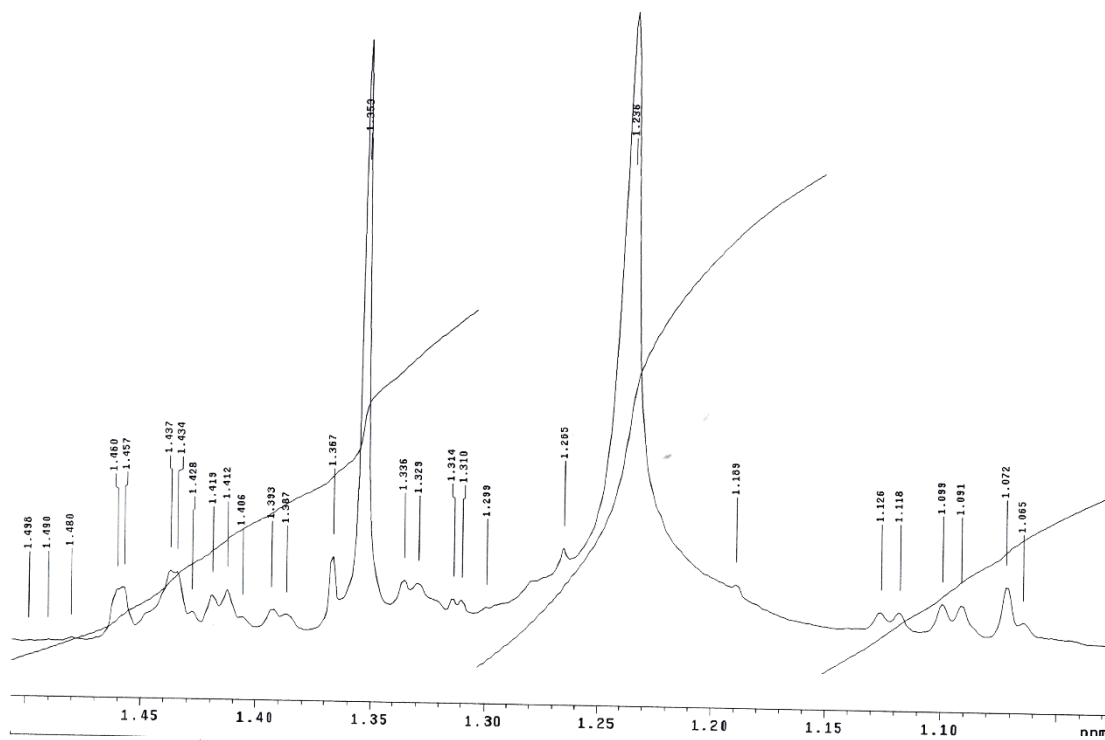
**Figure S123**  $^1\text{H}$  NMR spectrum of **23** (expanding 3.90-3.30 ppm; 500 MHz,  $\text{CDCl}_3$ )



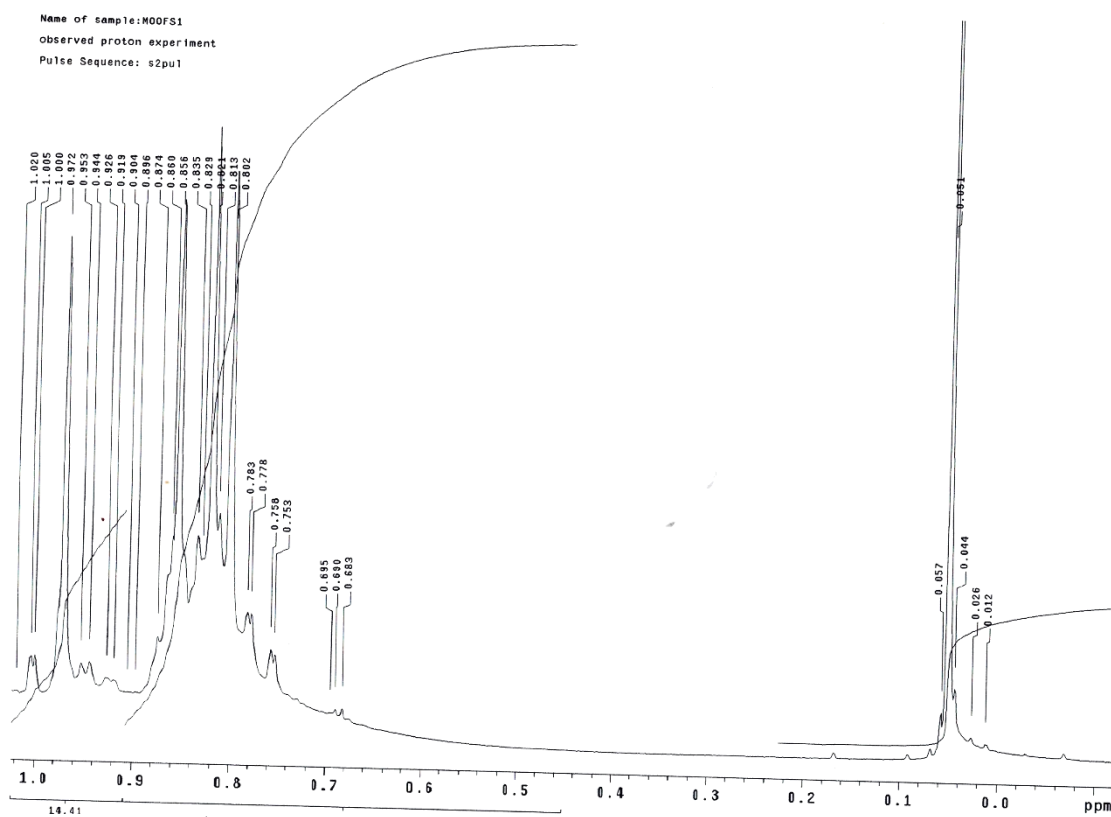
**Figure S124**  $^1\text{H}$  NMR spectrum of **23** (expanding 2.80-2.35 ppm; 500 MHz,  $\text{CDCl}_3$ )



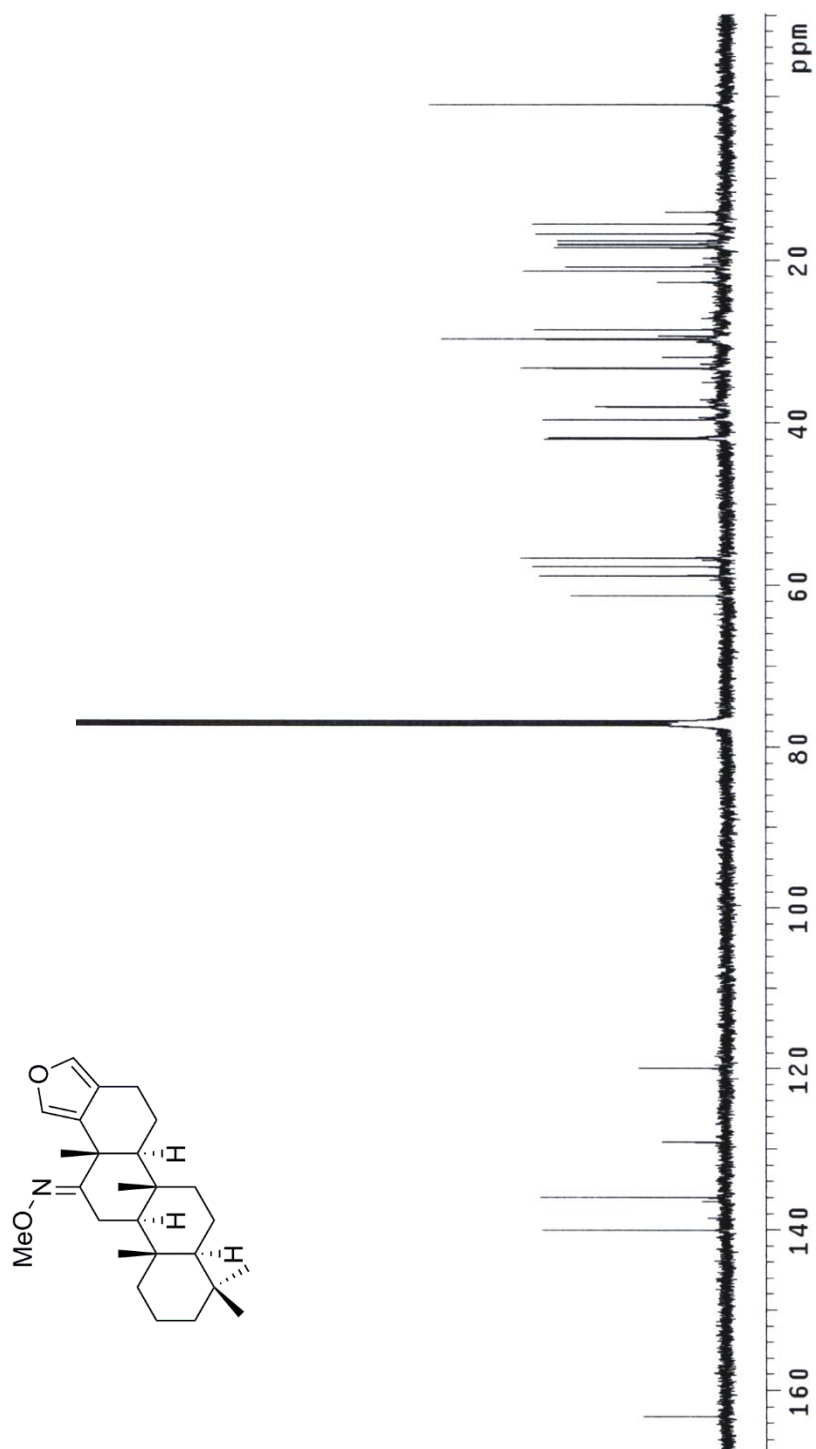
**Figure S125**  $^1\text{H}$  NMR spectrum of **23** (expanding 2.30-1.50 ppm; 500 MHz,  $\text{CDCl}_3$ )



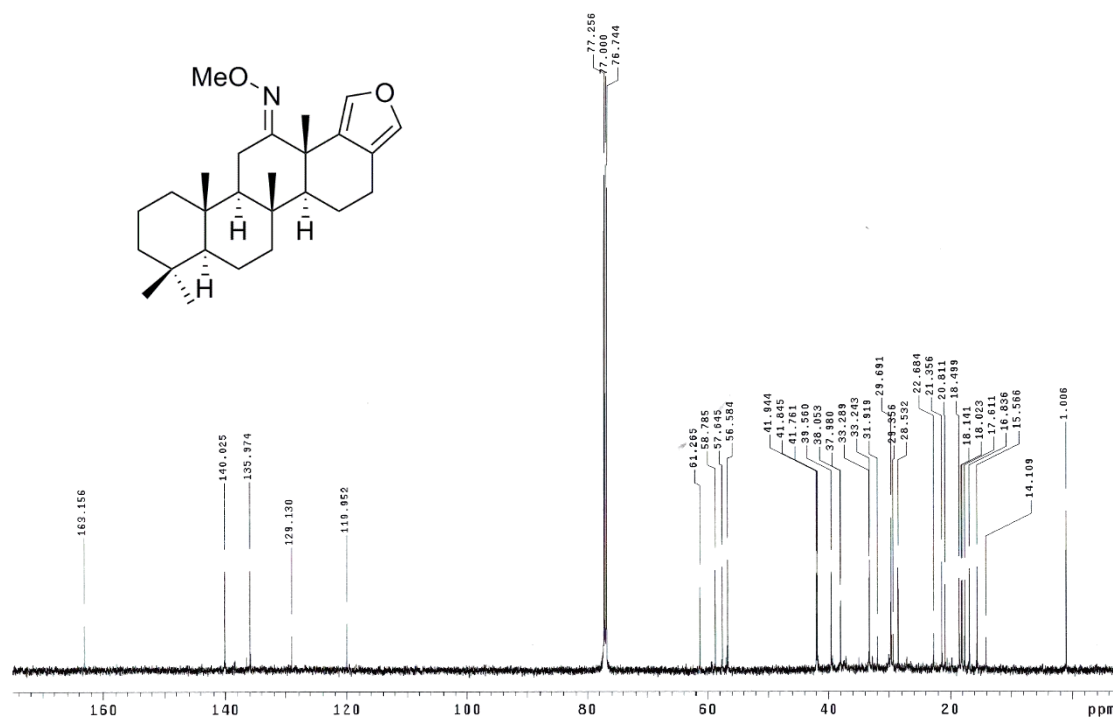
**Figure S126**  $^1\text{H}$  NMR spectrum of **23** (expanding 1.50-1.05 ppm; 500 MHz,  $\text{CDCl}_3$ )



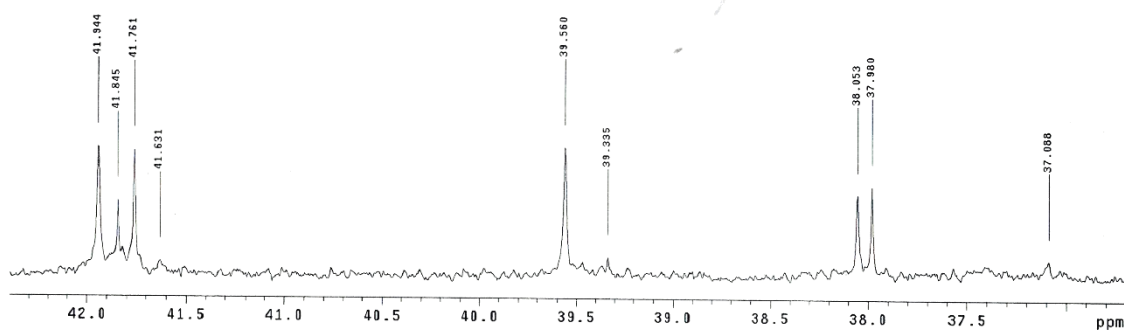
**Figure S127**  $^1\text{H}$  NMR spectrum of **23** (expanding 1.00-0.00 ppm; 500 MHz,  $\text{CDCl}_3$ )



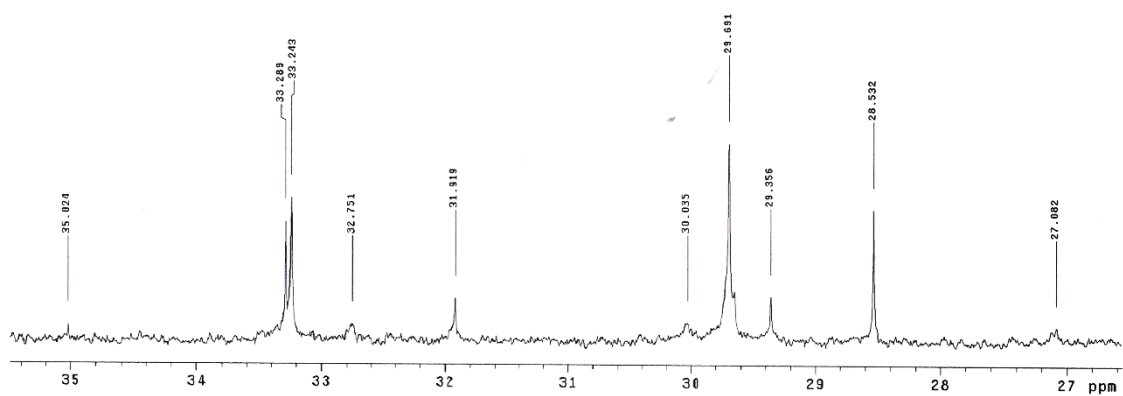
**Figure S128**  $^{13}\text{C}$  NMR spectrum of compound **23** (125MHz,  $\text{CDCl}_3$ )



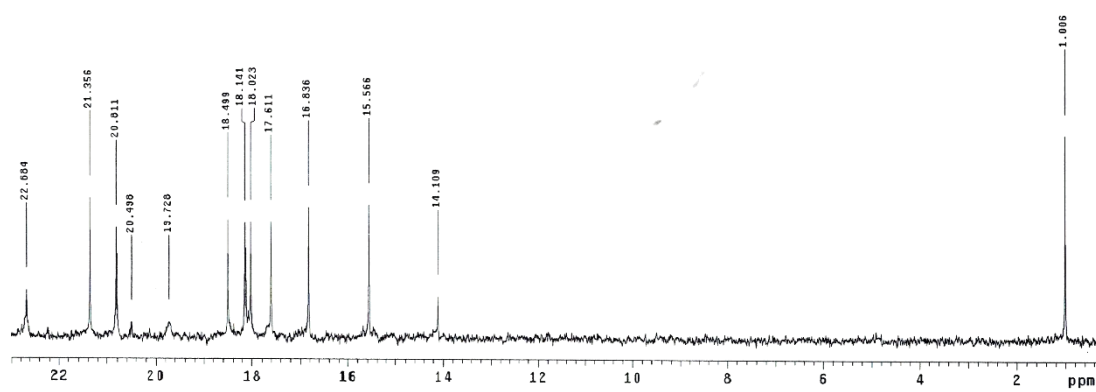
**Figure S129** <sup>13</sup>C NMR spectrum of **23** (peak picking tagged; 125 MHz, CDCl<sub>3</sub>)



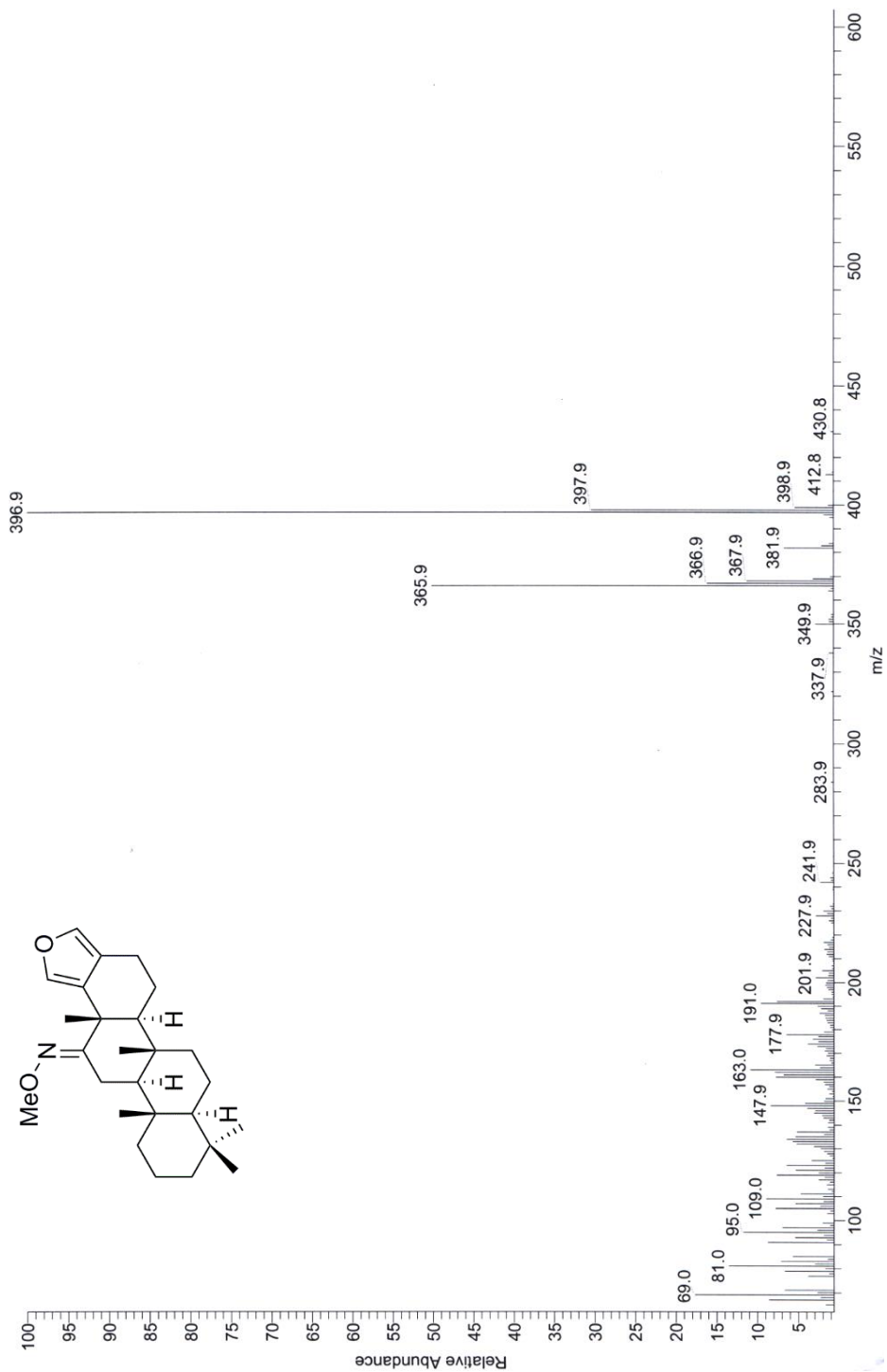
**Figure S130** <sup>13</sup>C NMR spectrum of **23** (expanding 42-37 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S131**  $^{13}\text{C}$  NMR spectrum of **23** (expanding 35-27 ppm; 125 MHz,  $\text{CDCl}_3$ )



**Figure S132**  $^{13}\text{C}$  NMR spectrum of **23** (expanding 21-0 ppm; 125 MHz,  $\text{CDCl}_3$ )



**Figure S133** EI mass spectrum of compound **23**



IR, NMR, and mass spectra of 24 (Figures S134-S144)

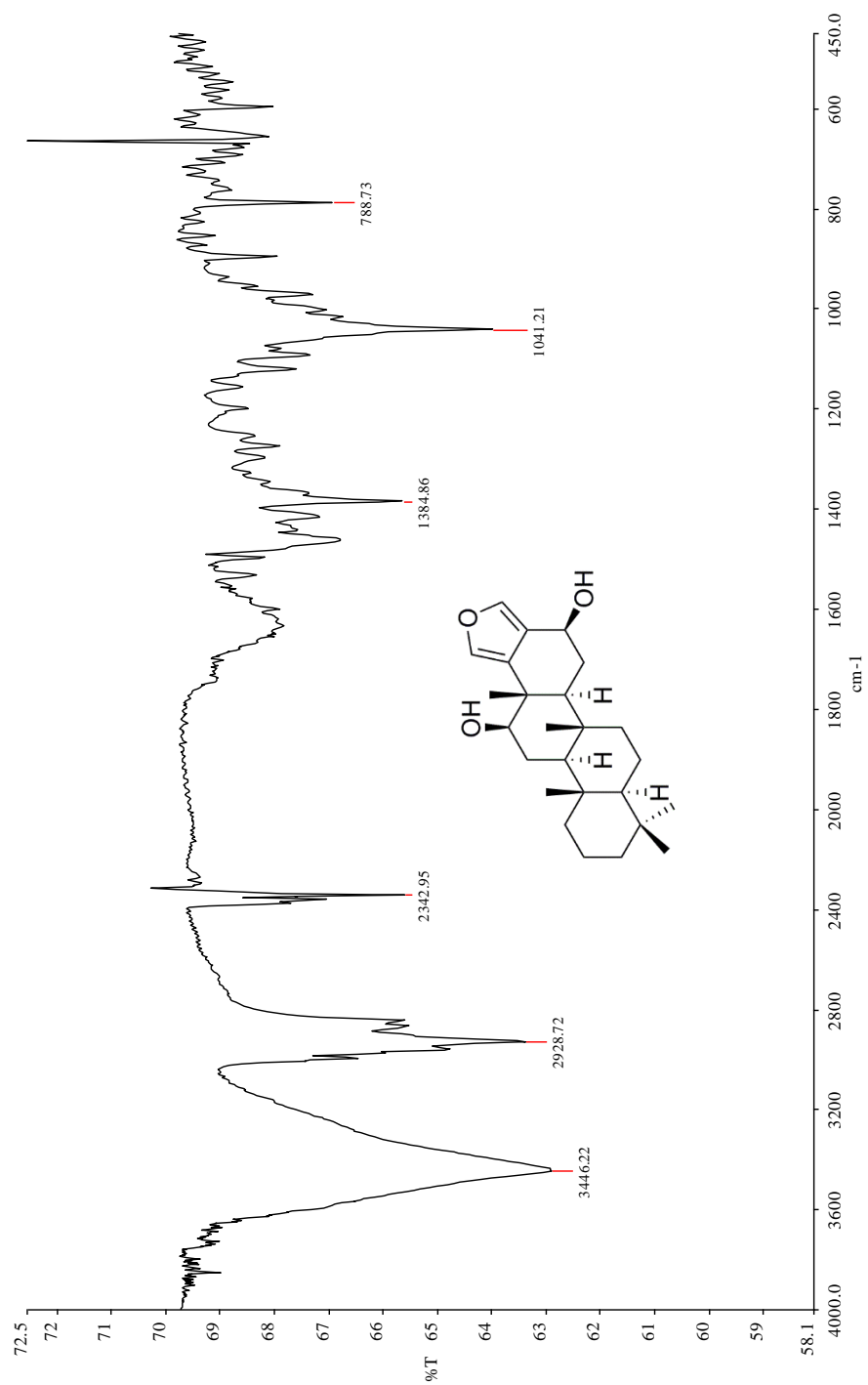
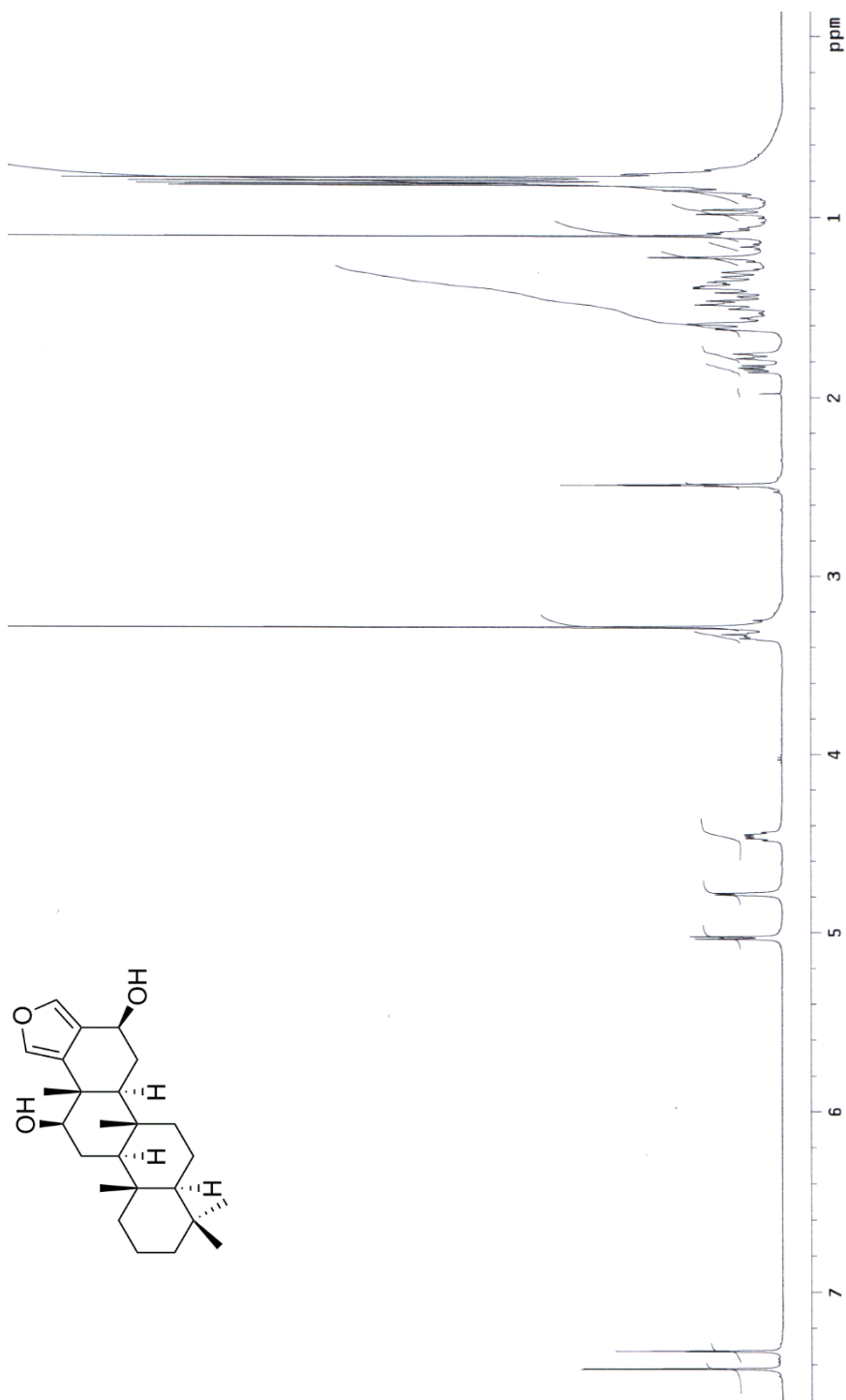
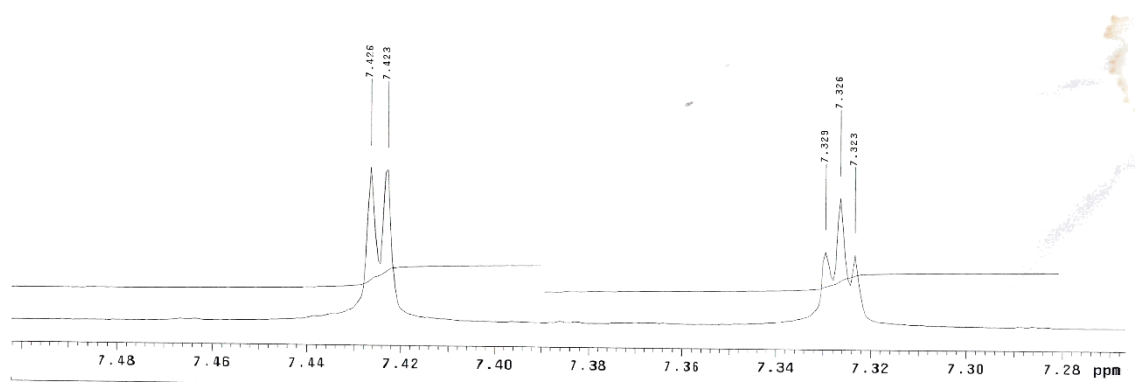
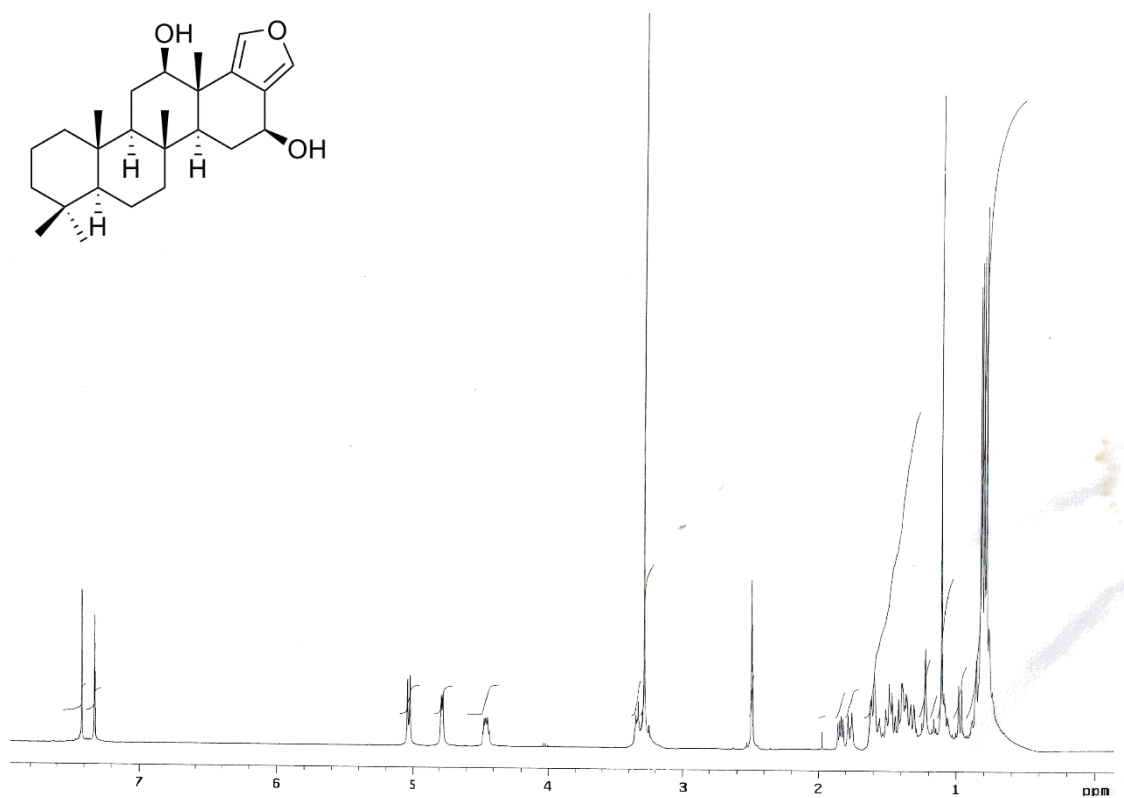
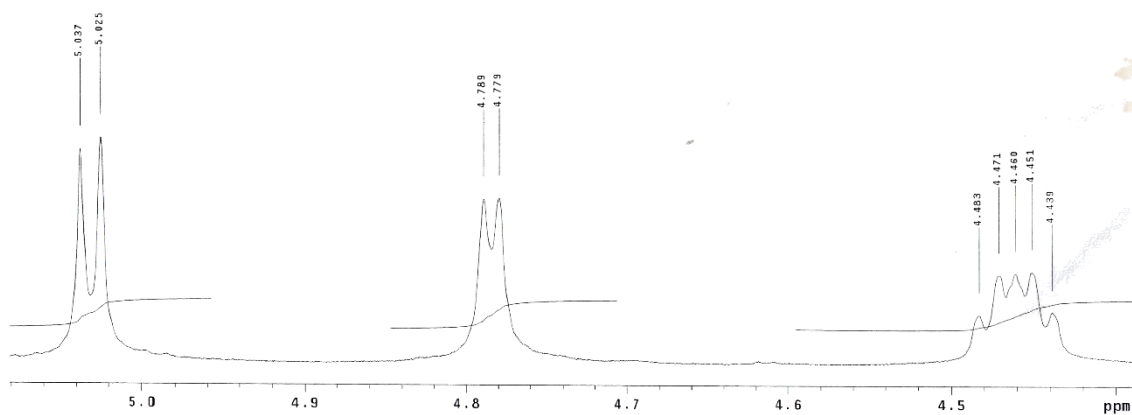


Figure S134 IR spectrum of compound 24

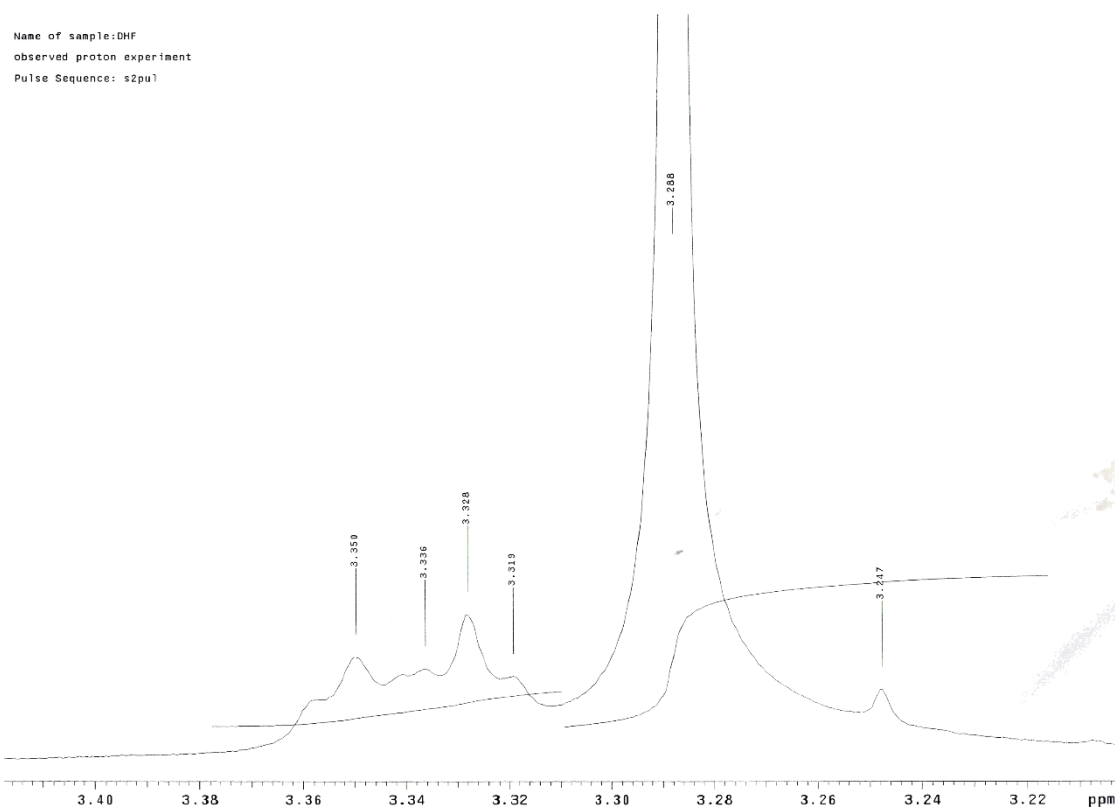


**Figure S135**  $^1\text{H}$  NMR spectrum of compound **24** (500MHz,  $\text{DMSO}-d_6$ )

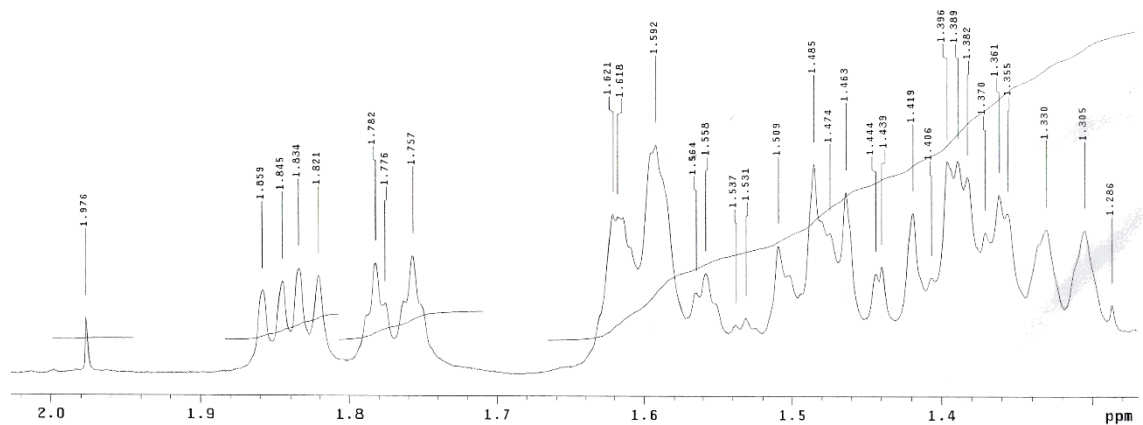




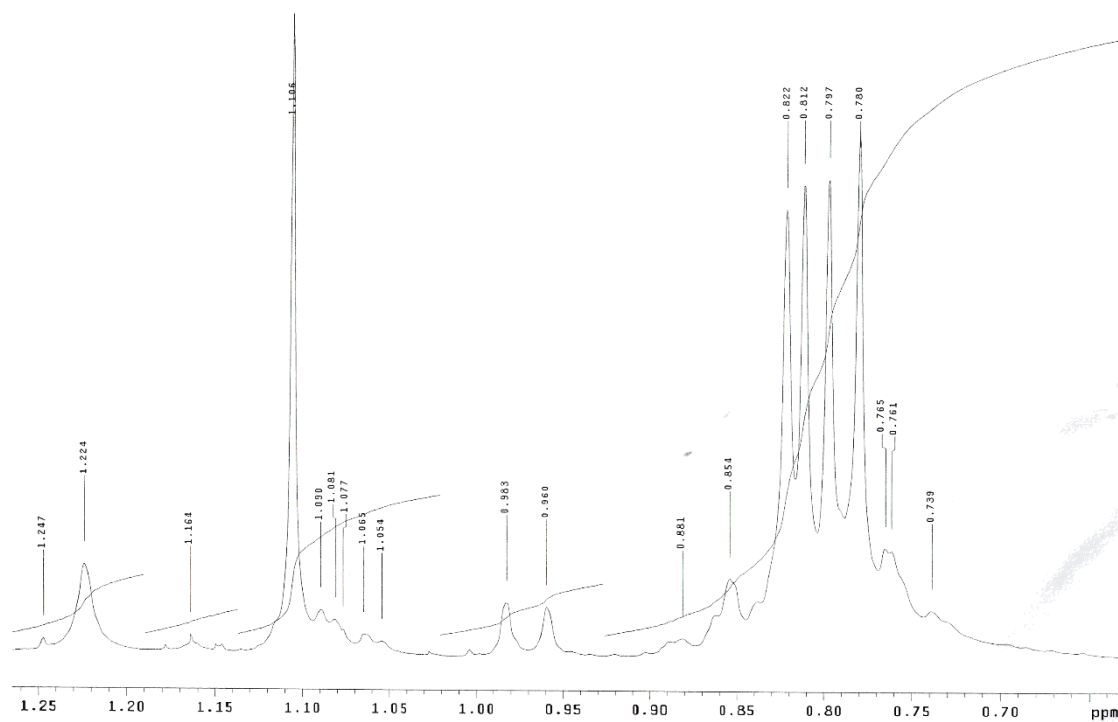
**Figure S138**  $^1\text{H}$  NMR spectrum of **24** (expanding 5.10-4.40 ppm; 500 MHz,  $\text{DMSO-}d_6$ )



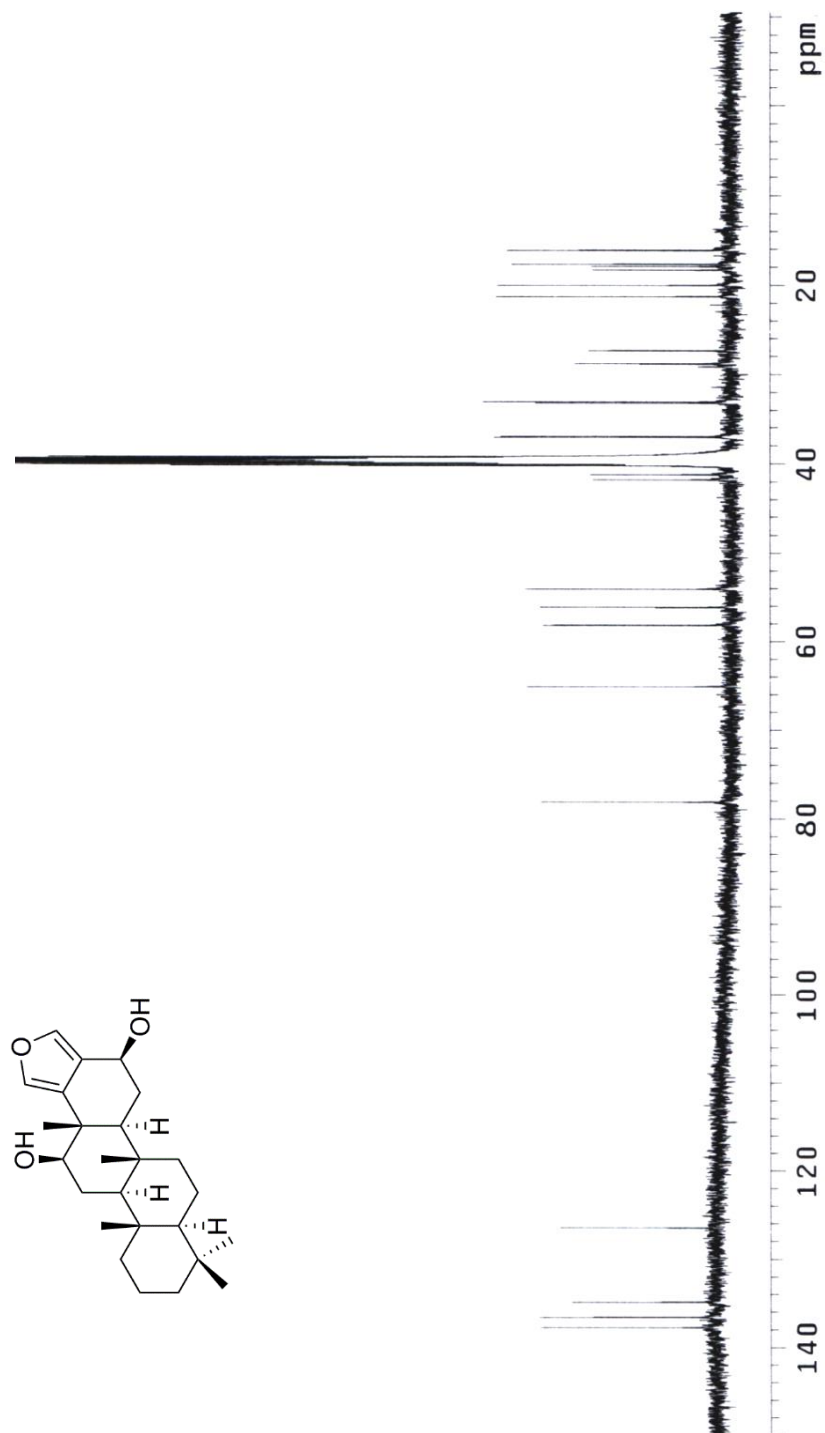
**Figure S139**  $^1\text{H}$  NMR spectrum of **24** (expanding 3.40-3.22 ppm; 500 MHz,  $\text{DMSO-}d_6$ )



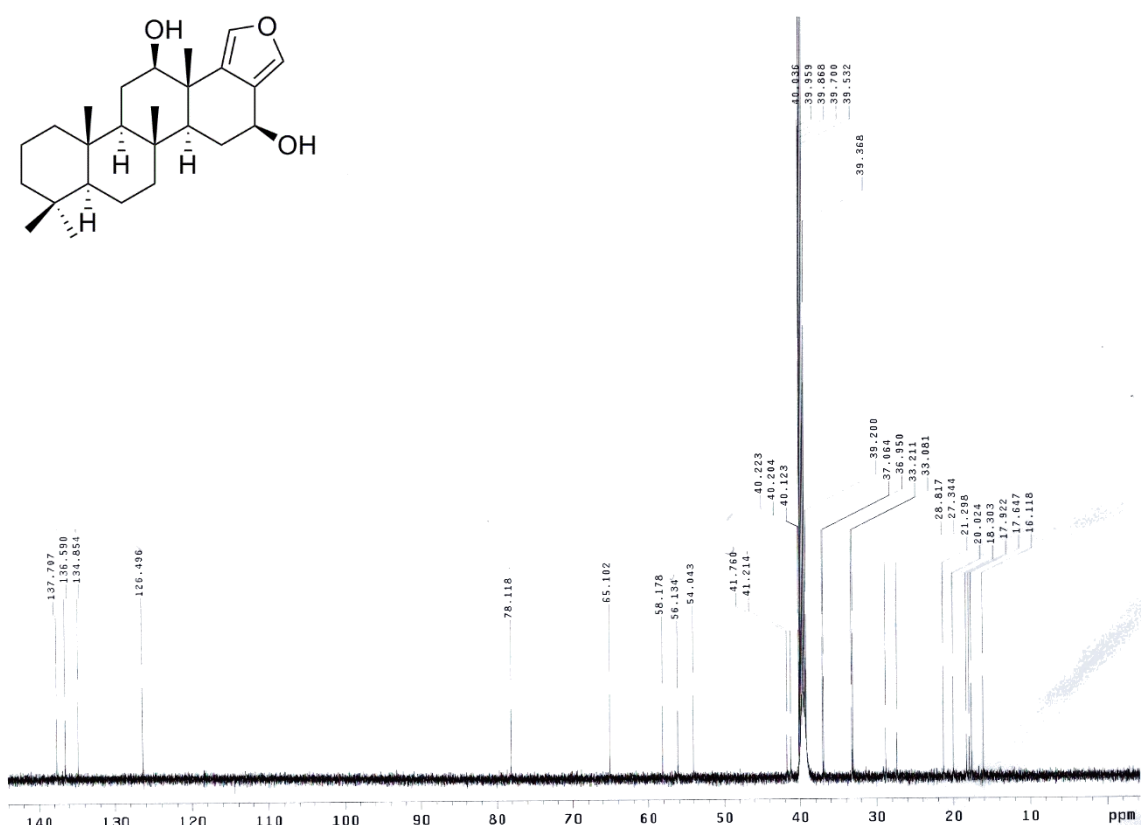
**Figure S140**  $^1\text{H}$  NMR spectrum of **24** (expanding 2.00-1.30 ppm; 500 MHz,  $\text{DMSO}-d_6$ )

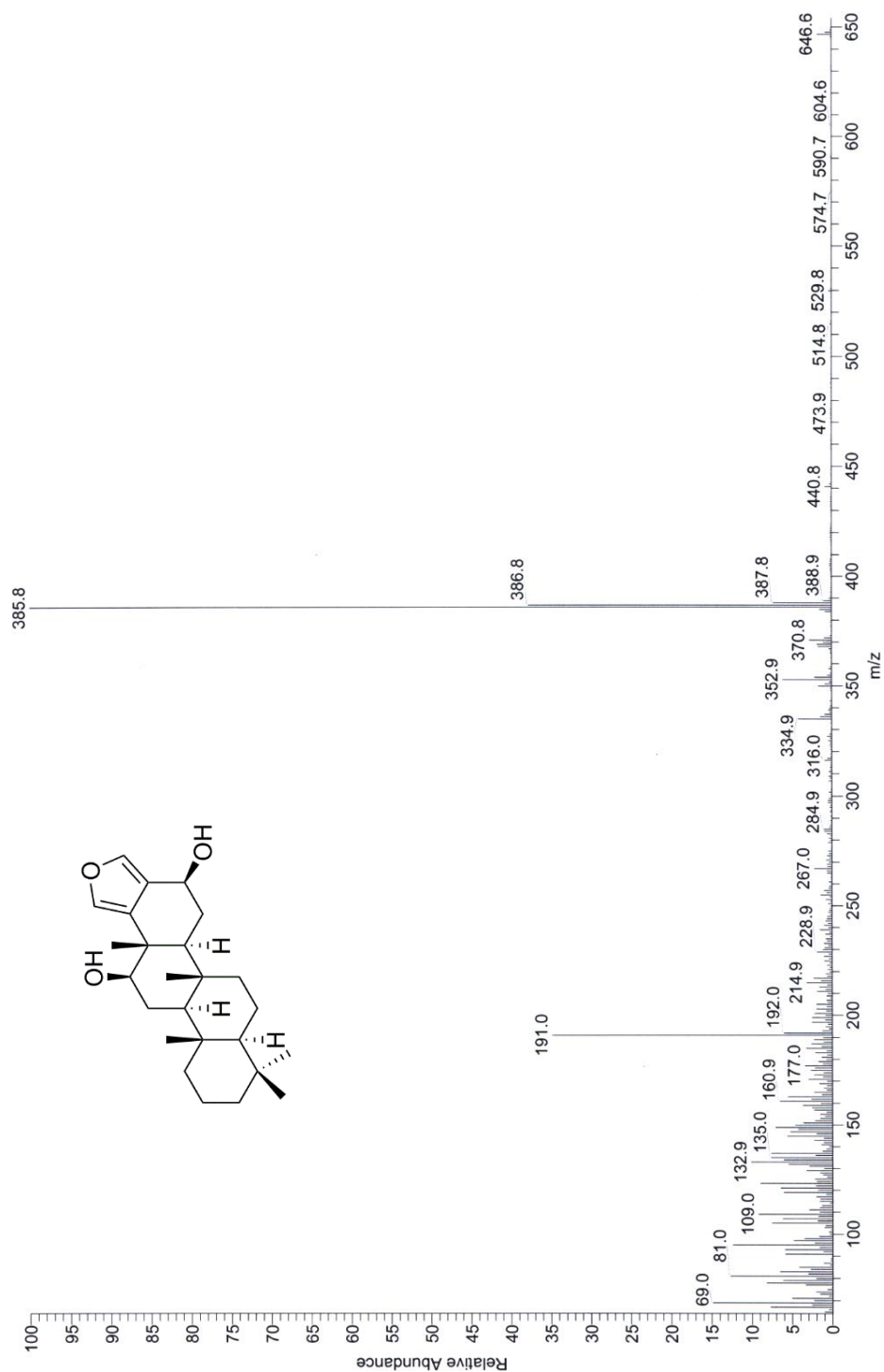


**Figure S141**  $^1\text{H}$  NMR spectrum of **24** (expanding 1.25-0.70 ppm; 500 MHz,  $\text{DMSO}-d_6$ )



**Figure S142**  $^{13}\text{C}$  NMR spectrum of compound **24** (125MHz,  $\text{DMSO}-d_6$ )





**Figure S144** EI mass spectrum of compound **24**



IR, NMR, and mass spectra of 25 (Figures S145-S150)

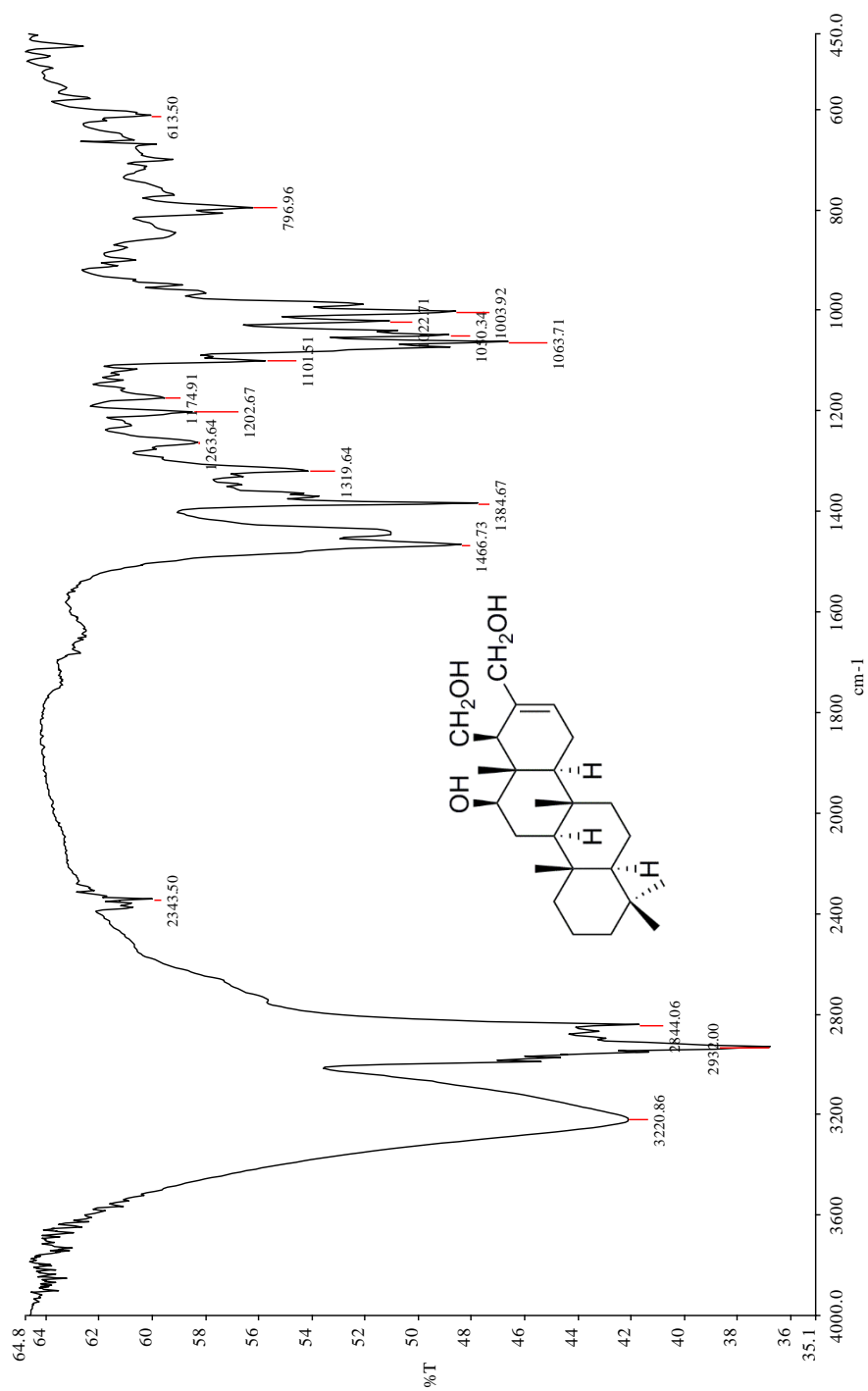
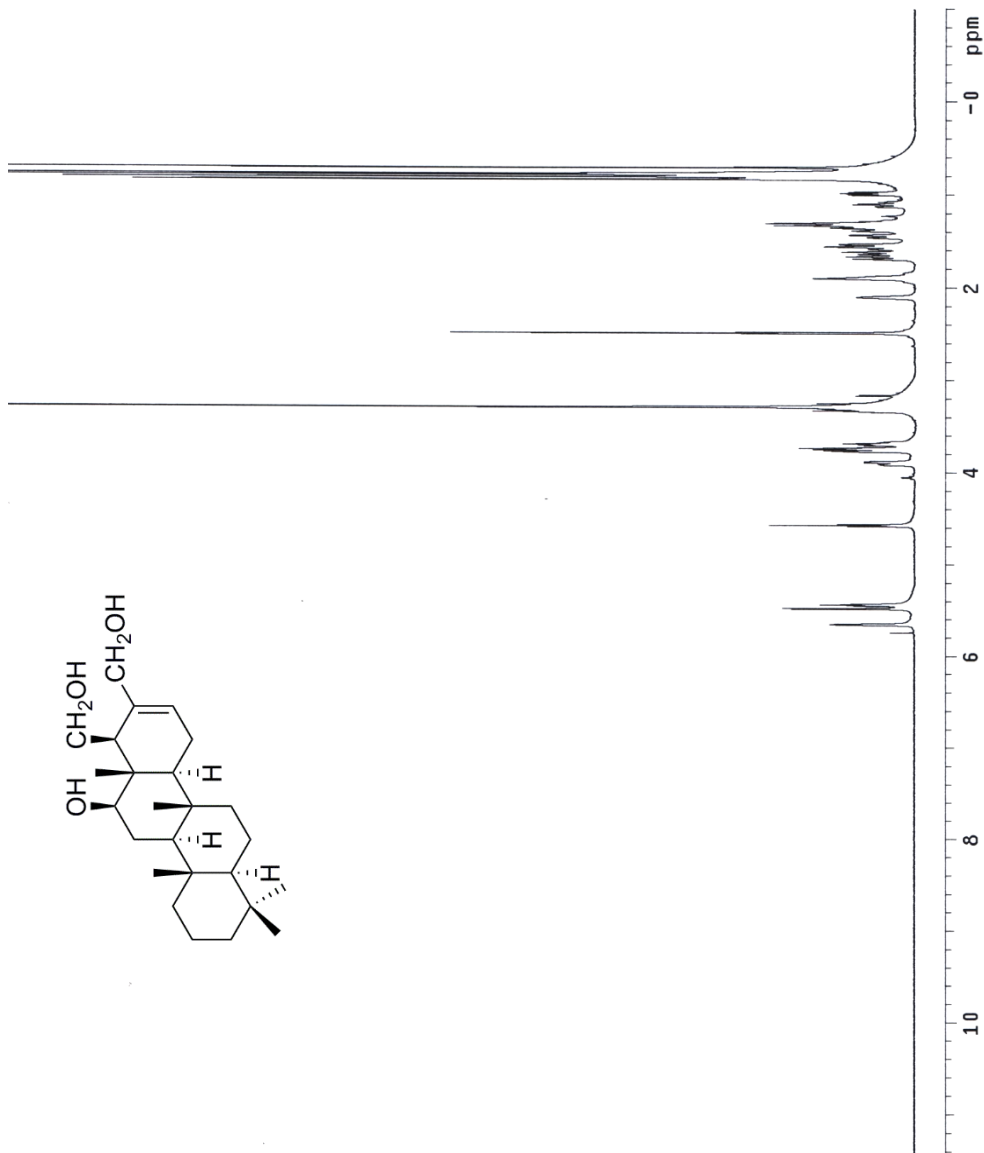
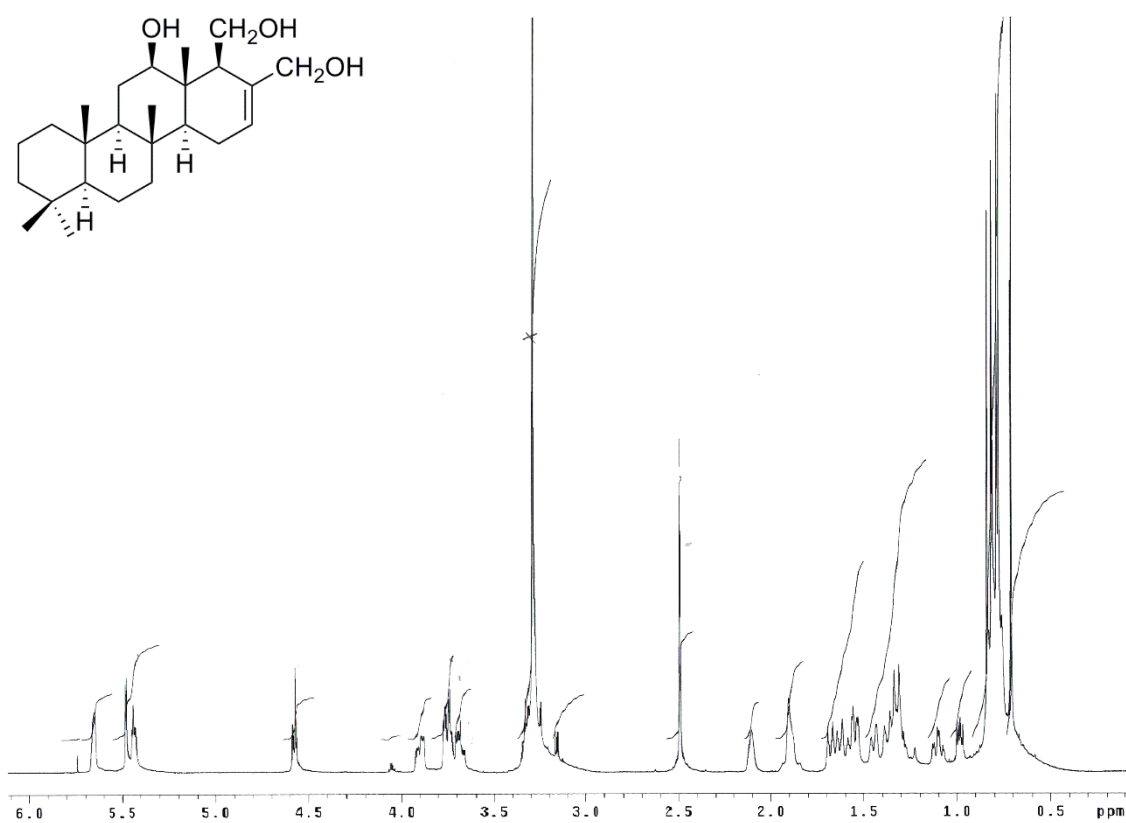


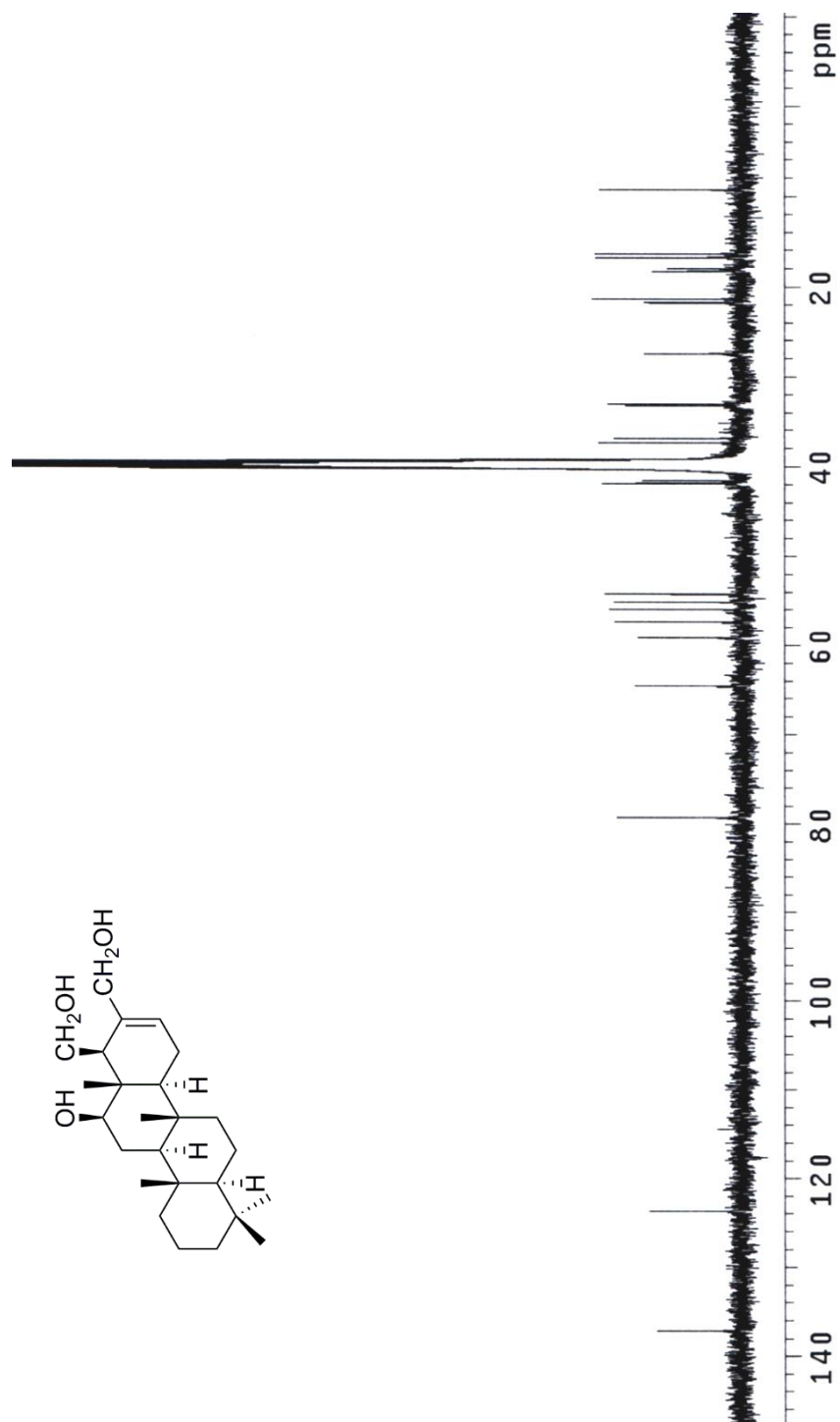
Figure S145 IR spectrum of compound 25



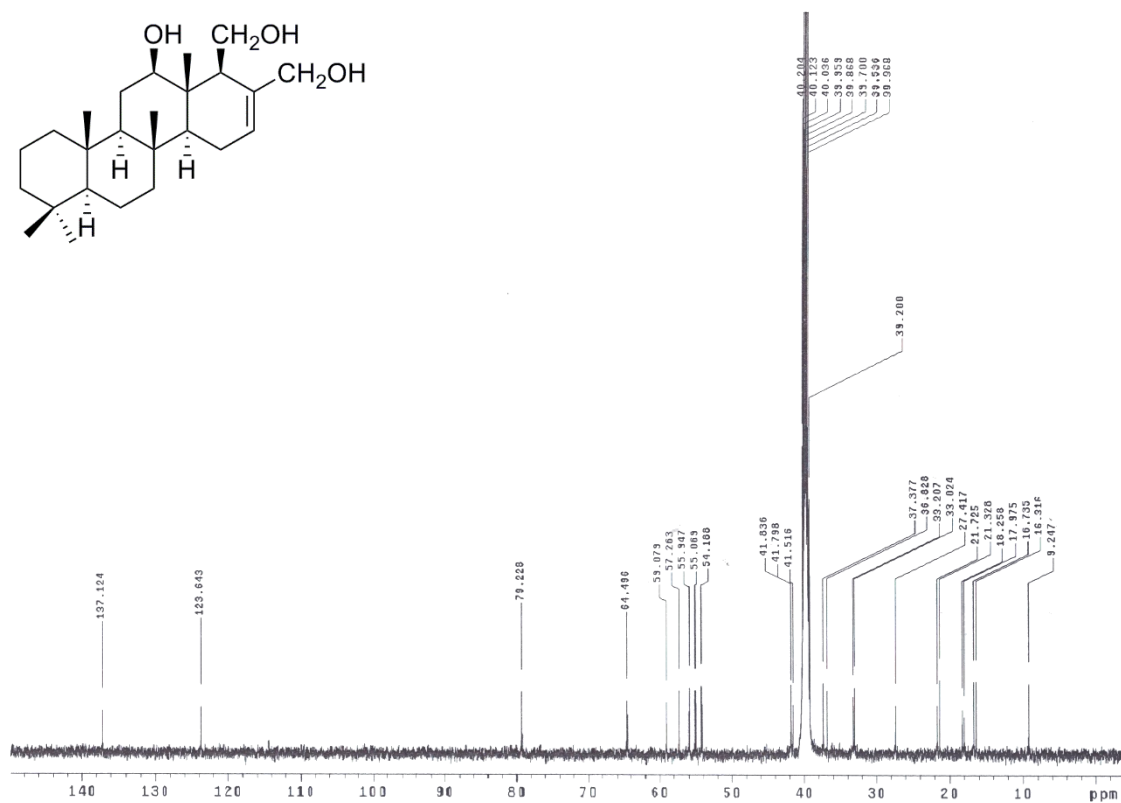
S-118



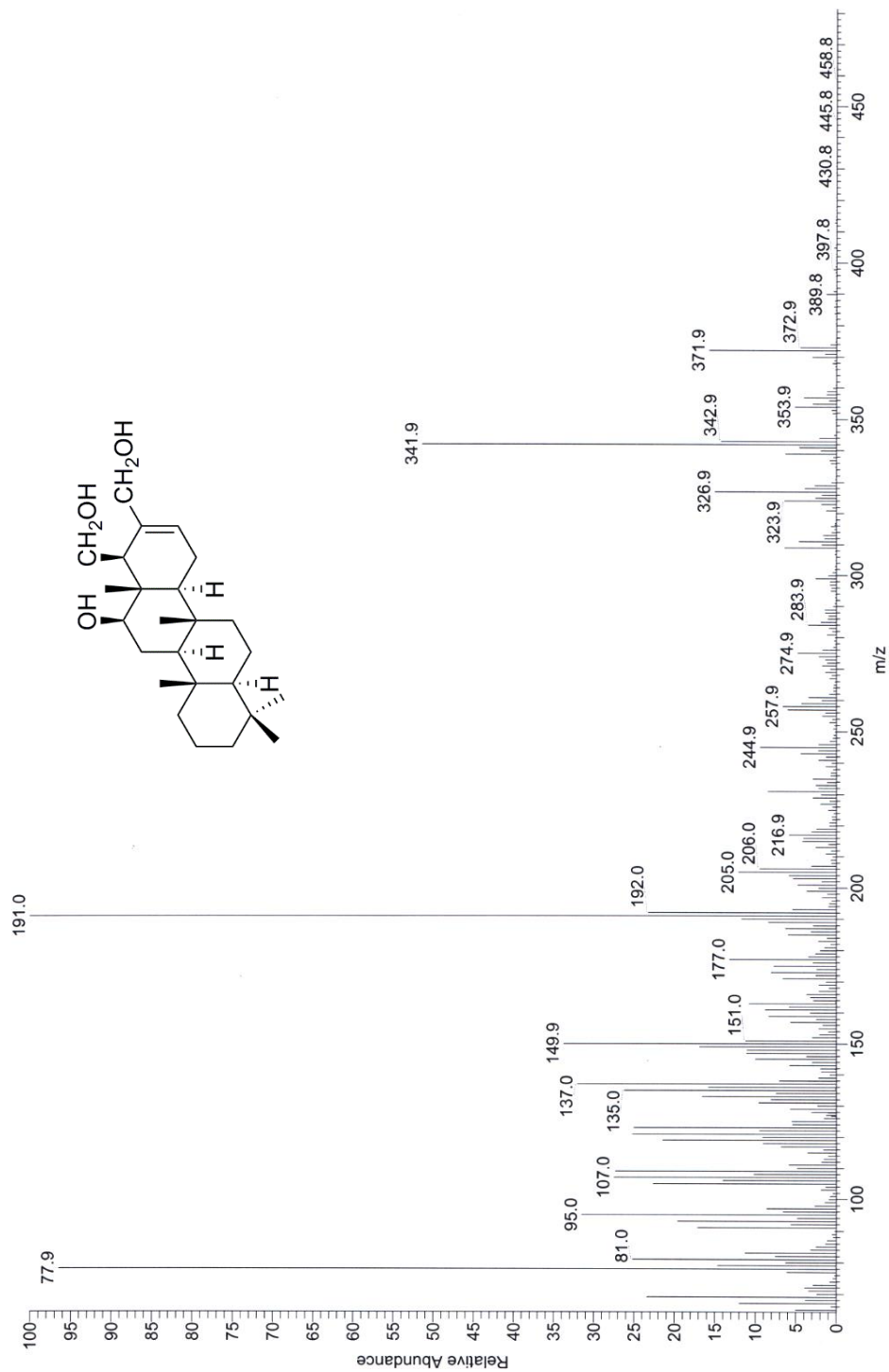
**Figure S147**  $^1\text{H}$  NMR spectrum of **25** (integration tagged; 500 MHz,  $\text{DMSO-}d_6$ )



**Figure S148**  $^{13}\text{C}$  NMR spectrum of compound **25** (125MHz,  $\text{DMSO-}d_6$ )



**Figure S149**  $^{13}\text{C}$  NMR spectrum of **25** (peak picking tagged; 125 MHz, DMSO- $d_6$ )



**Figure S150** EI mass spectrum of compound **25**

IR, NMR, and mass spectra of 26 (Figures S151-S161)

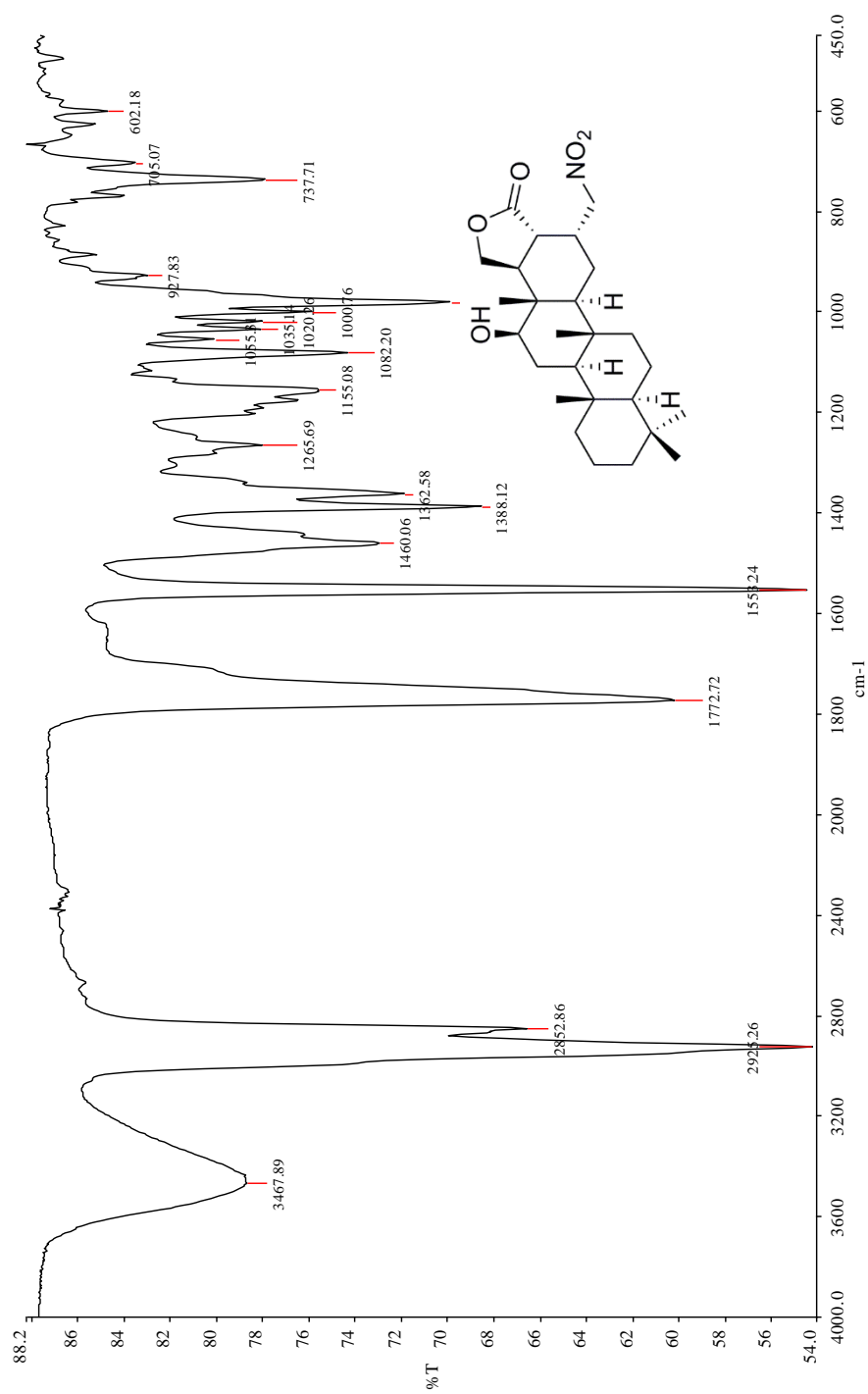
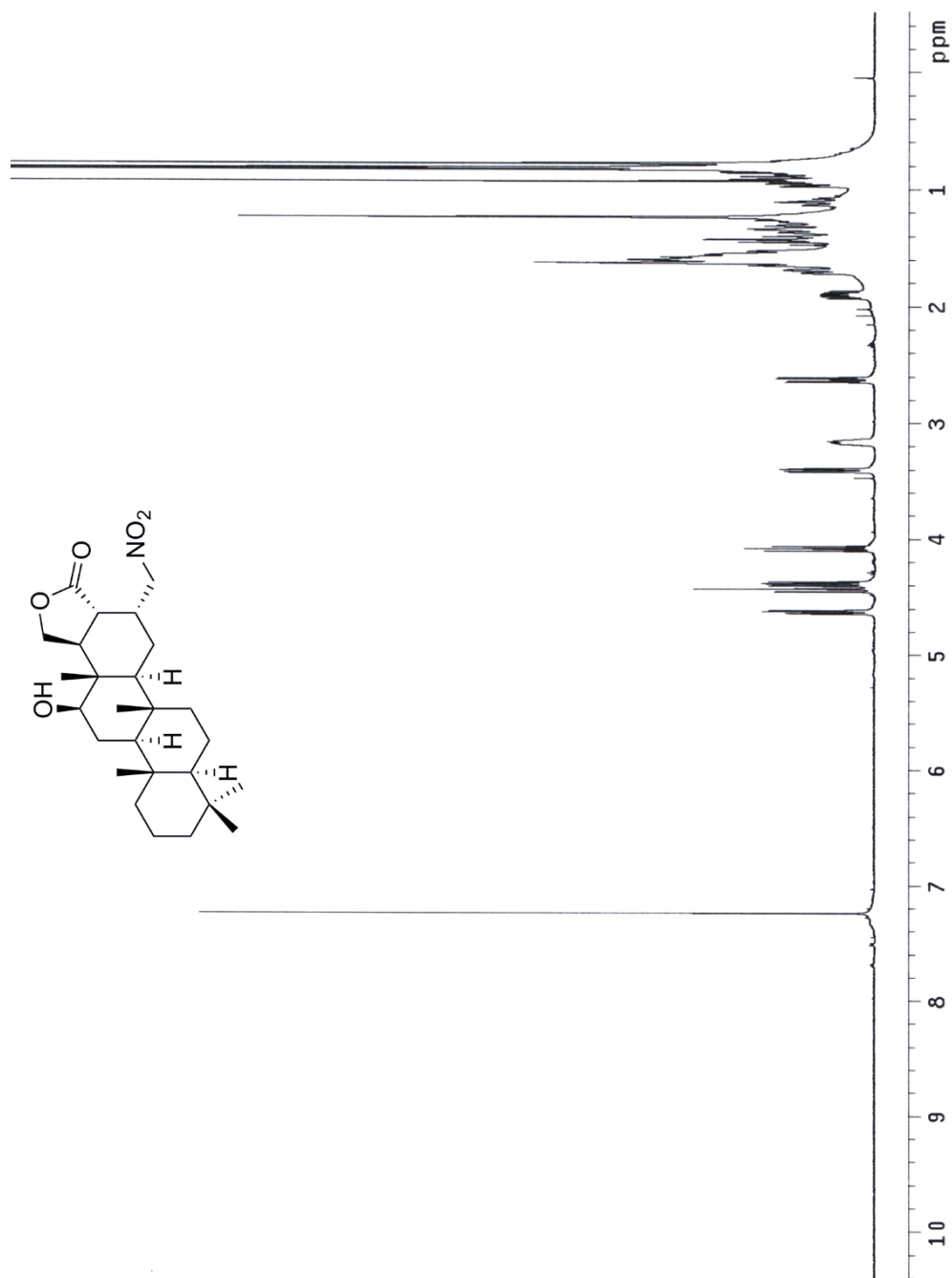
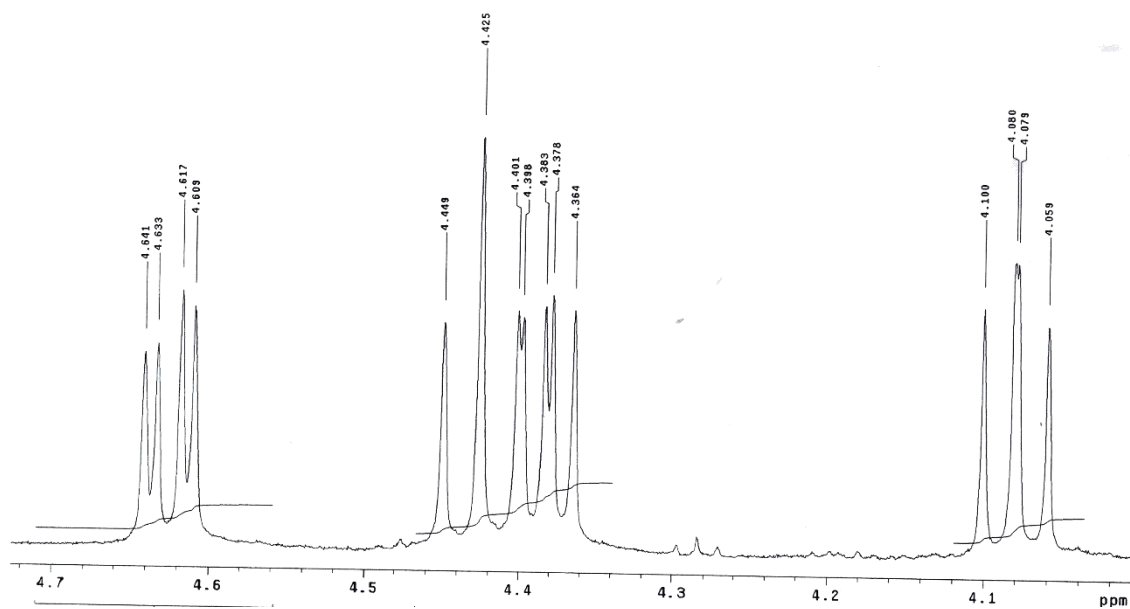
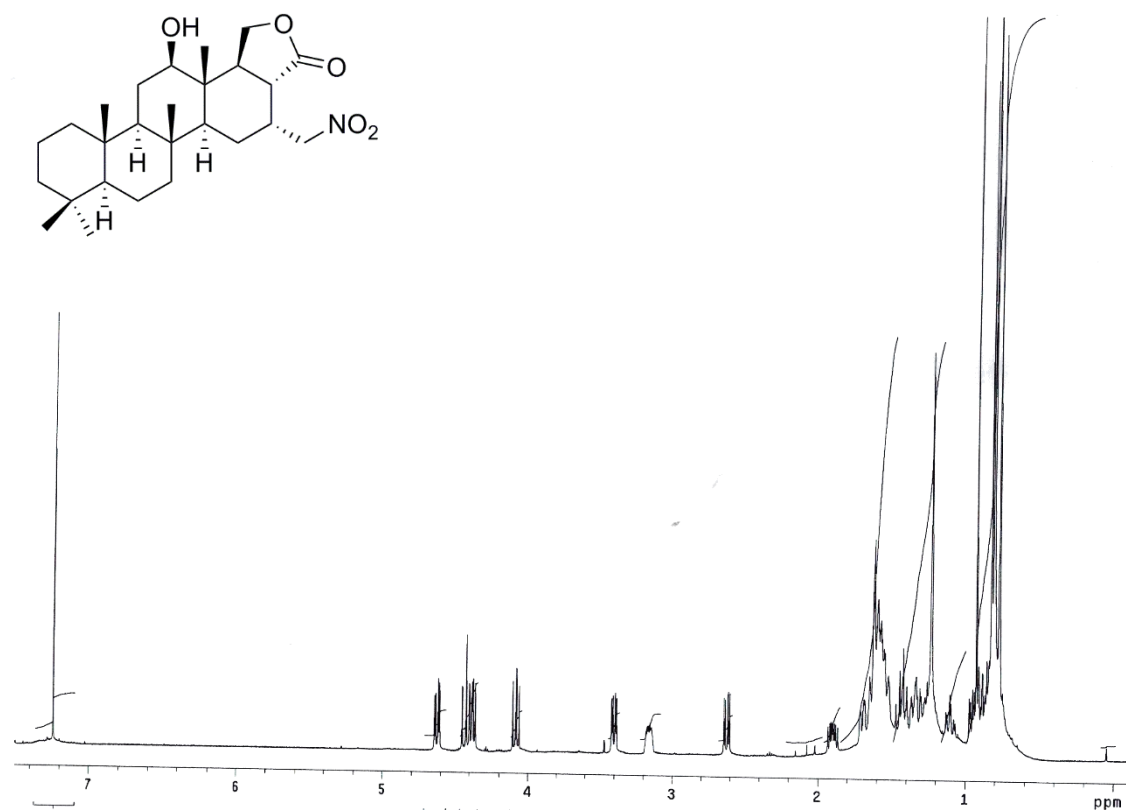


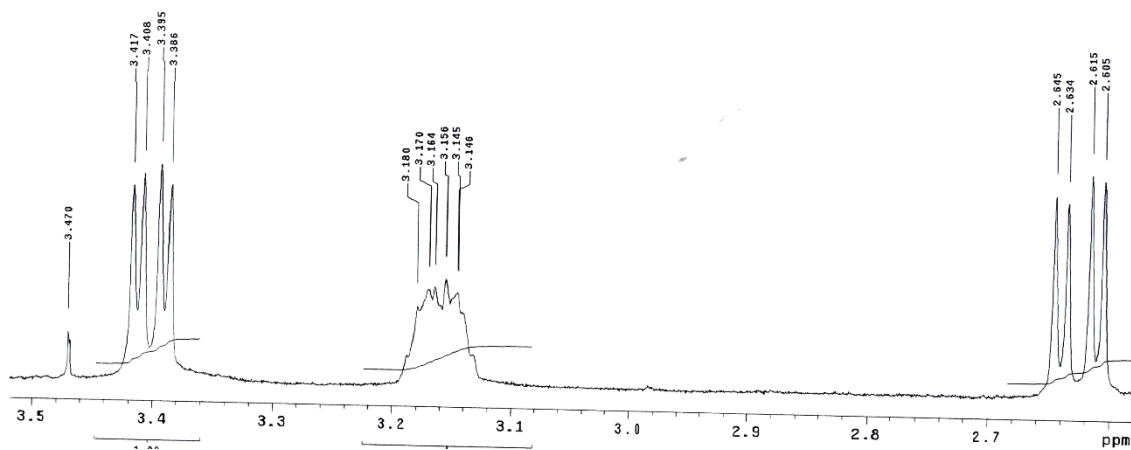
Figure S151 IR spectrum of compound 26



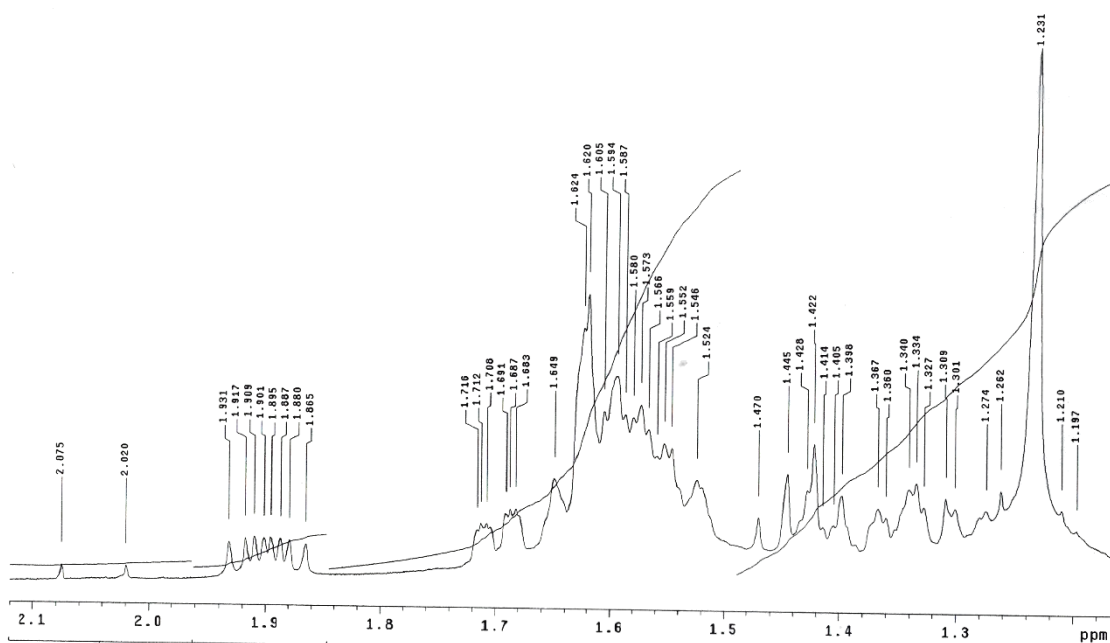
**Figure S152**  $^1\text{H}$  NMR spectrum of compound **26** (500MHz,  $\text{CDCl}_3$ )





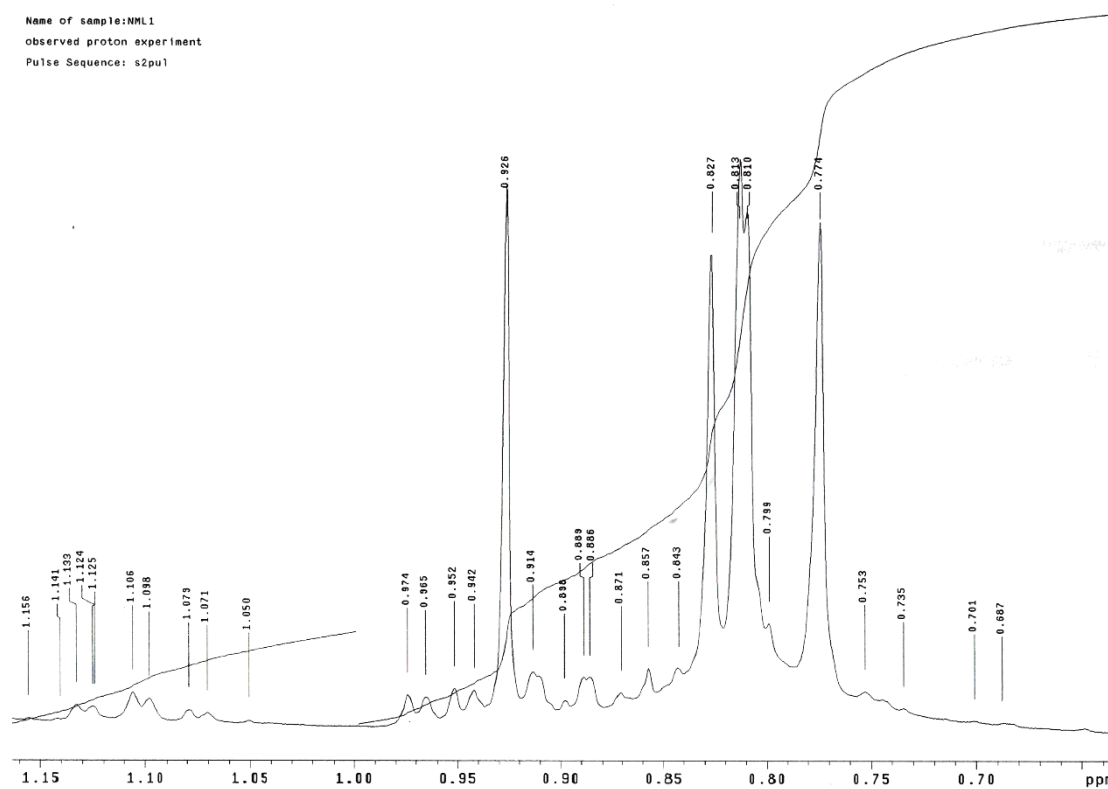


**Figure S155**  $^1\text{H}$  NMR spectrum of **26** (expanding 3.50-2.60 ppm; 500 MHz,  $\text{CDCl}_3$ )

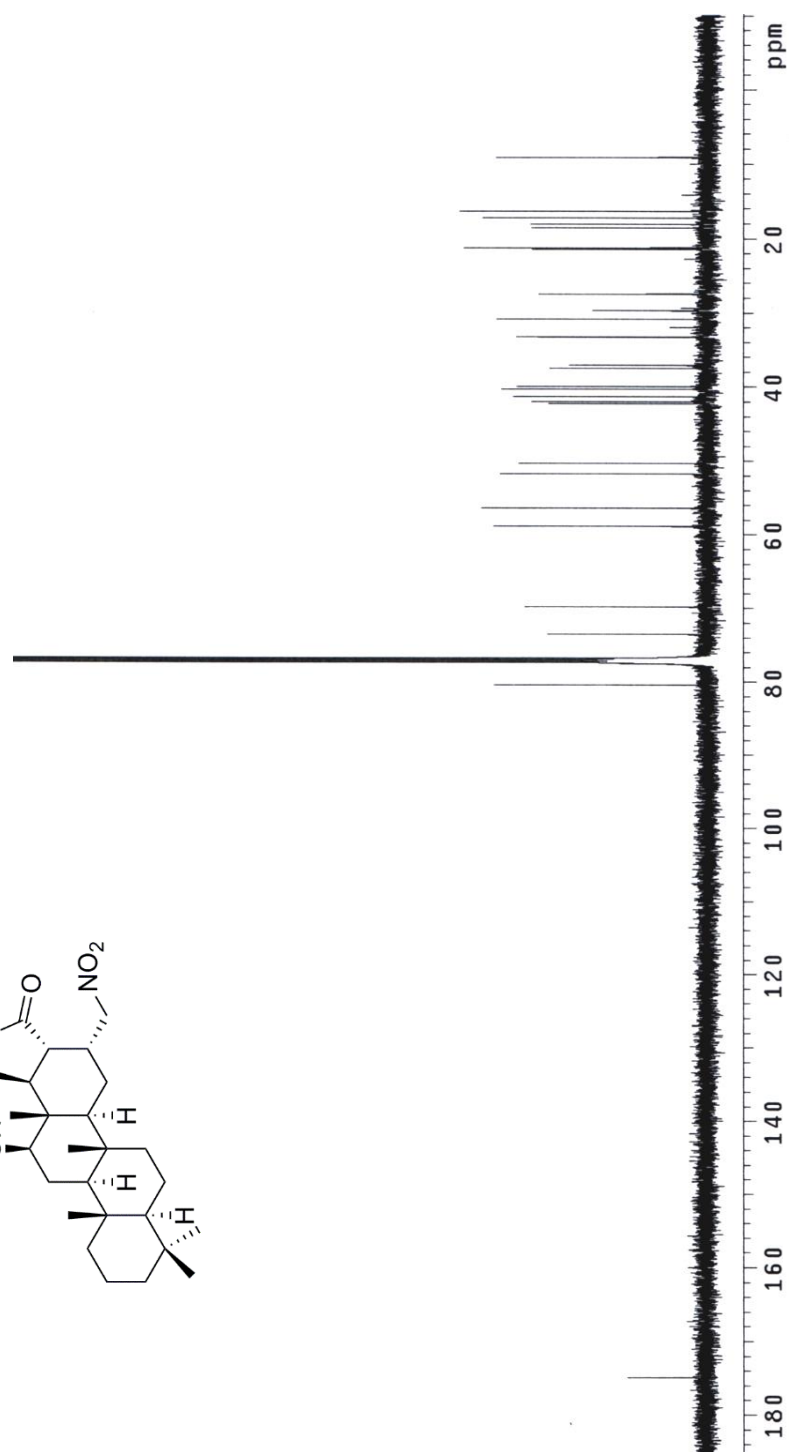
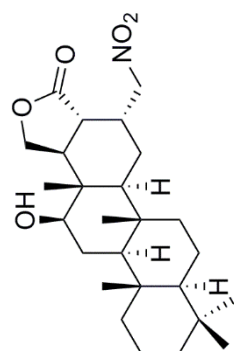


**Figure S156**  $^1\text{H}$  NMR spectrum of **26** (expanding 2.10-1.20 ppm; 500 MHz,  $\text{CDCl}_3$ )

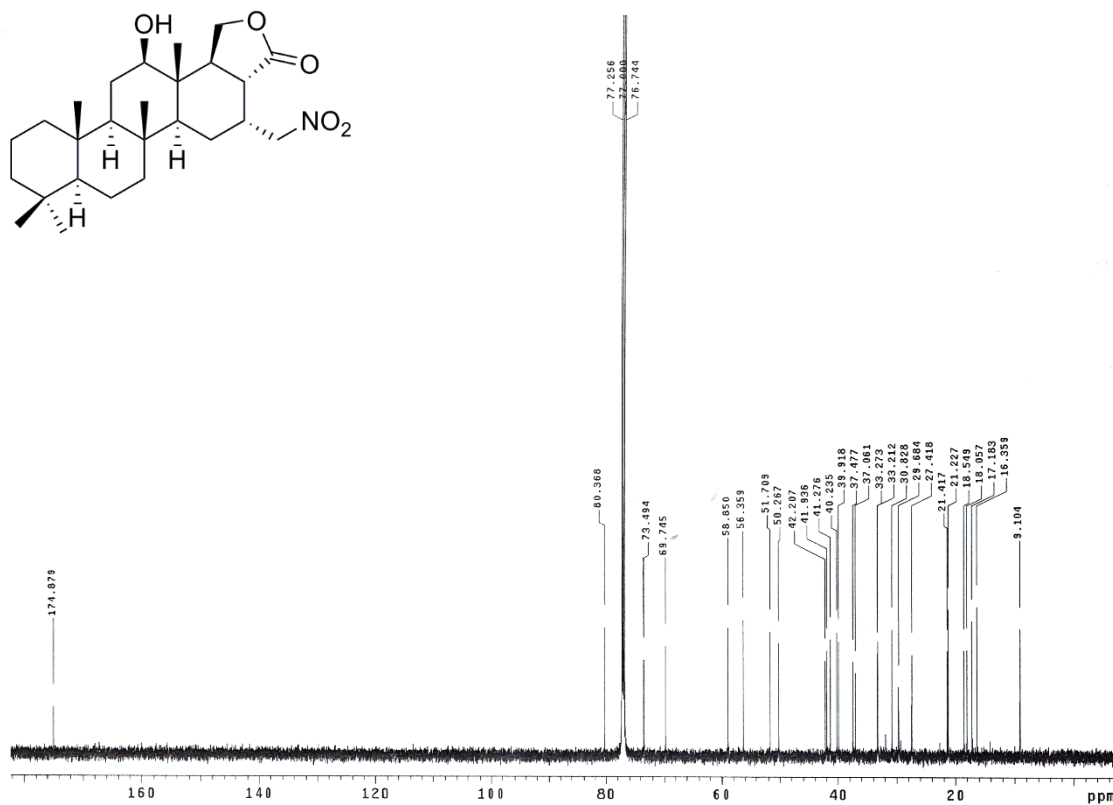
Name of sample: NML1  
observed proton experiment  
Pulse Sequence: s2pu1



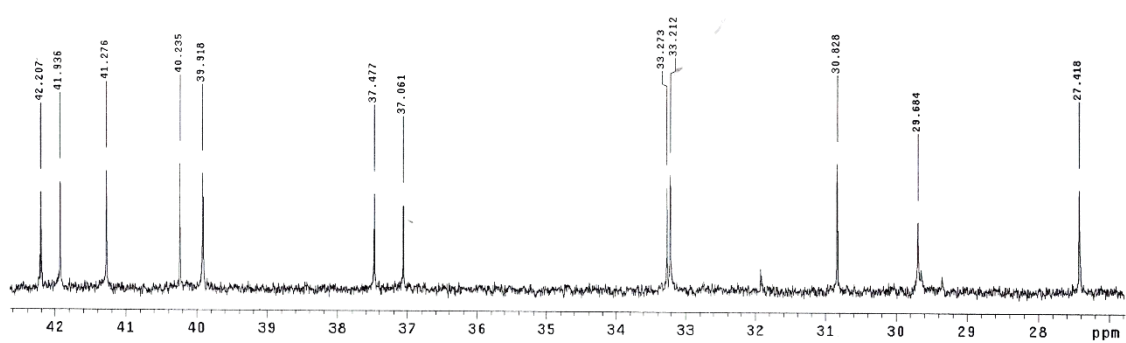
**Figure S157** <sup>1</sup>H NMR spectrum of **26** (expanding 1.15-0.70 ppm; 500 MHz, CDCl<sub>3</sub>)



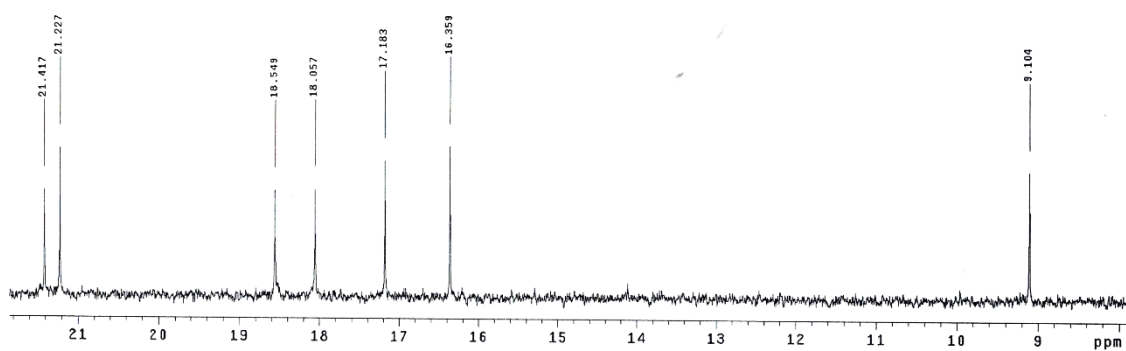
**Figure S158**  $^{13}\text{C}$  NMR spectrum of compound **26** (125MHz,  $\text{CDCl}_3$ )



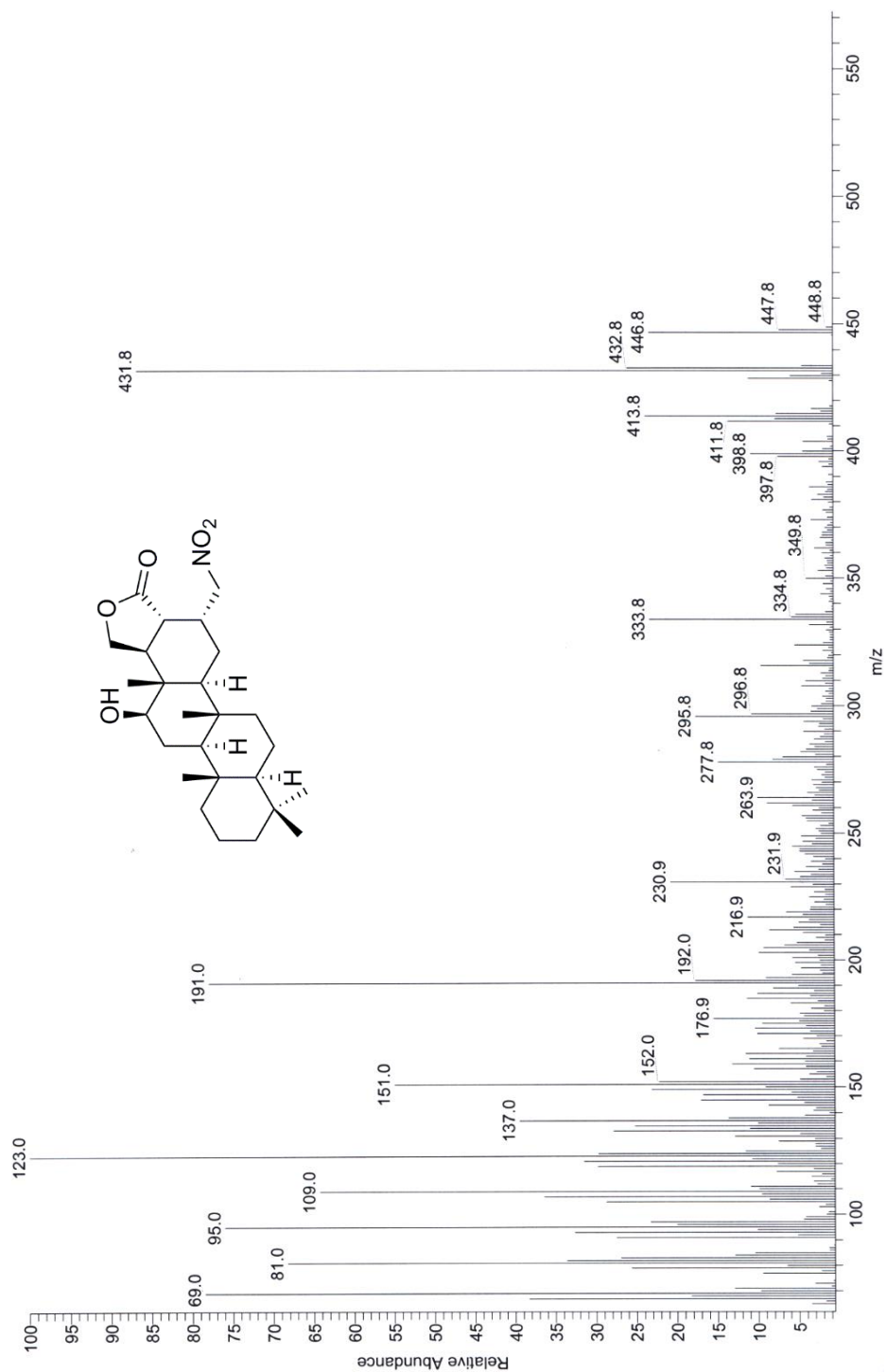
**Figure S158** <sup>13</sup>C NMR spectrum of **26** (peak picking tagged; 125 MHz, CDCl<sub>3</sub>)



**Figure S159** <sup>13</sup>C NMR spectrum of **26** (expanding 42.5-27.5 ppm; 125 MHz, CDCl<sub>3</sub>)



**Figure S160**  $^{13}\text{C}$  NMR spectrum of **26** (expanding 21.5-8.0 ppm; 125 MHz,  $\text{CDCl}_3$ )



**Figure S161** EI mass spectrum of compound **26**

IR, NMR, and mass spectra of 27 (Figures S162-S174)

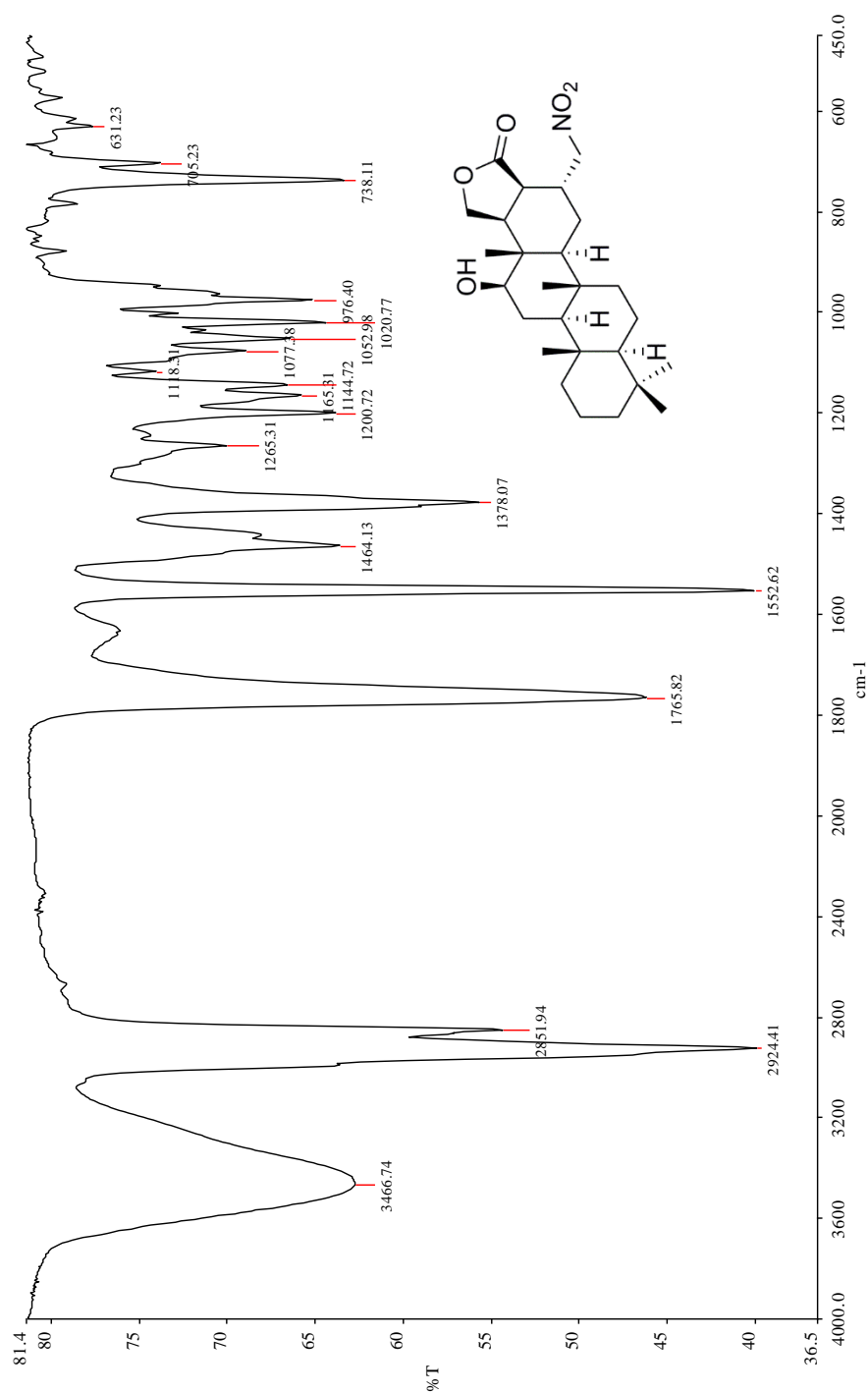
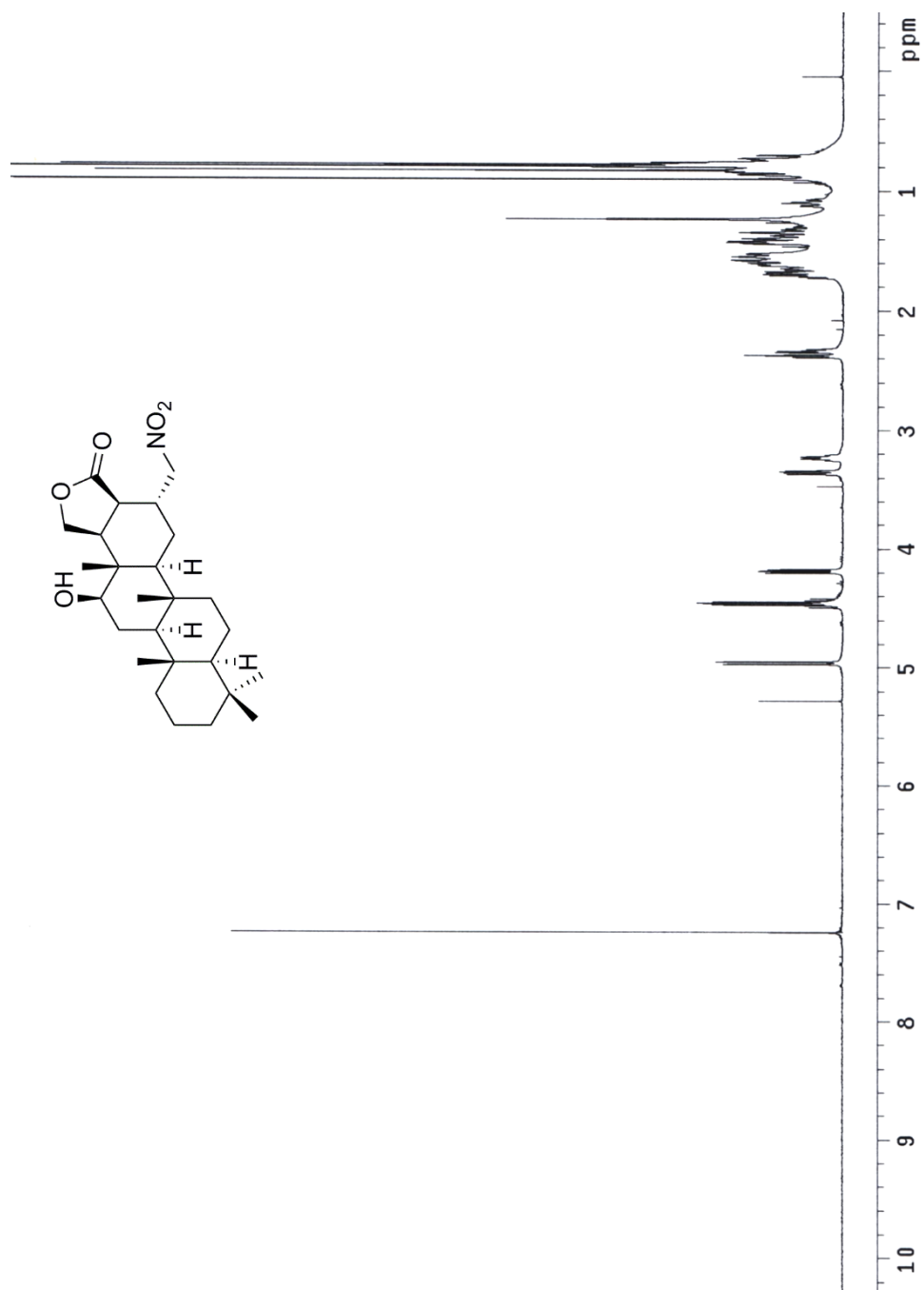
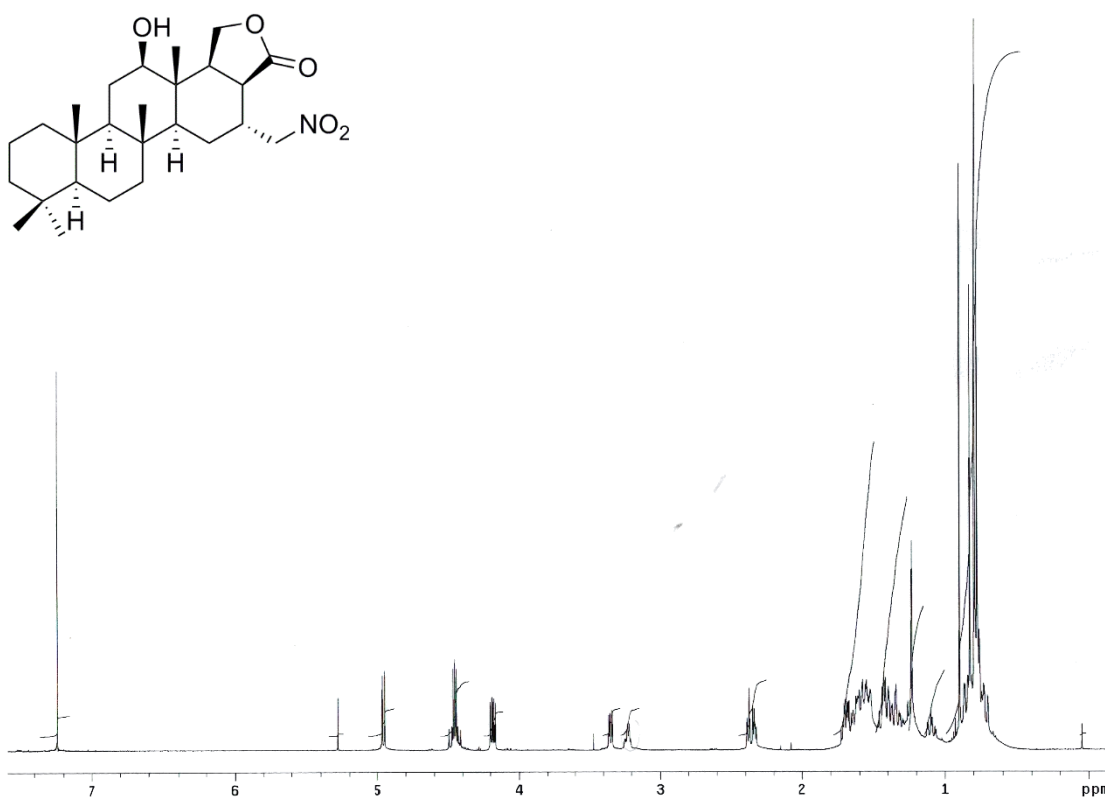


Figure S162 IR spectrum of compound 27

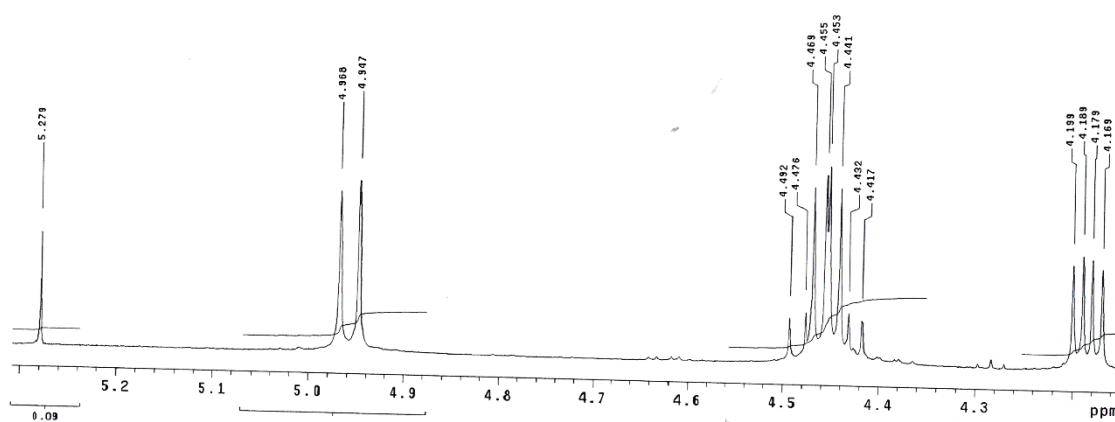




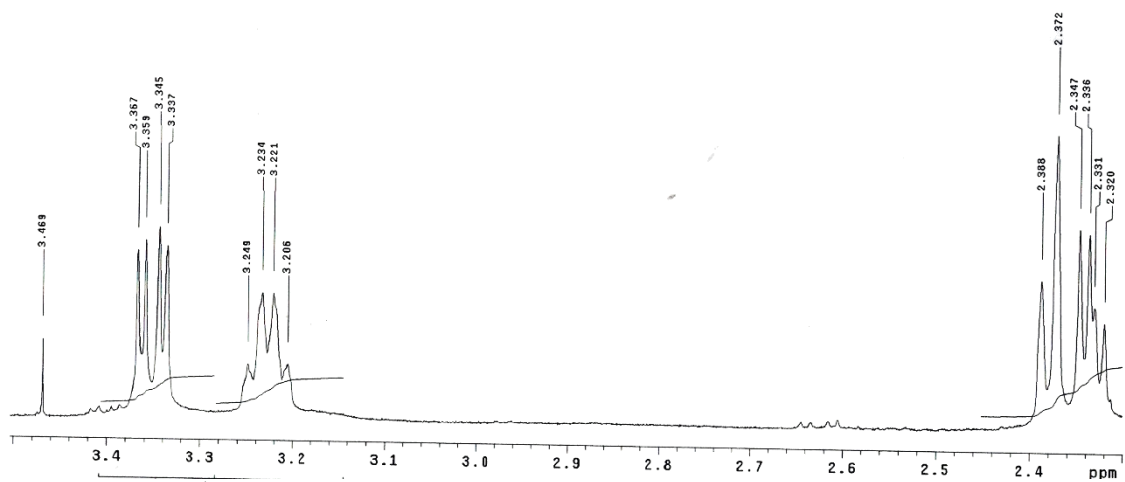
**Figure S163**  $^1\text{H}$  NMR spectrum of compound **27** (500MHz,  $\text{CDCl}_3$ )



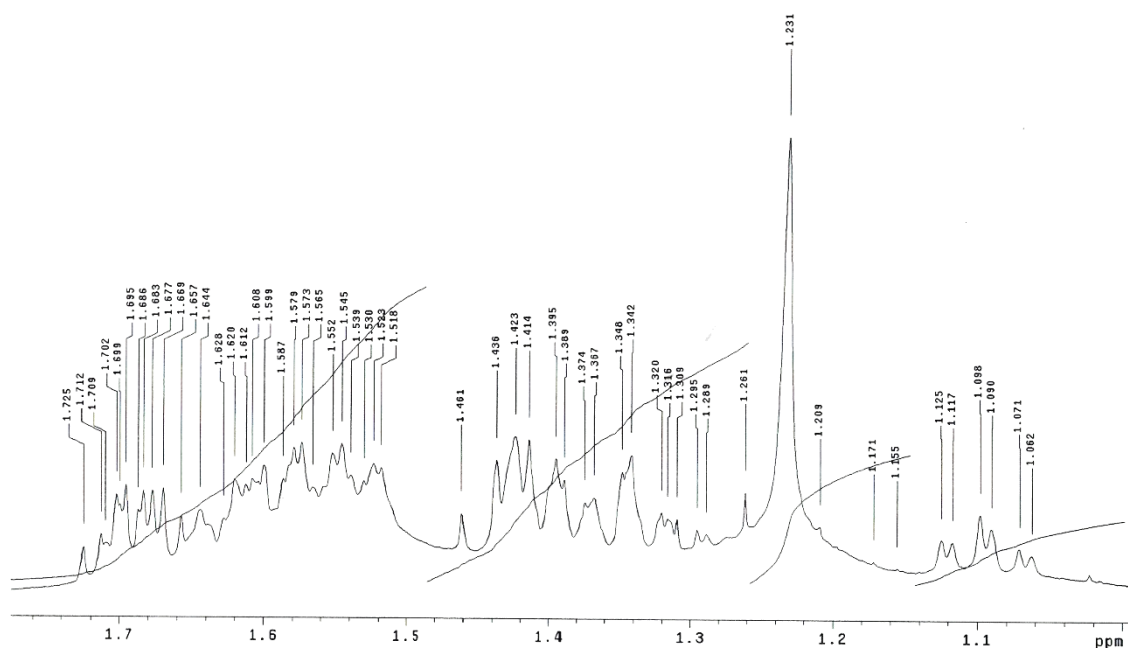
**Figure S164** <sup>1</sup>H NMR spectrum of **27** (integration tagged; 500 MHz, CDCl<sub>3</sub>)



**Figure S165** <sup>1</sup>H NMR spectrum of **27** (expanding 1.15-0.70 ppm; 500 MHz, CDCl<sub>3</sub>)

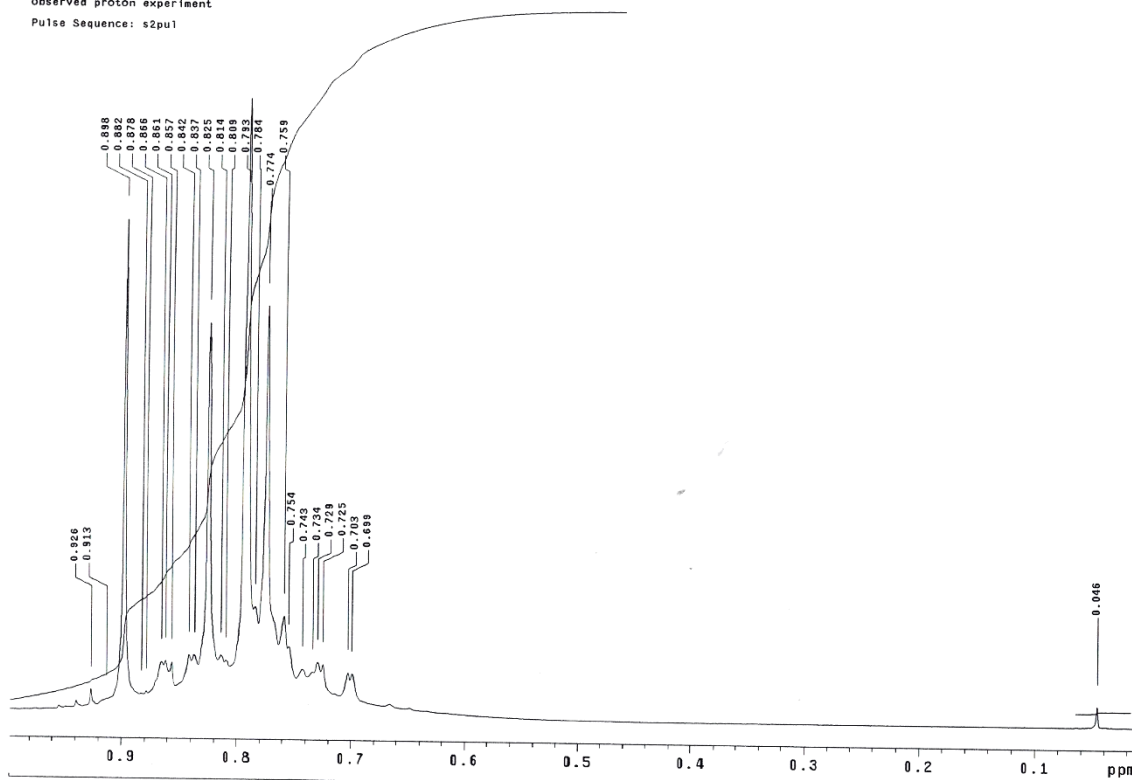


**Figure S166**  $^1\text{H}$  NMR spectrum of **27** (expanding 3.45-2.30 ppm; 500 MHz,  $\text{CDCl}_3$ )

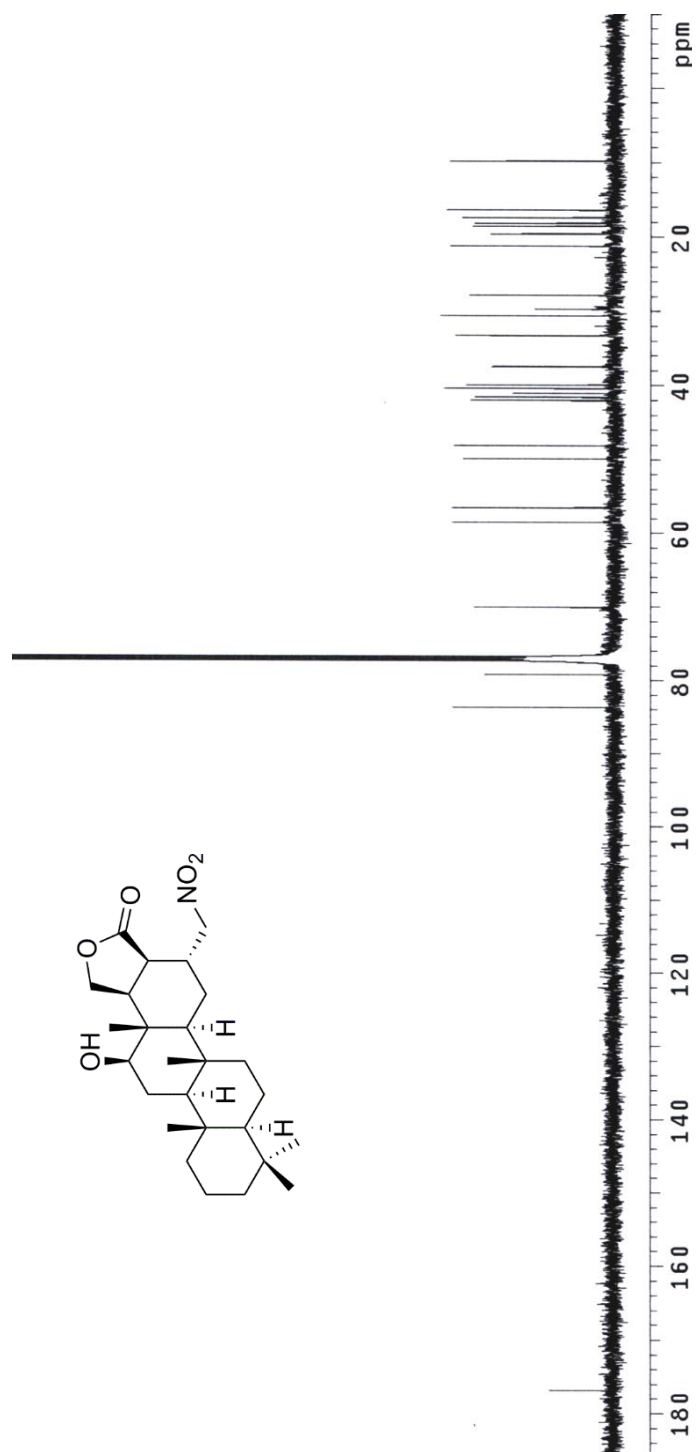


**Figure S167**  $^1\text{H}$  NMR spectrum of **27** (expanding 1.75-1.10 ppm; 500 MHz,  $\text{CDCl}_3$ )

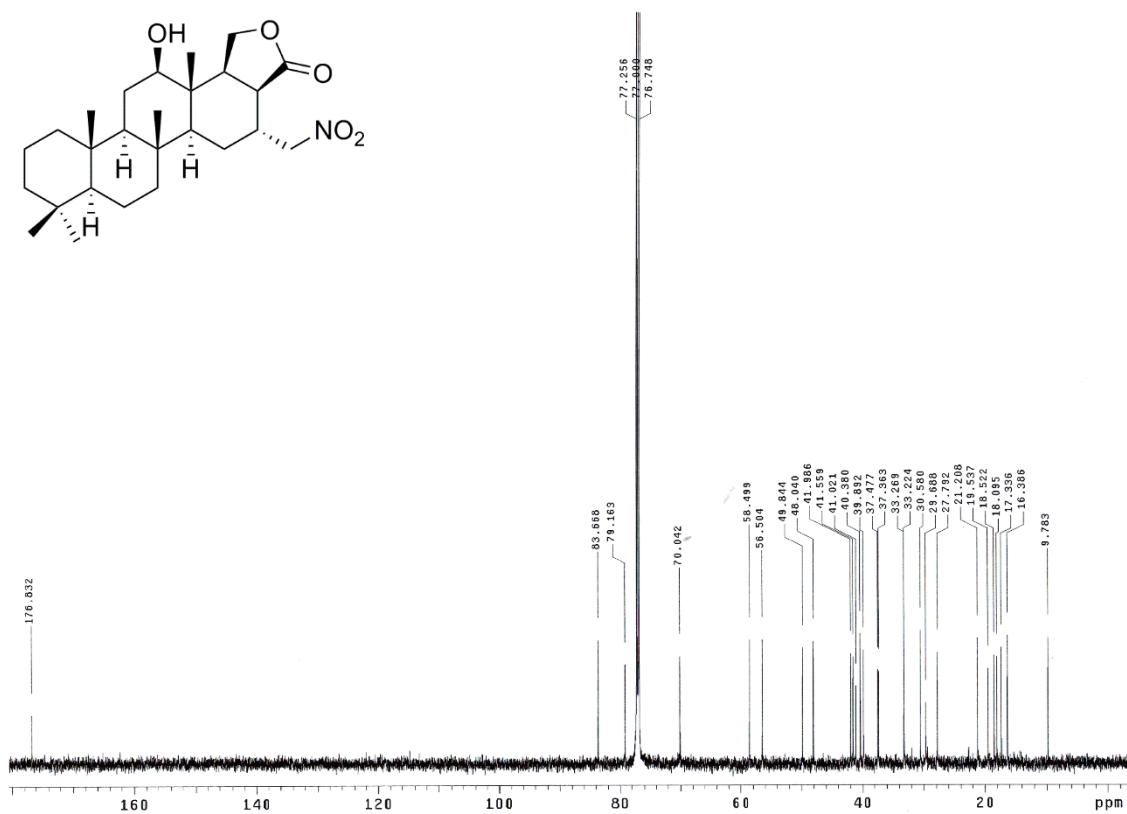
Name of sample: NML2  
Observed proton experiment  
Pulse Sequence: s2pu1



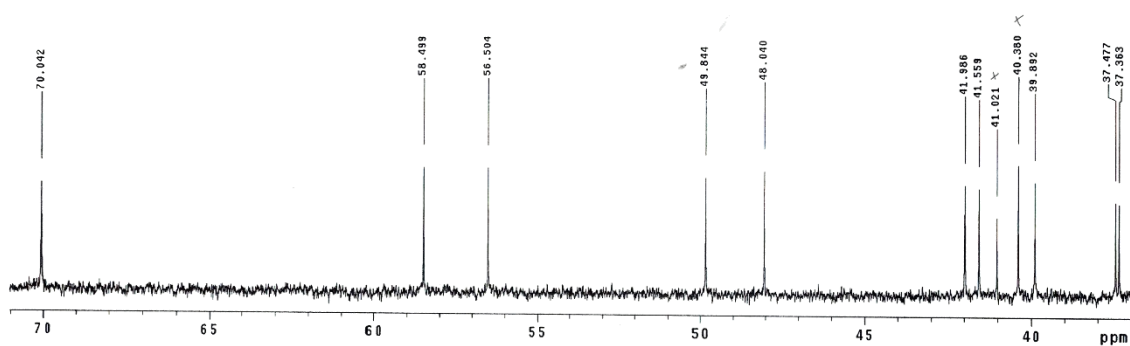
**Figure S168**  $^1\text{H}$  NMR spectrum of **27** (expanding 1.10-0.00 ppm; 500 MHz,  $\text{CDCl}_3$ )



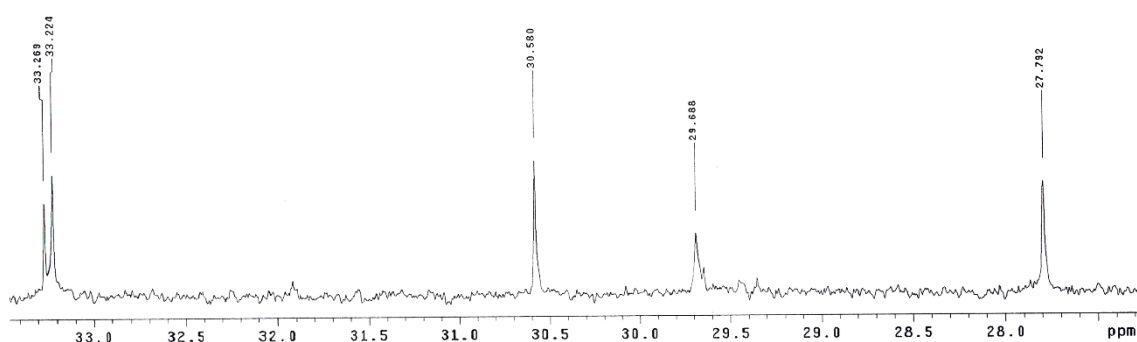
**Figure S169**  $^{13}\text{C}$  NMR spectrum of compound **27** (125MHz,  $\text{CDCl}_3$ )



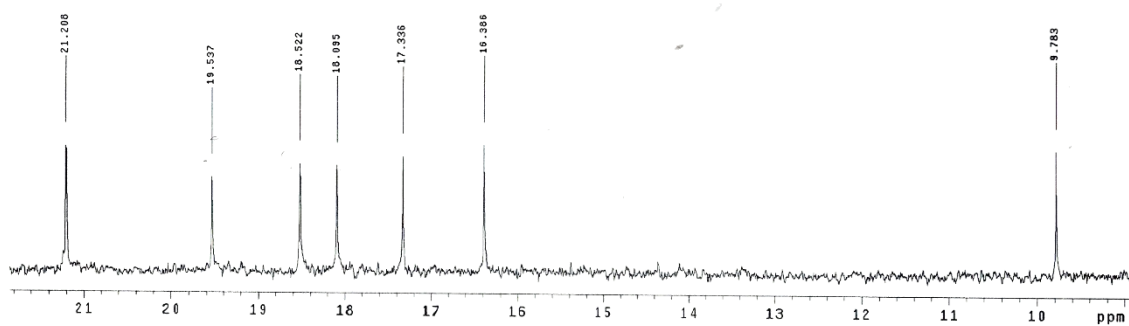
**Figure S170**  $^{13}\text{C}$  NMR spectrum of **27** (peak picking tagged; 125 MHz,  $\text{CDCl}_3$ )



**Figure S171**  $^{13}\text{C}$  NMR spectrum of **27** (expanding 70-37 ppm; 125 MHz,  $\text{CDCl}_3$ )



**Figure S172**  $^{13}\text{C}$  NMR spectrum of **27** (expanding 33.5-27.5 ppm; 125 MHz,  $\text{CDCl}_3$ )



**Figure S173**  $^{13}\text{C}$  NMR spectrum of **27** (expanding 21.5-9.5 ppm; 125 MHz,  $\text{CDCl}_3$ )





IR, NMR, and mass spectra of 28 (Figures S175-S184)

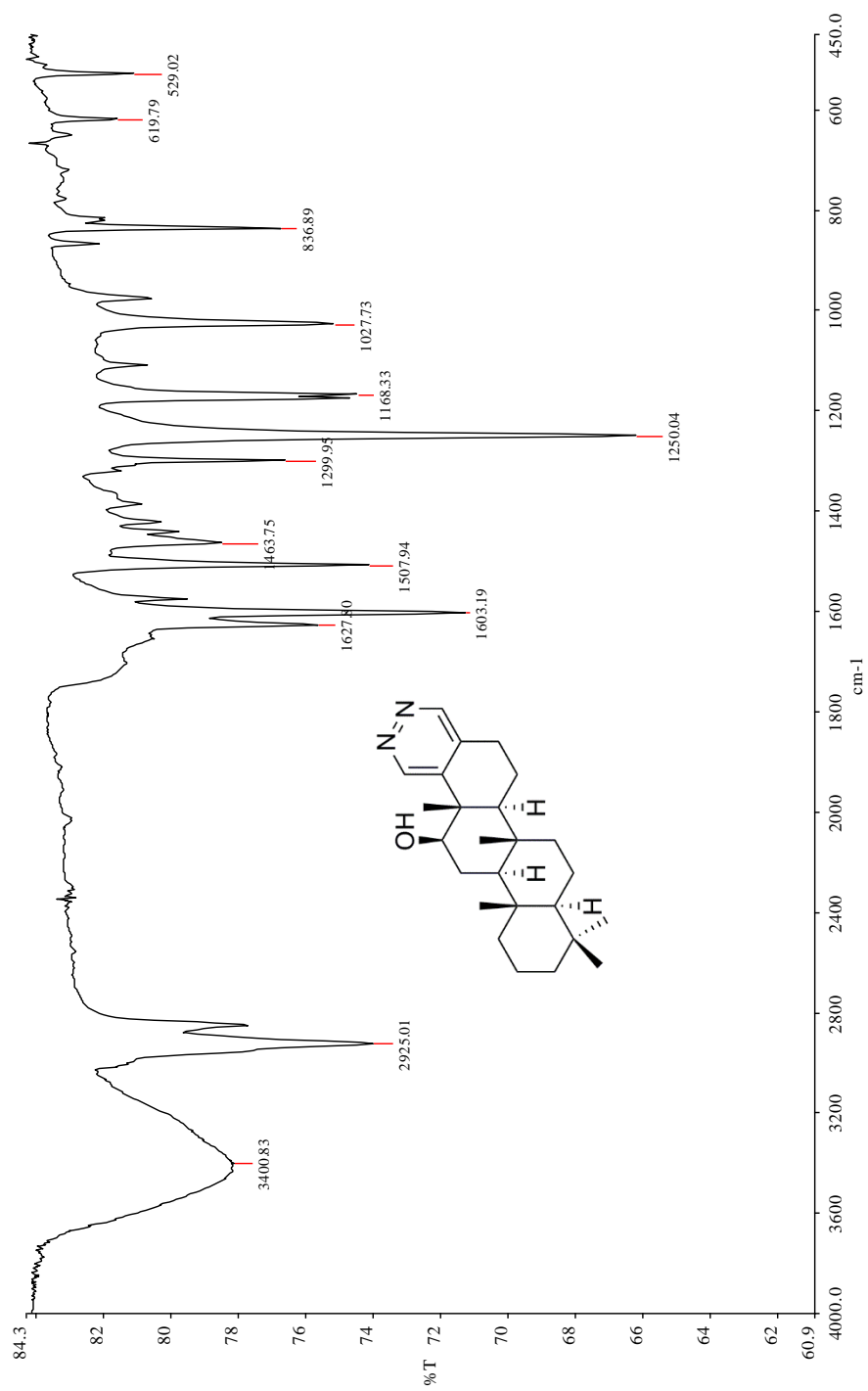
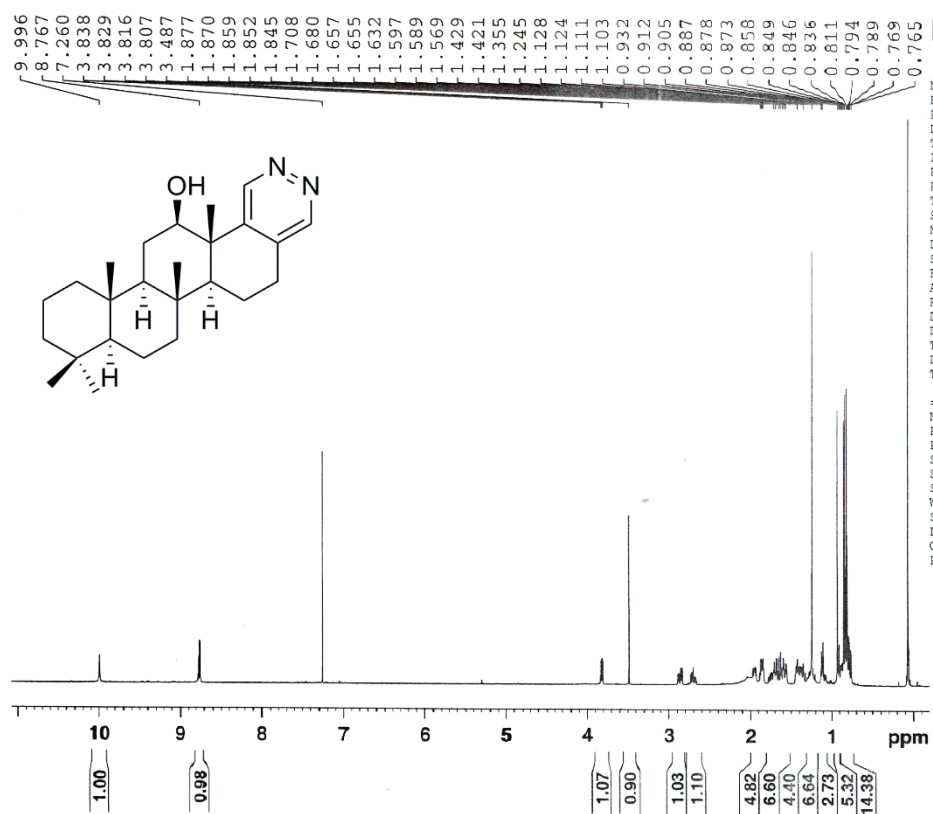


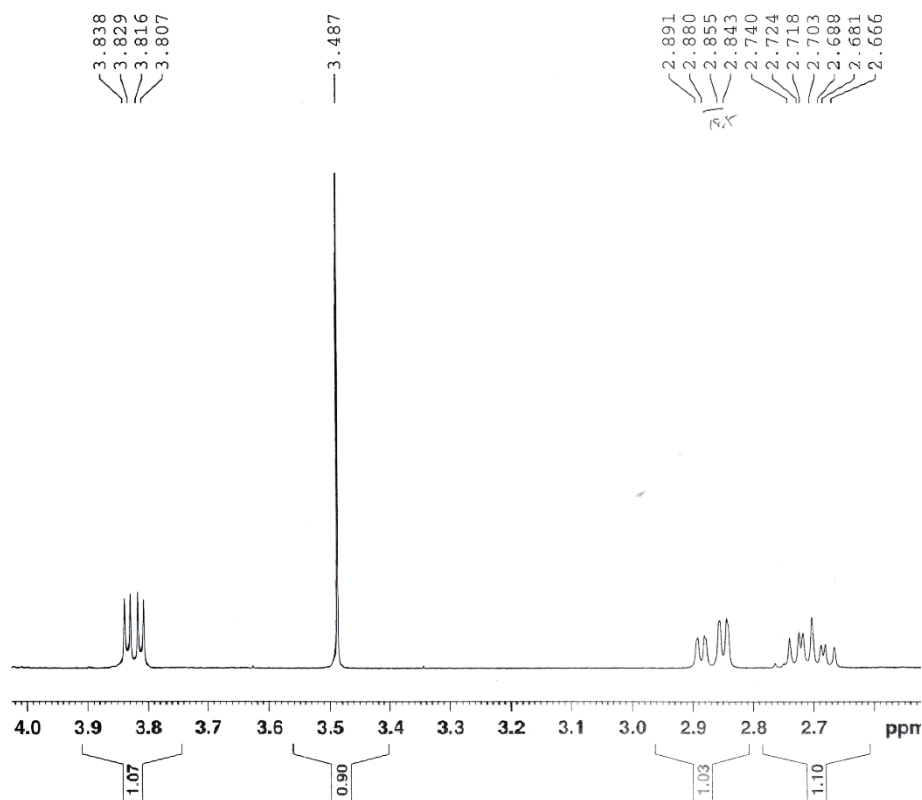
Figure S175 IR spectrum of compound 28



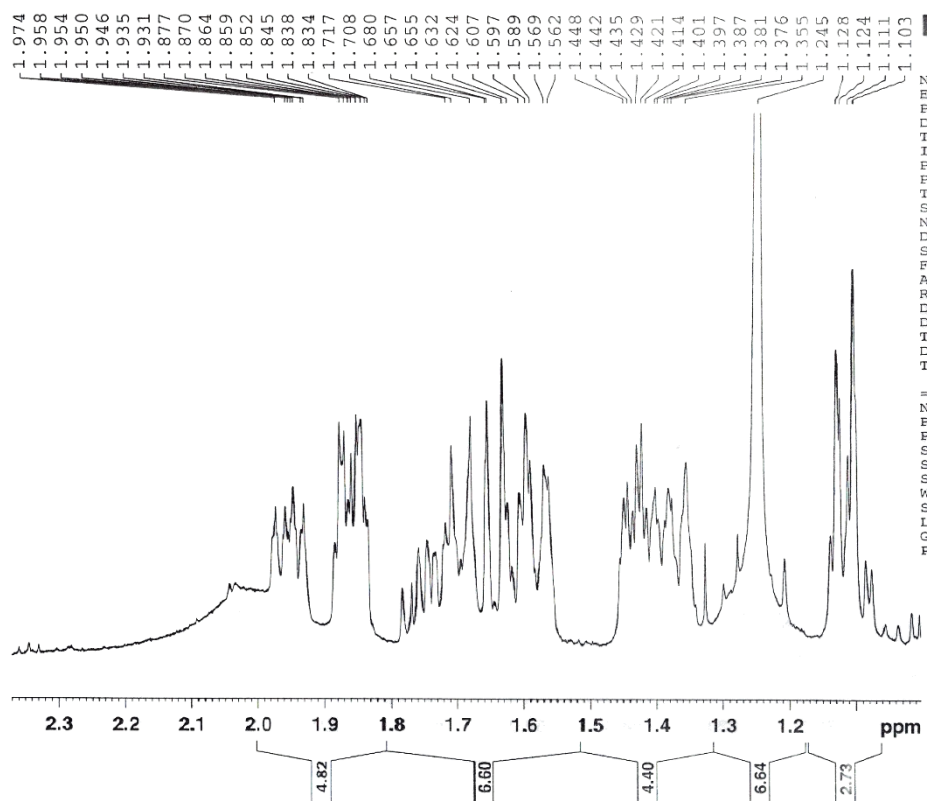
**Figure S176** <sup>1</sup>H NMR spectrum of compound **28** (500MHz, CDCl<sub>3</sub>)



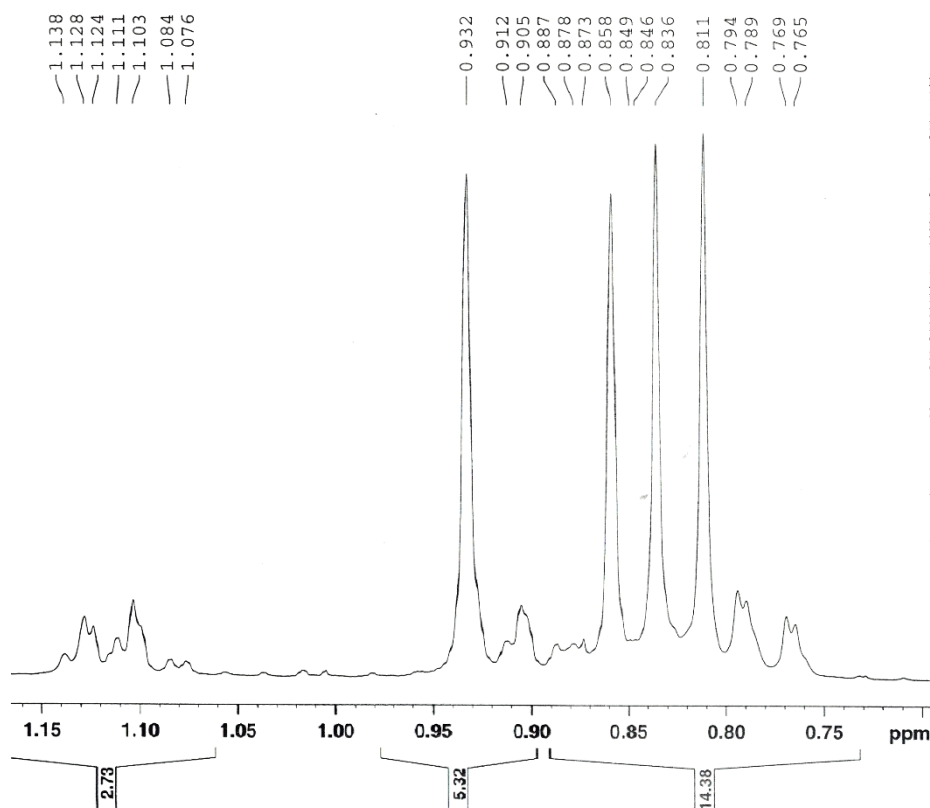
**Figure S177**  $^1\text{H}$  NMR spectrum of **28**  
(peak picked and integration tagged; 500 MHz,  $\text{CDCl}_3$ )



**Figure S178**  $^1\text{H}$  NMR spectrum of **28** (expanding 4.00-2.60 ppm; 500 MHz,  $\text{CDCl}_3$ )



**Figure S179**  $^1\text{H}$  NMR spectrum of **28** (expanding 2.30-1.00 ppm; 500 MHz,  $\text{CDCl}_3$ )



**Figure S180**  $^1\text{H}$  NMR spectrum of **28** (expanding 1.15-0.70 ppm; 500 MHz,  $\text{CDCl}_3$ )

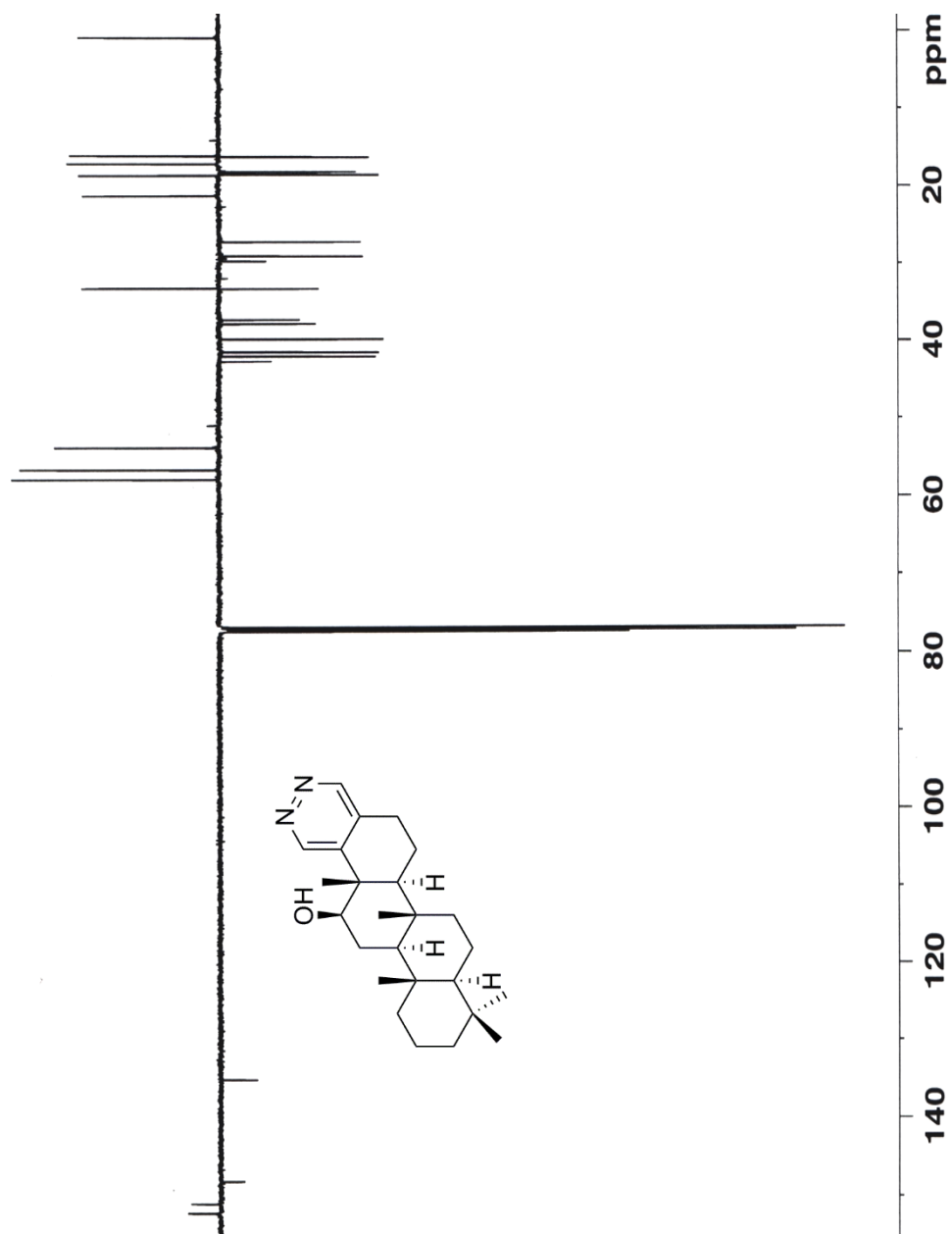
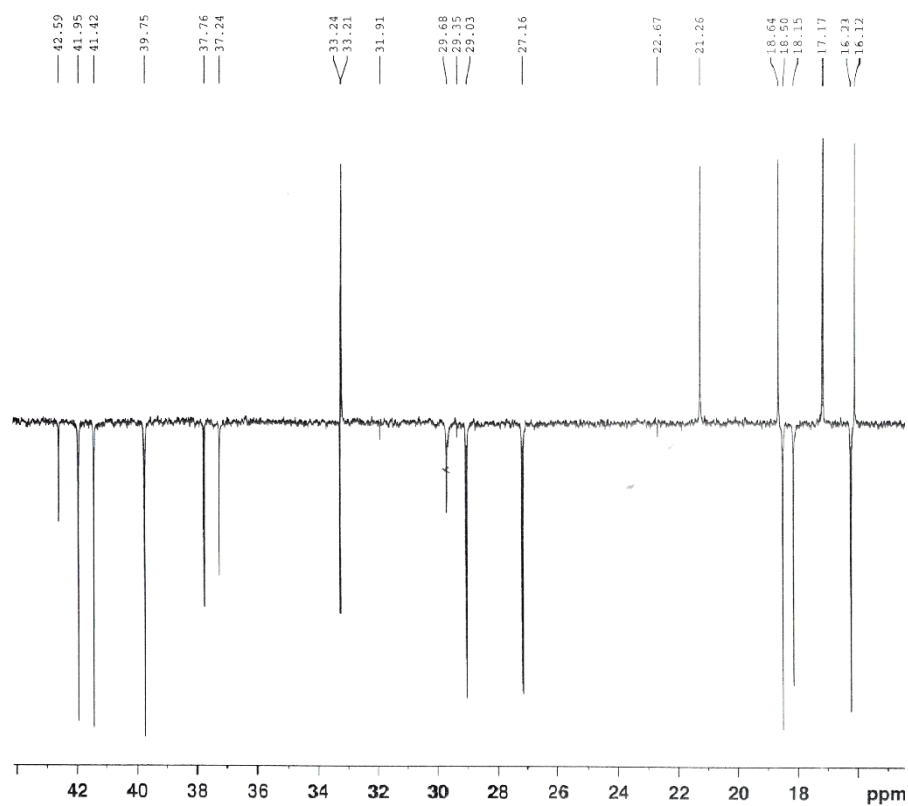
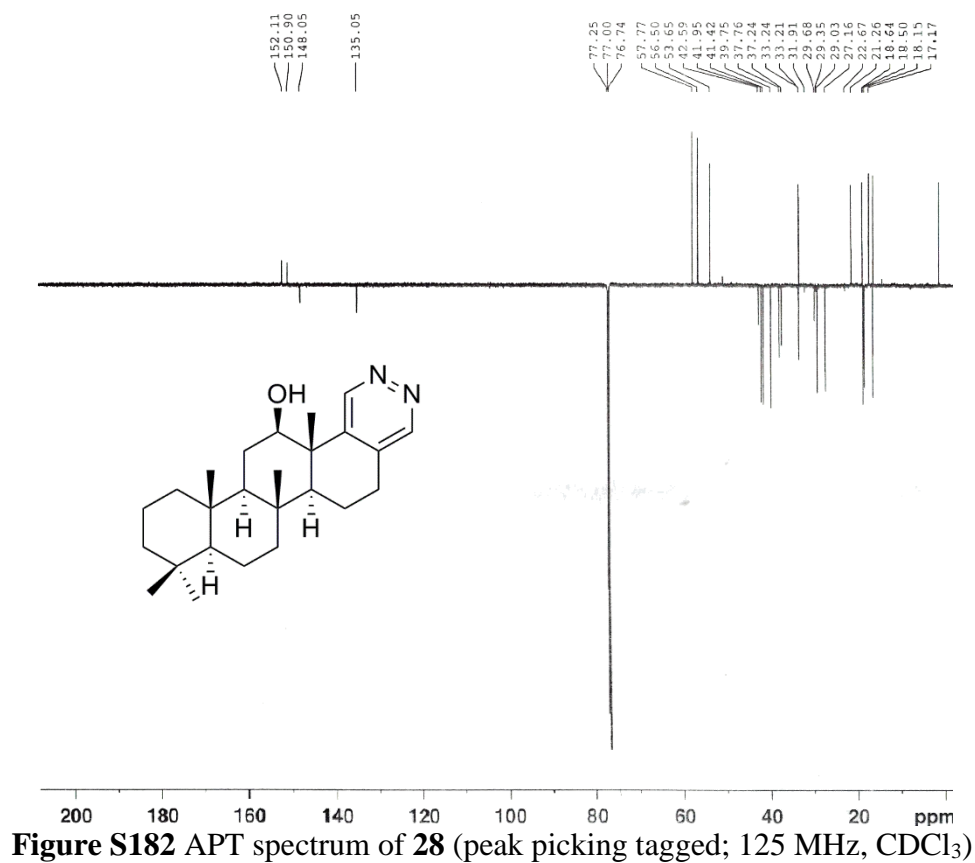
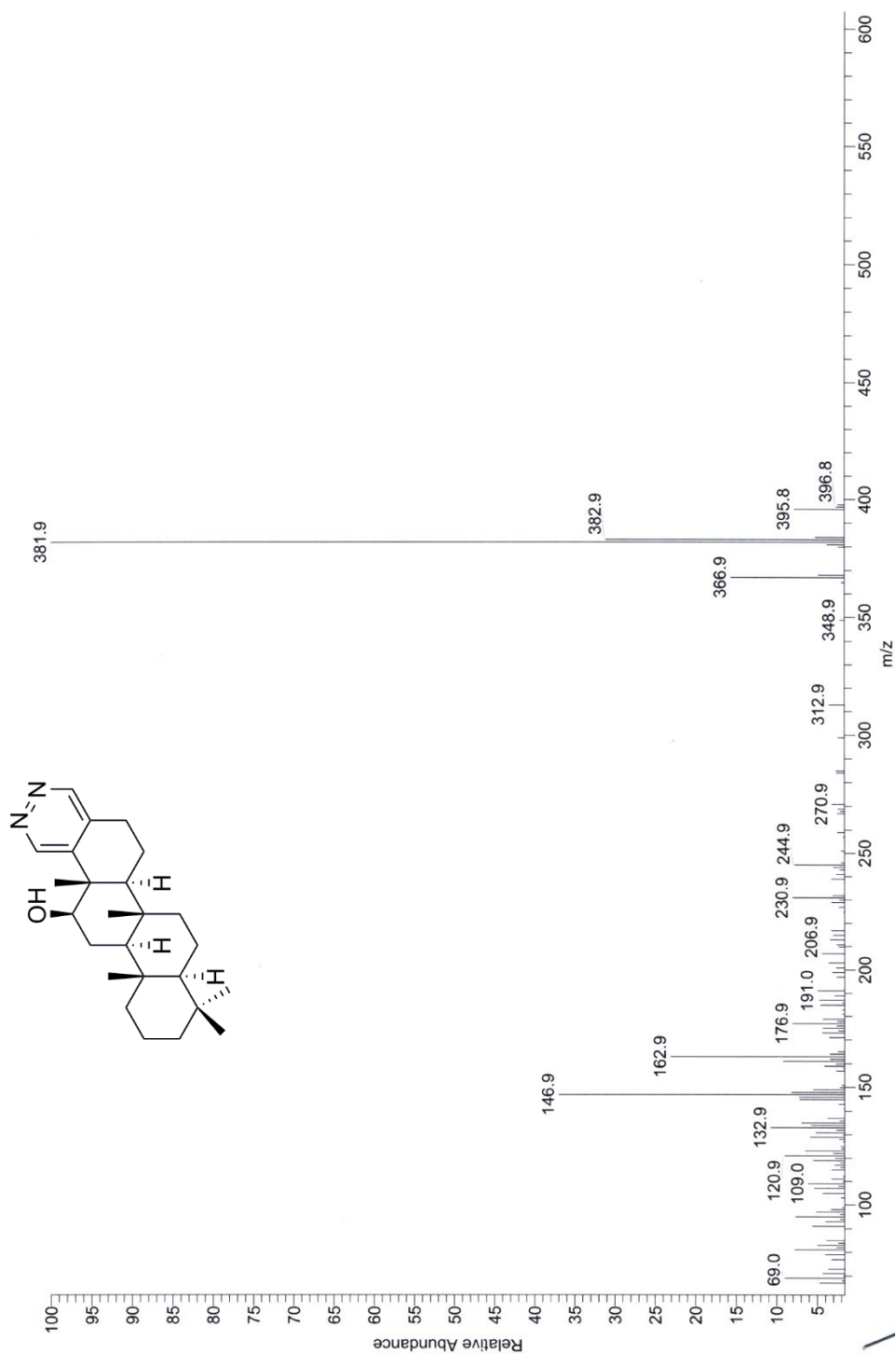
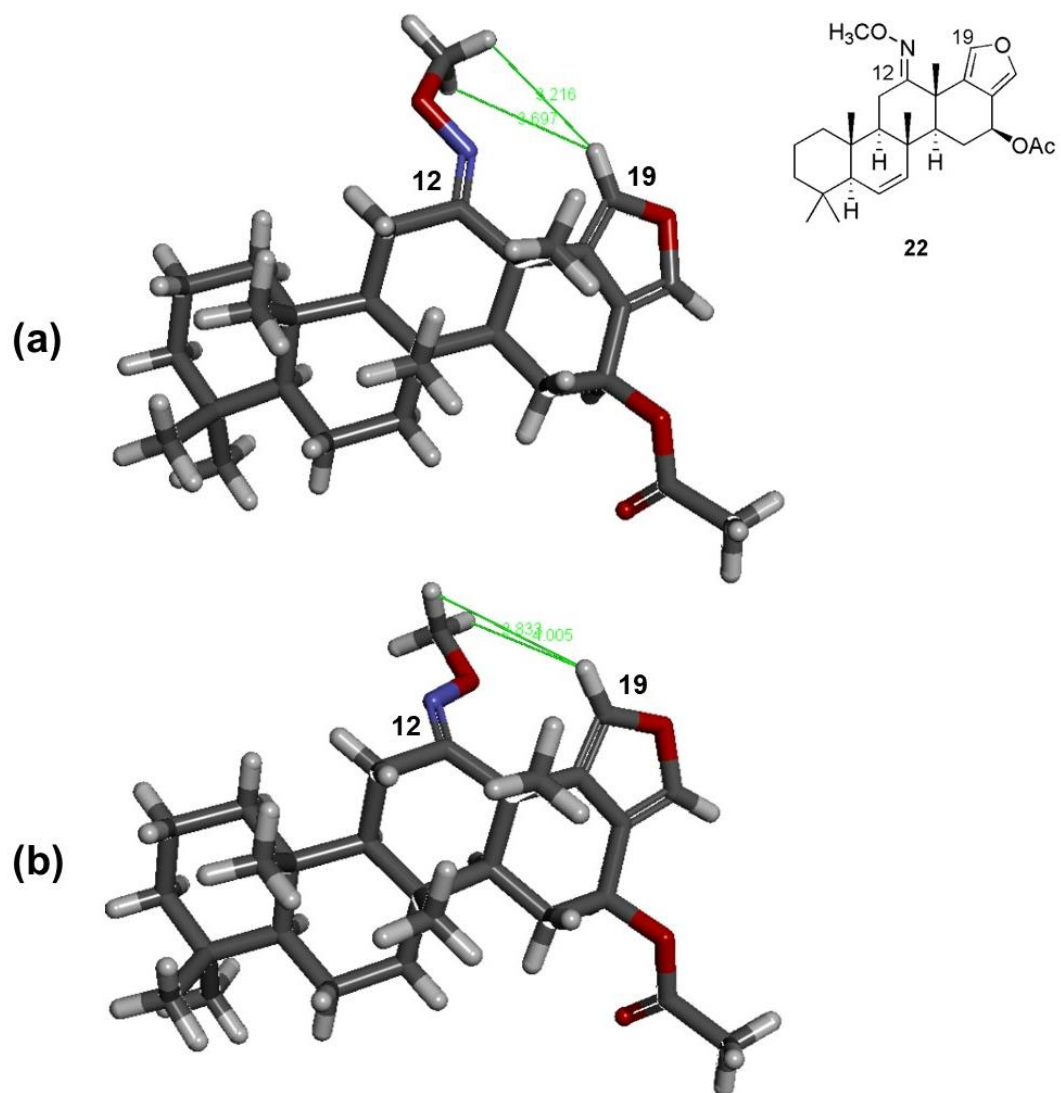


Figure S181 APT spectrum of compound 28 (125MHz, CDCl<sub>3</sub>)



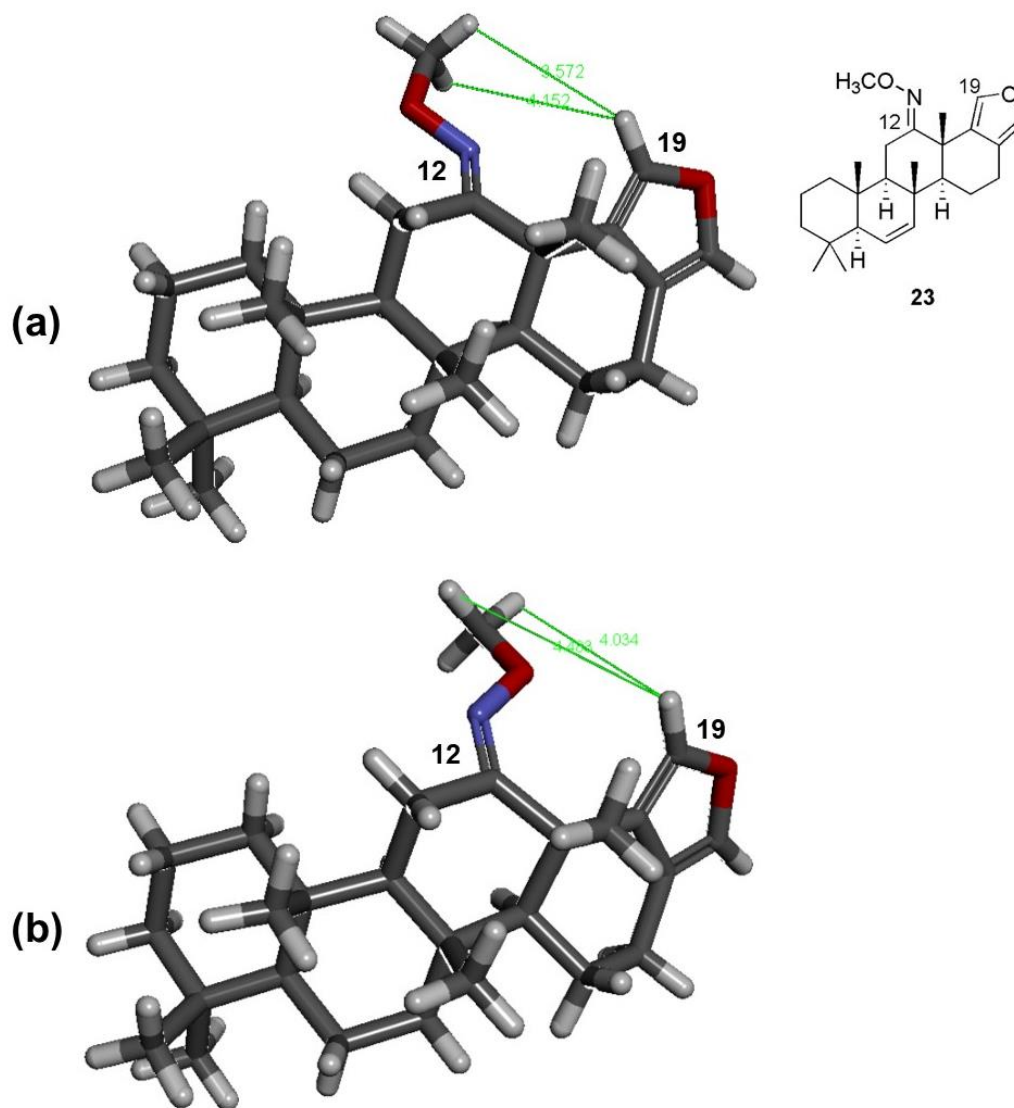


**Figure S184** EI mass spectrum of compound **28**



**Figure S185** Calculated interatomic distances between H-19 and 12-NOCH<sub>3</sub> for *E* (a) and *Z* (b) configuration of **22**





**Figure S186** Calculated interatomic distances between H-19 and 12-NOCH<sub>3</sub> for *E* (a) and *Z* (b) configuration of **23**

**Table S1.**  $\Delta\delta_{C\alpha}$  of compounds 20-23 (125 MHz,  $CDCl_3$ )

compounds	$\Delta\delta_{C-\alpha}$	
	$\Delta\delta_{C-11}$	$\Delta\delta_{C-13}$
20	18.0	6.9
21	18.1	6.9
22	17.4	7.3
23	18.2	7.3

**Table S2.** Calculated working molecular descriptors of scalaranes in the compound dataset

compounds	$E_{nb}$	$vsurf_{HD2}$	$vsurf_{CW3}$	$PEOE_{VSA+1}$	$\log P$ (o/w)
<b>1</b>	57.7132	0.9505	0.9557	26.8714	5.28
<b>2</b>	56.3187	0.9454	0.9279	26.8714	5.87
<b>3</b>	53.0447	0.9152	0.9293	17.7011	4.67
<b>4</b>	72.8694	0.9287	0.8554	36.9178	5.09
<b>5</b>	70.4747	1.0295	0.7958	36.9178	5.68
<b>6</b>	59.7575	1.2817	0.7741	8.5308	6.20
<b>7</b>	59.4938	1.4003	0.8831	34.7626	5.45
<b>8</b>	67.9628	1.6140	0.9164	41.1832	4.74
<b>9</b>	67.1199	1.3767	0.8771	13.4357	5.18
<b>10</b>	71.8821	1.2096	1.0112	13.4357	5.18
<b>11</b>	65.2619	1.5660	0.9022	4.2654	4.57
<b>12</b>	71.3779	1.3400	0.8851	13.4357	5.77
<b>13</b>	66.1311	0.8672	0.9223	55.3504	5.94
<b>14</b>	71.6745	0.7335	0.6549	54.7109	5.79
<b>24</b>	68.0062	1.1923	0.9876	55.3504	5.36
<b>21</b>	75.4527	0.5825	0.6262	43.7093	6.69
<b>20</b>	73.7781	0.7995	0.9068	52.8796	6.61
<b>22</b>	71.5506	0.5005	0.6829	90.6734	7.06
<b>26</b>	63.4330	1.3467	1.0819	32.6524	5.35
<b>27</b>	68.7942	1.5956	1.1775	32.6524	5.35
<b>28</b>	82.5506	0.9454	0.8572	51.1929	6.17
<b>30</b>	68.5747	1.0649	0.8404	47.5588	5.47