**Supporting Information related to the article**

# Novel vascular disrupting agents with a cyclohexanedione scaffold identified through a ligand-based virtual screening approach

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Includes:

**Chemistry procedures**

Melting points were obtained on a Reichert-Jung Kofler apparatus and are uncorrected. The elemental analysis was performed with a Heraeus CHN-O-RAPID instrument. The elemental compositions of the compounds agreed to within ±0.4% of the calculated values. For all the tested compounds, satisfactory elemental analysis was obtained supporting >95% purity. Electrospray mass spectra were measured on a quadrupole mass spectrometer equipped with an electrospray source (Hewlett-Packard, LC/MS HP 1100). $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian INNOVA 300 operating at 299 MHz ($^{1}H$) and 75 MHz ($^{13}C$), respectively, a Varian INNOVA-400 operating at 399 MHZ ($^{1}H$) and 99 MHz ($^{13}C$), respectively, and a VARIAN SYSTEM-500 operating a 499 MHz ($^{1}H$) and 125 MHz ($^{13}C$), respectively.

Analytical TLC was performed on silica gel 60 $F_{254}$ (Merck) precoated plates (0.2 mm). Spots were detected under UV light (254 nm) and/or charring with ninhydrin or phophomolibdic acid. Separations on silica gel were performed by preparative centrifugal circular thin-layer chromatography (CCTLC) on a Chromatotron$^{R}$ (Kiesegel 60 $PF_{254}$ gipshaltig (Merck)), with layer thickness of 1 and 2 mm and flow rate of 4 or 8 mL/min, respectively. Flash column chromatography was performed in a Biotage Horizon instrument.

Microwave reactions were performed using the Biotage Initiator 2.0 single-mode cavity instrument from Biotage (Uppsala). Experiments were carried out in sealed microwave process vials utilizing the standard absorbance level (400 W maximum power). The temperature was measured with an IR sensor on the outside of the reaction vessel.

**2-(1-((2-hydroxyphenyl)amino)propylidene)-5-phenylcyclohexane-1,3-dione (9).** EM (ES, positive mode): m/z 336 $(M+H)^{+}$. $^{1}H$-NMR (DMSO-$d_6$, 500 MHz) δ: 1.00 (t, 3H, *J* =7.3 Hz, $CH_3$), 2.60-2.64 (m, 2H, H-4, H-6), 2.80-2.87 (m, 4H, H-4, H-6, $CH_2$), 3.34-3.36 (m, 1H, H-5), 6.90 (td, 1H *J* = 7.6, 1.3 Hz, Ar), 7.01 (dd, 1 H, *J* = 8.1, 1.3 Hz, Ar), 7.17–7.28 (m, 3H, Ar), 7.31-7.36 (m, 4H, Ar), 10.15 (br s, 1H, OH), 14.80 (br s, 1H, NH).

**General procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines**

A microwave vial was charged with 2-acyl-5-phenylcyclohexane-1,3-dione (1.0 mmol), the appropriate aniline (1.5 mmol) and 4 Å molecular sieves in toluene (2 mL). The reaction vessel was sealed and heated in a

microwave reactor at 150 ºC for 2 h. After cooling, the solvent was evaporated. The resulting residue was purified as specified.

**2-(1-((3-Methoxyphenyl)amino)propylidene)-5-phenylcyclohexane-1,3-dione (14d).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 5-phenyl-2-propionylcyclohexane-1,3-dione (**12**) (40 mg, 0.16 mmol) and *m*-anisidine (27 µL, 0.24 mmol) in toluene. The residue was worked up and purified by CCTLC in the Chromatothron (hexane/ethyl acetate, 5:1) to yield 55 mg (98%) of **14d** as a white solid. Mp 104-106 ºC. EM (ES, positive mode): m/z 350 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 1.06 (t, 3H, *J* = 7.3 Hz, $CH_3$), 2.60-2.67 (m, 2H, H-4, H-6), 2.79-2.92 (m, 4H, H-4, H-6, $CH_2$), 3.35 (m, 1H, H-5), 3.79 (s, 3H, $OCH_3$), 6.87–6.94 (m, 2H, Ar), 7.01 (dd, 1H, *J* = 8.3, 2.5 Hz, Ar), 7.24 (ddd, 1H, *J* = 8.6, 5.1, 3.3 Hz, Ar), 7.33–7.35 (m, 4H, Ar), 7.41 (t, 1H, *J* = 8.0 Hz, Ar), 14.99 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 12.7 ($CH_3$), 23.4 ($CH_2$), 36.0 (C-5), 46.0 (C-4, C-6), 55.4 ($OCH_3$), 106.8 (NHC=*C*), 111.8, 113.9, 118.2, 126.5, 126.7, 128.5, 130.4, 134.0, 143.4, 160.0 (Ar), 177.1 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_3$): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.45; H, 6.49; N, 4.08.

**2-(1-((4-Methoxyphenyl)amino)propylidene)-5-phenylcyclohexane-1,3-dione (14e).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 5-phenyl-2-propionylcyclohexane-1,3-dione (**12**) (25 mg, 0.10 mmol) and *p*-anisidine (18 mg, 0.15 mmol) in toluene. The residue was worked up and purified by CCTLC in the Chromatothron (hexane/ ethyl acetate, 5:1) to yield 30 mg (86%) of **14e** as a white solid. Mp 122-124 ºC. EM (ES, positive mode): m/z 350 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 1.03 (t, 3H, *J* = 7.3 Hz, $CH_3$), 2.60-2.64 (m, 2H, H-4, H-6), 2.65-2.87 (m, 4H, H-4, H-6, $CH_2$), 3.32 (m, 1H, H-5), 3.80 (s, 3H, $OCH_3$), 7.02-7.07 (m, 2H, Ar), 7.20–7.29 (m, 3H, Ar), 7.33 (d, 2H, *J* = 1.1 Hz, Ar), 7.34 (s, 2H, Ar), 14.80 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 13.0 ($CH_3$), 23.7 ($CH_2$), 36.5 (C-5), 46.5 (C-4, C-6), 55.9 ($OCH_3$), 107.2 (NHC=*C*), 115.1, 127.0, 127.2, 127.8, 128.8, 128.9, 143.9, 159.1 (Ar), 178.0 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_3$): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.37; H, 6.54; N, 3.96.

**2-(1-((3,4-Dimethoxyphenyl)amino)propylidene)-5-phenylcyclohexane-1,3-dione (14f).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 5-phenyl-2-propionylcyclohexane-1,3-dione (**12**) (40 mg, 0.16 mmol) and 3,4-dimethoxyaniline (30 mg, 0.24 mmol) in toluene. The residue was worked up and purified by CCTLC in

the Chromatothron (hexane/ethyl acetate, 5:1) to yield 20 mg (33%) of **14f** as a white solid. Mp 209-211 ºC. EM (ES, positive mode): m/z 380 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 1.06 (t, 3H, *J* = 7.2 Hz, $CH_3$), 2.66 (m, 2H, H-4, H-6), 2.78-2.90 (m, 4H, H-4, H-6, $CH_2$), 3.39 (m, 1H, H-5), 3.77 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 6.85 (dd, 1H, *J* = 8.5, 2.4 Hz, Ar), 6.94 (d, 1H, *J* = 2.4 Hz, Ar), 7.04 (d, 1H, *J* = 8.5 Hz, Ar), 7.23 (dd, 1H, *J* = 8.7, 5.2, 3.4 Hz, Ar), 7.33 (d, 2H, *J* = 1.4 Hz, Ar), 7.34 (s, 2H, Ar), 14.82 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 13.2 ($CH_3$), 23.9 ($CH_2$), 36.5 (C-5), 46.5 (C-4, C-6), 56.1 ($OCH_3$), 56.2 ($OCH_3$), 107.2 (NHC=*C*), 110.2, 110.6, 112.2, 118.5, 127.0, 127.2, 128.9, 143.9, 148.8, 149.5 (Ar), 178.0 (NH*C*=C). Anal. calc. for ($C_{23}H_{25}NO_4$): C, 72.80; H, 6.64; N, 3.69. Found: C, 72.77; H, 6.59; N, 3.76.

**5-Phenyl-2-(1-((3,4,5-trimethoxyphenyl)amino)propylidene)cyclohexane-1,3-dione (14g).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 5-phenyl-2-propionyl-cyclochexane-1,3-dione (**12**) (40 mg, 0.16 mmol) and 3,4,5-trimethoxyaniline (44 mg, 0.24 mmol) in toluene. The residue was worked up and purified by CCTLC in the Chromatothron (hexane/ethyl acetate, 5:1) to yield 20 mg (30 %) of **14g** as a white solid. Mp 160-162 ºC. EM (ES, positive mode): m/z 410 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 1.10 (t, 3H, *J* = 7.1 Hz, $CH_3$), 2.61-2.68 (m, 2H, H-4, H-6), 2.78-2.92 (m, 4H, H-4, H-6, $CH_2$), 3.35 (m, 1H, H-5), 3.69 (s, 3H, $OCH_3$), 3.79 (s, 6H, $OCH_3$), 6.67 (s, 2H, Ar), 7.24 (ddd, 1 H, *J* = 8.3, 5.3, 3.3 Hz, Ar), 7.33 (d, 2H, *J* = 1.6 Hz, Ar), 7.34, 7.34 (s, 2H, Ar), 14.90 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 11.8 ($CH_3$), 22.5 ($CH_2$), 38.1 (C-5), 44.8 (C-4, C-6), 55.0 ($OCH_3$), 59.0 ($OCH_3$), 105.6 (NHC=*C*), 102.8, 125.4, 125.6, 127.3, 130.3, 135.7, 142.2, 152.1 (Ar), 173.3 (NH*C*=C). Anal. calc. for ($C_{24}H_{27}NO_5$): C, 70.40; H, 6.65; N, 3.42. Found: C, 70.70; H, 6.68; N, 3.62.

**2-(1-(Benzo[d][1,3]dioxol-5-ylamino)propylidene)-5-phenylcyclohexane-1,3-dione (14h).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 5-phenyl-2-propionylcyclohexane-1,3-dione (**12**) (40 mg, 0.16 mmol) and 3,4-methylenedioxyaniline (33 mg, 0.24 mmol) in toluene. The residue was worked up and purified by CCTLC in the Chromatothron (hexane/ethyl acetate, 5:1) to yield 58 mg (99%) of **14h** as a white solid. Mp 131-133 ºC. EM (ES, positive mode): m/z 364 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 1.03 (t, 3H, *J* = 7.3 Hz, $CH_3$), 2.60-2.64 (m, 2H, H-4, H-6), 2.79-2.89 (m, 4H, H-4, H-6, $CH_2$), 3.32 (m, 1H, H-5), 6.11 (s, 2H, $CH_2$), 6.79 (dd, 1H, *J* = 8.3, 2.1 Hz, Ar), 7.01 (m, 2H, Ar), 7.23 (m, 1H, Ar), 7.33 (m, 4H, Ar), 14.78 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 12.6 ($CH_3$), 23.3 ($CH_2$), 36.0 (C-5), 46.0 (C-4, C-6), 101.9

($CH_2$), 106.7 (NHC=*C*), 107.4, 108.4, 119.6, 126.5, 126.7, 128.5, 129.5, 143.4, 147.9, 149.9 (Ar), 177.8 (NH*C*=C). Anal. calc. for ($C_{22}H_{21}NO_4$): C, 72.71; H, 5.82; N, 3.85. Found: C, 73.02; H, 6.01; N, 3.96.

**5-Phenyl-2-(1-(phenylamino)propylidene)cyclohexane-1,3-dione (14i).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 5-phenyl-2-propionylcyclohexane-1,3-dione (**12**) (40 mg, 0.16 mmol) and aniline (22 μL, 0.24 mmol) in toluene. The residue was worked up and purified by CCTLC in the Chromatothron (hexane/ ethyl acetate, 5:1) to yield 41 mg (80 %) of **14i** as a white solid. Mp 112-114ºC. EM (ES, positive mode): m/z 320 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 1.04 (t, 3H, *J* = 7.3 Hz, $CH_3$), 2.62-2.66 (m, 2H, H-4, H-6), 2.81-2.88 (m, 4H, H-4, H-6, $CH_2$), 3.34 (m, 1H, H-5), 7.24 (m, 1H, Ar),7.34 (m, 6H, Ar), 7.45 (m, 1H, Ar),7.52 (m, 2H, Ar), 15.01 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 13.0 ($CH_3$), 23.8 ($CH_2$), 36.5 (C-5), 46.5 (C-4, C-6), 107.3 (NHC=*C*), 126.6, 127.0, 127.20, 128.5, 128.9, 130.1, 136.3, 143.9 (Ar), 177.5 (NH*C*=C). Anal. calc. for ($C_{21}H_{21}NO_2$): C, 78.97; H, 6.63; N, 4.391. Found: C, 78.68; H, 6.60; N, 4.21. Although this compound was mentioned in ref 1 no analitical or spectroscopical data were provided.

**5-Phenyl-2-(1-(*o*-tolylamino)propylidene)cyclohexane-1,3-dione (14j).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 5-phenyl-2-propionylcyclohexane-1,3-dione (**12**) (25 mg, 0.10 mmol) and *o*-toluidine (16 μL, 0.15 mmol) in toluene. The residue was worked up and purified by CCTLC in the Chromatothron (hexane/ethyl acetate, 5:1) to yield 25 mg (75%) of **14j** as a white solid. Mp 132-134 ºC. EM (ES, positive mode): m/z 334 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 0.98 (t, 3H, *J* = 7.3 Hz, $CH_3$), 2.18 (s, 3H, $CH_3$), 2.61-2.65 (m, 2H, H-4, H-6), 2.77-2.88 (m, 4H, H-4, H-6, $CH_2$), 3.35 (m, 1H, H-5), 7.24 (m, 1H, Ar), 7.28 (dd, 1H, *J* = 7.2, 2.1 Hz, Ar), 7.31-7.38 (m, 6H, Ar), 7.41 (dd, 1H, *J* = 7.0, 2.1 Hz, Ar), 14.88 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 12.7 ($CH_3$), 17.9 ($CH_3$), 23.8 ($CH_2$), 36.5 (C-5), 46.5 (C-4, C-6), 107.3 (NHC=*C*), 127.0, 127.2, 127.3, 127.4, 128.9, 129.0, 131.4, 134.1, 135.0 143.9 (Ar), 178.0 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_2$): C, 79.25; H, 6.95; N, 4.20. Found: C, 79.40; H, 6.15; N, 4.01.

**2-(1-((2-Chlorophenyl)amino)ethylidene)-5-phenylcyclohexane-1,3-dione (18a).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 2-acetyl-5-phenylcyclohexane-1,3-dione (**15b**) (35 mg, 0.15 mmol) and 2-chloroaniline (33 mg, 0.26 mmol) in toluene. The residue was worked up and purified by CCTLC in the

Chromatothron (hexane/ethyl acetate, 5:1) to yield 30 mg (59%) of **18a** as a white solid. Mp 125-127 ºC. EM (E-S, positive mode): m/z 340 $(M+H)^+$ with a Cl isotopic pattern. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ: 2.41 (s, 3H, $CH_3$), 2.41-2.67 (m, 2H, H-4, H-6), 2.84-2.88 (m, 2H, H-4, H-6), 3.38 (m, 1H, H-5), 7.25 (m, 1H, Ar), 7.34 (m, 4H, Ar), 7.49 (m, 3H, Ar), 7.68 (m, 1H,Ar), 15.07 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 20.1 ($CH_3$), 36.3 (C-5), 46.9 (C-4, C-6), 109.0 (NHC=*C*), 127.0, 127.2, 128.7, 129.0, 129.1, 129.7, 130.0, 130.6, 134.2, 143.8 (Ar), 173.0 (NH*C*=C). Anal. calc. for ($C_{20}H_{18}ClNO_2$): C, 70.69; H, 5.34; N, 4.12. Found: C, 70.94; H, 5.34; N, 4.20.

**2-(1-((2-Fluorophenyl)amino)ethylidene)-5-phenylcyclohexane-1,3-dione (18b).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 2-acetyl-5-phenylcyclohexane-1,3-dione (**15b**) (40 mg, 0.17 mmol) and 2-fluoroaniline (25 µL, 0.26 mmol) in toluene. The residue was worked up and purified by CCTLC in the Chromatothron (hexane/ethyl acetate, 5:1) to yield 45 mg (78%) of **18b** as a white solid. Mp 146-147 ºC. EM (ES, positive mode): m/z 324 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 2.44 (s, 3H, $CH_3$), 2.61-2.66 (m, 2H, H-4, H-6), 2.84-2.94 (m, 2H, H-4, H-6), 3.38 (m, 1H, H-5), 7.23 (m, 1H, Ar), 7.34 (m, 5H, Ar), 7.45 (m, 2H, Ar), 7.51 (td, 1H, *J* = 7.9, 1.3 Hz, Ar), 14.90 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 19.6 ($CH_3$), 35.9 (C-5), 45.3 (C-4, C-6), 108.8 (NHC=*C*), 116.4, 125.2, 126.5, 126.7, 128.2, 128.5, 129.8, 143.4, 154.9, 156.9 (Ar), 172.8 (NH*C*=C). Anal. calc. for ($C_{20}H_{18}FNO_2$): C, 74.29; H, 5.61; N, 4.33. Found: C, 73.99; H, 5.34; N, 4.29.

**5-Phenyl-2-(1-((2-(trifluoromethyl)phenyl)amino)ethylidene)cyclohexane-1,3-dione (18c).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 2-acetyl-5-phenylcyclohexane-1,3-dione (**15b**) (40 mg, 0.17 mmol) and 2-trifluoromethylaniline (33 µL, 0.26 mmol) in toluene. The residue was worked up and purified by CCTLC in the Chromatothron (hexane/ethyl acetate, 4:1) to yield 19 mg (30%) of **18c** as a white solid. Mp 167-169 ºC. EM (ES, positive mode): m/z 374 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 2.38 (s, 3H, $CH_3$), 2.54-2.70 (m, 2H, H-4, H-6), 2.80-2.95 (m, 2H, H-4, H-6), 3.36 (m, 1H, H-5), 7.24 (m, 1H, Ar), 7.44 (m, 4H, Ar), 7.65 (m, 2H, Ar), 7.82 (dd, 1H, *J* = 8.4, 6.9 Hz, Ar), 7.90 (m, 1H, Ar), 15.28 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 19.9 ($CH_3$), 36.0 (C-5), 45.0 (C-4, C-6), 108.6 (NHC=*C*), 126.9 ($CF_3$), 124.3, 124.6, 124.8, 126.8, 128.5, 128.8, 129.6, 133.0, 134.2, 143.4 (Ar), 173.0 (NH*C*=C). Anal. calc. for ($C_{21}H_{18}F_3NO_2$): C, 67.55; H, 4.86; N, 3.75. Found: C, 67.63; H, 4.74; N, 3.82.

**2-(1-((2,3-Difluorophenyl)amino)ethylidene)-5-phenylcyclohexane-1,3-dione (18d).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 2-acetyl-5-phenylcyclohexane-1,3-dione (**15b**) (40 mg, 0.17 mmol) and 2,3-difluoroaniline (26 μL, 0.26 mmol) in toluene. The residue was worked up and purified by flash chromatography (hexane/ethyl acetate) to yield 24 mg (41%) of **18d** as a white solid. Mp 131-133 ºC. EM (ES, positive mode): m/z 342 $(M+H)^+$.$^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 2.45 (s, 3H, $CH_3$), 2.57-2.67 (m, 2H, H-4, H-6), 2.85 (m, 2H, H-4, H-6), 3.37 (m, 1H, H-5), 7.24 (d, 1H, *J* = 4.2 Hz, Ar), 7.34 (m, 6H, Ar), 7.51 (m, 1H, Ar), 14.93 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 19.7 ($CH_3$), 35.8 (C-5), 45.4 (C-4, C-6), 109.0 (NHC=*C*), 116.8, 117.0, 123.7, 124.9, 126.5, 126.7, 128.5, 143.3, 149.1, 151.0 (Ar), 172.8 (NH*C*=C). Anal. calc. for ($C_{20}H_{17}F_2NO_2$): C, 70.37; H, 5.02; N, 4.10. Found: C, 70.41; H, 5.00; N, 3.98.

**2-(1-((2,6-Difluorophenyl)amino)ethylidene)-5-phenylcyclohexane-1,3-dione (18e).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 2-acetyl-5-phenylcyclohexane-1,3-dione (**15b**) (40 mg, 0.17 mmol) and 2,6-difluoroaniline (26 μL, 0.26 mmol) in toluene. The residue was worked up and purified by flash chromatography (hexane/ethyl acetate) to yield 20 mg (37%) of **18e** as a white solid. Mp 135-137 ºC. EM (ES, positive mode): m/z 342 $(M+H)^+$.$^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 2.37 (s, 3H, $CH_3$), 2.57-2.63 (m, 2H, H-4, H-6), 2.83 (m, 2H, H-4, H-6), 3.38 (m, 1H, H-5), 7.24 (d, 1H, *J* = 4.2 Hz, Ar), 7.34 (m, 6H, Ar), 7.54 (m, 1H, Ar), 14.61 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 19.4 ($CH_3$), 35.8 (C-5), 46.4 (C-4, C-6), 109.1 (NHC=*C*), 112.4, 113.8, 124.5, 126.7, 126.9, 128.5, 130.2, 143.3, 156.0, 157.9, (Ar), 173.5 (NH*C*=C). Anal. calc. for ($C_{20}H_{17}F_2NO_2$): C, 70.37; H, 5.02; N, 4.10. Found: C, 70.53; H, 4.99; N, 4.06.

**2-(1-((2,5-Dimethoxyphenyl)amino)ethylidene)-5-phenylcyclohexane-1,3-dione (18f).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 2-acetyl-5-phenyllcyclohexane-1,3-dione (**15b**) (40 mg, 0.17 mmol) and 2,5-dimethoxyaniline (40 mg, 0.26 mmol) in toluene. The residue was worked up and purified by flash chromatography (hexane/ethyl acetate) to yield 30 mg (48%) of **18f** as a white solid. Mp 183-185 ºC. EM (ES, positive mode): m/z 366 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ: 2.42 (s, 3H, $CH_3$), 2.57-2.64 (m, 2H, H-4, H-6), 2.72-2.85 (m, 2H, H-4, H-6), 3.39 (m, 1H, H-5), 3.73 (s, 3H, $OCH_3$), 3.77 (s, 3H, $OCH_3$), 6.95 (m, 2H, Ar), 7.12 (d, 1H, *J* = 9.9 Hz, Ar), 7.24 (m, 1H, Ar), 7.34 (m, 4H, Ar), 14.76 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.7 ($CH_3$), 36.1 (C-5), 46.6 (C-4, C-6), 55.7 ($OCH_3$), 56.1 ($OCH_3$), 108.4

(NHC=*C*), 112.9, 113.1, 113.9, 125.0, 126.5, 126.7, 128.5, 143.5, 147.2, 153.0 (Ar), 172.6 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_4$): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.20; H, 6.28; N, 3.54.

**2-(1-((2,6-Dimethoxyphenyl)amino)ethylidene)-5-phenylcyclohexane-1,3-dione (18g).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 2-acetyl-5-phenylcyclohexane-1,3-dione (**15b**) (100 mg, 0.43 mmol) and 2,6-dimethoxyaniline (100 mg, 0.65 mmol) in toluene. The residue was worked up and purified by flash chromatography (hexane/ethyl acetate) to yield 36 mg (23%) of **18g** as a white solid. Mp 159-160 ºC. EM (ES, positive mode): m/z 366 $(M+H)^+$.$^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 2.24 (s, 3H, $CH_3$), 2.55-2.59 (m, 2H, H-4, H-6), 2.77-2.87 (m, 2H, H-4, H-6), 3.35 (m, 1H, H-5), 3.81 (s, 6H, $OCH_3$), 6.82 (d, 2H, *J* = 8.52 Hz, Ar), 7.20–7.27 (m, 1H, Ar), 7.34 (m, 4H, Ar), 7.38 (d, 1H, *J* = 8.5 Hz, Ar), 14.39 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.4 ($CH_3$), 36.1 (C-5), 46.6 (C-4, C-6), 56.0 ($OCH_3$), 108.1 (NHC=*C*), 104.6, 112.8, 126.5, 126.7, 128.5, 129.6, 143.6, 154.5 (Ar), 174.0 (NH*C*=C), 196.9 (CO). Anal. calc. for ($C_{22}H_{23}NO_4$): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.60; H, 6.61; N, 3.92.

**(*E*)-4-Cyclohexylbut-3-en-2-one (20a).**

To a solution of cyclohexanecarbaldehyde (**19a**) (1.21 mL, 10 mmol) in a mixture of acetone/water (4 mL/5 mL), 1% aqueous solution of sodium hydroxide (5 mL) was rapidly added, and the reaction mixture was stirred at room temperature overnight. The crude reaction mixture was then neutralized by the addition of 1M HCl, extracted with $CH_2Cl_2$ (3 x 20 mL) and washed with brine (20 mL). The organic phase was dried over anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The residue was purified by flash column chromatography (hexane/ethyl acetate) to yield 984 mg (65%) of **20a** as an oil. EM (ES, positive mode): m/z 153 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ: 1.11-1.27 (m, 5H, H-2', H-3' H-4', H-5', H-6'), 1.69-1.70 (m, 5H, H-2', H-3' H-4', H-5', H-6'), 2.12 (m, 1H, H-1'), 2.18 (s, 3H, $CH_3$), 5.96 (d, 1H, *J* = 16.1 Hz, H-3), 6.78 (dd, 1H, *J* = 16.1, 6.7 Hz, H-4).

**[1,1'-Bi(cyclohexane)]-3,5-dione (21a).**

To a solution of 25% sodium ethoxide in ethanol (15 mL, 6.86 mmol), diethyl malonate (652 µL, 6.86 mmol) was added dropwise, keeping the temperature below 25 ºC. The mixture was further diluted with ethanol (1.2 mL) and heated at 60 ºC. Then, **20a** (950 mg, 6.24 mmol) in ethanol (2.2 mL) was added dropwise and the mixture was stirred at reflux and monitored by LC-MS until the corresponding starting material was consumed. The reaction mixture was treated with 6M sodium hydroxide (2.2 mmol) and heated

at 80 ºC for 2h. After cooling, ethanol was removed in vacuo and the resulting solution was washed with toluene (2x 10 mL). The aqueous layer was treated with 37% HCl until pH 2, refluxed for 1h and left to cool at room temperature. The solid thus formed was isolated by filtration to yield 840 mg (69%) of **21a** as a brown solid. Mp 144-146 ºC. EM (ES, positive mode): m/z 195 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 0.94-1.2 (m, 6H, H-1', H-2', H-3', H-4', H-5', H-6'), 1.62-1.77 (m, 6H, , H-2', H-3', H-4', H-5', H-6', H-5), 2.02-2.25 (m, 4H, H-4, H-6), 5.18 (s, 1H, H-2), 11.17 (br s, 1H, OH).

**5-Benzylcyclohexane-1,3-dione (21b).**

Following the described procedure for the synthesis of **21a,** a mixture of diethyl malonate (0.65 mL, 6.86 mmol), 25 % sodium ethoxide in ethanol (15 mL, 6.86 mmol) and (*E*)-5-phenylpent-3-en-2-one (**20b**)[2] (1.0 g, 6.25 mmol) in ethanol (2.2 mL) was stirred at reflux for 2 h before treatment with 6M NaOH (5 mL, 22 mmol) to yield 420 mg (33%) of **21b** as a brown oil. EM (ES, positive mode): m/z 203 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.03-2.16 (m, 4H, H-4, H-6), 2.24 (m, 1H, H-5), 2.64 (d, 2H, $J$ = 6.8 Hz, $CH_2$), 5.18 (s, 1H, H-2), 7.17-7.33 (m, 5H, Ar), 11.30 (br s, 1H, OH).

**4-Acetyl-[1,1'-bi(cyclohexane)]-3,5-dione (22a).**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with **21a** (300 mg, 1.54 mmol), acetylchloride (238 μL, 3.09 mmol), anhydrous $K_2CO_3$ (469 mg, 3.39 mmol), 1,2,4-triazole (43 mg, 0.62 mmol) and tetrabutyl ammonium bromide (248 mg, 0.77 mmol) in anhydrous DMF (4 mL) to yield 134 mg (36%) of **22a** as a yellow solid. Mp 52-54 ºC. EM (ES, positive mode): 237 m/z $(M+H)^+$. $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 1.12 (m, 6H, H-1', H-2', H-3', H-4', H-5', H-6'), 1.70 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 1.87 (m, 1H, H-5), 2.51 (s, 3H, $CH_3$), 2.50-2.64 (m, 4H, H-4, H-6).

**2-Acetyl-5-benzylcyclohexane-1,3-dione (22b).**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with **21b** (100 mg, 0.49 mmol), acetylchloride (75 μL, 0.98 mmol), anhydrous $K_2CO_3$ (150 mg, 1.08 mmol), 1,2,4-triazole (14 mg, 0.20 mmol) and tetrabutyl ammonium bromide (79 mg, 0.25 mmol) in anhydrous DMF (4 mL) to yield 46 mg (38 %) of **22b** as a yellow oil. EM (ES, positive mode): 245 m/z $(M+H)^+$. $^1$H-NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.17-2.43 (m, 5H, H-4, H-6, H-5), 2.48 (s, 3H, $CH_3$), 2.64 (d, 2H, $J$ = 5.5 Hz, $CH_2$), 3.51 (dd, 2H, $J$ = 6.7, 1.7 Hz, H-4, H-6), 7.20 (m, 3H, Ar), 7.30 (m, 2H, Ar).

**4-(1-((2-Methoxyphenyl)amino)ethylidene)-[1,1'-bi(cyclohexane)]-3,5-dione (23a).**

A solution of **22a** (100 mg, 0.42 mmol) and *o*-anisidine (72 µL, 0.63 mmol) in toluene was placed in an Ace pressure tube. Then, 4 Å molecular sieves were added, the vessel was sealed and heated at 110 ºC overnight. After cooling, the solvent was evaporated to dryness. The crude reaction mixture was purified by flash chromatography (hexane/ethyl acetate) to yield 128 mg (89%) of **23a** as a white solid. Mp 131-133 ºC. EM (ES, positive mode): m/z 342 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 0.93-1.20 (m, 6H, H-1', H-2', H-3', H-4', H-5', H-6'), 1.60-1.77 (m, 6H, H-5, H-2', H-3', H-4', H-5', H-6'), 2.30 (m, 2H, H-4, H-6), 2.36 (s, 3H, $CH_3$), 2.43 (m, 2H, H-4, H-6), 3.82 (s, 3H, $OCH_3$), 7.03 (t, 1H, *J* = 7.7 Hz, Ar), 7.18 (d, 1H, *J* = 8.1 Hz, Ar), 7.29 (d, 1H, *J* = 7.5 Hz, Ar), 7.37 (t, 1H, *J* = 7.8 Hz, Ar), 14.74 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.5 ($CH_3$), 25.9 (C-3', C-5'), 26.1 (C-4'), 29.2 (C-2', C-6'), 36.9 (C-5), 40.8 (C-1'), 42.2 (C-4, C-6), 55.8 ($OCH_3$), 108.4 (NHC=*C*), 112.3, 120.6, 124.5, 126.9, 129.1, 153.1 (Ar), 172.1 (NH*C*=C). Anal. calc. for ($C_{21}H_{27}NO_3$): C, 73.87; H, 7.97; N, 4.10. Found: C, 74.05; H, 8.15; N, 4.09.

**5-Benzyl-2-(1-((2-methoxyphenyl)amino)ethylidene)cyclohexane-1,3-dione (23b).**

A solution of **22b** (40 mg, 0.16 mmol) and *o*-anisidine (38 µL mg, 0.25 mmol) in toluene was placed in an Ace pressure tube. Then, 4 Å molecular sieves were added, the vessel was sealed and heated at 110 ºC overnight. After cooling, the solvent was evaporated to dryness. The crude reaction mixture was purified by flash chromatography (hexane/ethyl acetate) to yield 41 mg (73%) of **23b** as a white solid. Mp 165-167 ºC. EM (ES, positive mode): m/z 350 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 2.27 (m, 2H, H-4, H-6), 2.33 (m, 1H, H-5), 2.35 (s, 3H, $CH_3$), 2.38 (m, 2H, H-4, H-6), 2.60 (d, 2H, *J* = 5.6 Hz, $CH_2$), 3.81 (s, 3H, $OCH_3$), 7.02 (m, 1H, *J* = 7.6, 1.2 Hz, Ar), 7.18 (m, 2H, Ar), 7.22 (m, 2H, Ar), 7.28 (m, 2H, Ar), 7.31 (m, 1H, Ar), 7.37 (m, 1H, Ar), 14.72 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.6 ($CH_3$), 32.6 (C-5), 39.7 ($CH_2$), 46.5 (C-4, C-6), 55.7 ($OCH_3$), 108.6 (NHC=*C*), 112.3, 115.2, 117.9, 120.6, 124.5, 126.1, 126.9, 129.0, 129.2, 139.4 (Ar), 172.3 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_3$): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.86; H, 6.71; N, 4.08.

**2-(1-((2-Methoxyphenyl)amino)ethylidene)-5,5-dimethylcyclohexane-1,3-dione (23c).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with 2-acetyl-5,5-dimethyl-1,3-cyclohexanedione (**22c**) (100 mg, 0.59 mmol) and *o*-anisidine (93 µL, 0.82 mmol) in toluene to yield 134 mg (79%) of **23c** as a white solid. Mp 101-103 ºC. EM (ES, positive mode): m/z 288 $(M+H)^+$.$^1$H -NMR (DMSO-$d_6$, 500 MHz) δ: 0.98 (s, 6H, $CH_3$), 2.36 (m, 7H, H-4, H-6, $CH_3$), 3.83 (s, 3H, $OCH_3$), 7.01 (t, 1H, *J* = 7.5 Hz, Ar), 7.17 (d, 1 H, *J* = 8.1 Hz, Ar), 7.33 (m,

2H, Ar), 14.73 (br s, 1H, NH). $^{13}$C -NMR (DMSO-$d_6$, 125 MHz) δ: 20.0 ($CH_3$), 28.2 ($CH_3$), 30.2 (C-5), 52.7 (C-4, C-6), 56.2 ($OCH_3$), 108.3 (NHC=*C*), 112.7, 121.1, 124.6, 127.3, 129.7, 153.4 (Ar), 172.2 (NH*C*=C). Anal. calc. for ($C_{17}H_{21}NO_3$): C, 71.06; H, 7.37; N, 4.87. Found: C, 71.24; H, 7.61; N, 4.94.

**5-(3-Methoxyphenyl)cyclohexane-1,3-dione (24f)**

Following the procedure describe for the synthesis of **20a**, reaction of 3-methoxybenzaldehyde (0.97 mL, 8 mmol) and NaOH (4 mL) in acetone/water (3.2 mL/4 mL) afforded a residue that was purified by flash column chromatography (hexane/ethyl acetate 2:1) to yield 1.33 g (83%) of (*E*)-4-(3-methoxyphenyl)but-3-en-2-one as a yellow oil. EM (ES, positive mode): m/z 177 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ: 2.33 (s, 3H, $CH_3$), 3.80 (s, 3H, $OCH_3$), 6.80 (d, 1H, *J* = 16.4 Hz, H-3), 6.98-7.02 (m, 1H, Ar), 7.28-7.30 (m, 3H, Ar), 7.59 (d, 1H, *J* = 16.4 Hz, H-4). Then, following the described procedure for the synthesis of **21a**, a mixture of diethyl malonate (0.65 mL, 6.87 mmol), 25 % sodium ethoxide in ethanol (1.5mL, 8.87 mmol) and (*E*)-4-(3-methoxyphenyl)but-3-en-2-one (1.10 g, 6.24 mmol) in ethanol (2 mL) was stirred at reflux for 2 h before treatment with 6M NaOH (5 mL, 22 mmol) to yield 1.24 g (91%) of **24f** as a pale brown solid. Mp 85-87 ºC. EM (ES, positive mode): m/z 219 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.29 (m, 2H, H-4, H-6), 2.54-2.73 (m, 2H, H-4, H-6), 3.25 (m, 1H, H-5), 3.74 (s, 3H, $OCH_3$), 5.28 (s, 1H, H-2), 6.78-6.92 (m, 3H, Ar), 7.21-7.26 (m, 1H, Ar), 11.17 (br s, 1H, OH).

**2-Acetyl-5-(*o*-tolyl)cyclohexane-1,3-dione (25a).**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with 5-(*o*-tolyl)cyclohexane-1,3-dione (**24a**)[3] (100 mg, 0.49 mmol), acetylchloride (75 µL, 0.98 mmol), anhydrous $K_2CO_3$ (150 mg, 1.08 mmol), 1,2,4-triazole (14 mg, 0.20 mmol) and tetrabutyl ammonium bromide (79 mg, 0.25 mmol) in anhydrous acetonitrile (4 mL) to yield 38 mg (35 %) of **25a** as a yellow solid. Mp 165-167 ºC. EM (ES, positive mode): 245 m/z $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.31 (s, 3H, $CH_3$), 2.56 (s, 3H, $CH_3$), 2.63 (m, 2H, H-4, H-6), 2.93 (m, 2H, H-4, H-6), 3.60 (m, 1H, H-5), 7.11-7.33 (m, 4H, Ar).

**2-Acetyl-5-(2-fluorophenyl)cyclohexane-1,3-dione (25b).**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with 5-(2-fluorophenyl)cyclohexane-1,3-dione (**24b**)[3] (100 mg, 0.49 mmol), acetylchloride (75 µL, 0.98 mmol), anhydrous $K_2CO_3$ (150 mg, 1.08 mmol), 1,2,4-triazole (14 mg, 0.20 mmol) and tetrabutyl ammonium bromide

(79 mg, 0.25 mmol) in anhydrous acetonitrile (4 mL) to yield 59 mg (48%) of **25b** as a yellow solid. Mp 71-73ºC. EM (ES, positive mode): 249 m/z $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.55 (s, 3H, $CH_3$), 2.66-2.73 (m, 2H, H-4, H-6), 2.92-3.08 (m, 2H, H-4, H-6), 3.68 (m, 1H, H-5), 7.16-7.44 (m, 4H, Ar).

**2-Acetyl-5-(2,6-dimethylphenyl)cyclohexane-1,3-dione (25c).**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with 5-(2,6-dimethylphenyl)cyclohexane-1,3-dione (**24c**)[3] (400 mg, 1.85 mmol), acetylchloride (0.28 mL, 3.70 mmol), anhydrous $K_2CO_3$ (563 mg, 4.07 mmol), 1,2,4-triazole (51 mg, 0.74 mmol) and tetrabutyl ammonium bromide (298 mg, 0.93 mmol) in anhydrous acetonitrile (5 mL) to yield 139 mg (29%) of **25c** as a white solid. Mp 140-142 ºC. EM (ES, positive mode): 259 m/z $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.37 (s, 6H, $CH_3$), 2.56 (s, 3H, $CH_3$), 2.62-2.71 (m, 2H, H-4, H-6), 3.25 (m, 2H, H-4, H-6), 3.79 (m, 1H, H-5), 6.98-7.02 (m, 3H, Ar).

**2-Acetyl-5-(2,6-difluorophenyl)cyclohexane-1,3-dione (25d).**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with 5-(2,6-dimethylphenyl)cyclohexane-1,3-dione (**24d**)[3] (400 mg, 1.78 mmol), acetylchloride (0.26 mL, 3.57 mmol), anhydrous $K_2CO_3$ (543 mg, 3.93 mmol), 1,2,4-triazole (49 mg, 0.71 mmol) and tetrabutyl ammonium bromide (287 mg, 0.89 mmol) in anhydrous acetonitrile (5 mL) to yield 66 mg (14%) of **25d** as a white solid. Mp 88-90 ºC. EM (ES, positive mode): 267 m/z $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.54 (s, 3H, $CH_3$), 2.66 (m, 2H, H-4, H-6), 3.04 (m, 2H, H-4, H-6), 3.78 (m, 1H, H-5), 7.08-7.41 (m, 3H, Ar).

**2-Acetyl-5-(*m*-tolyl)cyclohexane-1,3-dione (25e)**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with 5-(*m*-tolyl)cyclohexane-1,3-dione (**24e**)[3] (200 mg, 1.00 mmol), acetylchloride (0.15 mL, 2.00 mmol), anhydrous $K_2CO_3$ (304 mg, 2.20 mmol), 1,2,4-triazole (28 mg, 0.40 mmol) and tetrabutyl ammonium bromide (161 mg, 0.50 mmol) in anhydrous acetonitrile (4 mL) to yield 110 mg (45%) of **25e** as a white solid. Mp 68-70 ºC. EM (ES, positive mode): 245 m/z $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.27 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$), 2.62-2.69 (m, 2H, H-4, H-6), 2.91 (m, 2H, H-4, H-6), 3.37 (m, 1H, H-5), 7.05-7.25 (m, 4H, Ar).

**2-Acetyl-5-(3-methoxyphenyl)cyclohexane-1,3-dione (25f)**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with **24f** (200 mg, 0.98 mmol), acetylchloride (0.14 mL, 1.84 mmol), anhydrous $K_2CO_3$ (276 mg, 2.00 mmol), 1,2,4-triazole (24 mg, 0.36 mmol) and tetrabutyl ammonium bromide (148 mg, 0.46 mmol) in anhydrous acetonitrile (4 mL) to yield 60 mg (50%) of **25f** as a white solid. Mp 110-112 ºC. EM (ES, positive mode): 261 m/z $(M+H)^+$. $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.55 (s, 3H, $CH_3$), 2.61 (m, 2H, H-4, H-6), 2.79 (m, 2H, H-4, H-6), 3.39 (m, 1H, H-5), 3.74 (s, 3H, $OCH_3$), 6.80-6.91 (m, 3H, Ar), 7.22-7.28 (m, 1H, Ar).

**2-Acetyl-5-(*p*-tolyl)cyclohexane-1,3-dione (25g)**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with 5-(*p*-tolyl)cyclohexane-1,3-dione (**24g**)[4] (200 mg, 1.00 mmol), acetylchloride (0.15 mL, 2.00 mmol), anhydrous $K_2CO_3$ (304 mg, 2.20 mmol), 1,2,4-triazole (28 mg, 0.40 mmol) and tetrabutylammonium bromide (161 mg, 0.50 mmol) in anhydrous acetonitrile (4 mL) to yield 217 mg (45%) of **25g** as a white solid. Mp 98-100 ºC. EM (ES, positive mode): 245 m/z $(M+H)^+$. $^1H$ NMR(DMSO-$d_6$, 300 MHz) δ (enol form): 2.27 (s, 3H, $CH_3$), 2.54 (s, 3H, $CH_3$), 2.64-2.69 (m, 2H, H-4, H-6), 2.91 (m, 2H, H-4, H-6), 3.36 (m, 1H, H-5), 7.14 (m, 2H, Ar), 7.21 (m, 2H, Ar).

**2-Acetyl-5-(4-methoxyphenyl)cyclohexane-1,3-dione (25h).**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with 5-(4-methoxyphenyl)cyclohexane-1,3-dione (**24h**)[4] (300 mg, 1.38 mmol), acetyl chloride (0.21 mL, 2.76 mmol), anhydrous $K_2CO_3$ (414 mg, 3.00 mmol), 1,2,4-triazole (36 mg, 0.54 mmol) and tetrabutylammonium bromide (222 mg, 0.69 mmol) in anhydrous acetonitrile (5.5 mL) to yield 180 mg (50%) of **25h** as a white solid. Mp 85-87 ºC. EM (ES, positive mode): 261 m/z $(M+H)^+$. $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.53 (s, 3H, $CH_3$), 2.66 (m, 2H, H-4, H-6), 2.88 (m, 2H, H-4, H-6), 3.34 (m, 1H, H-5), 3.72 (s, 4H, H-2, $OCH_3$), 6.88 (d, 2H, $J$ = 8.6 Hz, Ar), 7.23 (d, 2H, $J$ = 8.7 Hz, Ar).

**2-Acetyl-5-(4-chlorophenyl)cyclohexane-1,3-dione (25i)**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with 5-(4-chlorophenyl)cyclohexane-1,3-dione (**24i**) (200 mg, 0.90 mmol), acetylchloride (0.14 mL, 1.80 mmol), anhydrous $K_2CO_3$ (274 mg, 1.98 mmol), 1,2,4-triazole (25 mg, 0.36 mmol) and tetrabutyl ammonium bromide (145 mg, 0.45 mmol) in anhydrous acetonitrile (4 mL) to yield 352 mg (74%) of **25i** as a white solid. Mp 140-142 ºC. EM (ES, positive mode): 265 m/z $(M+H)^+$ with a Cl isotopic pattern. $^1H$ NMR (DMSO-$d_6$, 300 MHz)

δ (enol form): 2.55 (s, 3H, $CH_3$), 2.71 (m, 2H, H-4, H-6), 2.90 (m, 2H, H-4, H-6), 3.43 (m, 1H, H-5), 7.35-7.42 (m, 4H, Ar).

**2-Acetyl-5-(4-fluorophenyl)cyclohexane-1,3-dione (25j)**

Following the described procedure for the synthesis of **12**, a microwave vial was charged with 5-(4-fluorophenyl)cyclohexane-1,3-dione (**24j**) (100 mg, 0.48 mmol), acetylchloride (71 μL, 0.97 mmol), anhydrous $K_2CO_3$ (138 mg, 1.06 mmol), 1,2,4-triazole (13 mg, 0.19 mmol) and tetrabutyl ammonium bromide (77 mg, 0.24 mmol) in anhydrous acetonitrile (4 mL) to yield 71 mg (60 %) of **25j** as a white solid. Mp 110-112ºC. EM (ES, positive mode): 249 m/z $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ (enol form): 2.55 (s, 3H, $CH_3$), 2.71 (m, 2H H-4, H-6), 2.95 (m, 2H, H-4, H-6), 3.40 (m, 1H, H-5), 7.23-7.35 (m, 4H, Ar).

**2-(1-((2-Methoxyphenyl)amino)ethylidene)-5-(*o*-tolyl)cyclohexane-1,3-dione (26a).**

A solution of **25a** (90 mg, 0.37 mmol) and *o*-anisidine (63 μL, 0.55 mmol) in toluene was placed in an Ace pressure tube. Then, 4 Å molecular sieves were added, the vessel was sealed and heated at 110 ºC overnight. After cooling, the solvent was evaporated to dryness. The crude reaction mixture was purified by flash chromatography (hexane/ethyl acetate) to yield 60 mg (46%) of **26a** as a white solid. Mp 142-144 ºC. EM (ES, positive mode): m/z 350 $(M+H)^+$.$^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 2.32 (s, 3H, $CH_3$), 2.42 (s, 3H, $CH_3$), 2.55 (m, 2H, H-4, H-6), 2.80 (m, 2H, H-4, H-6), 3.51 (m, 1H, H-5), 3.84 (s, 3H, $OCH_3$), 7.05 (m, 1H, *J* = 7.7, 1.2 Hz, Ar), 7.17 (m, 4H, Ar), 7.32 (m, 2H, Ar), 7.39 (m, 1H, *J* = 8.0, 1.7 Hz, Ar), 14.79 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.7 ($CH_3$), 19.9 ($CH_3$), 32.1 (C-5), 45.1 (C-4, C-6), 55.8 ($OCH_3$), 108.3 (NHC=*C*), 112.3, 120.6, 124.5, 125.2, 126.2, 126.3, 126.9, 129.2, 130.3, 135.2, 141.4, 153.1 (Ar), 174.0 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_3$): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.78; H, 6.73; N, 3.84.

**5-(2-Fluorophenyl)-2-(1-((2-methoxyphenyl)amino)ethylidene)cyclohexane-1,3-dione (26b).**

A solution of **25b** (80 mg, 0.32 mmol) and *o*-anisidine (55 μL, 0.48 mmol) in toluene was placed in an Ace pressure tube. Then, 4 Å molecular sieves were added, the vessel was sealed and heated at 110 ºC overnight. After cooling, the solvent was evaporated to dryness. The crude reaction mixture was purified by flash chromatography (hexane/ethyl acetate) to yield 80 mg (71%) of **26b** as a white solid. Mp 133-135 ºC. EM (ES, positive mode): m/z 354 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 2.41 (s, 3H, $CH_3$), 2.60-2.63 (m, 2H, H-4, H-6), 2.84 (m, 2H, H-4, H-6), 3.60 (m, 1H, H-5), 3.84 (s, 3H, $OCH_3$), 7.04 (m, 1H, *J* = 7.6, 1.2 Hz, Ar), 7.20 (m, 3H, Ar), 7.32 (m, 2H, Ar), 7.39 (dd, 1H, *J* = 7.8, 1.7 Hz, Ar), 7.40 (dd, 1H, *J* = 7.8, 1.7 Hz, Ar), 14.75 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.7 ($CH_3$), 29.6 (C-5), 45.0 (C-4, C-6), 56.1

($OCH_3$), 108.1 (NHC=*C*), 108.3, 112.3, 115.3, 120.6, 124.4, 126.9, 127.8, 128.4, 129.3, 129.9, 153.1, 161.4 (Ar), 172.7 (NHC=C). Anal. calc. for ($C_{21}H_{20}FNO_3$): C, 71.37; H, 5.70; N, 3.96. Found: C, 71.09; H, 5.98; N, 4.02.

**5-(2,6-Dimethylphenyl)-2-(1-((2-methoxyphenyl)amino)ethylidene)cyclohexane-1,3-dione (26c).**

A solution of **25c** (130 mg, 0.50 mmol) and *o*-anisidine (85 µL, 0.75 mmol) in toluene was placed in an Ace pressure tube. Then, 4 Å molecular sieves were added, the vessel was sealed and heated at 110 ºC overnight. After cooling, the solvent was evaporated to dryness. The crude reaction mixture was purified by flash chromatography (hexane/ethyl acetate) to yield 120 mg (66%) of **26c** as a pale brown solid. Mp 140-142 ºC. EM (ES, positive mode): m/z 364 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 2.38 (s, 6H, $CH_3$), 2.42 (s, 3H, $CH_3$), 2.59 (m, 2H, H-4, H-6), 3.17 (m, 2H, H-4, H-6), 3.77 (m, 1H, H-5), 3.84 (s, 3H, $OCH_3$), 6.99 (m, 3H, Ar), 7.05 (t, 1H, *J* = 7.6 Hz, Ar), 7.20 (d, 1 H, *J* = 8.3 Hz, Ar), 7.32 (dd, 1H, *J* = 7.6, 1.7 Hz, Ar), 7.39 (m, 1H, Ar), 14.81 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.8 ($CH_3$), 21.5 ($CH_3$), 32.6 (C-5), 42.7 (C-4, C-6), 55.8 ($OCH_3$), 108.3 (NHC=*C*), 112.3, 120.6, 124.5, 126.2, 126.9, 129.2, 129.7, 136.1, 138.1, 153.1 (Ar), 172.7 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_4$): C, 76.01; H, 6.93; N, 3.85. Found: C, 76.30; H, 7.05; N, 3.79.

**5-(2,6-Difluorophenyl)-2-(1-((2-methoxyphenyl)amino)ethylidene)cyclohexane-1,3-dione (26d).**

A solution of **25d** (55 mg, 0.21 mmol) and *o*-anisidine (36 µL, 0.32 mmol) in toluene was placed in an Ace pressure tube. Then, 4 Å molecular sieves were added, the vessel was sealed and heated at 110 ºC overnight. After cooling, the solvent was evaporated to dryness. The crude reaction mixture was purified by flash chromatography (hexane/ethyl acetate) to yield 44 mg (56%) of **26d** as a white solid. Mp 141-142 ºC. EM (ES, positive mode): m/z 372 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 2.41 (s, 3H, $CH_3$), 2.55-2.60 (m, 2H, H-4, H-6), 2.96-3.03 (m, 2H, H-4, H-6), 3.71 (m, 1H, H-5), 3.84 (s, 3H, $OCH_3$), 7.04 (m, 1H, *J* = 7.6, 1.2 Hz, Ar), 7.10 (t, 2 H, *J* = 8.6 Hz, Ar), 7.20 (dd, 1H, *J* = 8.4, 1.2 Hz, Ar), 7.32 (dd, 1H, *J* = 7.8, 1.7 Hz, Ar), 7.36 (m, 1H, Ar), 7.40 (m, 1H, Ar), 14.72 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.8 ($CH_3$), 27.0 (C-5), 43.0 (C-4, C-6), 55.8 ($OCH_3$), 108.2 (NHC=*C*), 112.0, 112.3, 117.5, 120.6, 124.4, 126.9, 129.27, 153.1, 159.6, 162.1 (Ar), 172.9 (NH*C*=C). Anal. calc. for ($C_{21}H_{19}F_2NO_3$): C, 67.92; H, 5.16; N, 3.77. Found: C, 67.85; H, 4.98; N, 3.67 .

**2-(1-((2-Methoxyphenyl)amino)ethylidene)-5-(*m*-tolyl)cyclohexane-1,3-dione (26e).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with **25e** (50 mg, 0.20 mmol) and *o*-anisidine (42 μL, 0. 37 mmol) in toluene. The residue was worked up and purified by flash chromatography (hexane/ethyl acetate) to yield 54 mg (75%) of **26e** as a white solid. Mp 107-109 ºC. EM (ES, positive mode): m/z 350 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ: 2.30 (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$), 2.57-2.61 (m, 2H, H-4, H-6), 2.75-2.85 (m, 2H, H-4, H-6), 3.31 (m, 1H, H-5), 3.84 (s, 3H, $OCH_3$), 7.04 (m, 2H, Ar), 7.13 (m, 2H, Ar), 7.20 (m, 2H, Ar), 7.32 (dd, 1H, *J* = 7.7, 1.7 Hz, Ar), 7.39 (m, 1H, Ar), 14.78 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.5 ($CH_3$), 20.9 ($CH_3$), 35.9 (C-5), 46.2 (C-4, C-6), 55.6 ($OCH_3$), 108.2 (NHC=*C*), 112.1, 120.4, 123.6, 124.3, 126.7, 127.0, 127.2, 128.2, 129.0, 137.4, 143.3, 152.9 (Ar), 172.3 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_3$): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.66; H, 6.90; N, 4.02.

**5-(3-Methoxyphenyl)-2-(1-((2-methoxyphenyl)amino)ethylidene)cyclohexane-1,3-dione (26f).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with **25f** (60 mg, 0.23 mmol) and *o*-anisidine (39 μL, 0.35 mmol) in toluene. The residue was worked up and purified by flash chromatography (hexane/ethyl acetate) to yield 44 mg (52%) of **26f** as a white solid. Mp 127-129 ºC. EM (ES, positive mode): m/z 366 $(M+H)^+$.$^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 2.40 (s, 3H, $CH_3$), 2.56-2.63 (m, 2H, H-4, H-6), 2.78 (m, 2H, H-4, H-6), 3.38 (m, 1H, H-5), 3.75 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 6.80 (m, 1H, Ar), 6.90 (m, 2H, Ar), 7.04 (m, 1H, Ar), 7.20 (dd, 1H, *J* = 8.4, 1.2 Hz, Ar), 7.24 (t, 1H, *J* = 8.1 Hz, Ar), 7.31 (dd, 1H, *J* = 7.8, 1.7 Hz, Ar), 7.38 (m, 1H, *J* = 7.6, 1.7 Hz, Ar), 14.77 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 19.7 ($CH_3$), 36.1 (C-5), 45.4, 46.3 (C-4, C-6), 54.9 ($OCH_3$), 55.8 ($OCH_3$), 108.4 (NHC=*C*), 111.8, 112.3, 112.68, 118.9, 120.6, 124.5, 126.9, 129.2, 129.5, 145.2, 153.0, 159.4 (Ar), 172.4 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_4$): C, 72.31; H, 6.31; N, 3.94. Found: C, 72.43; H, 6.31; N, 3.84.

**2-(1-((2-Methoxyphenyl)amino)ethylidene)-5-(*p*-tolyl)cyclohexane-1,3-dione (26g).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with **25g** (50 mg, 0.20 mmol) and *o*-anisidine (35 μL, 0. 30 mmol) in toluene. The residue was worked up and purified by flash chromatography (hexane/ethyl acetate) to yield 41 mg (59%) of **26g** as a white solid. Mp 172-174 ºC. EM (ES, positive mode): m/z 350 $(M+H)^+$.$^1$H NMR (DMSO-$d_6$, 300 MHz) δ: 2.28 (s, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 2.56-2.61 (m, 2H, H-4, H-6), 2.78 (m, 2H, H-4, H-6), 3.27 (m, 1H, H-5), 3.83 (s, 3H, $OCH_3$), 7.05 (m, 1H, *J* = 7.6, 1.2 Hz, Ar), 7.13 (d, 2H, *J* = 7.9, 1.2 Hz, Ar),

7.21 (m, 3H, Ar), 7.31 (dd, 1H, *J* = 7.7, 1.7 Hz, Ar), 7.39 (m, 1H, Ar), 14.78 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.7 ($CH_3$), 20.6 ($CH_3$), 35.7 (C-5), 46.2 (C-4, C-6), 55.8 ($OCH_3$), 108.4 (NHC=*C*), 112.3, 120.6, 124.5, 126.6, 126.9, 129.0, 129.2, 135.5, 140.5, 153.1 (Ar), 172.4 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_3$): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.59; H, 6.39; N, 3.82.

**5-(4-Methoxyphenyl)-2-(1-((2-methoxyphenyl)amino)ethylidene)cyclohexane-1,3-dione (26h).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with **25h** (60 mg, 0.23 mmol) and *o*-anisidine (39 μL, 0. 35 mmol) in toluene. The residue was worked up and purified by flash chromatography (hexane/ethyl acetate) to yield 33 mg (39%) of **26h** as a white solid. Mp 140-142 ºC. EM (ES, positive mode): m/z 366 $(M+H)^+$.$^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 2.40 (s, 3H, $CH_3$), 2.55-2.61 (m, 2H, H-4, H-6), 2.77 (m, 2H, H-4, H-6), 3.29 (m, 1H, H-5), 3.73 (s, 3H, $OCH_3$), 3.83 (s, 3H, $OCH_3$), 6.89 (m, 2H, Ar), 7.04 (m, 1H, *J* = 7.6, 1.2 Hz, Ar), 7.19 (dd, 1H, *J* = 8.3, 1.2 Hz, Ar), 7.24 (m, 2H, Ar), 7.31 (dd, 1H, *J* = 7.8, 1.6 Hz, Ar), 7.38 (m, 1H, Ar), 14.79 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 19.7 ($CH_3$), 35.3 (C-5), 46.3 (C-4, C-6), 55.0 ($OCH_3$), 55.8 ($OCH_3$), 108.5 (NHC=*C*), 112.3, 113.9, 120.6, 124.5, 126.9, 127.7, 129.2, 135.5, 153.1, 157.9 (Ar), 172.4 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_4$): C, 72.31; H, 6.34; N, 3.83. Found: C, 72.38; H, 6.29; N, 4.01.

**5-(4-Chlorophenyl)-2-(1-((2-methoxyphenyl)amino)ethylidene)cyclohexane-1,3-dione (26i).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with **25i** (60 mg, 0.20 mmol) and *o*-anisidine (38 μL, 0.34 mmol) in toluene. The residue was worked up and purified by flash chromatography (hexane/ethyl acetate) to yield 70 mg (82%) of **26i** as a white solid. Mp 138-140 ºC. EM (ES, positive mode): m/z 370 $(M+H)^+$ with a Cl isotopic pattern. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ: 2.40 (s, 3H, $CH_3$), 2.57-2.63 (m, 2H, H-4, H-6), 2.81 (m, 2H, 2 H-4, H-6), 3.36 (m, 1H, H-5), 3.83 (s, 3H, $OCH_3$), 7.04 (m, 1H, *J* = 7.6, 1.3 Hz, Ar), 7.20 (dd, 1H, *J* = 8.3, 1.3 Hz, Ar), 7.32 (dd, 1H, *J* = 7.8, 1.5 Hz, Ar), 7.37 (m, 5H, Ar), 14.76 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 19.7 ($CH_3$), 35.5 (C-5), 45.6 (C-4, C-6), 55.8 ($OCH_3$), 108.4 (NHC=*C*), 112.3, 120.1, 124.5, 126.9, 128.4, 128.7, 129.2, 131.0, 142.5, 153.1 (Ar), 172.5 (NH*C*=C). Anal. calc. for ($C_{21}H_{20}ClNO_3$): C, 68.20; H, 5.45; N, 3.79. Found: C, 68.31; H, 5.64; N, 3.88.

**5-(4-Fluorophenyl)-2-(1-((2-methoxyphenyl)amino)ethylidene)cyclohexane-1,3-dione (26j).**

Following the general procedure for the reaction of 2-acyl-5-phenylcyclohexane-1,3-diones with anilines, a microwave vial was charged with **25j** (50 mg, 0.17 mmol) and *o*-anisidine (28 μL, 0.25 mmol) in toluene. The

residue was worked up and purified by flash chromatography (hexane/ethyl acetate) to yield 60 mg (99%) of **26j** as a white solid. Mp 126-128 ºC. EM (ES, positive mode): m/z 354 $(M+H)^+$.$^1$H NMR (DMSO-$d_6$, 500 MHz) δ: 2.40 (s, 3H, $CH_3$), 2.56-2.62 (m, 2H, H-4, H-6), 2.72-2.85 (m, 2H, H-4, H-6), 3.37 (m, 1H, H-5), 3.83 (s, 3H, $OCH_3$), 7.03 (m, 1H, *J* = 7.6, 1.3 Hz, Ar), 7.15 (m, 2H, Ar), 7.19 (dd, 1H, *J* = 8.5, 1.3 Hz, Ar), 7.31 (dd, 1H, *J* = 7.8, 1.6 Hz, Ar), 7.37 (m, 3H, Ar), 14.79 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 125 MHz) δ: 19.7 ($CH_3$), 35.4 (C-5), 45.6, 46.3 (C-4, C-6), 55.8 ($OCH_3$), 108.4 (NHC=*C*), 112.3, 115.2, 120.6, 124.5, 126.9, 128.6, 129.2, 139.7, 139.7, 153.1, 159.9, 161.8 (Ar), 172.5 (NH*C*=C). Anal. calc. for ($C_{21}H_{20}FNO_3$): C, 71.37; H, 5.70; N, 3.96. Found: C, 71.62; H, 5.84; N, 4.05.

**5-(3-Methoxyphenyl)-2-(1-(*o*-tolylamino)ethylidene)cyclohexane-1,3-dione (26k).**

A solution of **25k** (250 mg, 0.96 mmol) and *o*-tolylaniline (154 µL, 1.44 mmol) in toluene was placed in an Ace pressure tube. Then, 4 Å molecular sieves were added, the vessel was sealed and heated at 110 ºC overnight. After cooling, the solvent was evaporated to dryness. The crude reaction mixture was purified by flash chromatography (hexane/ethyl acetate) to yield 148 mg (42%) of **26k** as a white solid. Mp 105-107 ºC. EM (ES, positive mode): m/z 350 $(M+H)^+$.$^1$H NMR (DMSO-$d_6$, 300 MHz) δ: 2.20 (s, 3H, $CH_3$), 2. 37 (s, 3H, $CH_3$), 2.58-2.64 (m, 2H, H-4, H-6), 2.79-2.89 (m, 2H, H-4, H-6), 3.39 (m, 1H, H-5), 3.75 (s, 3H, $OCH_3$), 6.79-6.82 (m, 1H, Ar), 6.91 (m, 2H, Ar), 7.22-7.35 (m, 4H, Ar), 7.40 (m, 1H, Ar), 14.90 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 75 MHz) δ: 17.4 ($CH_3$), 19.6 ($CH_3$), 36.2 (C-5), 45.7 (C-4, C-6), 55.0 ($OCH_3$), 108.2 (NHC=*C*), 111.8, 112.687, 118.9, 126.5, 126.9, 128.1, 129.5, 131.0, 133.3, 135.1, 145.1, 159.4 (Ar), 172.6 (NH*C*=C). Anal. calc. for ($C_{22}H_{23}NO_3$): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.44; H, 6.51; N, 3.98.

**5-(3-Hydroxyphenyl)-2-(1-(*o*-tolylamino)ethylidene)cyclohexane-1,3-dione (26l).**

To a cooled solution of **26k** (150 mg, 0.43 mmol) in $CH_2Cl_2$, $BBr_3$ (800 µL, 0.78 mmol) was added and the mixture was stirred overnight at room temperature. The precipitate was filtered, washed with $CH_2Cl_2$ and purified by flash chromatography (hexane/ethyl acetate) to yield 34 mg (23%) of **26l** as a yellow oil. EM (ES, positive mode): m/z 336 $(M+H)^+$. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 2.20 (s, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$), 2.60 (m, 2H, H-4, H-6), 2.77 (m, 2H, H-4, H-6), 3.25 (m, 1H, H-5), 6.62 (ddd, 1H, *J* = 8.0, 2.4, 0.9 Hz, Ar), 6.70 (t, 1H, *J*= 1.9 Hz, Ar), 6.75 (m, 1H, Ar), 7.11 (t, 1H, *J* = 7.8 Hz, Ar), 7.26 (m, 1H, Ar), 7.32 (m, 2H, Ar), 7.40 (m, 1H, Ar), 9.35 (br s, 1H, OH), 14.91 (br s, 1H, NH).$^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 17.5 ($CH_3$), 19.7 ($CH_3$), 36.0 (C-5), 45.8 (C-4, C-6), 108.2 (NHC=*C*) 113.4, 113.6, 117.3, 126.6, 126.9, 128.1, 129.4,

131.0, 133.3, 135.2, 145.0, 157.4 (Ar), 172.6 (NH*C*=C). Anal. calc. for ($C_{21}H_{21}NO_3$): C, 75.20; H, 6.31; N, 4.18. Found: C, 74.98; H, 6.33; N, 4.05.

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**Table S1. SMILES strings from the VS hits tested.**

| Compound | SMILES string |
|---|---|
| Hit 1, compound **9** | O=C(CC(C1=CC=CC=C1)CC/2=O)C2=C(NC3=CC=CC=C3O)\CC |
| Hit 2 | O=C(C1=C(N2)C3=CC=CC=C3S1)N(CCN4CCOCC4)C2=S |
| Hit 3 | CC1=CC(N/C(C)=C2C(C(C=CC=C3)=C3C\2=O)=O)=NO1 |
| Hit 4 | O=C(NC1=CC=NC=C1)C(C(N2)=O)=C(O)C3=C2CCCC3 |
| Hit 5 | NC1=NC(NC2=CC=CC=C2)=C3C(CC(C4=CC=CC=C4)CC3=N1)=O |
| Hit 6 | OC1=C2C(N=CN2CC3=CC=CC=C3)=NC(N4CCOCC4)=N1 |

**Table S2. Anti-proliferative activity of the VS hits in endothelial and tumor cell lines.**

| | Endothelial cells $IC_{50}$ (μM) | Tumor cells $IC_{50}$ (μM) |
|---|---|---|
| **Compound** | **MEBC** | **L1210** |
| Hit 1, compound **9** | 13 ± 5 | 13 ± 1 |
| Hit 2 | ≥ 100 | |
| Hit 3 | > 100 | |
| Hit 4 | ≥ 100 | > 250 |
| Hit 5 | 57 ± 14 | |
| Hit 6 | ≥ 100 | > 250 |

**Sandra, may you complete the table?**

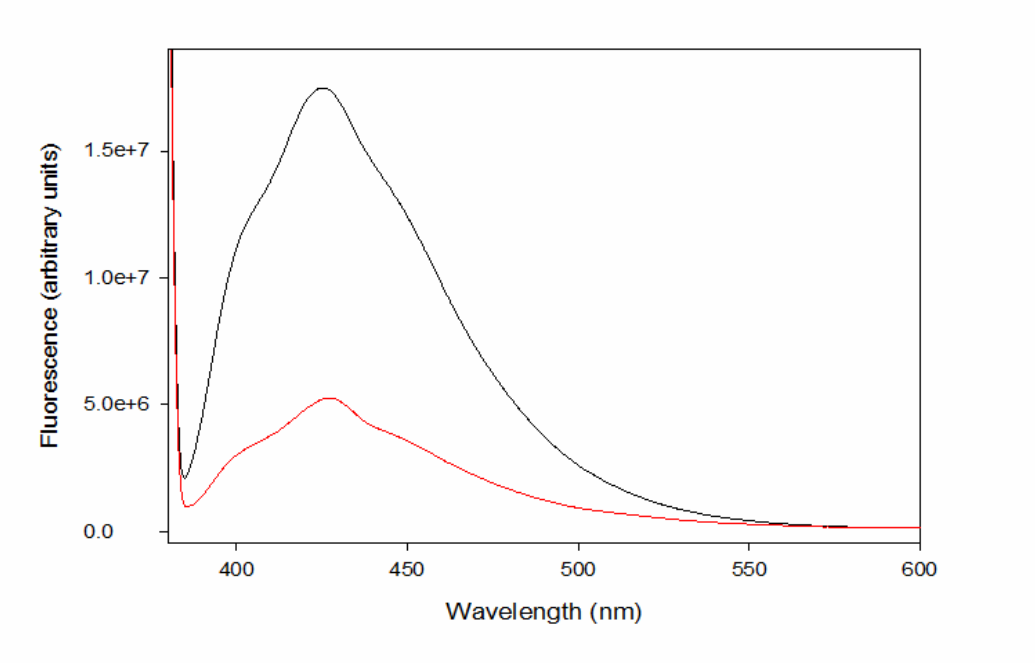


**Figure S1.** Displacement of MTC by hit **9**. Fluorescence emission spectra (excitation 374 nm) of MTC (10 μM) in the presence of 10 μM tubulin and in the absence (black line) or presence (red line) of **9** (20 μM).

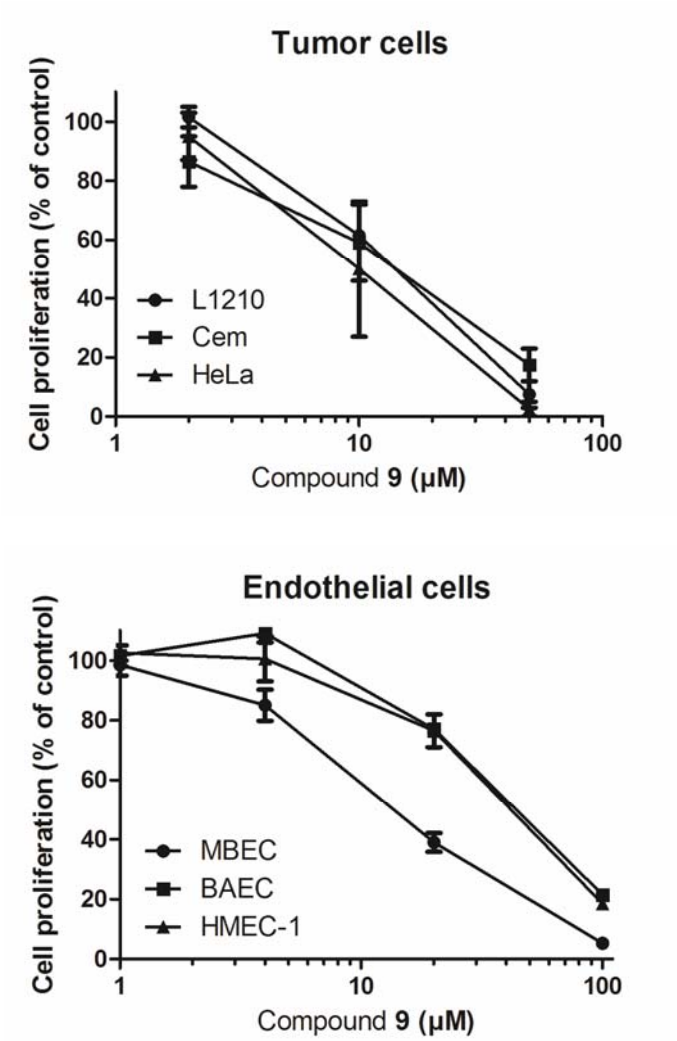


**Figure S2.** Dose-response curves of compound **9** in endothelial and tumor cells.

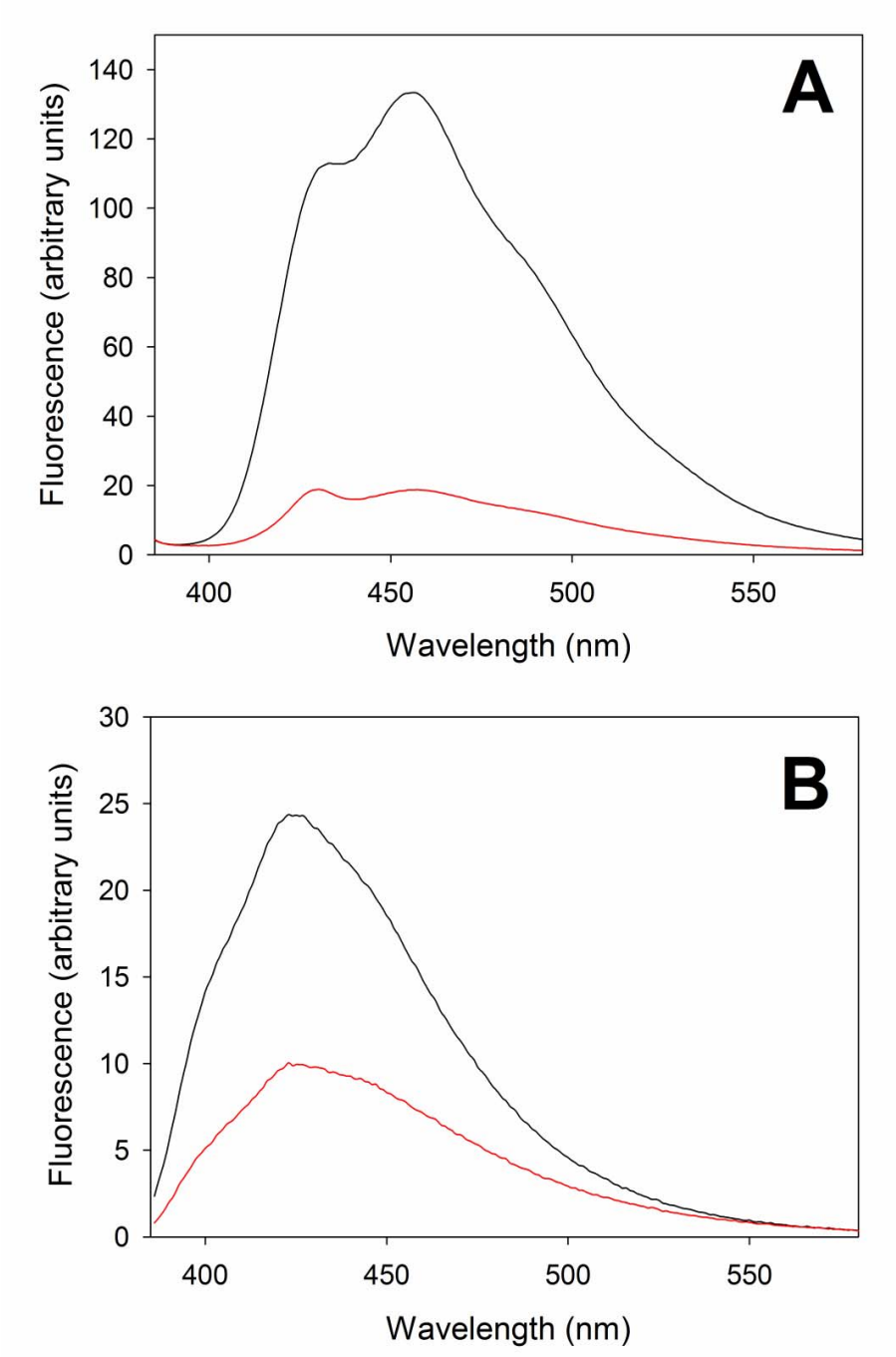


**Figure S3.** Displacement of R-PT (A) and MTC (B) by **16c**. (A) Fluorescence emission spectra (excitation 374 nm) of 0.2 μM R-PT in the presence of 0.2 μM tubulin and in the absence (black line) or presence of 20 μM **16c**. (B) Fluorescence emission spectra (excitation 374 nm) of 10 μM MTC in the presence of 10 μM tubulin and in the absence (black line) or presence of 20 μM **16c**.