**Supplementary Information**

# (*E*)-1-(3-(3-Hydroxy-4-Methoxyphenyl)-1-(3,4,5-Trimethoxyphenyl)allyl)-1*H*-1,2,4-Triazole and Related Compounds: Their Synthesis and Biological Evaluation as Novel Antimitotic Agents Targeting Breast Cancer

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**Supplementary Information**

## Experimental Chemistry

**Figure S1:** Bioavailability Radar for **22a, 22b, 23a** and **23b**.

**Figure S2:** The BOILED-Egg evaluation of passive gastrointestinal absorption (HIA) and brain penetration (BBB) of compound **22a, 22b, 23a** and **23b** as function of the position of the molecule in the WLOGP-*versus*-TPSA map.

**Figure S3-S18:** $^{1}$H-NMR and $^{13}$C NMR spectra

**Figure S19:** Overlay of Imidazole-chalcones with phenstatin, letrozole and phenstatin

**Table S1:** Standard COMPARE Analysis of compound **22b**

**Table S2:** Physicochemical descriptors of selected (*E*)-1-(3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)allyl)-1*H*-1,2,4-triazoles and related compounds.

**Table S3:** Pharmacokinetic interaction estimations with P-gp and CYP 450 isozymes of selected compounds.

**Table S4:** Drug-likeness of representative compounds assessed via lead-likeness and reactivity/toxicity filters for selected compounds.

## References

## Materials and methods: Chemistry

Melting points were measured on a Gallenkamp SMP 11 melting point apparatus and are uncorrected. Infra-red (IR) spectra were recorded as thin film on NaCl plates, or as potassium bromide discs on a Perkin Elmer FT-IR Spectum 100 spectrometer. $^{1}H$ and $^{13}C$ nuclear magnetic resonance (NMR) spectra were recorded at 27°C on a Bruker Avance DPX 400 spectrometer (400.13 MHz, $^{1}H$; 100.61 MHz, $^{13}C$) at 20 °C in $CDCl_3$ (internal standard tetramethylsilane TMS) or DMSO-$d_6$. For $CDCl_3$, $^{1}H$-NMR spectra were assigned relative to the TMS peak at 0.00 δ and $^{13}C$-NMR spectra were assigned relative to the middle $CDCl_3$ triplet at 77.00 ppm. Electrospray ionisation mass spectrometry (ESI-MS) on a liquid chromatography time-of-flight (TOF) mass spectrometer (Micromass LCT, Waters Ltd., Manchester, UK) equipped with electrospray ionization (ES) interface operated in the positive ion mode with High Resolution Mass measurement accuracies of < ±5 ppm. $R_f$ values are quoted for thin layer chromatography on silica gel Merck F-254 plates. Flash column chromatography was carried out on Merck Kieselgel 60 (particle size 0.040-0.063 mm) and also on Biotage SP4 instrument. All products isolated were homogenous on TLC. Analytical high-performance liquid chromatography (HPLC) for purity determination of products was performed using a Waters 2487 Dual Wavelength Absorbance detector, Waters 1525 binary HPLC pump, Waters In-Line Degasser AF and Waters 717plus Autosampler and Varian Pursuit XRs C18 reverse phase 150 x 4.6 mm chromatography column with detection at 254 nm.

**General method I: Preparation of chalcones 20a-h, 20j**.

To a solution of the appropriate aryl aldehyde (1 eq) in methanol (15-20 mL) containing KOH (50%) was added 1-(3,4,5-trimethoxyphenyl)ethan-1-one (1 eq) while stirring at ambient temperature for 24 h. After 24 h, water and HCl dil. were added to complete the precipitation. The solid product was then filtered and the product collected and recrystallised from methanol to afford the desired chalcone.

**(*E*)-3-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (20a)**. As per general method I, 3,4,5-trimethoxyacetophenone (1 eq, 4.7 mmol, 1 g) was reacted with 4-methoxybenzaldehyde (1 eq, 4.7 mmol, 0.64 g) and KOH 50% (10 mL) in methanol at RT for 24 h. The precipitate was filtered and recrystallised from methanol to afford the product, yield 67%, 1.04 g, white crystals, Mp. 96-100 °C [1]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 3227, 3005, 1654, 1591, 1579, 1457, 1408, 1318, 1245, 1155, 1120, 997, 973, 823, 664, 558. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3 H, $OCH_3$), 3.92 (s, 3 H, $OCH_3$), 3.93 (s, 6 H, 2×$OCH_3$), 6.93 (d, *J*=8.71 Hz, 2 H, Ar-H), 7.25 (s, 2 H, Ar-H), 7.34 (d, *J*=15.34 Hz, 1 H, C<u>H</u>=CH), 7.60 (d,

*J*=8.71 Hz, 2 H, Ar-H), 7.78 (d, *J*=15.34 Hz, 1 H, CH=C<u>H</u>). $^{13}$C NMR (101 MHz, $CDCl_3$) 55.41 ($OCH_3$), 56.38 (2×$OCH_3$), 60.96 (OCH), 105.99 (2×CH), 114.42 (2×CH), 119.42 (<u>C</u>H=CH), 127.60 (C), 130.21 (2×CH), 133.82 (C), 144.59 (C-O, CH=<u>C</u>H), 153.11 (2×C-O), 161.68 (C-O), 189.25 (C=O) ppm. HRMS (EI): Found 329.1374 $(M+H)^+$; $C_{19}H_{21}O_5$ requires 329.1389.

**(*E*)-3-(3-Hydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (20b)**. As per general method I, 3,4,5-trimethoxyacetophenone (1 eq, 7.13 mmol, 1.5 g) was reacted with 3-hydroxy-4-methoxybenzaldehyde (1 eq, 7.13 mmol, 1.08 g) and KOH 50% (10 mL) in methanol at RT for 24 h. The precipitate was filtered and recrystallised from methanol to afford the product, yield: 73%, 1.8 g, orange solid, Mp. 137-141 °C [2]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 3293, 2946, 2838, 1650, 1571, 1504, 1449, 1412, 1311, 1267, 1226, 1154, 1029, 976, 843, 745, 665. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 3.73 (s, 3 H, $OCH_3$), 3.81 (s, 3 H, $OCH_3$), 3.87 (s, 6 H, 2×$OCH_3$), 6.97 (d, *J*=8.29 Hz, 1 H, Ar-H), 7.27 (dd, *J*=8.29, 2.07 Hz, 1 H, Ar-H), 7.34 (d, *J*=2.07 Hz, 1 H, Ar-H), 7.37 (s, 2 H, Ar-H), 7.57 - 7.62 (m, 1 H, C<u>H</u>=CH), 7.65 - 7.70 (m, 1 H, CH=C<u>H</u>), 9.11 (s, 1 H, OH). $^{13}$C NMR (101 MHz, DMSO-$d_6$) 55.67 ($OCH_3$), 56.17 (2×$OCH_3$), 60.16 ($OCH_3$), 105.99 (2×CH), 111.81 (CH), 114.86 (CH), 119.23 (CH), 122.30 (<u>CH</u>=CH), 127.67 (C), 133.29 (C), 141.72 (C-O), 144.38 (CH=<u>CH</u>), 146.69 (C-O), 150.29 (C-O), 152.86 (2×C-O), 187.71 (C=O) ppm. HRMS (EI): Found 343.1187 $(M-H)^+$; $C_{19}H_{19}O_6$ requires 343.1182.

**(*E*)-1,3-Bis(3,4,5-trimethoxyphenyl)prop-2-en-1-one (20c)**. As per general method I, 3,4,5-trimethoxyacetophenone (1 eq, 7.1 mmol, 1.5 g) was reacted with 3,4,5-trimethoxybenzaldehyde (1 eq, 7.1 mmol, 1.39 g) and KOH 50% (10 mL) in methanol for 24 h. The precipitate was filtered and recrystallised from methanol, yield: 80%, 2.2 g, pale yellow crystals, Mp. 123-125°C [3]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 3385, 3001, 2919, 1660, 1578, 1501, 1466, 1324, 1266, 1225, 1148, 1120, 993, 971, 852, 830, 778, 725. $^1$H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3 H, $OCH_3$), 3.91 (s, 6 H, $OCH_3$), 3.93 (s, 3 H, $OCH_3$), 3.93 (s, 6 H, 2×$OCH_3$), 6.85 (s, 2 H, Ar-H), 7.24 (s, 2 H, Ar-H), 7.31 (d, *J*=15.34 Hz, 1 H, C<u>H</u>=CH), 7.70 (d, *J*=15.76 Hz, 1 H, CH=C<u>H</u>). $^{13}$C NMR (101 MHz, $CDCl_3$) 56.29 (2×$OCH_3$), 56.51 (2×$OCH_3$), 60.99 (2x×$OCH_3$), 105.77 (2×CH), 106.28 (2×CH), 121.34 (<u>CH</u>=CH), 126.44 (C), 130.36 (C), 142.56 (C-O), 144.96 (C-O, CH=<u>CH</u>), 153.15 (2xC-O), 153.51 (2×C-O), 189.44 (C=O) ppm. HRMS (EI): Found 411.1420 $(M+Na)^+$ $C_{21}H_{24}NaO_7$ requires 411.1420.

**(*E*)-3-(3,4-Dimethoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (20d):** As per general method I, 3,4,5-trimethoxyacetophenone (1 eq, 7.14 mmol, 1.5 g) was reacted with

3,4-dimethoxybenzaldehyde (1 eq, 7.14 mmol, 1.19 g) and KOH 50% (10 mL) in methanol for 24 h. The precipitate was filtered and recrystallised from methanol. Yield 90%, 2.3 g, yellow solid, Mp. 130-133 °C [1]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 3333, 2994, 2943, 2835, 1649, 1580, 1568, 1501, 1410, 1329, 1313, 1263, 1225, 1153, 1120, 1023, 997, 829, 806, 763, 698, 662. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 6 H, 2×$OCH_3$), 3.94 (s, 9 H, 3×$OCH_3$), 6.90 (d, *J*=8.29 Hz, 1 H, Ar-H), 7.14 (d, *J*=1.66 Hz, 1 H, Ar-H), 7.25 (d, *J*=1.66 Hz, 3 H, Ar-H), 7.31 (d, *J*=15.76 Hz, 1 H, CH=CH), 7.75 (d, *J*=15.76 Hz, 1 H, CH=CH). $^{13}C$ NMR (101 MHz, $CDCl_3$) 189.41 (C=O), 153.10 (2×C-O), 151.43 (C-O), 149.23 (C-O), 144.92 (CH=CH), 142.35 (C-O), 133.79 (C), 127.84 (C), 122.85 (CH), 119.85 (CH=CH), 111.15 (CH), 110.47 (CH), 106.13 (2×CH), 60.95 ($OCH_3$), 56.43 (2×$OCH_3$), 56.01 ($OCH_3$), 55.99 ($OCH_3$) ppm. HRMS (EI): Found 381.1314 $(M+Na)^+$; $C_{20}H_{22}NaO_6$ requires 381.1314.

**(*E*)-3-(4-Ethoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (20e):** As per general method I, 3,4,5-trimethoxyacetophenone (1 eq, 4.7 mmol, 1.0 g) was reacted with 4-ethoxybenzaldehyde (1 eq, 4.7 mmol, 0.71 g, 0.67 mL) and KOH 50% (10 mL) in methanol for 24 h. The precipitate was filtered and recrystallised from methanol. Yield: 56%, 0.25 g, yellow solid, Mp. 73-77 °C [4] . IR: $\nu_{max}$ (ATR) $cm^{-1}$: 2998, 2933, 2820, 1678, 1586, 1567, 1407, 1355, 1329, 1215, 1174, 992, 887, 856, 750, 653. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 1.43 (t, *J*=7.05 Hz, 3 H, $CH_3$), 3.92 (s, 3 H, $OCH_3$), 3.94 (s, 6 H, 2×$OCH_3$), 4.07 (q, *J*=6.91 Hz, 2 H, $CH_2$), 6.92 (d, *J*=8.71 Hz, 2 H), 7.24 - 7.25 (m, 2 H, Ar-H), 7.34 (d, *J*=15.76 Hz, 1 H, CH=CH), 7.58 (d, *J*=8.71 Hz, 2 H), 7.78 (d, *J*=15.34 Hz, 1 H, CH=CH). $^{13}C$ NMR (101 MHz, $CDCl_3$) 14.71 ($CH_3$), 56.39 (2×$OCH_3$), 60.97 ($OCH_3$), 63.67 ($CH_2$), 106.00 (2×CH), 114.89 (2×CH), 119.28 (CH=CH), 127.42 (C), 130.23 (2×CH), 133.86 (C), 144.71 (C-O, CH=CH), 153.11 (2xC-O), 161.12 (C-OEt), 189.30 (C=O) ppm. HRMS (EI): Found 365.1346 $(M+Na)^+$; $C_{20}H_{22}NaO_5$ requires 365.1346.

**(*E*)-3-(4-Fluorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (20f):** As per general method I, 3,4,5-trimethoxyacetophenone (1 eq, 7.14 mmol, 1.5 g) was reacted with 4-fluorobenzaldehyde (1 eq, 7.14 mmol, 0.89 g) and KOH 50% (10 mL) in methanol. The reaction was stirred at RT for 24 h. The precipitate was filtered and recrystallised from methanol. Yield: 81%, 1.8 g, yellow crystals, Mp. 127-130 °C [5]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 2947, 1692, 1625, 1600, 1572, 1525, 1424, 1346, 1314, 1277, 1199, 1088, 977, 815, 757. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3 H, $OCH_3$), 3.94 (s, 6 H, 2×$OCH_3$ ), 7.11 (t, *J*=8.50 Hz, 2 H, Ar-H), 7.26 (s, 2 H, Ar-H), 7.39 (d, *J*=15.34 Hz, 1 H, CH=CH), 7.63 (dd, *J*=8.71, 5.39 Hz, 2 H, Ar-H), 7.77 (d, *J*=15.76 Hz, 1 H, CH=CH). $^{13}C$ NMR (101 MHz, $CDCl_3$) 56.43

(2×$OCH_3$), 60.98 ($OCH_3$), 106.11 (2×CH), 116.03 (CH), 116.25 (CH), 121.43 (CH=CH), 130.29 (C), 130.37 (2xCH), 131.13 (C), 143.41 (C-O, CH=CH), 153.17 (2xC-O), 165.31 (C-F), 188.97 (C=O) ppm. LRMS (EI): Found 339.21 $(M+Na)^+$; $C_{18}H_{17}FNaO_4$ requires 339.10.

**(*E*)-3-Phenyl-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (20g):** As per general method I, 3,4,5-trimethoxyacetophenone (1 eq, 4.76 mmol, 1.0 g) was reacted with benzaldehyde (1 eq, 4.76 mmol, 0.505 g, 0.48 mL) and KOH 50% (10 mL) in methanol for 24 h. The precipitate was filtered and recrystallised from methanol. Yield: 86%, 1.22 g, yellow crystals, Mp. 80-84 °C [6]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 2941, 2838, 1656, 1571, 1450, 1412, 1335, 1228, 1155, 1121, 992, 844, 763, 634. $^1H$ NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3 H, $OCH_3$), 3.94 (s, 6 H, 2×$OCH_3$), 7.27 (s, 2 H, Ar-H), 7.40 - 7.44 (m, 3 H, Ar-H), 7.47 (d, *J*=15.76 Hz, 1 H, CH=CH), 7.64 (dd, *J*=6.84, 2.70 Hz, 2 H, Ar-H), 7.80 (d, *J*=15.34 Hz, 1 H, CH=CH). $^{13}C$ NMR (101 MHz, $CDCl_3$) 56.41 (2×$OCH_3$), 60.98 ($OCH_3$), 106.11 (2×CH), 121.80 (CH=CH), 128.42 (4×CH), 128.96 (CH), 130.55 (C), 133.49 (C), 144.74 (C-O, CH=CH), 153.15 (2×C-O), 189.25 (C=O) ppm. LRMS (EI): Found 321.29 $(M+Na)^+$; $C_{18}H_{18}NaO_4$ requires 321.11.

**(*E*)-3-(4-Nitrophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (20h):** As per general method I, 3,4,5-trimethoxyacetophenone (1 eq, 7.14 mmol, 1.5 g) was reacted with 4-nitrobenzaldehyde (1 eq, 7.14 mmol, 1.08 g) and KOH 50% (10 mL) in methanol at RT for 24 h. The precipitate was filtered and recrystallised from methanol. Yield: 83%, 2.02 g, yellow solid Mp. 197-200 °C [5]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 3294, 1526, 1294, 1221, 1085, 1031, 773. $^1H$ NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3 H, $OCH_3$), 3.95 (s, 6 H, 2×$OCH_3$), 7.27 (s, 2 H, Ar-H), 7.57 (d, *J*=15.76 Hz, 1 H, CH=CH), 7.78 (d, *J*=8.71 Hz, 2 H, Ar-H), 7.81 (d, *J*=15.76, 1 H, CH=CH), 8.28 (d, *J*=8.71 Hz, 2 H, Ar-H). $^{13}C$ NMR (101 MHz, $CDCl_3$) 188.27 (C=O), 153.27 (2×C-O), 148.54 (C-$NO_2$), 143.11 (C-O, CH=CH), 141.42 (C), 132.75 (C), 128.92 (2×CH), 125.39 (CH=CH), 124.21 (2×CH), 106.30 (2×CH), 61.03 ($OCH_3$), 56.48 (2×$OCH_3$) ppm. HRMS (EI): Found 344.1127 $(M+H)^+$; $C_{18}H_{18}NO_6$ requires 344.1134.

**(*E*)-3-(4-Hydroxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (20j).** As per general method I, 3,4,5-trimethoxyacetophenone (1 eq, 7.14 mmol, 1.5 g) was reacted with 4-hydroxybenzaldehyde (1 eq, 7.14 mmol, 0.87 g) and KOH 50% (10 mL) in methanol at RT for 24 h. The precipitate was filtered and recrystallised from methanol. Yield: 27%, 0.60 g, yellow solid, Mp. 200-204 °C [7]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 3142, 2945, 2833, 1638, 1586, 1551, 1438, 1342, 1306, 1275, 1231, 1168, 984, 824, 813, 702, 668. $^1H$ NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3 H, $OCH_3$) 3.96 (s, 6 H, 2×$OCH_3$) 6.88 - 6.93 (m, 2 H, Ar-H) 7.28 (s, 2 H, Ar-H) 7.36 (d, *J*=15.76 Hz, 1 H, CH=CH) 7.57 - 7.59 (m, 2 H, Ar-H) 7.79 (d, *J*=15.76 Hz, 1 H,

CH=CH). $^{13}$C NMR (101 MHz, $CDCl_3$) 189.54 (C=O), 158.20 (C-OH), 153.08 (2×C-O), 144.81 (C-O, CH=CH), 133.72 (C), 130.46 (2×CH), 127.56 (C), 119.31 (CH=CH), 115.99 (2×CH), 106.04 (2×CH), 60.96 ($OCH_3$), 56.37 (2×$OCH_3$) ppm. HRMS (EI): Found 313.1083 $(M-H)^+$; $C_{18}H_{18}O_5$ requires 313.1076.

**(E)-3-(4-Chlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one 20k:**

General Procedure I was followed using 1-(3,4,5-trimethoxyphenyl)ethan-1-one (1 equiv; 2.37 mmol; 500 mg), 4-chlorobenzaldehyde (1 equiv; 2.37 mmol; 334 mg), MeOH (30 mL) and 70 drops of 50% KOH solution to afford the pure product **20l** as a white powder (91%)[8]. $^1$H NMR (400 MHz, $CDCl_3$): δ ppm 7.75 (d, J = 15.7 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 15.7 Hz, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.25 (s, 2H), 3.94 (s, 6H), 3.92 (s, 3H). $^{13}$C NMR (400MHz, $CDCl_3$): ppm 188.91, 153.18, 143.26, 142.84, 136.32, 133.34, 133.25, 129.55, 129.34, 122.02, 106.10, 61.05, 56.48 ppm.

**General method II: Preparation of (*E*)-1,3-Diarylprop-2-en-1-ols (21a-c)**

To a solution of the appropriate chalcone (1 eq) in methanol (25 mL), a suspension of $NaBH_4$ (1 eq) in methanol (10 mL) and THF (10 mL) was slowly added. The reaction mixture was stirred (0-20 °C) and monitored by TLC until the reaction was complete. $NaHCO_3$ (sat., 5 mL) was then added and the reaction mixture was concentrated. The reaction residue was extracted with ethyl acetate, washed with water and brine and dried over sodium sulphate. No further purification was required.

**(*E*)-3-(4-Methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-ol (21a)**: As per general method II (*E*)-3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **(20a) (**1 eq, 1.5 mmol, 0.5 g) was treated with sodium borohydride (1 eq, 1.5 mmol, 0.06 g) in methanol (10 mL) and THF (10 mL). Yield: 100%, 1.45 g, white solid, Mp. 113-116 °C [1]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 3379, 2836, 1693, 1508, 1458, 1421, 1243, 1123, 1037, 1020, 848, 767. $^1$H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3 H, $OCH_3$), 3.84 (s, 3 H, $OCH_3$), 3.87 (s, 6 H, 2×$OCH_3$), 5.30 (d, *J*=9.54 Hz, 1 H, CH-OH), 6.23 (dd, *J*=15.76, 7.05 Hz, 1 H, CH=CH), 6.59 (d, *J*=16.59 Hz, 1 H, CH=CH), 6.66 (s, 2 H, Ar-H), 6.83 - 6.87 (m, 2 H, Ar-H), 7.32 - 7.36 (m, 2 H, Ar-H).$^{13}$C NMR (101 MHz, $CDCl_3$) 55.29 ($OCH_3$), 56.13 (2×$OCH_3$), 60.82 ($OCH_3$), 75.44 (CH-OH), 103.12 (2×CH), 114.01 (2×CH), 127.85 (CH=CH), 129.07 (C), 129.14 (CH=CH), 130.42 (2×CH), 135.76 (C), 138.73 (C-O), 153.38 (2×C-O), 159.44 (C-O) ppm. HRMS (EI): Found 329.1383 $(M-H)^+$; $C_{19}H_{21}O_5$ requires 329.1389.

**(*E*)-5-(3-Hydroxy-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)-2-methoxyphenol (21b)**: As per general method II (*E*)-3-(3-hydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **(20b)** (1 eq, 5.22 mmol, 1.9 g) was treated with sodium borohydride (1 eq, 5.22 mmol, 0.2 g) in methanol (10 mL) and THF (10 mL). Yield: 100%, 1.8 g, yellow oil [1]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 3448, 2988, 2971, 2939, 1582, 1503, 1454, 1416, 1327, 1233, 1120, 1044, 911, 829, 598, 561. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3 H, $OCH_3$), 3.85 (s, 6 H, 2×$OCH_3$), 3.87 (s, 3 H, $OCH_3$), 5.27 (d, *J*=6.63 Hz, 1 H, CH-OH), 6.20 (dd, *J*=15.76, 6.63 Hz, 1 H, CH=CH), 6.54 - 6.60 (m, 1 H, CH=CH), 6.64 (s, 2 H, Ar-H), 6.78 (d, *J*=8.29 Hz, 1 H, Ar-H), 6.86 (dd, *J*=8.29, 2.07 Hz, 1 H, Ar-H), 7.01 (d, *J*=2.07 Hz, 1 H, Ar-H). $^{13}C$ NMR (101 MHz, $CDCl_3$) 153.09 (2xC-O), 148.80 (C-O), 144.64 (C-OH), 142.29 (C-O), 131.67 (C), 128.53 (C), 124.46 (CH=CH), 122.98 (CH=CH), 119.83 (CH), 112.69 (CH), 110.55 (CH), 106.71 (CH), 105.93 (CH), 68.04 (CH-OH), 60.98 ($OCH_3$), 56.35 ($OCH_3$), 56.26 ($OCH_3$), 56.21 ($OCH_3$) ppm. HRMS (APCI): Found 343.1185 $(M-3H)^+$ $C_{19}H_{19}O_6$ requires 343.1182.

**(*E*)-1,3-Bis(3,4,5-trimethoxyphenyl)prop-2-en-1-ol (21c)**: As per general method II (*E*)-1,3-bis(3,4,5-trimethoxyphenyl)prop-2-en-1-one **(20c)** (1 eq, 1.28 mmol, 0.5 g) was reacted with sodium borohydride (2 eq, 2.57 mmol, 0.1 g) in methanol and THF. Yield: 93%, 0.46 g, yellow solid, Mp. 58-62 °C [9]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 3494, 2938, 2836, 1582, 1503, 1453, 1416, 1325, 1231, 1119, 1001, 818, 778, 731, 700, 663. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 2 H, Ar-H), 6.59 (s, 2 H, Ar-H), 6.51 (d, *J* = 16.6 Hz, 1 H, CH=CH), 6.14 (dd, *J* = 15.8, 6.8 Hz, 1 H, CH=CH), 4.69 (d, *J* = 6.8 Hz, 1 H, CH-OH), 3.86 (s, 6 H, 2×$OCH_3$), 3.84 (s, 6 H, $OCH_3$), 3.82 (s, 3 H, $OCH_3$), 3.81 (s, 3 H, $OCH_3$). $^{13}C$ NMR (101 MHz, $CDCl_3$) 153.37 (2×C-O), 153.26 (2×C-O), 137.98 (C-O), 137.37 (C-O), 136.65 (C), 132.13 (C), 131.46 (CH=CH), 129.31 (CH=CH), 103.68 (2xCH), 103.57 (2×CH), 84.30 (CH-OH), 60.88 ($OCH_3$), 60.80 ($OCH_3$), 56.13 (2×$OCH_3$), 56.07 (2×$OCH_3$) ppm. HRMS (EI): Found 413.1556 $(M+Na)^+$; $C_{21}H_{26}NaO_7$ requires 413.1576.

**3-(3-Hydroxy-4-methoxyphenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-ol (25a):** As per general method II above, 3-(3-hydroxy-4-methoxyphenyl)-4,5,6-trimethoxy-2,3-dihydro-1*H*-inden-1-one **(24a) (**1 eq, 1.21 mmol, 0.42 g) was reacted with sodium borohydride (2 eq, 2.42 mmol, 0.10 g) in methanol and THF. Yield: 86% (0.36 g) brown resin [10]. IR: $\nu_{max}$ (ATR) $cm^{-1}$: 3405, 2969, 2936, 2988, 1691, 1594, 1465, 1431, 1414, 1507, 1265, 1049, 1113, 1023, 727, 761, 590. $^{1}H$ NMR (400 MHz, $CDCl_3$) δ 1.89 - 1.95 (m, 1 H, $CH_2$), 2.95 (ddd, *J*=13.79, 8.40, 7.26 Hz, 1 H, $CH_2$), 3.46 (s, 3 H, $OCH_3$), 3.82 (s, 3 H, $OCH_3$ ), 3.86 (s, 3 H,

$OCH_3$), 3.90 (s, 3 H, $OCH_3$), 4.25 (dd, *J*=8.29, 5.39 Hz, 1 H, CH), 5.14 (dd, *J*=7.26, 4.77 Hz, 1 H, CH-OH), 5.59 (s, 1 H, OH), 6.70 (d, *J*=2.07 Hz, 1 H, Ar-H), 6.75 (s, 1 H, Ar-H), 6.80 - 6.82 (m, 2 H, Ar-H). $^{13}$C NMR (101 MHz, $CDCl_3$) 46.21 ($CH_2$), 46.42 (C), 55.93 ($OCH_3$), 56.12 (2×$OCH_3$), 60.79 ($OCH_3$), 75.87 (CH-OH), 102.65 (CH), 110.45 (CH), 113.89 (CH), 118.82 (CH), 139.62 (C), 140.56 (C), 142.61 (C), 144.92 (C-O), 145.44 (2xC-O), 150.11 (C-O) 154.15 (C-O) ppm. HRMS (EI): Found 345.1334 $(M-H)^+$; $C_{19}H_{21}O_6$ requires 345.1338.

**General method III synthesis of anthracene-base chalcones 31a, 31b**

NaOH (1.3 equiv; 6 mmol, 240 mg) was dissolved in 50% aqueous ethanol (20 mL). The required ketone (5.02 mmol) was dissolved EtOH (20 mL) and then added before adding a solution of anthracene-9-carbaldehyde (5.02 mmol; 1.035 g) dissolved EtOH (40 mL) . The mixture was left to stir at RT for 24 h. The resulting suspension was filtered, washed with minimal EtOH to afford the crude product before recrystallization from minimal hot EtOH to afford the pure product .

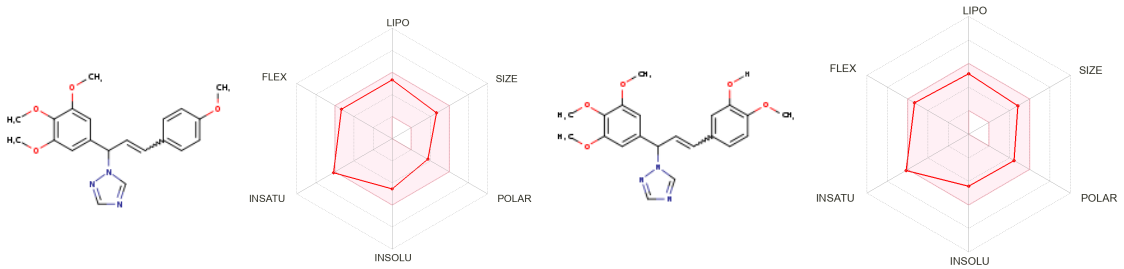
**(*E*)-3-(anthracen-9-yl)-1-(4-iodophenyl)prop-2-en-1-one 31a**

General procedure III was followed using 1-(4-iodophenyl)ethan-1-one (1 equiv; 5.02 mmol; 1.235 g) to afford the product as yellow needle-like crystals (66%) Mp. 167-173 $^{o}$C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.54 (m, 5 H, 4×ArH, 1xC=CH), 7.75 - 7.80 (m, 2 H, ArH), 7.84 - 7.89 (m, 2 H, ArH), 7.99 - 8.05 (m, 2 H, ArH), 8.24 - 8.29 (m, 2 H, ArH), 8.46 (br.s, 1 H, ArH), 8.80 (d, *J*=16.17 Hz, 1 H, C=CH). $^{13}$C NMR (101 MHz, $CDCl_3$) ppm 101.06, 125.17, 125.46, 126.54, 128.65, 128.96, 129.63, 130.06, 129.86, 130.33, 131.28, 137.12, 138.05, 142.46, 188.80 (C=O). $IR_{Vmax}$ (ATR): 3045.07 (Ar C-H), 1593.90 (C=O), 1618.99 (*trans* C=C) 1658.74, 1577.36, 1515.35, 1439.81 (Ar C=C), 669.23 (C-I) $cm^{-1}$.

**(*E*)-3-(Anthracen-9-yl)-1-(pyridin-4-yl)prop-2-en-1-one 31b**

Preparation from 4-acetylpyridine (5.02 mmol, 0.55 mL) and 9-anthracenecarboxaldehyde (5.02 mmol, 1.035 g), according to the general procedure II above; orange crystals (49%), Mp. 170-173 $^{o}$C. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.48 (d, 1H, CH=C), 7.49 - 7.56 (m, 3H, ArH), 7.80 - 7.85 (m, 2H, ArH), 7.98 - 8.05 (m, 2H, ArH), 8.21 - 8.28 (m, 2H, Ar H), 8.46 (br.s, 1H), 8.80 - 8.87 (m, 3H, ArH, C=CH). $^{13}$C NMR (101 MHz, $CDCl_3$) ppm 121.57, 124.92, 125.49, 126.75, 129.03 129.09, 129.64, 129.84, 131.23, 143.86, 143.90, 150.94, 188.94 (C=O). IR *v* max (KBr): 3047.23, 2971.86 (Ar C-H), 1587 (C=O), 1621.69 (*trans* C=C), 1661. 62, 1597.45, 1518.42, 1441.76 (Ar C=C), 1266.30 (C-N) $cm^{-1}$.

**22a** **22b**




**23a** **23b**

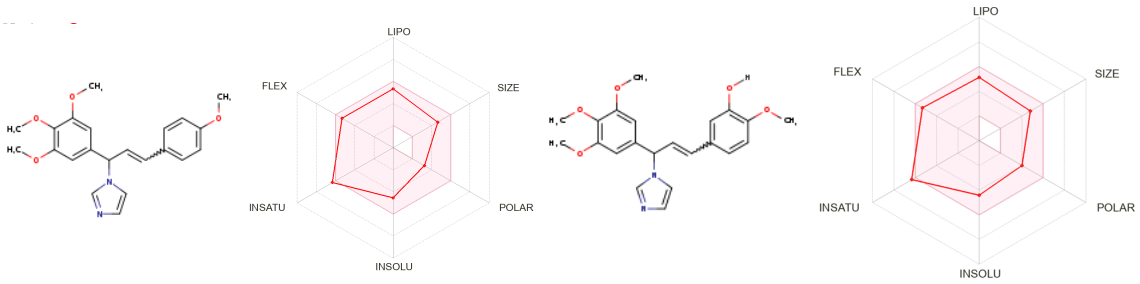
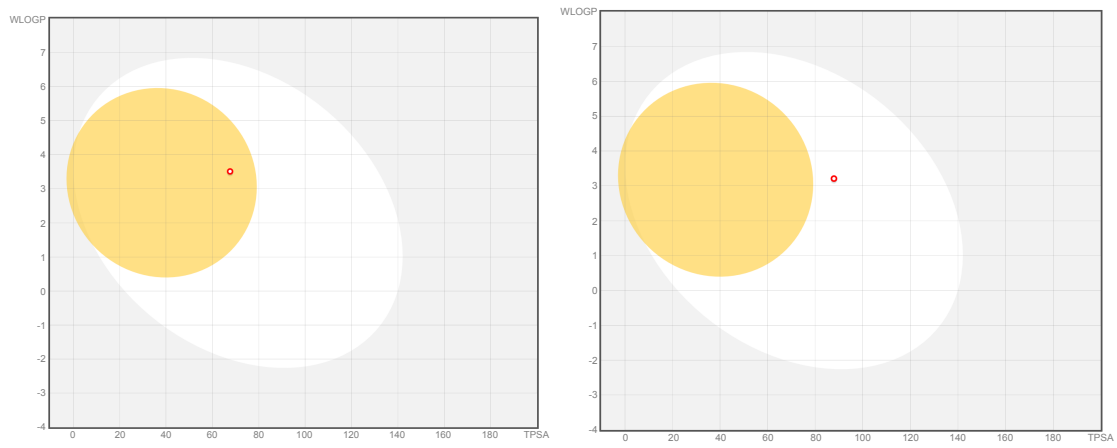



**Figure S1:** Bioavailability Rader for **22a, 22b, 23a** and **23b**.

The following six physicochemical properties are considered for analysis of drug-likeness: lipophilicity (XLOGP3), size (MW), polarity (TPSA, topological polar surface area), solubility (logS), saturation ($fsp^3$) and flexibility (number of rotatable bonds). A physicochemical range on each axis is depicted as a pink area in which the radar plot of the molecule has to fall entirely to be considered drug-like. The pink area represents the optimal range for each properties (lipophilicity: XLOGP3 between −0.7 and +5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 $Å^2$, solubility: log *S* not higher than 6, saturation: fraction of carbons in the $sp^3$ hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds. (SwissADME http://www.swissadme.ch).

**22a** **22b**




**23a** **23b**

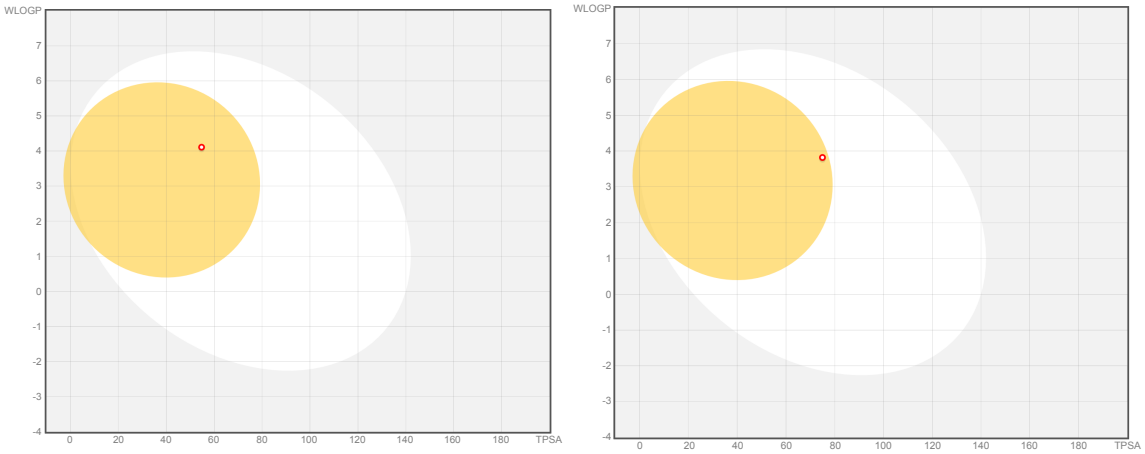






**Figure S2:** The BOILED-Egg allows evaluation of passive gastrointestinal absorption (HIA) and brain penetration (BBB) of compound **22a, 22b, 23a** and **23b** as function of the position of the molecule in the WLOGP-*versus*-TPSA map.

Boiled-Egg is a visual prediction model for the evaluation of passive gastrointestinal absorption (HIA) and blood-brain-barrier (BBB) penetration. The data for compound **22b** is visually analysed on the same 2D map with WLOGP and TPSA plot. (SwissADME http://www.swissadme.ch).

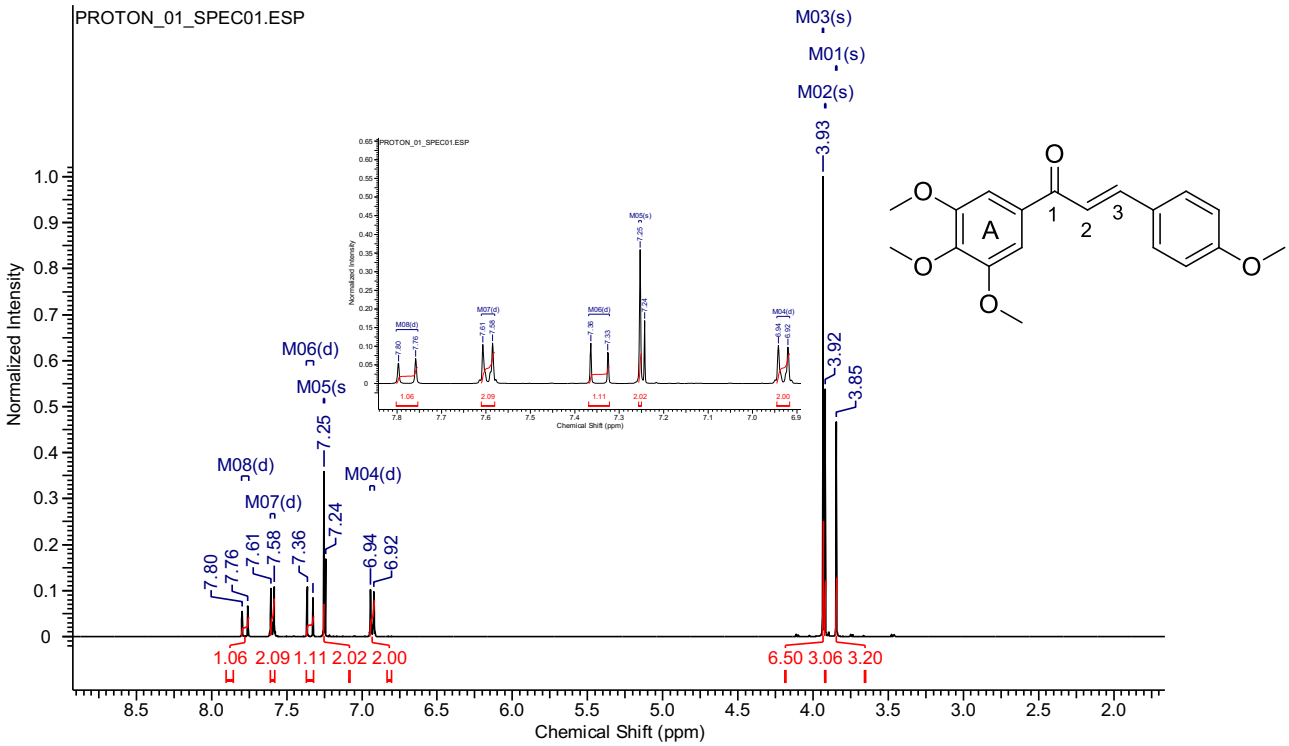



**Figure S3: $^{1}$H-NMR spectrum of compound 20a ($CDCl_3$)**

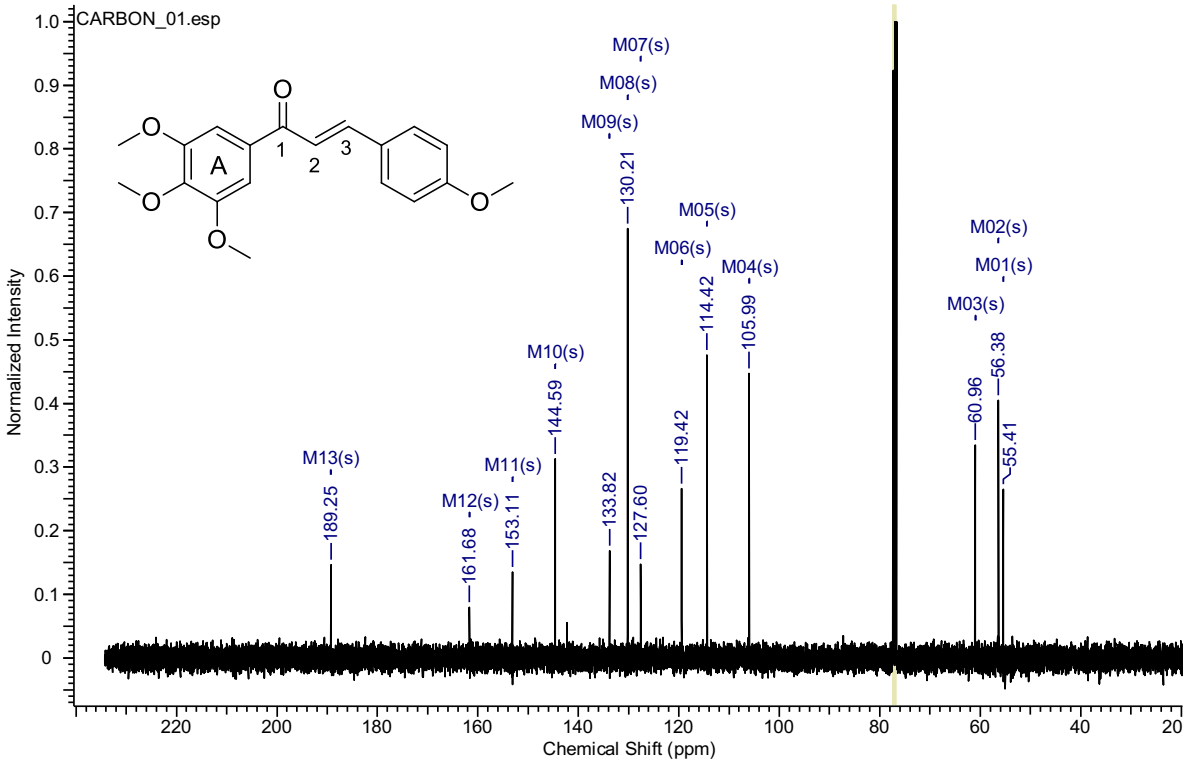



**Figure S4: $^{13}$C-NMR spectrum of compound 20a ($CDCl_3$)**

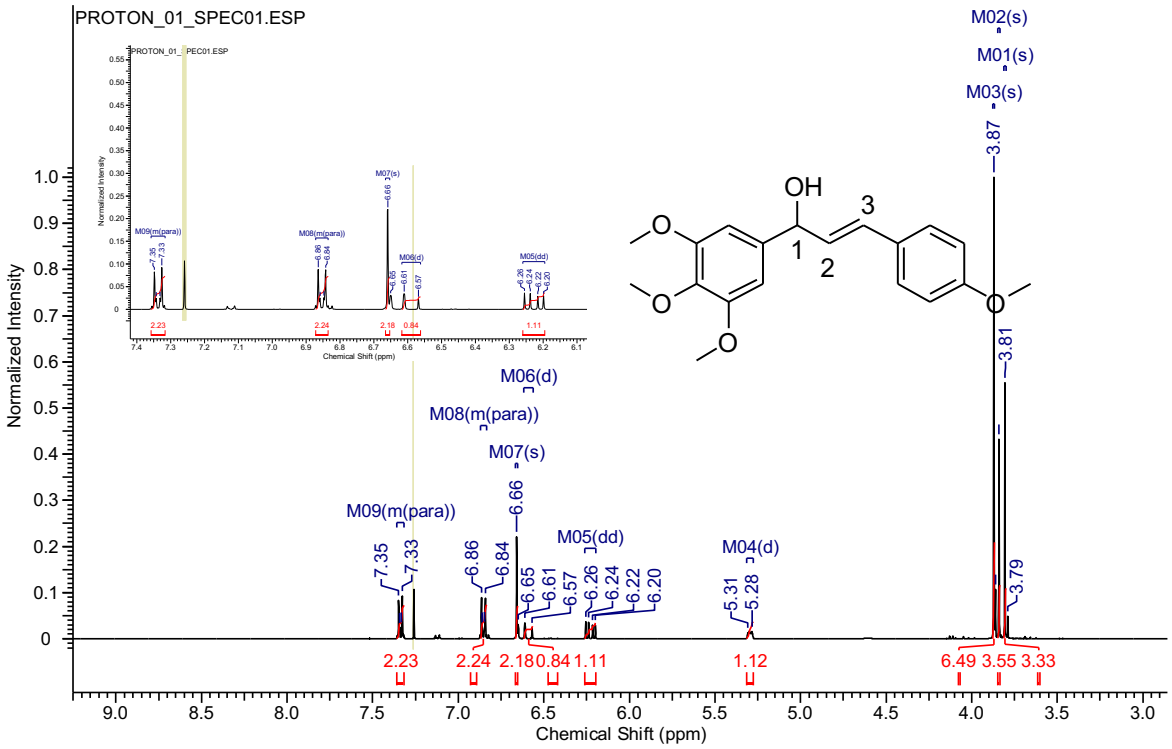



**Figure S5: $^{1}$H-NMR spectrum of compound 21a ($CDCl_3$)**

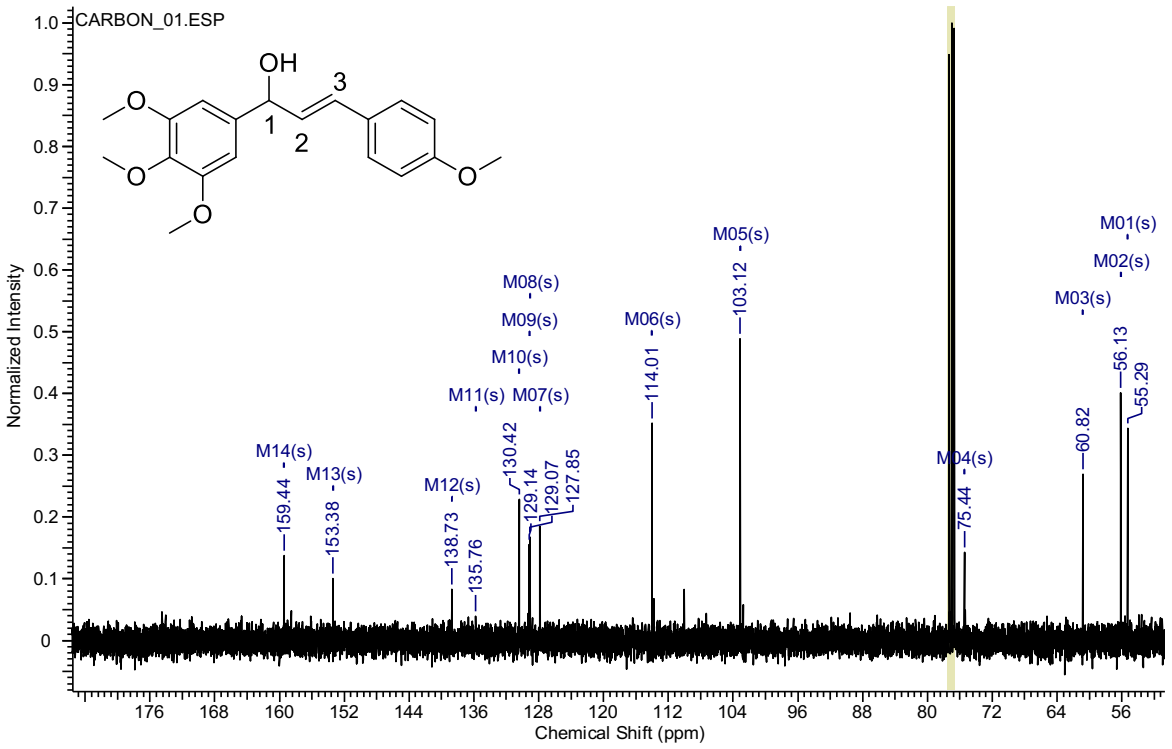



**Figure S6: $^{13}$C-NMR spectrum of compound 21a ($CDCl_3$)**

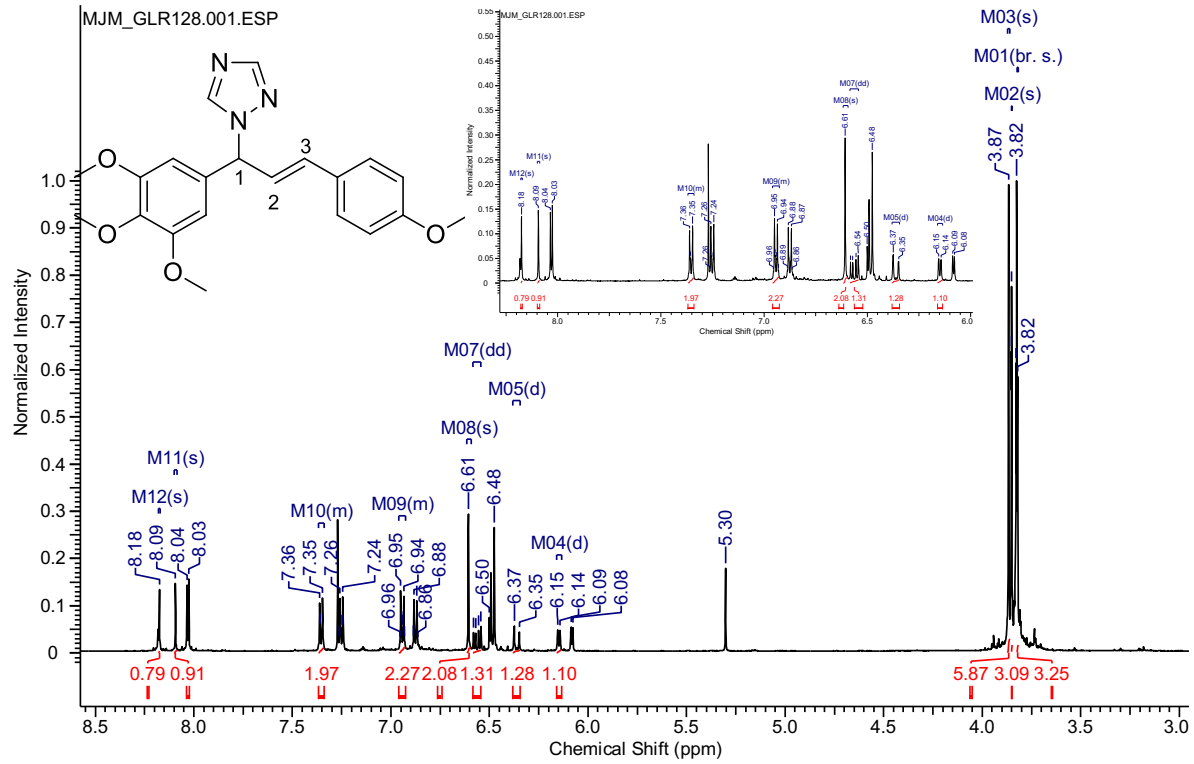



**Figure S7: $^{1}$H-NMR spectrum of compound 22a ($CDCl_3$)**

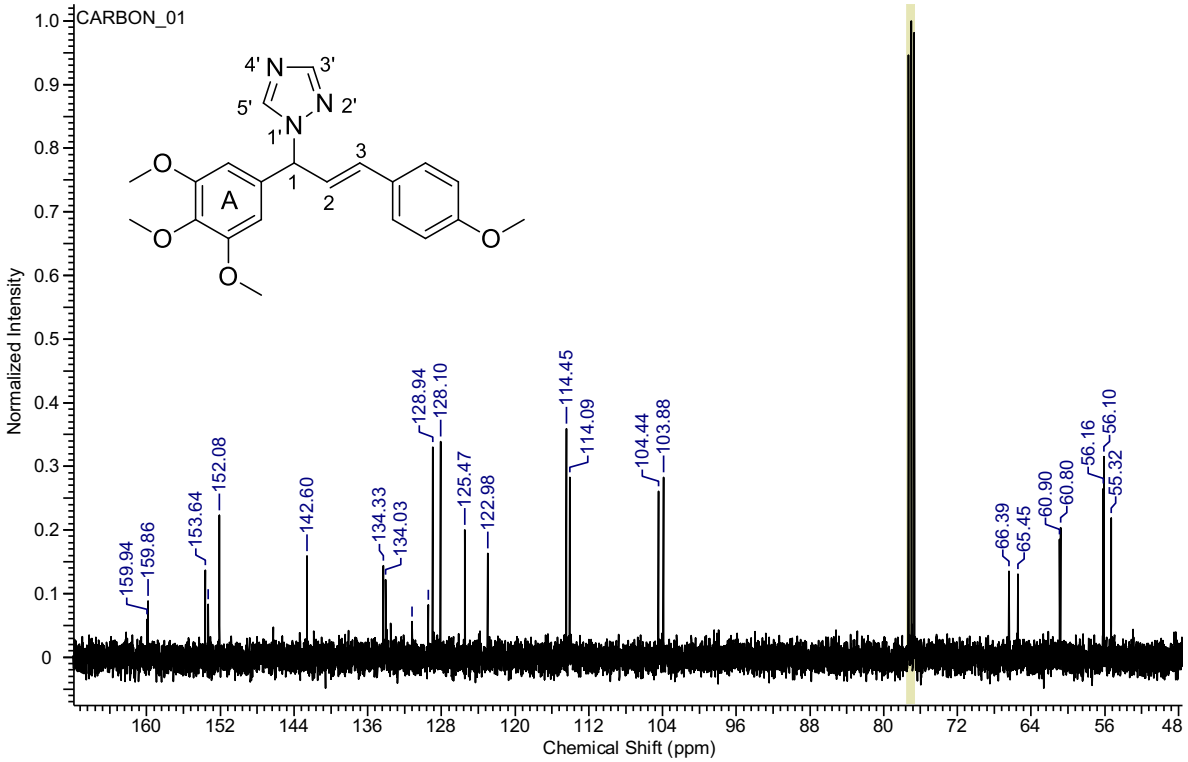



**Figure S8: $^{13}$C-NMR spectrum of compound 22a ($CDCl_3$)**

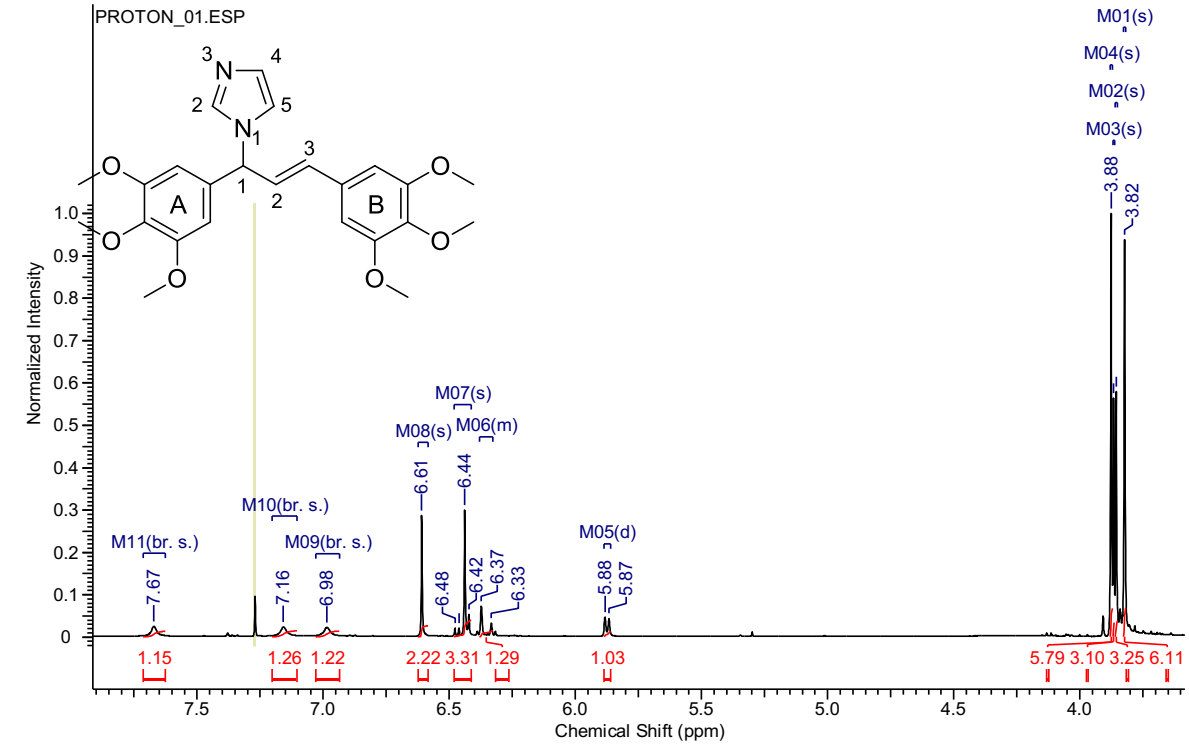



**Figure S9: $^{1}$H-NMR spectrum of compound 23c ($CDCl_3$)**

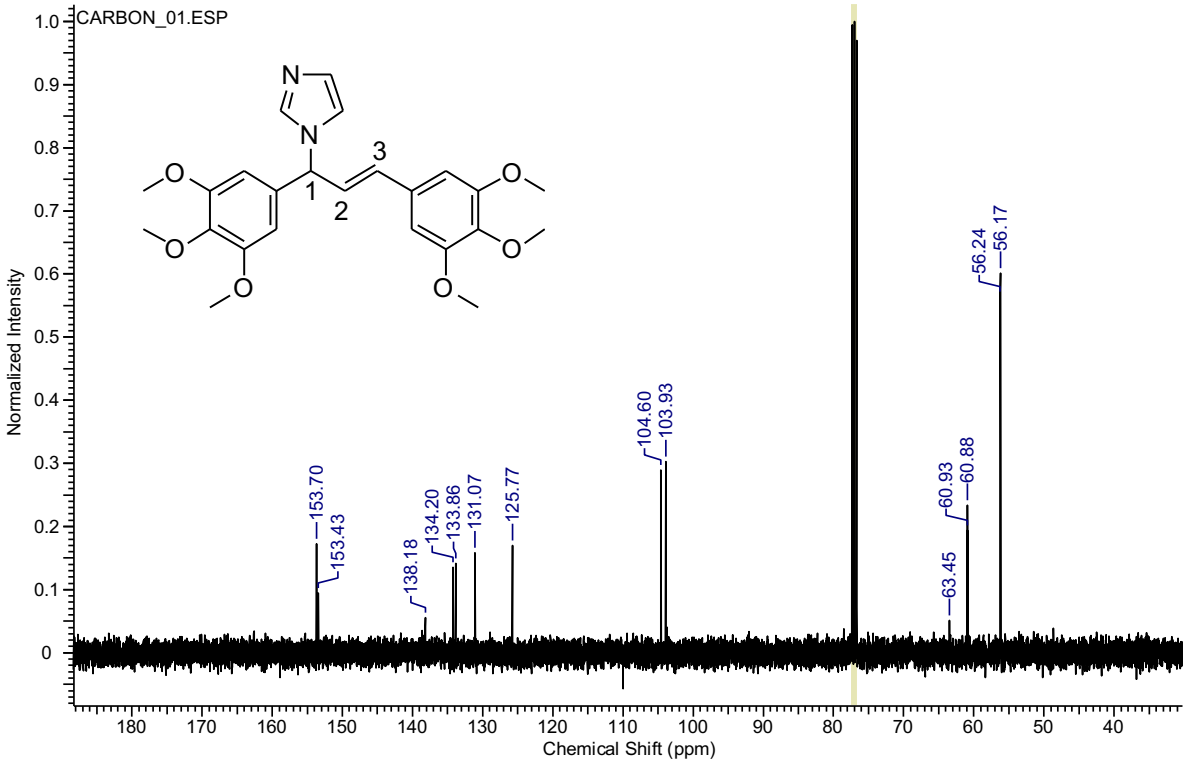



**Figure S10: $^{13}$C-NMR spectrum of compound 23c ($CDCl_3$)**

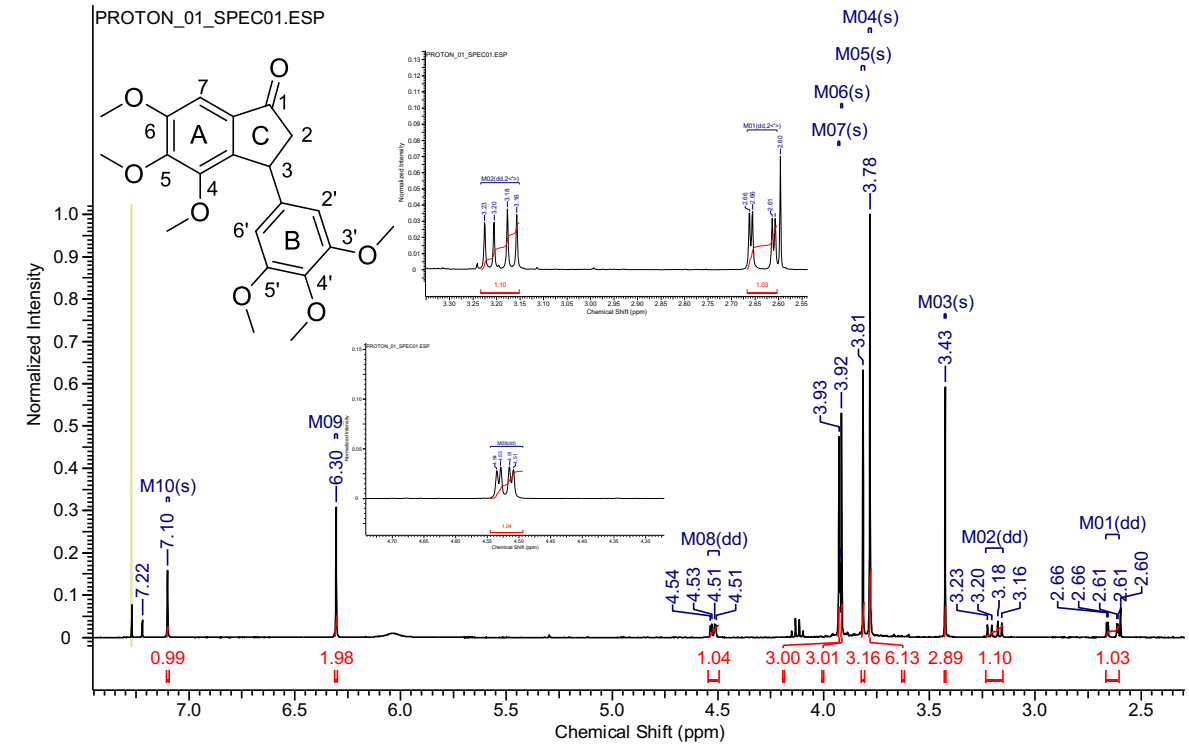



**Figure S11: $^{1}$H-NMR spectrum of compound 24b ($CDCl_3$)**

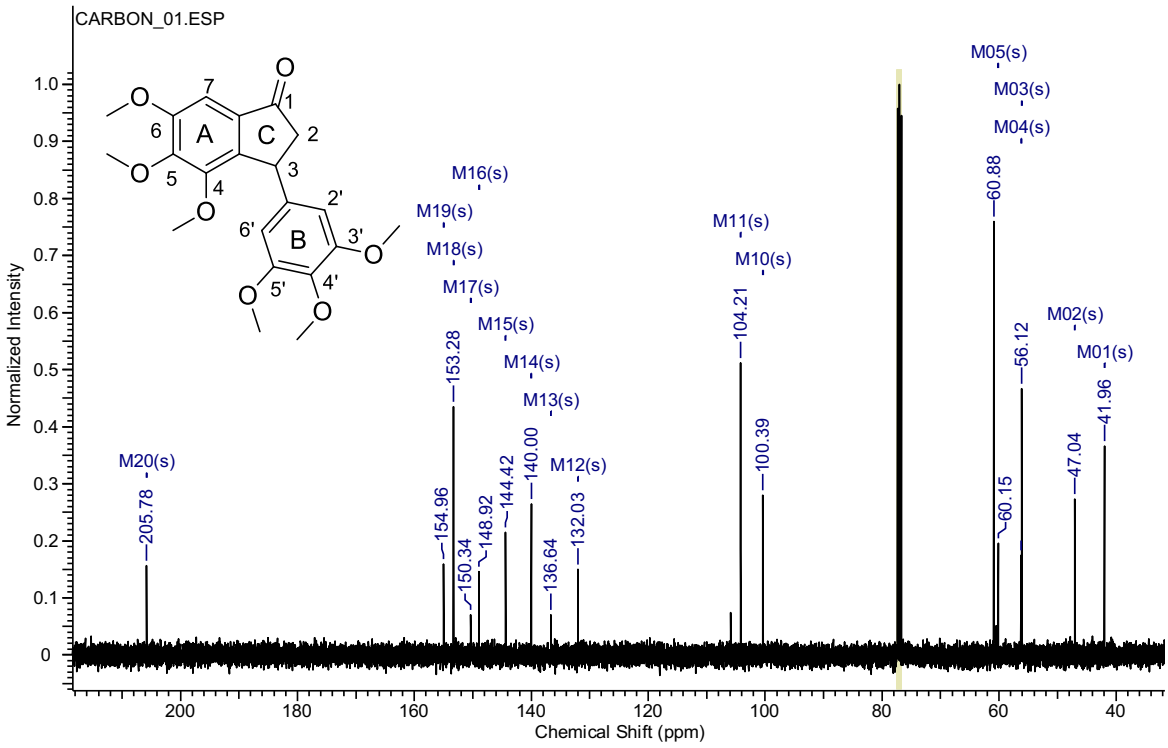



**Figure S12: $^{13}$C-NMR spectrum of compound 24b ($CDCl_3$)**

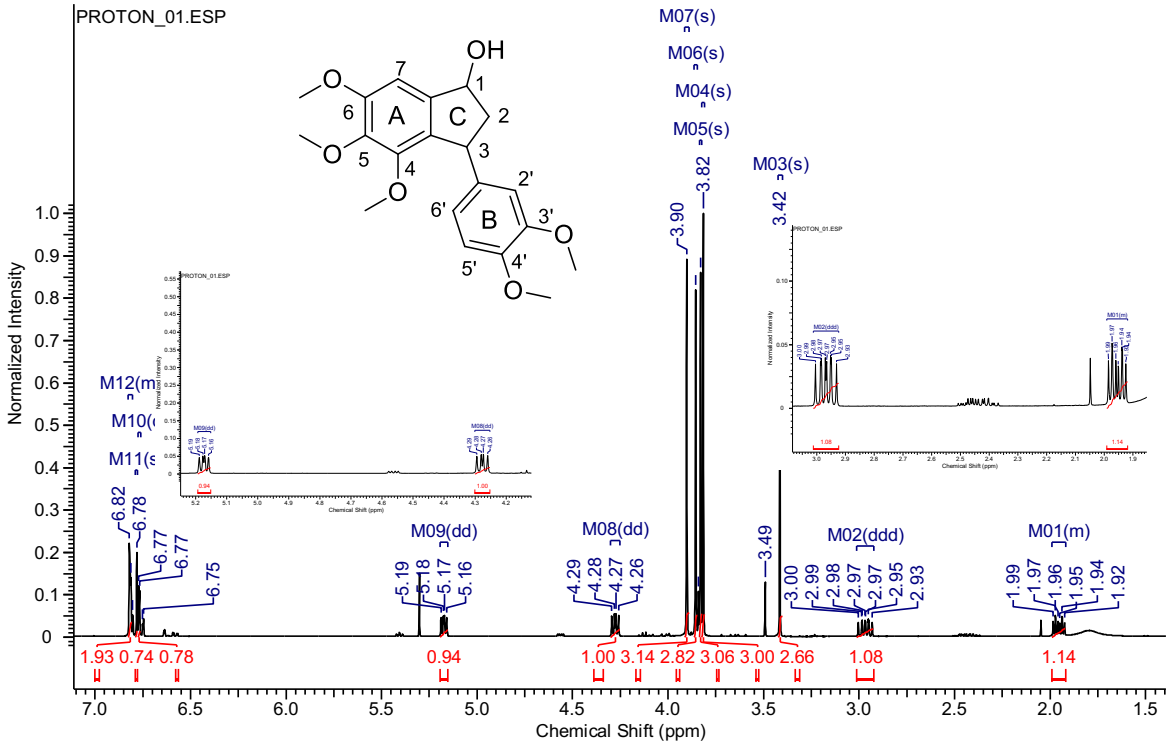



**Figure S13: $^{1}$H-NMR spectrum of compound 25c ($CDCl_3$)**

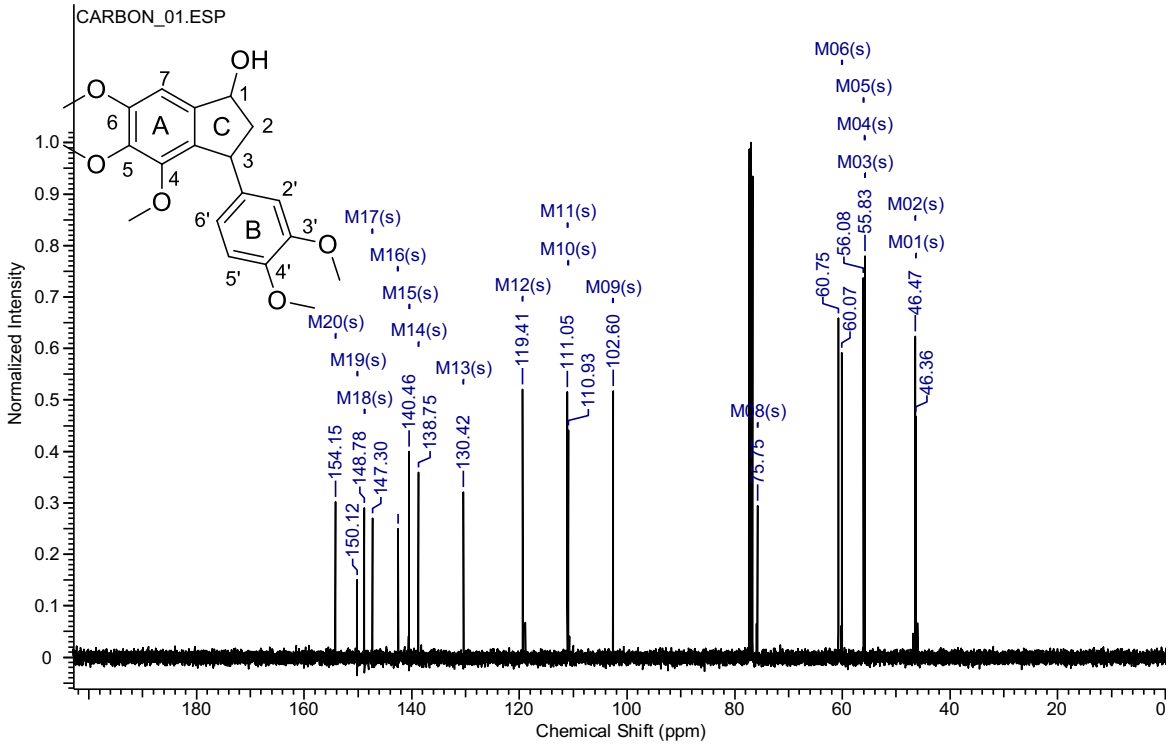



**Figure S14: $^{13}$C-NMR spectrum of compound 25c ($CDCl_3$)**

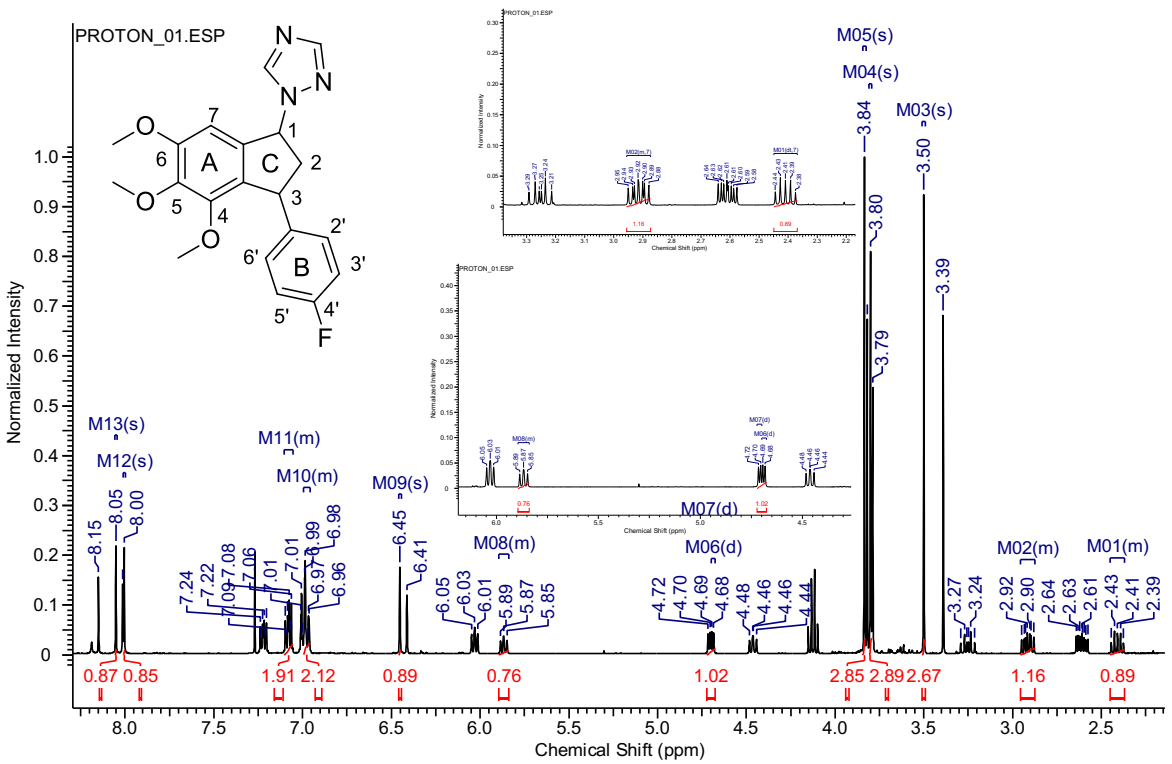



**Figure S15: $^{1}$H-NMR spectrum of compound 26d ($CDCl_3$)**

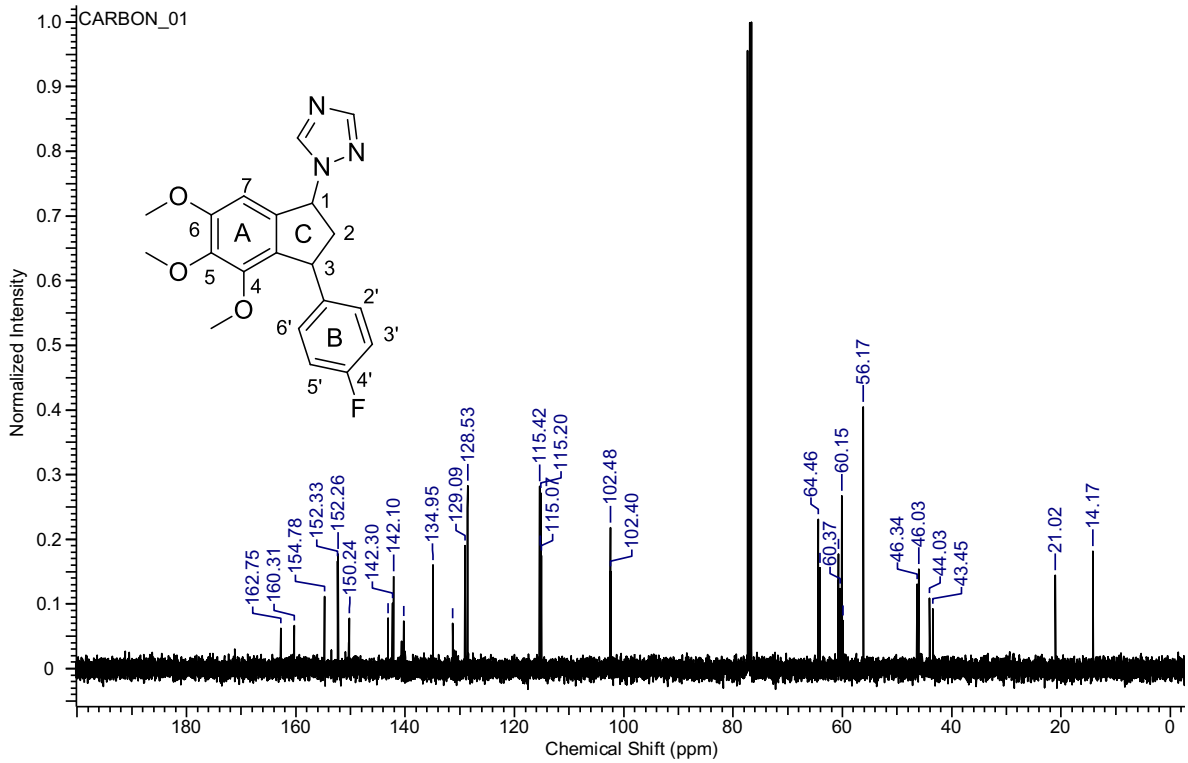



**Figure S16: $^{13}$C-NMR spectrum of compound 26d ($CDCl_3$)**

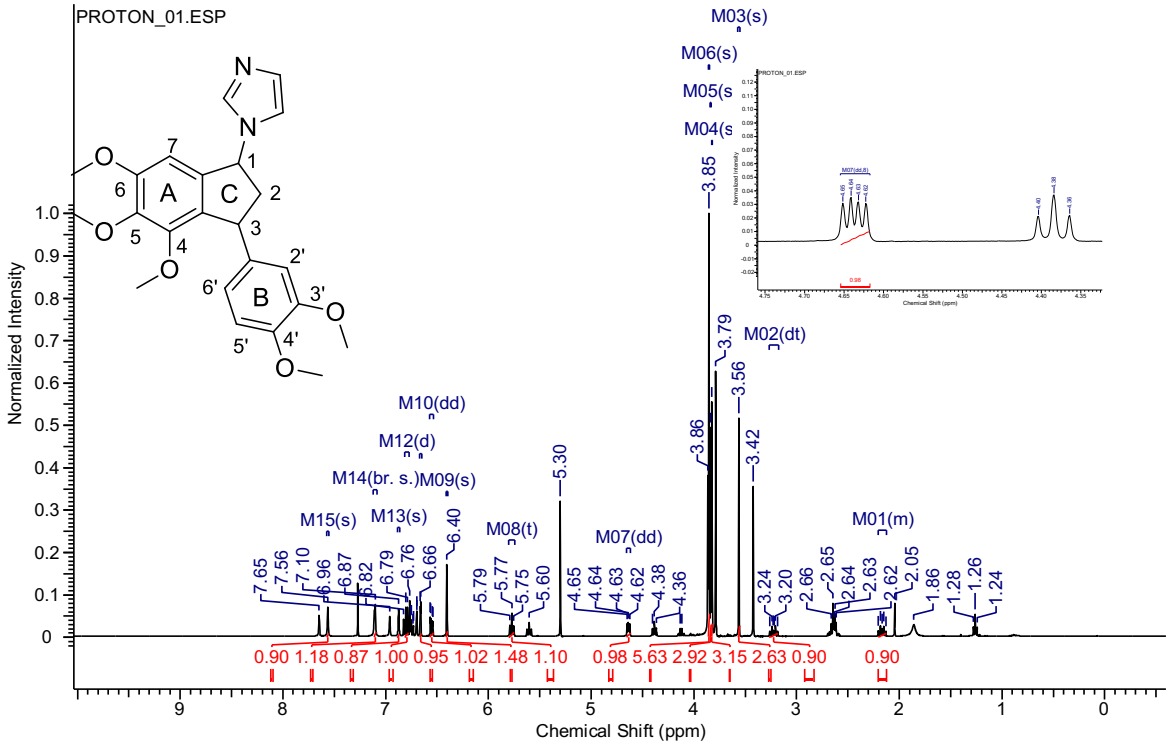



**Figure S17: $^{1}$H-NMR spectrum of compound 27c ($CDCl_3$)**

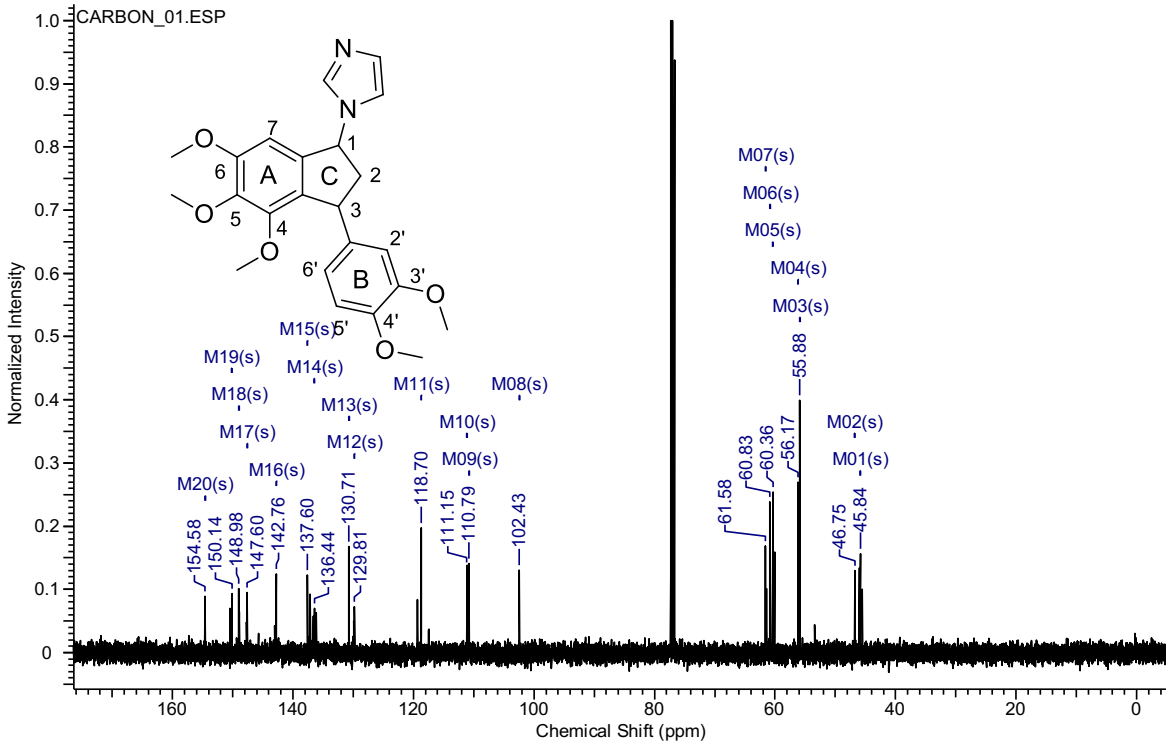



**Figure S18: $^{13}$C-NMR spectrum of compound 27c ($CDCl_3$)**

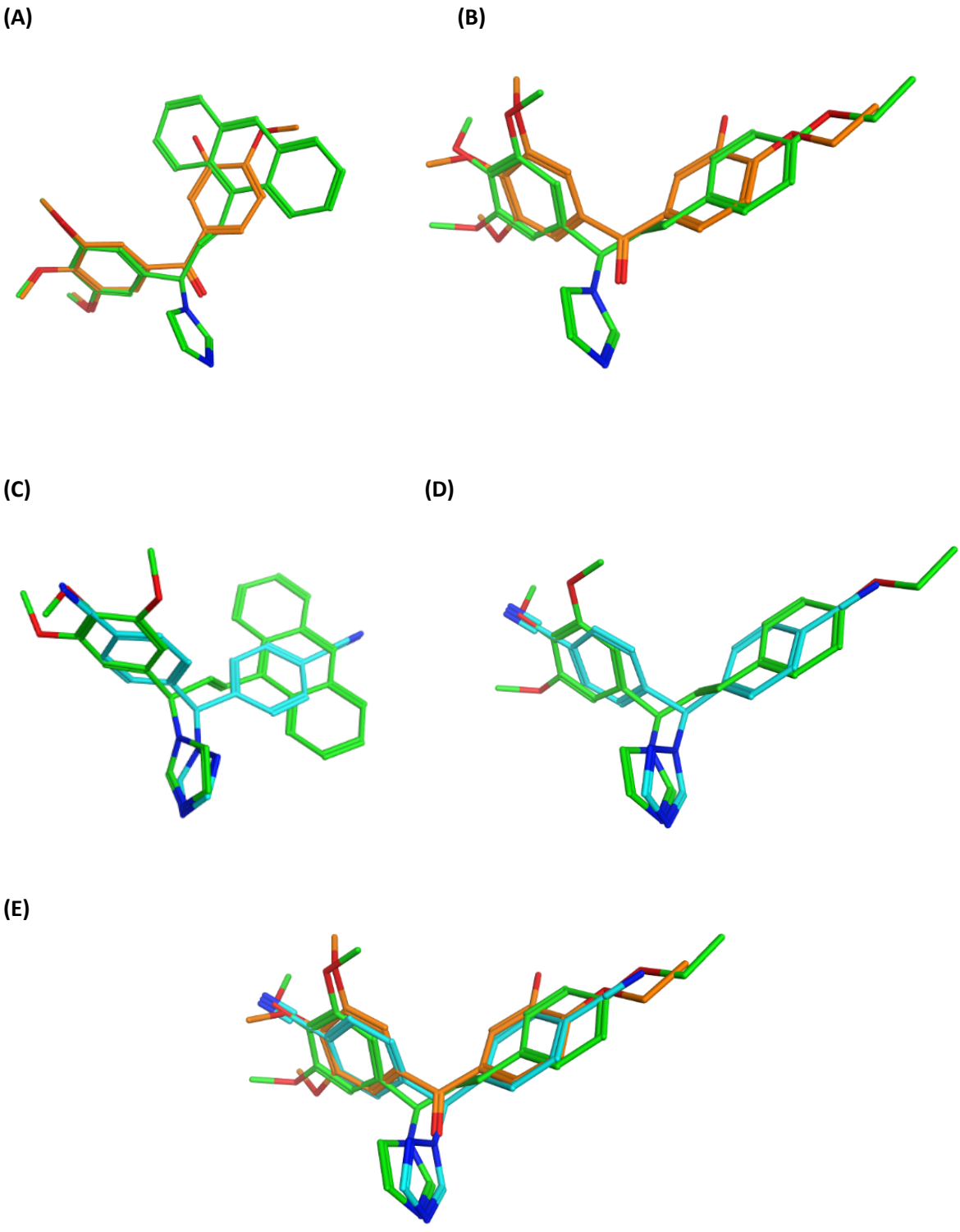



**Figure S19:** Overlay of **(A)** anthracene based imidazole-chalcone with phenstatin; **(B)** imidazole-chalcone with Phenstatin; **(C)** anthracene-based chalcone and letrozole; **(D)** imidazole-chalcone with letrozole and **(E)** imidazole-chalcone with letrozole and phenstatin

**Table S1: Standard COMPARE Analysis of compound 22b**

| Rank | Compound | *r* |
|---|---|---|
| | **Based on $GI_{50}$ mean graph** | |
| 1 | Glycoxalic acid | 0.595 |
| 2 | Dichloroallyl lawsone | 0.592 |
| 3 | S-Trityl-L-cysteine | 0.58 |
| 4 | Vinblastine sulfate | 0.578 |
| 5 | DUP785 (brequinar) | 0.569 |
| | **Based on TGI mean graph** | |
| 1 | Paclitaxel (Taxol) hiConc:-6.0 | 0.703 |
| 2 | S-Trityl-L-cysteine | 0.648 |
| 3 | Vinblastine sulfate | 0.643 |
| 4 | Paclitaxel (Taxol) hiConc:-4.6 | 0.641 |
| 5 | Rhizoxin | 0.586 |

The target set was the standard agent database and the target set endpoints were selected to be equal to the seed end points. Standard COMPARE analysis was performed. Correlation values (*r*) are Pearson correlation coefficients. Paclitaxel appears at different concentrations as the drug has been tested by the NCI at multiple concentration ranges. $LC_{50}$ values all > 0.1 mM.

**Table S2:** Physicochemical descriptors of selected (*E*)-1-(3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)allyl)-1*H*-1,2,4-triazoles and related compounds [a].

| Cpd No. | MW | Molar Refractivity ($m^3$/mol) | Num. HBD | Num. HBA | Num. Rot Bonds | TPSA (Å$^2$) | Log P (consensus)[c] | Water Solubility (mg/mL)[d] | Solubility Class[e] | GI Absorption[b] |
|---|---|---|---|---|---|---|---|---|---|---|
| **22a** | 381.43 | 106.16 | 0 | 6 | 8 | 67.63 | 3.21 | 1.12e-02 | Moderately soluble | High |
| **22b** | 397.42 | 108.18 | 1 | 7 | 8 | 87.86 | 2.89 | 1.60e-02 | Moderately soluble | High |
| **22c** | 441.48 | 119.14 | 0 | 8 | 10 | 86.09 | 3.23 | 9.11e-03 | Moderately soluble | High |
| **22d** | 411.45 | 112.65 | 0 | 7 | 9 | 76.86 | 3.24 | 1.02e-02 | Moderately soluble | High |
| **22e** | 369.39 | 99.62 | 0 | 6 | 7 | 58.40 | 3.55 | 8.81e-03 | Moderately soluble | High |
| **22f** | 351.40 | 99.67 | 0 | 5 | 7 | 58.40 | 3.24 | 1.20e-02 | Moderately soluble | High |
| **22g** | 396.40 | 108.49 | 0 | 7 | 8 | 104.22 | 2.69 | 1.19e-02 | Moderately soluble | High |
| **23a** | 380.44 | 108.36 | 0 | 5 | 8 | 54.74 | 3.43 | 1.12e-02 | Moderately soluble | High |
| **23b** | 396.44 | 110.39 | 1 | 6 | 8 | 74.97 | 3.09 | 1.59e-02 | Moderately soluble | High |
| **23c** | 440.49 | 121.35 | 0 | 7 | 10 | 73.20 | 3.41 | 9.22e-03 | Moderately soluble | High |
| **23d** | 410.46 | 114.85 | 0 | 6 | 9 | 63.97 | 3.43 | 1.02e-02 | Moderately soluble | High |
| **23e** | 368.40 | 101.83 | 0 | 5 | 7 | 45.51 | 3.76 | 8.78e-03 | Moderately soluble | High |
| **23f** | 384.86 | 106.88 | 0 | 4 | 7 | 45.51 | 3.98 | 3.36e-03 | Moderately soluble | High |
| **26a** | 397.42 | 105.91 | 1 | 7 | 6 | 87.86 | 2.67 | 2.30e-02 | Moderately soluble | High |
| **26b** | 441.48 | 116.87 | 0 | 8 | 8 | 86.09 | 2.97 | 1.31e-02 | Moderately soluble | High |
| **26c** | 411.45 | 110.38 | 0 | 7 | 7 | 76.86 | 2.95 | 1.47e-02 | Moderately soluble | High |
| **26d** | 369.39 | 97.35 | 0 | 6 | 5 | 58.40 | 3.33 | 1.27e-02 | Moderately soluble | High |
| **26e** | 351.40 | 97.39 | 0 | 5 | 5 | 58.40 | 3.03 | 1.73e-02 | Moderately soluble | High |
| **27a** | 396.44 | 108.11 | 1 | 6 | 6 | 74.97 | 2.85 | 2.29e-02 | Moderately soluble | High |
| **27b** | 440.49 | 119.07 | 0 | 7 | 8 | 73.20 | 3.16 | 1.33e-02 | Moderately soluble | High |
| **27c** | 410.46 | 112.58 | 0 | 6 | 7 | 63.97 | 3.18 | 1.47e-02 | Moderately soluble | High |
| **27d** | 424.49 | 117.39 | 0 | 6 | 8 | 63.97 | 3.48 | 8.73e-03 | Moderately soluble | High |
| **27e** | 368.40 | 99.56 | 0 | 5 | 5 | 45.51 | 3.55 | 1.26e-02 | Moderately soluble | High |
| **27f** | 350.41 | 99.60 | 0 | 4 | 5 | 45.51 | 3.24 | 1.72e-02 | Moderately soluble | High |
| **27g** | 395.41 | 108.42 | 0 | 6 | 6 | 91.33 | 2.65 | 1.71e-02 | Moderately soluble | High |
| **27h** | 425.43 | 114.91 | 0 | 7 | 7 | 100.56 | 2.62 | 1.55e-02 | Moderately soluble | High |
| **27i** | 366.41 | 101.62 | 1 | 5 | 5 | 65.74 | 2.83 | 2.48e-02 | Moderately soluble | High |
| **30** | 466.53 | 131.28 | 0 | 7 | 11 | 73.20 | 3.96 | 3.22e-03 | Moderately soluble | High |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **33a** | 486.35 | 130.12 | 0 | 1 | 4 | 17.82 | 5.88 | 1.43e-05 | Poorly soluble | Low |
| **33b** | 361.44 | 115.20 | 0 | 2 | 4 | 30.71 | 4.49 | 7.26e-04 | Moderately soluble | High |

[a]SwissADME http://www.swissadme.ch; [b]according to the white of the BOILED-Egg; [c]Average of all five predictions; [d]Topological method to predict Water Solubility included in SwissADME using an implementation of the ESOL model; [e] Solubility class: Log S scale: Insoluble < -10 < Poorly < -6 < Moderately < -4 < Soluble < -2 Very < 0 < Highly

**Table S3:** Pharmacokinetic interaction estimations with P-gp and CYP 450 isozymes of (*E*)-1-(3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)allyl)-1*H*-1,2,4-triazoles and related compounds)[a]

| Cpd No. | BBB permeable[b] | P-gp substrate | CYP1A2 Inhibitor | CYP2C19 inhibitor | CYP2C9 inhibitor | CYP2D6 Inhibitor | CYP3A4 Inhibitor | Skin permeation Coefficient (cm/s) | Abbott Bioavailability Score[c] |
|---|---|---|---|---|---|---|---|---|---|
| **22a** | Yes | No | Yes | Yes | Yes | No | Yes | -5.91 | 0.55 |
| **22b** | No | No | No | Yes | No | No | Yes | -6.26 | 0.55 |
| **22c** | No | No | No | Yes | Yes | No | No | -6.32 | 0.55 |
| **22d** | Yes | No | Yes | Yes | Yes | No | No | -6.12 | 0.55 |
| **22e** | Yes | No | Yes | Yes | Yes | No | No | -5.75 | 0.55 |
| **22f** | Yes | No | Yes | Yes | Yes | No | No | -5.71 | 0.55 |
| **22g** | No | No | Yes | Yes | Yes | No | Yes | -6.11 | 0.55 |
| **23a** | Yes | No | Yes | Yes | Yes | Yes | Yes | -5.90 | 0.55 |
| **23b** | Yes | No | Yes | Yes | Yes | Yes | No | -6.25 | 0.55 |
| **23c** | Yes | No | No | Yes | Yes | No | No | -6.31 | 0.55 |
| **23d** | Yes | No | Yes | Yes | Yes | No | Yes | -6.11 | 0.55 |
| **23e** | Yes | No | Yes | Yes | Yes | Yes | Yes | -5.74 | 0.55 |
| **23f** | Yes | No | Yes | Yes | Yes | Yes | Yes | -5.46 | 0.55 |
| **26a** | No | No | Yes | No | Yes | Yes | Yes | -6.59 | 0.55 |
| **26b** | No | No | No | No | Yes | Yes | Yes | -6.64 | 0.55 |
| **26c** | Yes | No | Yes | No | Yes | Yes | Yes | -6.45 | 0.55 |
| **26d** | Yes | No | No | Yes | Yes | Yes | Yes | -6.08 | 0.55 |
| **26e** | Yes | No | Yes | Yes | Yes | Yes | Yes | -6.04 | 0.55 |
| **27a** | Yes | Yes | No | No | Yes | Yes | Yes | -6.57 | 0.55 |
| **27b** | Yes | No | No | No | Yes | Yes | Yes | -6.64 | 0.55 |
| **27c** | Yes | No | No | No | Yes | Yes | Yes | -6.43 | 0.55 |
| **27d** | Yes | Yes | No | No | Yes | Yes | Yes | -6.26 | 0.55 |
| **27e** | Yes | Yes | Yes | Yes | Yes | Yes | Yes | -6.06 | 0.55 |
| **27f** | Yes | Yes | Yes | Yes | Yes | Yes | Yes | -6.02 | 0.55 |
| **27g** | No | No | Yes | Yes | Yes | Yes | Yes | -6.42 | 0.55 |
| **27h** | No | No | Yes | Yes | Yes | Yes | Yes | -6.62 | 0.55 |
| **27i** | Yes | Yes | Yes | Yes | No | Yes | Yes | -6.37 | 0.55 |
| **30** | No | No | No | Yes | Yes | No | No | -6.01 | 0.55 |
| **33a** | No | Yes | Yes | Yes | Yes | No | No | -4.42 | 0.55 |
| **33b** | Yes | Yes | Yes | Yes | Yes | No | Yes | -4.88 | 0.55 |

[a] SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules http://www.swissadme.ch; [b]According to the yolk of the BOILED-Egg; [c]The bioavailability score is the parameter which predict the probability of more than 10% oral bioavailability in rat based on PSA (potential surface area) and Lipinski rule-of-five. This parameter falls on four classes of probabilities (11%, 17%, 56% or 85%) and allows to filter off the molecules with cell-permeability issues

**Table S4:** Drug-likeness of representative compounds assessed via lead-likeness and reactivity/toxicity filters for (*E*)-1-(3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)allyl)-1*H*-1,2,4-triazoles and related compounds [a ,d]

| Cpd No. | Lipinski | Ghose | Veber | Egan | Muegge | PAINS[b] | Brenk[c] | Lead-likeness | Synthetic accessibility |
|---|---|---|---|---|---|---|---|---|---|
| **22a** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 3 alerts | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 | 3.85 |
| **22b** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 2 violations: MW>350, Rotors>7 | 3.93 |
| **22c** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 | 4.20 |
| **22d** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 | 4.04 |
| **22e** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 2 violations: MW>350, XLOGP3>3.5 | 3.69 |
| **22f** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 2 violations: MW>350, XLOGP3>3.5 | 3.70 |
| **22g** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 1 alert: nitro group | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 | 3.75 |
| **23a** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 | 3.71 |
| **23b** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 2 violations: MW>350, Rotors>7 | 3.80 |
| **23c** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 | 4.07 |
| **23d** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 | 3.92 |
| **23e** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 2 violations: MW>350, XLOGP3>3.5 | 3.56 |
| **23f** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 2 violations: MW>350, XLOGP3>3.5 | 3.57 |
| **26a** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 1 violation: MW>350 | 4.01 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **26b** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 2 violations: MW>350, Rotors>7 | 4.27 |
| **26c** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 1 violation: MW>350 | 4.12 |
| **26d** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 1 violation: MW>350 | 3.81 |
| **26e** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 1 violation: MW>350 | 3.82 |
| **27a** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 1 violation: MW>350 | 3.90 |
| **27b** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 2 violations: MW>350, Rotors>7 | 4.17 |
| **27c** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 1 violation: MW>350 | 4.01 |
| **27d** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 | 4.15 |
| **27e** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 1 violation: MW>350 | 3.71 |
| **27f** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 1 violation: MW>350 | 3.71 |
| **27g** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 1 alert: nitro group | No; 1 violation: MW>350 | 3.82 |
| **27h** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 1 alert: nitro group | No; 1 violation: MW>350 | 4.04 |
| **27i** | Yes; 0 violation | Yes | Yes | Yes | Yes | 0 alerts | 0 alerts | No; 1 violation: MW>350 | 3.75 |
| **30** | Yes; 0 violation | No; 1 violation: MR>130 | No; 1 violation: Rotors >10 | Yes | Yes | 0 alerts | 0 alerts | No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5 | 4.16 |
| **33a** | Yes; 1 violation: MLOGP>4.15 | No; 3 violations: MW>480, WLOGP>5.6, MR>130 | Yes | No; 1 violation: WLOGP>5.88 | No; 1 violation: XLOGP3>5 | 0 alert | 2 alerts: iodine, polycyclic aromatic hydrocarbon 2 | No; 2 violations: MW>350, XLOGP3>3.5 | 3.72 |
| **33b** | Yes; 0 violation | No; 1 violation: WLOGP>5.6 | Yes | Yes | No; 1 violation: XLOGP3>5 | 0 alert | 1 alert: polycyclic aromatic hydrocarbon 2 | No; 2 violations: MW>350, XLOGP3>3.5 | 3.48 |

[a]SwissADME http://www.swissadme.ch [b]Pan Assay Interference Structures: (PAINS); [c]Brenk Structural Alert e.g. Michael acceptor, more than 2 esters; nitro group, oxygen-nitrogen single bond, phthalimide, alkyl halide; [d]Additional druglikeness assessment methods including Ghose, Veber and Muegge filters together with medicinal chemistry structure alert assessments PAINS (pan assay interference compounds) and Brenk filters were used to identify

compounds which are potentially toxic, chemically reactive, metabolically unstable compounds or having poor pharmacokinetics.

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