SUPPLEMENTARY MATERİAL

Triad Pyrazole-Thiazole-Coumarin Heterocyclic Core Effectively Inhibit HSP and Drive Cancer Cells To Apoptosis

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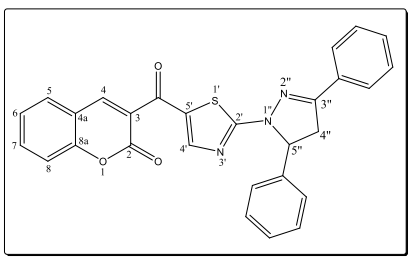
3-(2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-2*H*-chromen-2-one (PTC-1)



Color: Yellow, Yield 0,372 g, 78%, mp 275-277 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3042, 3029 (Ar-H); 2970, 2957, 2940 (alifatic C-H), 1718 (C=O, lactone); 1619 (C=O, ketone); 1603, 1564, 1544, 1505, 1490 (C=N and C=C). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 8.03 (s, CH, coumarin); 7.81 (s, CH, thiazole); 7.80-7.26 (m, 14H, Ar-H); 5.77-5.71 (dd, J_{cis}= 4.9 Hz, J_{trans}= 11.6 Hz, 1H, C_5H-pyrazole); 4.02-3.93 (dd, J_{gem}= 17.7 Hz, J_{trans}= 11.7 Hz, 1H, C_4H-pyrazole); 3.39-3.32 (dd, J_{gem}= 17.7 Hz, J_{cis}= 5.0 Hz, 1H, C_4H-pyrazole). ^{13}C-NMR (75 MHz; $CDCl_3$, ppm): δ 180.8 (C=O, ketone); 170.3 (C=N, thiazole); 158.2 (C=O, lactone); 155.4; 154.5; 151.1; 140.6; 133.4; 132.6; 130.8; 130.5; 129.7; 129.2; 129.0; 128.9; 128.2; 126.9; 126.7; 125.7; 124.9; 118.2; 116.9 (C=C and C=N); 63.7 (C_5-pyrazole);

43.9 (C_4-pyrazole). HRMS: m/z (M + H) calcd. for $C_{28}H_{19}N_3O_3S$: 478.1220; found: 478.1217. Elemental analysis calcd: C, 70.42; H, 4.01; N, 8.80; S, 6.71. Found: C, 70.09; H, 3.85; N, 8.74; S, 6.42 %.

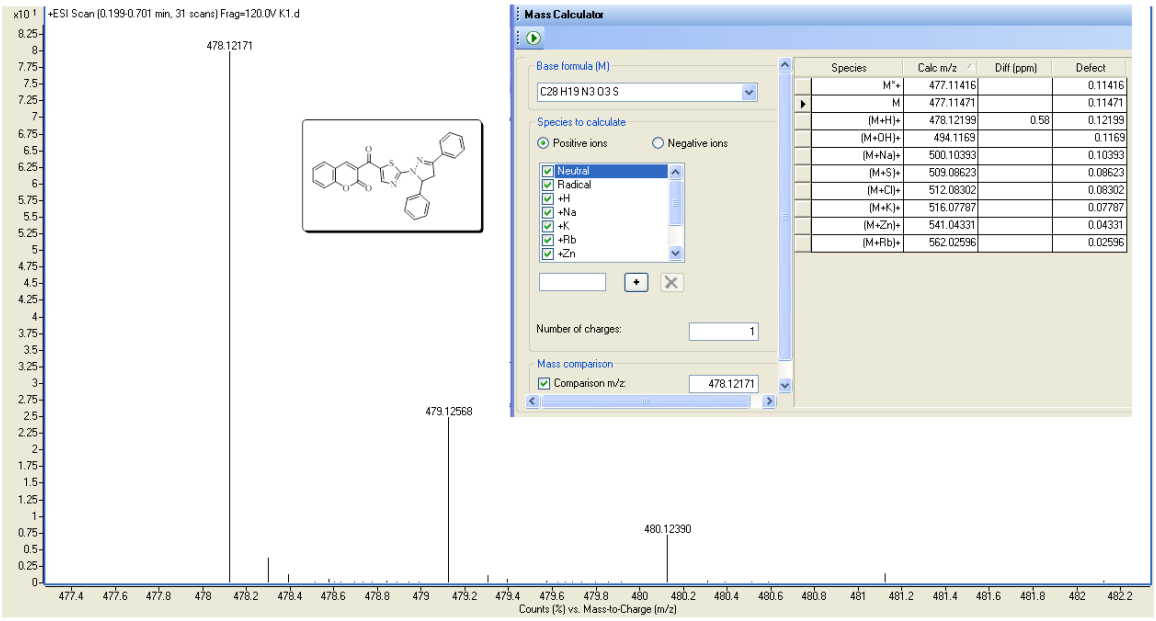


Figure S1: HRMS spectra of PTC-1

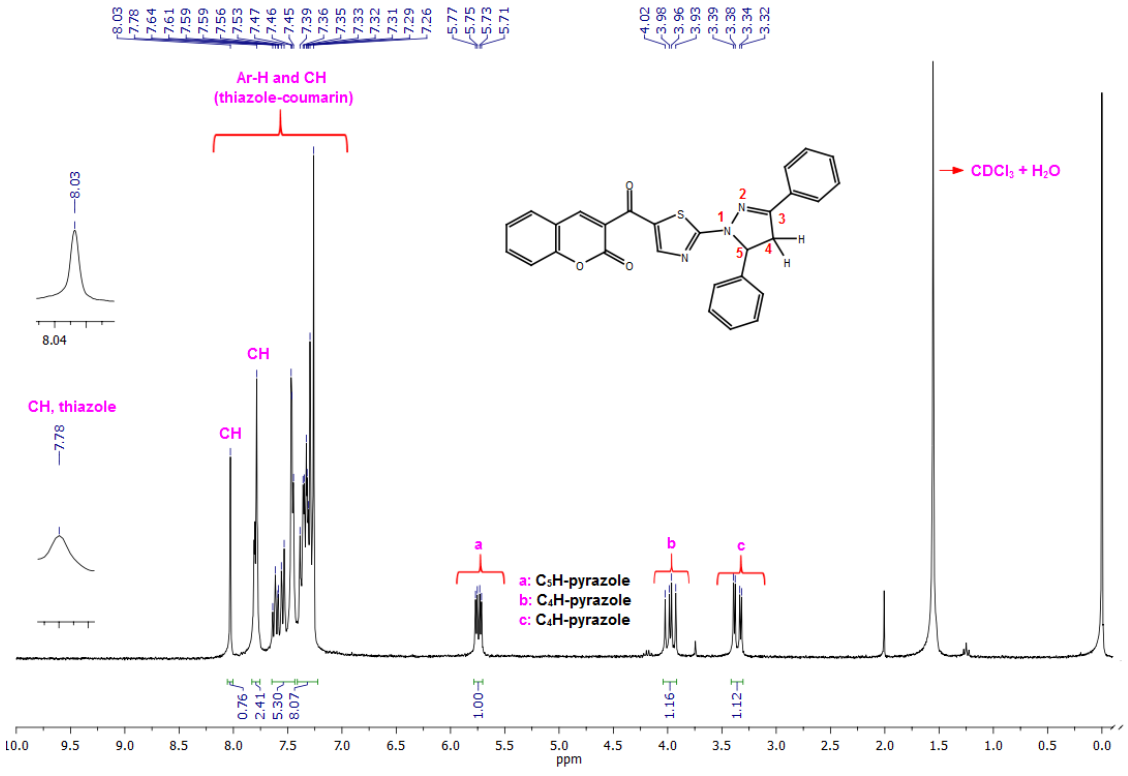


Figure S2: ^{1}H-NMR spectra of PTC-1

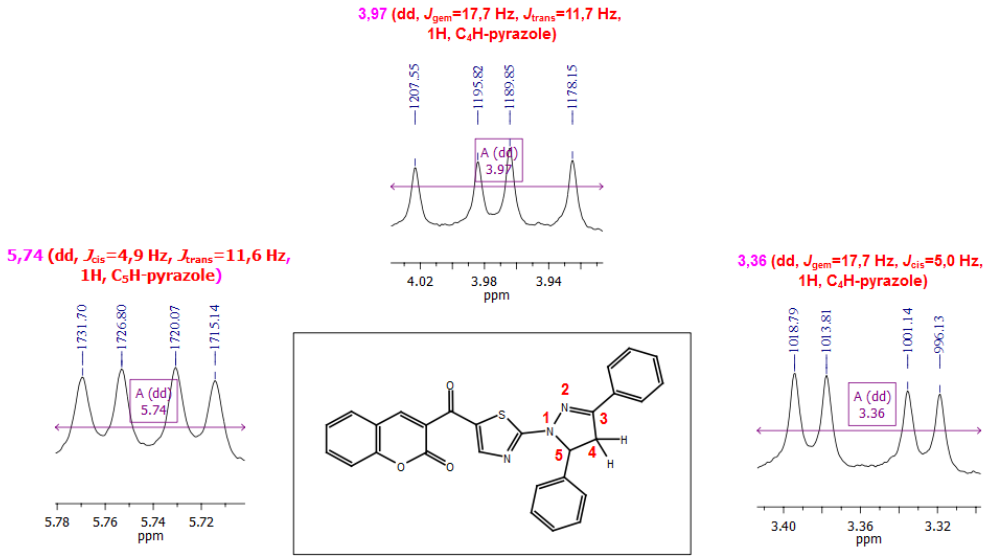


Figure S3: ^{1}H NMR splitting of the pyrazole protons (C_4H- and C_5H-) of compound PTC-1

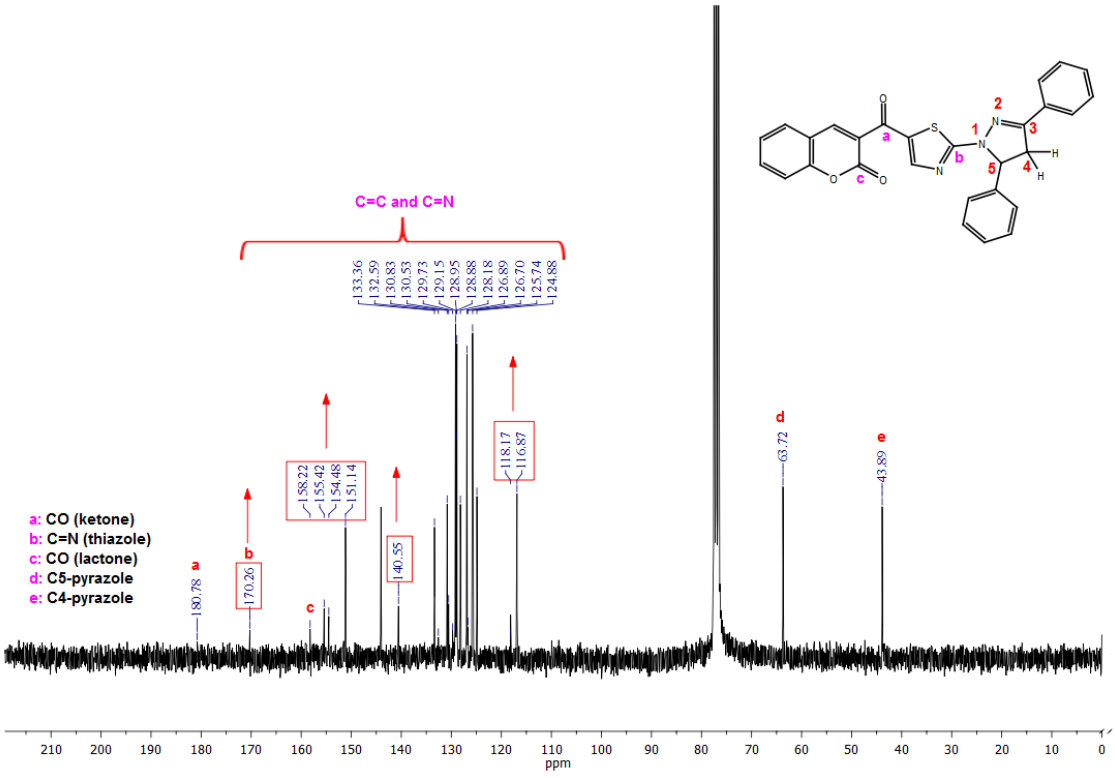
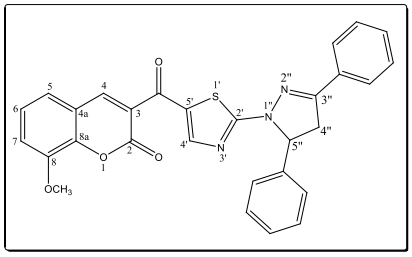


Figure S4: ^{13}C NMR spectra of PTC-1

3-(2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-8-methoxy-2*H*-chromen-2-one (PTC-2)



Color: Yellow, Yield 0,355 g, 70%, mp 198-200 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3060, 3028, 3006 (Ar-H); 2973, 2943, 2843 (alifatic C-H), 1712 (C=O, lactone); 1627 (C=O, ketone); 1601, 1576, 1532, 1505, 1489, 1475 (C=N and C=C), 1248 (C-O). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 8.01 (s, CH, coumarin); 7.79 (s, CH, thiazole); 7.81-7.10 (m, 13H, Ar-H); 5.77-5.71 (dd, J_{cis}= 4.9 Hz, J_{trans}= 11.7 Hz, 1H, C_5H-pyrazole); 4.02-3.92 (dd, 1H, C_4H-pyrazole); 3.97 (s, 3H, OCH_3); 3.39-3.31 (dd, J_{gem}= 17.7 Hz, J_{cis}= 5.0 Hz, 1H, C_4H-pyrazole). ^{13}C-NMR (75 MHz; $CDCl_3$, ppm): δ 180.8 (C=O, ketone); 170.2 (C=N, thiazole); 157.7 (C=O, lactone); 155.4; 151.2; 147.2; 144.4; 144.2; 140.6; 130.8; 130.5; 129.7; 129.1; 129.0; 128.9; 128.2; 126.9; 125.7; 124.7; 120.2; 118.8; 115.1 (C=C and C=N); 63.7 (C_5-pyrazole); 56.3 (OCH_3); 43.9 (C_4-pyrazole). HRMS: m/z (M + H) calcd. for $C_{29}H_{21}N_3O_4S$: 508,1326; found: 508,1322. Elemental analysis calcd: C, 68.62; H, 4.17; N, 8.28; S, 6.32. Found: C, 68.36; H, 4.00; N, 8.15; S, 6.02 %.

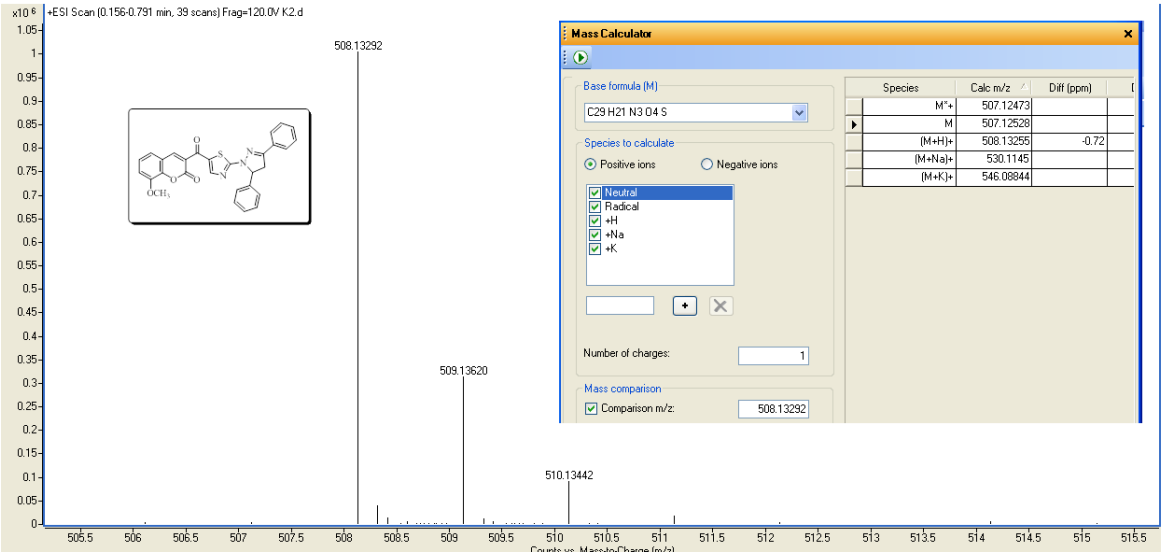


Figure S5: HRMS spectra of PTC-2

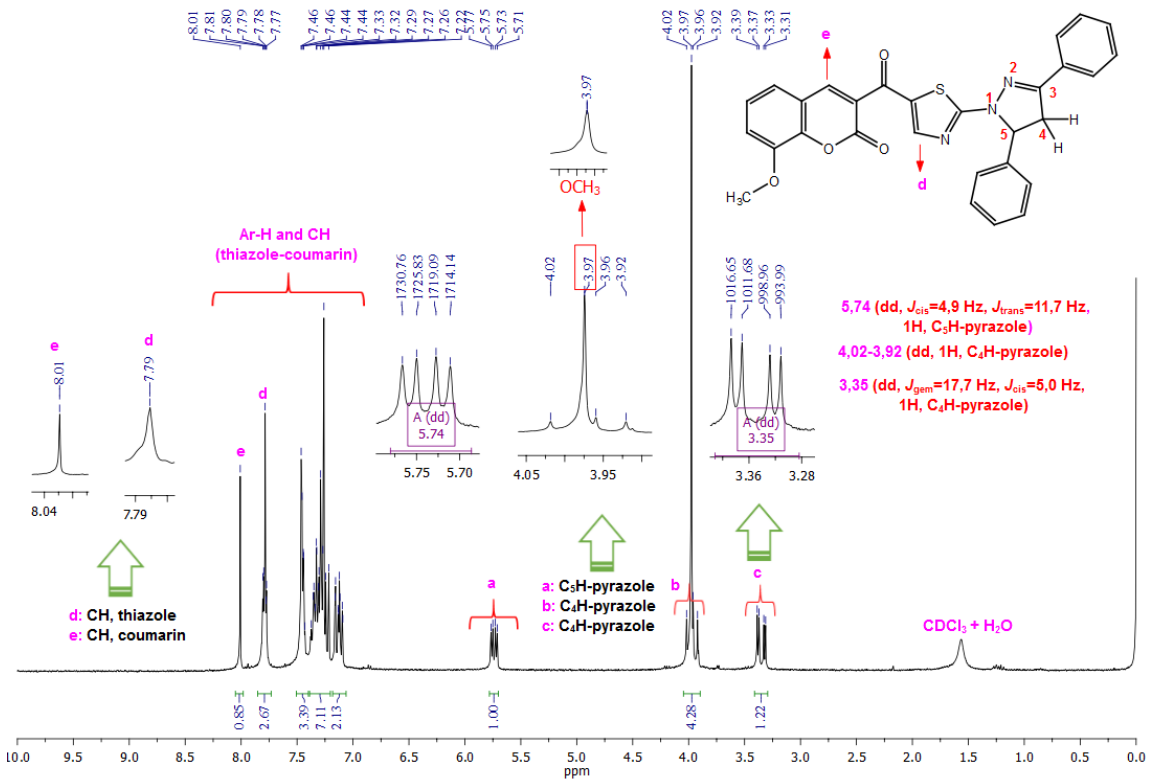


Figure S6: ^{1}H NMR spectra of PTC-2

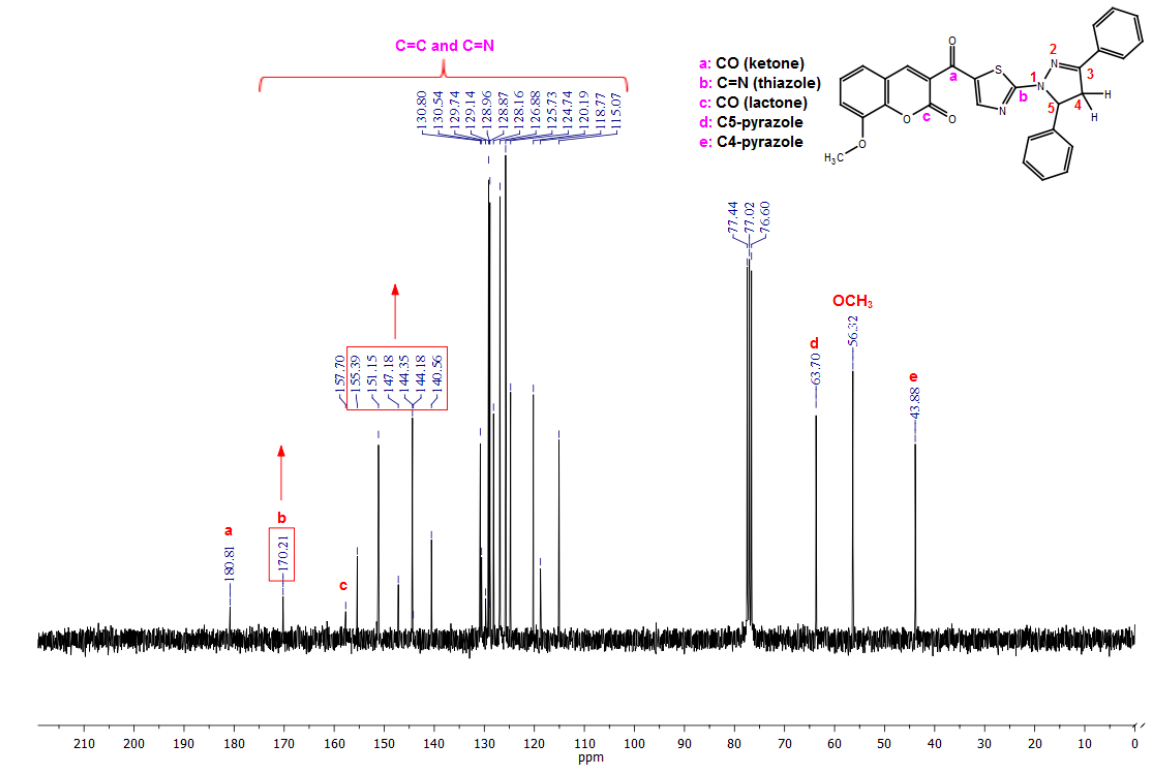
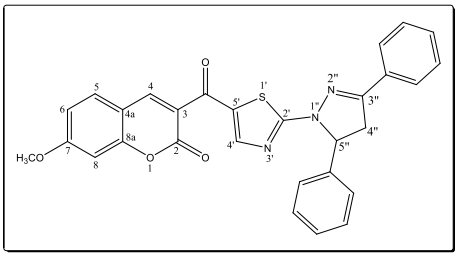


Figure S7: ^{13}C NMR spectra of PTC-2

3-(2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-7-methoxy-2*H*-chromen-2-one (PTC-3)



Color: Yellow, Yield 0,375 g, 74%, mp 248-250 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3096, 3057, 3035, 3006 (Ar-H); 2971, 2944, 2840 (alifatic C-H), 1722 (C=O, lactone); 1626 (C=O, ketone); 1615, 1561, 1537, 1504, 1488 (C=N and C=C), 1239 (C-O). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 8.03 (s, CH, coumarin); 7.81 (s, CH, thiazole); 7.80-6.84 (m, 13H, Ar-H); 5.77-5.72 (dd, J_{cis}= 5.0 Hz, J_{trans}= 11.7 Hz, 1H, C_5H-pyrazole); 4.02-3.92 (dd, J_{gem}= 17.7 Hz, J_{trans}= 11.7 Hz, 1H, C_4H-pyrazole); 3.90 (s, 3H, OCH_3); 3.39-3.31 (dd, J_{gem}= 17.7 Hz, J_{cis}= 5.0 Hz, 1H, C_4H-pyrazole). ^{13}C-NMR (75 MHz; $CDCl_3$, ppm): δ 181.1 (C=O, ketone); 170.1 (C=N, thiazole); 164.4 (C-OCH_3); 158.6 (C=O, lactone); 156.7; 155.2; 150.7; 144.8; 140.6; 130.8; 130.6; 130.1; 130.0; 129.1; 128.9; 128.1; 126.8; 125.7; 122.9; 113.5; 111.8; 100.6 (C=C and C=N); 63.7 (C_5-pyrazole); 55.9 (OCH_3); 43.9 (C_4-pyrazole). HRMS: m/z (M + H) calcd. for $C_{29}H_{21}N_3O_4S$: 508.1326; found: 508.1322. Elemental analysis calcd: C, 68.62; H, 4.17; N, 8.28; S, 6.32. Found: C, 68.94; H, 4.05; N, 8.12; S, 5.97 %.

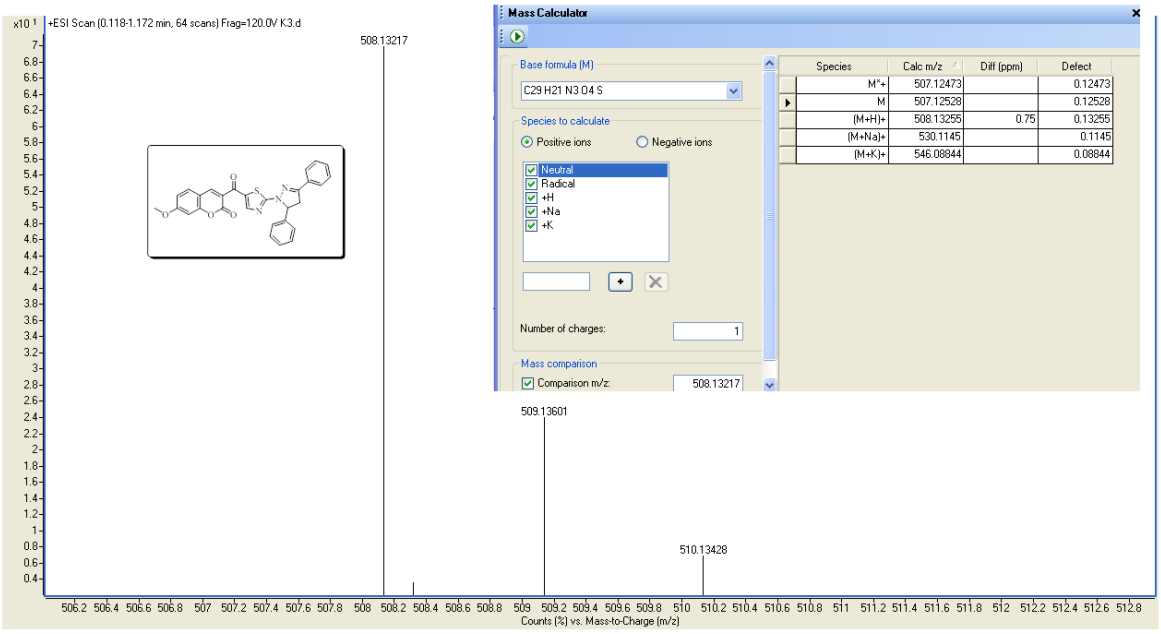


Figure S8: HRMS spectra of PTC-3

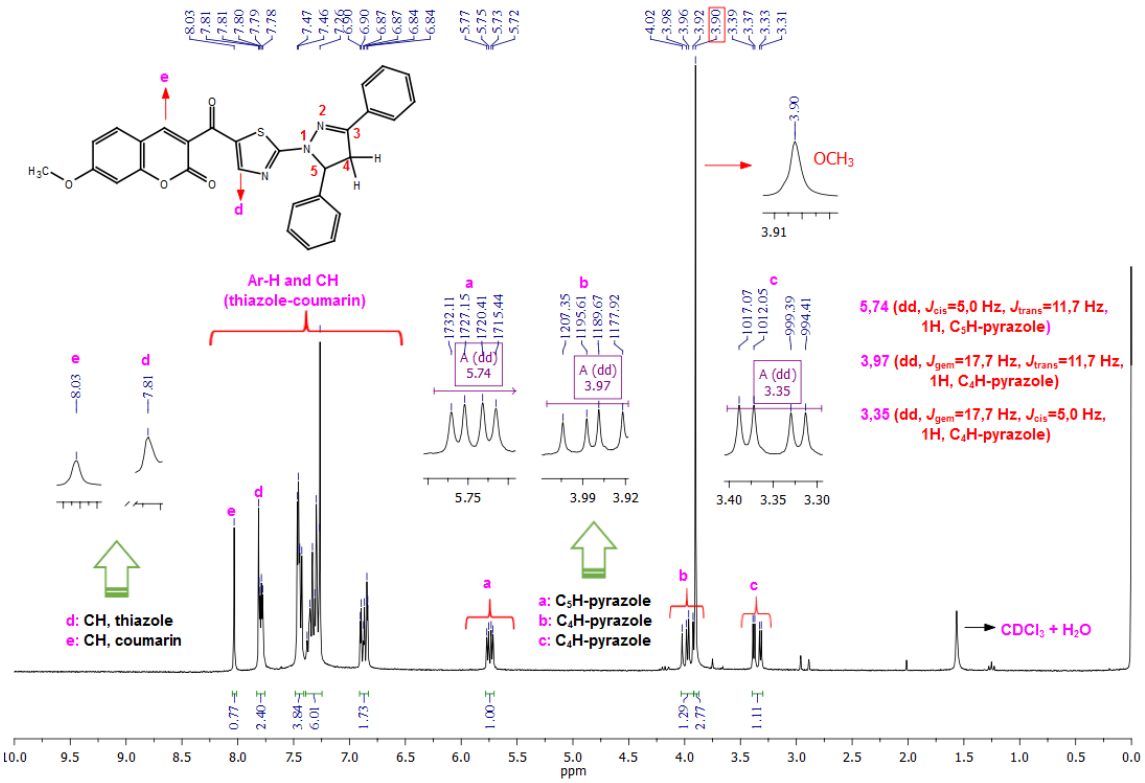


Figure S9: ^{1}H NMR spectra of PTC-3

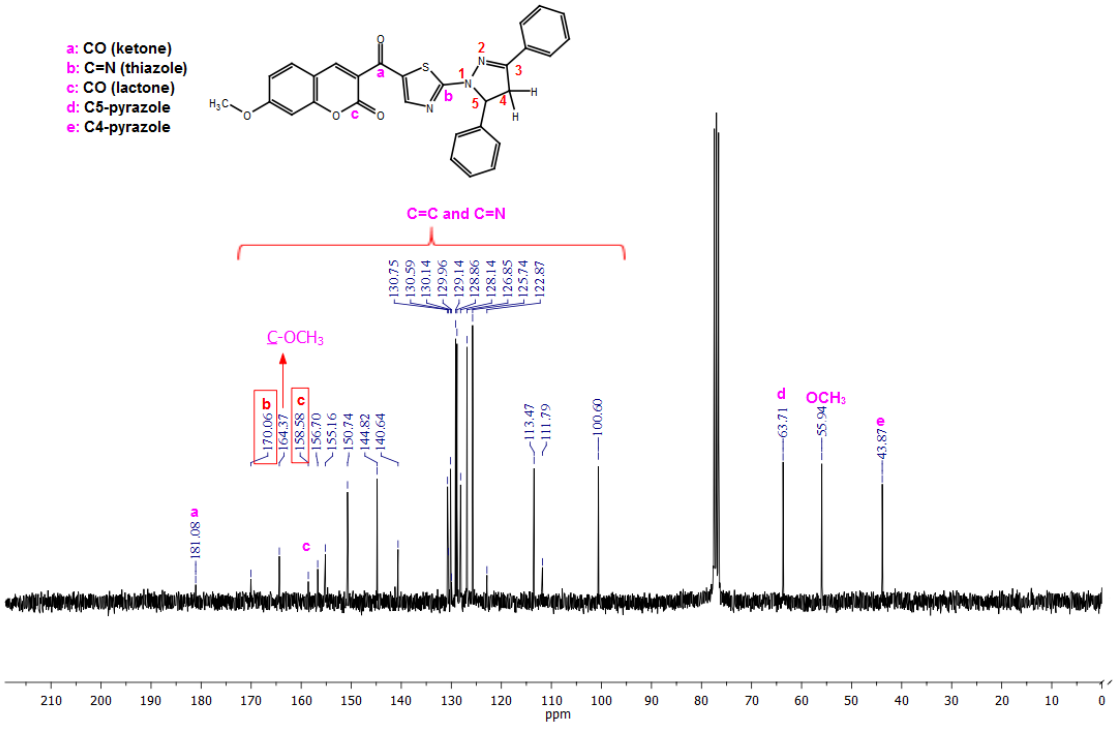
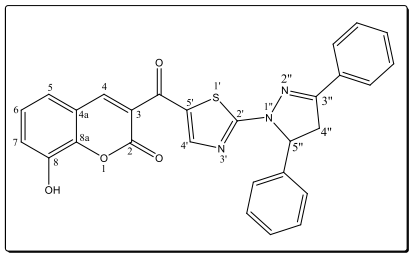


Figure S10: ^{13}C NMR spectra of PTC-3

3-(2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-8-hydroxy-2*H*-chromen-2-one (PTC-4)



Color: Yellow, Yield 0,340 g, 69%, mp 254-256 ºC, FT-IR (ATR, cm^{-1}): υ_{max} 3361 (O-H), 3060, 3036, 3028 (Ar-H); 2939, 2925, 2918 (alifatic C-H), 1724 (C=O, lactone); 1632 (C=O, ketone); 1622, 1606, 1586, 1564, 1535, 1509, 1493, 1470 (C=N and C=C). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 8.03 (s, CH, coumarin); 7.77 (s, CH, thiazole); 7.81-7.21 (m, 13H, Ar-H); 5.97 (s, 1H, OH); 5.78-5.72 (dd, J_{cis}= 5.0 Hz, J_{trans}= 11.7 Hz, 1H, C_5H-pyrazole); 4.03-3.93 (dd, J_{gem}= 17.7 Hz, J_{trans}= 11.7 Hz, 1H, C_4H-pyrazole); 3.40-3.32 (dd, J_{gem}= 17.7 Hz, J_{cis}= 5.0 Hz, 1H, C_4H-pyrazole). ^{13}C-NMR (75 MHz; DMSO-d_6, ppm): δ 181.6 (C=O, ketone); 169.4 (C=N, thiazole); 158.1 (C=O, lactone); 157.6; 153.0; 145.0; 144.9; 141.5; 131.4; 130.6; 129.4; 129.4; 129.3; 128.2; 127.5; 126.4; 126.3; 126.2; 125.2; 120.0; 120.0; 119.7 (C=C and C=N); 63.9 (C_5-pyrazole); 44.2 (C_4-pyrazole). HRMS: m/z (M + H) calcd. for $C_{28}H_{19}N_3O_4S$: 494.1169; found: 494,1166. Elemental analysis calcd: C, 68.14; H, 3.88; N, 8.51; S, 6.50. Found: C, 67.87; H, 3.66; N, 8.21; S, 6.20 %.

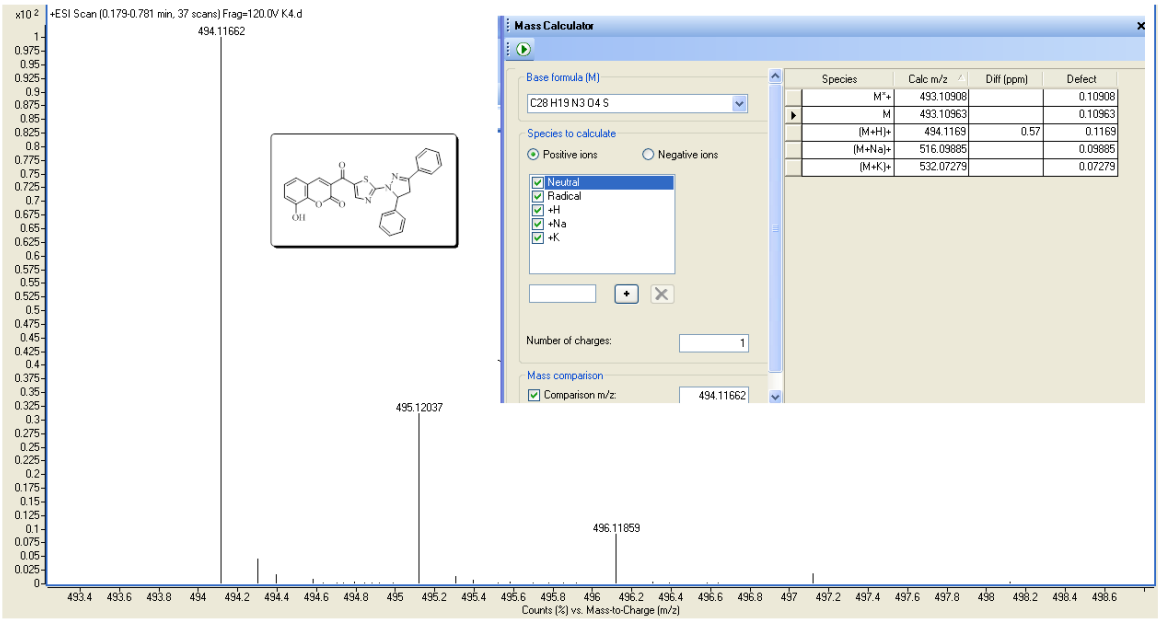


Figure S11: HRMS spectra of PTC-4

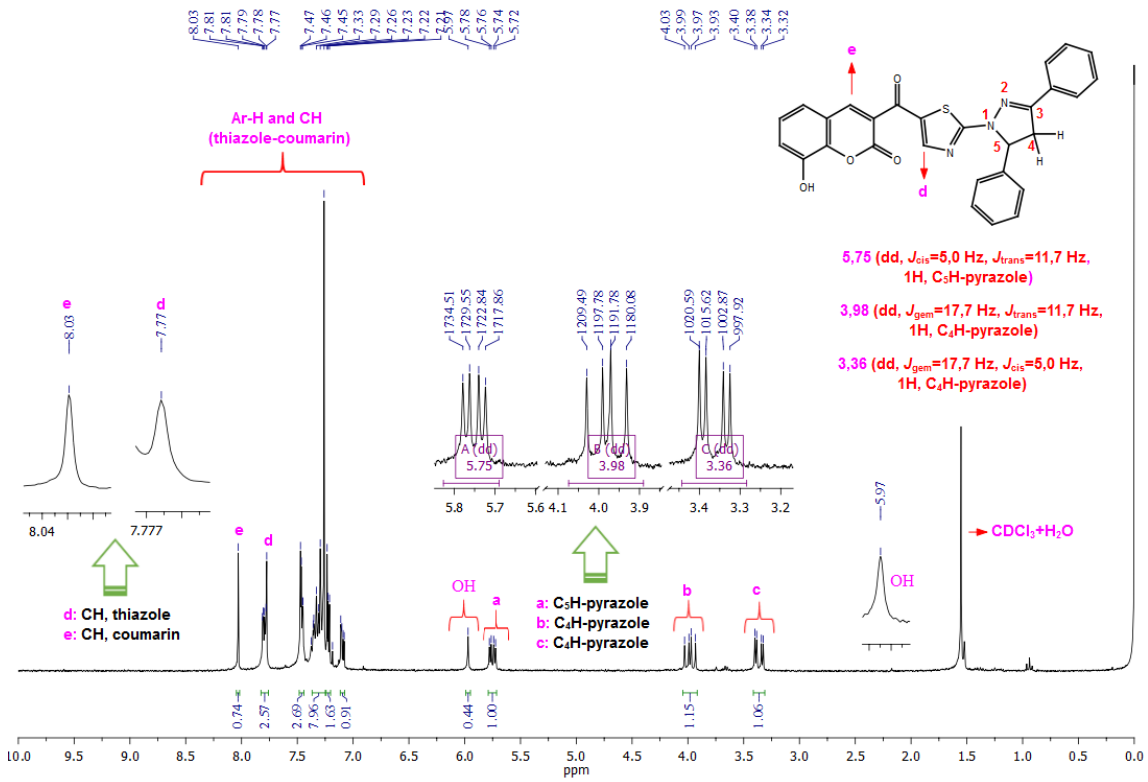


Figure S12: ^{1}H NMR spectra of PTC-4

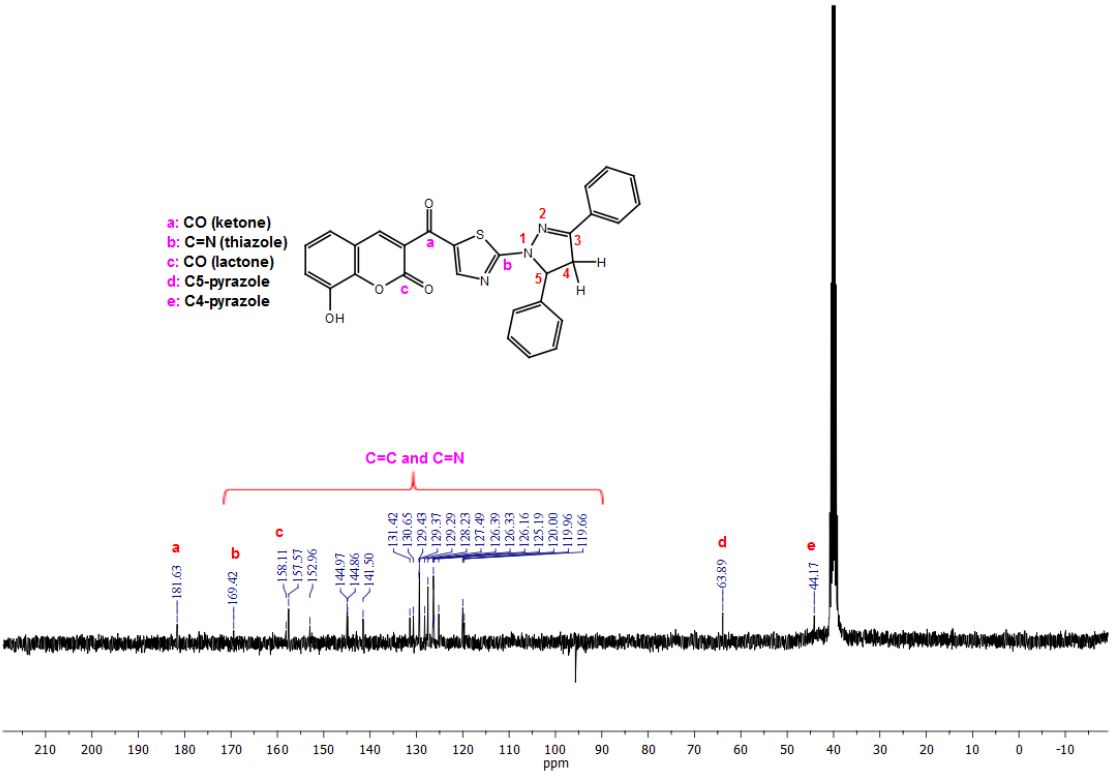
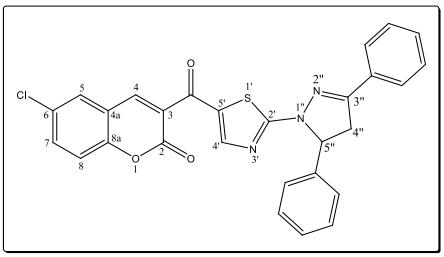


Figure S13: ^{13}C NMR spectra of PTC-4

6-chloro-3-(2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-2*H*-chromen-2-one (PTC-5)



Color: Yellow, Yield 0,430 g, 84%, mp 250-253 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3086, 3059, 3029, 3009 (Ar-H); 2971, 2956, 2907 (alifatic C-H), 1718 (C=O, lactone); 1618 (C=O, ketone); 1602, 1564, 1542, 1505, 1489 (C=N and C=C). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 7.93 (s, CH, coumarin); 7.76 (s, CH, thiazole); 7.81-7.26 (m, 13H, Ar-H); 5.77-5.72 (dd, J_{cis}= 4.9 Hz, J_{trans}= 11.7 Hz, 1H, C_5H-pyrazole); 4.03-3.93 (dd, J_{gem}= 17.7 Hz, J_{trans}= 11.7 Hz, 1H, C_4H-pyrazole); 3.40-3.33 (dd, J_{gem}= 17.7 Hz, J_{cis}= 5.0 Hz, 1H, C_4H-pyrazole). ^{13}C-NMR (75 MHz; $CDCl_3$, ppm): δ 180.2 (C=O, ketone); 170.4 (C=N, thiazole); 157.6 (C=O, lactone); 155.6; 152.8; 151.4; 142.5; 140.5; 133.2; 130.9; 130.5; 130.2; 129.5; 129.2; 128.9; 128.2; 128.0; 127.8; 126.9; 125.8; 119.1; 118.3 (C=C and C=N); 63.7 (C_5-pyrazole); 43.9 (C_4-pyrazole). HRMS: m/z (M + H) calcd. for $C_{28}H_{18}ClN_3O_3S$: 512.0830; found: 512.0825. Elemental analysis calcd: C, 65.69; H, 3.54; N, 8.21; S, 6.26. Found: C, 65.32; H, 3.31; N, 7.94; S, 5.95 %.

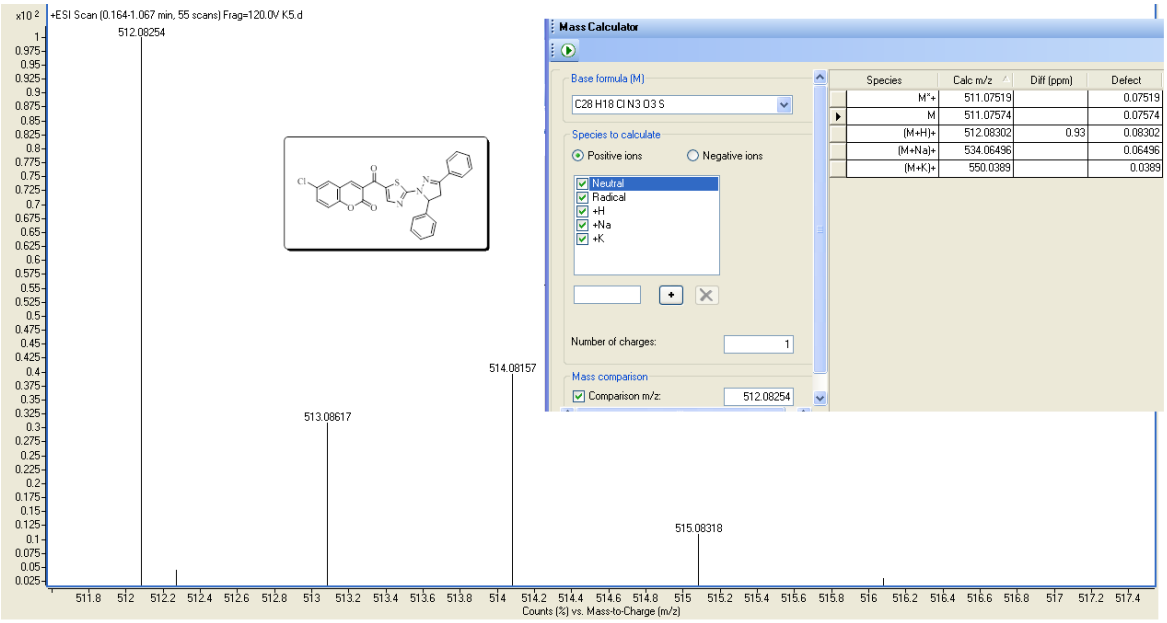


Figure S14: HRMS spectra of PTC-5

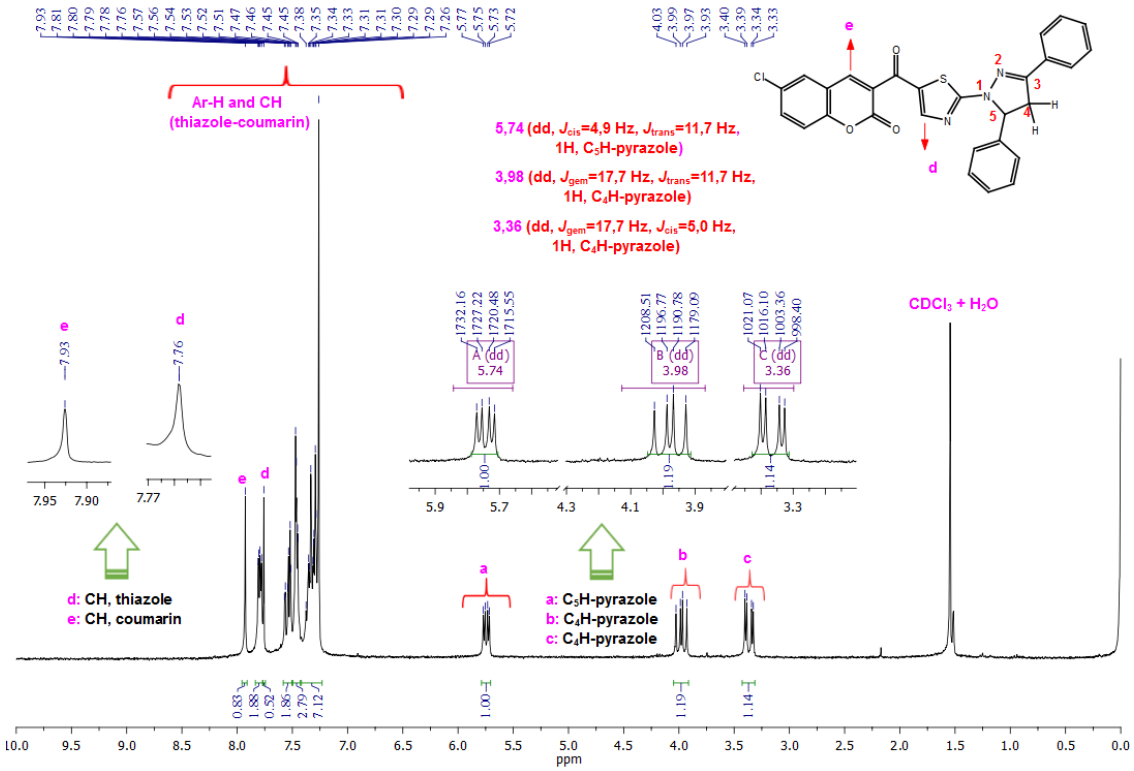


Figure S15: ^{1}H NMR spectra of PTC-5

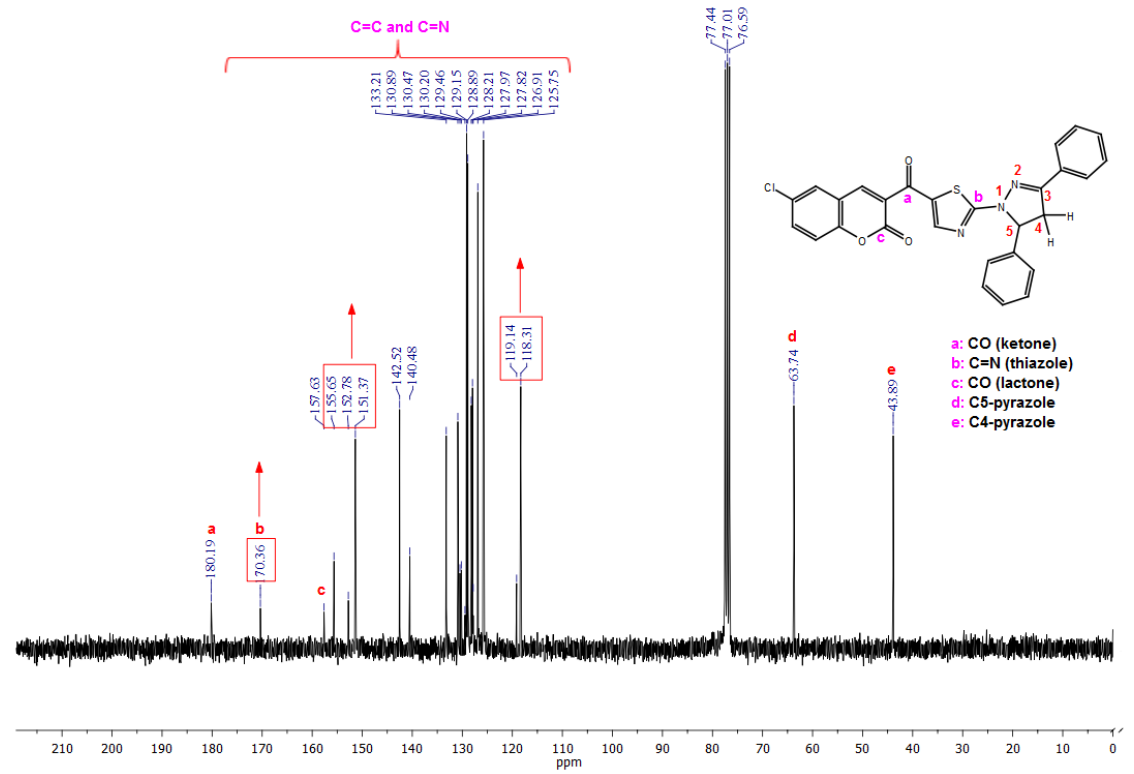
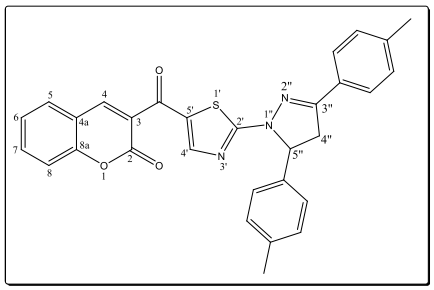


Figure S16: ^{13}C NMR spectra of PTC-5

3-(2-(3,5-di *p*-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-2*H*-chromen-2-one (PTC-6)



Color: Yellow, Yield 0,409 g, 81%, mp 234-235 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3052, 3030 (Ar-H); 2948, 2923, 2858 (alifatic C-H), 1738 (C=O, lactone); 1618 (C=O, ketone); 1609, 1581, 1553, 1535, 1494 (C=N and C=C). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 8.02 (s, CH, coumarin); 7.78 (s, CH, thiazole); 7.69-7.15 (m, 12H, Ar-H); 5.71-5.65 (dd, J_{cis}= 4.9 Hz, J_{trans}= 11.6 Hz, 1H, C_5H-pyrazole); 3.97-3.88 (dd, J_{gem}= 17.6 Hz, J_{trans}= 11.6 Hz, 1H, C_4H-pyrazole); 3.35-3.28 (dd, J_{gem}= 17.7 Hz, J_{cis}= 4.9 Hz, 1H, C_4H-pyrazole); 2.41 and 2.32 (s, 6H, 2 x Ar-CH_3). ^{13}C-NMR (75 MHz; $CDCl_3$, ppm): δ 180.7 (C=O, ketone); 170.3 (C=N, thiazole); 158.2 (C=O, lactone); 154.5; 151.3; 143.9; 141.3; 137.9; 137.7; 133.3; 129.8; 129.6; 129.5; 128.9; 127.8; 126.9; 126.7; 125.8; 125.7; 124.9; 118.2; 116.8 (C=C and C=N); 63.5 (C_5-pyrazole); 44.0 (C_4-pyrazole); 21.6; 21,1 (2 x Ar-CH_3). HRMS: m/z (M + H) calcd. for $C_{30}H_{23}N_3O_3S$: 506.1533; found: 506.1526. Elemental analysis calcd: C, 71.27; H, 4.59; N, 8.31; S, 6.34. Found: C, 71.05; H, 4.40; N, 8.03; S, 6.01 %.

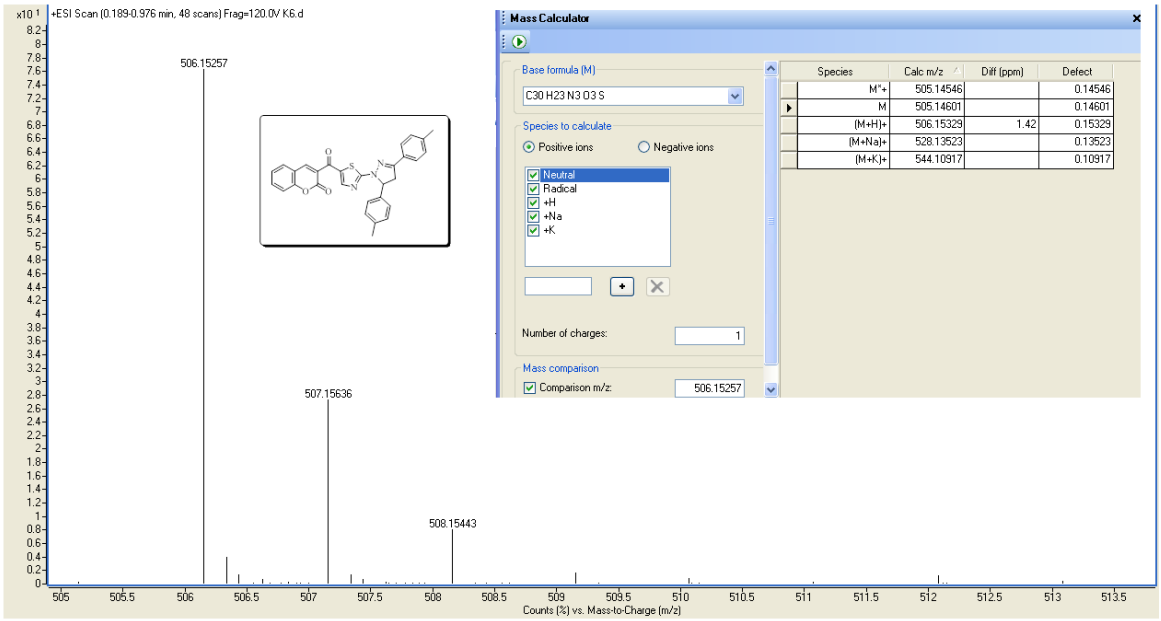


Figure S17: HRMS spectra of PTC-6

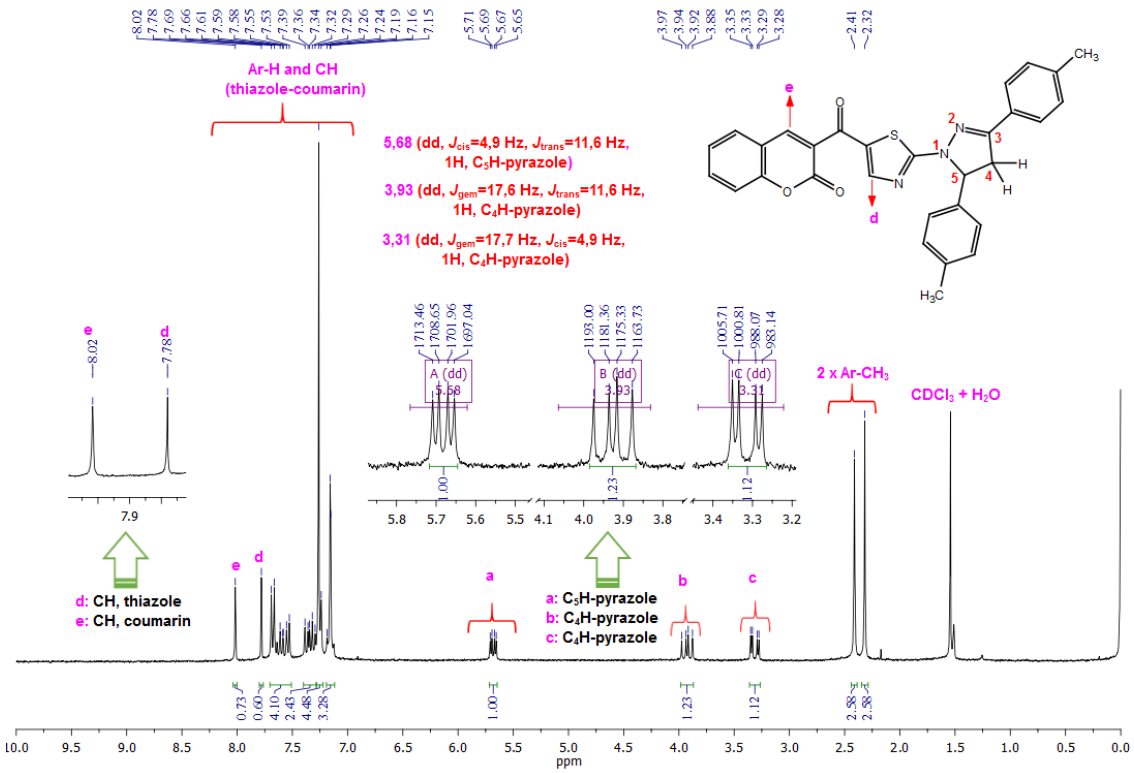


Figure S18: ^{1}H NMR spectra of PTC-6

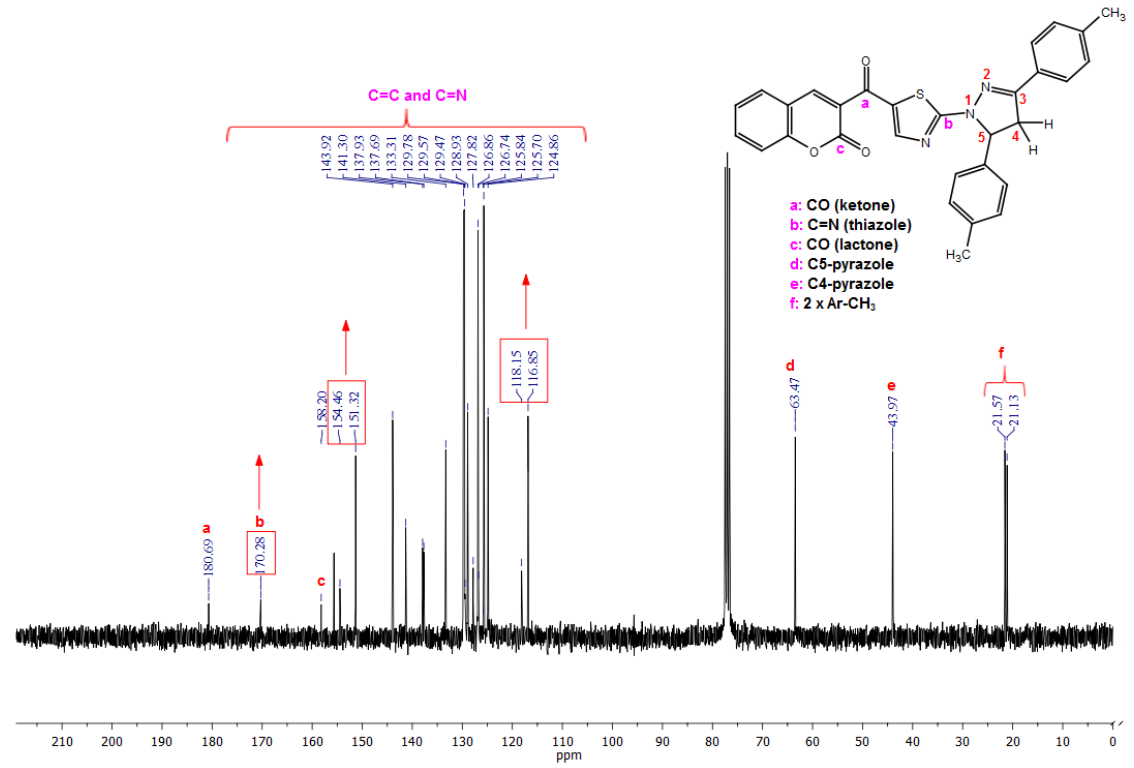
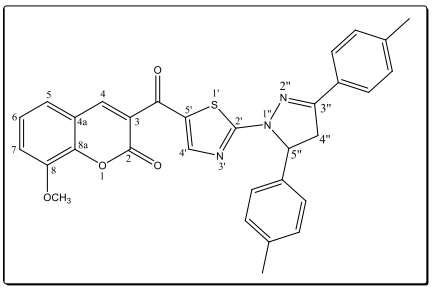


Figure S19: ^{13}C NMR spectra of PTC-6

3-(2-(3,5-di*p*-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-8-methoxy-2*H*-chromen-2-one (PTC-7)



Color: Yellow, Yield 0,396 g, 74%, mp 146-148 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3026, 3004 (Ar-H); 2936, 2920, 2839 (alifatic C-H), 1721 (C=O, lactone); 1621 (C=O, ketone); 1608, 1576, 1538, 1489, 1472 (C=N and C=C), 1242 (C-O). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 8.00 (s, CH, coumarin); 7.78 (s, CH, thiazole); 7.69-7.09 (m, 11H, Ar-H); 5.71-5.65 (dd, J_{cis}= 4.8 Hz, J_{trans}= 11.6 Hz, 1H, C_5H-pyrazole); 3.98 (s, 3H, OCH_3); 3.98-3.88 (dd, 1H, C_4H-pyrazole); 3.35-3.27 (dd, J_{gem}= 17.7 Hz, J_{cis}= 4.8 Hz, 1H, C_4H-pyrazole); 2.41 and 2.32 (s, 6H, 2 x Ar-CH_3). ^{13}C-NMR (75 MHz; DMSO-d_6, ppm): δ 181.3 (C=O, ketone); 169.3 (C=N, thiazole); 157.9 (C=O, lactone); 157.6; 153.1; 146.8; 144.6; 143.6; 141.4; 138.5; 137.4; 130.0; 129.8; 129.0; 127.9; 127.4; 126.4; 126.3; 125.1; 121.1; 119.3; 115.8 (C=C and C=N); 63.6 (C_5-pyrazole); 56.6 (-OCH_3); 44.1 (C_4-pyrazole); 21.6; 21.1 (2 x Ar-CH_3). HRMS: m/z (M + H) calcd. for $C_{31}H_{25}N_3O_4S$: 536.1638; found: 536.1638. Elemental analysis calcd: C, 69.52; H, 4.70; N, 7.85; S, 5.99. Found: C, 69.24; H, 4.42; N, 7.57; S, 5.99 %.

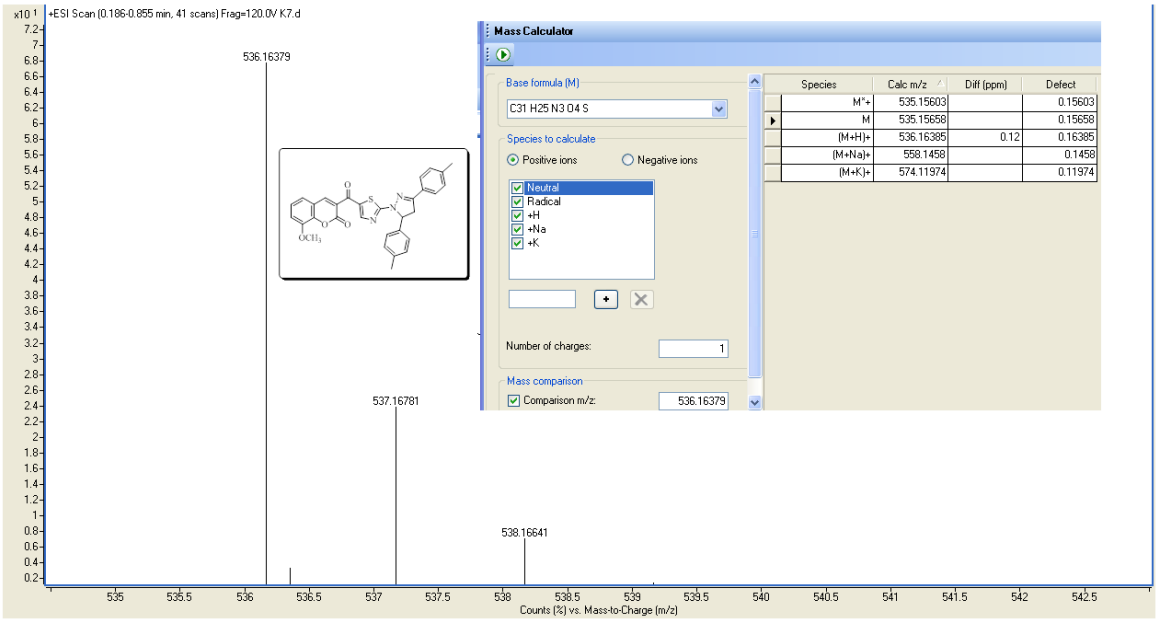


Figure S20: HRMS spectra of PTC-7

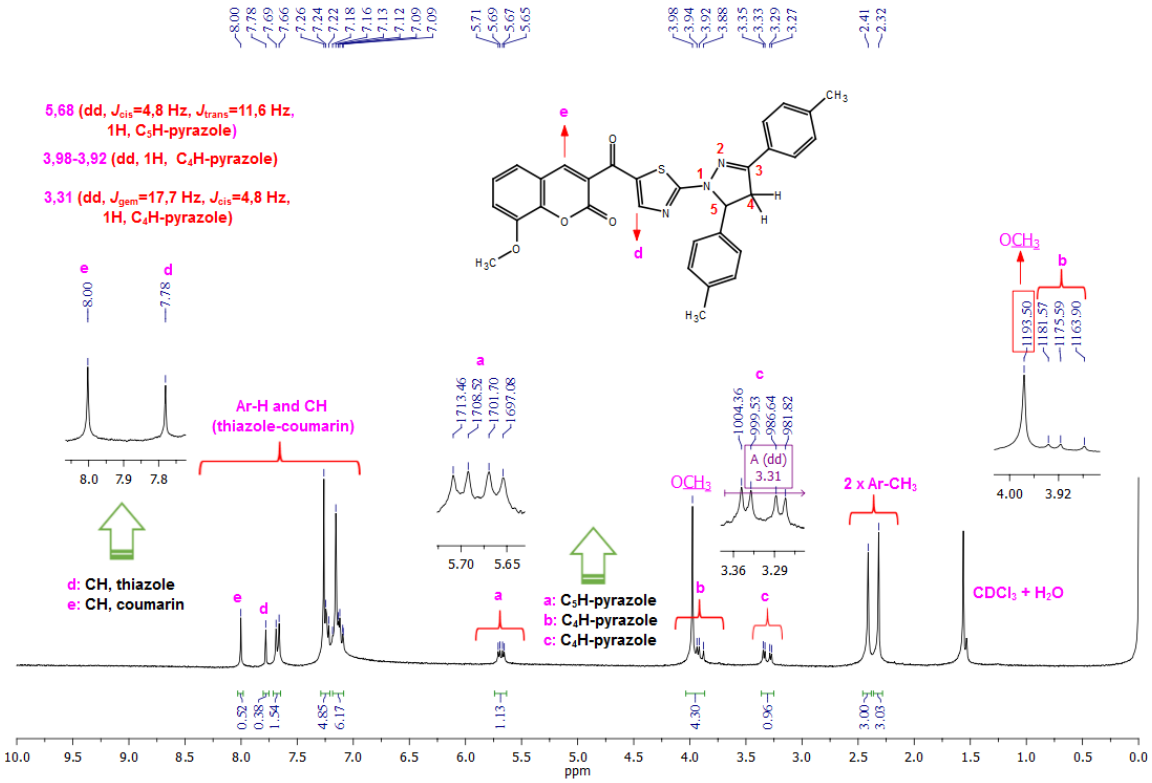


Figure S21: ^{1}H NMR spectra of PTC-7

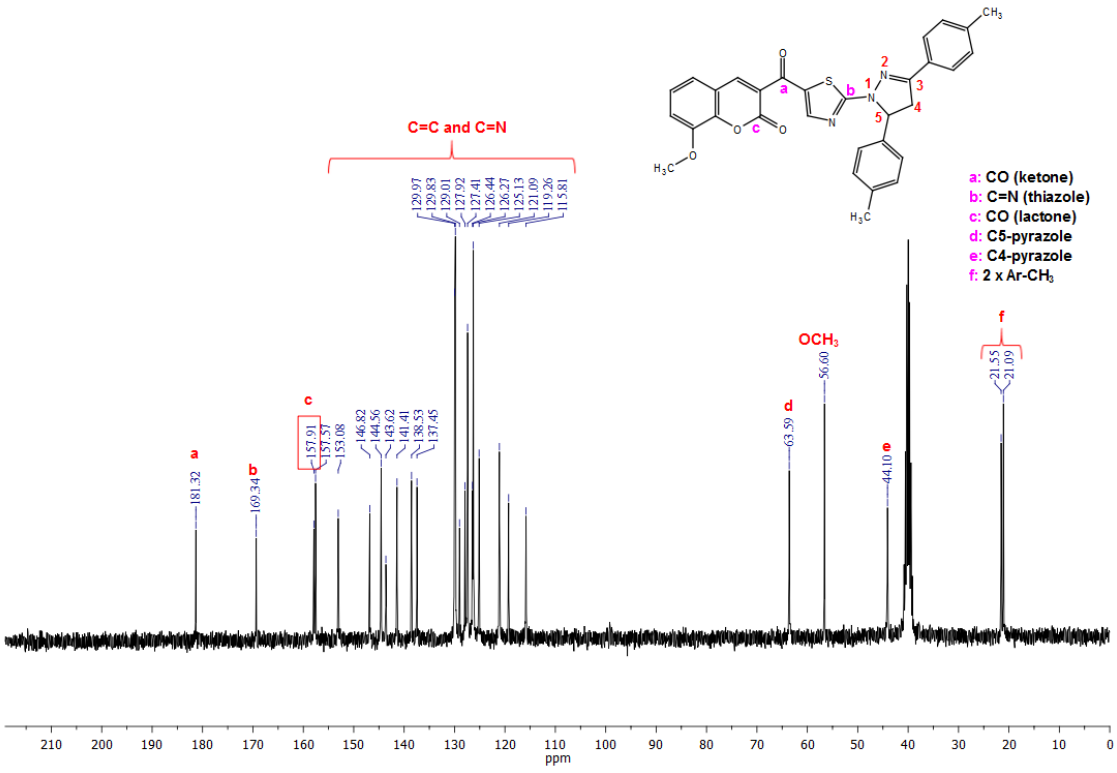
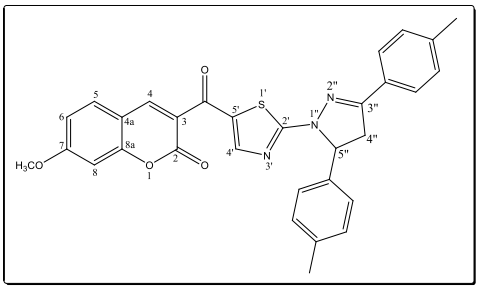


Figure S22: ^{13}C NMR spectra of PTC-7

3-(2-(3,5-di*p*-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-7-methoxy-2H-chromen-2-one (PTC-8)



Color: Yellow, Yield 0,348 g, 65%, mp 246-248 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3088, 3073, 3034 (Ar-H); 2986, 2953, 2919, 2855 (alifatic C-H), 1724 (C=O, lactone); 1615 (C=O, ketone); 1596, 1580, 1537, 1497, 1460 (C=N and C=C), 1216 (C-O). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 8.02 (s, CH, coumarin); 7.81 (s, CH, thiazole); 7.69-6.84 (m, 11H, Ar-H); 5.71-5.65 (dd, J_{cis}= 4.8 Hz, J_{trans}= 11.6 Hz, 1H, C_5H-pyrazole); 3.97-3.88 (dd, J_{gem}= 17.6 Hz, J_{trans}= 11.6 Hz, 1H, C_4H-pyrazole); 3.90 (s, 3H, OCH_3); 3.35-3.27 (dd, J_{gem}= 17.6 Hz, J_{cis}= 4.9 Hz, 1H, C_4H-pyrazole); 2.41 and 2.32 (s, 6H, 2 x Ar-CH_3). ^{13}C-NMR (75 MHz; $CDCl_3$, ppm): δ 181.0 (C=O, ketone); 170.1 (C=N, thiazole); 164.3 (-C-OCH_3); 158.6 (C=O, lactone); 156.7; 155.4; 150.9; 144.7; 141.2; 137.9; 137.8; 130.1; 129.8; 129.7; 129.6; 127.9; 126.8; 125.7; 122.9; 113.4; 111.8; 100.6 (C=C and C=N); 63.5 (C_5-pyrazole); 56.0 (-OCH_3); 44.0 (C_4-pyrazole); 21.6; 21.1 (2 x Ar-CH_3). HRMS: m/z (M + H) calcd. for $C_{31}H_{25}N_3O_4S$: 536.1638; found: 536.1638. Elemental analysis calcd: C, 69.52; H, 4.70; N, 7.85; S, 5.99. Found: C, 69.32; H, 4.33; N, 7.68; S, 5.63 %.

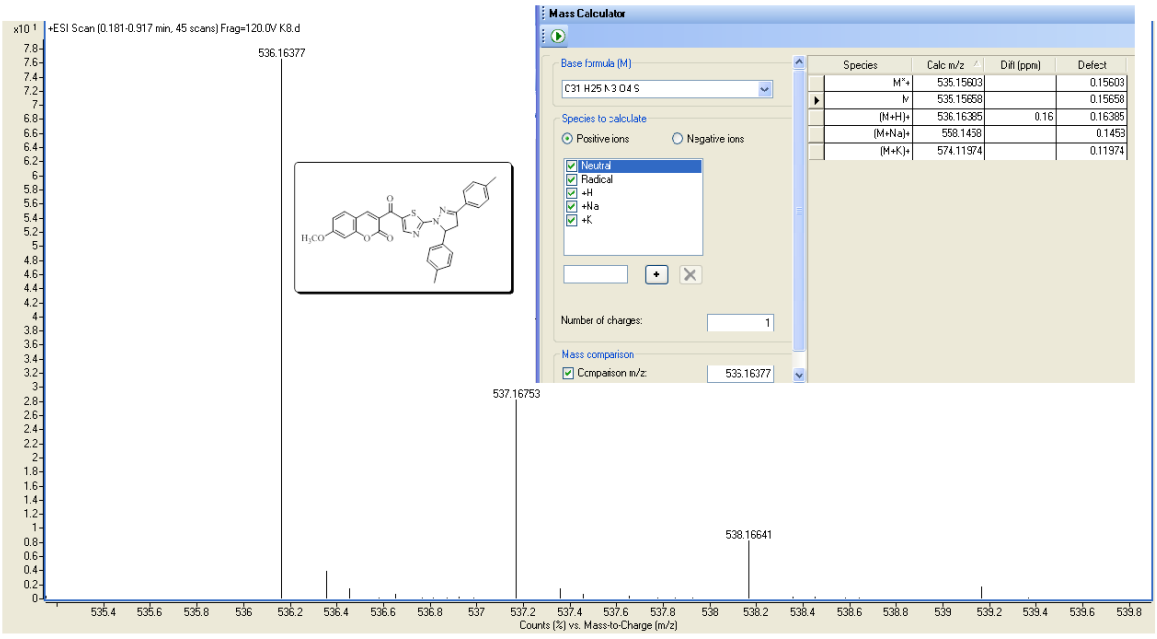


Figure S23: HRMS spectra of PTC-8

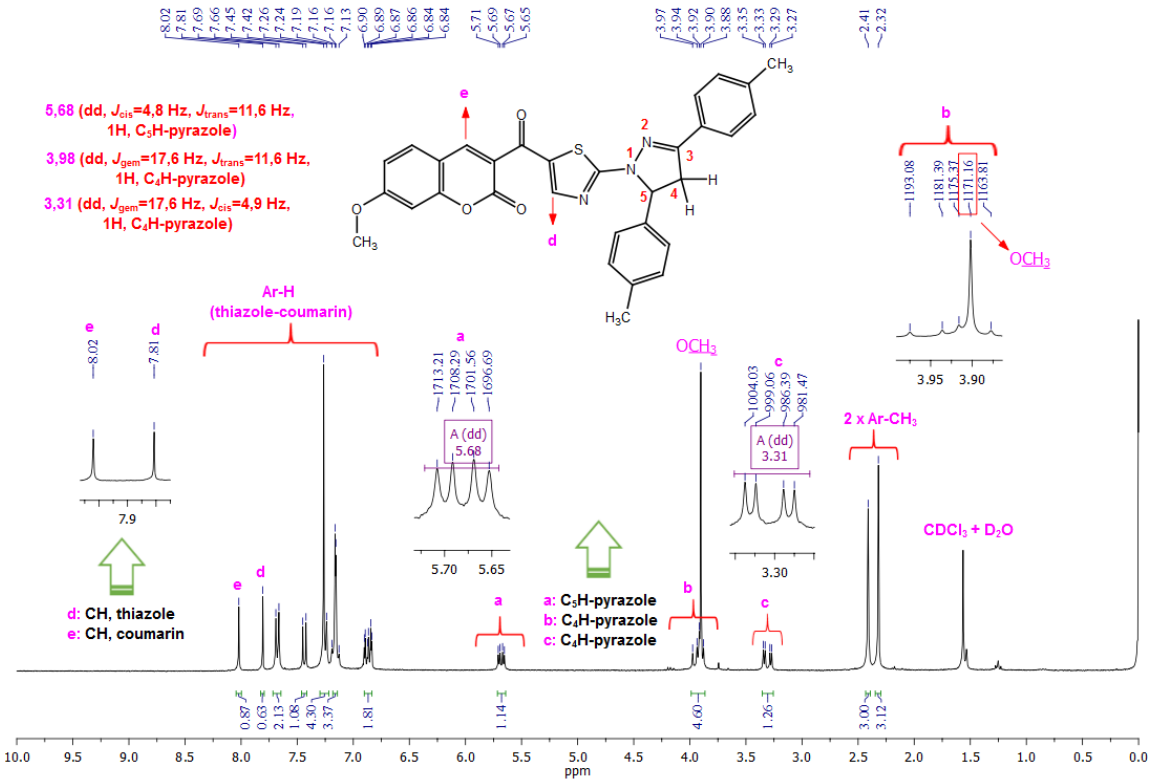


Figure S24: ^{1}H NMR spectra of PTC-8

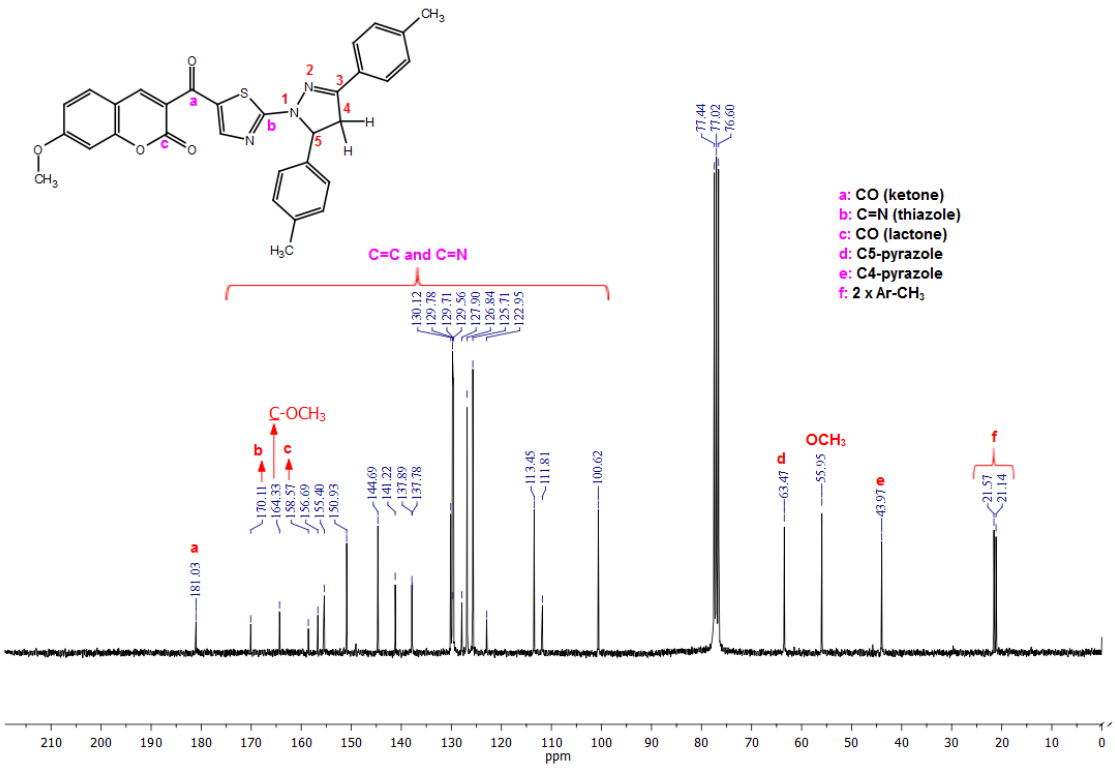
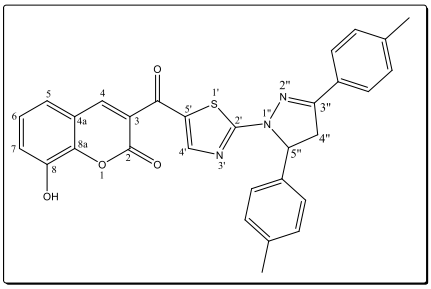


Figure S25: ^{13}C NMR spectra of PTC-8

3-(2-(3,5-di*p*-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-8-hydroxy-2*H*-chromen-2-one (PTC-9)



Color: Yellow, Yield 0,417 g, 80%, mp 302-304 ºC, FT-IR (ATR, cm^{-1}): υ_{max} 3367 (O-H), 3096, 3056, 3035, 3006 (Ar-H); 2933, 2917, 2858 (alifatic C-H), 1730 (C=O, lactone); 1626 (C=O, ketone); 1608, 1599, 1579, 1543, 1502, 1471 (C=N and C=C). ^{1}H-NMR (300 MHz; DMSO-d_6, ppm): δ 8.31 (s, CH, coumarin); 7.97 (s, CH, thiazole); 7.76-7.15 (m, 11H, Ar-H); 5.78-5.73 (dd, J_{cis}= 4.7 Hz, J_{trans}= 11.6 Hz, 1H, C_5H-pyrazole); 4.14-4.04 (dd, J_{gem}= 18.2 Hz, J_{trans}= 11.6 Hz, 1H, C_4H-pyrazole); 3.39-3.32 (in DMSO-d_6, dd, 1H, C_4H-pyrazole); 2.38 and 2.26 (s, 6H, 2 x Ar-CH_3). ^{13}C-NMR (75 MHz; DMSO-d_6, ppm): δ 181.5 (C=O, ketone); 169.3 (C=N, thiazole); 158.1 (C=O, lactone); 157.6; 153.0; 145.0; 144.8; 142.9; 141.4; 138.6; 137.5; 130.0; 130.0; 129.0; 128.0; 127.6; 127.4; 126.3; 126.2; 125.2; 120.0; 119.6 (C=C and C=N); 63.6 (C_5-pyrazole); 44.1 (C_4-pyrazole); 21.6; 21.1 (2 x Ar-CH_3). HRMS: m/z (M + H) calcd. for $C_{30}H_{23}N_3O_4S$: 522.1482; found: 522.1483. Elemental analysis calcd: C, 69.08; H, 4.44; N, 8.06; S, 6.15. Found: C, 69.40; H, 4.38; N, 7.70; S, 5.88 %.

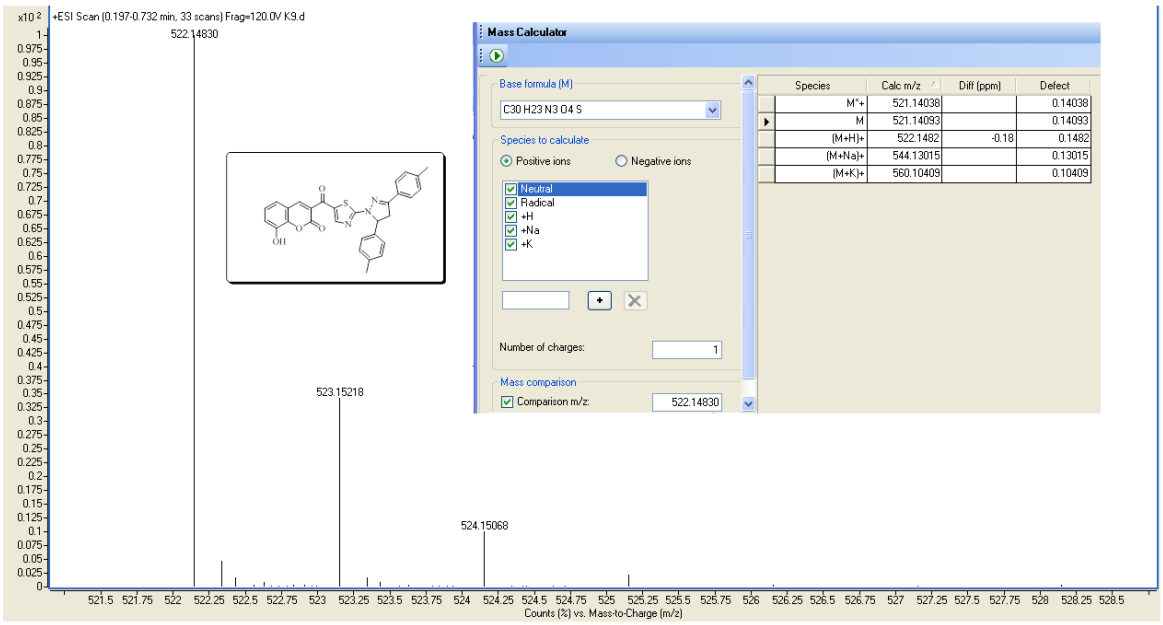


Figure S26: HRMS spectra of PTC-9

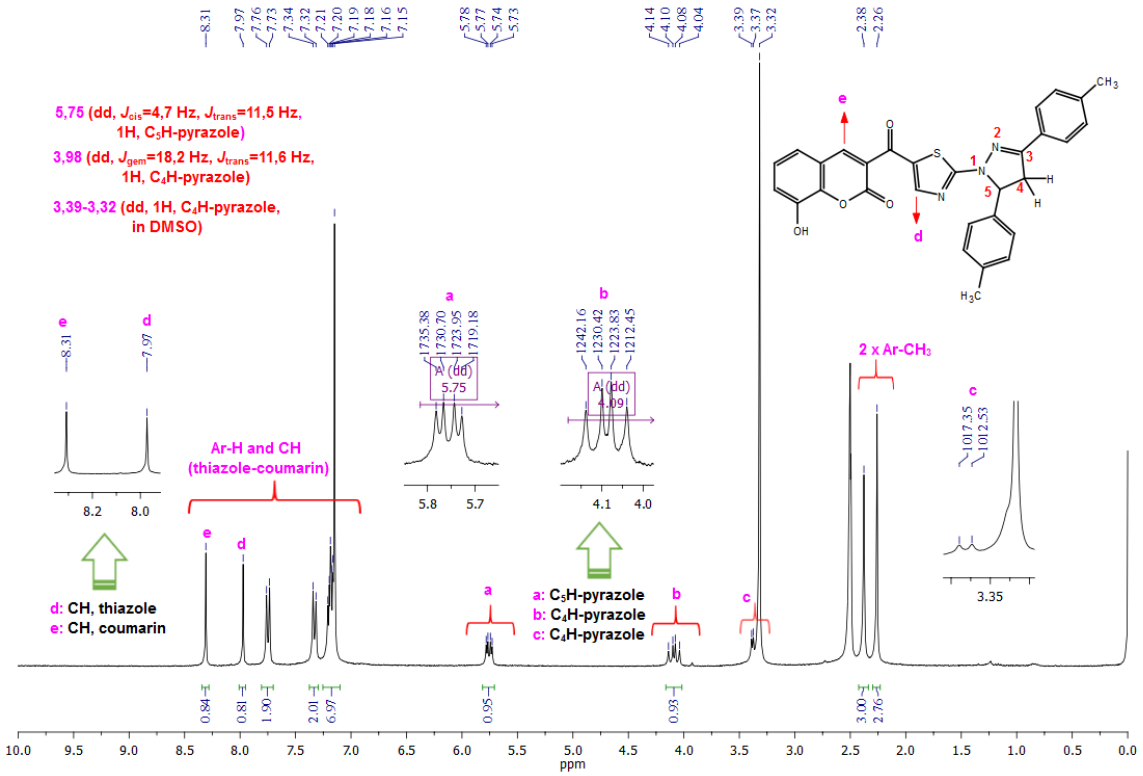


Figure S27: ^{1}H NMR spectra of PTC-9

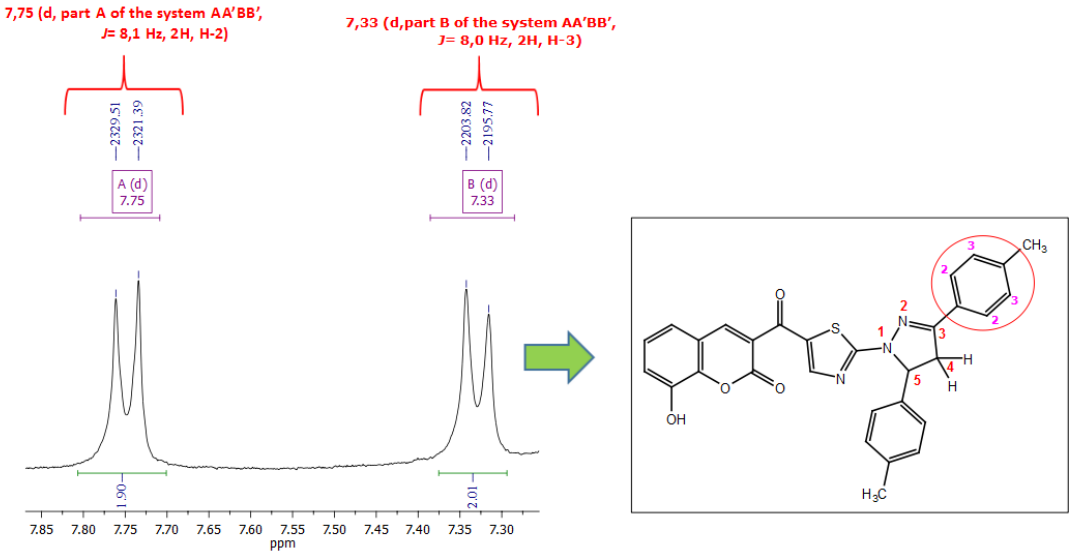


Figure S28: ^{1}H NMR splitting of *p*-disubstituted benzene group protons in compound PTC-9

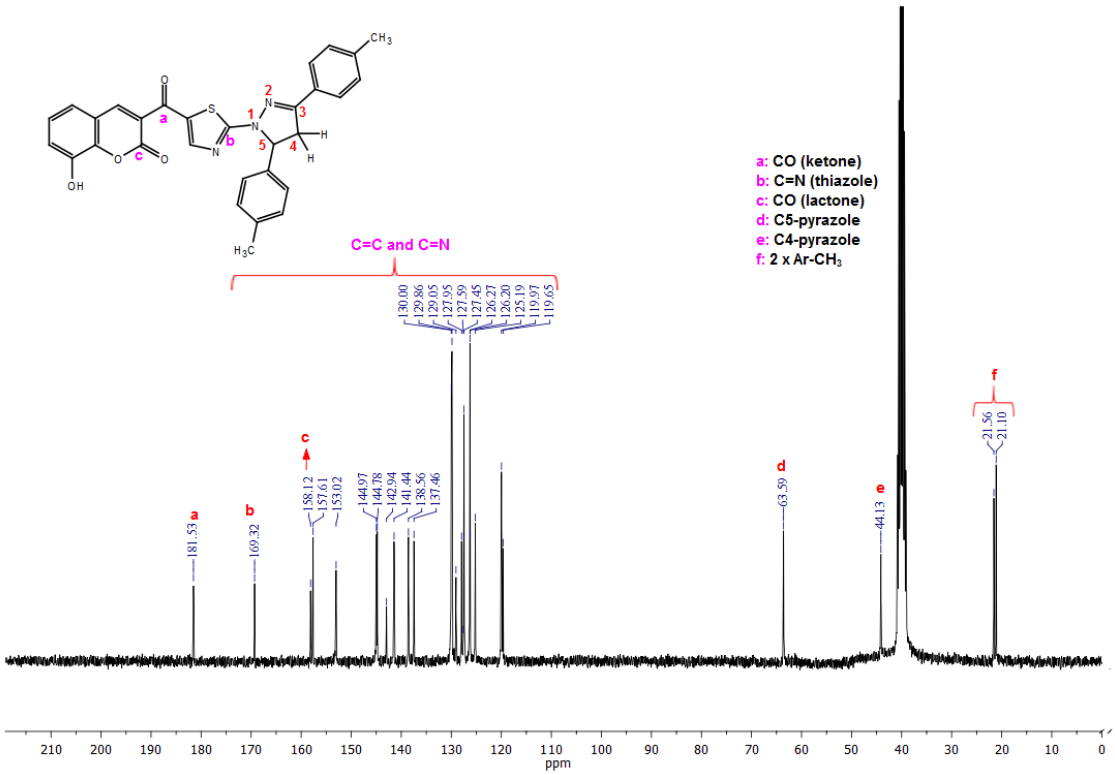
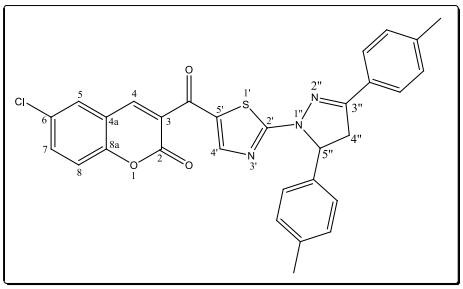


Figure S29: ^{13}C NMR spectra of PTC-9

6-chloro-3-(2-(3,5-dip-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-2*H*-chromen-2-one (PTC-10)



Color: Yellow, Yield 0,410 g, 76%, mp 231-232 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3079, 3060, 3030, 3006 (Ar-H); 2924, 2872 (alifatic C-H), 1727 (C=O, lactone); 1619 (C=O, ketone); 1602, 1584, 1537, 1517, 1496 (C=N and C=C). ^{1}H-NMR (300 MHz; DMSO-d$_6$, ppm): δ 8.31 (s, CH, coumarin); 8.00 (s, CH, thiazole); 7.90-7.15 (m, 11H, Ar-H); 5.79-5.73 (dd, J_{cis}= 4.7 Hz, J_{trans}= 11.6 Hz, 1H, C$_5$H-pyrazole); 4.14-4.04 (dd, J_{gem}= 18.2 Hz, J_{trans}= 11.6 Hz, 1H, C$_4$H-pyrazole); 3.40-3.32 (dd, 1H, C$_4$H-pyrazole, in DMSO-*d*$_6$); 2.38 and 2.26 (s, 6H, 2 x Ar-CH$_3$). ^{13}C-NMR (75 MHz; DMSO-*d*$_6$, ppm): δ 180.9 (C=O, ketone); 169.4 (C=N, thiazole); 157.8 (C=O, lactone); 157.8; 153.5; 152.9; 143.1; 141.5; 138.5; 137.5; 133.1; 130.0; 129.8; 129.0; 128.9; 128.8; 127.9; 127.5; 127.2; 126.3; 120.2; 118.7 (C=C and C=N); 63.6 (C$_5$-pyrazole); 44.1 (C$_4$-pyrazole); 21.6; 21.1 (2 x Ar-CH$_3$). HRMS: m/z (M + H) calcd. for C$_{30}$H$_{22}$ClN$_3$O$_3$S: 540.1143; found: 540.1147. Elemental analysis calcd: C, 66.72; H, 4.11; N, 7.78; S, 5.94. Found: C, 66.70; H, 4.17; N, 7.46; S, 5.82 %.

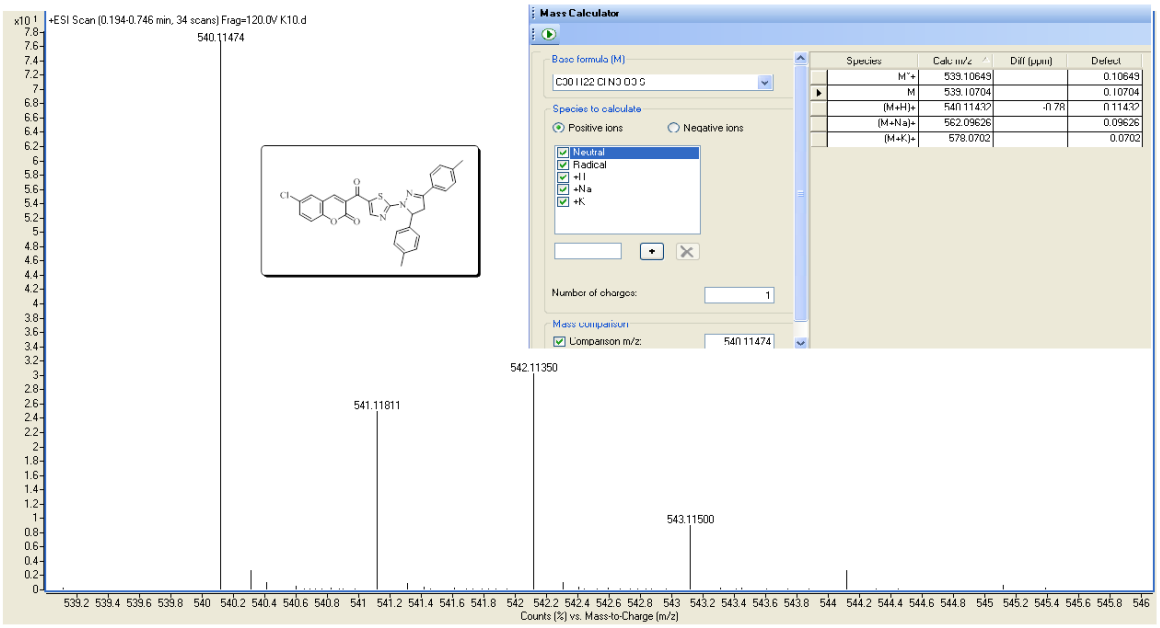


Figure S30: HRMS spectra of PTC-10

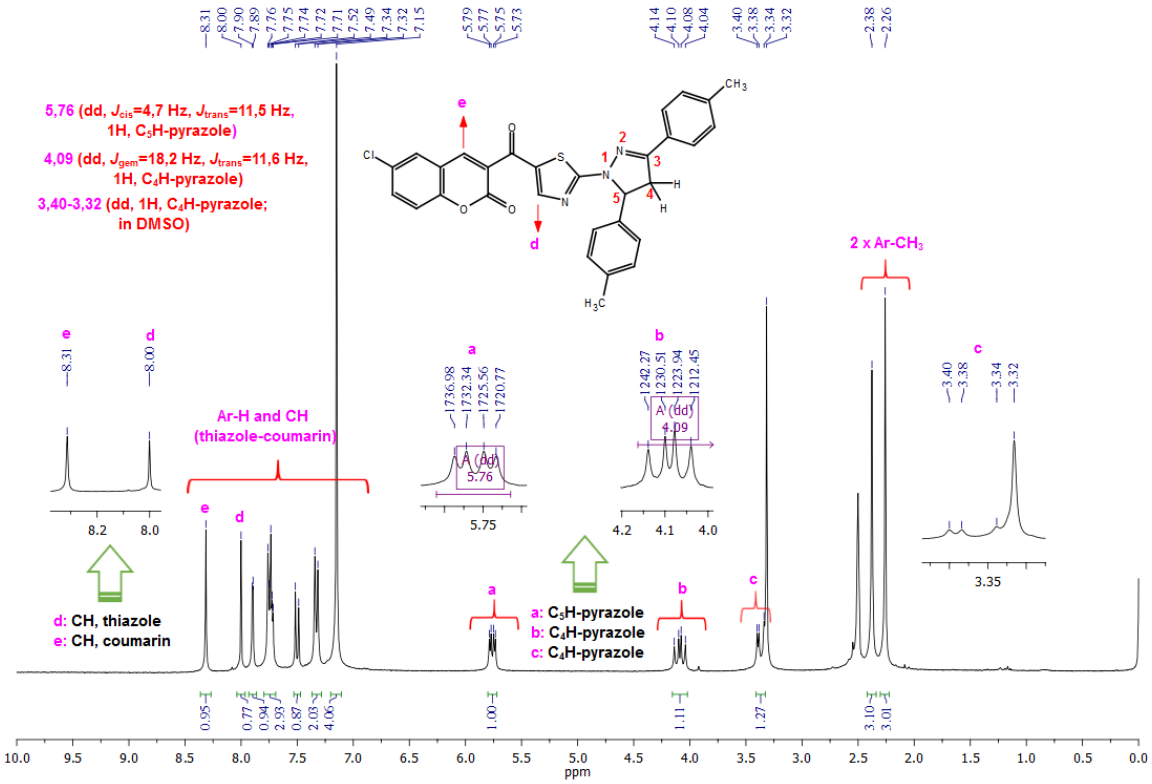


Figure S31: ^{1}H NMR spectra of PTC-10

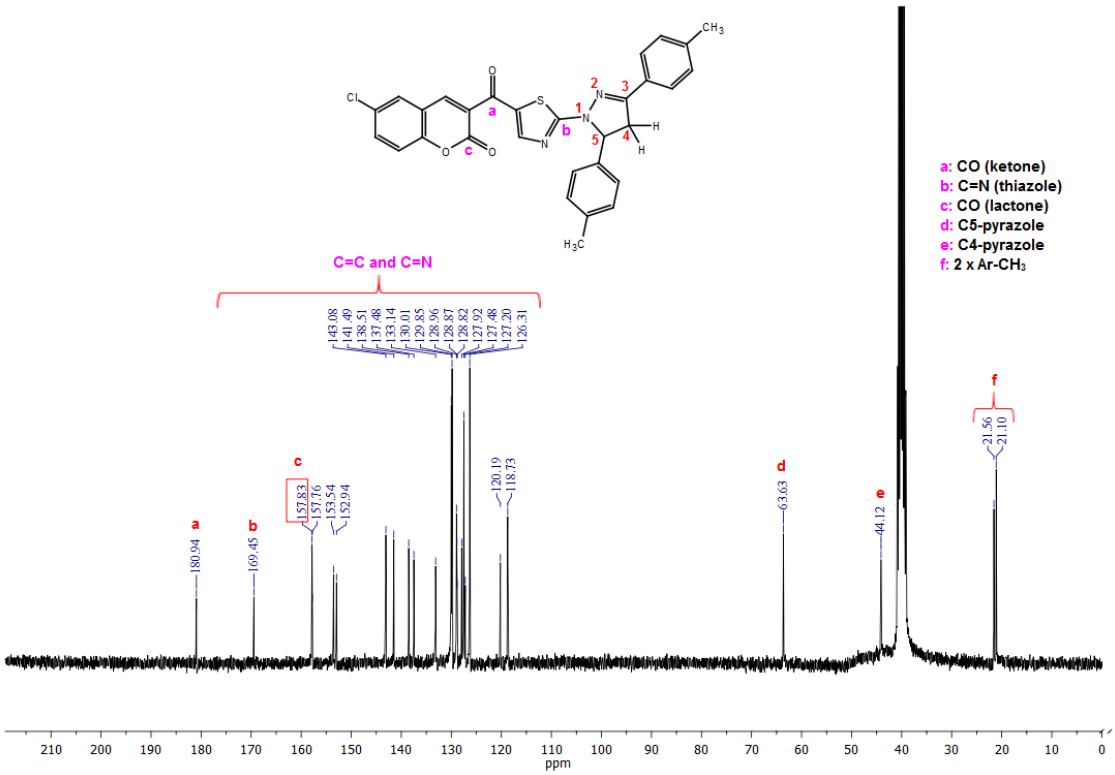
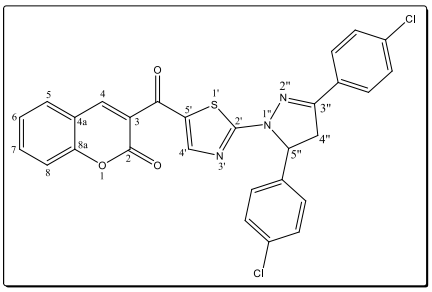


Figure S32: ^{13}C NMR spectra of PTC-10

3-(2-(3,5-bis(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-2*H*-chromen-2-one (PTC-11)



Color: Yellow, Yield 0,393 g, 72%, mp 138-141 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3072, 3038 (Ar-H); 2966, 2924 (alifatic C-H), 1740 (C=O, lactone); 1616 (C=O, ketone); 1609, 1597, 1562, 1537, 1503, 1481 (C=N and C=C). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 8.04 (s, CH, coumarin); 7.78 (s, CH, thiazole); 7.72-7.20 (m, 12H, Ar-H); 5.74-5.68 (dd, J_{cis}= 5.2 Hz, J_{trans}= 11.8 Hz, 1H, C_5H-pyrazole); 3.99-3.90 (dd, J_{gem}= 17.7 Hz, J_{trans}= 11.8 Hz, 1H, C_4H-pyrazole); 3.32-3.24 (dd, J_{gem}= 17.7 Hz, J_{cis}= 5.2 Hz, 1H, C_4H-pyrazole). ^{13}C-NMR (75 MHz; $CDCl_3$, ppm): δ 180.9 (C=O, ketone); 170.0 (C=N, thiazole); 158.2 (C=O, lactone); 154.5; 154.0; 150.8, 144.3; 138.9; 137.0; 134.1; 133.5; 130.1; 129.4; 129.2; 129.0; 128.9; 128.0; 127.3; 126.6; 124.9; 118.1; 116.9 (C=C and C=N); 63.3 (C_5-pyrazole); 43.6 (C_4-pyrazole). HRMS: m/z (M + H) calcd. for $C_{28}H_{17}Cl_2N_3O_3S$: 546.0440; found: 546.0442. Elemental analysis calcd: C, 61.55; H, 3.14; N, 7.69; S, 5.87. Found: C, 61.24; H, 3.34; N, 7.64; S, 5.62 %.

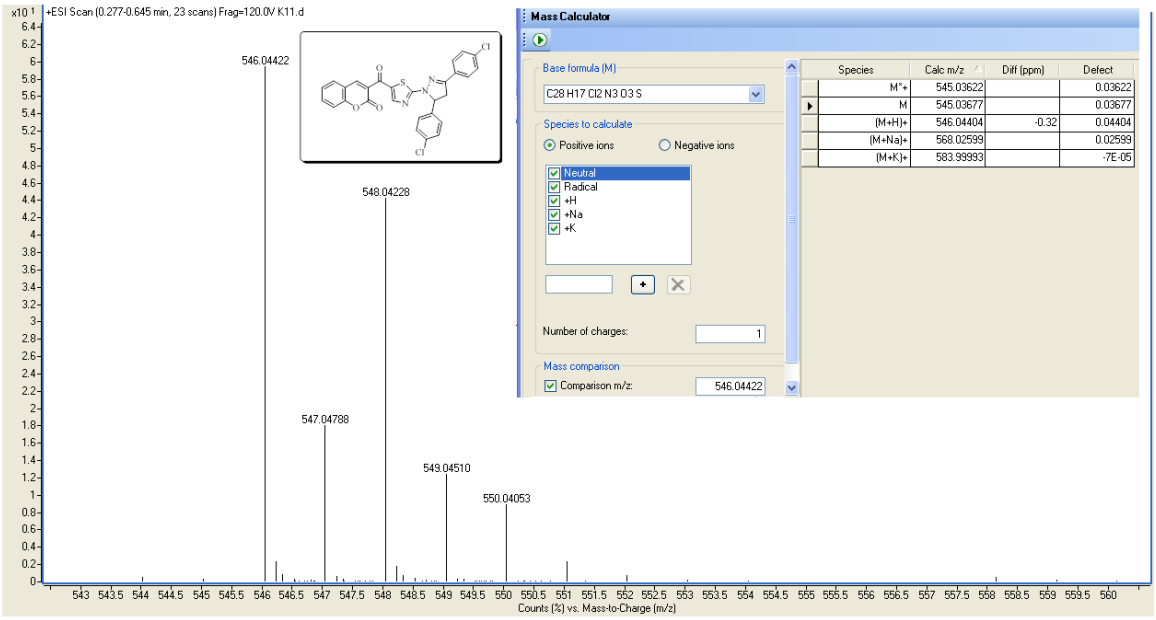


Figure S33: HRMS spectra of PTC-11

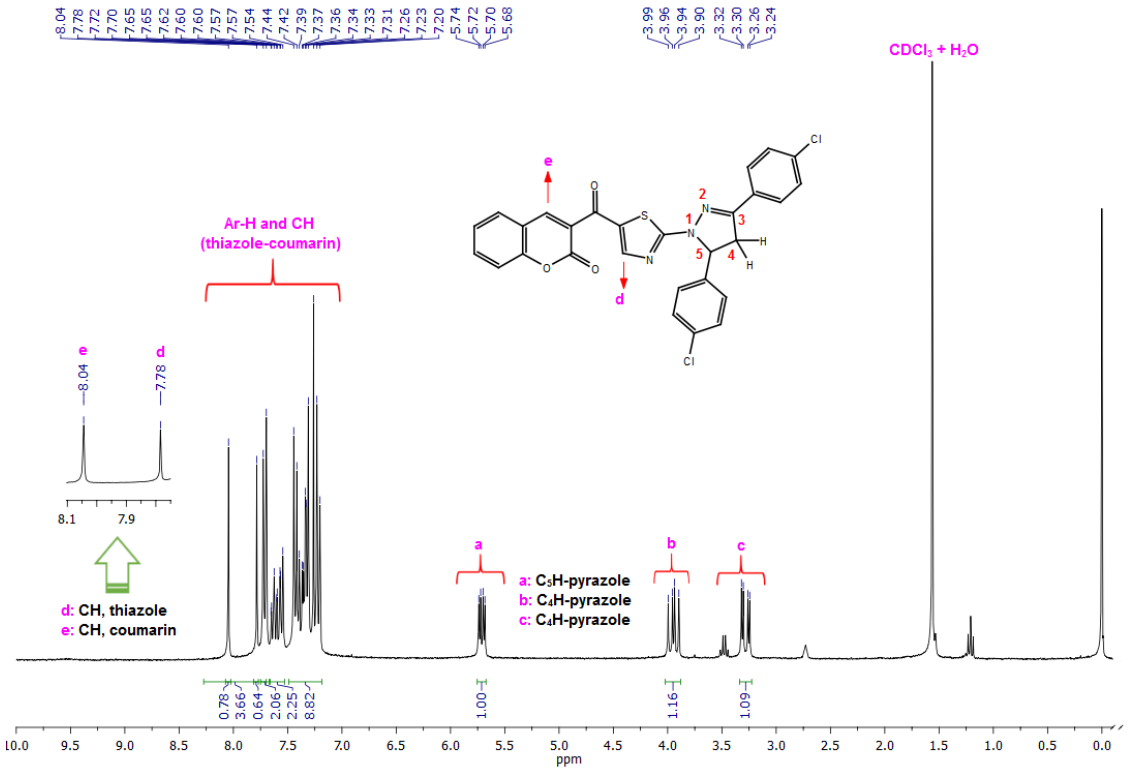


Figure S34: ^{1}H NMR spectra of PTC-11

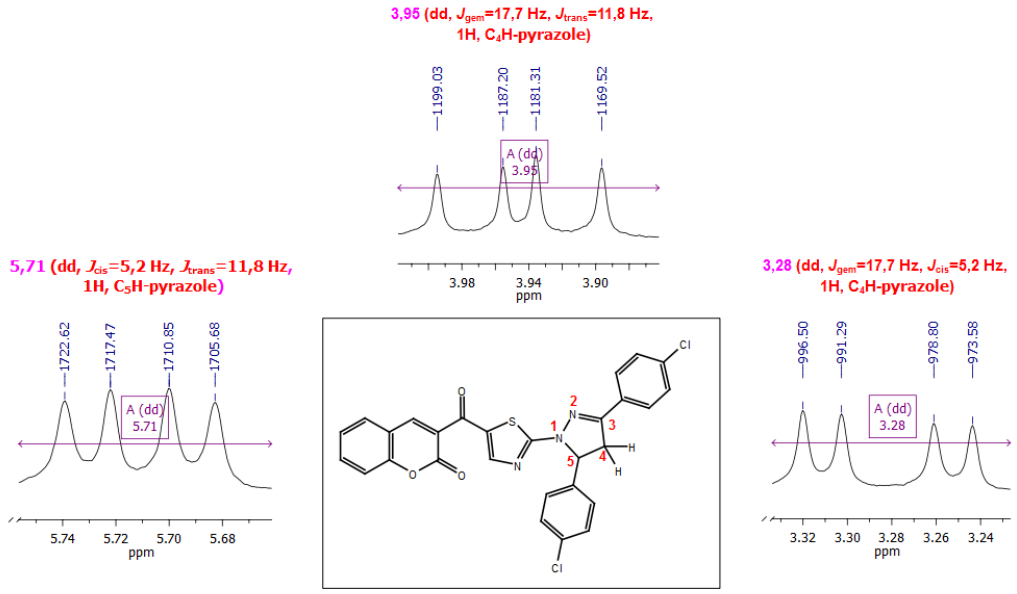


Figure S35: ^{1}H NMR splitting of pyrazole protons (C_4H- and C_5H-) of compound PTC-11

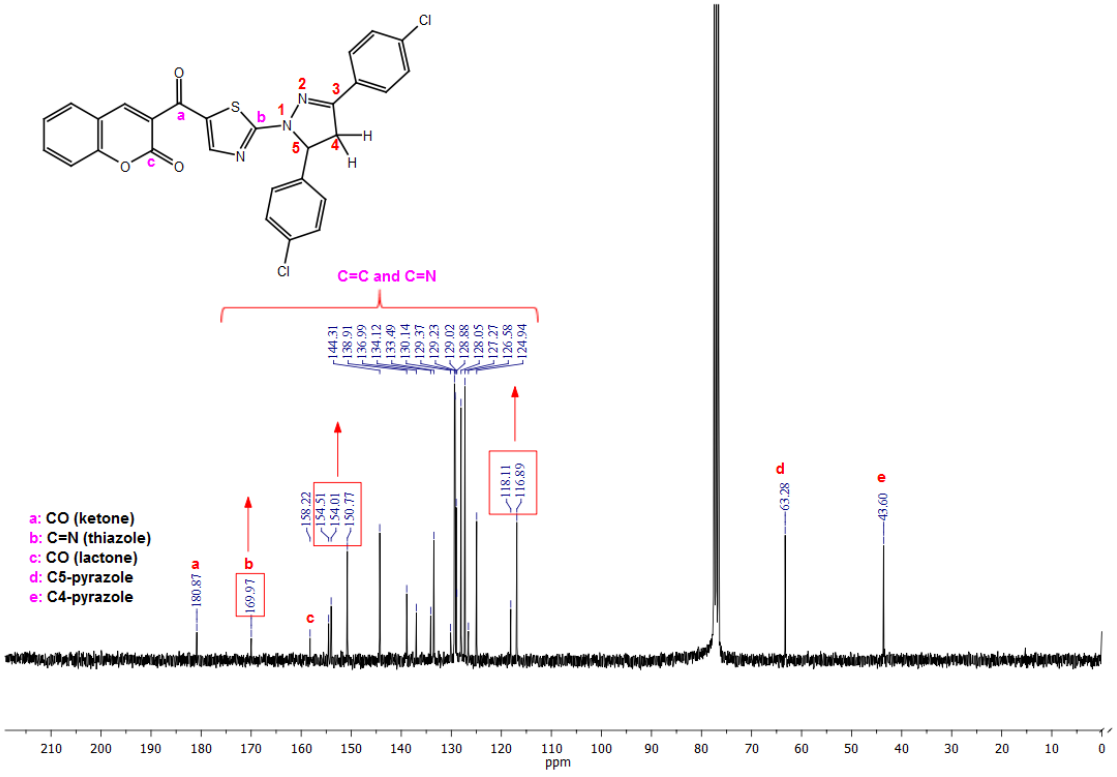
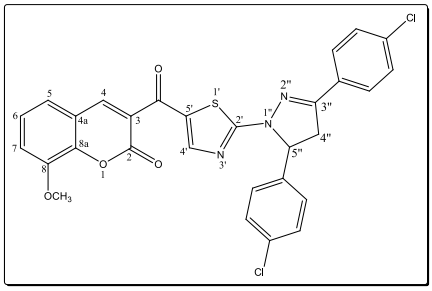


Figure S36: ^{13}C NMR spectra of PTC-11

3-(2-(3,5-bis(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-8-methoxy-2*H*-chromen-2-one (PTC-12)



Color: Yellow, Yield 0,367 g, 64%, mp 222-223 ºC, FT-IR (ATR, cm^{-1}): υ_{max} 3088, 3054, 3031, 3008 (Ar-H); 2951, 2913, 2850 (alifatic C-H), 1714 (C=O, lactone); 1630 (C=O, ketone); 1605, 1576, 1525, 1506, 1488, 1476 (C=N and C=C), 1252 (C-O). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 8.03 (s, CH, coumarin); 7.78 (s, CH, thiazole); 7.72-7.10 (m, 11H, Ar-H); 5.74-5.68 (dd, J_{cis}= 5.2 Hz, J_{trans}= 11.8 Hz, 1H, C_5H-pyrazole); 4.00-3.90 (dd, J_{gem}= 17.6 Hz, J_{trans}= 11.7 Hz, 1H, C_4H-pyrazole); 3.98 (s, 3H, OCH_3); 3.31-3.24 (dd, J_{gem}= 17.7 Hz, J_{cis}= 5.2 Hz, 1H, C_4H-pyrazole). ^{13}C-NMR (75 MHz; $CDCl_3$, ppm): δ 180.9 (C=O, ketone); 169.9 (C=N, thiazole); 157.7 (C=O, lactone); 154.0; 150.8; 147.2; 144.6; 144.2; 138.9; 136.9; 134.1; 130.1; 129.4; 129.2; 128.9; 128.0; 127.3; 126.8; 124.8; 120.2; 118.8; 115.2 (C=C and C=N); 63.3 (C_5-pyrazole); 56.3 (-OCH_3); 43.6 (C_4-pyrazole). HRMS: m/z (M + H) calcd. for $C_{29}H_{19}Cl_2N_3O_4S$: 576.0546; found: 576.0555. Elemental analysis calcd: C, 60.42; H, 3.32; N, 7.29; S, 5.56. Found: C, 60.12; H, 3.43; N, 7.26; S, 5.88 %.

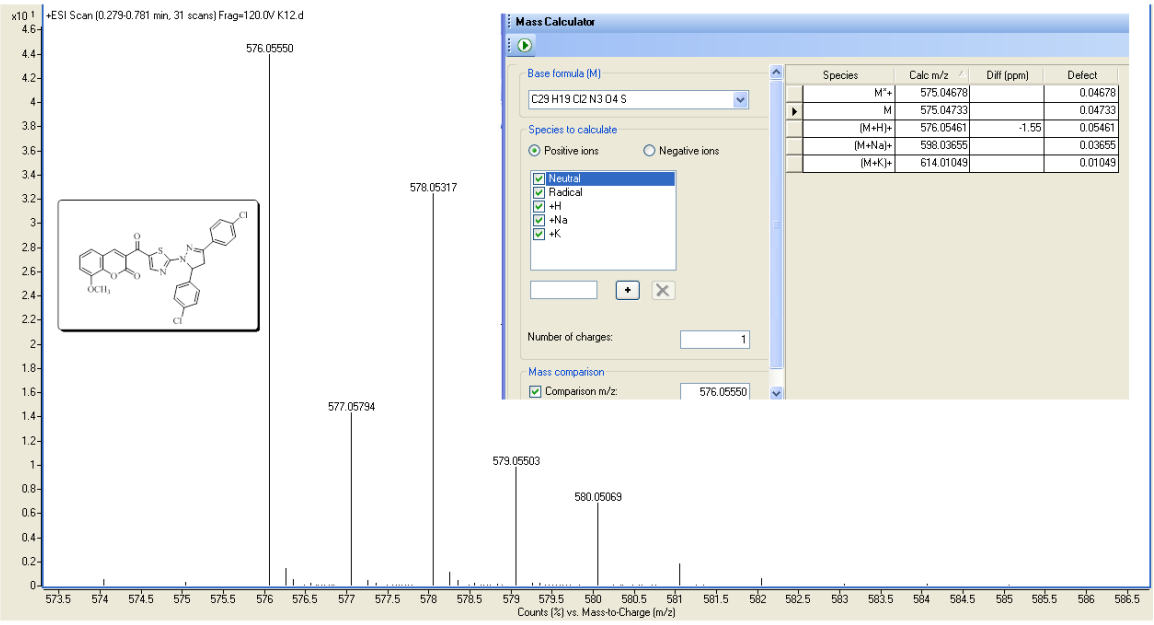


Figure S37: HRMS spectra of PTC-12

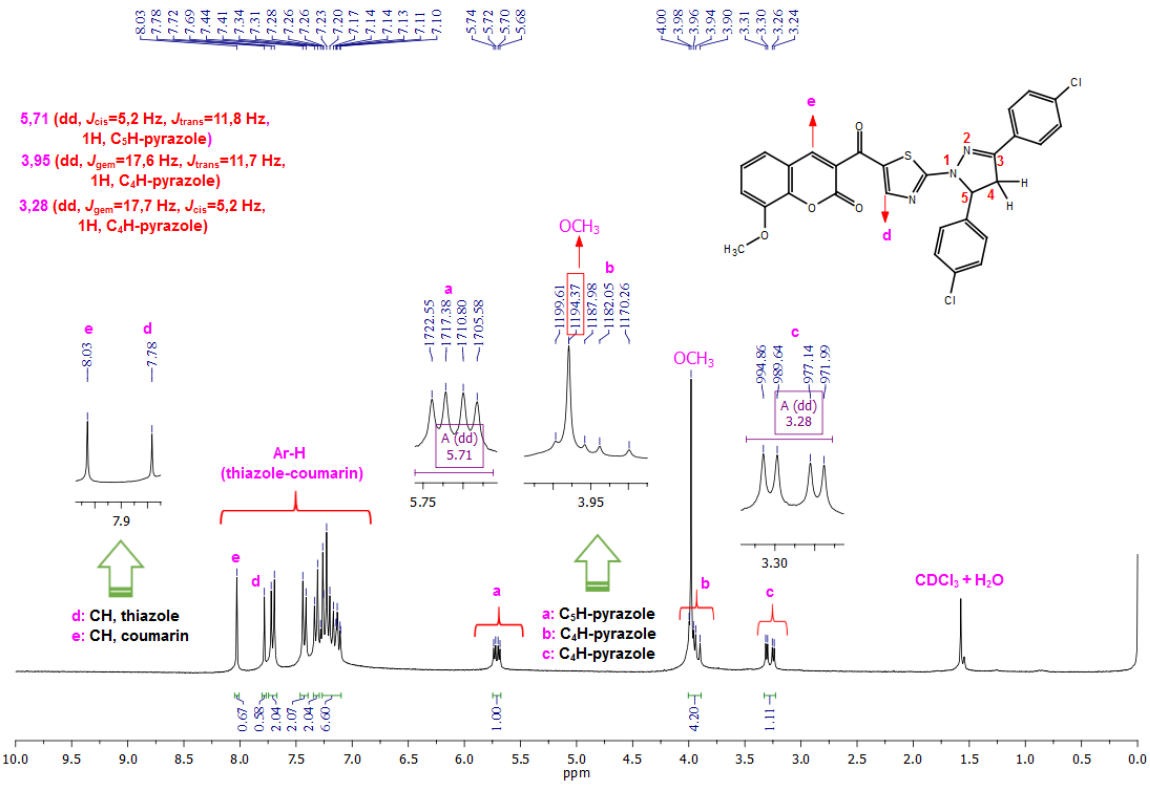


Figure S38: ^{1}H NMR spectra of PTC-12

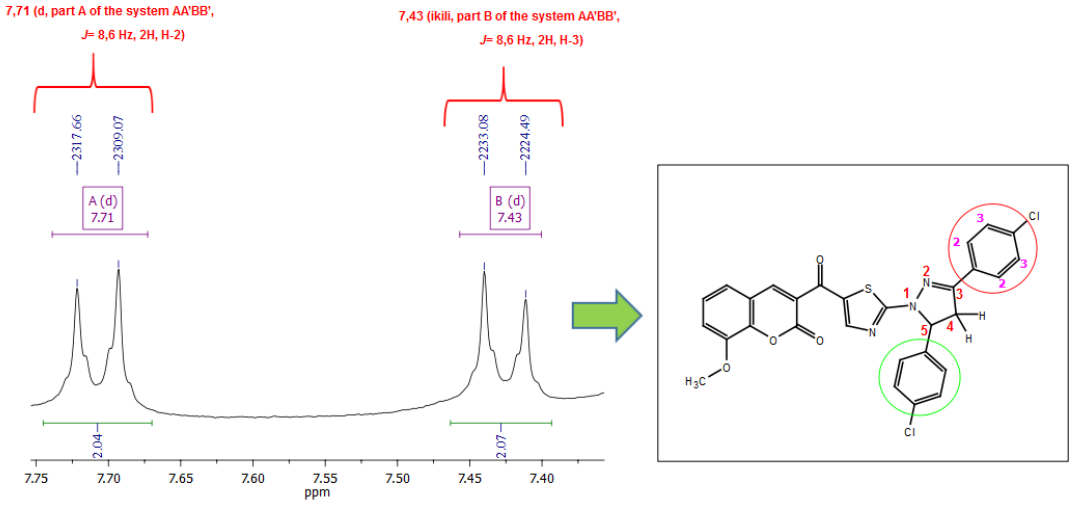


Figure S39: ^{1}H NMR splitting of *p*-disubstituted benzene group protons in compound PTC-12

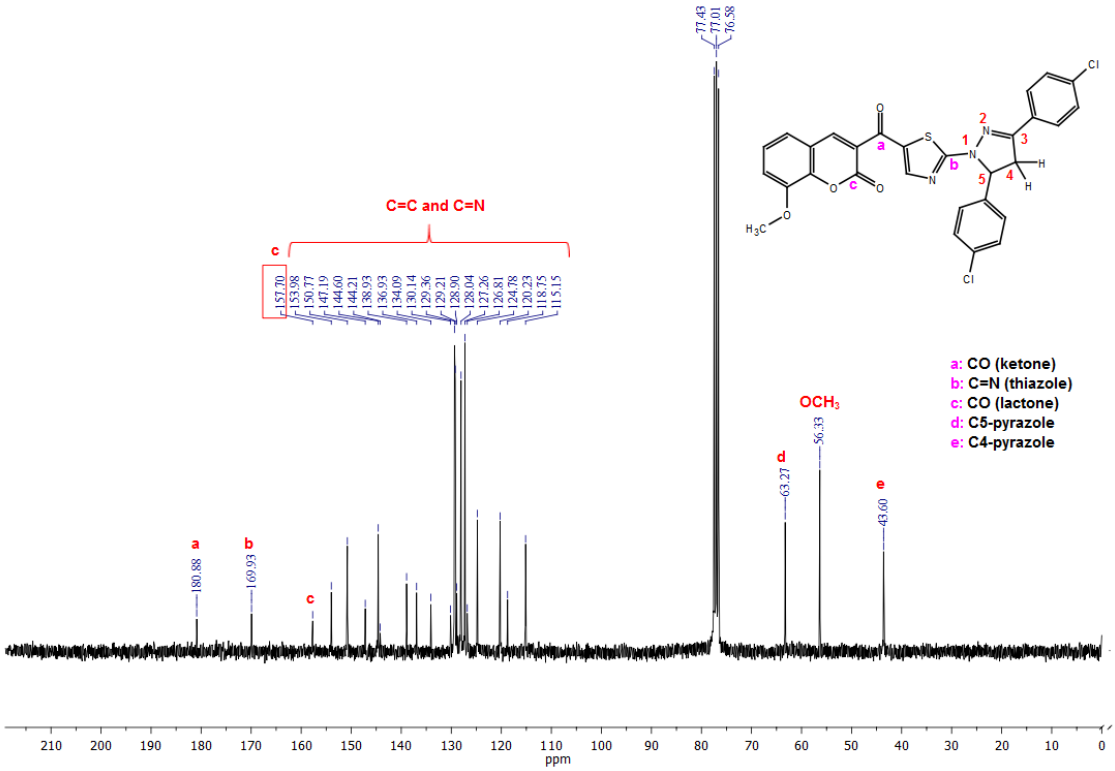
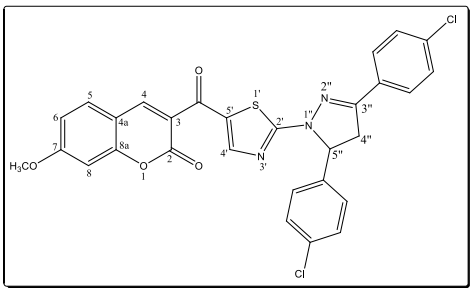


Figure S40: ^{13}C NMR spectra of PTC-12

3-(2-(3,5-bis(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-7-methoxy-2*H*-chromen-2-one (PTC-13)



Color: Yellow, Yield 0,478 g, 83%, mp 201-203 ºC, FT-IR (ATR, cm^{-1}): υ_{max} 3099, 3067, 3056, 3022 (Ar-H); 2986, 2958, 2914, 2847 (alifatic C-H), 1708 (C=O, lactone); 1622 (C=O, ketone); 1598, 1564, 1524, 1510, 1499, 1478 (C=N and C=C), 1237 (C-O). ^{1}H-NMR (300 MHz; $CDCl_3$, ppm): δ 8.05 (s, CH, coumarin); 7.81 (s, CH, thiazole); 7.72-6.84 (m, 11H, Ar-H); 5.74-5.68 (dd, J_{cis}= 5.2 Hz, J_{trans}= 11.7 Hz, 1H, C_5H-pyrazole); 3.99-3.90 (dd, 1H, C_4H-pyrazole); 3.90 (s, 3H, OCH_3); 3.31-3.23 (dd, J_{gem}= 17.7 Hz, J_{cis}= 5.2 Hz, 1H, C_4H-pyrazole). ^{13}C-NMR (75 MHz; $CDCl_3$, ppm): δ 181.1 (C=O, ketone); 169.8 (C=N, thiazole); 164.5 (-C-OCH_3); 158.6 (C=O, lactone); 156.7; 153.8; 150.4; 145.1; 139.0; 136.9; 134.0; 130.4; 130.2; 129.3; 129.2; 129.0; 128.0; 127.3; 122.7; 113.5; 111.8; 100.6 (C=C and C=N); 63.3 (C_5-pyrazole); 56.0 (-OCH_3); 43.6 (C_4-pyrazole). HRMS: m/z (M + H) calcd. for $C_{29}H_{19}Cl_2N_3O_4S$: 576.0546; found: 576.0547. Elemental analysis calcd: C, 60.42; H, 3.32; N, 7.29; S, 5.56. Found: C, 60.30; H, 3.33; N, 7.21; S, 5.37 %.

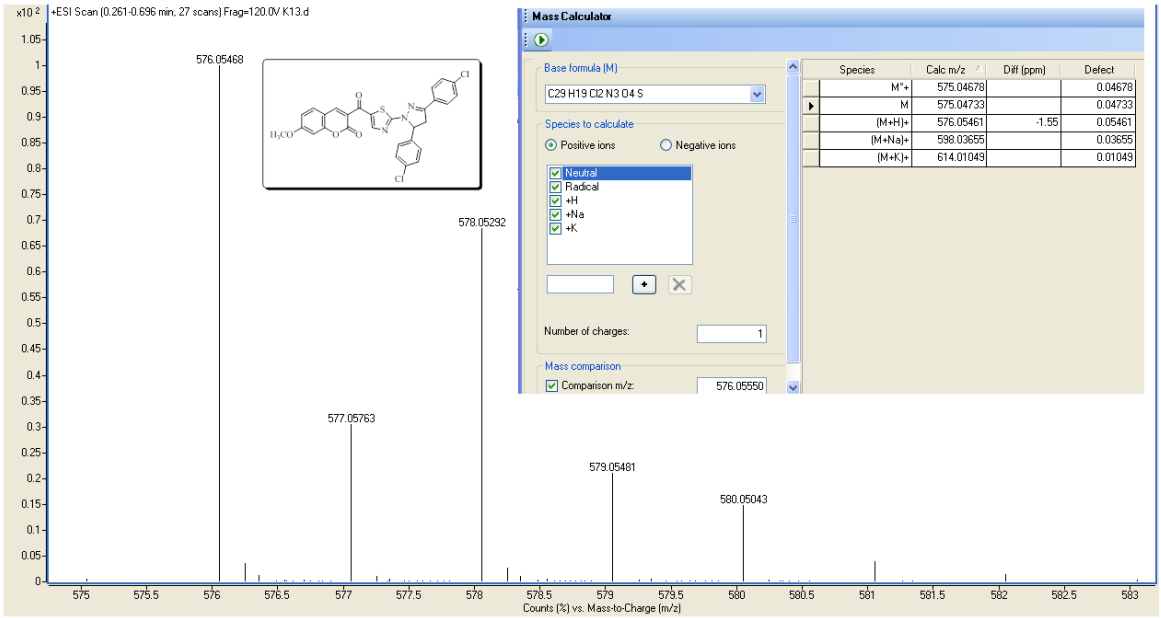


Figure S41: HRMS spectra of PTC-13

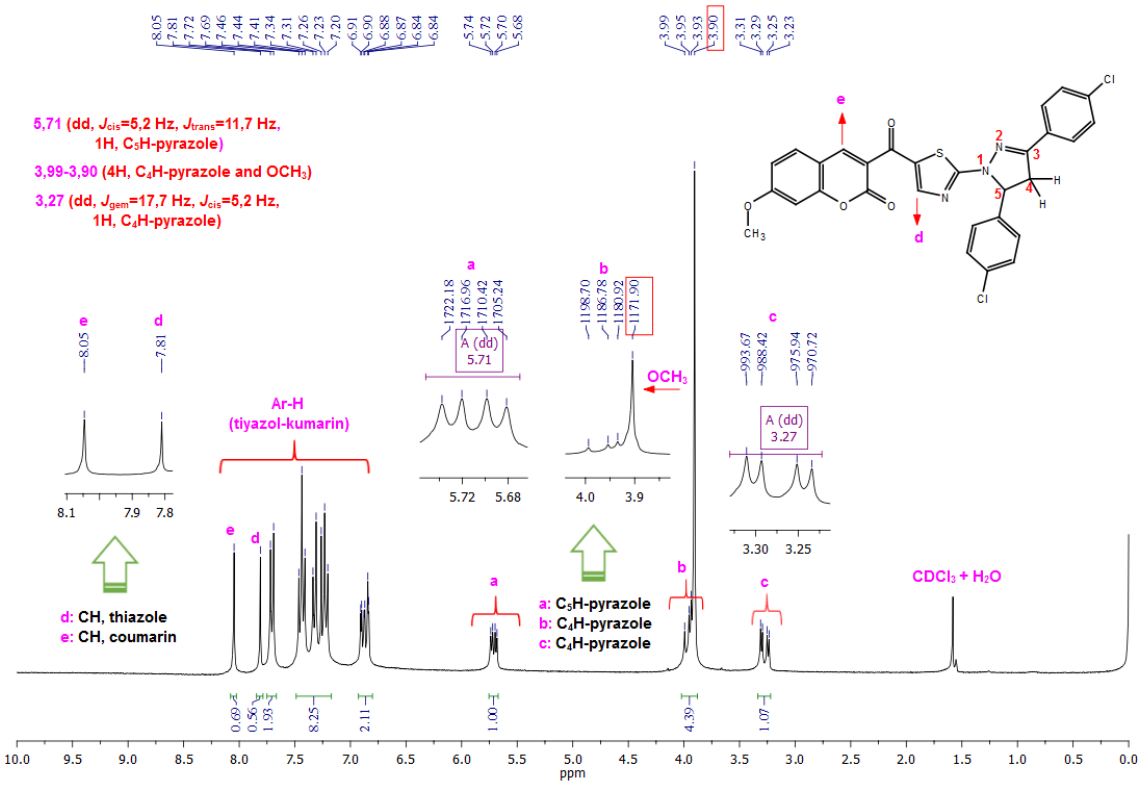


Figure S42: ^{1}H NMR spectra of PTC-13

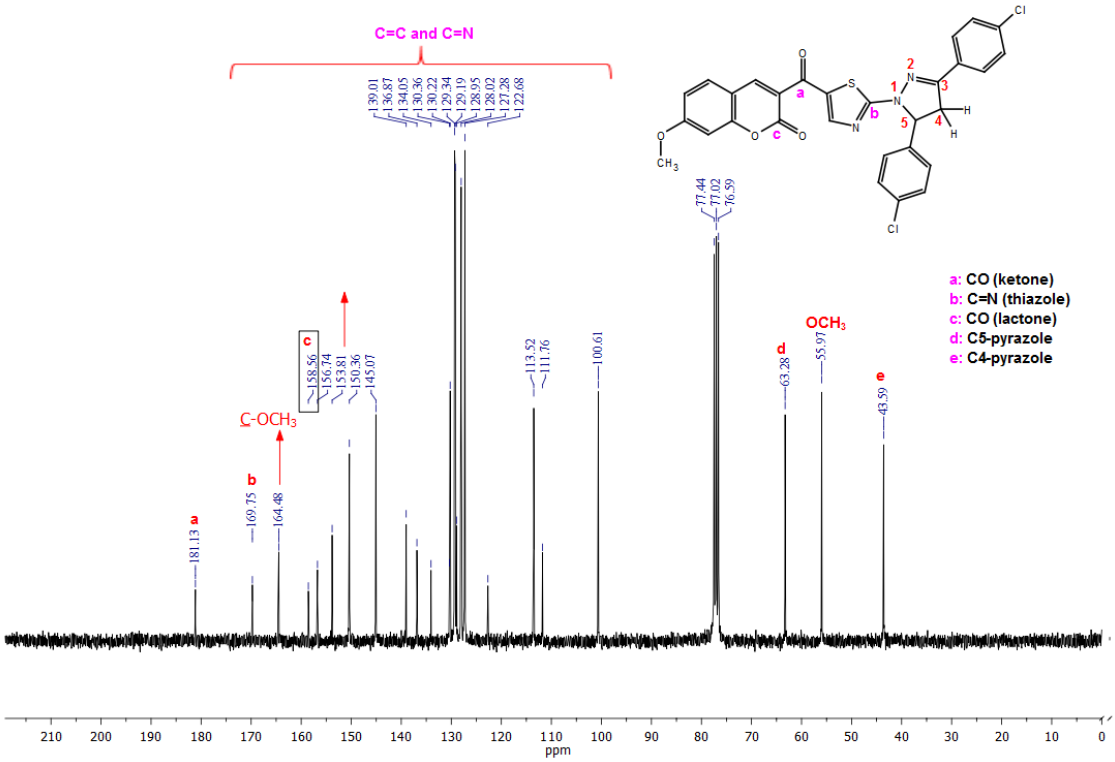
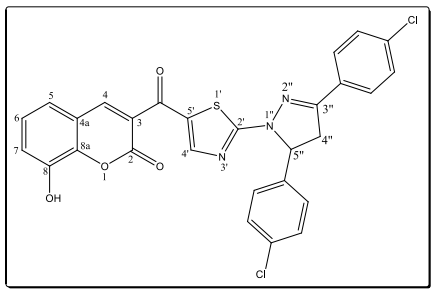


Figure S43: ^{13}C NMR spectra of PTC-13

3-(2-(3,5-bis(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-8-hydroxy-2*H*-chromen-2-one (PTC-14)



Color: Yellow, Yield 0,421 g, 75%, mp 307-308 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3378 (O-H), 3104, 3089, 3075 (Ar-H); 2987, 2967 (alifatic C-H), 1724 (C=O, lactone); 1628 (C=O, ketone); 1603, 1583, 1543, 1509, 1492 (C=N and C=C). ^{1}H-NMR (300 MHz; DMSO-d_6, ppm): δ 10.31 (s, 1H, OH); 8.32 (s, CH, coumarin); 8.00 (s, CH, thiazole); 7.86 (d, part A of the system AB, J=8.7 Hz, 2H, H-2); 7.59 (d, part B of the system AB, J=8.7 Hz, 2H, H-3); 7.42 (d, part A of the system AB, J=8.5 Hz, 2H, H-2'); 7.32 (d, part B of the system AB, J=8.6 Hz, 2H, H-3'); 7.21-7.17 (m, 3H, Ar-H); 5.86-5.80 (dd, J_{cis}= 5.3 Hz, J_{trans}= 11.7 Hz, 1H, C$_5$H-pyrazole); 4.17-4.07 (dd, J_{gem}= 18.3 Hz, J_{trans}= 11.7 Hz, 1H, C$_4$H-pyrazole); 3.47-3.39 (dd, J_{gem}= 18.5 Hz, J_{cis}= 5.4 Hz, 1H, C$_4$H-pyrazole). ^{13}C-NMR (75 MHz; DMSO-d_6, ppm): δ 181.7 (C=O, ketone); 169.3 (C=N, thiazole); 158.1 (C=O, lactone); 156.5; 152.8; 145.0; 144.9; 143.0; 140.3; 136.0; 132.8; 129.6; 129.5; 129.4; 129.3; 129.2; 128.5; 126.2; 126.1; 125.2; 120.0; 119.6 (C=C and C=N); 63.5 (C$_5$-pyrazole); 43.8 (C$_4$-pyrazole). HRMS: m/z (M + H) calcd. for $C_{28}H_{17}Cl_2N_3O_4S$: 562.0390; found: 562.0394. Elemental analysis calcd: C, 59.79; H, 3.05; N, 7.47; S, 5.70. Found: C, 59.52; H, 2.94; N, 7.40; S, 5.41 %.

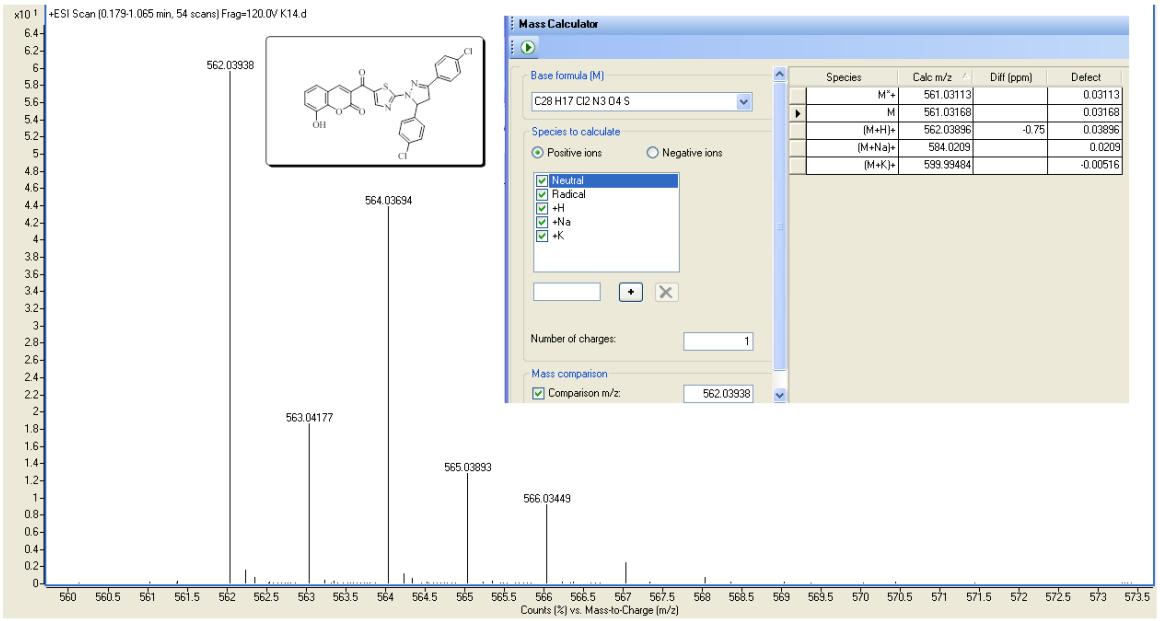


Figure S44: HRMS spectra of PTC-14

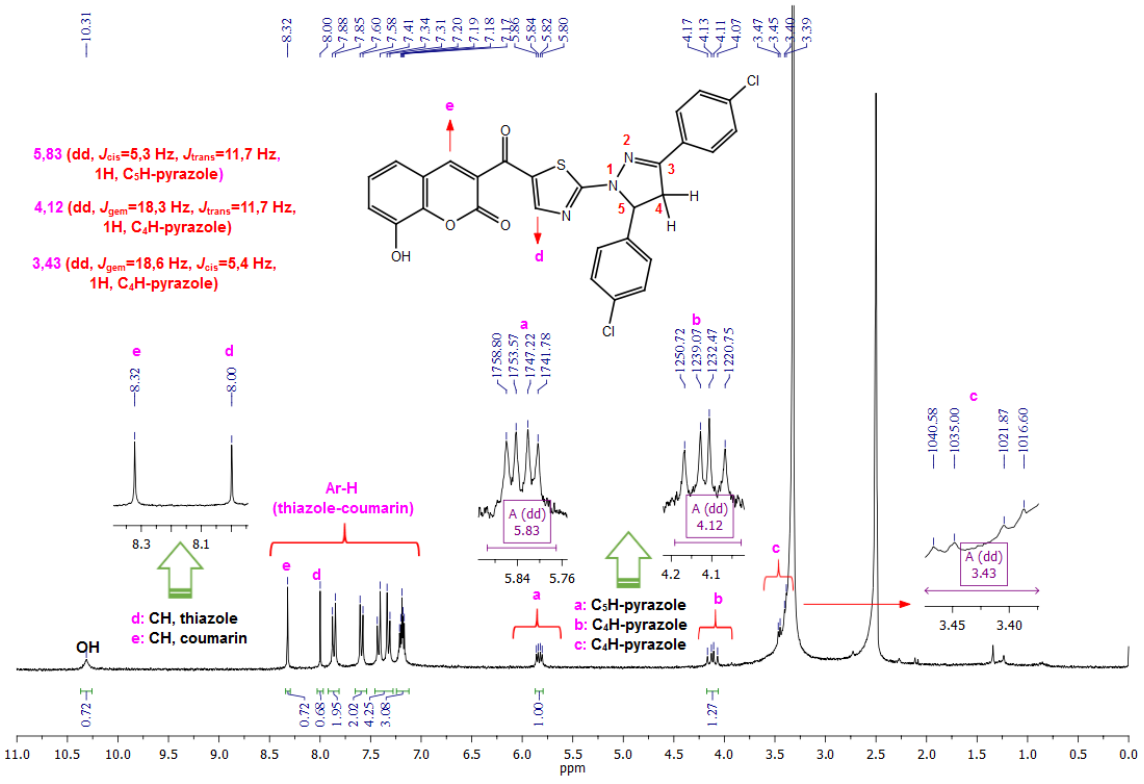


Figure S45: ^{1}H NMR spectra of PTC-14

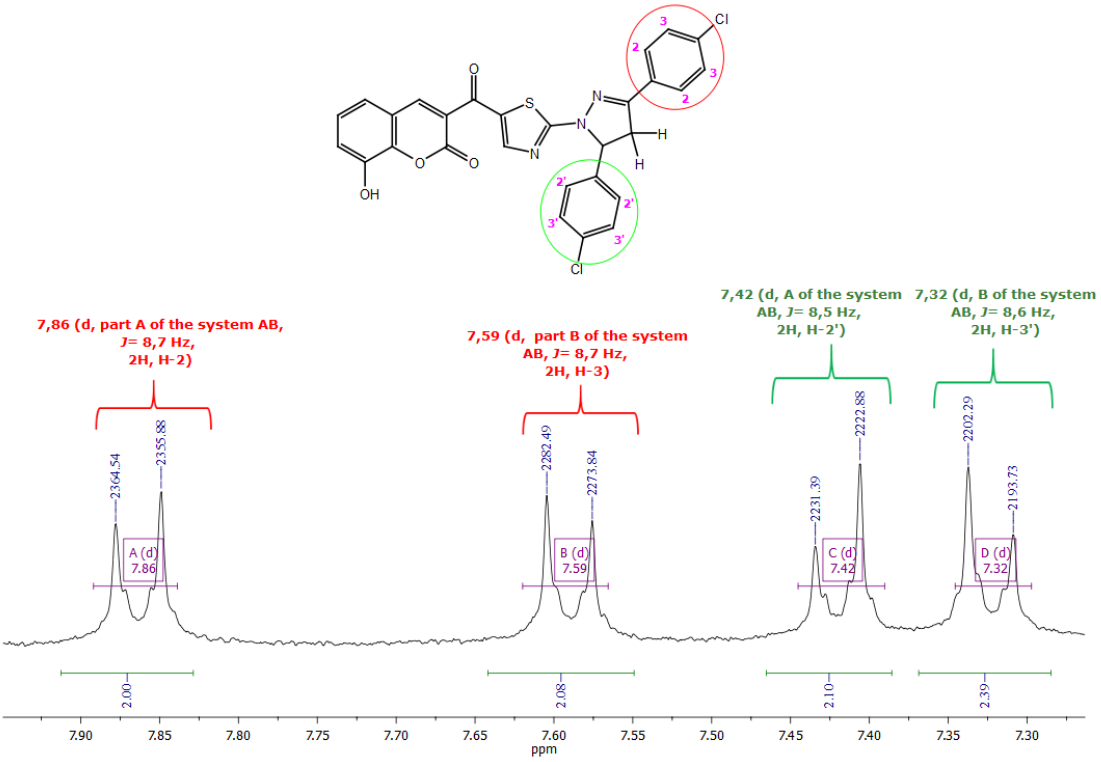


Figure S46: ^{1}H NMR splitting of *p*-disubstituted benzene group protons in compound PTC-14

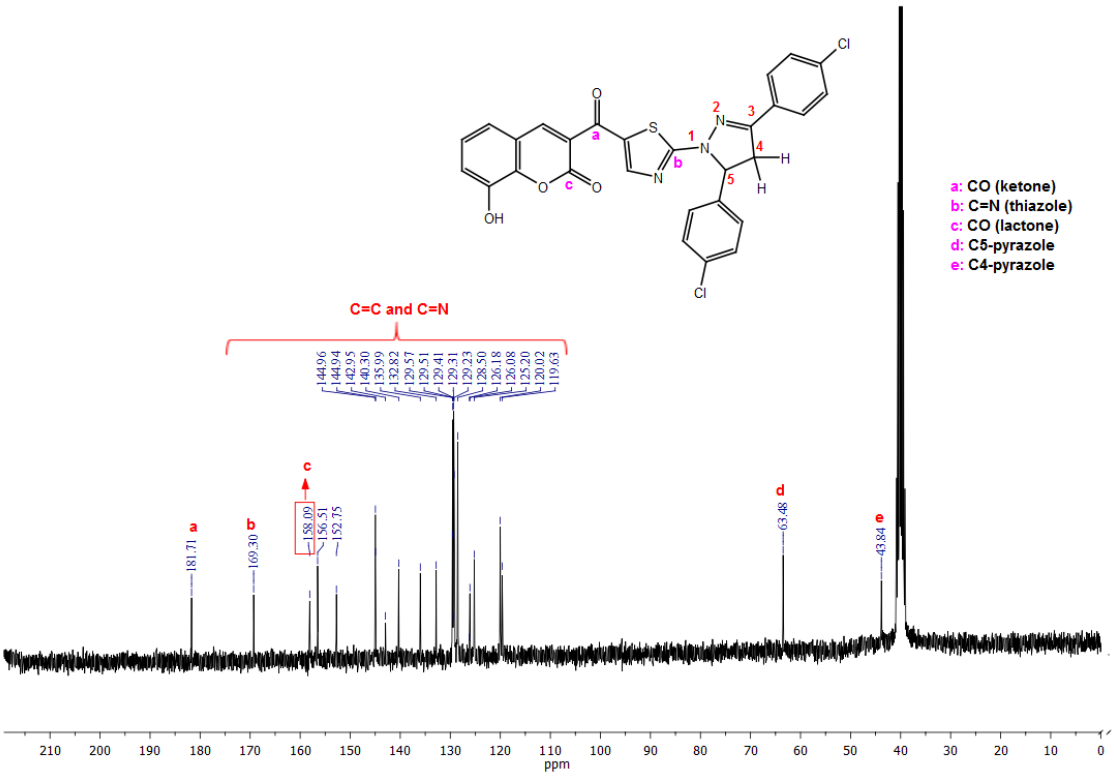
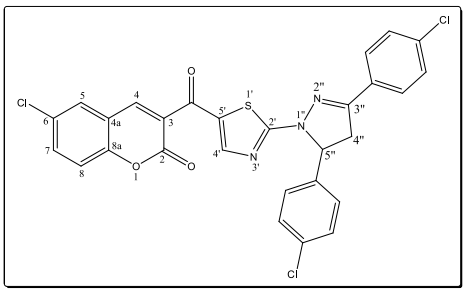


Figure S47: ^{13}C NMR spectra of PTC-14

3-(2-(3,5-bis(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazole-5-carbonyl)-6-chloro-2*H*-chromen-2-one (PTC-15)



Color: Yellow, Yield 0,435 g, 75%, mp : 252-254 ^{o}C, FT-IR (ATR, cm^{-1}): υ_{max} 3090, 3050 (Ar-H); 2985, 2974 (alifatic C-H), 1724 (C=O, lactone); 1631 (C=O, ketone); 1613, 1593, 1555, 1535, 1504, 1488 (C=N and C=C). ^{1}H-NMR (300 MHz; CDCl, ppm): δ 7.95 (s, CH, coumarin); 7.76 (s, CH, thiazole); 7.73-7.20 (m, 11H, Ar-H); 5.74-5.69 (dd, J_{cis}= 5.2 Hz, J_{trans}= 11.8 Hz, 1H, C$_5$H-pyrazole); 4.00-3.90 (dd, J_{gem}= 17.9 Hz, J_{trans}= 11.8 Hz, 1H, C$_4$H-pyrazole); 3.33-3.25 (dd, J_{gem}= 17.8 Hz, J_{cis}= 5.2 Hz, 1H, C$_4$H-pyrazole). ^{13}C-NMR (75 MHz; DMSO-d_6, ppm): δ 181.1 (C=O, ketone); 169.4 (C=N, thiazole); 157.7 (C=O, lactone); 156.7; 156.1; 153.3; 153.0; 143.2; 140.3; 140.2; 136.0; 133.2; 132.8; 129.5; 129.3; 129.3; 129.2; 129.0; 128.9; 128.6; 120.2; 118.7 (C=C and C=N); 63.5 (C$_5$-pyrazole); 43.8 (C$_4$-pyrazole). HRMS: m/z (M + H) calcd. for C$_{28}$H$_{16}$Cl$_3$N$_3$O$_3$S: 580.0051; found: 580.0055. Elemental analysis calcd: C, 57.90; H, 2.78; N, 7.23; S, 5.52. Found: C, 58.26; H, 3.04; N, 7.24; S, 5.73 %.

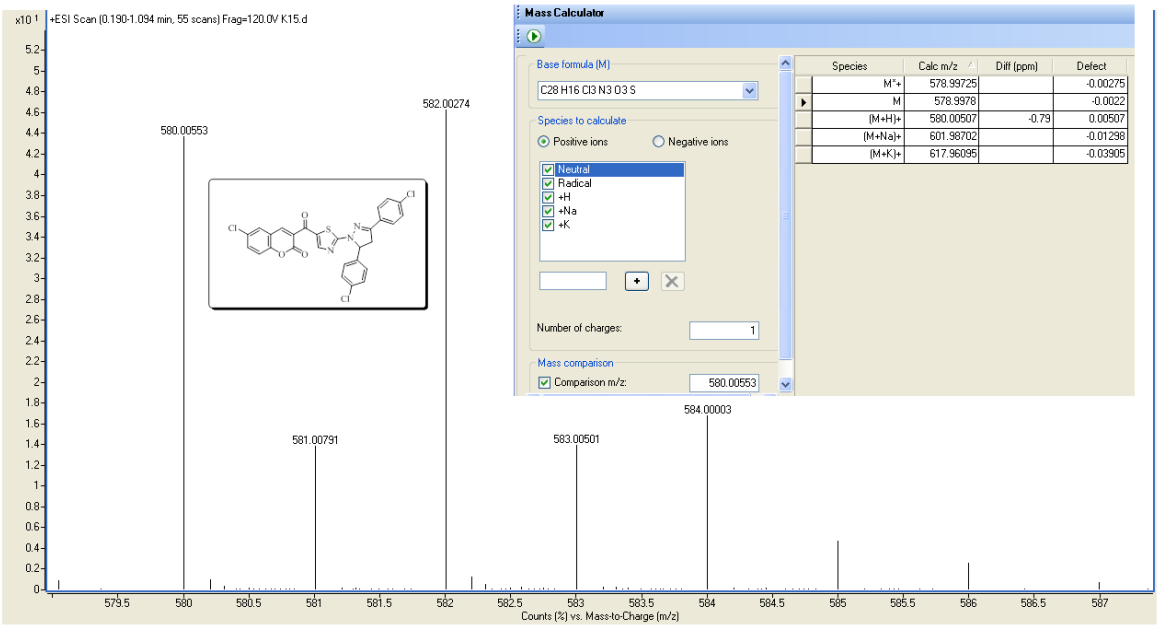


Figure S48: HRMS spectra of PTC-15

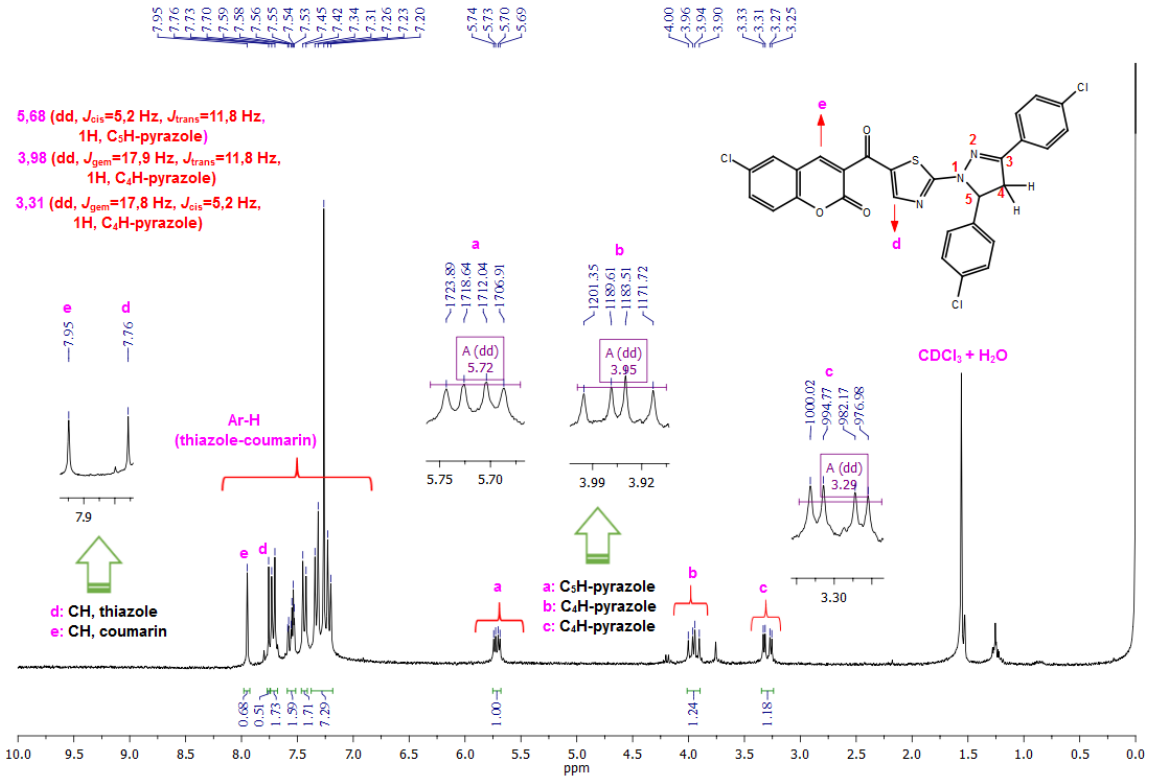


Figure S49: ^{1}H NMR spectra of PTC-15

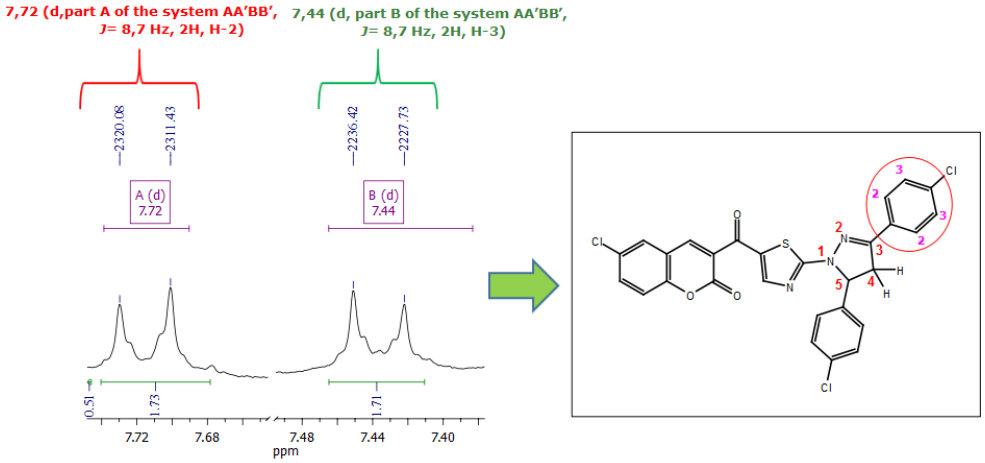


Figure S50: ^{1}H NMR splitting of *p*-disubstituted benzene group protons in compound PTC-15

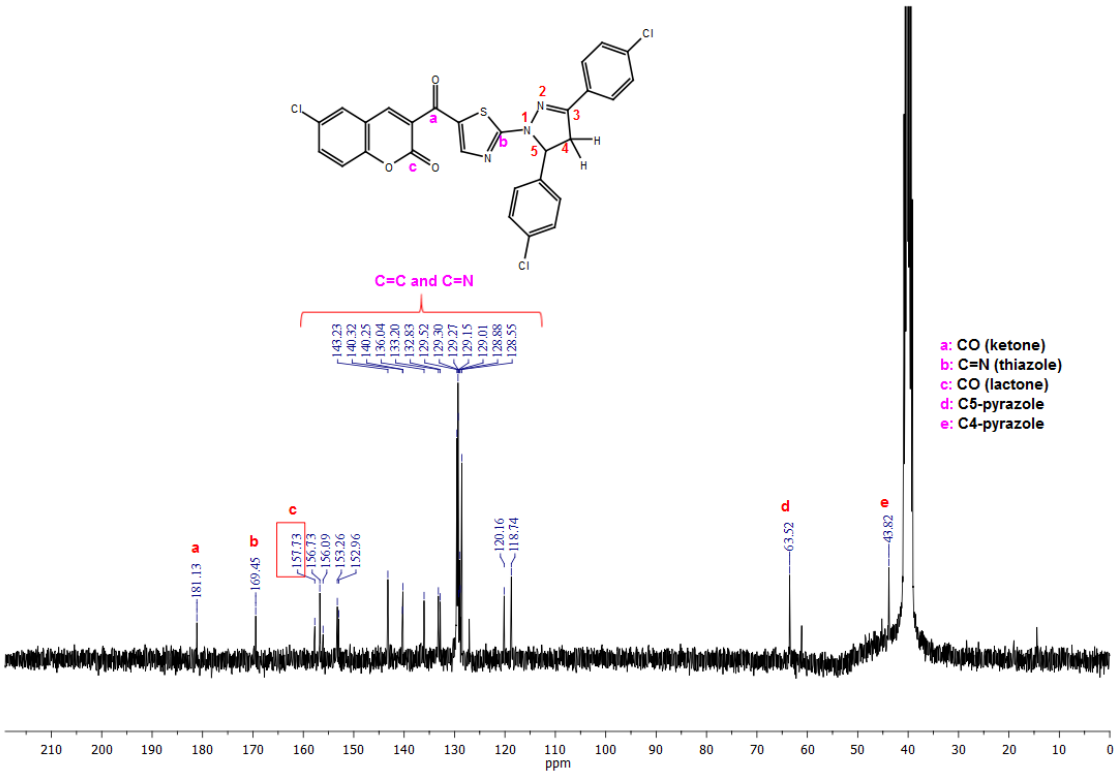


Figure S51: ^{13}C NMR spectra of PTC-15

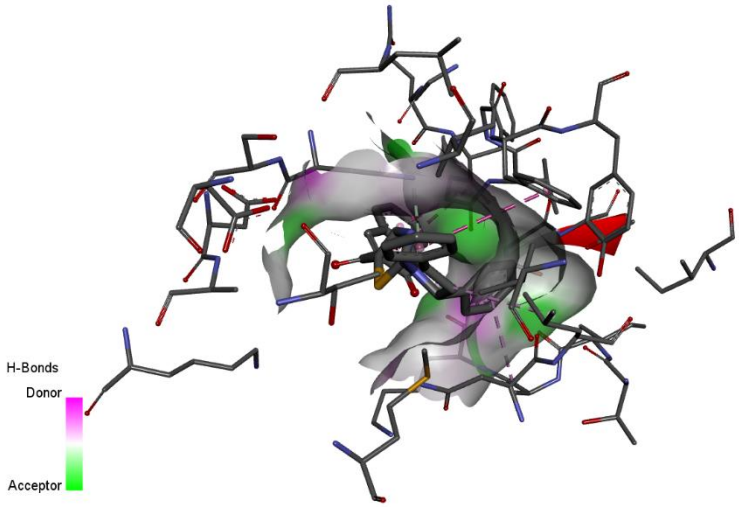


Figure S52. 3D molecular docking results of the PTC-1+HSP90/PDB: 1YC4.

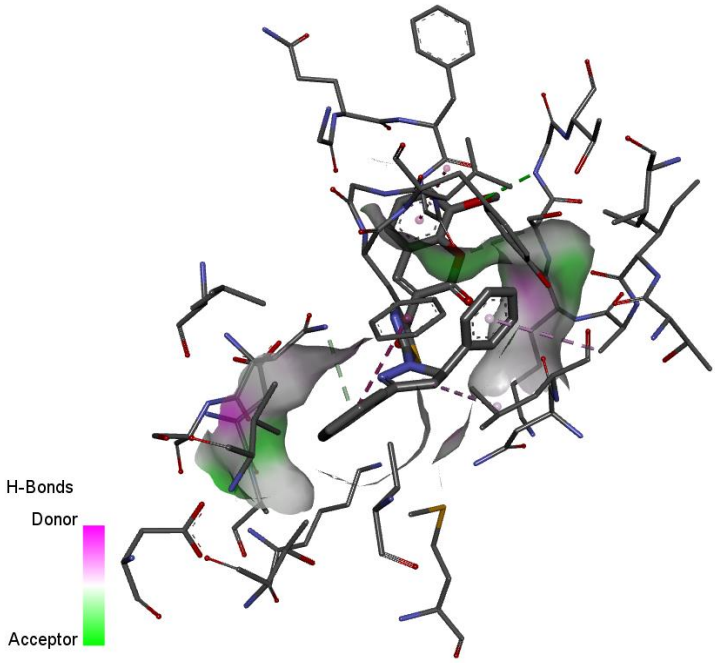


Figure S53. 3D molecular docking results of the PTC-2+HSP90/PDB: 1YC4.

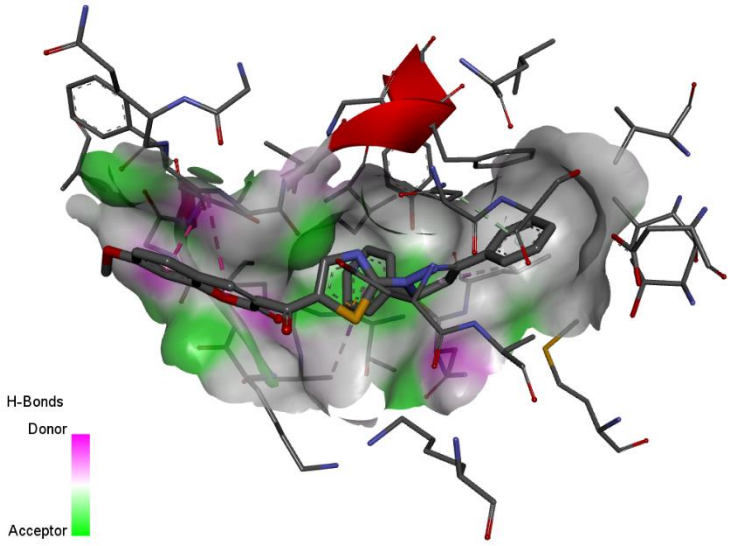


Figure S54. 3D molecular docking results of the PTC-3+HSP90/PDB: 1YC4.

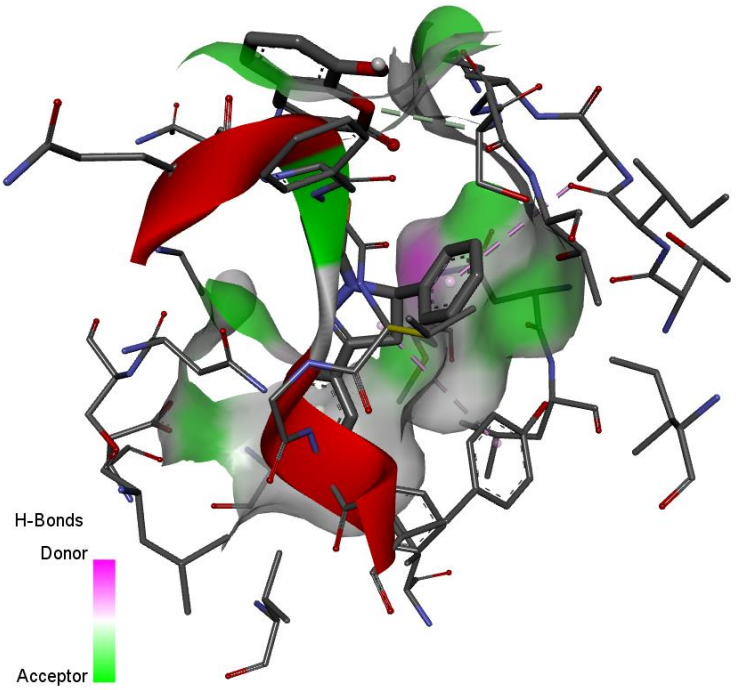


Figure S55. 3D molecular docking results of the PTC-4+HSP90/PDB: 1YC4.

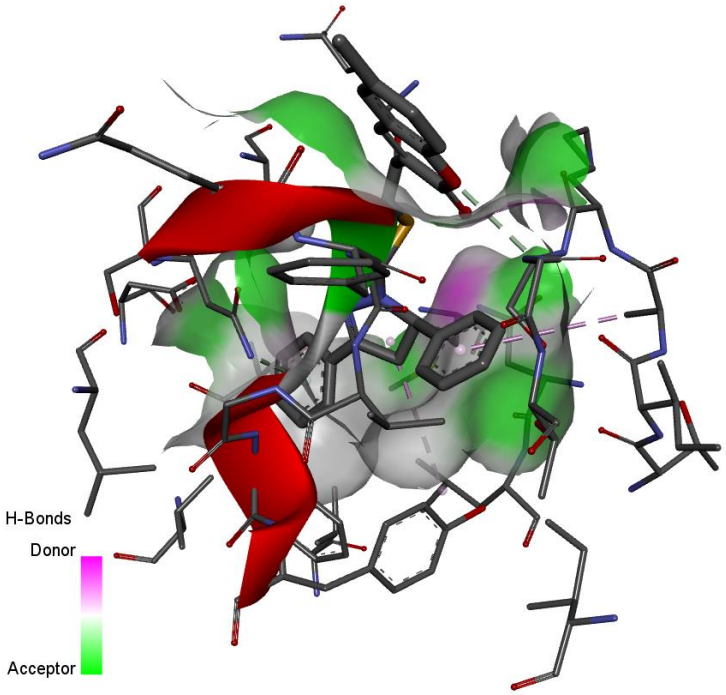


Figure S56. 3D molecular docking results of the PTC-5+HSP90/PDB: 1YC4.

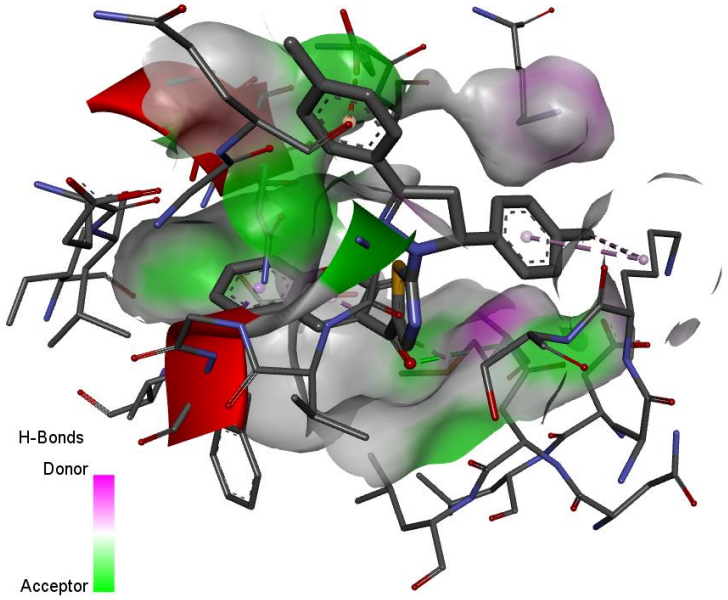


Figure S57. 3D molecular docking results of the PTC-6+HSP90/PDB: 1YC4.

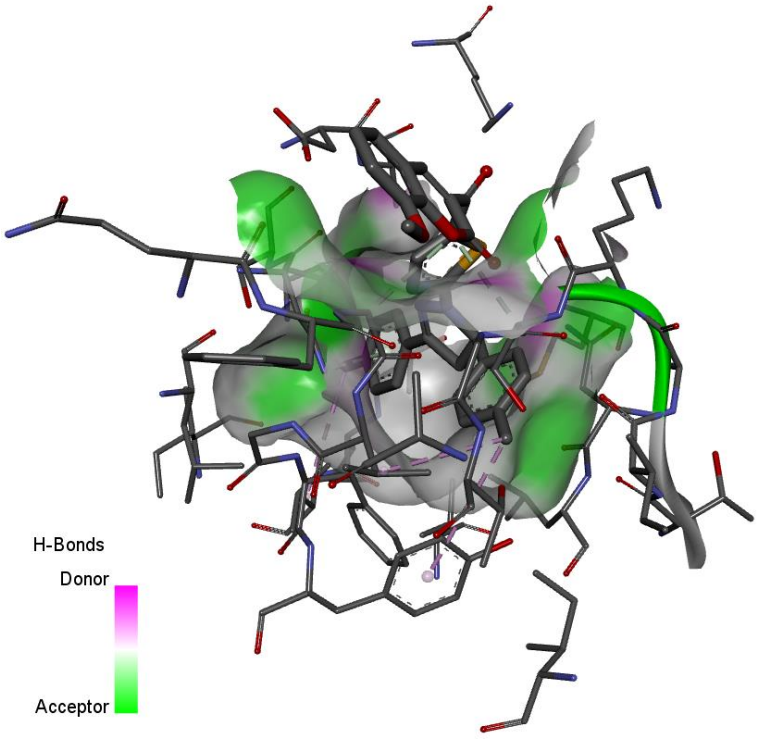


Figure S58. 3D molecular docking results of the PTC-7+HSP90/PDB: 1YC4.

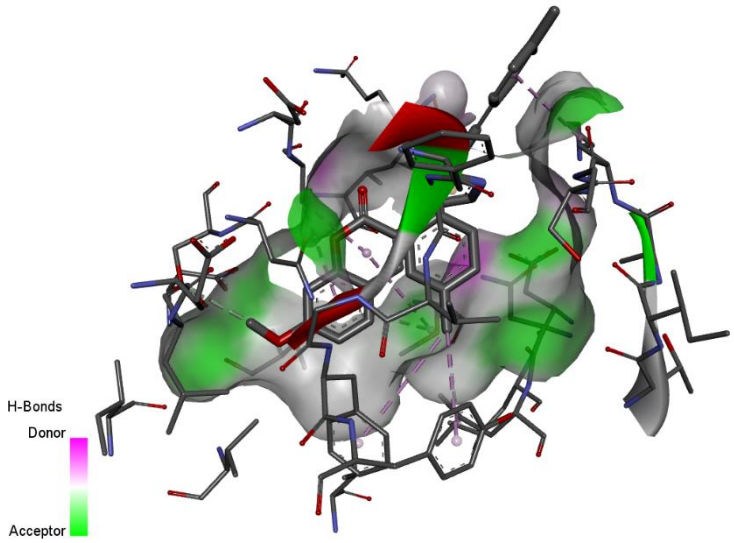


Figure S59. 3D molecular docking results of the PTC-8+HSP90/PDB: 1YC4.

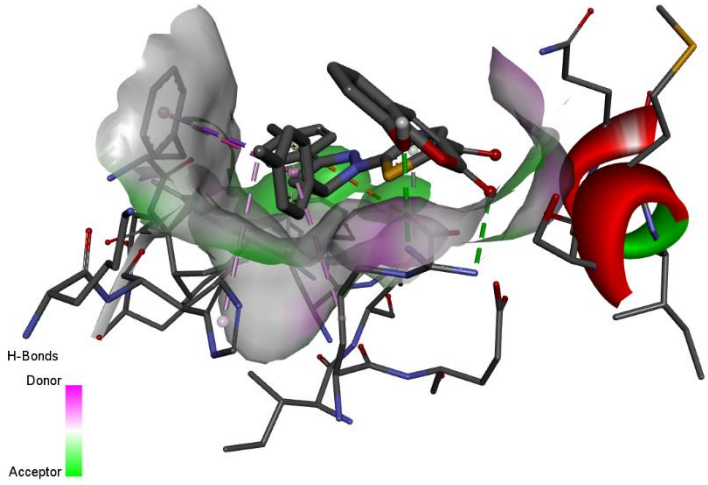


Figure S60. 3D molecular docking results of the PTC-9+HSP90/PDB: 1YC4.

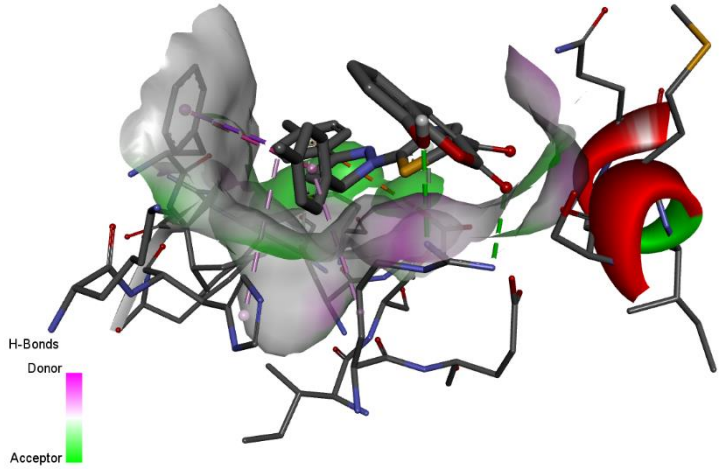


Figure S61. 3D molecular docking results of the PTC-11+HSP90/PDB: 1YC4.

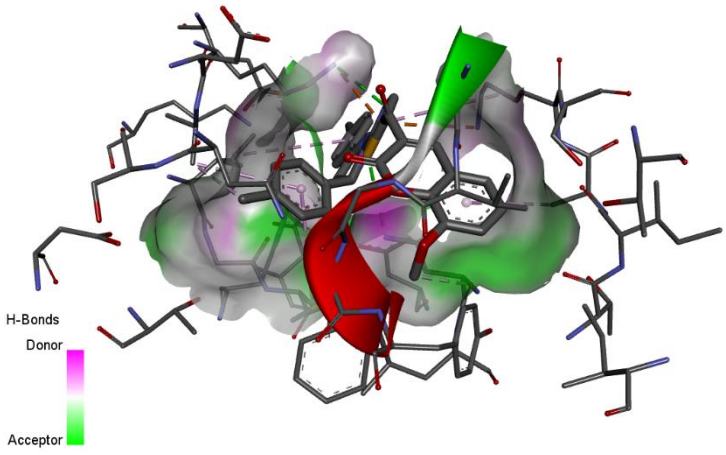


Figure S62. 3D molecular docking results of the PTC-12+HSP90/PDB: 1YC4.

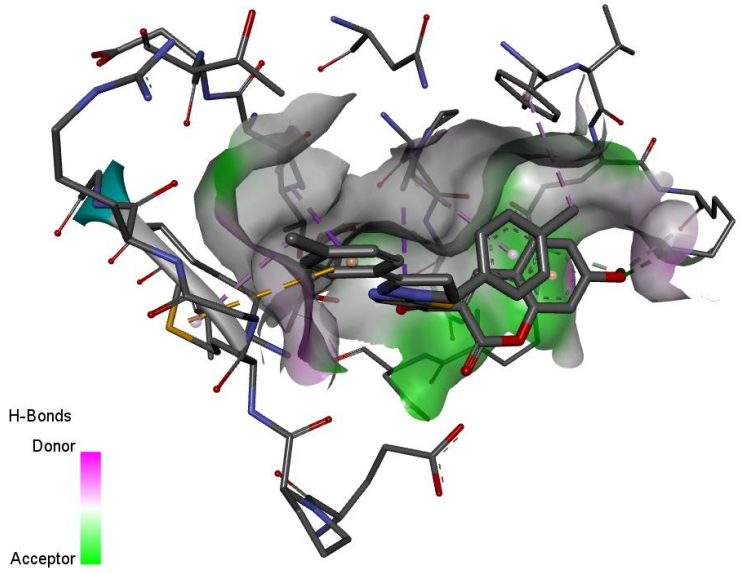


Figure S63. 3D molecular docking results of the PTC-13+HSP90/PDB: 1YC4.

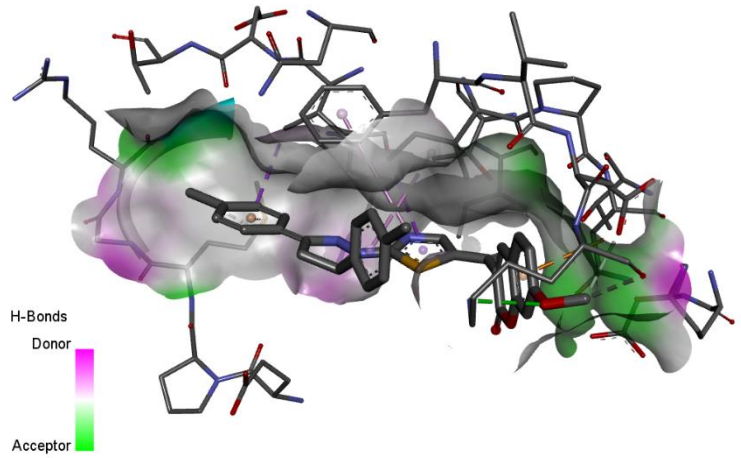


Figure S64. 3D molecular docking results of the PTC-14+HSP90/PDB: 1YC4.

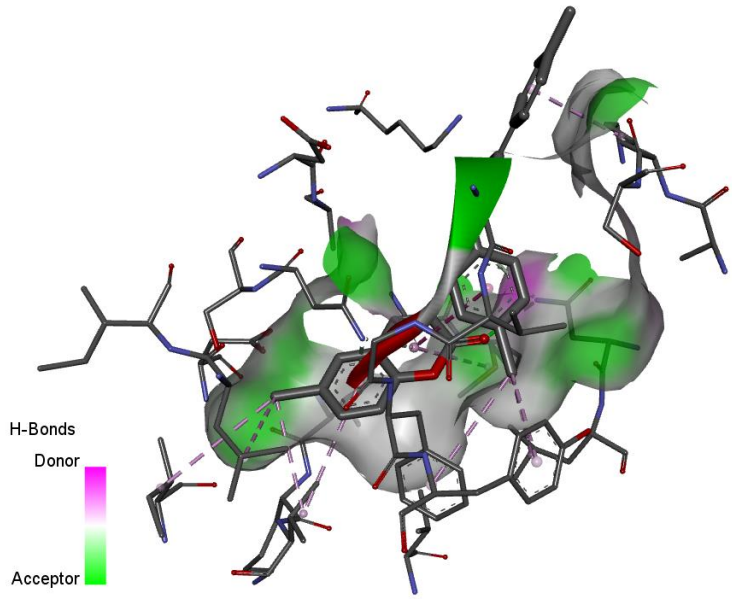


Figure S65. 3D molecular docking results of the PTC-15+HSP90/PDB: 1YC4.

Table S1. Important computed physicochemical properties of the PTC1-15 series

Compound	MW	n_{Rot}	HBA	HBD	Mlog *P*	TPSA	log *S* (Ali)	MR	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Lipinski rule violation
PTC1	477.53	5	5	0	3.55	104.01	-8.23	143.85	+	-	+	-	-	0
PTC2	507.56	6	6	0	3.21	113.24	-8.39	150.34	+	-	+	-	+	1; MW>50
PTC3	507.56	6	6	0	3.21	113.24	-8.39	150.34	+	-	+	-	+	1; MW>50
PTC4	493.53	5	6	1	3.02	124.24	-8.28	145.87	+	-	+	-	-	0
PTC5	511.98	5	5	0	4.01	104.01	-8.89	148.86	+	-	+	-	-	1; MW>50
PTC6	505.59	5	5	0	3.94	104.01	-8.99	153.78	+	-	+	-	-	1; MW>50
PTC7	535.61	6	6	0	3.60	113.24	-9.15	160.27	-	-	+	-	+	1; MW>50
PTC8	535.61	6	6	0	3.60	113.24	-9.15	160.27	-	-	+	-	+	1; MW>50
PTC9	521.59	5	6	1	3.40	124.24	-9.04	155.81	-	-	+	-	-	1; MW>50
PTC10	540.03	5	5	0	4.39	104.01	-9.64	158.79	-	-	+	-	-	2; MW>50 and Mlog *P*>4.15
PTC11	546.42	5	5	0	4.47	104.01	-9.54	153.87	-	-	+	-	-	2; MW>50 and Mlog *P*>4.15
PTC12	576.45	6	6	0	4.13	113.24	-9.70	160.36	-	-	+	-	-	1; MW>50
PTC13	576.45	6	6	0	4.13	113.24	-9.70	160.36	-	-	+	-	-	1; MW>50
PTC14	562.42	5	6	1	3.94	124.24	-9.59	155.89	-	-	+	-	-	1; MW>50
PTC15	580.87	5	5	0	4.93	104.01	-10.18	158.88	-	-	+	-	-	2; MW>50 and Mlog *P*>4.15

Table S2. Selected pharmacokinetic parameters of PTC1-15 series

Compound	Blood brain barrier	Human intestinal absorption	P-glycoprotein inhibitor	hERG	Carcinogen	Acute oral toxicity
PTC1	+(0.8949)	+(0.9865)	NI(0.8687)	WI(0.8835)	NC(0.8222)	III(0.6442)
PTC2	+(0.6433)	+(0.9685)	NI(0.5978)	WI(0.9468)	NC(0.8395)	III(0.6181)
PTC3	+(0.6666)	+(0.9732)	NI(0.7094)	WI(0.8974)	NC(0.8306)	III(0.6047)
PTC4	+(0.6007)	+(0.9250)	NI(0.9049)	WI(0.9614)	NC(0.7956)	III(0.6278)
PTC5	+(0.8230)	+(0.9889)	NI(0.8800)	WI(0.8431)	NC(0.7619)	III(0.6509)
PTC6	+(0.8158)	+(0.9896)	NI(0.8541)	WI(0.8990)	NC(0.7832)	III(0.6675)
PTC7	+(0.5912)	+(0.9544)	I(0.7375)	WI(0.9570)	NC(0.8011)	III(0.5944)
PTC8	+(0.6152)	+(0.9611)	I(0.6954)	WI(0.9157)	NC(0.7878)	III(0.5821)
PTC9	+(0.5970)	+(0.9413)	NI(0.8944)	WI(0.9671)	NC(0.7577)	III(0.6502)
PTC10	+(0.7280)	+(0.9915)	NI(0.8698)	WI(0.8635)	NC(0.7082)	III(0.6685)
PTC11	+(0.8230)	+(0.9889)	NI(0.8800)	WI(0.8431)	NC(0.7619)	III(0.6509)
PTC12	+(0.5644)	+(0.9745)	NI(0.7127)	WI(0.9289)	NC(0.7820)	III(0.6249)
PTC13	+(0.5901)	+(0.9783)	NI(0.7432)	WI(0.8604)	NC(0.7691)	III(0.6145)
PTC14	-(0.5335)	+(0.9384)	NI(0.8930)	WI(0.9458)	NC(0.7370)	III(0.6285)
PTC15	+(0.8230)	+(0.9889)	NI(0.8800)	WI(0.8431)	NC(0.7619)	III(0.6509)

I: Inhibitor; NI: Non Inhibitor; WI: Weak Inhibitor; NC: Non-Carcinogens