Supporting Information

Synthesis and characterization of a bidirectional photoswitchable antagonist toolbox for real-time GPCR photopharmacology

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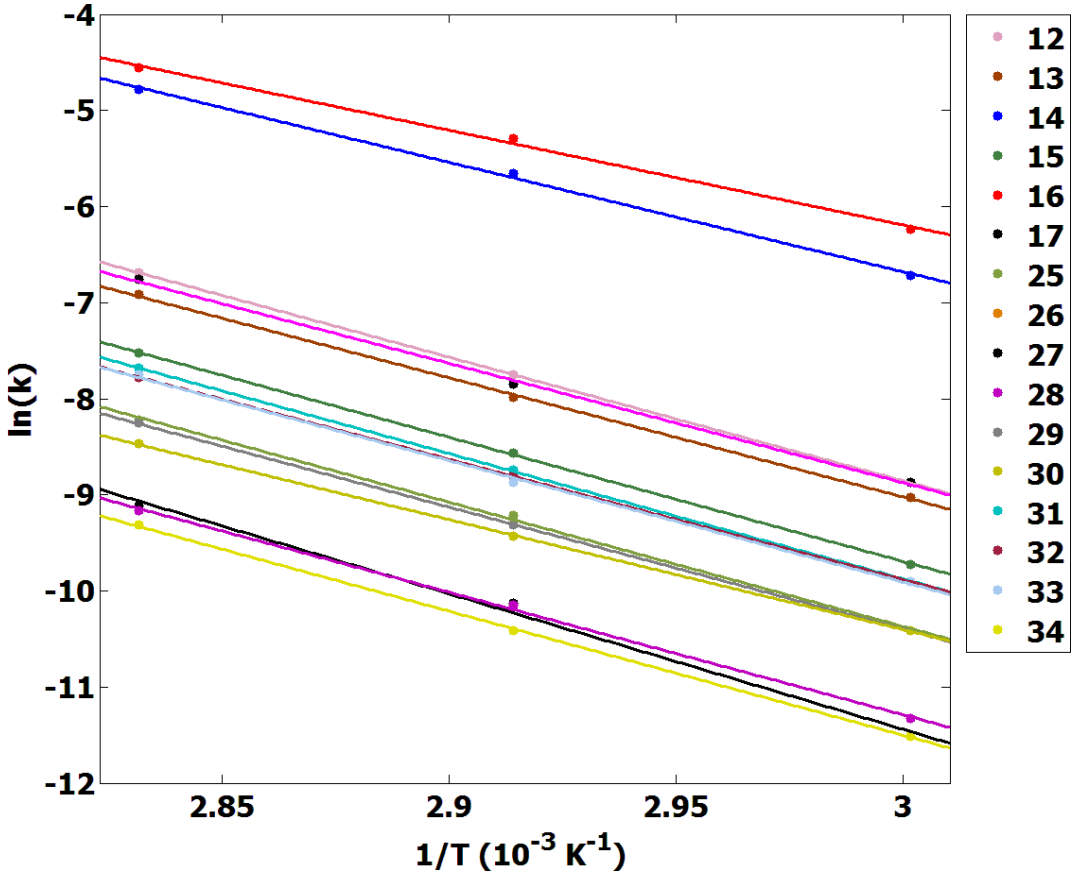


Figure S1: Arrhenius plots for all compounds measured at a compound concentration of 25 µM in 50 mM Tris-HCl pH 7.4 buffer + 1% DMSO-d_6. Values in Table 1 are extrapolations of the linear fits presented in this plot. R^2 values for all fits were over 0.99.

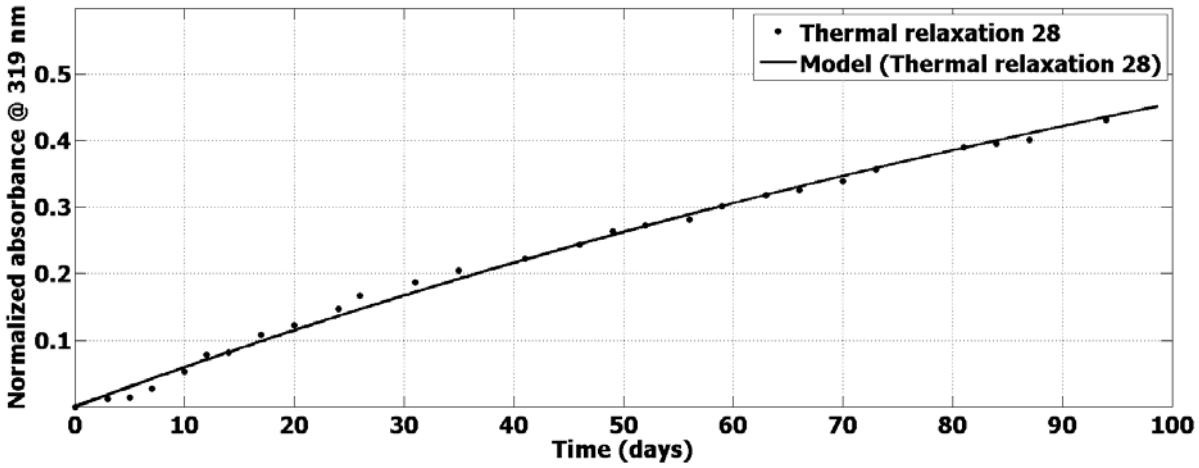


Figure S2: Thermal relaxation curve of 25 μM of compound 28 in 50 mM Tris-HCl pH 7.4 buffer containing 1% DMSO-d_6 at 20 ± 3 °C normalized using the >99% *trans* samples as reference. The sample was illuminated for 10 minutes at 360 ± 20 nm prior to thermal relaxation. The relaxation was followed by recording absorbance at 319 nm. An exponential fit was used to obtain the thermal relaxation half-life (t½ = 114 days). R^2 = 0.9956.

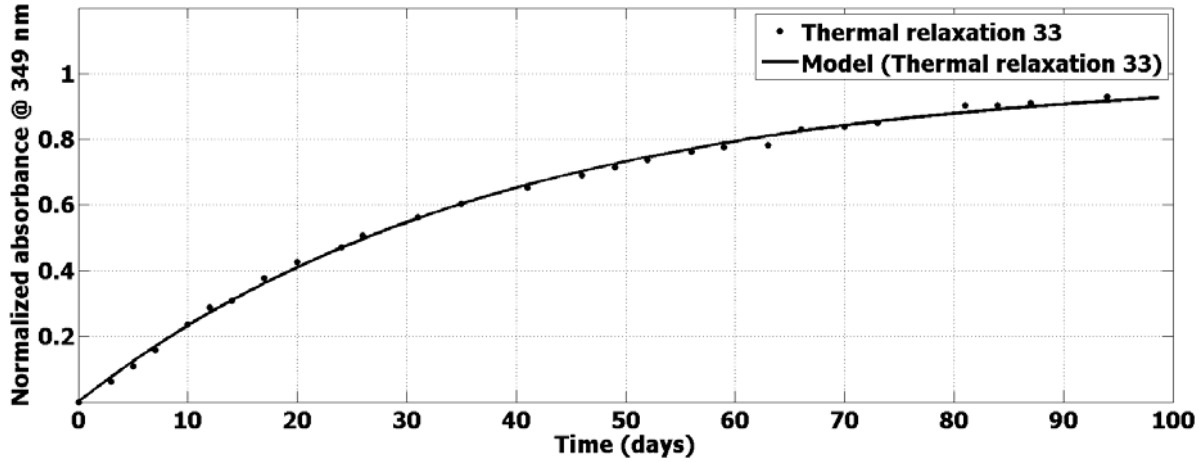


Figure S3: Thermal relaxation curve of 25 μM of compound 33 in 50 mM Tris-HCl pH 7.4 buffer containing 1% DMSO-d_6 at 20 ± 3 °C normalized using the >99% *trans* samples as reference. The sample was illuminated for 10 minutes at 360 ± 20 nm prior to thermal relaxation. The relaxation was followed by recording absorbance at 349 nm. An exponential fit was used to obtain the thermal relaxation half-life (t½ = 26.3 days). R^2 = 0.9982.

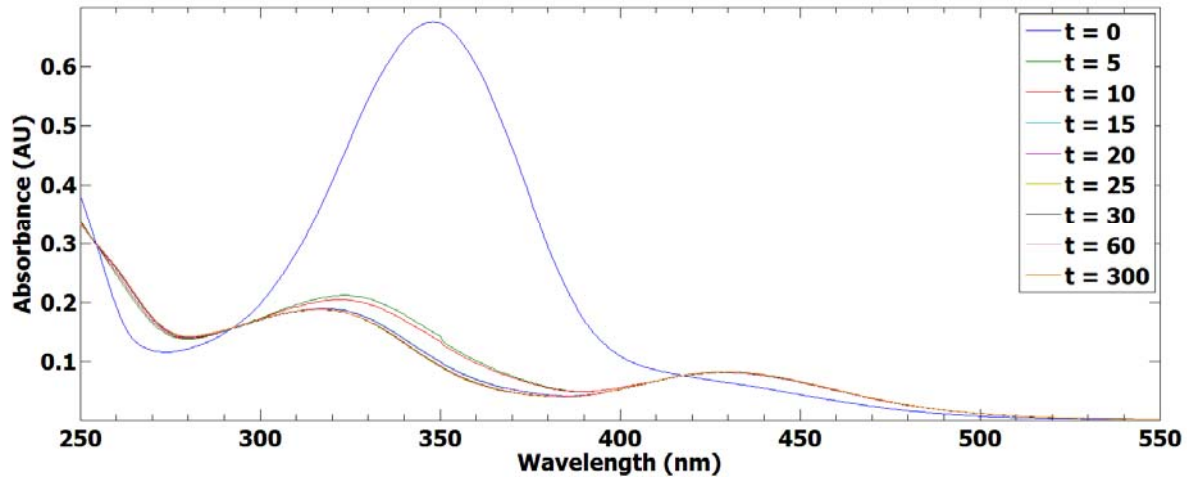


Figure S4: Illumination of 25 µM of compound 33 (*trans*) in 50 mM Tris-HCl pH 7.4 buffer containing 1% DMSO-d_6 using 360 ± 20 nm. Value t is in seconds.

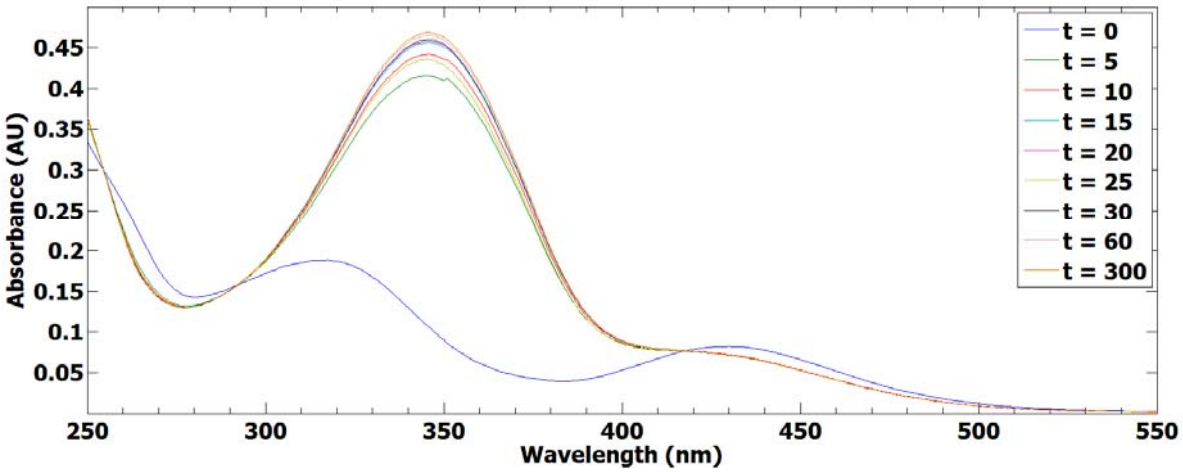


Figure S5: Illumination of 25 µM of compound 33 (PSS *cis,* obtained as shown in Figure S4) in 50 mM Tris-HCl pH 7.4 buffer containing 1% DMSO-d_6 using 434 ± 9 nm. Value t is in seconds.

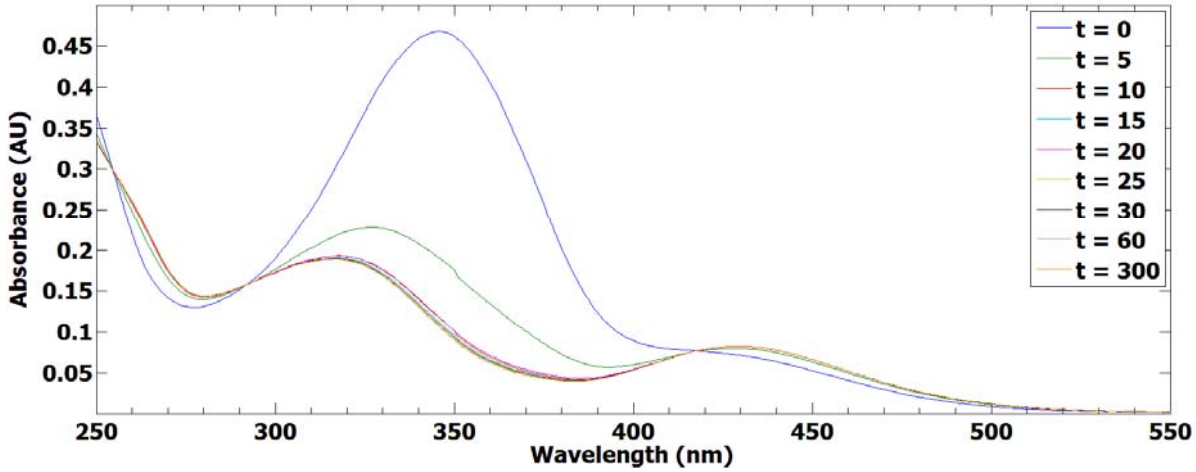


Figure S6: Illumination of 25 µM of compound 33 (PSS *trans*, obtained as shown in Figure S5) in 50 mM Tris-HCl pH 7.4 buffer containing 1% DMSO-d_6 using 360 ± 20 nm. Value t is in seconds.

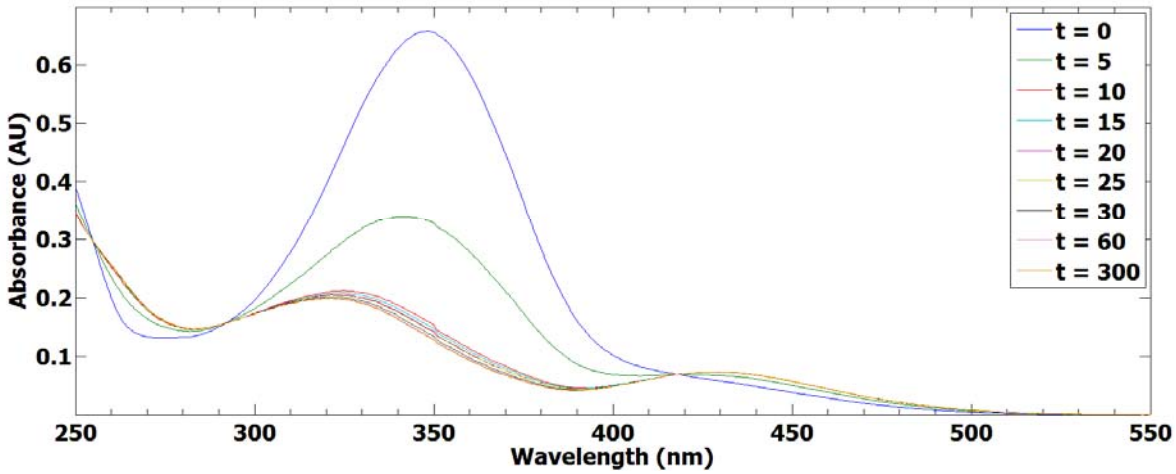


Figure S7: Illumination of 25 µM of compound 33 (*trans*) in a pH 7.4 buffer containing 15 mM HEPES, 64 mM NaCl, 25 mM KCl, 0.4 mM $CaCl_2$ and 0.8 mM $MgCl_2$ containing 1% DMSO-d_6 using 360 ± 20 nm. Value t is in seconds.

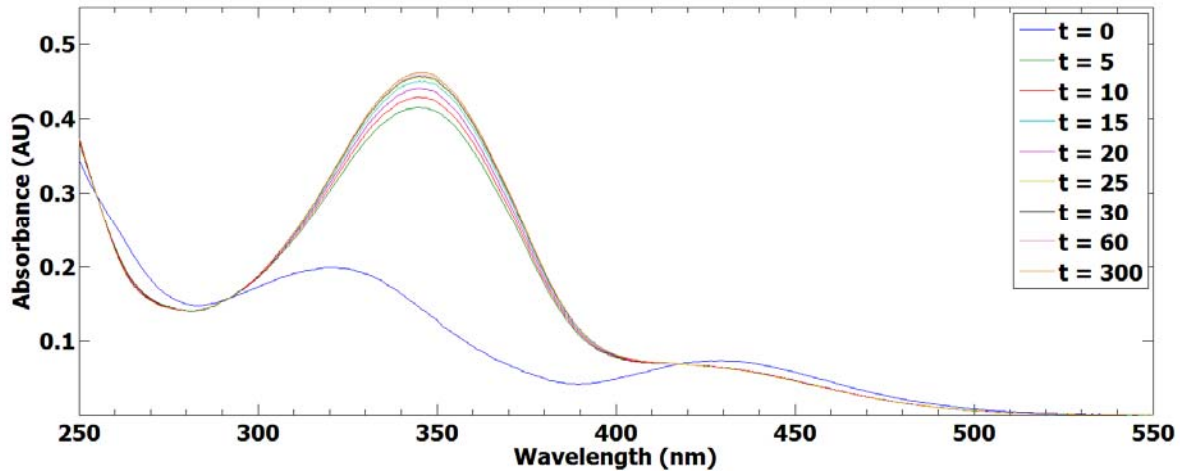


Figure S8: Illumination of 25 µM of compound 33 (PSS *cis,* obtained as shown in Figure S7) in a pH 7.4 buffer containing 15 mM HEPES, 64 mM NaCl, 25 mM KCl, 0.4 mM $CaCl_2$ and 0.8 mM $MgCl_2$ containing 1% DMSO-d_6 using 434 ± 9 nm. Value t is in seconds.

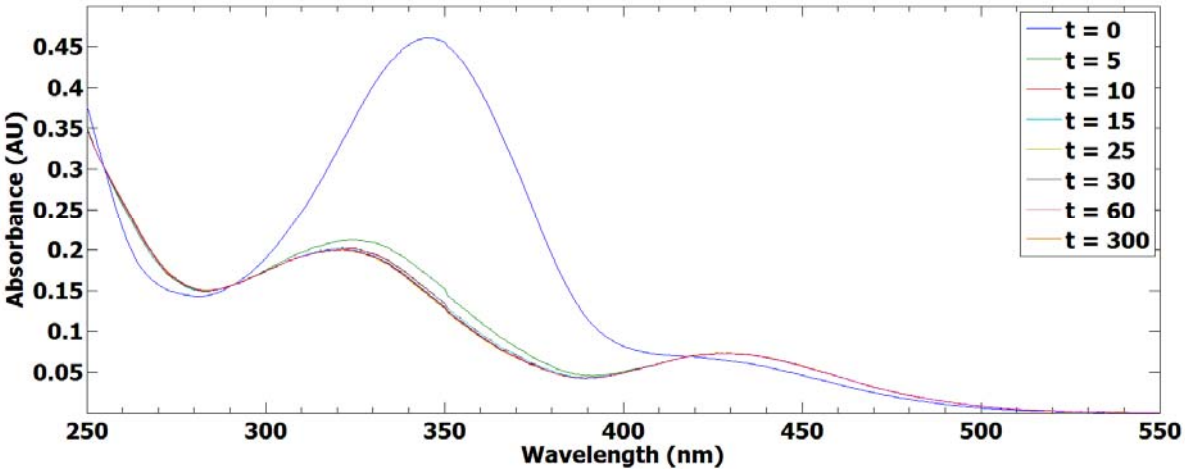


Figure S9: Illumination of 25 µM of compound 33 (PSS *trans,* obtained as shown in Figure S8) in a pH 7.4 buffer containing 15 mM HEPES, 64 mM NaCl, 25 mM KCl, 0.4 mM $CaCl_2$ and 0.8 mM $MgCl_2$ containing 1% DMSO-d_6 using 360 ± 20 nm. Value t is in seconds.

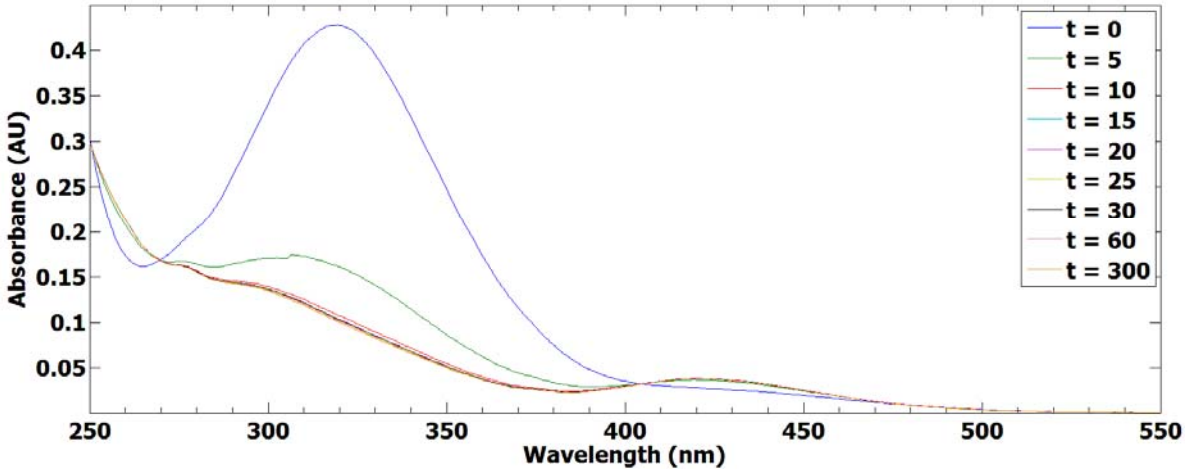


Figure S10: Illumination of 25 µM of compound 28 (*trans*) in 50 mM Tris-HCl pH 7.4 buffer containing 1% DMSO-d_6 using 360 ± 20 nm. Value t is in seconds.

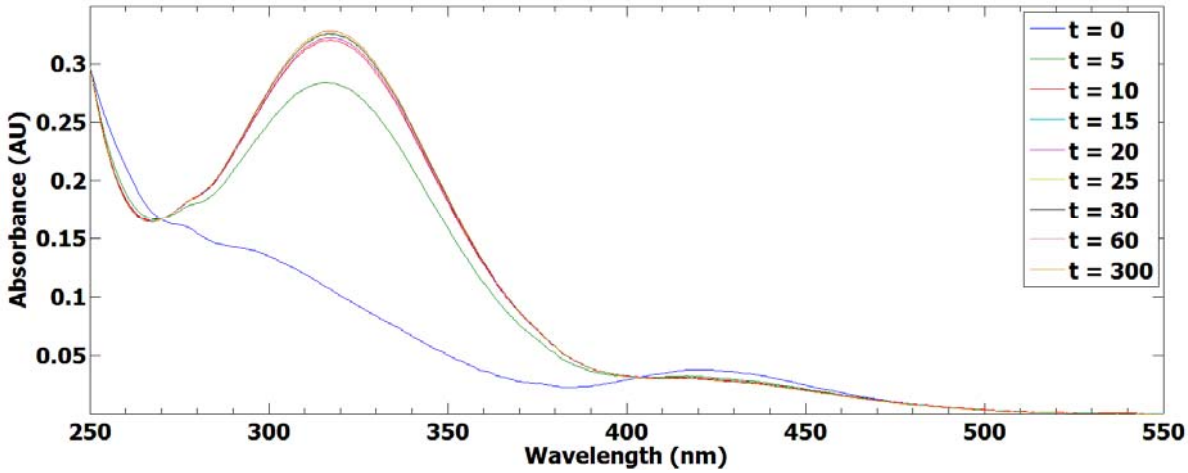


Figure S11: Illumination of 25 µM of compound 28 (PSS *cis,* obtained as shown in Figure S10) in 50 mM Tris-HCl pH 7.4 buffer containing 1% DMSO-d_6 using 434 ± 9 nm. Value t is in seconds.

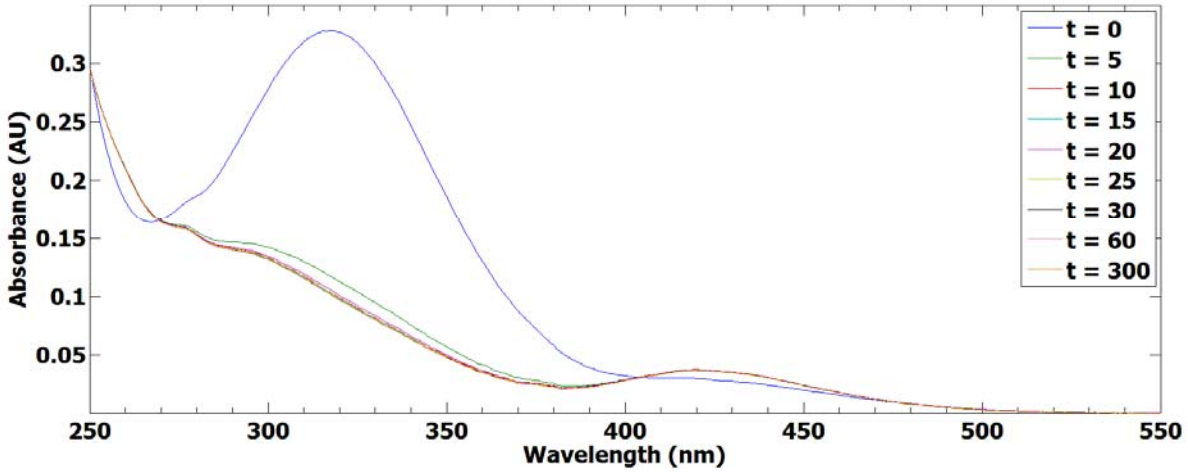


Figure S12: Illumination of 25 μM of compound 28 (PSS *trans,* obtained as shown in Figure S11) in 50 mM Tris-HCl pH 7.4 buffer containing 1% DMSO-d_6 using 360 ± 20 nm. Value t is in seconds.

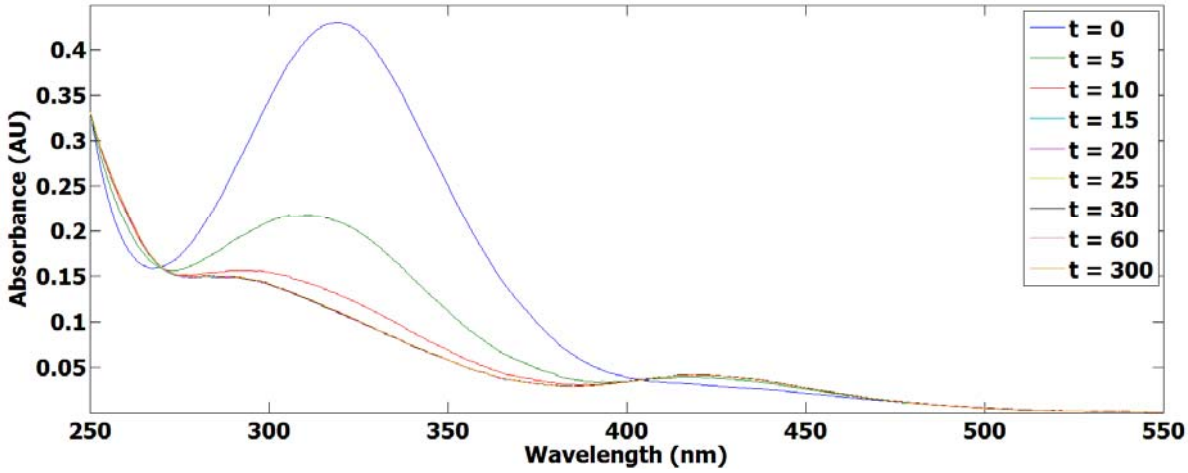


Figure S13: Illumination of 25 μM of compound 28 (*trans*) in a pH 7.4 buffer containing 15 mM HEPES, 64 mM NaCl, 25 mM KCl, 0.4 mM $CaCl_2$ and 0.8 mM $MgCl_2$ containing 1% DMSO-d_6 using 360 ± 20 nm. Value t is in seconds.

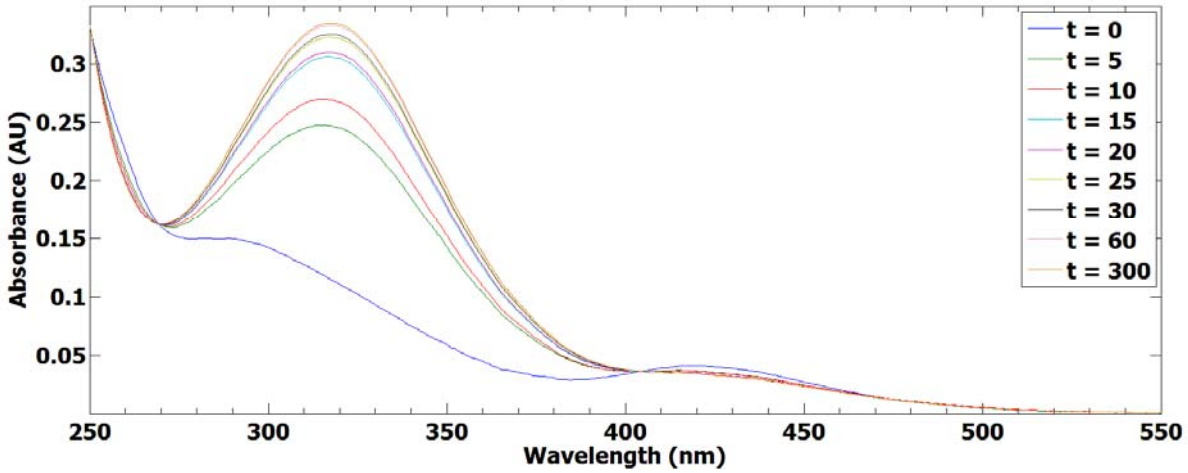


Figure S14: Illumination of 25 µM of compound 28 (PSS *cis,* obtained as shown in Figure S13) in a pH 7.4 buffer containing 15 mM HEPES, 64 mM NaCl, 25 mM KCl, 0.4 mM $CaCl_2$ and 0.8 mM $MgCl_2$ containing 1% DMSO-d_6 using 434 ± 9 nm. Value t is in seconds.

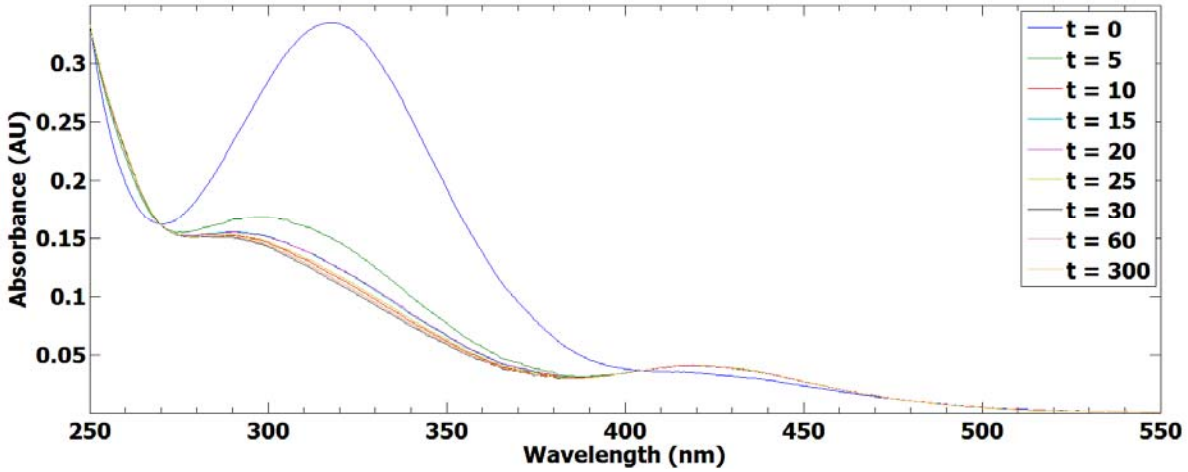


Figure S15: Illumination of 25 µM of compound 28 (PSS *trans,* obtained as shown in Figure S14) in a pH 7.4 buffer containing 15 mM HEPES, 64 mM NaCl, 25 mM KCl, 0.4 mM $CaCl_2$ and 0.8 mM $MgCl_2$ containing 1% DMSO-d_6 using 360 ± 20 nm. Value t is in seconds.

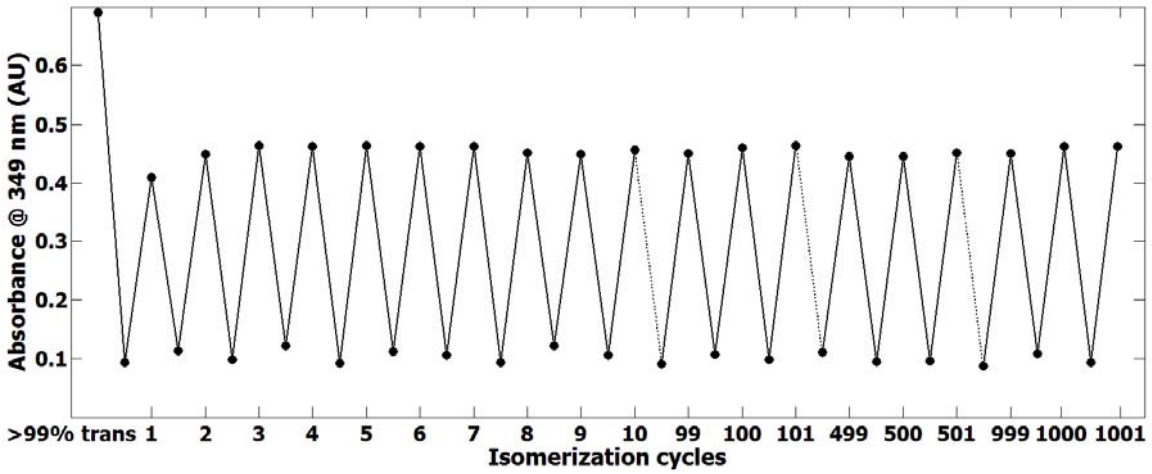


Figure S16: Repeated isomerization cycles of 25 μM of compound 33 in a pH 7.4 buffer containing 15 mM HEPES, 64 mM NaCl, 25 mM KCl, 0.4 mM $CaCl_2$, 0.8 mM $MgCl_2$ and 1% DMSO-d_6 analyzed at 349 nm. PSS *cis* was obtained by using illuminations for 20 seconds at 360 ± 20 nm. PSS *trans* was obtained by using illuminations for 20 seconds at 434 ± 9 nm. The dotted lines indicate larger numbers of cycles which are not presented here.

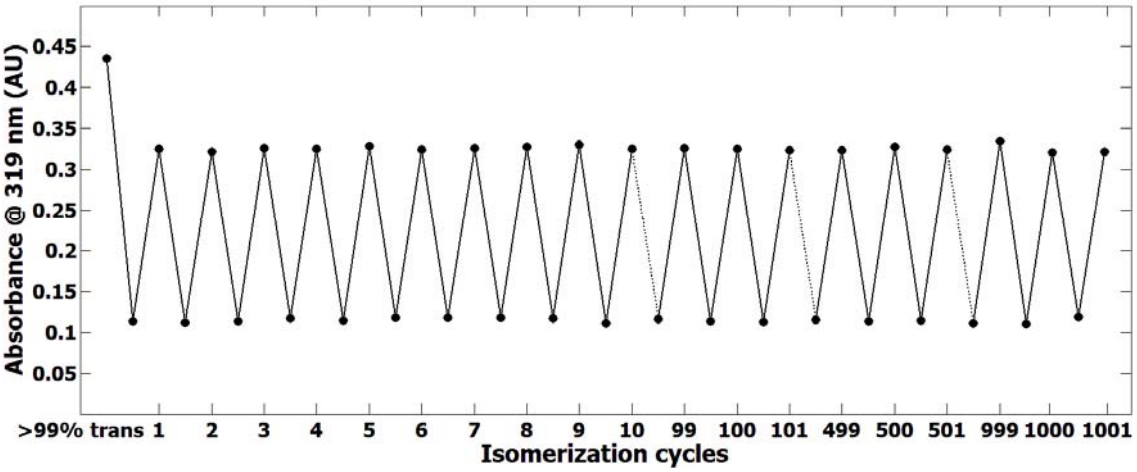


Figure S17: Repeated isomerization cycles of 25 μM of compound 28 in a pH 7.4 buffer containing 15 mM HEPES, 64 mM NaCl, 25 mM KCl, 0.4 mM $CaCl_2$, 0.8 mM $MgCl_2$ and 1% DMSO-d_6 analyzed at 319 nm. PSS *cis* was obtained by using illuminations for 20 seconds at 360 ± 20 nm. PSS *trans* was obtained by using illuminations for 20 seconds at 434 ± 9 nm. The dotted lines indicate larger numbers of cycles which are not presented here.

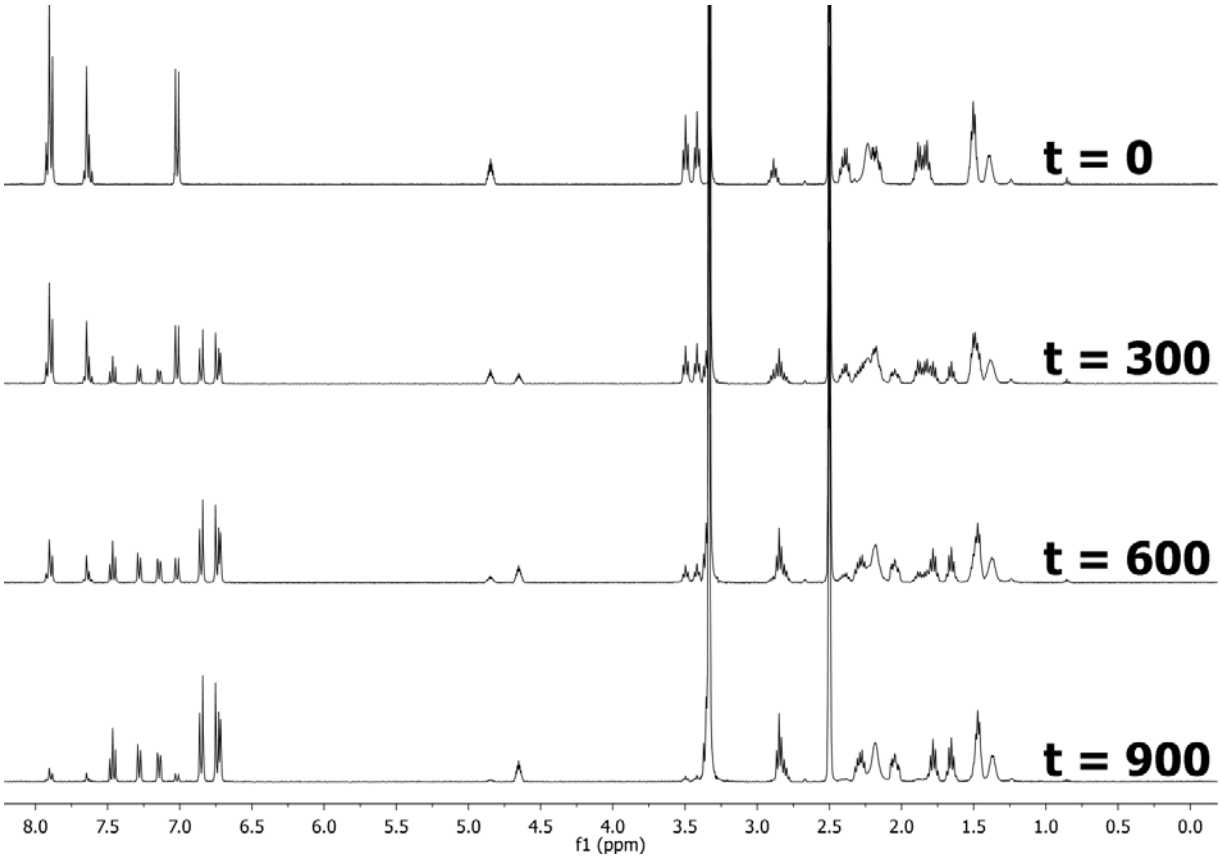
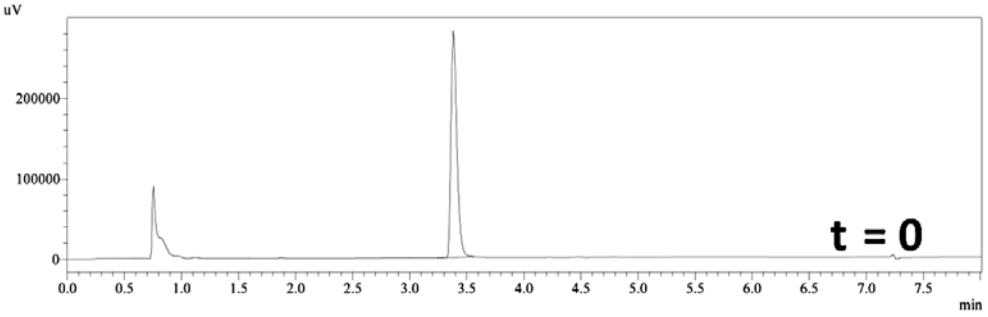
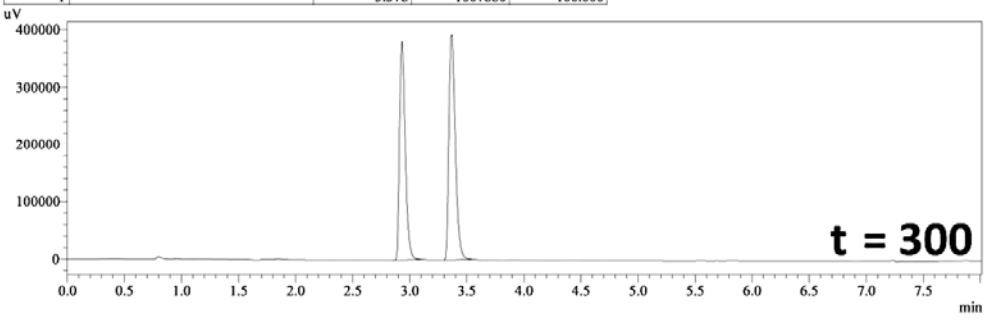


Figure S18: ^{1}H-NMR spectra of an illumination with 360 ± 20 nm of 10 mM of compound 33 in DMSO-d_6. Value t is illumination time in seconds.



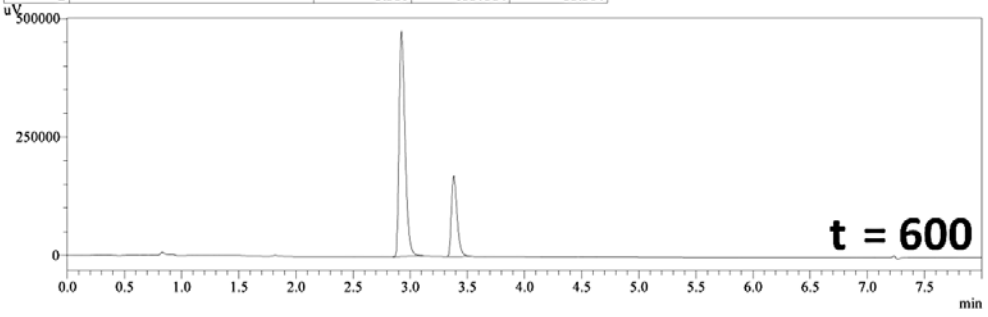
PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.378	1007880	100.000



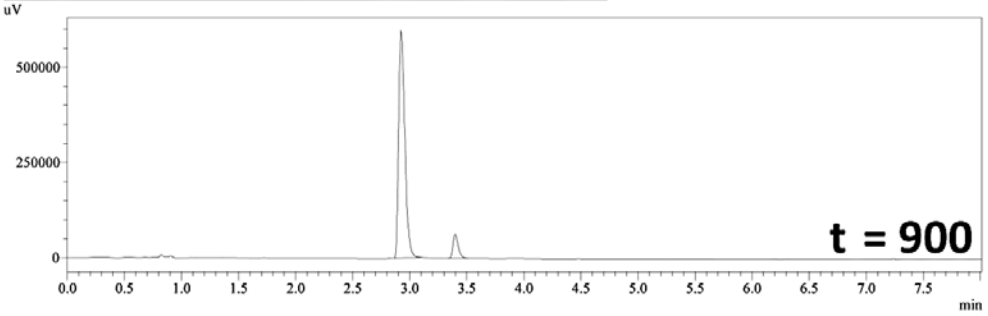
PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		2.926	1336189	46.496
2		3.361	1537564	53.504



PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		2.920	1726634	74.916
2		3.377	578140	25.084



PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		2.920	2252756	91.773
2		3.393	201943	8.227

Figure S19: LC chromatograms corresponding to the experiment and ^{1}H-NMR spectra shown in Figure S18. Value t is illumination time in seconds.

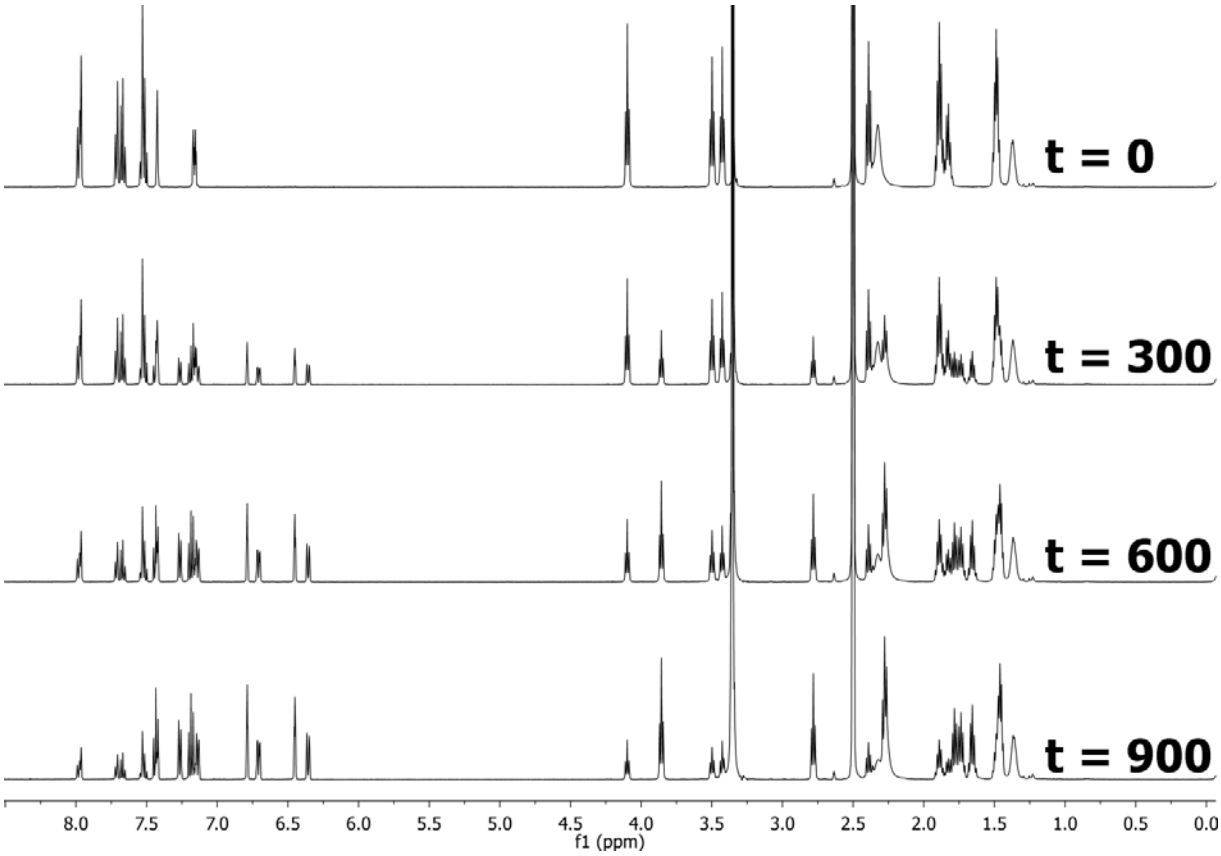
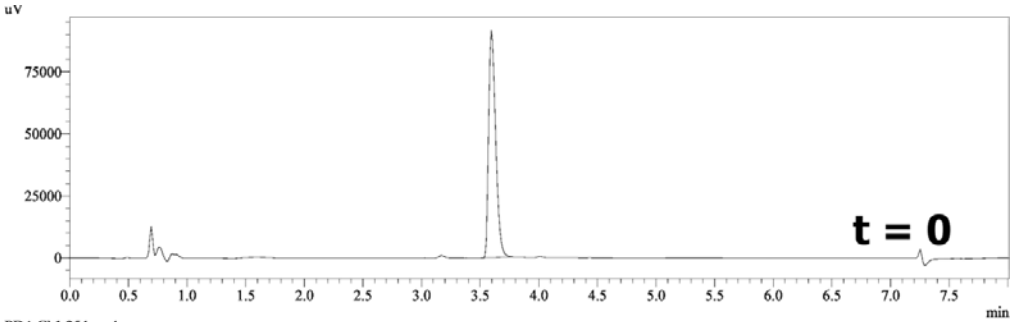
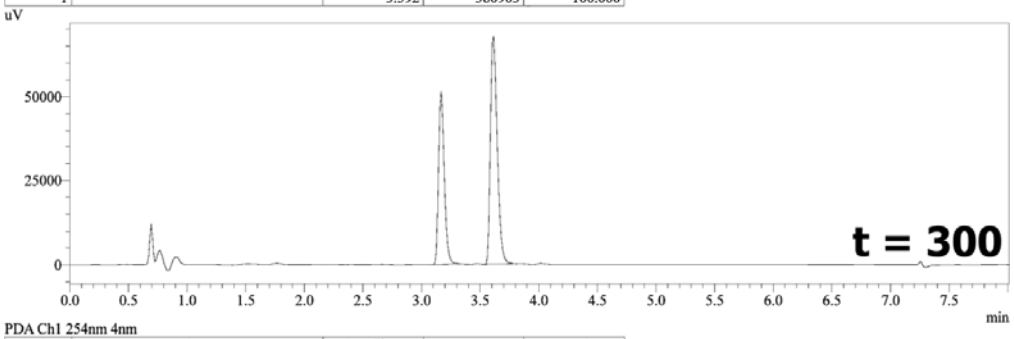


Figure S20: ^{1}H-NMR spectra of an illumination with 360 ± 20 nm of 10 mM of compound 28 in DMSO-d_6. Value t is illumination time in seconds.



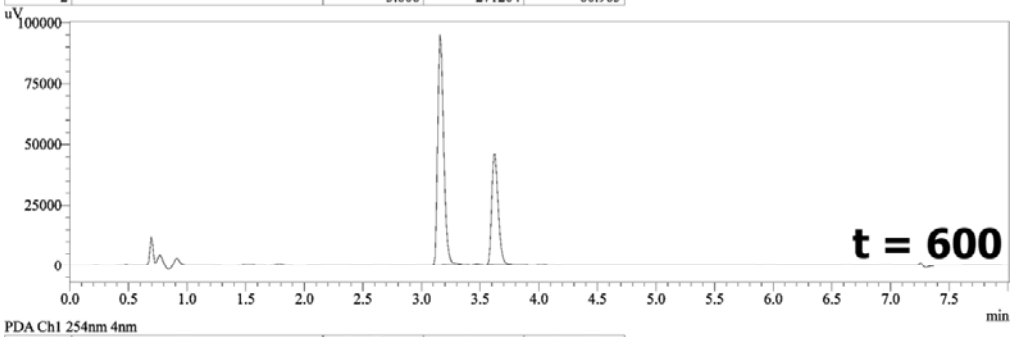
PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.592	380903	100.000



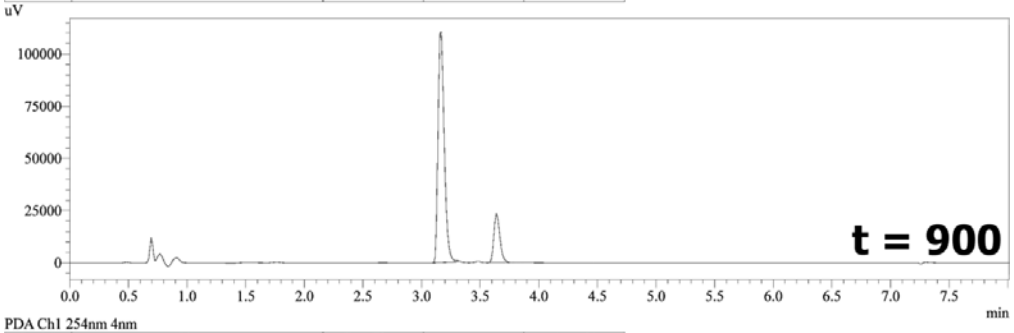
PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.161	173644	39.035
2		3.606	271204	60.965



PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.155	336409	65.925
2		3.616	173885	34.075



PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.158	405411	83.074
2		3.634	82602	16.926

Figure S21: LC chromatograms corresponding to the experiment and ^{1}H-NMR spectra shown in Figure S20. Value t is illumination time in seconds.

Table S1: Correlation between ^{1}H-NMR and LC-MS area percentages of 10 mM compound in DMSO-d_6 under illumination with 360 ± 20 nm for the indicated duration. Aliquots were diluted 100 times in Tris-HCl pH 7.4 buffer prior to LC-MS analysis. The photostationary states of the compounds were not reached at any of the chosen time points.

Compound 33

time (s)	^{1}H-NMR		LC-MS	
	% trans	*% cis*	*% trans*	*% cis*
0	>95	<5	>99	<1
300	58.53	41.47	53.50	46.50
600	26.81	73.19	25.08	74.92
900	7.00	93.00	8.23	91.77

Compound 28

time (s)	^{1}H-NMR		LC-MS	
	% trans	*% cis*	*% trans*	*% cis*
0	>95	<5	>99	<1
300	66.74	33.26	60.96	39.04
600	38.88	61.12	34.07	65.93
900	24.56	75.44	16.93	83.07

Table S2: Overview of binding affinities of 33 and 28 on the hH_1R, hH_2R, hH_3R and hH_4R transiently expressed on HEK293T cells. Competition binding experiments were performed at least in triplicates. N/A=not applicable.

Compound 33

Receptor	pK_i (>99% *trans*) ± SEM	pK_i (PSS *cis*) ± SEM	pK_i-shift
hH_1R	6.65 ± 0.13	5.61 ± 0.07	-1.05
hH_2R	< 5	< 5	N/A
hH_3R	8.76 ± 0.09	7.71 ± 0.09	-1.05
hH_4R	< 5	< 5	N/A

Compound 28

Receptor	pK_i (>99% *trans*) ± SEM	pK_i (PSS *cis*) ± SEM	pK_i-shift
hH_1R	< 5	6.23 ± 0.01	> 1.3
hH_2R	< 5	< 5	N/A
hH_3R	6.19 ± 0.11	7.32 ± 0.04	1.13
hH_4R	< 5	< 5	N/A

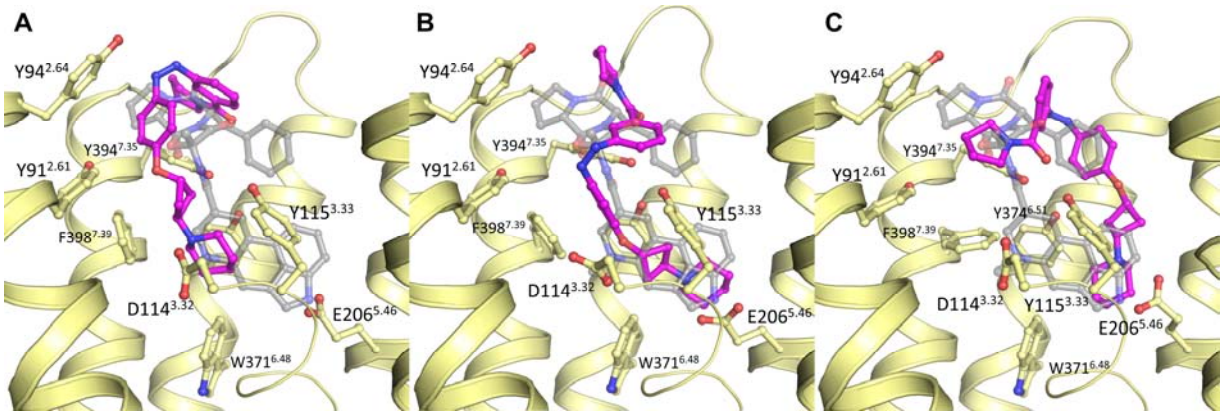


Figure S22: Overview of the three distinct binding modes obtained for compounds 28 and 33 using docking into a series of H_3R homology models (before performing MD simulations). A) Binding mode 1: D114$^{3.32}$ serves as the ionic anchor and the ligand moves via TMs 2, 3, and 7 towards the extracellular vestibule (ECV). B) Binding mode 2: E206$^{5.46}$ serves as the ionic anchor and the ligand moves from TM5 to TM3 and upward via TMs 2, 3, and 7 towards the ECV. C) Binding mode 3: E206$^{5.46}$ serves as the ionic anchor and the ligands moves upwards via TMs 5 and 6 towards the ECV. The *cis* isomer of 33 is shown with magenta carbon atoms and the binding mode of ergotamine in 5-HT_{1B} (PDB ID 4IAR) is shown with transparent gray carbon atoms. For clarity purposes the binding modes of 28 and the *trans* isomer of 33, parts of the ribbon/cartoon for ECL1/TM3 and ECL2, and the label for Y374$^{6.51}$ (in panel A and B) are not shown.

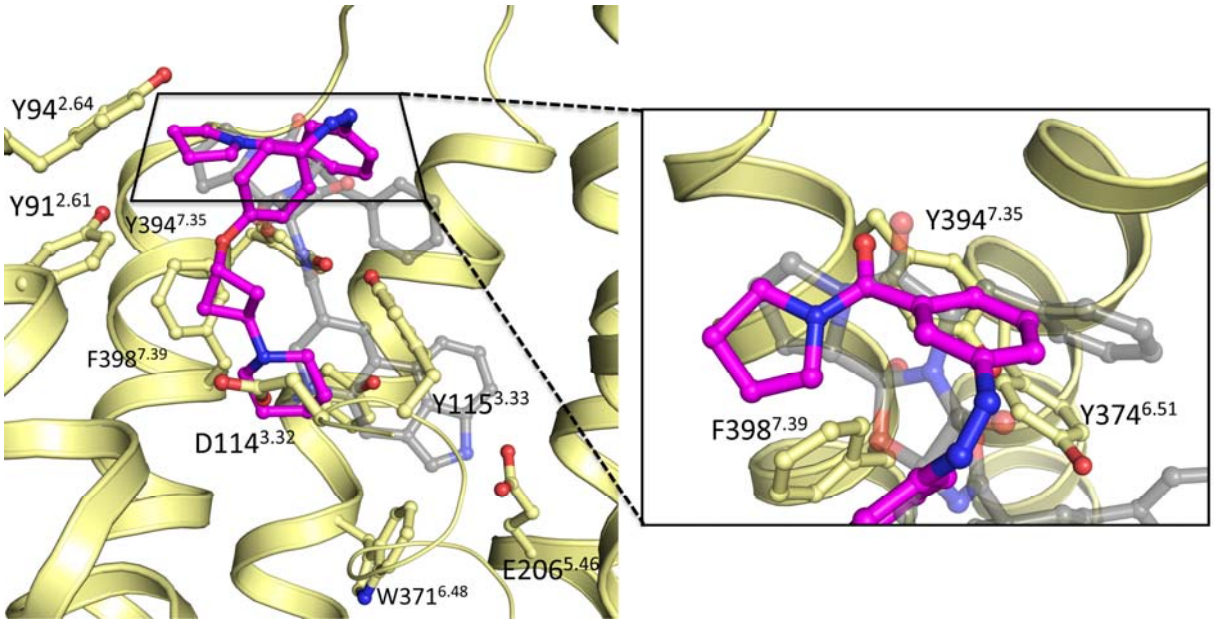


Figure S23: The similarity between the proposed binding mode for the *cis*-isomer of compound 33 after MD simulation and the binding mode of ergotamine in 5-HT_{1B} (PDB ID 4IAR). The inset highlights the overlay of the carboxamide moiety of 33 with the pyrrolidine of ergotamine.

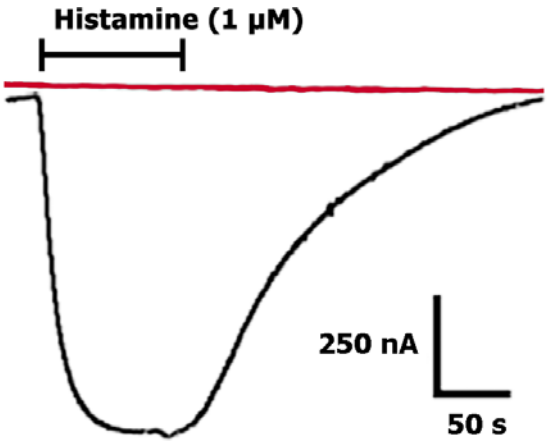


Figure S24: TEVC time trace of 1 µM histamine on H_3R-GIRK expressing *Xenopus* oocytes (black) or non-injected *Xenopus* oocytes (red) in a continuous perfusion system.

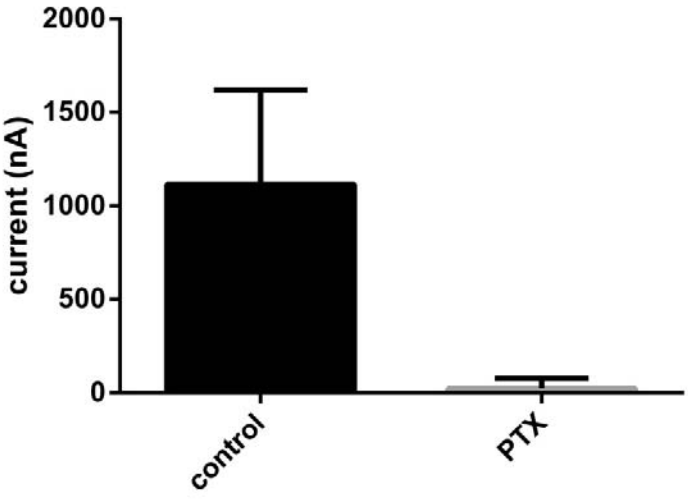


Figure S25: Response at 1 µM histamine (control) and 1 µM histamine after injection of 1.37 ng of pertussis toxin (PTX) on GIRK–H_3R expressing *Xenopus* oocytes.

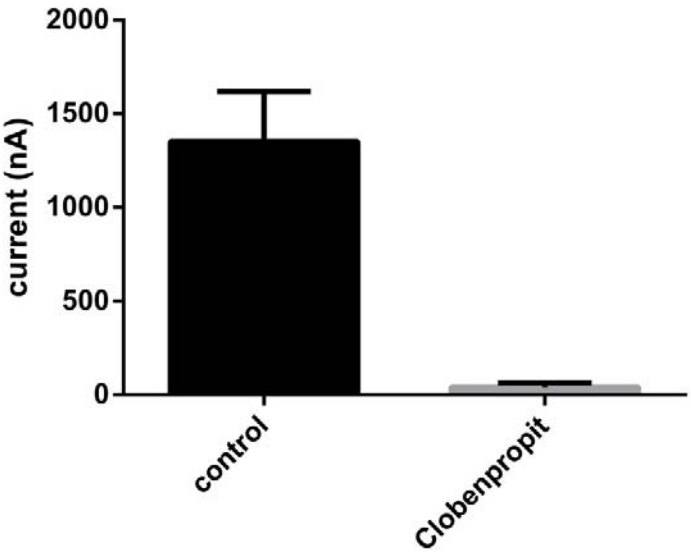


Figure S26: Response at 1 µM histamine (control) and 1 µM histamine in competition with 1 µM clobenpropit on GIRK–H_3R expressing *Xenopus* oocytes.

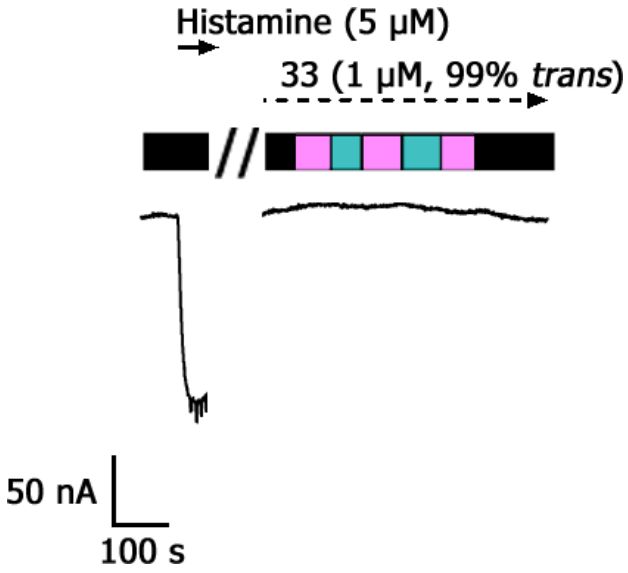


Figure S27: TEVC time trace of 5 µM histamine and 1 µM of 33 on H_3R-GIRK expressing *Xenopus* oocytes in a continuous perfusion system using illuminations at 360 ± 20 nm (magenta), 434 ± 9 nm (cyan) or without illumination (black).

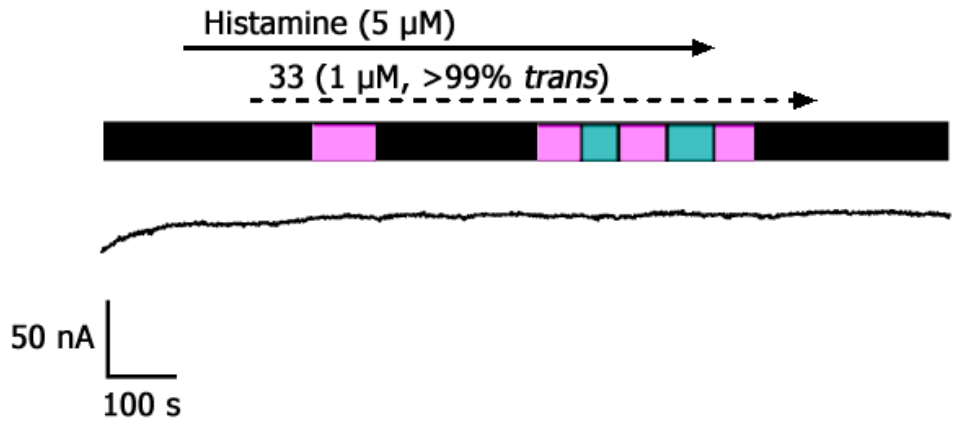


Figure S28: TEVC time trace of 5 µM histamine and 1 µM of 33 on non-injected *Xenopus* oocytes in a continuous perfusion system using illuminations at 360 ± 20 nm (magenta), 434 ± 9 nm (cyan) or without illumination (black).

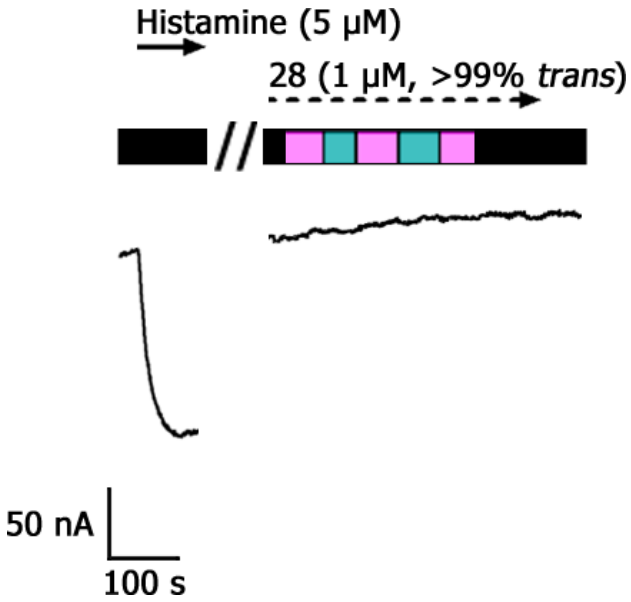


Figure S29: TEVC time trace of 5 µM histamine and 1 µM of 28 on H_3R-GIRK expressing *Xenopus* oocytes in a continuous perfusion system using illuminations at 360 ± 20 nm (magenta), 434 ± 9 nm (cyan) or without illumination (black).

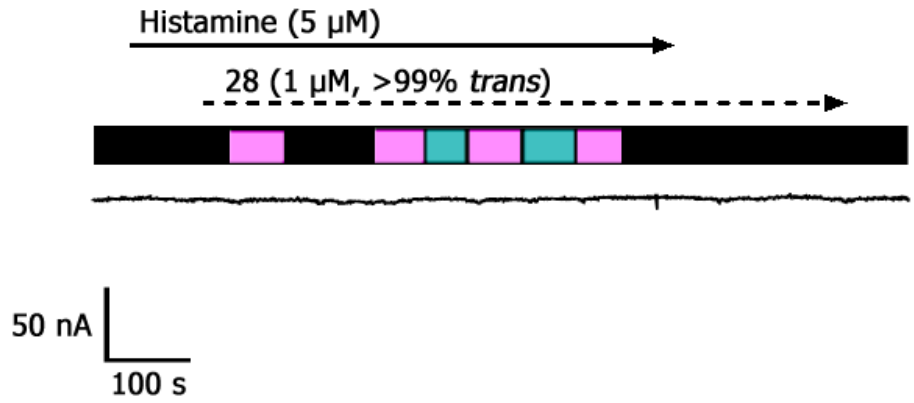


Figure S30: TEVC time trace of 5 µM histamine and 1 µM of 28 on non-injected *Xenopus* oocytes in a continuous perfusion system using illuminations at 360 ± 20 nm (magenta), 434 ± 9 nm (cyan) or without illumination (black).

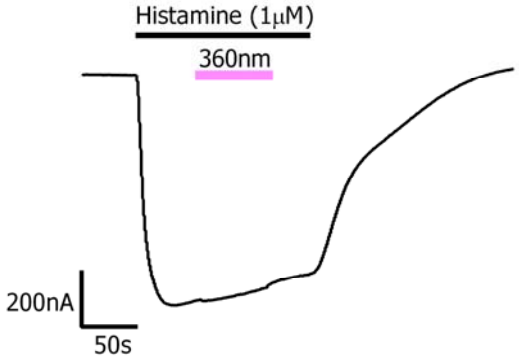


Figure S31: TEVC time trace of 1 µM histamine on GIRK–H_3R expressing *Xenopus* oocytes using illumination at 360 ± 20 nm (magenta).

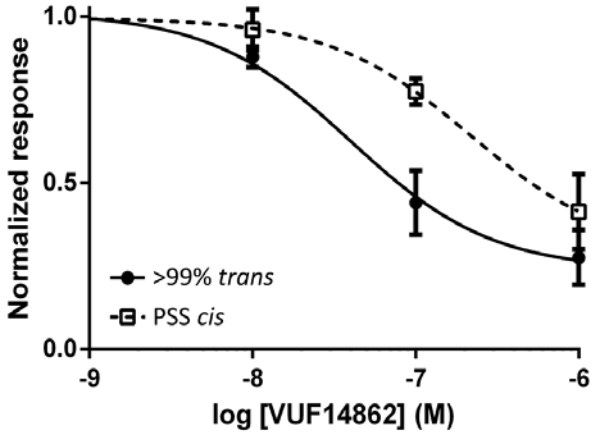


Figure S32: Concentration-response relationship for activation of GIRK current of 1 µM histamine in competition with 33 (VUF14862) on *Xenopus* oocytes expressing H_3R coupled to GIRK measured using TEVC.

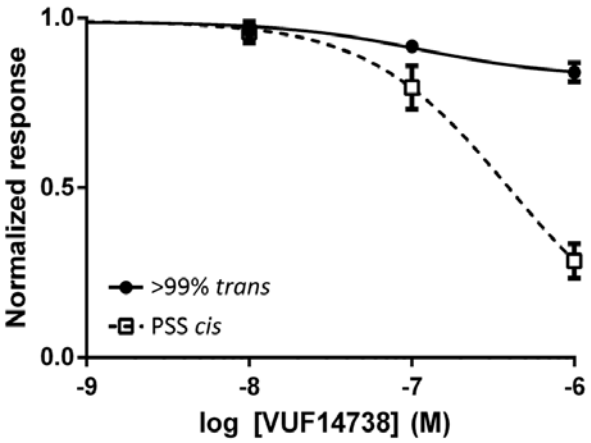


Figure S33: Concentration-response relationship for activation of GIRK current of 1 µM histamine in competition with 28 (VUF14738) on *Xenopus* oocytes expressing H_3R coupled to GIRK measured using TEVC.

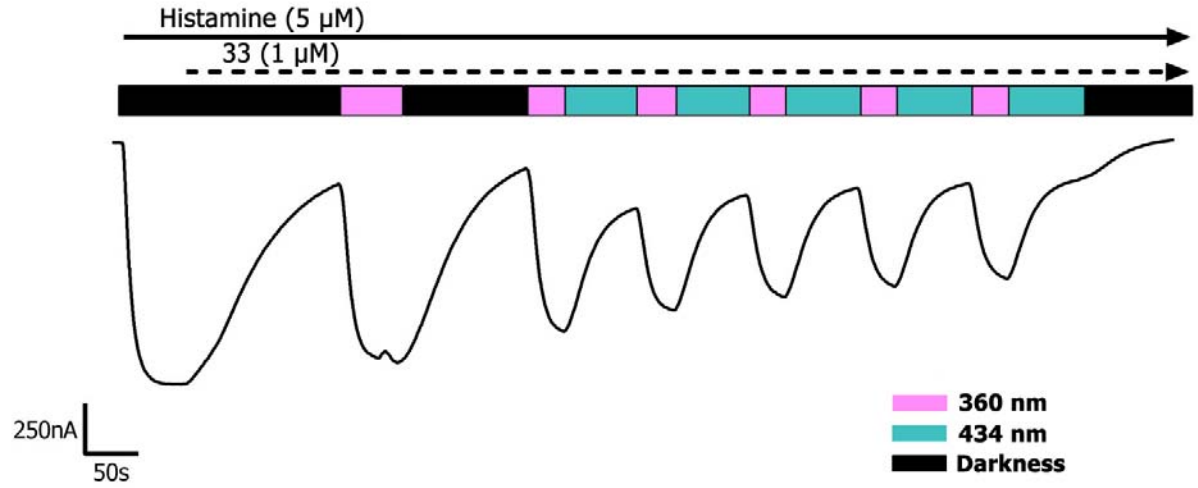


Figure S34: TEVC time trace of 5 µM histamine in competition with 1 µM of compound 33 (>99% *trans*) on GIRK–H_3R expressing *Xenopus* oocytes in a continuous perfusion system using illuminations at 360 ± 20 nm (magenta), 434 ± 9 nm (cyan) or without illumination (black, perfusion with >99% *trans* compound still ongoing).

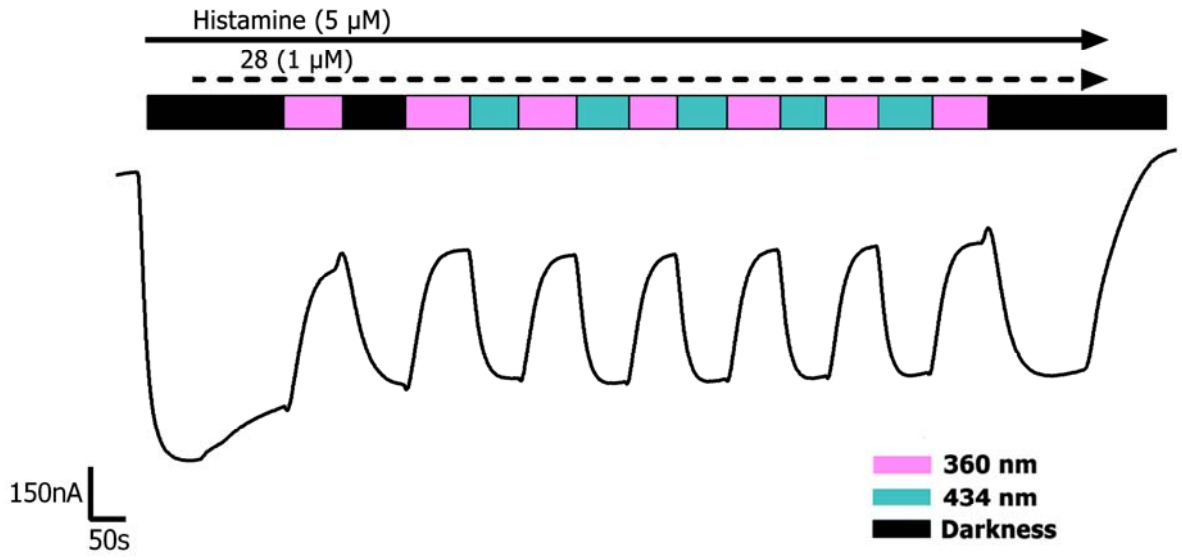


Figure S35: TEVC time trace of 5 µM histamine in competition with 1 µM of compound 28 (>99% *trans*) on GIRK–H_3R expressing *Xenopus* oocytes in a continuous perfusion system using illuminations at 360 ± 20 nm (magenta), 434 ± 9 nm (cyan) or without illumination (black, perfusion with >99% *trans* compound still ongoing).

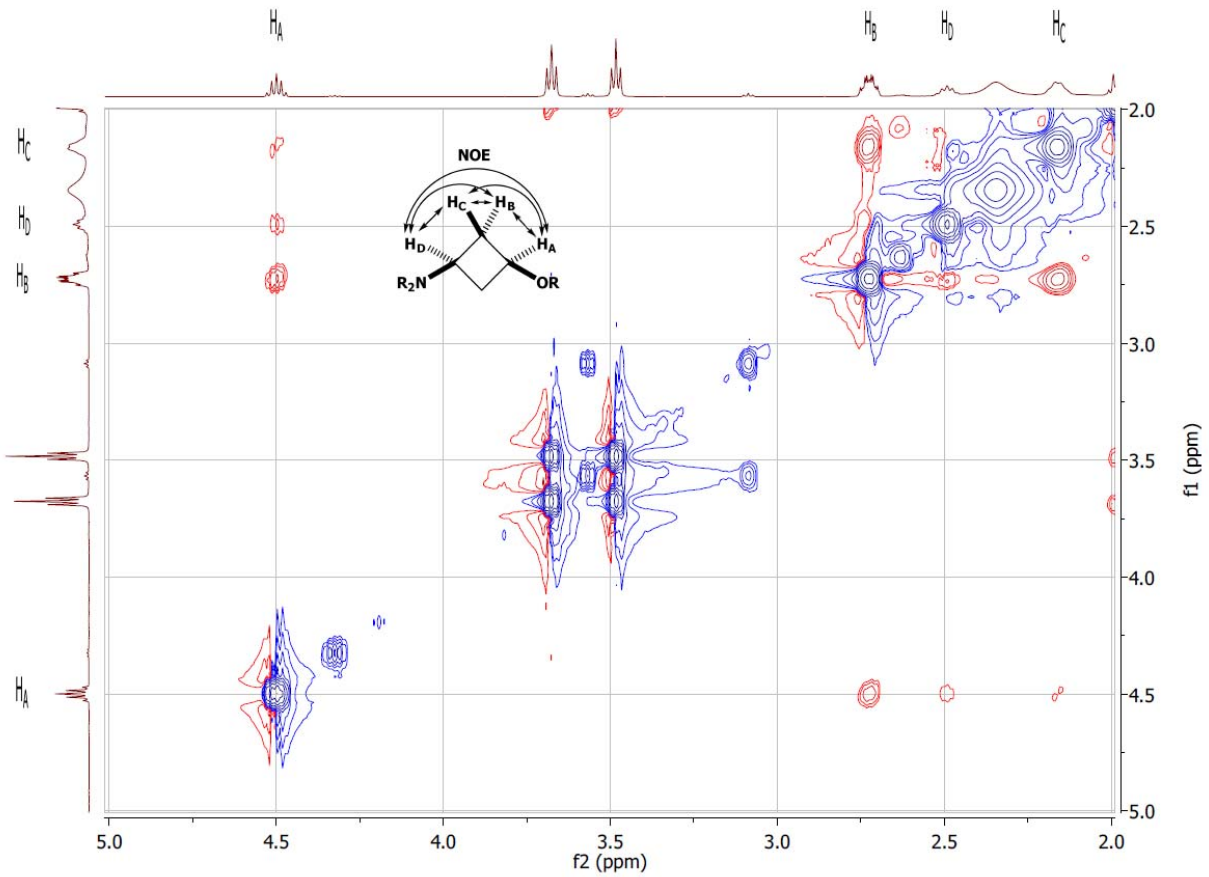


Figure S36: Characteristic section of a 500 MHz NOESY spectrum of compound 32 in $CDCl_3$.

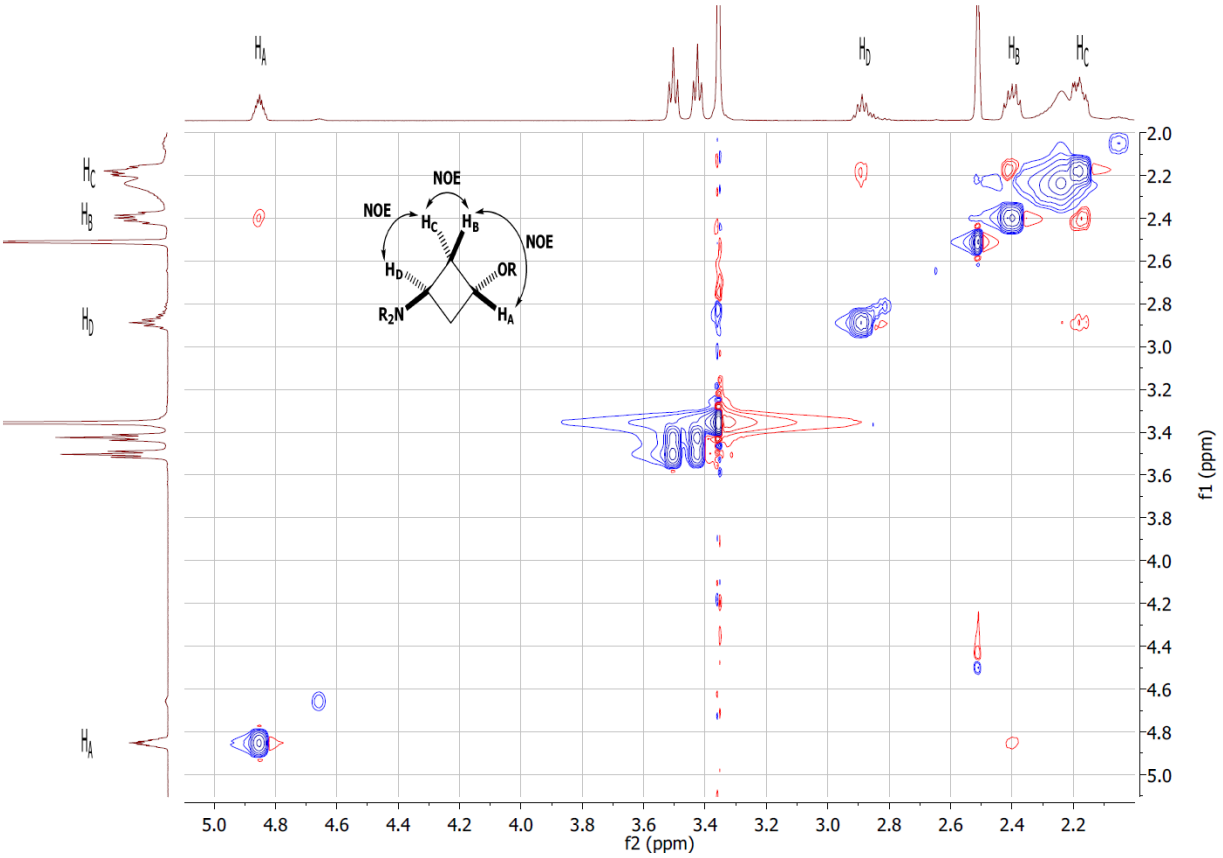


Figure S37: Characteristic section of a 500 MHz NOESY spectrum of compound 33 in DMSO-d_6.

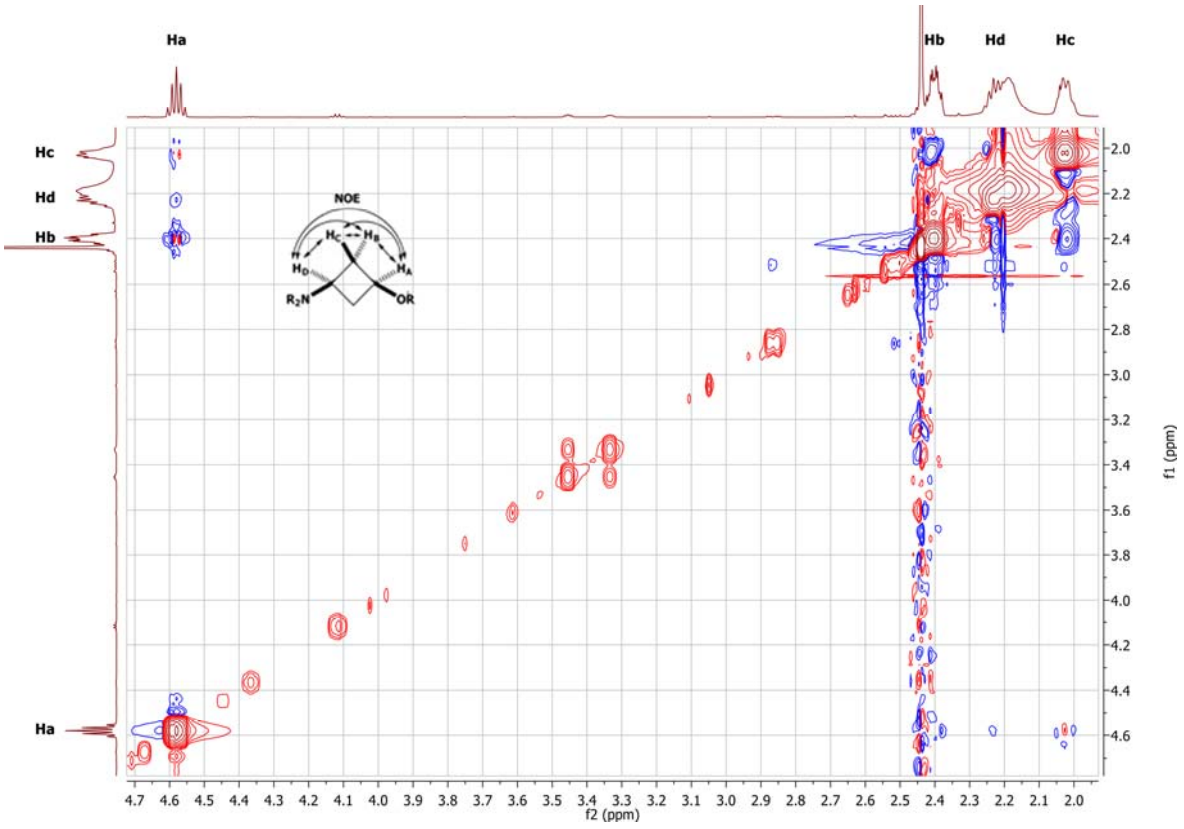


Figure S38: Characteristic section of a 600 MHz NOESY spectrum of compound 36 in $CDCl_3$.

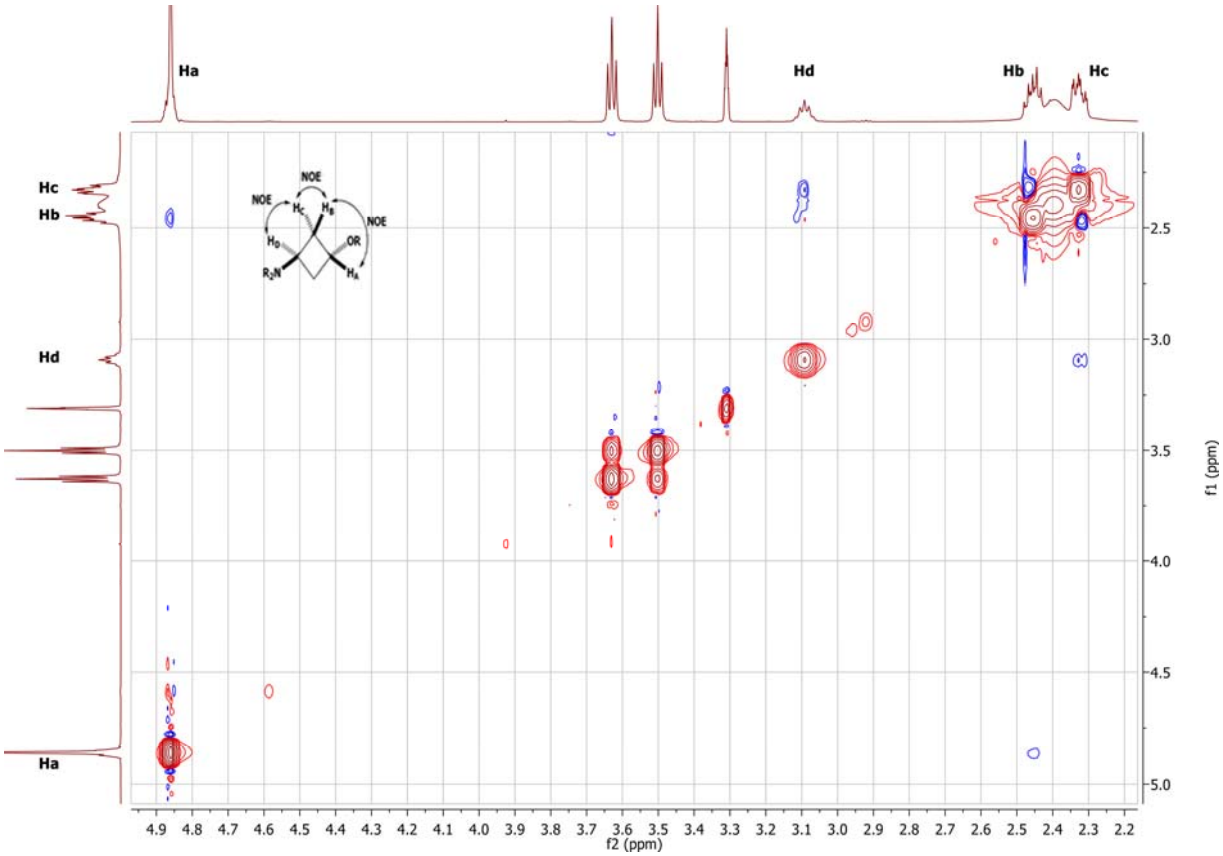
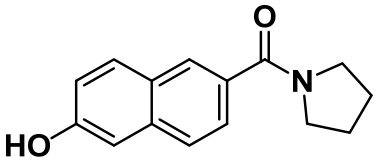


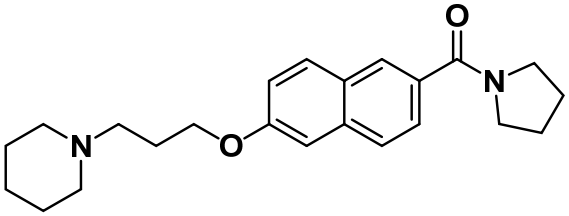
Figure S39: Characteristic section of a 600 MHz NOESY spectrum of compound 34 in CD_3OD.

Chemical procedures



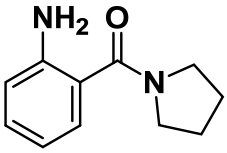
(6-Hydroxynaphthalen-2-yl)(pyrrolidin-1-yl)methanone (**38**)

This procedure was based on a literature description.[1] To a stirred solution of 6-hydroxy-2-naphthoic acid (1.00 g, 5.31 mmol) in DMF (20 mL) was added DIPEA (3.71 mL, 21.3 mmol), pyrrolidine (0.527 mL, 6.38 mmol) and TBTU (2.05 g, 6.38 mmol). The solution was left to stir overnight at RT, after which the solution was diluted with H_2O (50 mL). The mixture was extracted using EtOAc (3x40 mL). The combined organic phases were dried over Na_2SO_4 and evaporated *in vacuo*. The resulting off-white solid was recrystallized from H_2O: MeOH 9:1 to yield the product as white highly crystalline flakes (1.25 g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.93 (bs, 1H), 8.00 – 7.93 (m, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.50 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.18 – 7.08 (m, 2H), 3.56 – 3.42 (m, 4H), 1.96 – 1.73 (m, 4H). LC-MS: t_R= 3.36 min, purity: > 99%, M/z $[M+H]^+$: 242.



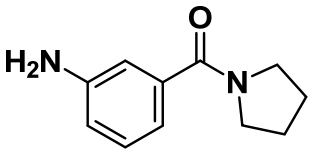
(6-(3-(Piperidin-1-yl)propoxy)naphthalen-2-yl)(pyrrolidin-1-yl)methanone (**1**)

This procedure was based on a literature description.[1] To a stirred solution of di-*tert*-butylazodicarboxylate (954 mg, 4.14 mmol), PPh_3 (1.09 g, 4.14 mmol) and 3-(piperidin-1-yl)propan-1-ol (356 mg, 2.49 mmol) in THF (20 mL) was added **38** (500 mg, 2.07 mmol) after which the flask was flushed with nitrogen gas and sealed. The obtained solution was stirred for 5 days at RT. The reaction mixture was concentrated *in vacuo*. Et_2O (20 mL) was added and the precipitated triphenylphosphine oxide was removed by filtration. After evaporation of Et_2O the solids were recrystallized using H_2O: MeOH 4:1. Addition of a few drops of H_2O to the mother liquor gave a second crop of crystals. The combined crops yielded 752 mg (99%, 2.05 mmol) of highly crystalline white needles. ^{1}H NMR (500 MHz, CD_3OD) δ 7.98 (d, *J* = 1.6 Hz, 1H), 7.83 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.56 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.19 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.15 (t, *J* = 6.1 Hz, 2H), 3.64 (t, *J* = 7.0 Hz, 2H), 3.55 (t, *J* = 6.7 Hz, 2H), 2.63 – 2.35 (m, 6H), 2.11 – 1.97 (m, 4H), 1.91 (p, *J* = 6.7 Hz, 2H), 1.64 (p, *J* = 5.7 Hz, 4H), 1.55 – 1.43 (m, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 172.0, 159.6, 137.0, 132.8, 131.1, 129.3, 128.1, 128.0, 125.7, 120.9, 107.5, 67.5, 57.2, 55.5, 51.1, 47.6, 27.4, 27.3, 26.5, 25.4, 25.2; LC-MS: t_R= 3.02 min, purity: >99%, M/z $[M+H]^+$: 367; HRMS calcd. for $C_{23}H_{31}N_2O_2$ $[M+H]^+$ = 367.2380, found 367.2376.



(2-Aminophenyl)(pyrrolidin-1-yl)methanone (**5**)

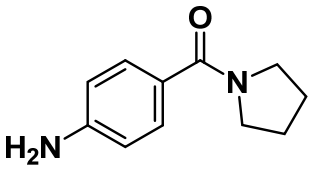
To a stirred solution of **2** (1.63 g, 12.1 mmol) in DMF (9.82 mL) were added DIPEA (2.44 mL, 15.7 mmol), HOBt. H_2O (1.23 g, 8.06 mmol), pyrrolidine (0.650 mL, 7.86 mmol) and EDCI.HCl (1.53 g, 7.98 mmol). The mixture was stirred overnight at RT, after which it was concentrated *in vacuo* and partitioned between DCM (40 mL) and H_2O (40 mL). The aqueous phase was extracted with DCM (3x40 mL). The combined organic phases were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified via flash column chromatography using EtOAc: TEA 95:5 as eluent to yield the product as an off-white solid (1.21 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.09 (m, 2H), 6.76 – 6.66 (m, 2H), 4.55 (bs, 2H), 3.63 (bs, 2H), 3.47 (bs, 2H), 2.15 – 1.64 (m, 4H); LC-MS: t_R= 3.16 min, purity: >99%, M/z $[M+H]^+$= 191.



(3-Aminophenyl)(pyrrolidin-1-yl)methanone (**6**)

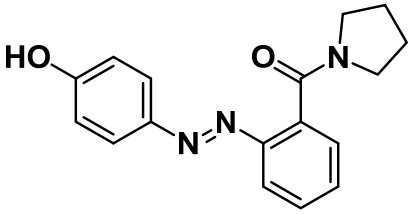
To a stirred solution of **3** (1.09 g, 7.91 mmol) in DMF (6.5 mL) were added DIPEA (1.64 mL, 10.6 mmol), HOBt.H_2O (0.808 g, 5.27 mmol), pyrrolidine (0.43 mL, 5.2 mmol) and EDCI.HCl (1.02 g, 5.32 mmol). The reaction mixture was stirred overnight at RT, after which H_2O (30 mL) was added. The mixture was extracted using DCM (4x30 mL). The combined organic phases were dried over Na_2SO_4, evaporated *in vacuo* and coevaporated twice using toluene. The crude product was purified via flash column chromatography using EtOAc: TEA 95:5 as eluent to yield the product as an off-white solid (0.96 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, *J* = 7.7 Hz, 1H), 6.88 – 6.77 (m, 2H), 6.74 – 6.65 (m, 1H), 3.72

(bs, 2H), 3.60 (t, *J* = 7.0 Hz, 2H), 3.40 (t, *J* = 6.6 Hz, 2H), 2.00 – 1.88 (m, 2H), 1.84 (p, *J* = 6.4 Hz, 2H); LC-MS: t_R= 2.42 min, purity: >99%, M/z $[M+H]^+$: 191.



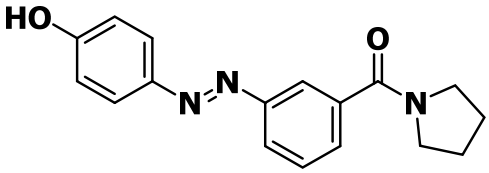
(4-Aminophenyl)(pyrrolidin-1-yl)methanone (**7**)

To a stirred solution of **4** (6.49 g, 47.3 mmol) in DMF (39.5 mL) were added DIPEA (9.76 mL, 56.0 mmol), HOBt.H_2O (4.83 g, 31.6 mmol), pyrrolidine (2.61 mL, 31.6 mmol) and EDCI.HCl (6.05 g, 31.6 mmol). The solution was stirred overnight at RT, after which H_2O (100 mL) was added. The mixture was extracted using DCM (3x100 mL). The combined organic phases were dried over Na_2SO_4 and evaporated *in vacuo* to yield the product as a tan solid (5.06 g, 81%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 2H), 6.68 – 6.54 (m, 2H), 4.16 (bs, 2H), 3.72 – 3.39 (m, 4H), 2.05 – 1.71 (m, 4H); LC-MS: t_R= 2.54 min, purity 96.19%, M/z $[M+H]^+$: 191.



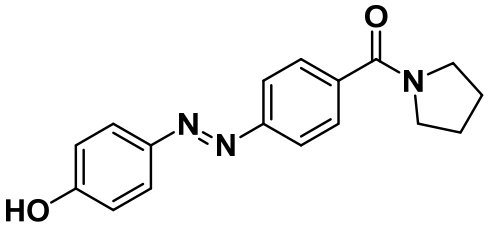
(E)-(2-((4-Hydroxyphenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**9**)

Aniline **5** (0.644 g, 3.39 mmol) was dissolved in ice-cooled 1.0 M aq. HCl (8.46 mL, 8.46 mmol). $NaNO_2$ (0.234 g, 3.39 mmol) dissolved in H_2O (3.6 mL) was added. After 5 min, phenol (1.59 g, 16.9 mmol) dissolved in 2.5 M aq. NaOH solution (8.40 mL, 21.0 mmol) was added at once. After 30 min, the mixture was acidified to pH 4 by means of a 3.0 M aq. HCl solution and aq. sat. NH_4Cl. The collected precipitate was suspended in H_2O (50 mL) and heated to 70 °C for 15 min, after which the solids were collected by hot filtration and washed with ice cold H_2O. The product was an orange solid (605 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 1H), 7.67 – 7.61 (m, 2H), 7.54 – 7.42 (m, 3H), 6.93 – 6.87 (m, 2H), 3.71 (t, *J* = 7.1 Hz, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 1.93 (p, *J* = 6.8 Hz, 2H), 1.81 (p, *J* = 6.7 Hz, 2H); LC-MS: t_R= 4.03 min, purity: 98.30%, M/z $[M+H]^+$: 296.



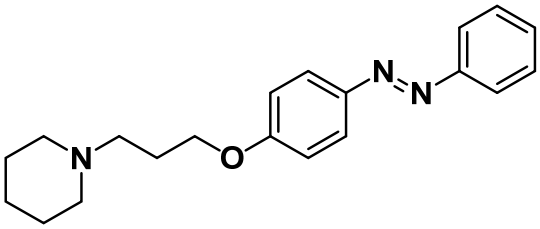
(E)-(3-((4-Hydroxyphenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**10**)

Aniline **6** (0.634 g, 3.33 mmol) was dissolved in ice-cooled 1.0 M aq. HCl (8.33 mL, 8.33 mmol) solution. $NaNO_2$ (0.303 g, 4.39 mmol) dissolved in H_2O (4.1 mL) was added and the mixture stirred for 5 min. Phenol (1.57 g, 16.7 mmol) dissolved in 2.50 M aq. NaOH (8.26 mL, 20.7 mmol) was added at once. After 30 min, the mixture was acidified to pH 4 by means of a 3.0 M aq. HCl solution and aq. sat. NH_4Cl. The precipitate was collected and washed with ice cold H_2O. The crude product was suspended in H_2O and heated to 50 °C for 30 min. The solids were collected by hot filtration and washed with cold H_2O. The product was obtained as orange crystals (0.646 g, 66%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 – 7.77 (m, 4H), 7.68 – 7.52 (m, 2H), 7.01 – 6.83 (m, 2H), 3.63 (t, *J* = 6.9 Hz, 2H), 3.51 (t, *J* = 6.7 Hz, 2H), 2.10 – 1.82 (m, 4H); LC-MS: t_R= 4.03 min, purity: 96.49%, M/z $[M+H]^+$: 296.



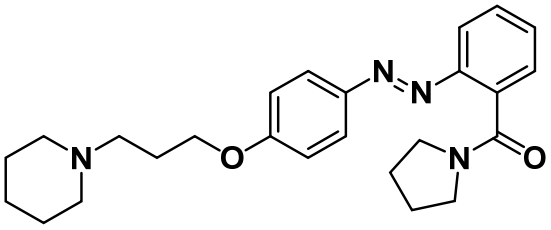
(E)-(4-((4-Hydroxyphenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**11**)

Aniline **7** (1.41 g, 7.09 mmol) was dissolved in ice-cooled 1.0 M aq. HCl solution (17.7 mL, 17.7 mmol). $NaNO_2$ (0.646 g, 9.36 mmol) dissolved in H_2O (3.20 mL) was added and the mixture was stirred for 5 min. Phenol (3.33 g, 35.4 mmol) dissolved in a 2.5 M aq. NaOH solution (17.6 mL, 44.0 mmol) and added in one portion. After 30 min, the mixture was acidified to pH 4 by means of a 3.0 M aq. HCl solution and aq. sat. NH_4Cl. The precipitate was collected and washed with H_2O (2x10 mL).The product was obtained as orange crystals (1.86 g, 81%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 – 7.80 (m, 4H), 7.72 – 7.60 (m, 2H), 6.97 – 6.87 (m, 2H), 3.62 (t, *J* = 6.9 Hz, 2H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.02 (p, *J* = 6.4 Hz, 2H), 1.93 (p, *J* = 6.1 Hz, 2H); LC-MS: t_R= 3.97 min, purity: 97.58%, M/z $[M+H]^+$: 296.



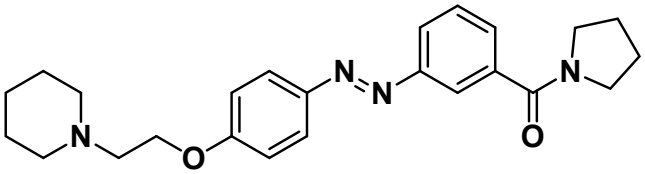
(E)-1-(3-(4-(Phenyldiazenyl)phenoxy)propyl)piperidine (**12**)

Phenol **8** (0.200 g, 1.01 mmol), 1-(3-chloropropyl)piperidine.HCl (0.172 g, 1.06 mmol), KI (0.019 g, 0.11 mmol) and K_2CO_3 (0.450 g, 3.26 mmol) were added to DMF (6.3 mL). This mixture was stirred overnight at 60°C, after which the reaction mixture was concentrated *in vacuo*. The residue was partitioned between DCM (40 mL) and H_2O (40 mL). The organic phase was washed with 2.5 M aq. NaOH solution (2x20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by flash column chromatography with a gradient of *n*-heptane: EtOAc: TEA 45:45:10 to EtOAc: TEA 90:10. This yielded the product as orange needles (0.22 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.84 (m, 4H), 7.53 – 7.47 (m, 2H), 7.46 – 7.40 (m, 1H), 7.04 – 6.96 (m, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 2.50 (t, *J* = 7.3 Hz, 2H), 2.47 – 2.32 (m, 4H), 2.07 – 1.97 (m, 2H), 1.61 (p, *J* = 5.7 Hz, 4H), 1.51 – 1.39 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 152.9, 147.0, 130.4, 129.1, 124.9, 122.7, 114.8, 67.0, 56.0, 54.8, 26.9, 26.1, 24.5; LC-MS: t_R= 3.70 min, purity: > 99%, M/z $[M+H]^+$: 324, An injection peak is visible below 1.0 min; HRMS calcd. for $C_{20}H_{26}N_3O$ $[M+H]^+$ = 324.2070, found 324.2082.



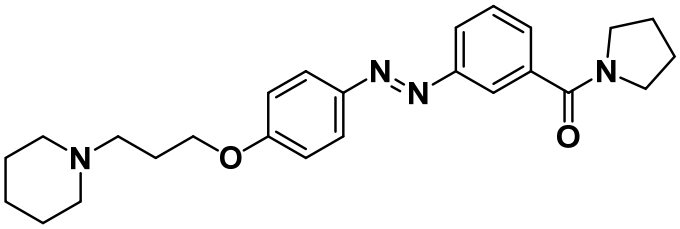
(E)-(2-((4-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**13**)

Phenol **9** (0.300 g, 0.995 mmol), 1-(3-chloropropyl)piperidine.HCl (0.194 g, 1.20 mmol), KI (0.017 g, 0.10 mmol) and K_2CO_3 (0.413 g, 2.99 mmol) were added to DMF (5.93 mL). The mixture was stirred at overnight at 60 °C after which the solvent was evaporated *in vacuo*. The residue was partitioned between DCM (20 mL) and H_2O (20 mL). The organic phase was washed with H_2O (20 mL) and 2.5 M aq. NaOH solution (4x 20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by means of flash column chromatography using a gradient from *n*-heptane: EtOAc: TEA 10:9:1 to EtOAc: TEA 9:1. This yielded the product as orange crystals (0.28 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.75 (m, 3H), 7.52 – 7.43 (m, 3H), 7.02 – 6.92 (m, 2H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.71 (t, *J* = 7.0 Hz, 2H), 3.07 (t, *J* = 6.7 Hz, 2H), 2.55 – 2.31 (m, 6H), 2.02 (p, *J* = 6.7 Hz, 2H), 1.91 (p, *J* = 6.8 Hz, 2H), 1.78 (p, *J* = 6.8 Hz, 2H), 1.61 (p, *J* = 5.6 Hz, 4H), 1.51 – 1.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 162.1, 148.3, 147.0, 136.4, 130.7, 129.7, 127.5, 125.1, 118.1, 114.9, 67.0, 56.0, 54.8, 48.4, 45.7, 26.9, 26.1, 26.0, 24.9, 24.5; LC-MS: t_R= 3.72 min, purity: >99%, M/z $[M+H]^+$: 421; HRMS calcd. for $C_{25}H_{33}N_4O_2$ $[M+H]^+$ = 421.2598, found 421.2619.



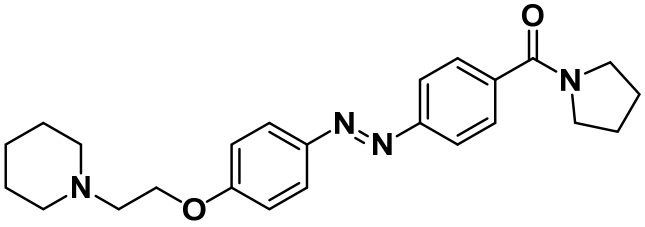
(E)-(3-((4-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**14**)

Phenol **10** (0.141 g, 0.477 mmol), 1-(2-chloroethyl)piperidine.HCl (0.087 g, 0.59 mmol), KI (0.011 g, 0.066 mmol) and K_2CO_3 (0.211 g, 1.53 mmol) were added to DMF (3.0 mL). The obtained mixture was stirred overnight at 60 °C, after which the solvent was evaporated *in vacuo.* The residue was partitioned between DCM (20 mL) and H_2O (20 mL). The organic phase was washed with H_2O (20 mL) and 2.5 M aq. NaOH (2x 20 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from *n*-heptane: EtOH 10:1 to yield the product as orange crystals (63 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 8.00 (m, 1H), 7.95 – 7.87 (m, 3H), 7.63 – 7.57 (m, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.05 – 6.99 (m, 2H), 4.20 (t, *J* = 6.0 Hz, 2H), 3.68 (t, *J* = 7.0 Hz, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 2.83 (t, *J* = 6.0 Hz, 2H), 2.63 – 2.45 (m, 4H), 1.98 (p, *J* = 6.8 Hz, 2H), 1.89 (p, *J* = 6.8 Hz, 2H), 1.63 (p, *J* = 5.6 Hz, 4H), 1.50 – 1.39 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 161.7, 152.5, 147.0, 138.2, 129.3, 129.0, 125.0, 124.3, 121.0, 115.0, 66.4, 57.9, 55.2, 49.8, 46.4, 26.5, 26.0, 24.6, 24.2; LC-MS: t_R= 3.63 min, purity: >99%, M/z $[M+H]^+$: 407; HRMS calcd. for $C_{24}H_{31}N_4O_2$ $[M+H]^+$ = 407.2442, found 407.2453.



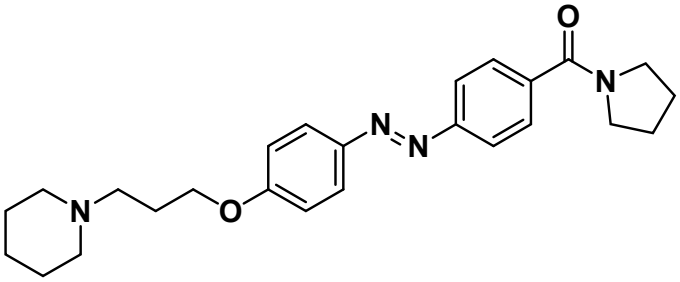
(E)-(3-((4-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**15**)

Phenol **10** (0.149 g, 0.505 mmol), 1-(3-chloropropyl)piperidine.HCl (0.099 g, 0.61 mmol), KI (8.0 mg, 0.048 mmol) and K_2CO_3 (0.210 g, 1.52 mmol) were added to DMF (3.0 mL). The mixture was stirred overnight at 60 °C, after which it was concentrated *in vacuo.* DCM (20 mL) and H_2O (20 mL) were added and the layers were partitioned. The organic phase was washed using 2.5 M NaOH (2x20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from n-heptane: EtOH 10:1 to yield the product as orange crystals (0.10 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 1H), 7.96 – 7.86 (m, 3H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.04 – 6.96 (m, 2H), 4.10 (t, *J* = 6.3 Hz, 2H), 3.68 (t, *J* = 6.9 Hz, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 2.63 – 2.30 (m, 6H), 2.10 – 1.94 (m, 4H), 1.89 (p, *J* = 6.7 Hz, 2H), 1.62 (p, *J* = 5.6 Hz, 4H), 1.51 – 1.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 162.0, 152.6, 146.9, 138.3, 129.3, 129.0, 125.1, 124.3, 121.0, 114.9, 67.0, 56.0, 54.8, 49.8, 46.4, 26.8, 26.6, 26.0, 24.6, 24.5; LC-MS: t_R= 3.33 min, purity: >99%, M/z $[M+H]^+$: 421; HRMS calcd. for $C_{25}H_{33}N_4O_2$ $[M+H]^+$ = 421.2598, found 421.2606.



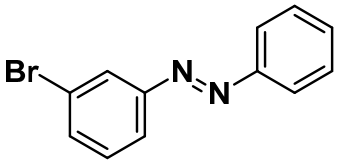
(E)-(4-((4-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**16**)

Phenol **11** (0.145 g, 0.491 mmol), 1-(2-chloroethyl)piperidine.HCl (0.086 g, 0.58 mmol), KI (0.011 g, 0.066 mmol) and K_2CO_3 (0.218 g, 1.58 mmol) were added in DMF (3.0 mL). The mixture was stirred at 60 °C for 16 hours, after which the solvent was evaporated *in vacuo*. DCM (20 mL) and H_2O (20 mL) were added to the residue. The organic phase was washed using 2.5 M NaOH solution (2x20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was recrystallized from *n*-heptane: EtOH 20:1 to yield the product as orange crystals (38 mg, 19%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 – 7.87 (m, 4H), 7.68 – 7.60 (m, 2H), 7.20 – 7.12 (m, 2H), 4.19 (t, *J* = 5.8 Hz, 2H), 3.50 (t, *J* = 6.8 Hz, 2H), 3.42 (t, *J* = 6.4Hz, 2H), 2.71 (bs, 2H), 2.46 (bs, 4H), 1.94 – 1.77 (m, 4H), 1.51 (p, *J* = 5.5 Hz, 4H), 1.43 – 1.33 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 161.7, 153.4, 147.1, 138.8, 128.2, 125.1, 122.5, 115.0, 66.4, 57.9, 55.2, 49.7, 46.4, 26.6, 26.0, 24.6, 24.2; LC-MS: t_R= 4.28 min, purity: >99%, M/z $[M+H]^+$= 407; HRMS calcd. for $C_{24}H_{31}N_4O_2$ $[M+H]^+$ = 407.2442, found 407.2424.



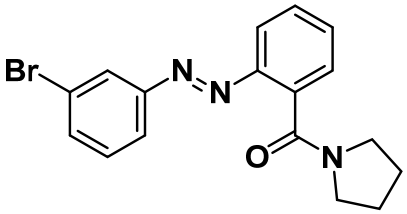
(E)-(4-((4-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**17**)

Phenol **11** (0.145 g, 0.491 mmol), 1-(3-chloropropyl)piperidine. HCl (0.096 g, 0.59 mmol), KI (0.010 g, 0.060 mmol) and K_2CO_3 (0.237 g, 1.72 mmol) were added to DMF (3.0 mL). The mixture was stirred overnight at 60 °C. The solvent was evaporated *in vacuo*, after which the crude was partitioned between DCM (20 mL) and H_2O (20 mL). The organic phase was washed using 2.5 M aq. NaOH solution (2x20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was recrystallized from EtOAc to yield the product as orange crystals (80 mg, 39%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 4H), 7.69 – 7.62 (m, 2H), 7.05 – 6.97 (m, 2H), 4.11 (t, *J* = 6.3 Hz, 2H), 3.67 (t, *J* = 7.0 Hz, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 2.74 – 2.29 (m, 4H), 2.21 – 2.02 (m, 2H), 2.02 – 1.94 (m, 2H), 1.94 – 1.84 (m, 2H), 1.82 – 1.31 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2, 162.1, 153.5, 147.0, 138.7, 128.2, 125.1, 122.5, 114.9, 67.0, 56.0, 54.8, 49.7, 46.4, 26.8, 26.6, 26.1, 24.6, 24.5; LC-MS: t_R= 3.98 min, purity >99%, M/z $[M+H]^+$: 421; HRMS: $C_{25}H_{33}N_4O_2^+$ M/z calc. 421.2598, M/z found. 421.2593.



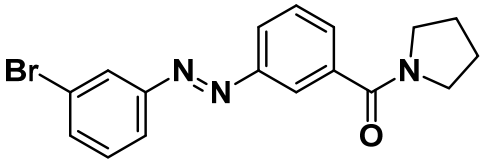
(E)-1-(3-Bromophenyl)-2-phenyldiazene (**20**)

To a stirred solution of nitrosobenzene (1.89 g, 17.6 mmol) in glacial AcOH (20 mL) was added aniline **18** (1.92 mL, 17.6 mmol). The solution was heated to 80 °C and stirred for 7 hours. The reaction mixture was added to toluene (50 mL). The organic phase was washed with 1.0 M aq. H_2SO_4 solution (50 mL) and 1% aq. NaOH solution (50 mL), dried over Na_2SO_4 and evaporated *in vacuo.* The crude product was subjected to flash column chromatography using *n*-heptane as eluent to afford the product as a sticky orange oil (1.91 g, 42%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.09 – 8.03 (m, 1H), 7.98 – 7.83 (m, 3H), 7.64 – 7.48 (m, 4H), 7.46 – 7.34 (m, 1H); LC-MS: t_R= 5.99 min, purity: > 99%, M/z $[M+H]^+$: 261 (^{79}Br) + 263 (^{81}Br).



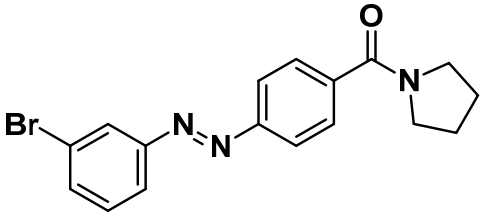
(E)-(2-((3-Bromophenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**21**)

Aniline **18** (0.316 mL, 2.91 mmol) was dissolved in DCM (10 mL). Oxone™ (3.57 g, 5.81 mmol) was added as a solution in H_2O (40 mL). The biphasic mixture was stirred vigorously at RT. After 3 hours, the layers were partitioned and the organic phase was washed with 1.0 M aq. HCl (10 mL), aq. sat. $NaHCO_3$ (10 mL) and transferred to a round bottomed flask. Aniline **5** (503 mg, 2.64 mmol) and AcOH (10 mL) were added and the solution was stirred overnight at RT. The solution was evaporated *in vacuo* after which EtOAc (20 mL) was added. The organic phase was washed with aq. sat. $NaHCO_3$ (2x20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was subjected to flash column chromatography using *n*-heptane: EtOAc 9:1 as eluent to yield the product as an orange viscous oil (622 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 1H), 7.86 – 7.79 (m, 2H), 7.63 – 7.57 (m, 1H), 7.57 – 7.47 (m, 3H), 7.39 (t, *J* = 7.9 Hz, 1H), 3.74 (t, *J* = 7.0 Hz, 2H), 3.09 (t, *J* = 6.7 Hz, 2H), 1.95 (p, *J* = 6.9 Hz, 2H), 1.82 (p, *J* = 6.7 Hz, 2H); LRMS: M/z $[M+H]^+$: 358 (^{79}Br) + 360 (^{81}Br).



(E)-(3-((3-Bromophenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**22**)

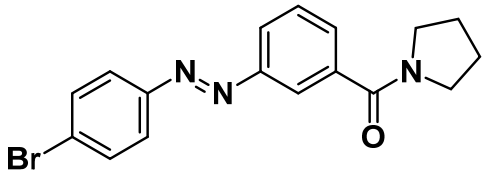
Aniline **18** (0.285 mL, 2.69 mmol) was dissolved in DCM (9.00 mL). Oxone™ (3.31 g, 5.38 mmol) was added as a solution in H_2O (36.0 mL). The biphasic mixture was stirred vigorously at RT. After 2.5 hours, the layers were partitioned and the organic phase was washed with 1.0 M aq. HCl (5 mL), aq. sat. $NaHCO_3$ (5 mL), brine (5 mL) and transferred to a round bottomed flask. Aniline **6** (0.511 g, 2.69 mmol) and AcOH (13.4 mL) were added and the solution was stirred overnight at RT. The solution was evaporated *in vacuo* after which EtOAc (40 mL) was added. The organic phase was washed with aq. sat. $NaHCO_3$ (2x40 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was subjected to flash column chromatography using a gradient from *n*-heptane: EtOAc: TEA 80:20:1 to *n*-heptane: EtOAc: TEA 10:90:1 to yield the product as an orange viscous oil (472 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.02 (m, 2H), 7.97 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.88 (dt, *J* = 7.9, 1.3 Hz, 1H), 7.67 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.65 – 7.52 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 3.69 (t, *J* = 6.9 Hz, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 2.06 – 1.85 (m, 4H); LC-MS: t_R= 5.47 min, purity: 95.81%, M/z $[M+H]^+$: 358 (^{79}Br) + 360 (^{81}Br).



(E)-(4-((3-Bromophenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**23**)

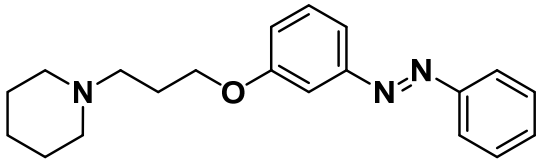
Aniline **18** (0.570 mL, 5.38 mmol) was dissolved in DCM (9.00 mL). Oxone™ (6.61 g, 10.8 mmol) was added as a solution in H_2O (36.0 mL). The biphasic mixture was stirred vigorously at RT. After 3 hours, the layers were partitioned and the organic phase was washed with 1.0 M aq. HCl (5 mL), aq. sat. $NaHCO_3$ (5 mL), brine (5 mL) and transferred to a round bottomed flask. Aniline **7** (0.516 g, 2.71 mmol) and AcOH (13.6 mL) were added and the solution was stirred overnight at RT. The solution was evaporated *in vacuo* after which EtOAc (40 mL) was added. The organic phase was washed with aq. sat. $NaHCO_3$ (2x40 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was subjected to flash column chromatography using a gradient from *n*-heptane: EtOAc: TEA 80:20:1 to *n*-heptane: EtOAc: TEA 10:90:1 to yield the

product as an orange solid (718 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (t, *J* = 1.9 Hz, 1H), 7.97 – 7.92 (m, 2H), 7.92 – 7.87 (m, 1H), 7.71 – 7.65 (m, 2H), 7.64 – 7.60 (m, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 3.76 – 3.61 (m, 2H), 3.55 – 3.40 (m, 2H), 2.06 – 1.85 (m, 4H); LC-MS: t_R= 5.55 min, purity: 97.56%, M/z $[M+H]^+$= 358 (^{79}Br) + 360 (^{81}Br).



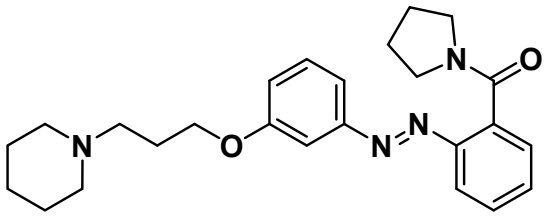
(E)-(3-((4-Bromophenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**24**)

To a stirred solution of aniline **19** (0.482 g, 2.80 mmol) in DCM (9.33 mL) was added OXONE™ (3.45 g, 5.60 mmol) in H_2O (37.3 mL). The obtained biphasic solution was stirred vigorously. After 4 hours, the layers were partitioned and the aqueous phase was extracted using DCM (2x20 mL). The combined organic phases were washed using 1.0 M aq. HCl (25 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated to a volume of about 5 mL. The concentrate was added to a solution of AcOH (9.3 mL) and aniline **6** (0.350 g, 1.84 mmol). The mixture was stirred at RT overnight. The volatiles were evaporated *in vacuo* and the residue was taken up in EtOAc. The mixture was washed with aq. sat. $NaHCO_3$ (2x20 mL) and brine (20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The remaining oil was subjected to flash column chromatography with a gradient from EtOAc: *n*-heptane 1:1 to EtOAc: *n*-heptane 9:1 to yield the product as an orange powder (480 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (t, *J* = 1.9 Hz, 1H), 7.99 – 7.93 (m, 1H), 7.84 – 7.76 (m, 2H), 7.69 – 7.61 (m, 3H), 7.56 (t, *J* = 7.7 Hz, 1H), 3.80 – 3.58 (m, 2H), 3.58 – 3.37 (m, 2H), 2.10 – 1.94 (m, 2H), 1.94 – 1.83 (m, 2H); LC-MS: t_R= 5.50 min, purity: 97.16%, M/z $[M+H]^+$: 358 (^{79}Br) + 360 (^{81}Br).



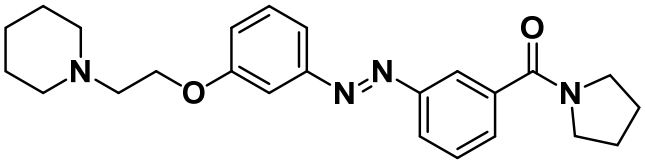
(E)-1-(3-(3-(Phenyldiazenyl)phenoxy)propyl)piperidine (**25**)

Cs_2CO_3 (484 mg, 1.49 mmol) was added to an oven-dried microwave tube and flame-dried under vacuum. Catalyst $[PdCl(C_3H_5)]_2$ (18 mg, 0.048 mmol) and Rockphos™ (53.8 mg, 0.115 mmol) were added. The tube was evacuated and backfilled with nitrogen three times. Bromide **20** (250 mg, 0.957 mmol) was dissolved in toluene (957 μL) and this solution was added to the reaction vial via a syringe. Then, 3-(piperidin-1-yl)propan-1-ol (286 μL, 1.91 mmol) was added via a syringe. The tube was heated in a sand bath at 90 °C for 72 hours. The mixture was cooled to RT, filtered over Celite® and the filter cake was washed with THF. The solvent was evaporated *in vacuo* and the residue was subjected to flash column chromatography using a gradient from *n*-heptane: EtOAc: TEA 95:95:10 to EtOAc: TEA 95:5 followed by reverse phase LC purification with a gradient from H_2O: ACN: formic acid 95:5:1 to H_2O: ACN: formic acid 5:95:1. This yielded the product as an orange oil (62 mg, 20%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 – 7.86 (m, 2H), 7.65 – 7.54 (m, 3H), 7.54 – 7.47 (m, 2H), 7.42 – 7.37 (m, 1H), 7.17 – 7.08 (m, 1H), 4.10 (t, *J* = 6.4 Hz, 2H), 2.39 (t, *J* = 7.1 Hz, 2H), 2.37 – 2.24 (m, 4H), 1.89 (p, *J* = 6.7 Hz, 2H), 1.49 (p, *J* = 5.6 Hz, 4H), 1.41 – 1.33 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 159.5, 153.1, 151.8, 131.6, 130.3, 129.5, 122.6, 118.3, 116.4, 106.3, 66.3, 55.1, 54.2, 26.3, 25.6, 24.2; LC-MS: *cis*-**25:** t_R= 3.59 min, purity: 3.91%, M/z $[M+H]^+$: 324; *trans*-**25**: t_R= 4.39 min, purity: 96.09%, M/z $[M+H]^+$: 324; HRMS calcd. for $C_{20}H_{26}N_3O$ $[M+H]^+$ = 324.2070, found 324.2066.



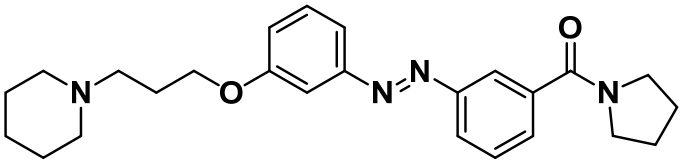
(E)-(2-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**26**)

Cs_2CO_3 (635 mg, 1.95 mmol) was added to an oven-dried microwave vial and flame-dried under vacuum. Catalyst $[(C_3H_5)PdCl]_2$ (23 mg, 0.063 mmol) and Rockphos (70.7 mg, 0.151 mmol) were added. The tube was evacuated and backfilled three times with nitrogen. Bromide **21** (450 mg, 1.26 mmol) was dissolved in toluene (1.26 mL) and this solution was added to the reaction vial via a syringe. Then, 3-(piperidin-1-yl)propan-1-ol (375 μL, 2.51 mmol) was added via a syringe. The tube was heated in a sand bath at 90 °C for 72 hours. The mixture was cooled to RT, filtered over Celite® and the filter cake was washed with THF (10 mL). The solvent was evaporated *in vacuo* and the residue was subjected to flash column chromatography using a gradient from *n*-heptane: EtOAc: TEA 95:95:10 to EtOAc: TEA 95:5 followed by reverse phase column chromatography using a gradient for H_2O: ACN: formic acid 95:5:1 to H_2O: ACN: formic acid 5:95:1. The product was obtained as an orange powder (62 mg, 12%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 – 7.75 (m, 1H), 7.66 – 7.56 (m, 2H), 7.56 – 7.43 (m, 3H), 7.26 (t, *J* = 2.1 Hz, 1H), 7.18 – 7.13 (m, 1H), 4.06 (t, *J* = 6.5 Hz, 2H), 3.53 (t, *J* = 7.0 Hz, 2H), 3.02 (t, *J* = 6.7 Hz, 2H), 2.45 – 2.22 (m, 6H), 1.96 – 1.80 (m, 4H), 1.76 (p, *J* = 6.7 Hz, 2H), 1.49 (p, *J* = 5.6 Hz, 4H), 1.42 – 1.33 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.9, 159.5, 153.1, 147.2, 136.9, 131.9, 130.5, 129.7, 127.5, 119.0, 117.5, 117.3, 105.2, 66.2, 55.1, 54.2, 47.8, 45.3, 26.2, 25.6, 25.6, 24.3, 24.2; LC-MS: t_R= 3.60 min, purity: 93.94%, M/z $[M+H]^+$: 421; HRMS calcd. for $C_{25}H_{33}N_4O_2$ $[M+H]^+$ = 421.2598, found 421.2593.



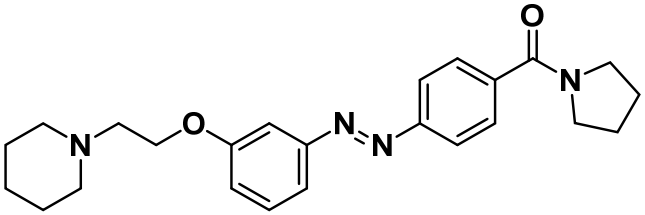
(E)-(3-((3-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**27**)

Cs_2CO_3 (423 mg, 1.30 mmol) was added to an oven-dried microwave vial and and flame-dried under vacuum. Catalyst $[(C_3H_5)PdCl]_2$ (15 mg, 0.042 mmol) and Rockphos (47.1 mg, 0.100 mmol) were added. The tube was evacuated and backfilled three times with nitrogen. Bromide **22** (300 mg, 0.837 mmol) was dissolved in toluene (837 μL) and this solution was added to the reaction vial via a syringe. Then, 2-(piperidin-1-yl)ethanol (222 μL, 1.67 mmol) was added via a syringe. The tube was heated in a sand bath at 90 °C for 72 hours. The mixture was cooled to RT, filtered over Celite® and the filter cake was washed with THF (10 mL). The solvent was evaporated *in vacuo* and the residue was subjected to flash column chromatography using a gradient from *n*-heptane: EtOAc: TEA 95:95:10 to EtOAc: TEA 95:5 to yield the product as orange crystals (0.16 g, 47%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.01 – 7.94 (m, 2H), 7.74 – 7.69 (m, 1H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.44 (t, *J* = 2.0 Hz, 1H), 7.17 (dt, *J* = 7.5, 2.0 Hz, 1H), 4.16 (t, *J* = 5.8 Hz, 2H), 3.50 (t, *J* = 6.9 Hz, 2H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.68 (t, *J* = 5.9 Hz, 2H), 2.48 – 2.35 (m, 4H), 1.94 – 1.77 (m, 4H), 1.49 (p, *J* = 5.6 Hz, 4H), 1.41 – 1.33 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.3, 159.4, 153.1, 151.5, 138.5, 130.3, 129.9, 129.6, 124.2, 120.5, 118.6, 116.5, 106.7, 66.0, 57.4, 54.4, 49.0, 46.0, 26.0, 25.6, 24.0 (2 overlapping carbon signal according to HSQC); LC-MS: t_R= 3.26 min, purity: 96.19%, M/z $[M+H]^+$: 407; HRMS calcd. for $C_{24}H_{31}N_4O_2$ $[M+H]^+$ = 407.2442, found 407.2434.



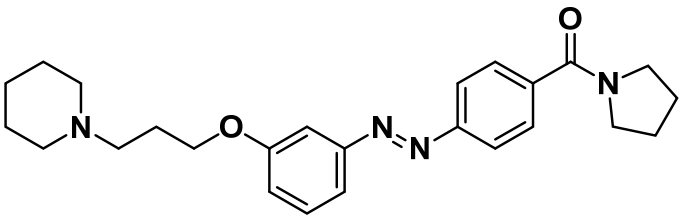
(E)-(3-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**28**)

Cs_2CO_3 (142 mg, 0.436 mmol) was added to an oven-dried microwave tube and flame-dried under vacuum. Catalyst $[(C_3H_5)PdCl]_2$ (6.1 mg, 0.017 mmol) and Rockphos (22 mg, 0.047 mmol) were added. The tube was evacuated and backfilled three times with nitrogen. Bromide **22** (104 mg, 0.289 mmol) was dissolved in toluene (279 μL) and this solution was added to the reaction vial via a syringe. Then, 3-(piperidin-1-yl)propan-1-ol (85 μL, 0.56 mmol) was added via a syringe. The tube was heated in a 90 °C sand bath for 23 hours. The mixture was cooled to RT, filtered over Celite® and the filter cake was washed with MeOH (10 mL). The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography using EtOAc: *n*-heptane: TEA 35:64:1 to EtOAc: TEA 99:1 to yield the product as an orange viscous oil (40 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.02 (m, 1H), 8.00 – 7.93 (m, 1H), 7.68 – 7.62 (m, 1H), 7.60 – 7.51 (m, 2H), 7.46 – 7.38 (m, 2H), 7.05 (dd, *J* = 7.9, 2.4 Hz, 1H), 4.10 (t, *J* = 6.3 Hz, 2H), 3.68 (t, *J* = 6.9 Hz, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.56 – 2.47 (m, 2H), 2.43 (bs, 4H), 2.07 – 1.95 (m, 4H), 1.90 (p, *J* = 6.6 Hz, 2H), 1.61 (p, *J* = 5.6 Hz, 4H), 1.50 – 1.38 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 159.9, 153.8, 152.3, 138.3, 129.9, 129.7, 129.4, 124.6, 121.3, 118.7, 117.4, 106.5, 66.9, 56.1, 54.8, 49.8, 46.4, 26.9, 26.6, 26.1, 24.6, 24.6. LC-MS: t_R= 3.85 min, purity: >99%, M/z $[M+H]^+$: 421; HRMS calcd. for $C_{25}H_{33}N_4O_2$ $[M+H]^+$ = 421.2598, found 421.2616.



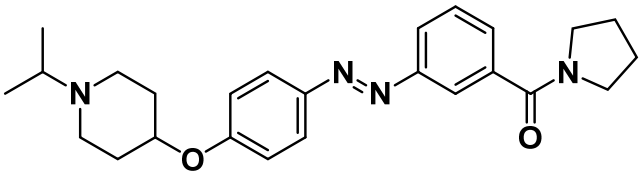
(E)-(4-((3-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**29**)

Cs_2CO_3 (217 mg, 0.667 mmol) was added to an oven-dried microwave vial and flame-dried under vacuum. Catalyst $[PdCl(C_3H_5)]_2$ (7.9 mg, 0.021 mmol) and Rockphos (24 mg, 0.052 mmol) were added. The tube was evacuated and backfilled three times with nitrogen. Bromide **23** (154 mg, 0.430 mmol) was dissolved in toluene (430 μL) and this solution was added to the reaction vial via a syringe. Then, 2-(piperidin-1-yl)ethanol (114 μL, 0.858 mmol) was added via a syringe. The tube was heated in a sand bath at 90 °C for 72 hours. The mixture was cooled to RT, filtered through Celite® and the filter cake was washed with THF (5 mL). The solvent was evaporated *in vacuo* and the residue was subjected to flash column chromatography using a gradient from *n*-heptane: EtOAc: TEA 95:95:10 to EtOAc: TEA 95:5 followed by reverse phase column chromatography with a gradient from H_2O: ACN: formic acid 95:5:1 to H_2O: ACN: formic acid 5:95:1. This yielded an orange oil which crystallized upon storage (72 mg, 41%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 – 7.89 (m, 2H), 7.76 – 7.70 (m, 2H), 7.57 – 7.49 (m, 2H), 7.46 – 7.42 (m, 1H), 7.18 (dt, *J* = 7.1, 2.3 Hz, 1H), 4.17 (t, *J* = 5.9 Hz, 2H), 3.49 (t, *J* = 6.8 Hz, 2H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.69 (t, *J* = 5.8 Hz, 2H), 2.47 – 2.40 (m, 4H), 1.92 – 1.79 (m, 4H), 1.50 (p, *J* = 5.6 Hz, 4H), 1.42 – 1.34 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.4, 159.4, 153.1, 152.1, 139.7, 130.4, 128.4, 122.4, 118.7, 116.6, 106.7, 66.0, 57.4, 54.5, 48.9, 46.0, 26.0, 25.6, 24.0, 24.0; LC-MS: t_R= 3.41 min, purity: 95.75%, M/z $[M+H]^+$= 407; HRMS calcd. for $C_{24}H_{31}N_4O_2$ $[M+H]^+$ = 407.2442, found 407.2439.



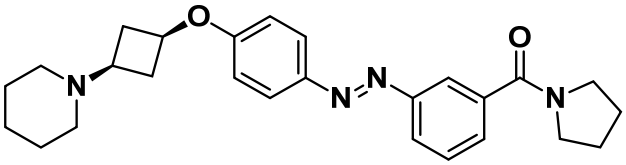
(E)-(4-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**30**)

Cs_2CO_3 (142 mg, 0.436 mmol) was added to an oven-dried microwave tube and flame-dried under vacuum. Catalyst $[PdCl(C_3H_5)]_2$ (6.7 mg, 0.018 mmol) and RockPhos (20.4 mg, 0.0435 mmol) were added. The tube was evacuated and backfilled three times with nitrogen. Bromide **23** (101 mg, 0.281 mmol) was dissolved in toluene (279 μL) and this solution was added to the reaction vial via a syringe. Then, 3-(piperidin-1-yl)propan-1-ol (85 μL, 0.56 mmol) was added via a syringe. The tube was heated to 90 °C in a sand bath for 23 hours. The mixture was cooled to RT, filtered over Celite® and the filter cake was washed with MeOH (10 mL). The solvent was evaporated *in vacuo* and the residue was purified by flash column chromatography using a gradient from *n*-heptane: EtOAc: TEA 64:35:1 to EtOAc: TEA 99:1 followed by column chromatography using an isocratic elution with EtOAc: *n*-heptane: TEA 71:25:4. The product was obtained as a viscous orange oil (45 mg, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.58 – 7.52 (m, 1H), 7.46 – 7.38 (m, 2H), 7.05 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.11 (t, *J* = 6.3 Hz, 2H), 3.67 (t, *J* = 6.9 Hz, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 2.67 – 2.33 (m, 6H), 2.06 (p, *J* = 6.6 Hz, 2H), 2.01 – 1.94 (m, 2H), 1.94 – 1.84 (m, 2H), 1.64 (p, *J* = 5.6 Hz, 4H), 1.51 – 1.40 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 159.8, 153.9, 153.2, 139.4, 129.9, 128.2, 122.9, 118.8, 117.6, 106.5, 66.8, 56.1, 54.7, 49.7, 46.4, 26.7, 26.6, 25.8, 24.6, 24.4; LC-MS: t_R= 3.43 min, purity: >99%, M/z $[M+H]^+$: 421; HRMS calcd. for $C_{25}H_{33}N_4O_2$ $[M+H]^+$ = 421.2598, found 421.2615.



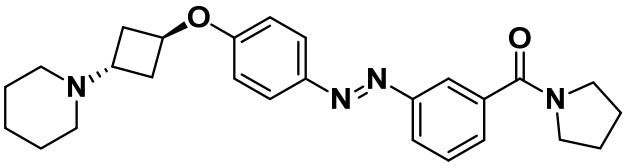
(E)-(3-((4-((1-Isopropylpiperidin-4-yl)oxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**31**)

Phenol **10** (0.150 g, 0.508 mmol), 1-isopropylpiperidin-4-ol (0.218 g, 1.52 mmol) and PPh_3 (0.400 g, 1.52 mmol) were dissolved in ice-cooled THF (9.0 mL). DEAD (0.241 mL, 1.52 mmol) in THF (6.0 mL) was added to the solution. The reaction mixture was stirred at 0 °C for 2 hours and at RT for 16 hours aq. sat. NH_4Cl solution (12 mL) was added. The mixture was extracted using EtOAc (3x30 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude residue was purified using flash column chromatography with a gradient from EtOAc: *n*-heptane: TEA 75:24:1 to EtOAc: TEA 99:1. The compound was heated in *n*-heptane. The mixture was cooled and filtered. The filtrate was evaporated *in vacuo* to yield the product as a yellow fluffy powder (156 mg, 73%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.96 – 7.84 (m, 4H), 7.69 – 7.59 (m, 2H), 7.17 – 7.09 (m, 2H), 4.54 – 4.45 (m, 1H), 3.49 (t, *J* = 6.9 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.77 – 2.62 (m, 3H), 2.40 – 2.30 (m, 2H), 2.04 – 1.94 (m, 2H), 1.88 (p, *J* = 6.7 Hz, 2H), 1.82 (p, *J* = 6.2 Hz, 2H), 1.67 – 1.56 (m, 2H), 0.97 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.4, 160.4, 151.7, 145.8, 138.4, 129.5, 129.1, 124.9, 123.9, 120.2, 116.1, 73.5, 53.6, 49.0, 46.0, 45.3, 31.1, 26.0, 24.0, 18.1; LC-MS: t_R= 3.46 min, purity: >99%, M/z $[M+H]^+$: 421; HRMS calcd. for $C_{25}H_{33}N_4O_2$ $[M+H]^+$ = 421.2598, found 421.2617.



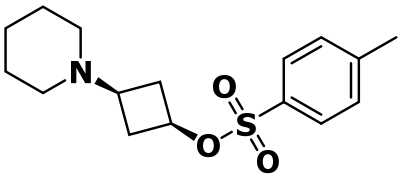
(3-((E)-(4-((1s,3s)-3-(Piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**32**)

Cs_2CO_3 (0.205 g, 0.628 mmol) was added to an oven-dried microwave tube and and flame-dried under vacuum. Bromide **24** (0.150 g, 0.419 mmol) was dissolved in toluene (1.20 mL) and added to the vial. Rockphos (0.031 g, 0.067 mmol), cyclobutanol **35** (0.130 g, 0.837 mmol) and $[(C_3H_5)PdCl]_2$ (7.6 mg, 0.021 mmol) were subsequently added to the vial. The flask was evacuated and backfilled three times with nitrogen. The microwave vial was heated in a sand bath at 90 °C and for 24 hours. The mixture was cooled to RT, filtered over Celite® and the filter cake was washed with MeOH (10 mL). The solvent was evaporated *in vacuo*, after which the crude product was subjected to flash column chromatography using a gradient from *n*-heptane: EtOAc: TEA 50:45:5 to EtOAc: TEA 95:5 to yield the product as orange crystals (68 mg, 38%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.99 (m, 1H), 7.93 – 7.85 (m, 3H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 6.94 – 6.88 (m, 2H), 4.50 (p, *J* = 7.1 Hz, 1H), 3.68 (t, *J* = 7.0 Hz, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 2.77 – 2.68 (m, 2H), 2.54 – 2.05 (m, 7H), 1.98 (p, *J* = 6.9 Hz, 2H), 1.89 (p, *J* = 6.8 Hz, 2H), 1.69 – 1.55 (m, 4H), 1.51 – 1.39 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 160.4, 152.5, 146.9, 138.2, 129.3, 129.0, 125.0, 124.3, 121.0, 115.4, 65.7, 52.6, 51.0, 49.8, 46.4, 35.6, 26.6, 25.4, 24.6, 24.3; LC-MS: t_R= 3.28 min, purity: >99%, M/z $[M+H]^+$: 433; HRMS calcd. for $C_{26}H_{33}N_4O_2$ $[M+H]^+$ = 433.2598, found 433.2610; *Cis*-stereochemistry was proven by 2D NOE NMR (see Figure S36).



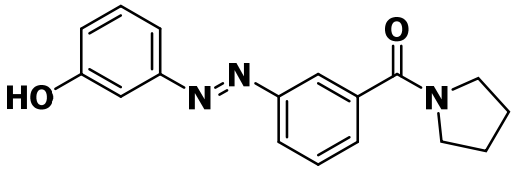
(3-((E)-(4-((1r,3s)-3-(Piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**33**)

Phenol **10** (0.100 g, 0.339 mmol), cyclobutanol **35** (0.105 g, 0.677 mmol) and PPh_3 (0.266 g, 1.02 mmol) were dissolved in ice-cooled THF (6.0 mL). DEAD (0.161 mL, 1.02 mmol) in THF (4 mL) was added to the solution. After 23 hours at RT, aq. sat. $NaHCO_3$ solution (8 mL) was added. The mixture was extracted with EtOAc (3x20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified using flash column chromatography with a gradient from *n*-heptane: EtOAC: TEA 82:17:1 to EtOAc: TEA 99:1. The compound was heated in *n*-heptane. The mixture was cooled and filtered. The filtrate was evaporated *in vacuo* to yield the product as a yellow fluffy solid (48 mg, 33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 – 7.85 (m, 4H), 7.68 – 7.59 (m, 2H), 7.06 – 6.98 (m, 2H), 4.85 (tt, *J* = 6.9, 3.5 Hz, 1H), 3.50 (t, *J* = 6.8 Hz, 2H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.94 – 2.82 (m, 1H), 2.45 – 2.35 (m, 2H), 2.33 – 2.12 (m, 6H), 1.95 – 1.77 (m, 4H), 1.50 (p, *J* = 5.4 Hz, 4H), 1.44 – 1.34 (m, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.4, 160.3, 151.7, 146.0, 138.4, 129.5, 129.1, 124.9, 123.9, 120.2, 115.6, 70.0, 56.4, 50.5, 49.0, 46.0, 33.1, 26.0, 25.3, 24.1, 24.0; LC-MS: t_R= 3.34 min, purity: >99%, M/z $[M+H]^+$: 433; HRMS calcd. for $C_{26}H_{33}N_4O_2$ $[M+H]^+$ = 433.2598, found 433.2603; *Trans*-stereochemistry was proven by 2D NOE NMR (see Figure S37).



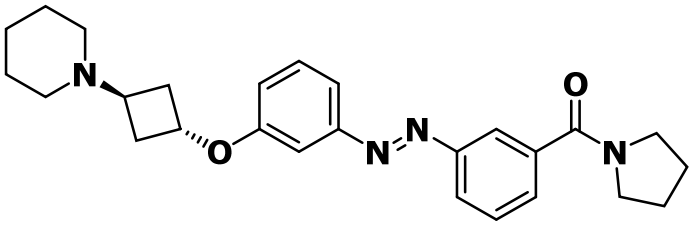
(1s,3s)-3-(piperidin-1-yl)cyclobutyl 4-methylbenzenesulfonate (**36**)

This procedure was based on a literature description[2]. 1-methylimidazole (0.339 mL, 4.25 mmol) and cyclobutanol **35** (330 mg, 2.13 mmol) were mixed in anhydrous DCM (3.5 mL) after which 4-toluenesulfonyl chloride (689 mg, 3.61 mmol) was added. The solution was stirred at RT for 48 hours. Aq. satd. $NaHCO_3$ (3 mL) was added and the layers were partitioned. The organic phase was dried over Na_2SO_4, and evaporated *in vacuo*. The crude product was further purified using flash column chromatography eluting with DCM : MeOH : 28% aq. NH_3 (990:9:1) to yield the product as an off-white colored solid (280 mg, 43%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.58 (p, *J* = 7.5 Hz, 1H), 2.47 – 2.37 (m, 5H), 2.28 – 2.10 (m, 5H), 2.07 – 1.98 (m, 2H), 1.54 (p, *J* = 5.8 Hz, 4H), 1.45 – 1.35 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.8, 134.2, 129.9, 128.0, 68.8, 52.4, 50.9, 36.0, 25.5, 24.2, 21.8; LC-MS: t_R= 2.84 min, purity: 88.5%, M/z $[M+H]^+$: 310; *cis*-stereochemistry was proven by 2D NOE NMR (see Figure S38).



(E)-(3-((3-hydroxyphenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**37**)

Aniline **6** (670 mg, 3.52 mmol) was added to a mixture of Oxone^{tm} (4.33 g, 7.04 mmol) dissolved in water (44 mL) and DCM (11 mL). The mixture was stirred at RT for 6 hours. The layers were separated and the organic phase was washed with 10% aq. sodium thiosulfate (5 mL), 1 M aq. HCl solution (5 mL) and brine (5 mL). The organic phase was added to a flask containing 3-((*tert*-butyldimethylsilyl)oxy)aniline (715 mg, 3.20 mmol) and acetic acid (11 mL). After stirring overnight at RT the solution was evaporated to dryness and anhydrous THF (33 mL) and 1 M TBAF solution in THF (6.40 mL, 6.40 mmol) were added at ice-bath temperature. After 10 minutes aq. satd. $NaHCO_3$ (40 mL) and EtOAc (30 mL) were added and the mixture was extracted using EtOAc (3x 30 mL). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was subjected to preparative reverse phase chromatography on C-18 functionalized silica eluting with a gradient from H_2O:ACN:HCOOH 949:50:1 to ACN:formic acid:HCOOH 100:899:1 to yield the product as an orange solid (120 mg, 13%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.23 (t, *J* = 2.1 Hz, 1H), 6.98 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.72 (t, *J* = 7.0 Hz, 2H), 3.48 (t, *J* = 6.6 Hz, 2H), 1.99 (p, *J* = 6.9 Hz, 2H), 1.90 (p, *J* = 6.7 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.7, 157.5, 153.6, 152.3, 137.6, 129.9, 129.4, 129.3, 124.6, 121.3, 119.2, 117.0, 108.0, 50.0, 46.7, 26.5, 24.6; LC-MS: t_R= 4.09 min, purity: >98%, M/z $[M+H]^+$: 296.



(3-((E)-(3-((1r,3s)-3-(piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (**34**)

Phenol **37** (120 mg, 0.406 mmol) was dissolved in anhydrous DMF (433 µL) after which sodium hydride (60% dispersion in mineral oil, 20.0 mg, 0.500 mmol) was added. The solution was stirred for 30 minutes at RT after which tosylate **36** (97 mg, 0.313 mmol) was added and the solution was stirred overnight at 90 °C. EtOAc (5 mL) was added to the solution. The mixture was washed using ice-cold brine (2 x 2 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo* to obtain an orange crude product which was purified using flash column chromatography eluting with a gradient from cyclohexane:EtOAc + 5% TEA 8:2 to EtOAc + 5% TEA:MeOH 19:1 to yield the product as a sticky orange oil (80 mg, 59%). ^{1}H NMR (600 MHz, CD_3OD) δ 8.06 – 8.03 (m, 1H), 8.01 (dt, *J* = 7.4, 1.8 Hz, 1H), 7.69 – 7.61 (m, 2H), 7.58 – 7.53 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 2.1 Hz, 1H), 7.01 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.86 (s, 1H), 3.63 (t, J = 7.0 Hz, 2H), 3.50 (t, *J* = 6.7 Hz, 2H), 3.09 (p, *J* = 7.5 Hz, 1H), 2.54 – 2.24 (m, 8H), 2.01 (p, *J* = 6.8 Hz, 2H), 1.92 (p, *J* = 6.7 Hz, 2H), 1.64 (p, *J* = 5.7 Hz, 4H), 1.50 (s, 2H). The signal at 4.86 ppm is obscured by the peak of H_2O; ^{13}C NMR (151 MHz, CD_3OD) δ 170.8, 159.7, 155.0, 153.7, 139.3, 131.2, 130.7, 130.6, 125.6, 122.1, 119.9, 118.1, 108.5, 70.4, 58.7, 52.0, 50.9, 47.5, 34.3, 27.3, 26.1, 25.3, 24.9; LC-MS: t_R= 3.69 min, purity: >99%, M/z $[M+H]^+$: 433; HRMS calcd. for $C_{26}H_{33}N_4O_2$ $[M+H]^+$ = 433.2598, found 433.2606; *Trans*-stereochemistry was proven by 2D NOE NMR (see Figure S39).

Chemical analyses

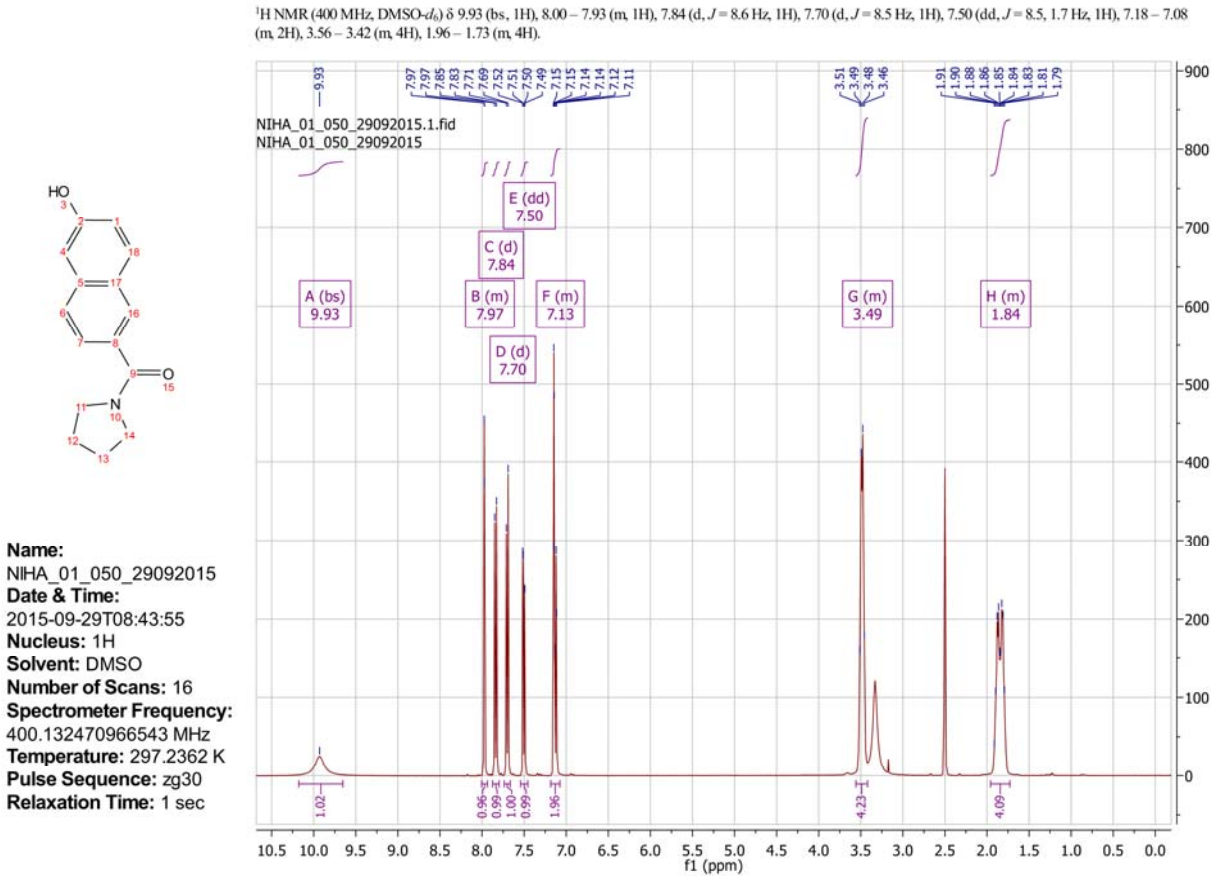


Figure S40: ^{1}H-NMR spectrum of (6-Hydroxynaphthalen-2-yl)(pyrrolidin-1-yl)methanone (38)

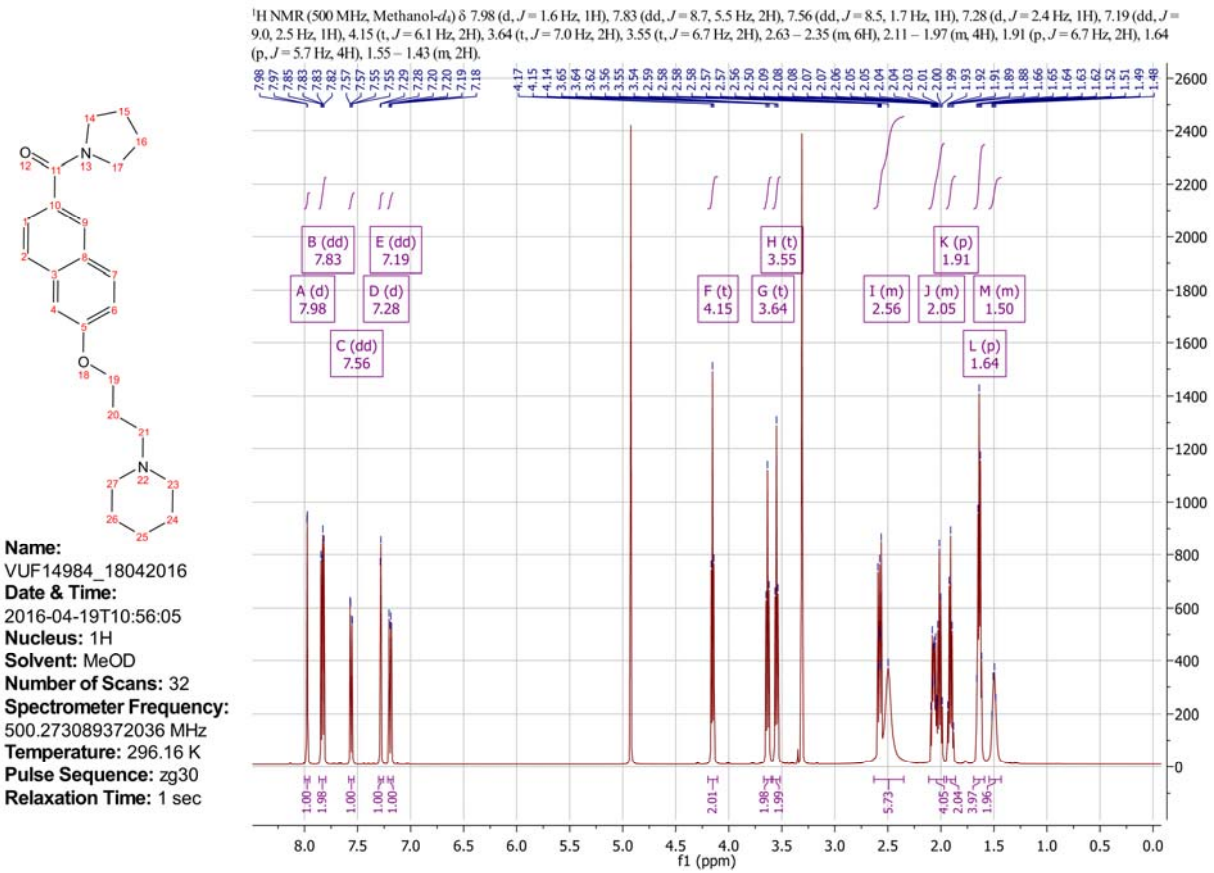


Figure S41: ^{1}H-NMR spectrum of (6-(3-(Piperidin-1-yl)propoxy)naphthalen-2-yl)(pyrrolidin-1yl)methanone (1)

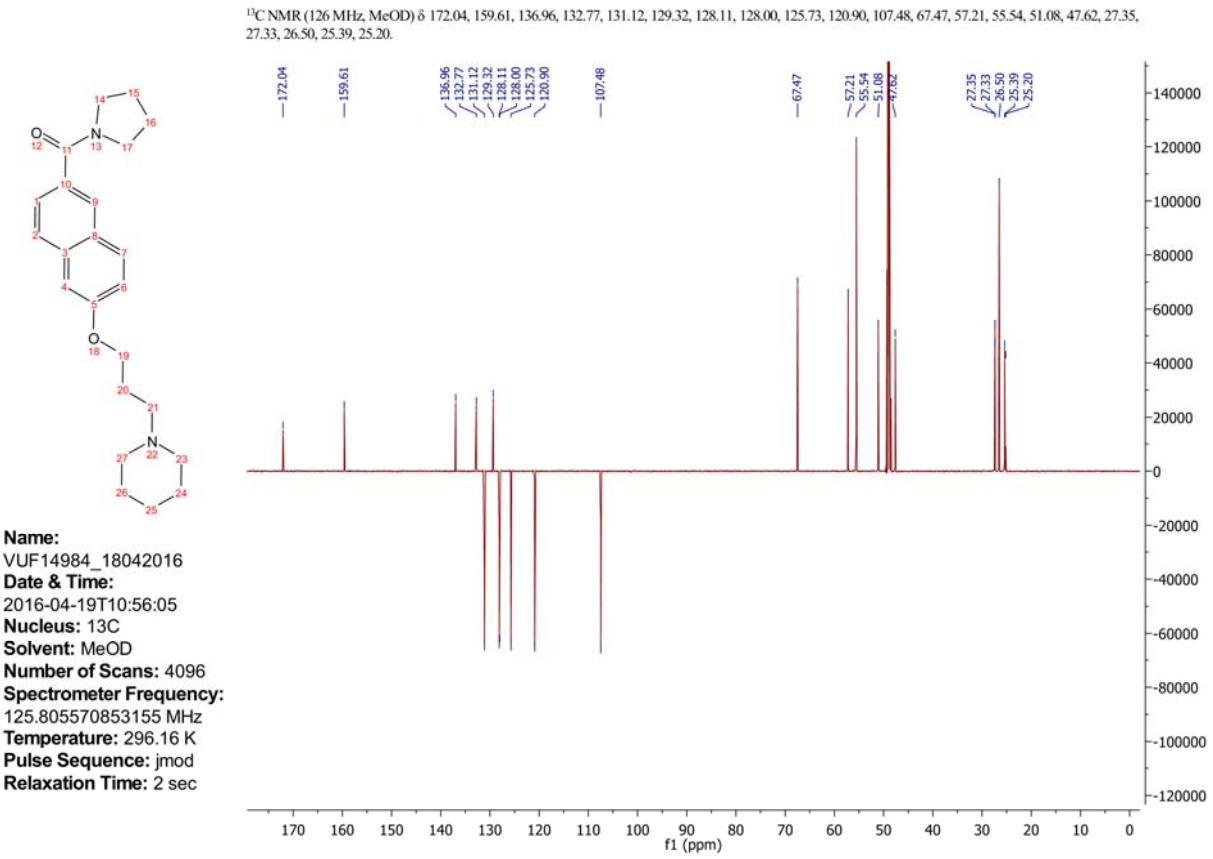


Figure S42: ^{13}C-NMR spectrum of (6-(3-(Piperidin-1-yl)propoxy)naphthalen-2-yl)(pyrrolidin-1yl)methanone (1)

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Sample ID	:
Tray#	: 1
Vial#	: 24
Injection Volume	: 10
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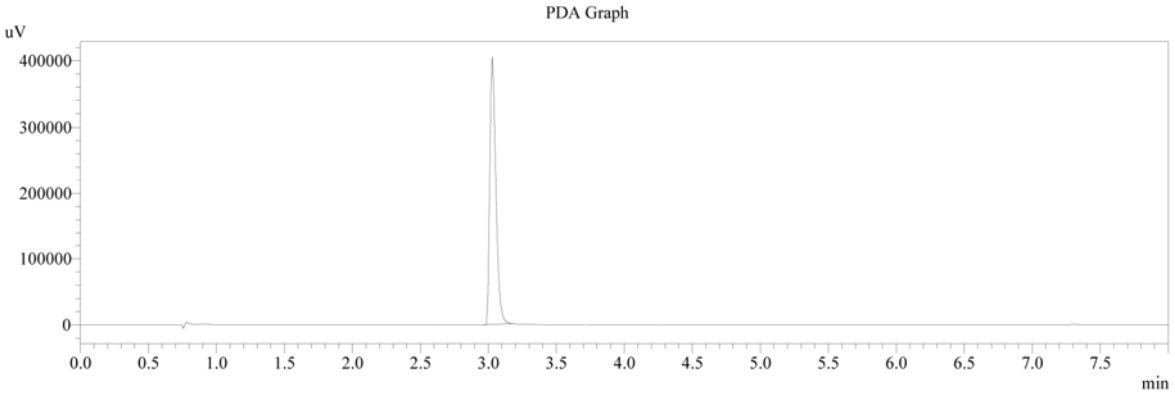
Background File	: VUFBlanco_IRRA_2_13052015.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Data\Installatie NOV 2009\Tuning ESI POS + NEG JAN2010.lct
Processed by	: Admin
Modified Date	: 1/29/2016 10:52:32 AM



PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.024	1252683	100.000

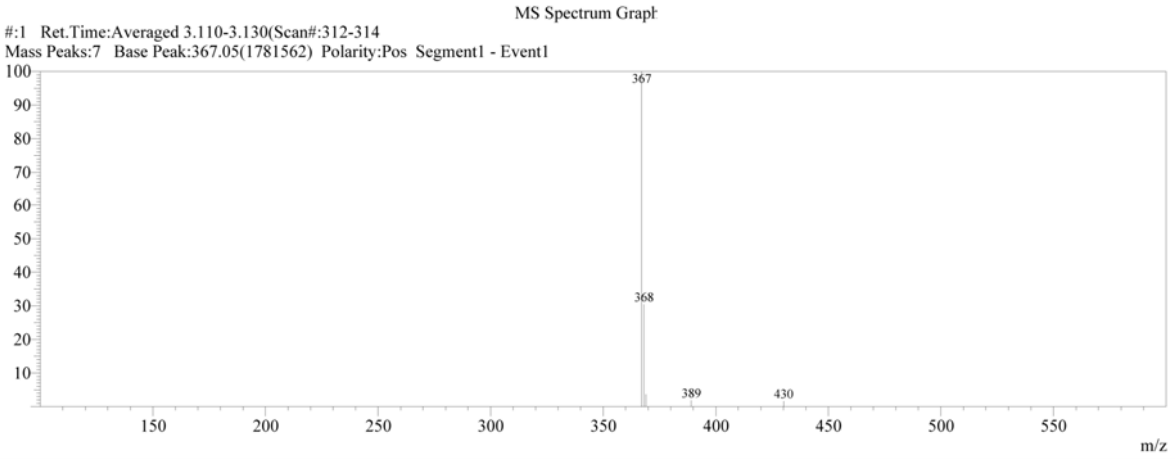


Figure S43: LC-MS chromatogram of (6-(3-(Piperidin-1-yl)propoxy)naphthalen-2-yl)(pyrrolidin-1yl)methanone (1)

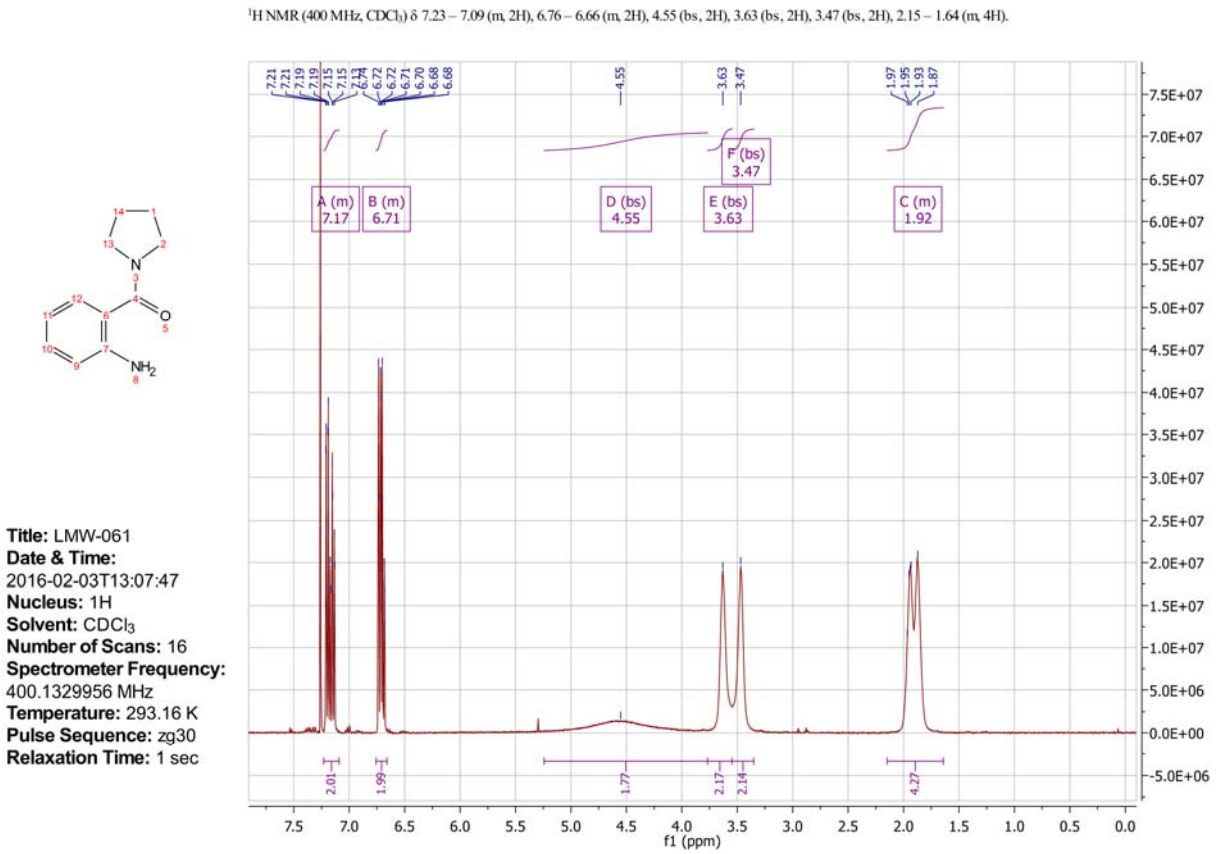


Figure S44: ^{1}H-NMR spectrum of (2-Aminophenyl)(pyrrolidin-1-yl)methanone (5)

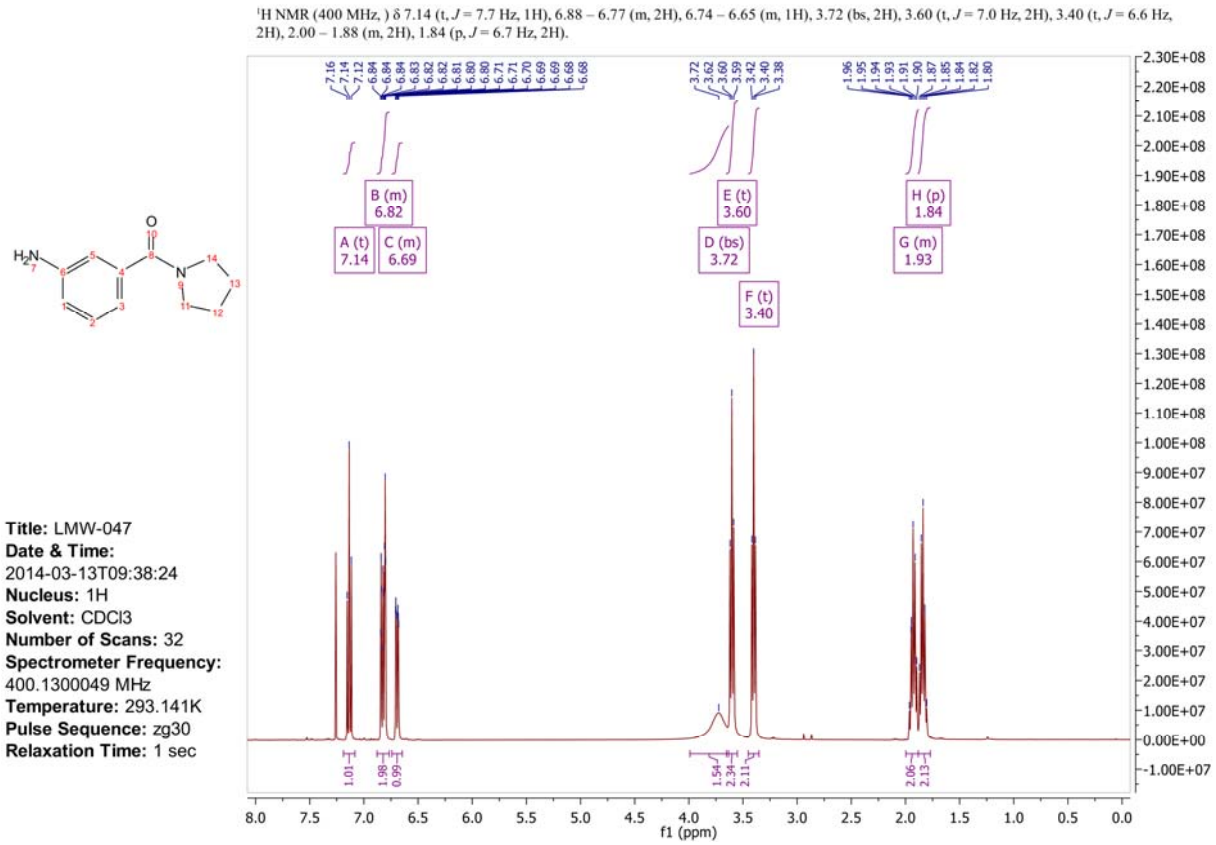


Figure S45: ^{1}H-NMR spectrum of (3-Aminophenyl)(pyrrolidin-1-yl)methanone (6)

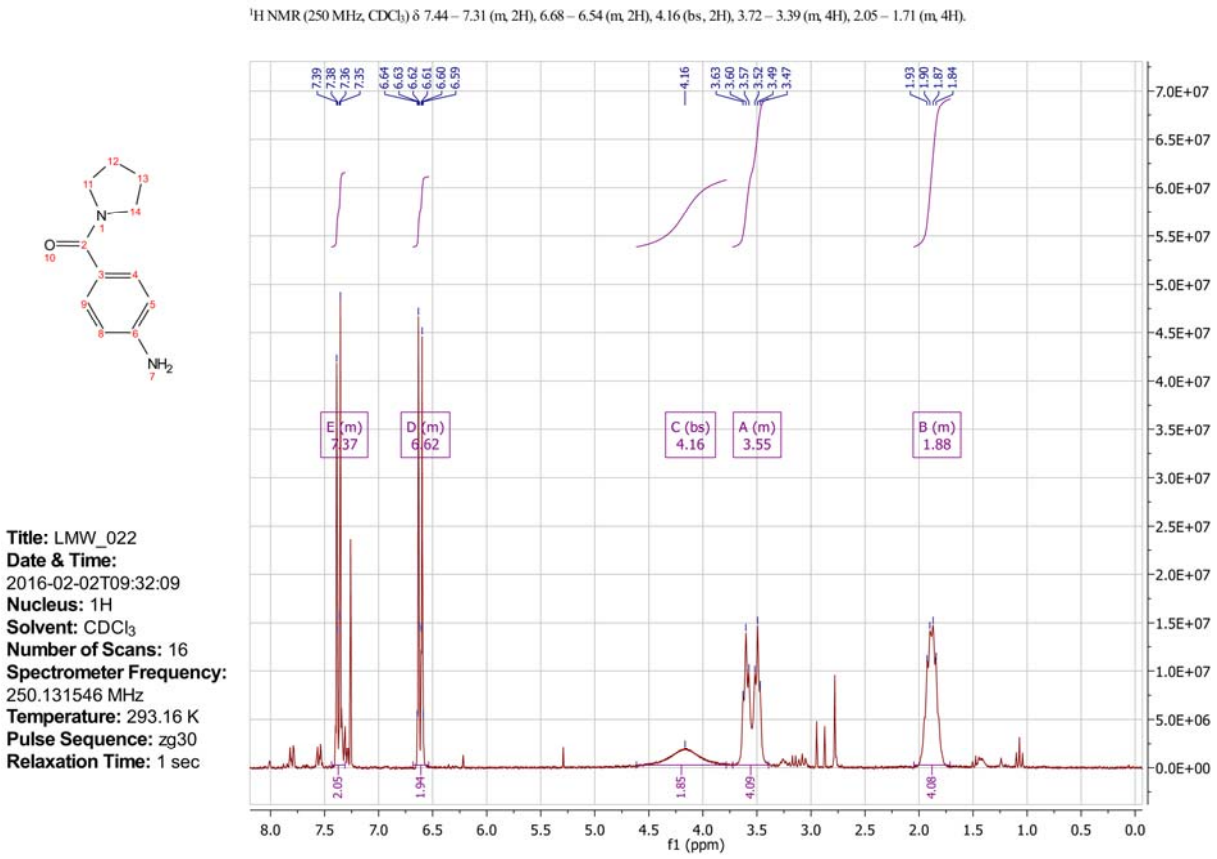


Figure S46: ^{1}H-NMR spectrum of (4-Aminophenyl)(pyrrolidin-1-yl)methanone (7)

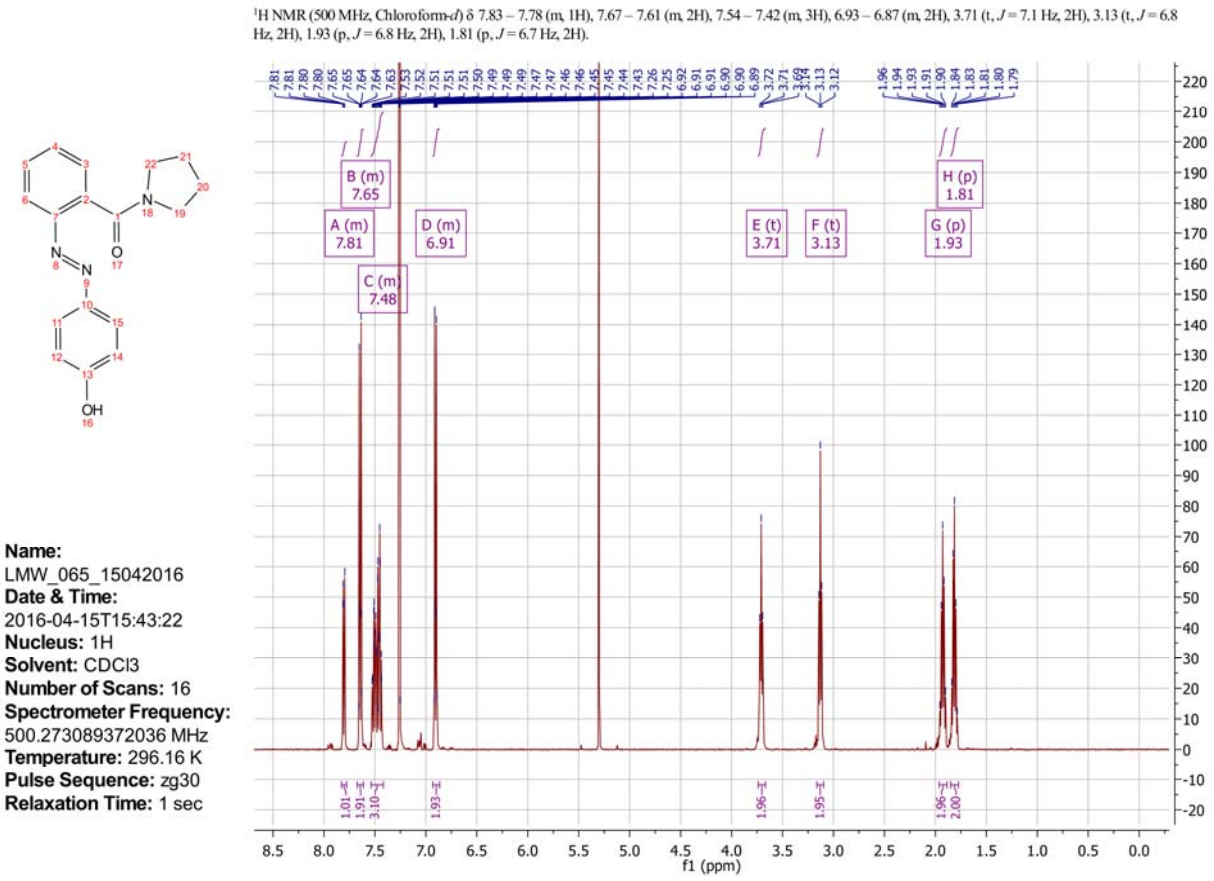
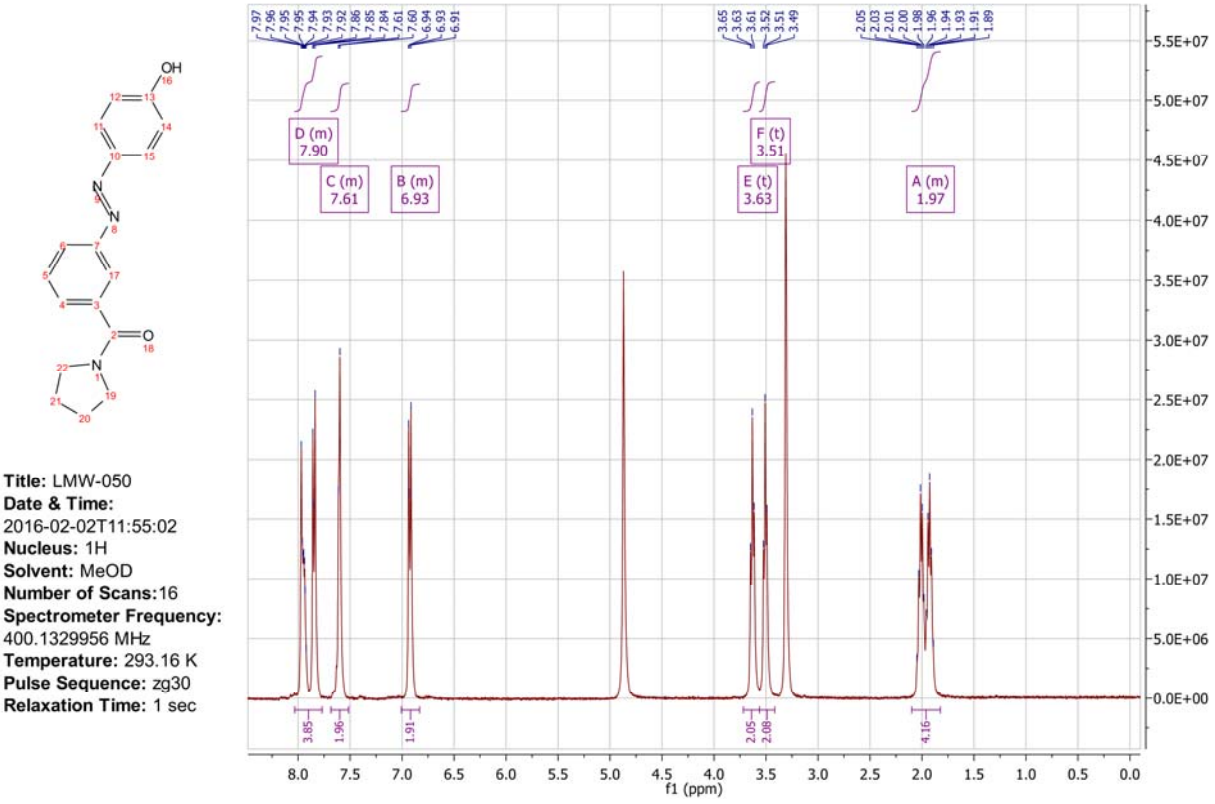


Figure S47: ^{1}H-NMR spectrum of (E)-(2-((4-Hydroxyphenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (9)

^{1}H NMR (400 MHz, MeOD) δ 8.03 – 7.77 (m, 4H), 7.68 – 7.52 (m, 2H), 7.01 – 6.83 (m, 2H), 3.63 (t, *J* = 6.9 Hz, 2H), 3.51 (t, *J* = 6.7 Hz, 2H), 2.10 – 1.82 (m, 4H).



Title: LMW-050
Date & Time: 2016-02-02T11:55:02
Nucleus: 1H
Solvent: MeOD
Number of Scans: 16
Spectrometer Frequency: 400.1329956 MHz
Temperature: 293.16 K
Pulse Sequence: zg30
Relaxation Time: 1 sec

Figure S48: ^{1}H-NMR spectrum of (E)-(3-((4-Hydroxyphenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (10)

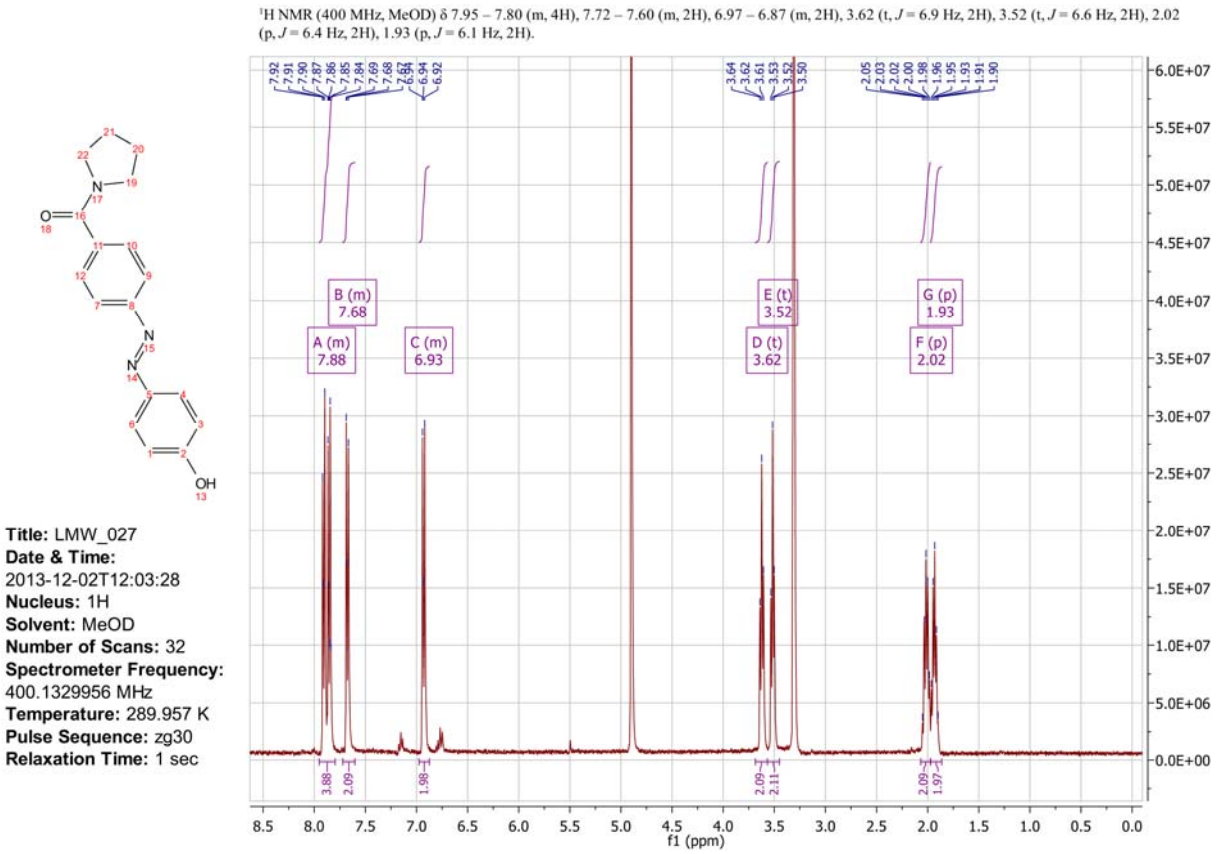


Figure S49: ^{1}H-NMR spectrum of (E)-(4-((4-Hydroxyphenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (11)

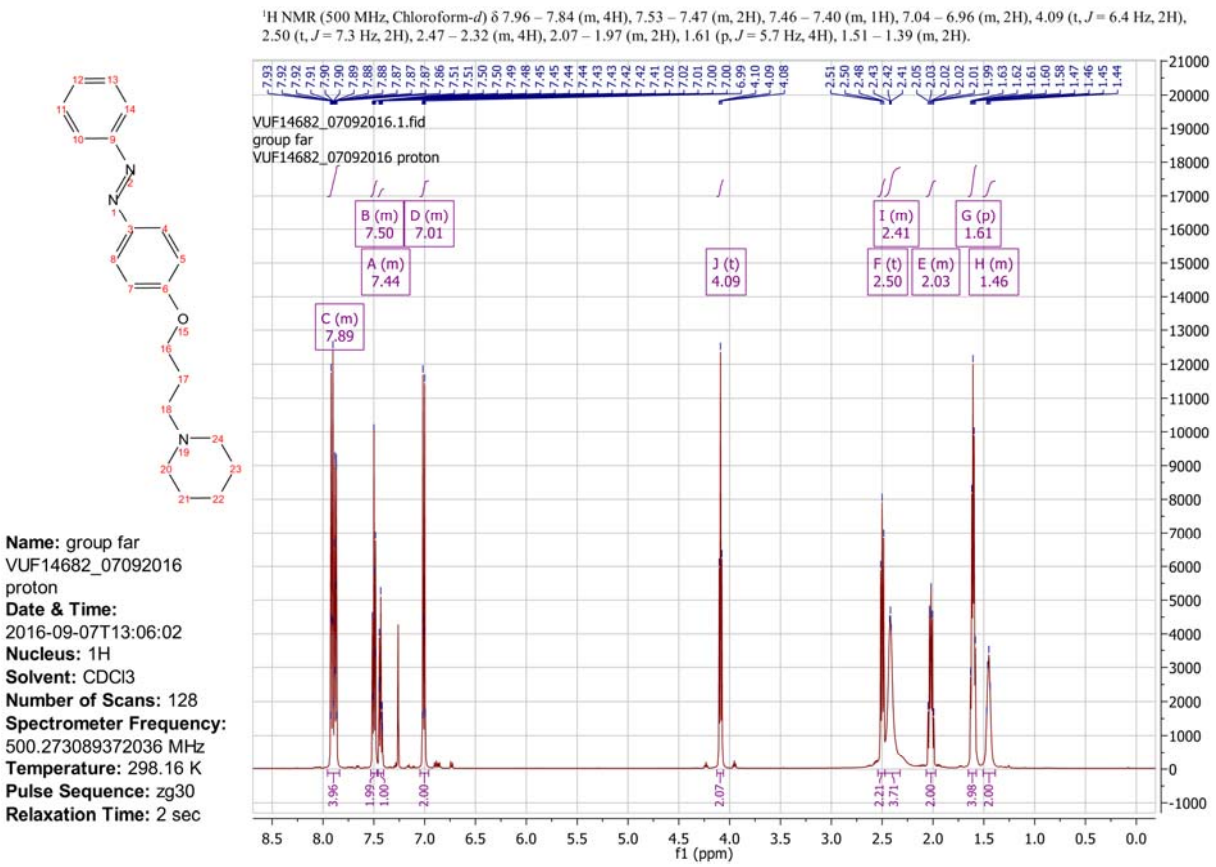


Figure S50: ^{1}H-NMR spectrum of (E)-1-(3-(4-(Phenyldiazenyl)phenoxy)propyl)piperidine (12)

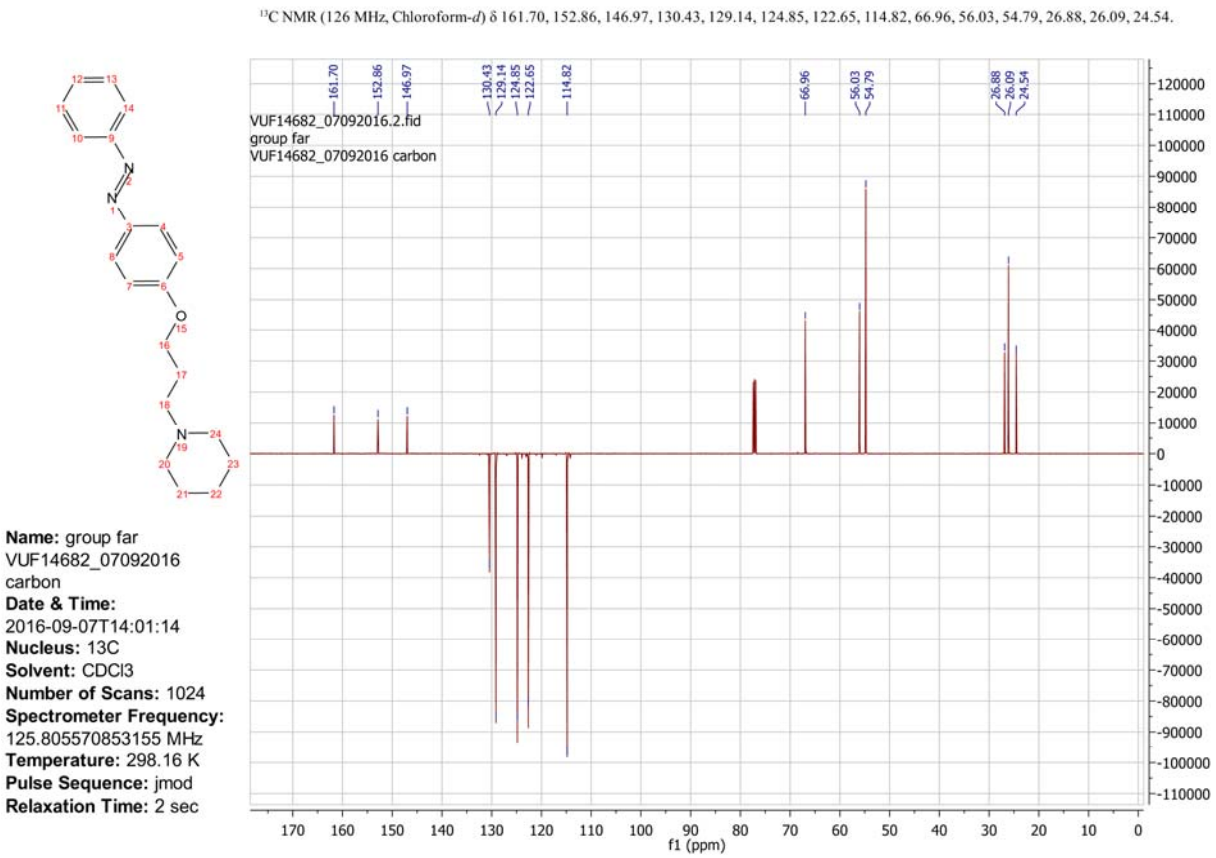


Figure S51: ^{13}C-NMR spectrum of (E)-1-(3-(4-(Phenyldiazenyl)phenoxy)propyl)piperidine (12)

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Sample ID	:
Tray#	: 1
Vial#	: 6
Injection Volume	: 10
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Background File	: BLANCO_DARK_27012016.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
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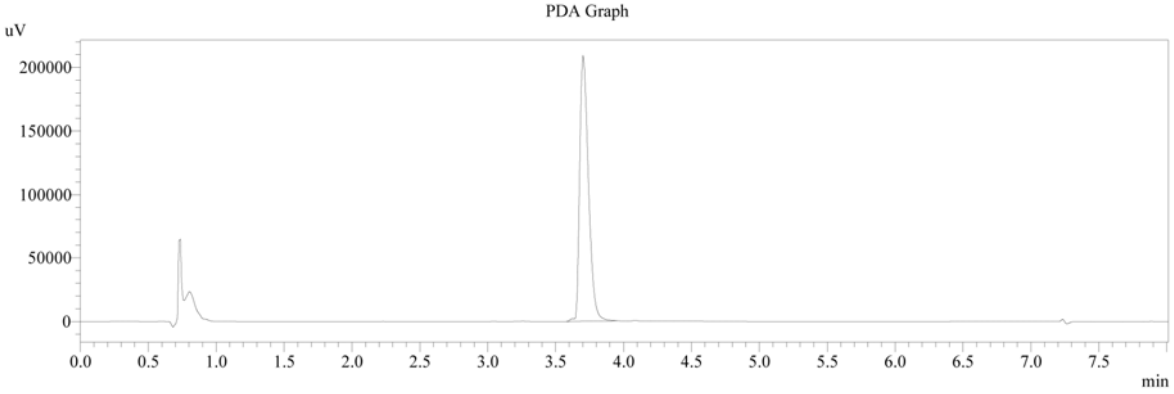
Processed by	: Admin
Modified Date	: 9/9/2016 3:44:37 PM

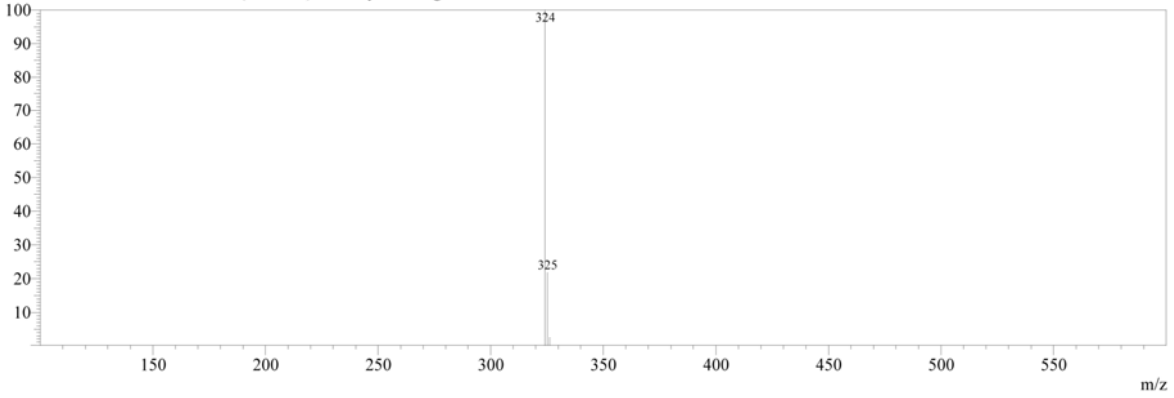


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.697	946043	100.000

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.820-3.840(Scan#:383-385)
Mass Peaks:3 Base Peak:324.15(3197093) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.660<->4.150(367<->416
Mass Peaks:3 Base Peak:324.15(3197093) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	324.15	3197093	100.00				3	326.20	74880	2.34			
2	325.15	700306	21.90										

Figure S52: LC-MS chromatogram of (E)-1-(3-(4-(Phenyldiazenyl)phenoxy)propyl)piperidine (12)

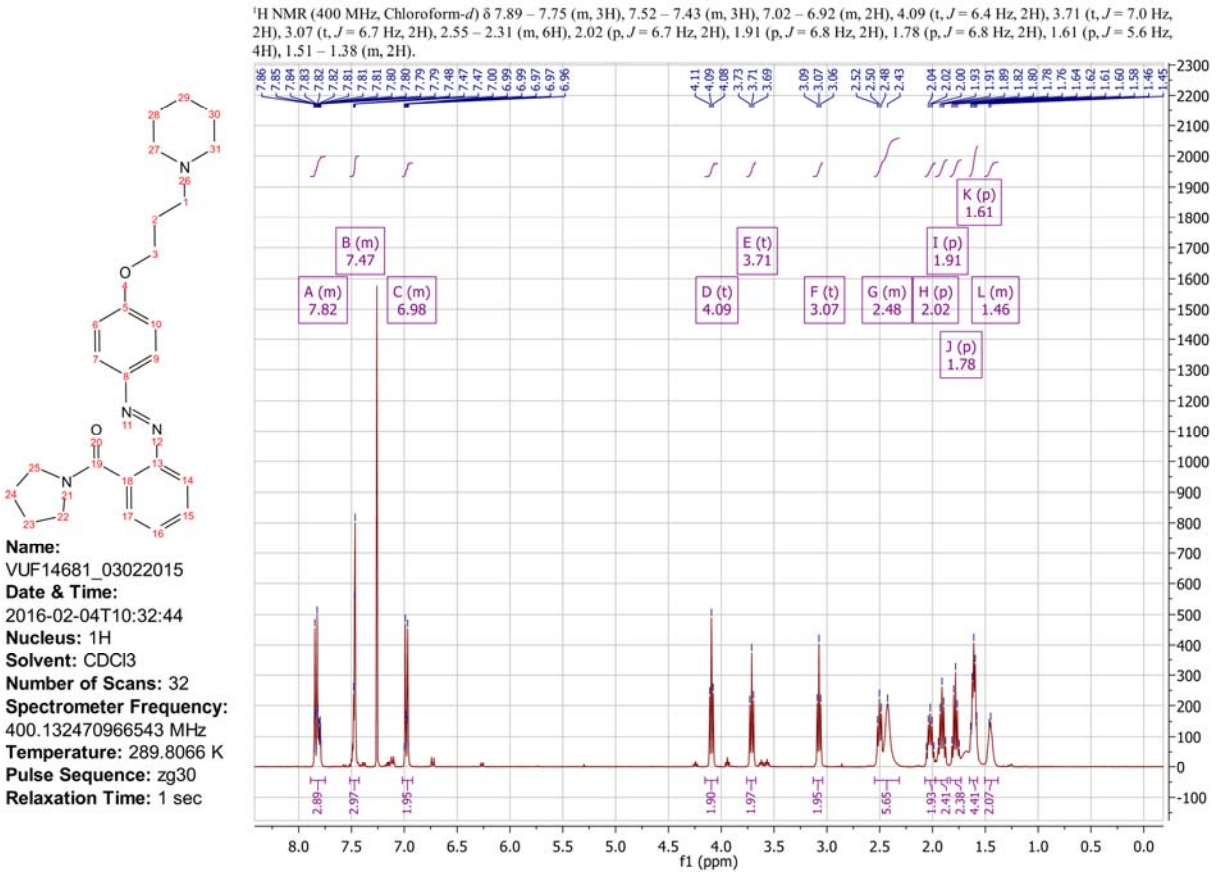


Figure S53: ^{1}H-NMR spectrum of (E)-(2-((4-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (13)

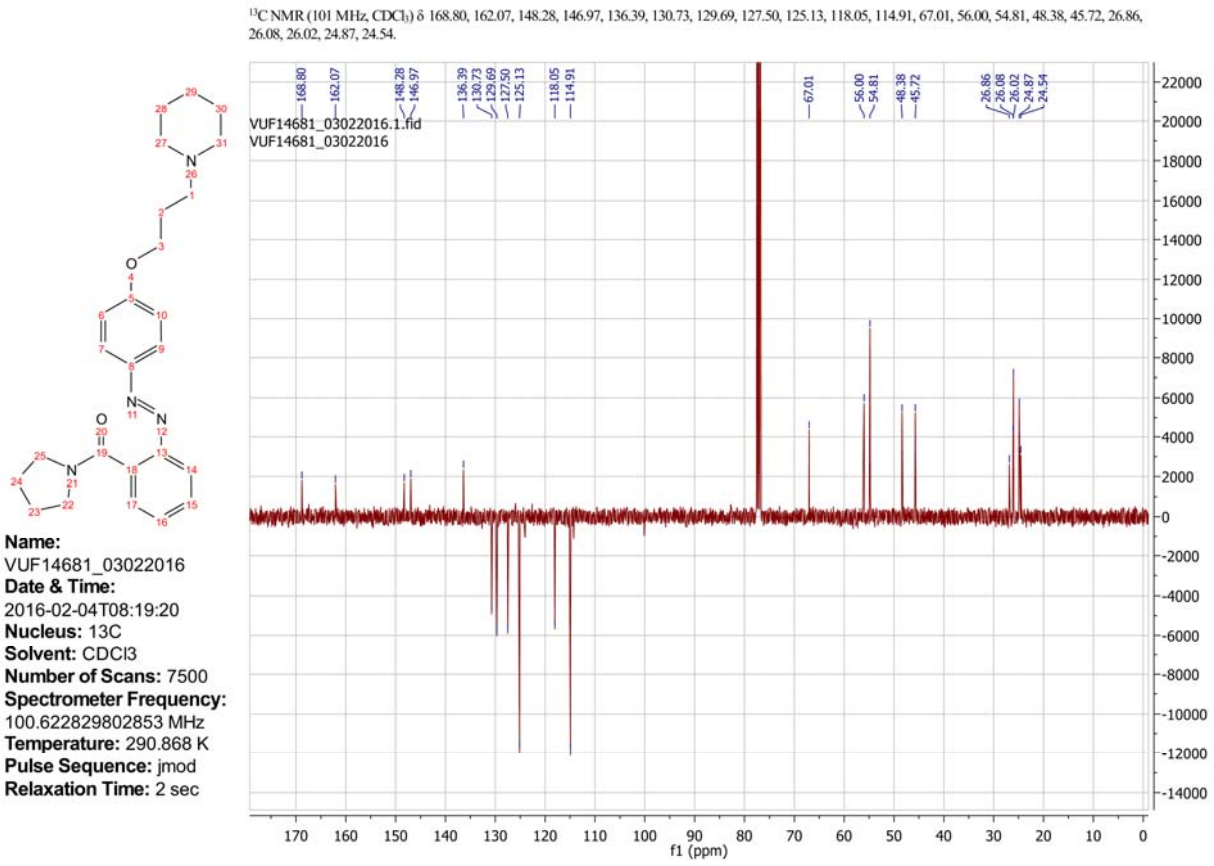
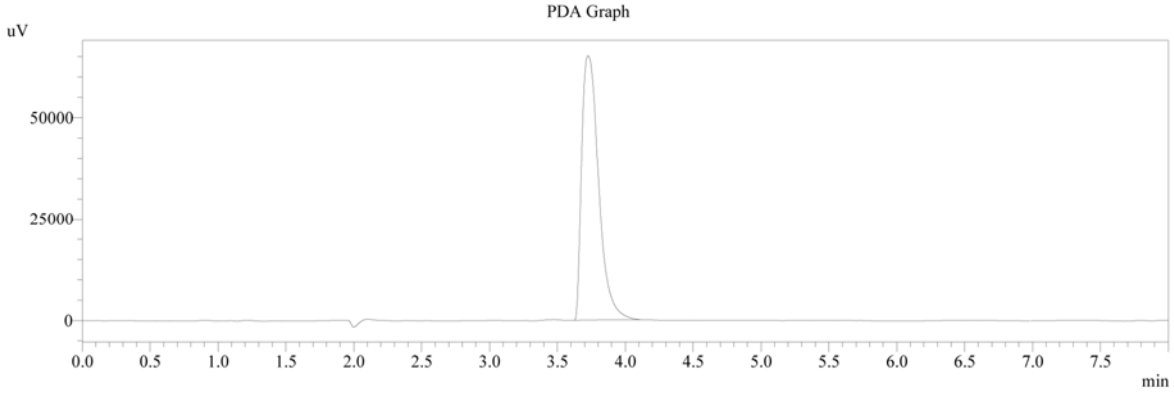


Figure S54: ^{13}C-NMR spectrum of (E)-(2-((4-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (13)

Acquired by	: Admin
Date Acquired	: 10/17/2014 10:20:23 AM
Sample Name	: VUF14681_D_17102014
Sample ID	:
Tray#	: 1
Vial#	: 14
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2014\2014-wk42\VUF14681_D_17102014.lcd
Background File	: DMSOd6_blanco_D_17102014.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Data\Installatie NOV 2009\Tuning ESI POS + NEG JAN2010.lct
Processed by	: Admin
Modified Date	: 11/4/2014 12:05:03 PM

PDA Graph

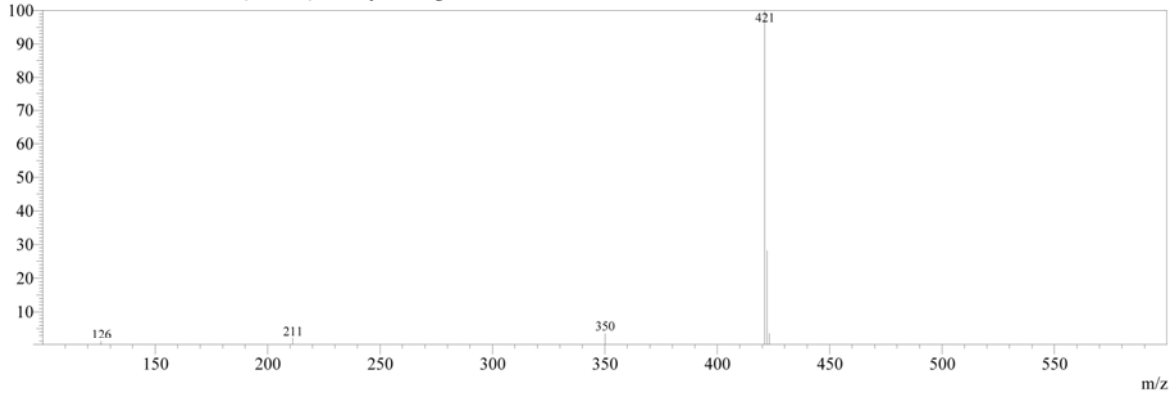


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.721	564010	100.000

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.810-3.830(Scan#:382-384)
Mass Peaks:7 Base Peak:421.20(1330263) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.660<->4.160(367<->417
Mass Peaks:7 Base Peak:421.20(1330263) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	125.95	14554	1.09				5	422.15	376164	28.28			
2	211.20	26598	2.00				6	423.20	48661	3.66			
3	350.05	47548	3.57				7	863.45	14334	1.08			
4	421.20	1330263	100.00										

Figure S55: LC-MS chromatogram of (E)-(2-((4-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (13)

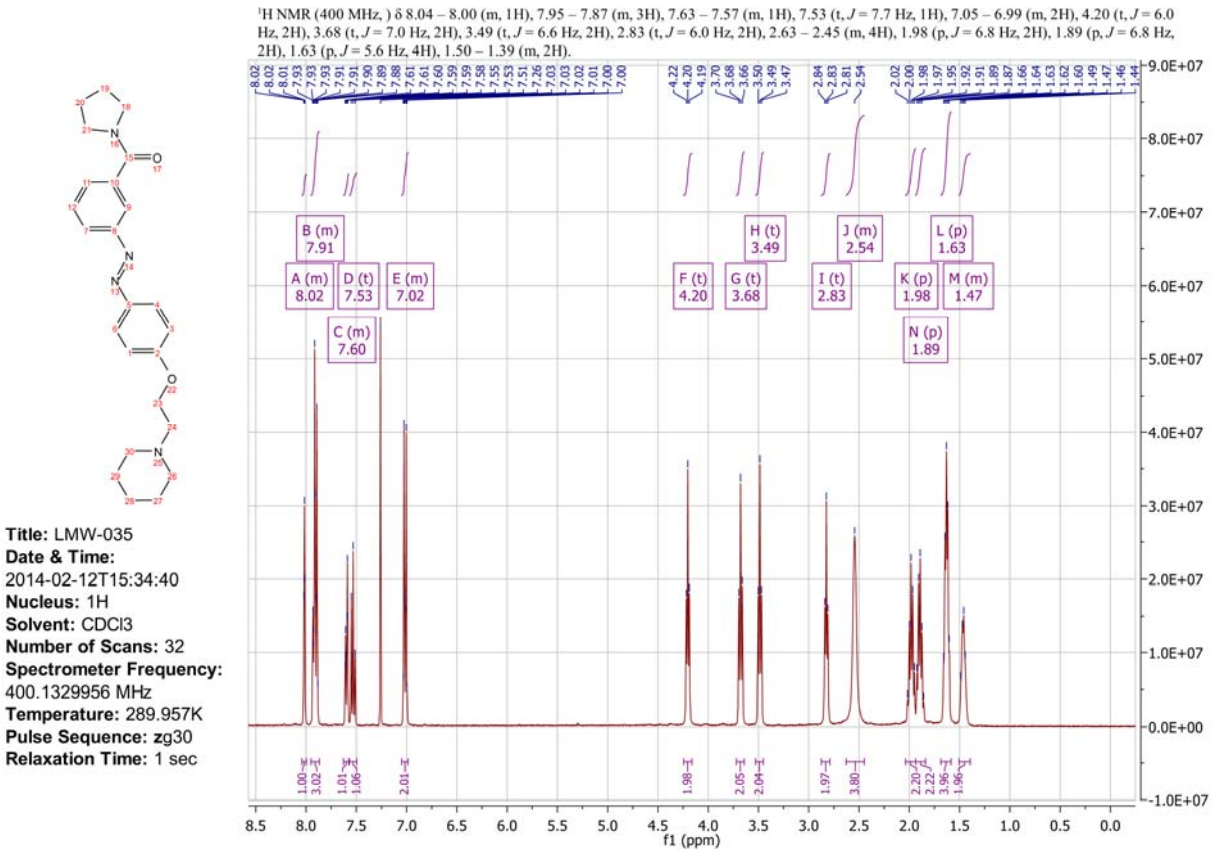


Figure S56: ^{1}H-NMR spectrum of (E)-(3-((4-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (14)

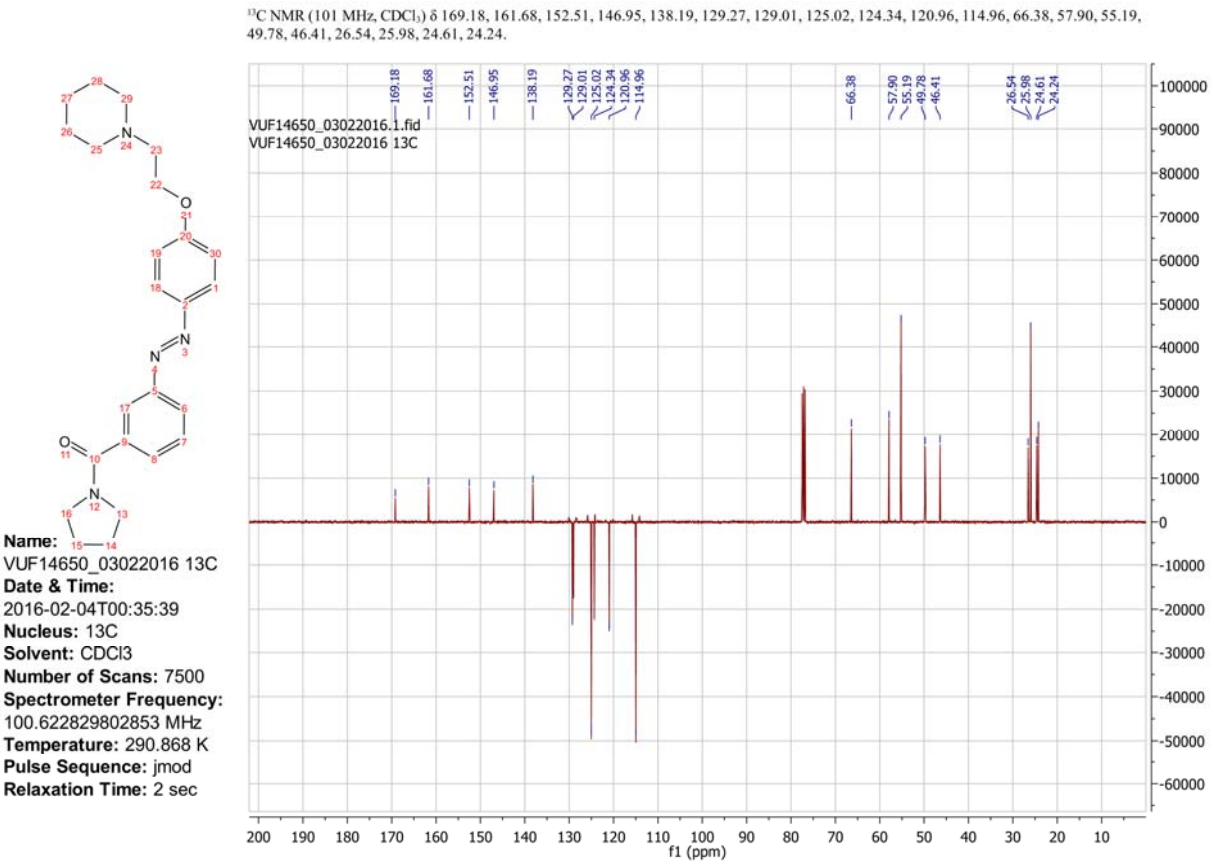


Figure S57: ^{13}C-NMR spectrum of (E)-(3-((4-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (14)

Acquired by	: Admin
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Sample ID	:
Tray#	: 1
Vial#	: 23
Injection Volume	: 10
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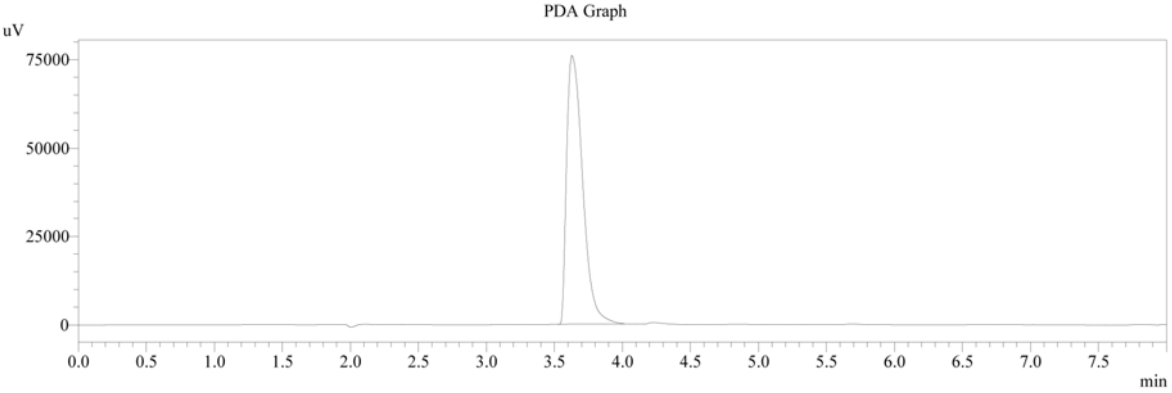
Background File	: DMSOd6_blanco_D2_22102014.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Data\Installatie NOV 2009\Tuning ESI POS + NEG JAN2010.lct
Processed by	: Admin
Modified Date	: 10/27/2014 10:06:16 AM

PDA Graph

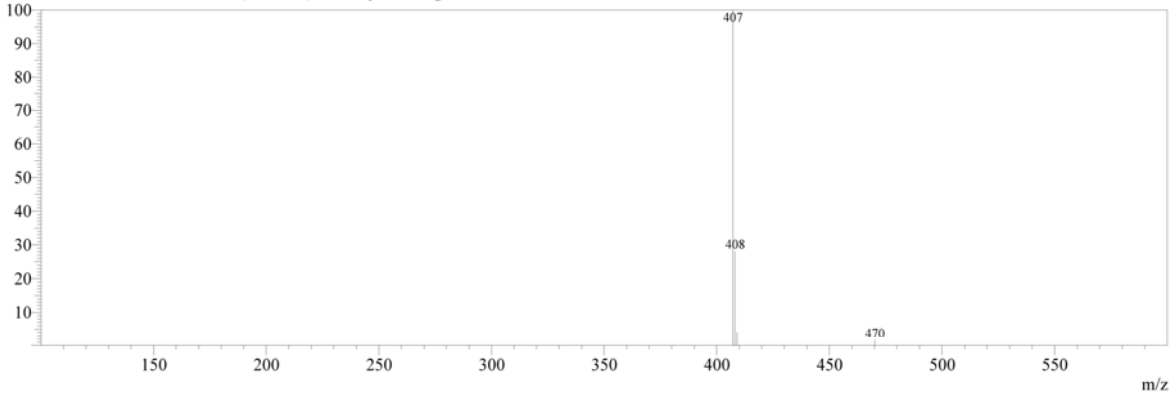


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.625	624778	100.000

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.720-3.740(Scan#:373-375)
Mass Peaks:4 Base Peak:407.10(1511516) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.570<->4.100(358<->411
Mass Peaks:4 Base Peak:407.10(1511516) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	407.10	1511516	100.00				3	409.05	61386	4.06			
2	408.10	423644	28.03				4	470.15	23393	1.55			

Figure S58: LC-MS chromatogram of (E)-(3-((4-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (14)

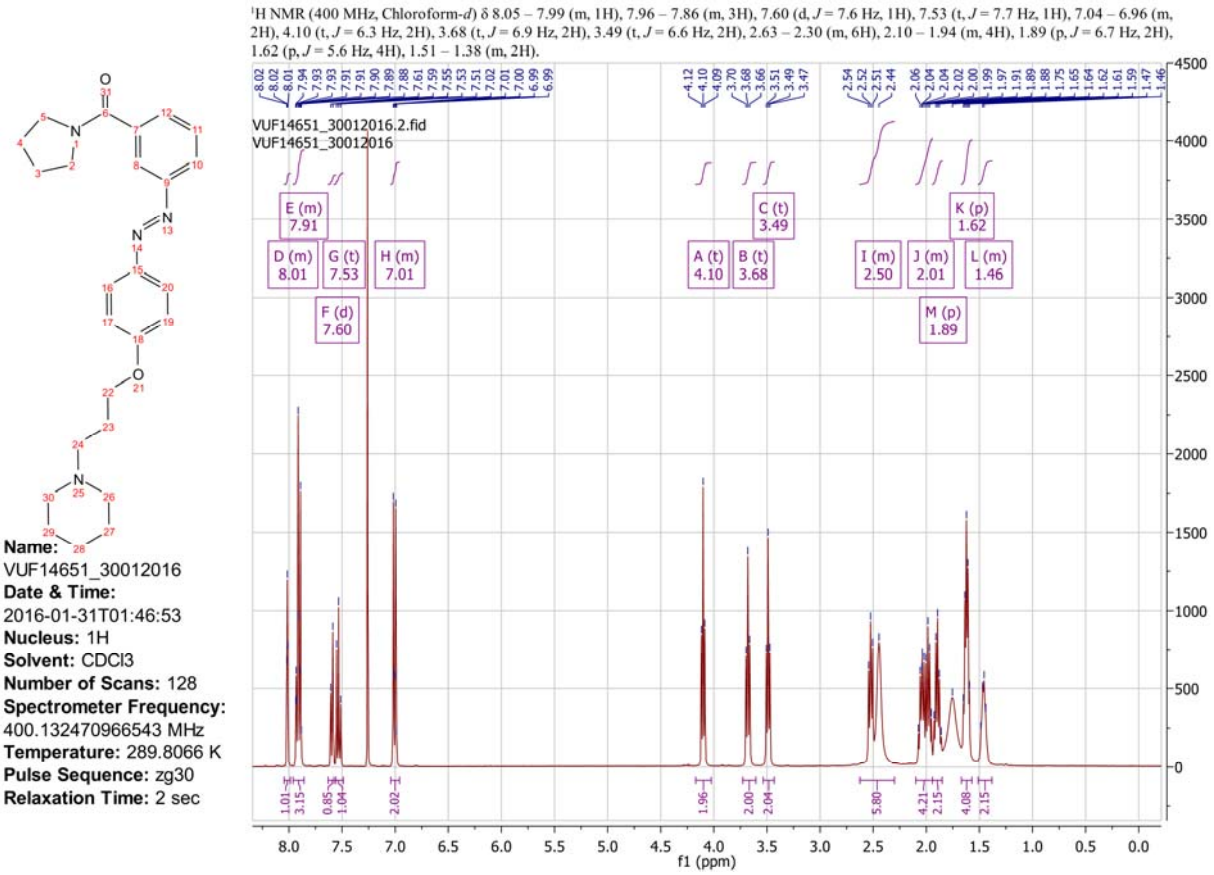


Figure S59: ^{1}H-NMR spectrum of (E)-(3-((4-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (15)

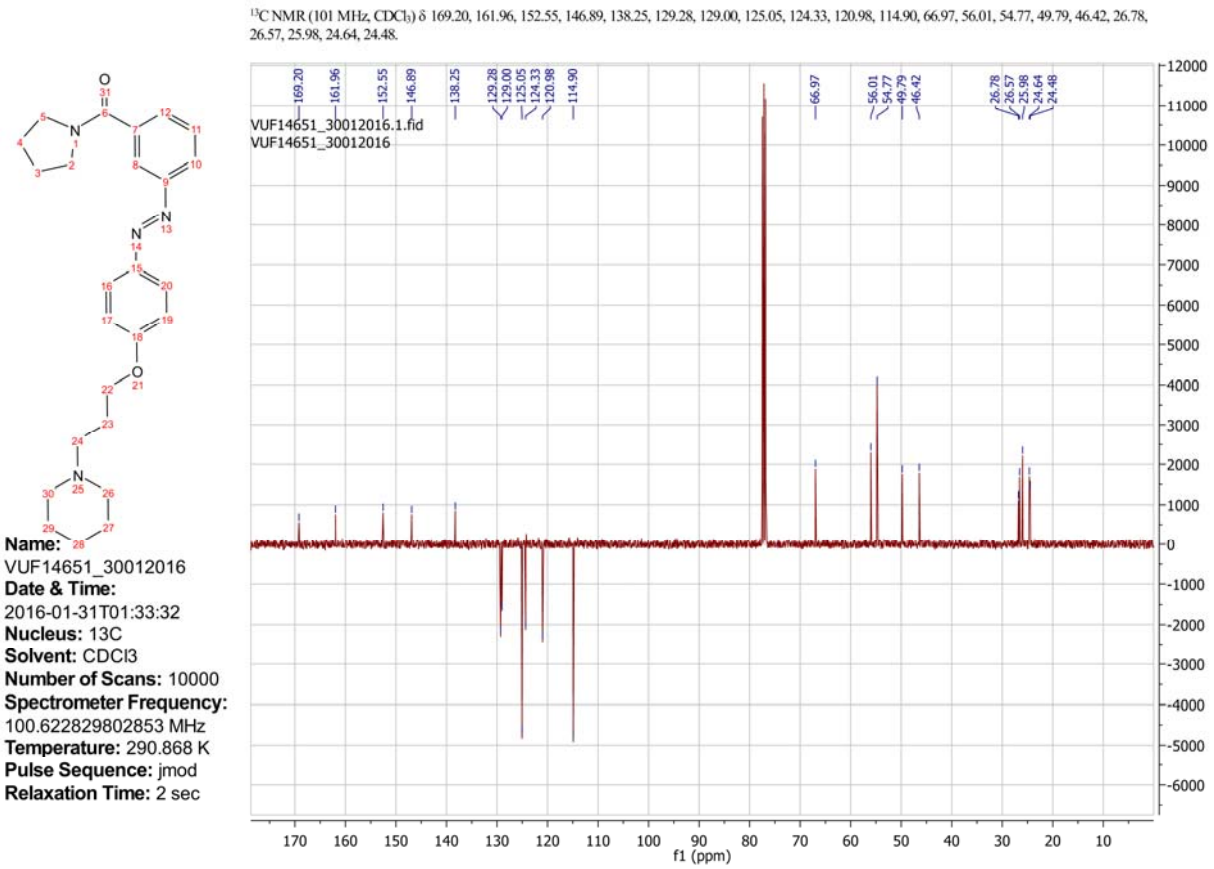
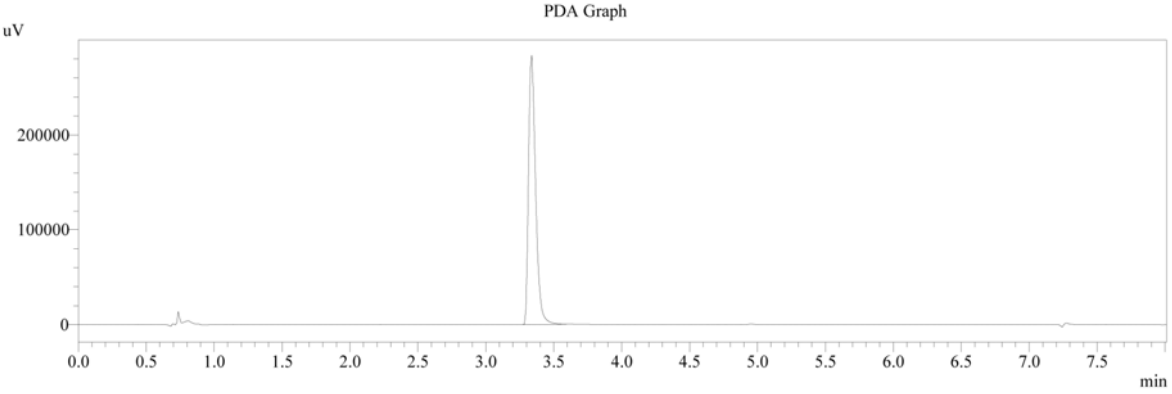


Figure S60: ^{13}C-NMR spectrum of (E)-(3-((4-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (15)

Acquired by	: Admin
Date Acquired	: 1/28/2016 1:01:57 PM
Sample Name	: VUF14651_DARK_28012015
Sample ID	:
Tray#	: 1
Vial#	: 18
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2016\2016 - wk04\VUF14651_DARK_28012015.lcd
Background File	: BLANCO_DARK_1_28012015.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Tuning File\Tuning-ESI-pos-neg01072015.lct
Processed by	: Admin
Modified Date	: 9/9/2016 4:09:54 PM

PDA Graph

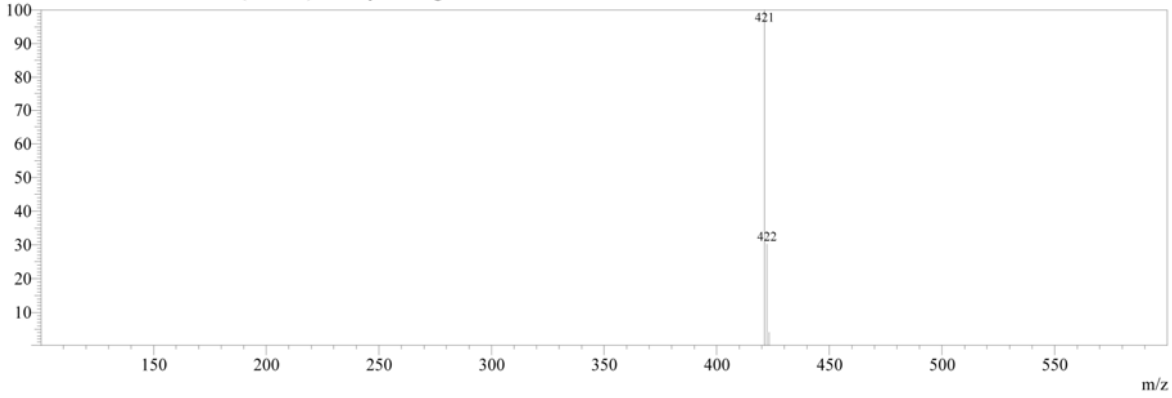


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.331	1024665	100.000

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.440-3.460(Scan#:345-347)
Mass Peaks:5 Base Peak:421.20(2070197) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.300<->3.670(331<->368
Mass Peaks:5 Base Peak:421.20(2070197) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	421.20	2070197	100.00				4	863.35	22163	1.07			
2	422.20	627485	30.31				5	864.35	33542	1.62			
3	423.20	86274	4.17										

Figure S61: LC-MS chromatogram of (E)-(3-((4-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (15)

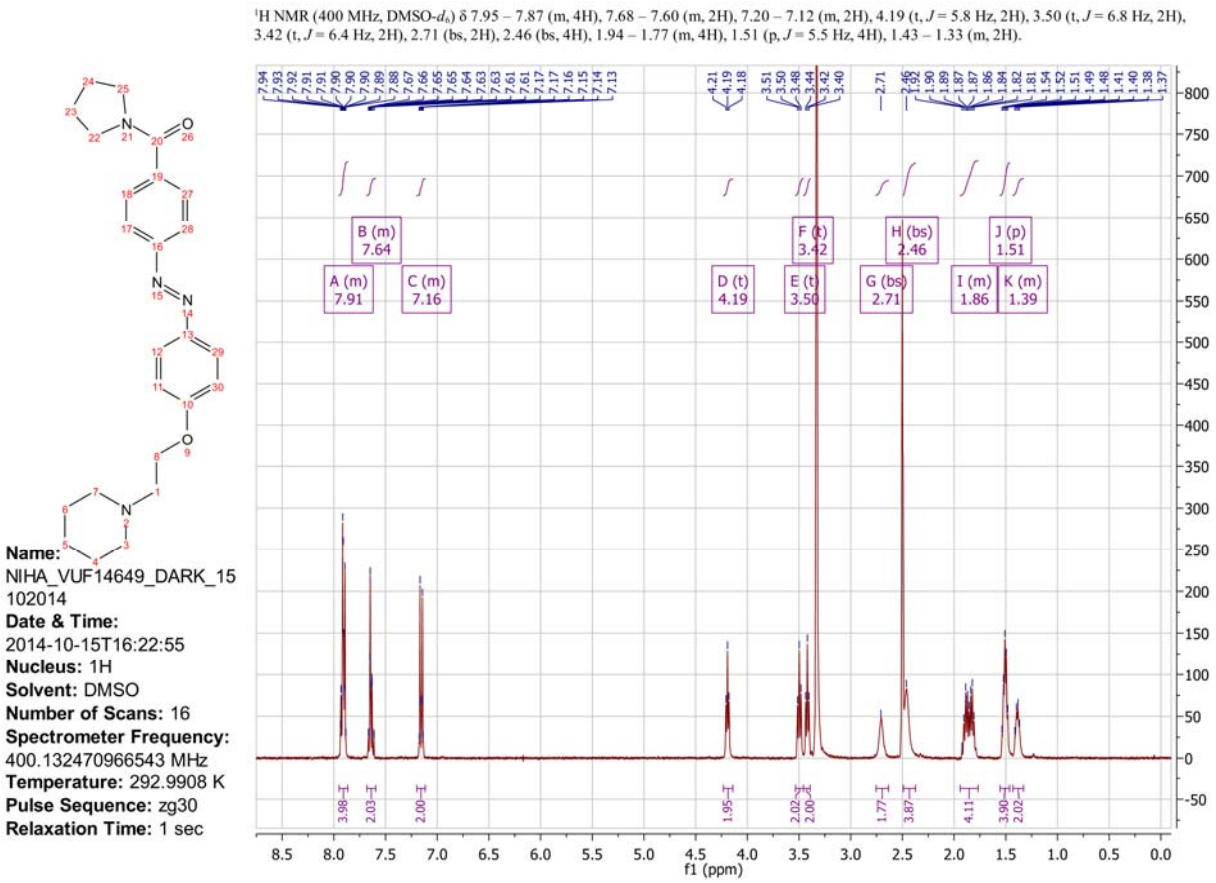


Figure S62: ^{1}H-NMR spectrum of (E)-(4-((4-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (16)

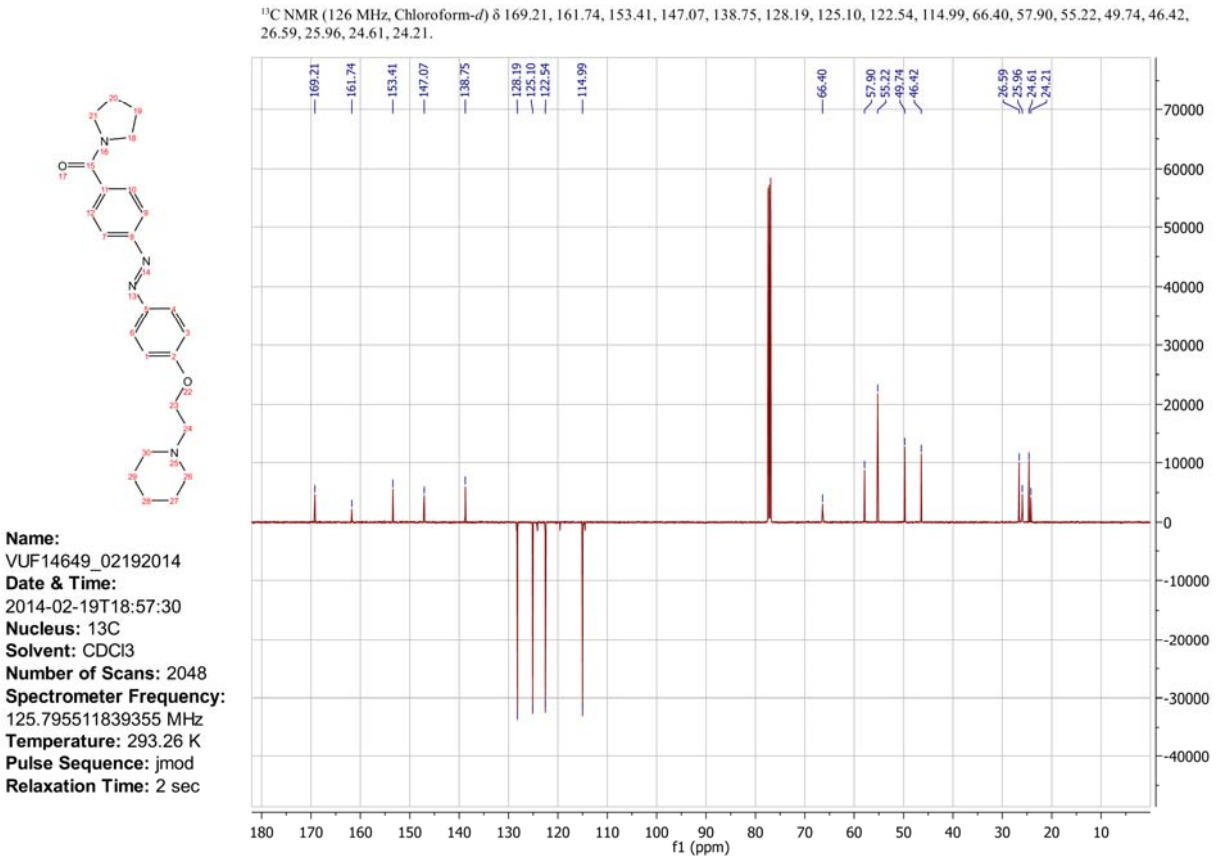
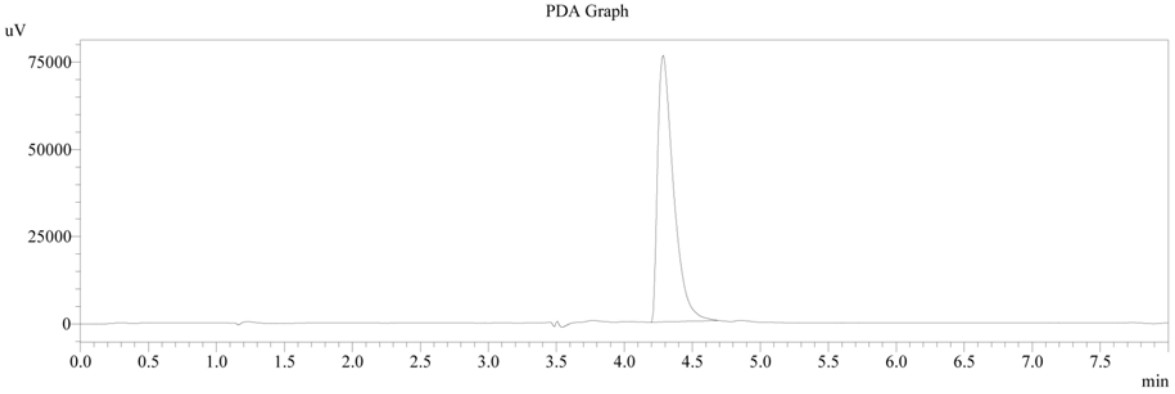


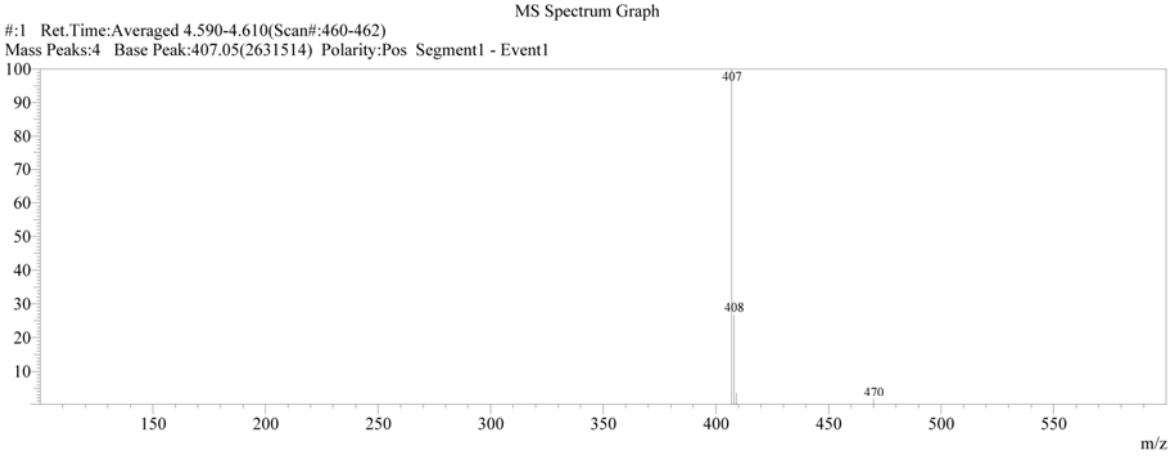
Figure S63: ^{13}C-NMR spectrum of (E)-(4-((4-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (16)

Acquired by	: Admin
Date Acquired	: 3/12/2015 3:21:32 PM
Sample Name	: NIHA_VUF14649_DARK_12032015
Sample ID	:
Tray#	: 1
Vial#	: 29
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2015\2015-wk10\NIHA_VUF14649_DARK_12032015.lcd
Background File	: NIHA_blanco_DARK_12032015.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Data\Installatie NOV 2009\Tuning ESI POS + NEG JAN2010.lct
Processed by	: Admin
Modified Date	: 9/9/2016 3:48:59 PM



PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		4.280	619781	100.000



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 4.370<->5.080(438<->509
Mass Peaks:4 Base Peak:407.05(2631514) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	407.05	2631514	100.00				3	409.05	93984	3.57			
2	408.05	705084	26.79				4	470.10	43322	1.65			

Figure S64: LC-MS chromatogram of (E)-(4-((4-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (16)

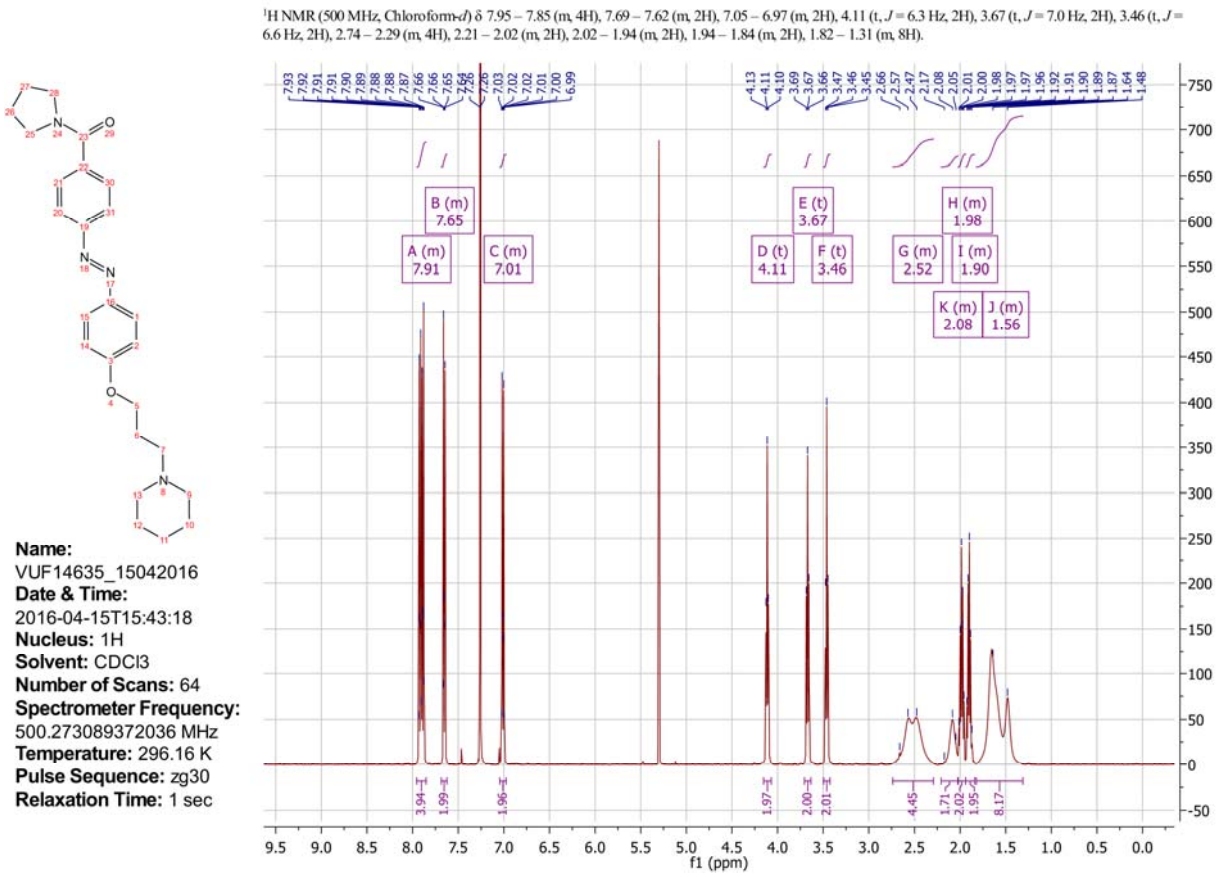


Figure S65: ^{1}H-NMR spectrum of (E)-(4-((4-(2-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (17)

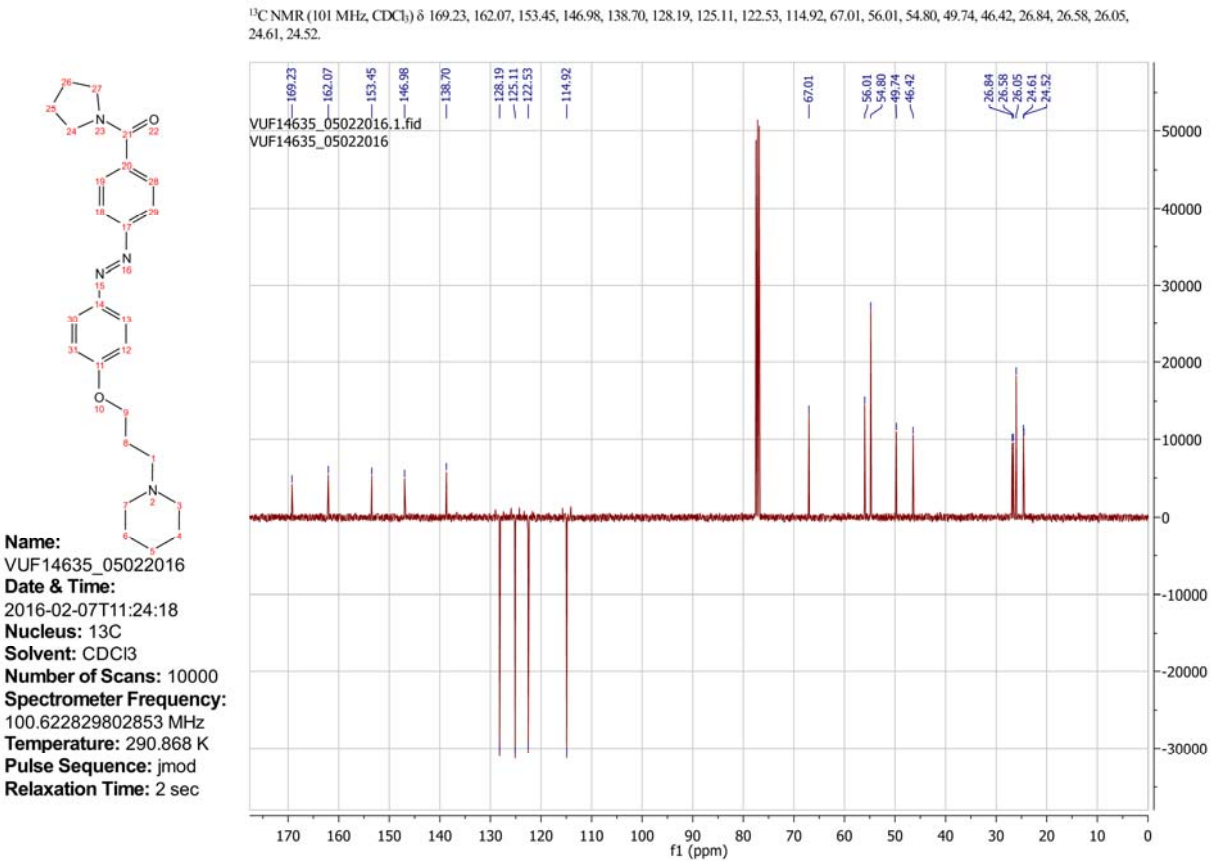
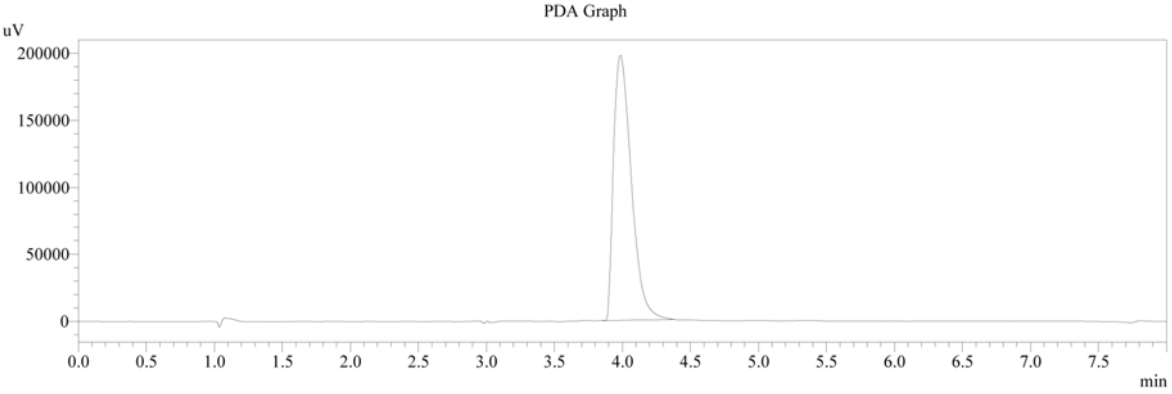


Figure S66: ^{13}C-NMR spectrum of (E)-(4-((4-(2-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (17)

Acquired by	: Admin
Date Acquired	: 2/12/2015 12:55:36 PM
Sample Name	: NIHA_VUF14635_dark_12022015
Sample ID	:
Tray#	: 1
Vial#	: 7
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2015\2015-wk06\NIHA_VUF14635_dark_12022015.lcd
Background File	: NIHA_blanco_IRR_12022015.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Data\Installatie NOV 2009\Tuning ESI POS + NEG JAN2010.lct
Processed by	: Admin
Modified Date	: 2/13/2015 3:32:13 PM

PDA Graph

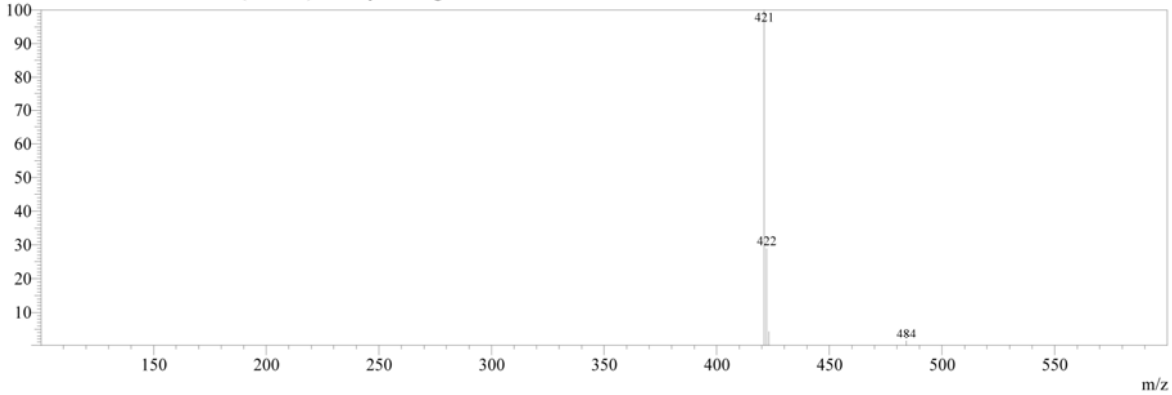


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.980	1802470	100.000

MS Spectrum Graph

#:1 Ret.Time:Averaged 4.230-4.250(Scan#:424-426)
Mass Peaks:4 Base Peak:421.05(4248061) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.890<->4.830(390<->484
Mass Peaks:4 Base Peak:421.05(4248061) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	421.05	4248061	100.00				3	423.10	186966	4.40			
2	422.05	1231546	28.99				4	484.10	58394	1.37			

Figure S67: LC-MS chromatogram of (E)-(4-((4-(2-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (17)

^{1}H NMR (250 MHz, Chloroform-*d*) δ 8.09 – 8.03 (m, 1H), 7.98 – 7.83 (m, 3H), 7.64 – 7.48 (m, 4H), 7.46 – 7.34 (m, 1H).

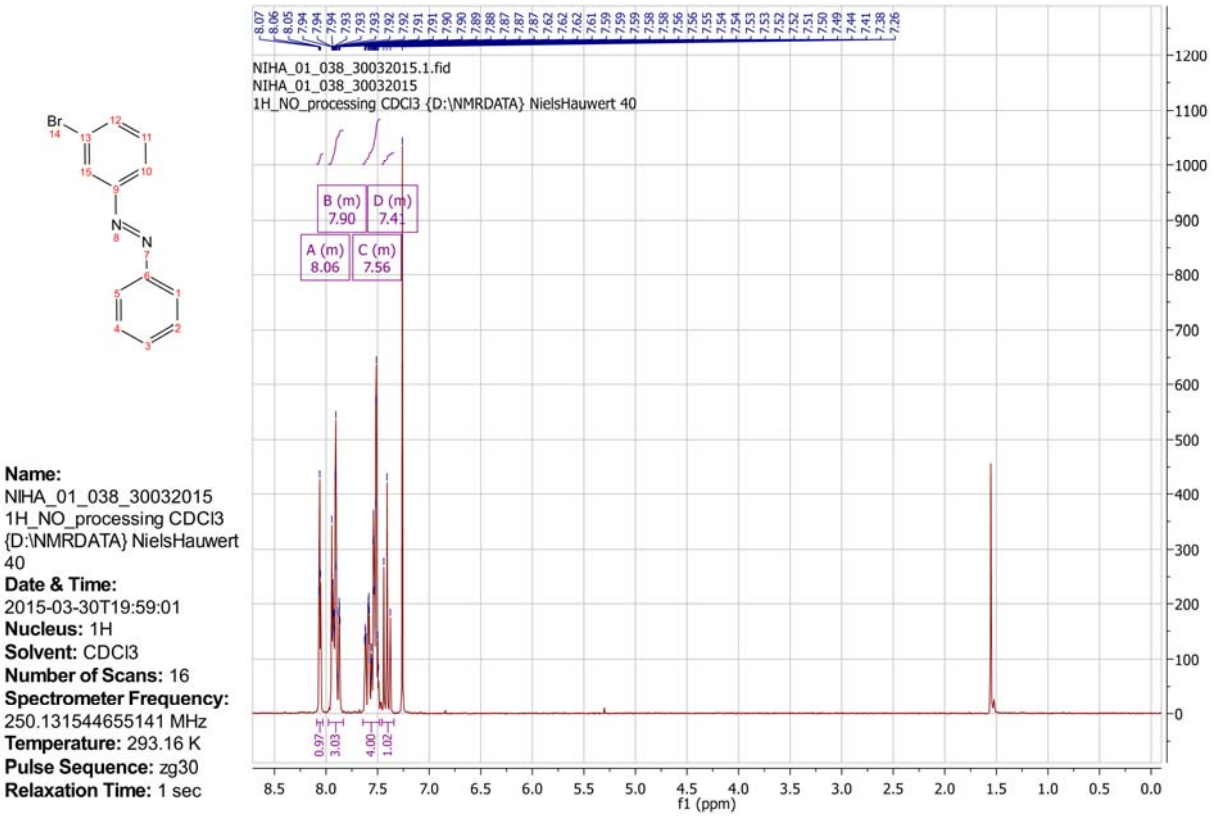


Figure S68: ^{1}H-NMR spectrum of (E)-1-(3-Bromophenyl)-2-phenyldiazene (20)

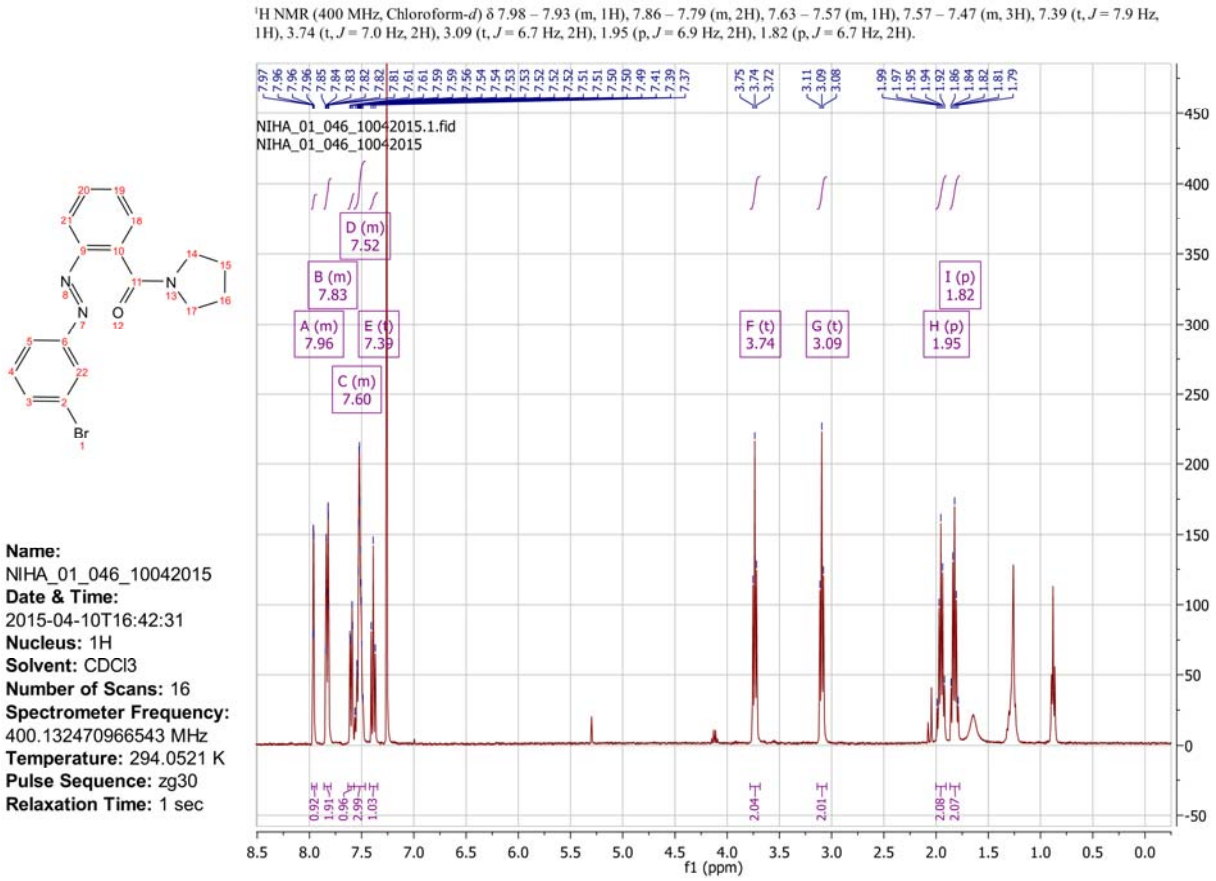


Figure S69: ^{1}H-NMR spectrum of (E)-(2-((3-Bromophenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (21)

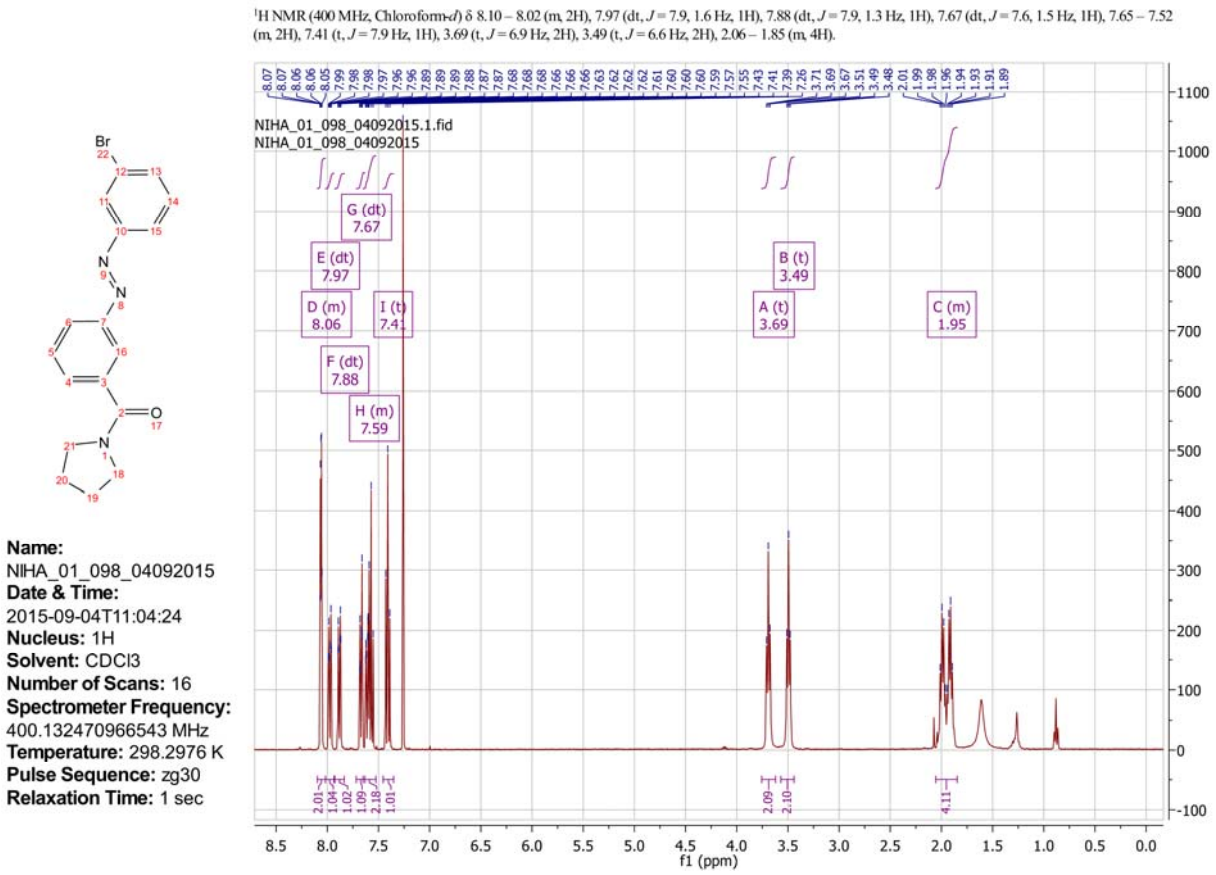


Figure S70: ^{1}H-NMR spectrum of (E)-(3-((3-Bromophenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (22)

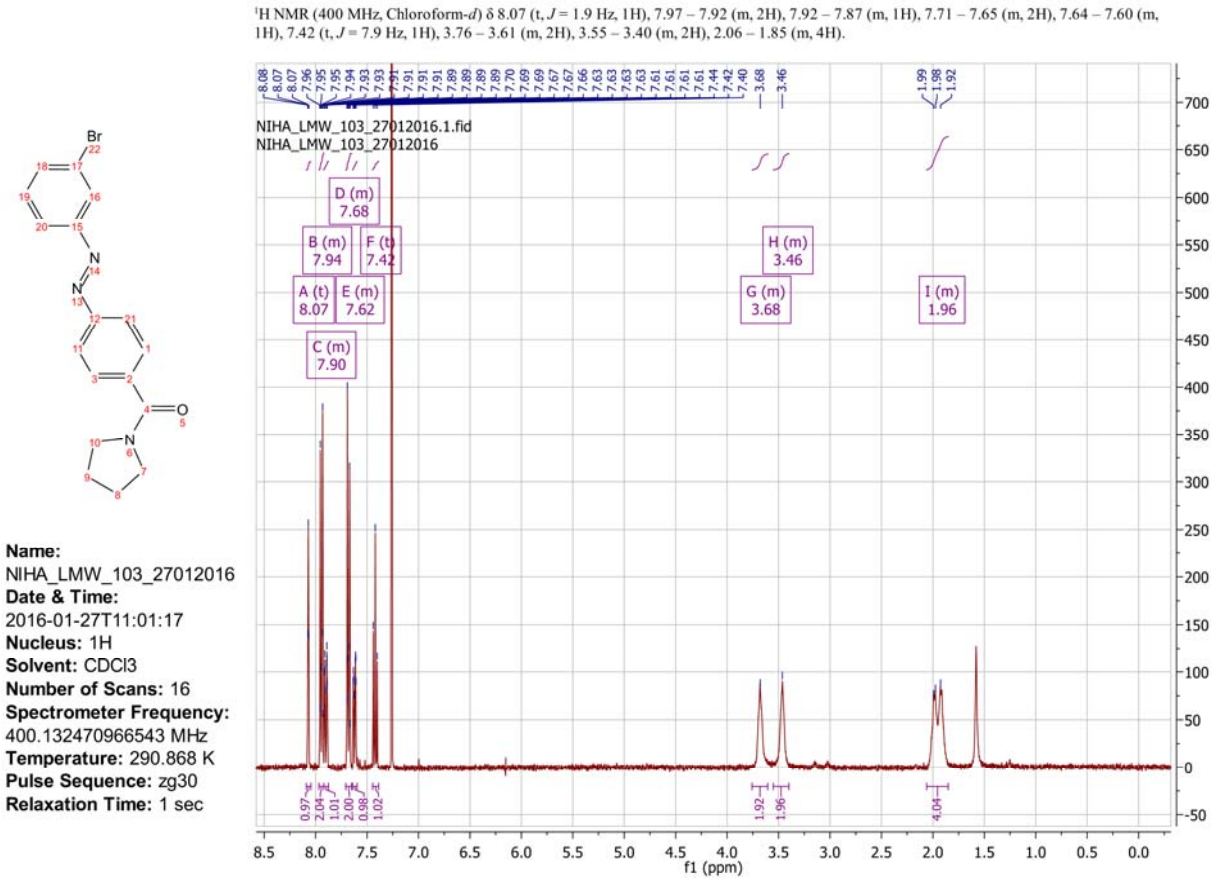


Figure S71: ^{1}H-NMR spectrum of (E)-(4-((3-Bromophenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (23)

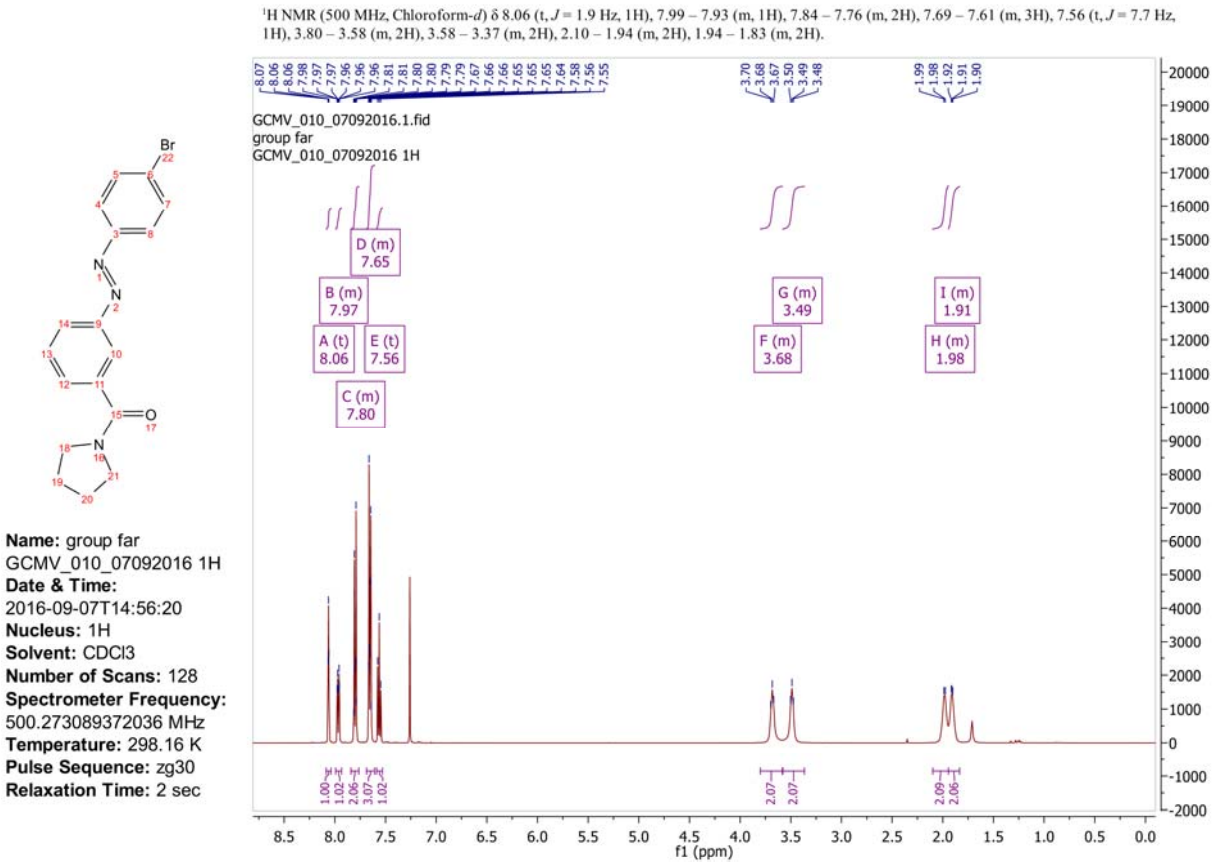


Figure S72: ^{1}H-NMR spectrum of (E)-(3-((4-Bromophenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (24)

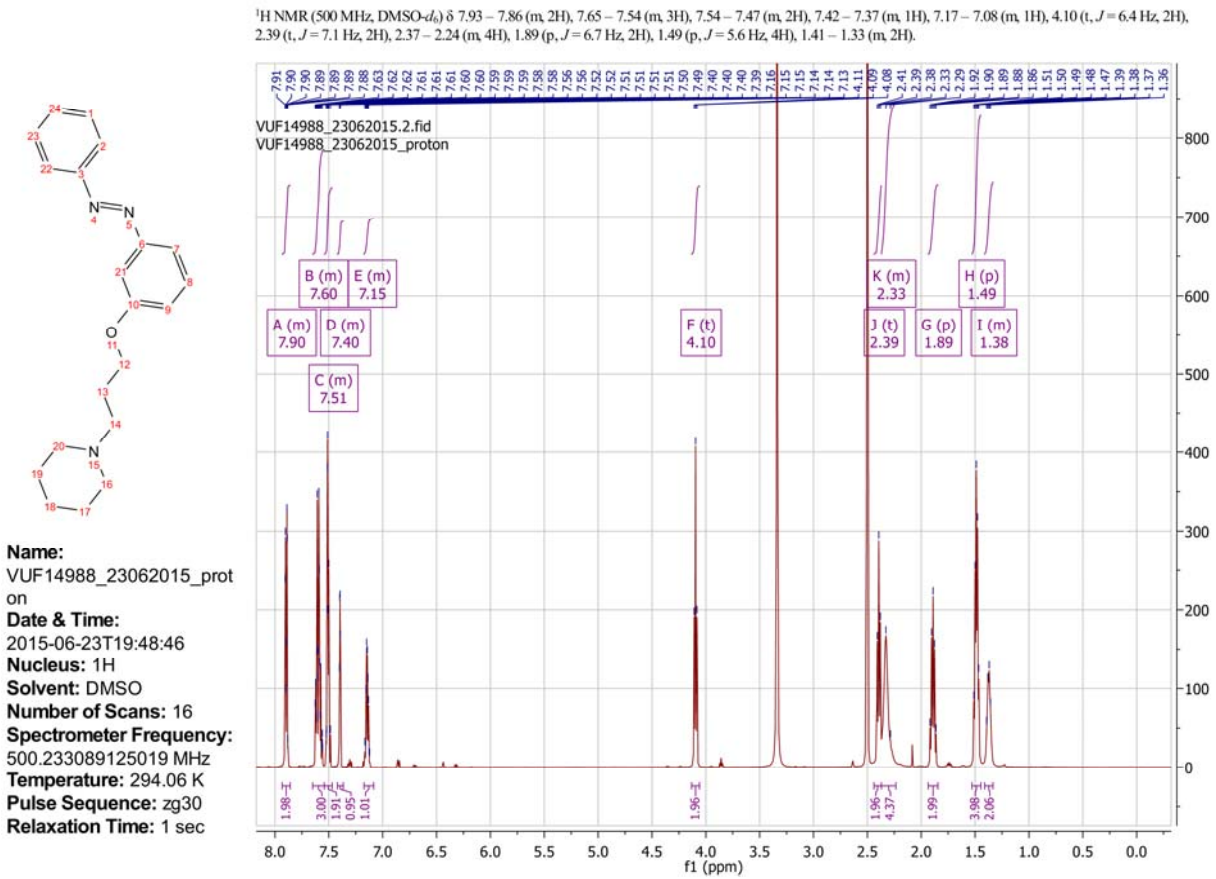


Figure S73: ^{1}H-NMR spectrum of (E)-1-(3-(3-(Phenyldiazenyl)phenoxy)propyl)piperidine (25)

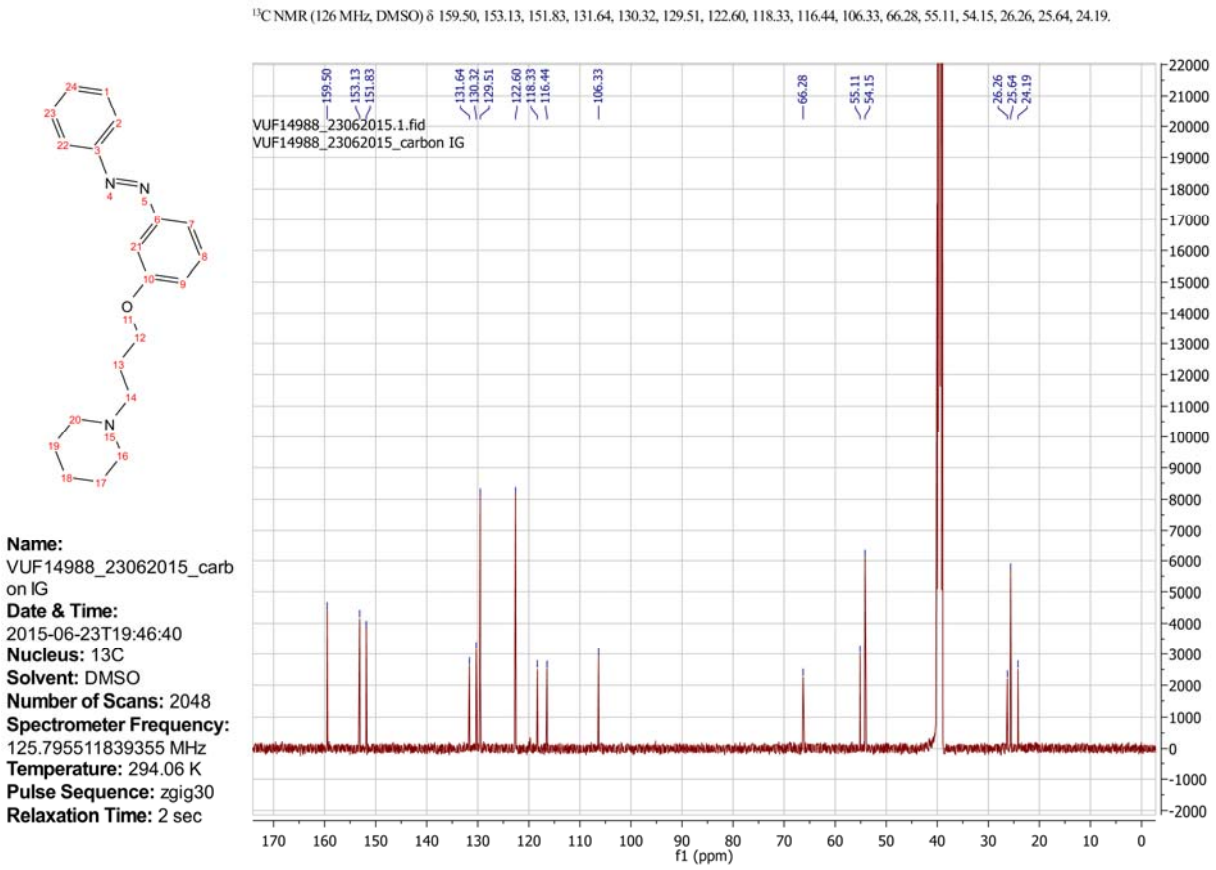
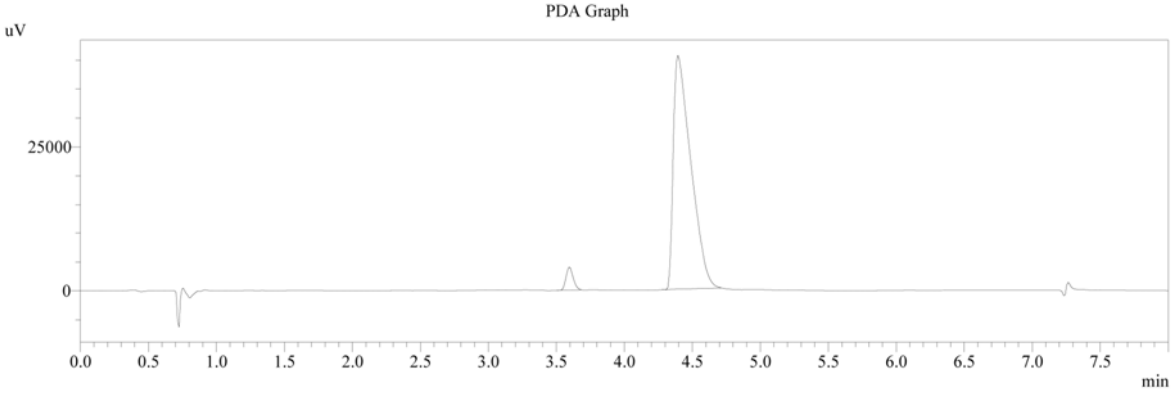


Figure S74: ^{13}C-NMR spectrum of (E)-1-(3-(3-(Phenyldiazenyl)phenoxy)propyl)piperidine (25)

Acquired by	: Admin
Date Acquired	: 8/6/2015 12:35:36 PM
Sample Name	: VUF14988_DARK_06082015
Sample ID	:
Tray#	: 1
Vial#	: 13
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2015\2015-wk32\VUF14988_DARK_06082015.lcd
Background File	: BLANCO_IRRA_2_06082015.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Tuning File\Tuning-ESI-pos-neg01072015.lct
Processed by	: Admin
Modified Date	: 9/9/2016 7:46:42 PM

PDA Graph

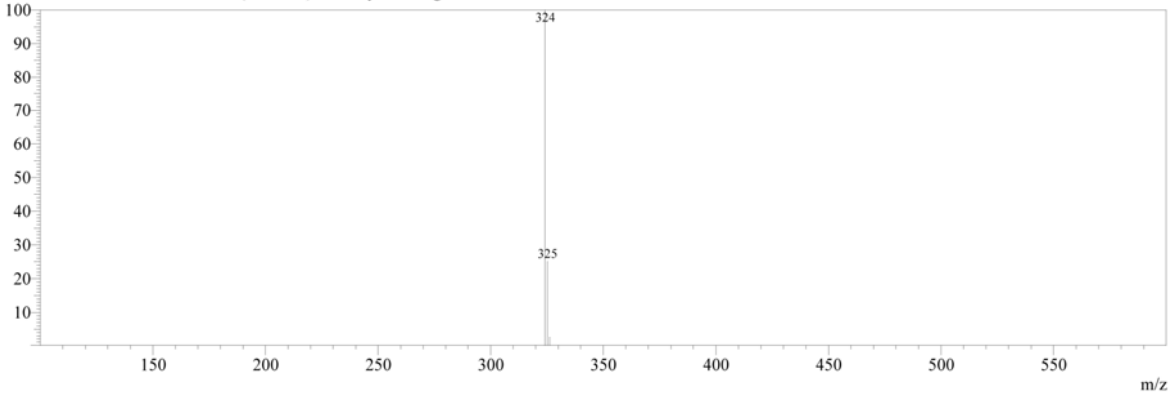


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.591	14810	3.910
2		4.391	364012	96.090

MS Spectrum Graph

#:1 Ret.Time:Averaged 4.470-4.490(Scan#:448-450)
Mass Peaks:3 Base Peak:324.15(2820517) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 4.350<->4.850(436<->486
Mass Peaks:3 Base Peak:324.15(2820517) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	324.15	2820517	100.00				3	326.15	76056	2.70			
2	325.15	711354	25.22										

Figure S75: LC-MS chromatogram of (E)-1-(3-(3-(Phenyldiazenyl)phenoxy)propyl)piperidine (25)

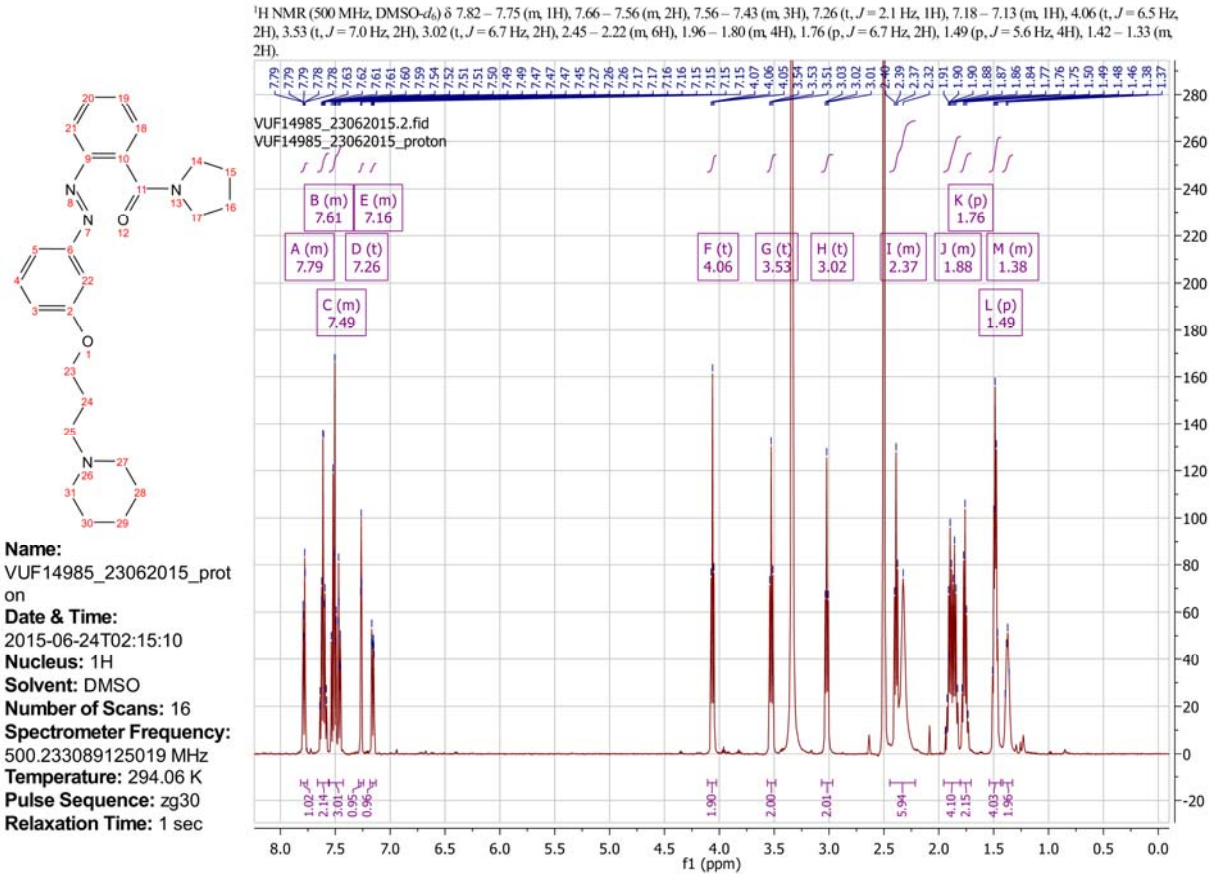


Figure S76: ^{1}H-NMR spectrum of (E)-(2-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (26)

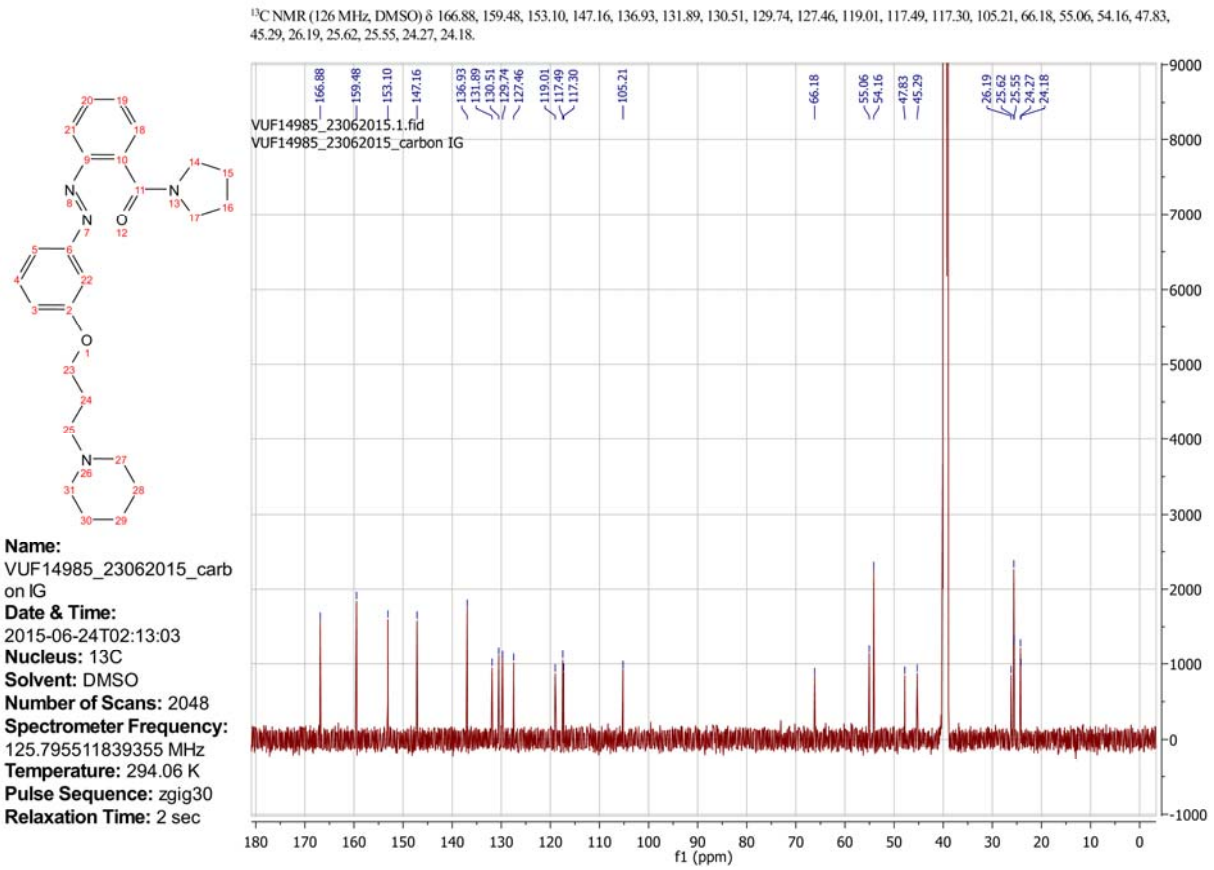
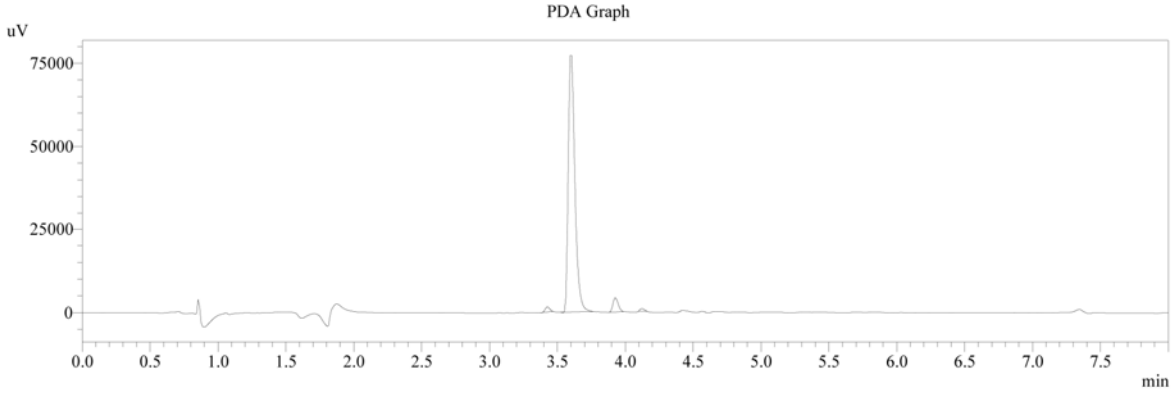


Figure S77: ^{13}C-NMR spectrum of (E)-(2-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (26)

Acquired by	: Admin
Date Acquired	: 5/28/2015 11:24:34 AM
Sample Name	: VUF14985_DARK_28052015
Sample ID	:
Tray#	: 1
Vial#	: 22
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2015\2015-wk22\VUF14985_DARK_28052015.lcd
Background File	: Blanco_IRRA2_28052015.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Data\Installatie NOV 2009\Tuning ESI POS + NEG JAN2010.lct
Processed by	: Admin
Modified Date	: 2/4/2016 2:55:21 PM

PDA Graph

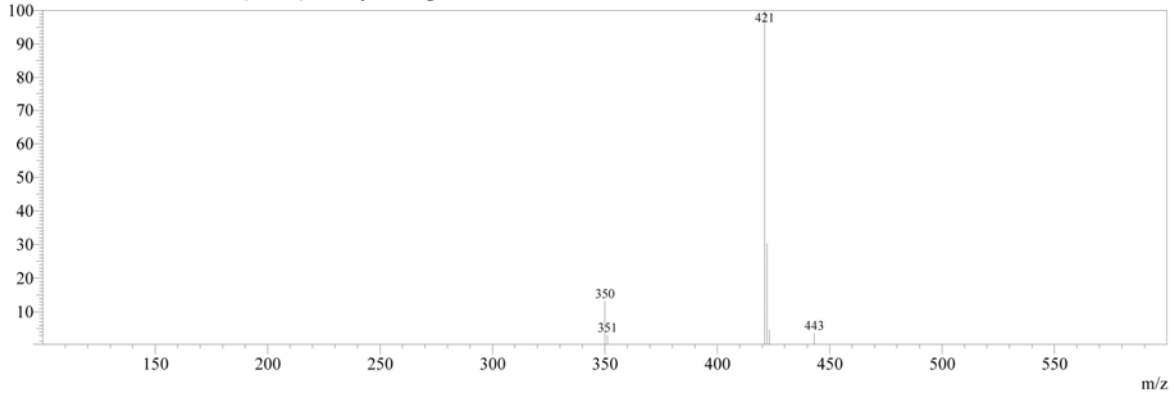


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.421	3665	1.309
2		3.595	263105	93.939
3		3.921	11575	4.133
4		4.117	1736	0.620

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.680-3.700(Scan#:369-371)
Mass Peaks:7 Base Peak:421.05(645985) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.580<->3.910(359<->392
Mass Peaks:7 Base Peak:421.05(645985) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	350.00	85374	13.22				5	423.10	29907	4.63			
2	351.05	20253	3.14				6	443.10	24270	3.76			
3	421.05	645985	100.00				7	863.45	10037	1.55			
4	422.10	196135	30.36										

Figure S78: LC-MS chromatogram of (E)-(2-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (26)

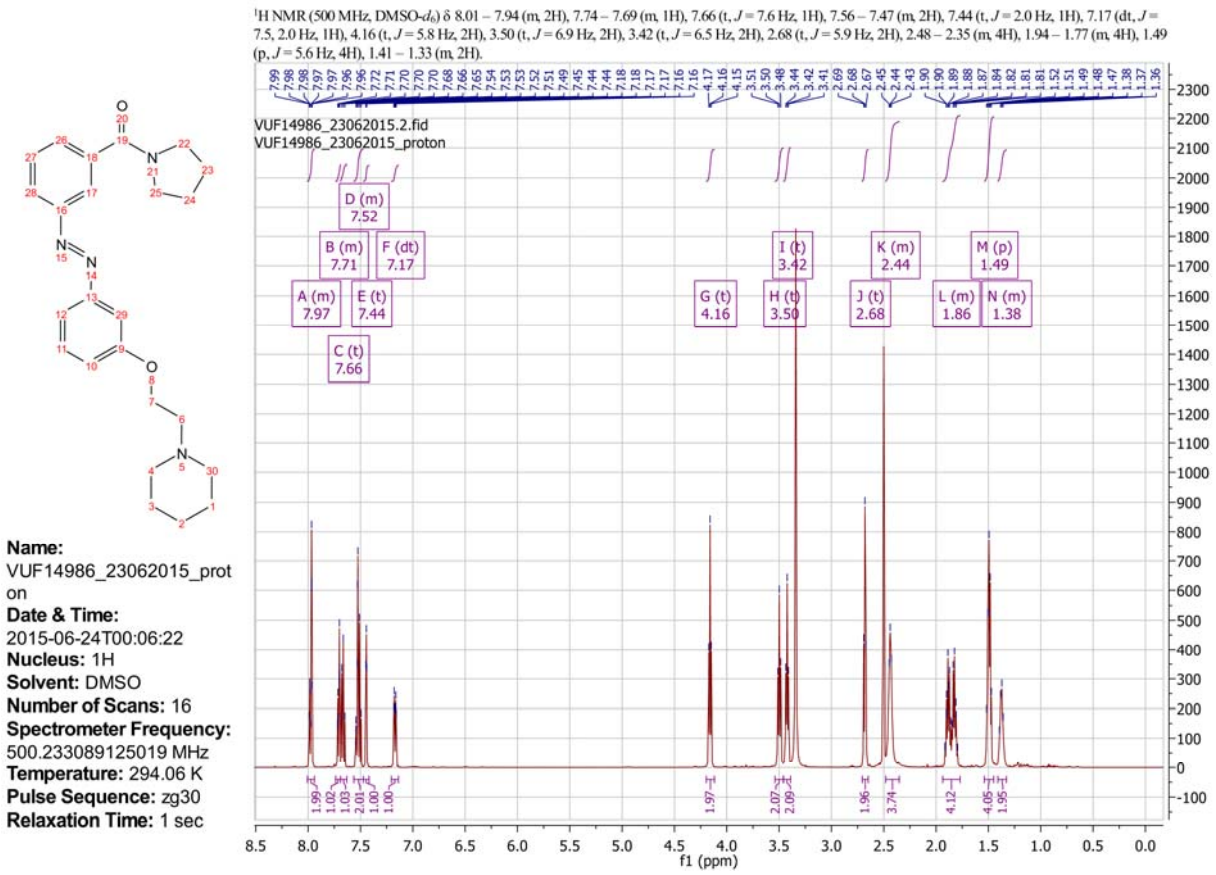


Figure S79: ^{1}H-NMR spectrum of (E)-(3-((3-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (27)

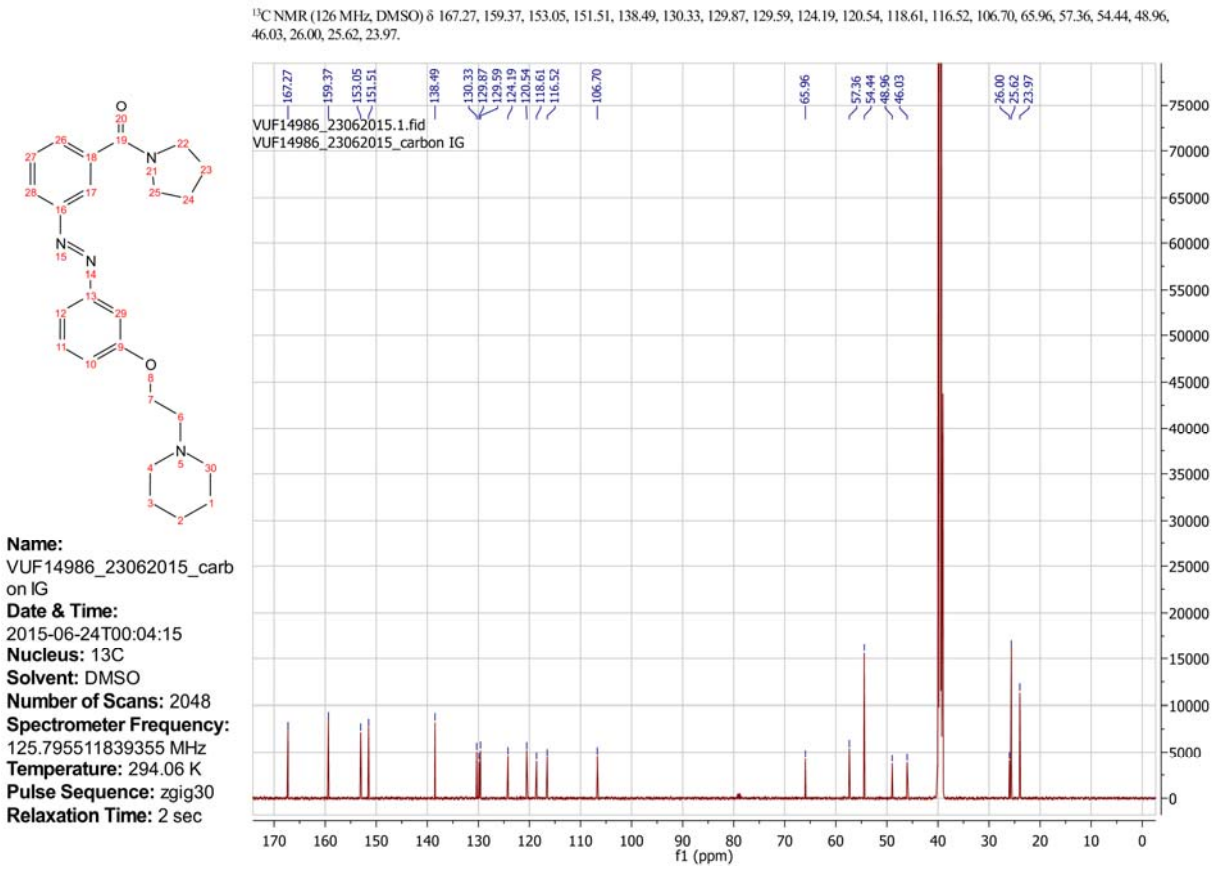


Figure S80: ^{13}C-NMR spectrum of (E)-(3-((3-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (27)

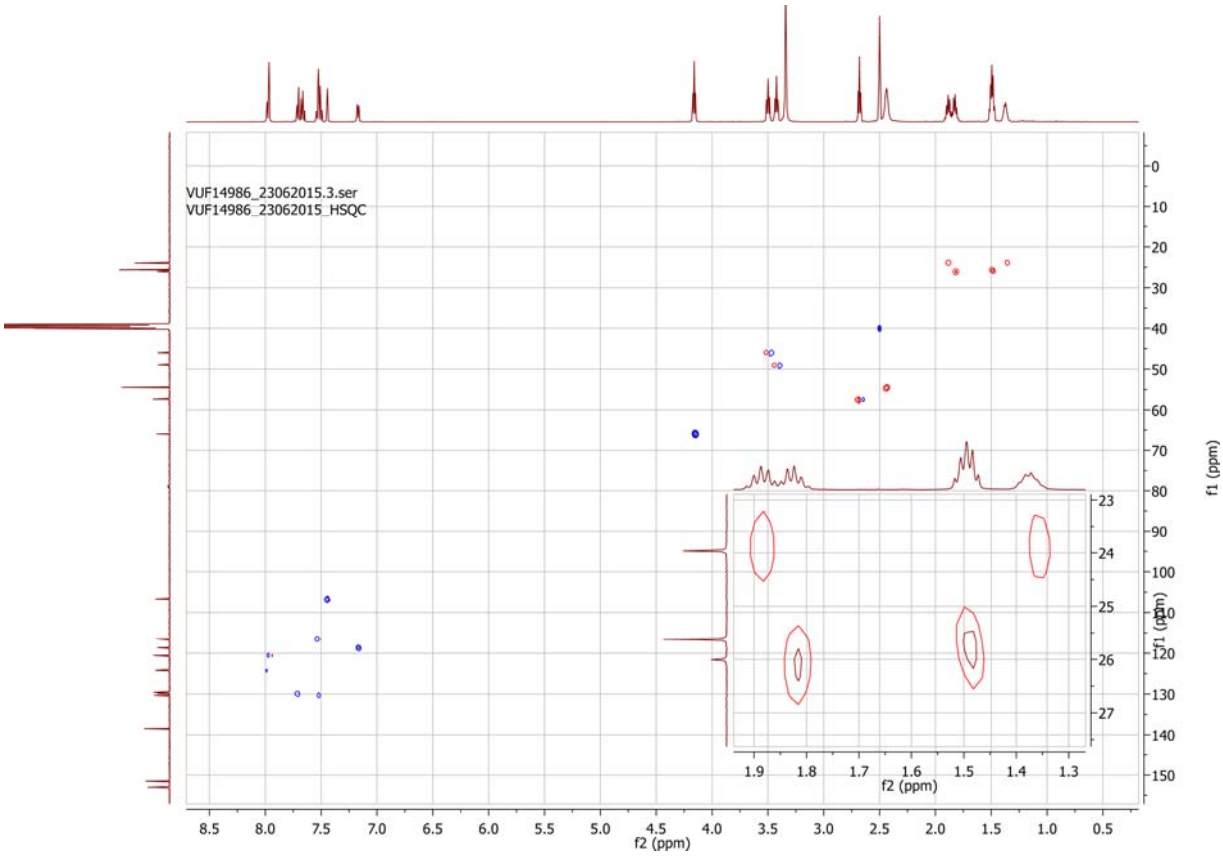
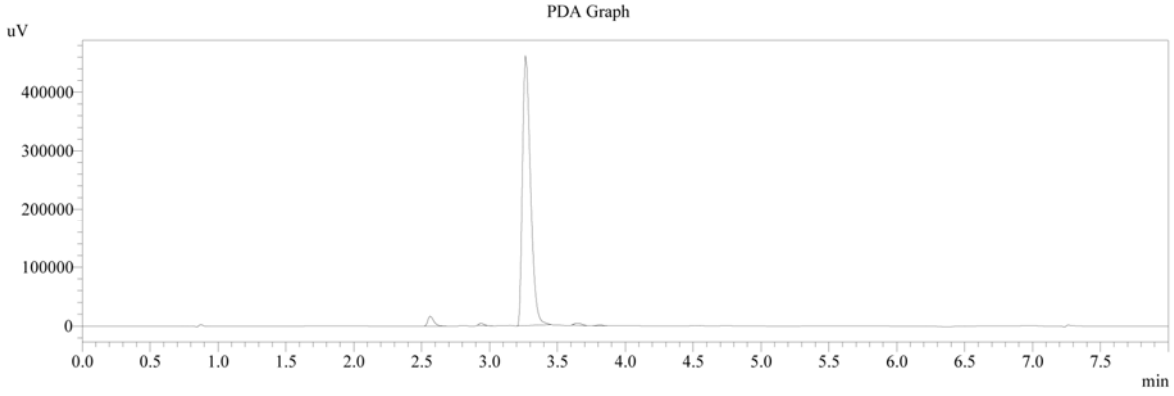


Figure S81: HSQC-NMR spectrum of (E)-(3-((3-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (27)

Acquired by	: Admin
Date Acquired	: 2/4/2016 1:59:59 PM
Sample Name	: vuf14986_04022016
Sample ID	:
Tray#	: 1
Vial#	: 39
Injection Volume	: 1
Data File	: C:\LabSolutions\Data\2016\2016 - wk05\vuf14986_04022016.lcd
Background File	: AZOBLANCO_0402016.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Tuning File\Tuning-ESI-pos-neg01072015.lct
Processed by	: Admin
Modified Date	: 2/4/2016 2:51:53 PM

PDA Graph

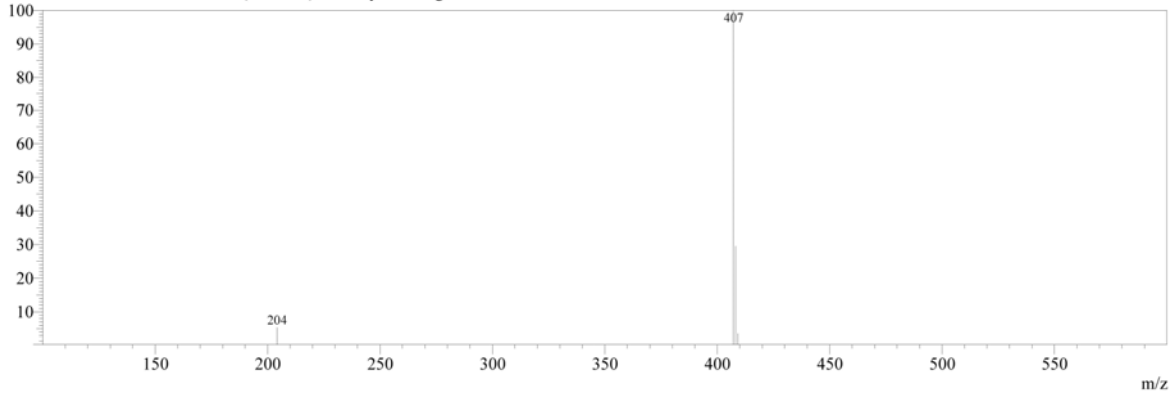


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		2.559	50352	2.514
2		2.932	7821	0.390
3		3.261	1926642	96.186
4		3.646	14072	0.703
5		3.806	4146	0.207

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.480-3.500(Scan#:349-351)
Mass Peaks:6 Base Peak:407.20(2520203) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.300<->3.760(331<->377
Mass Peaks:6 Base Peak:407.20(2520203) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	204.10	135636	5.38				4	409.25	90508	3.59			
2	407.20	2520203	100.00				5	835.45	85635	3.40			
3	408.20	745204	29.57				6	836.35	27961	1.11			

Figure S82: LC-MS chromatogram of (E)-(3-((3-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (27)

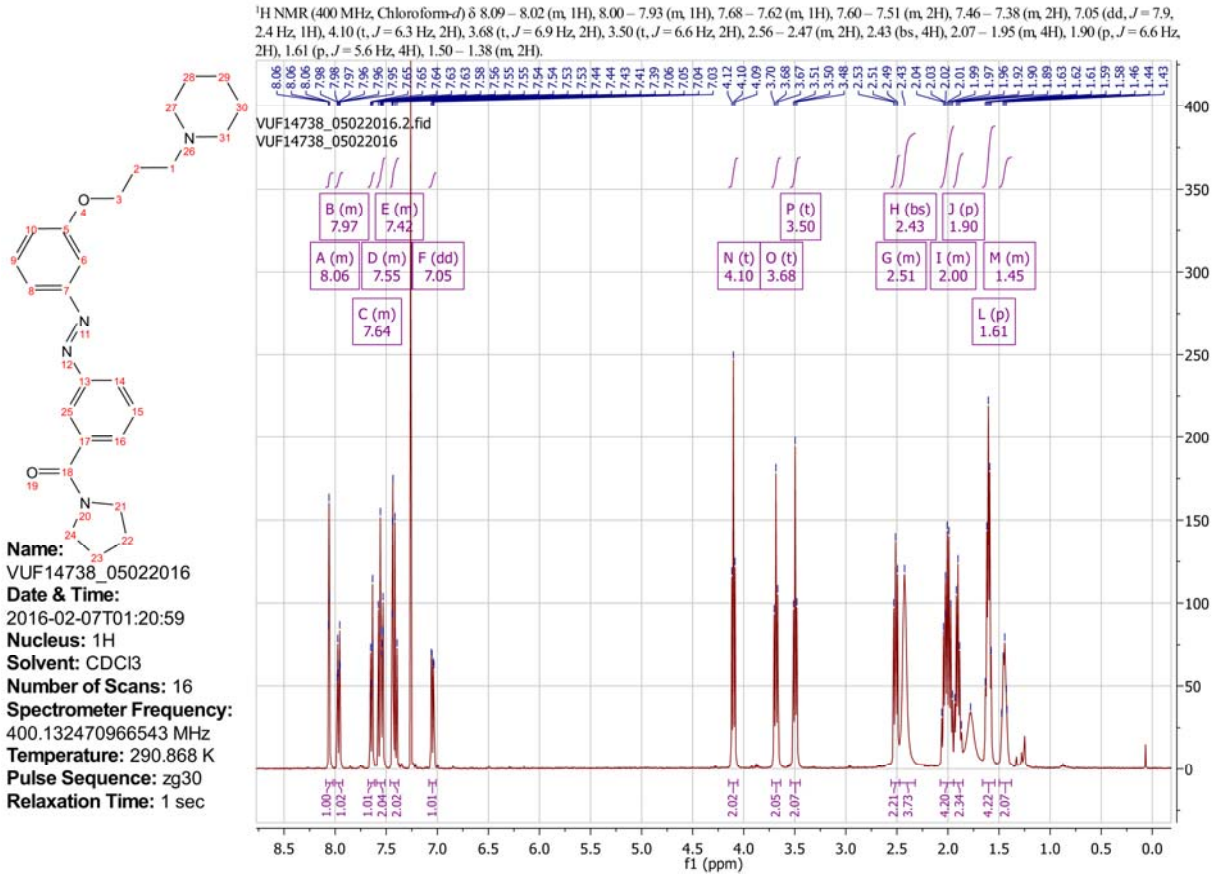


Figure S83: ^{1}H-NMR spectrum of (E)-(3-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (28)

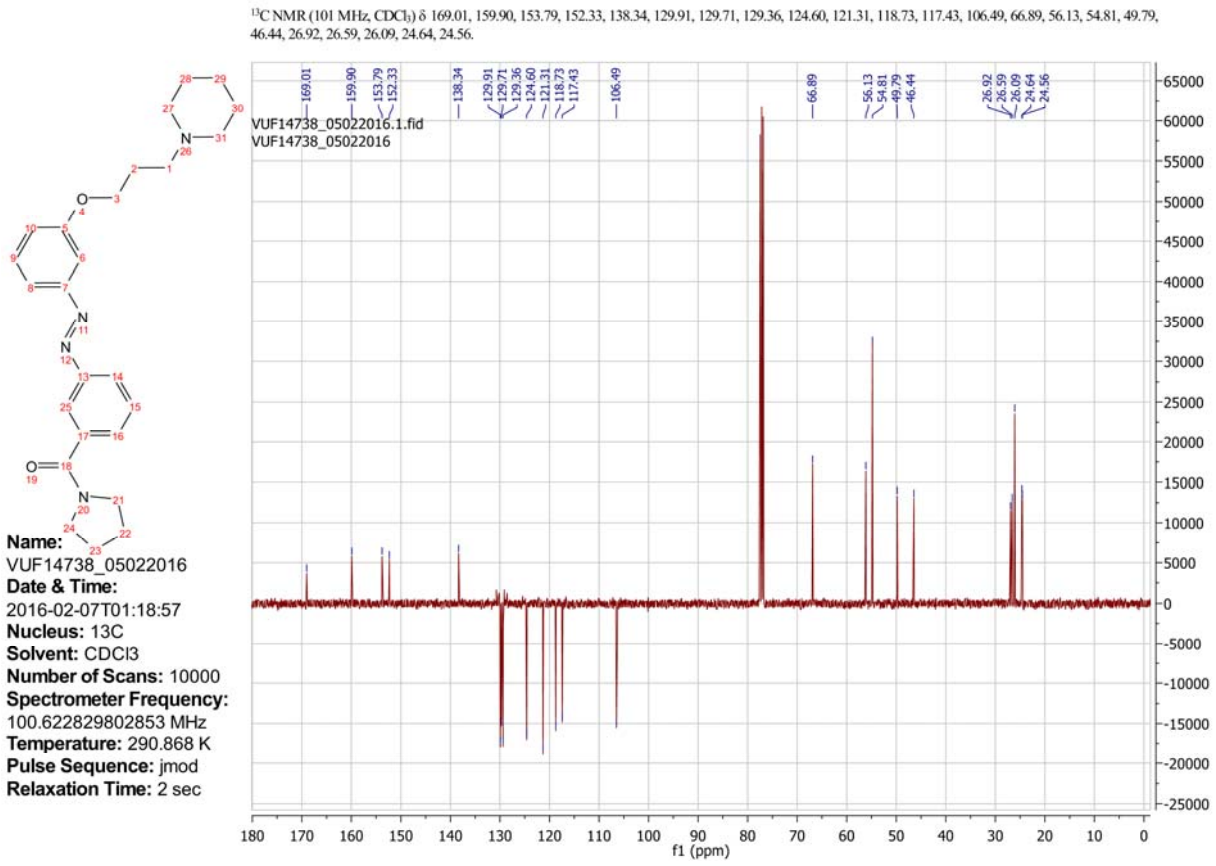
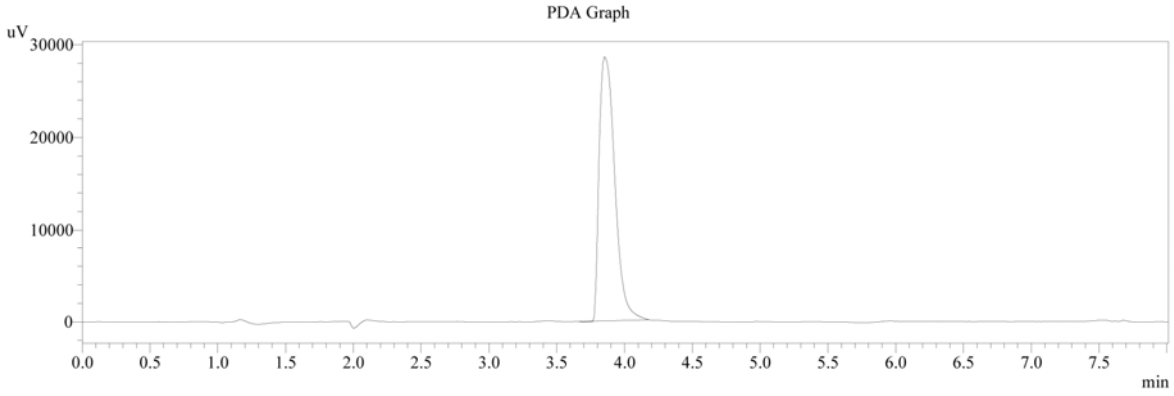


Figure S84: ^{13}C-NMR spectrum of (E)-(3-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (28)

Acquired by : Admin
Date Acquired : 10/17/2014 10:37:46 AM
Sample Name : VUF14738_D_17102014
Sample ID :
Tray# : 1
Vial# : 16
Injection Volume : 10
Data File : C:\LabSolutions\Data\2014\2014-wk42\VUF14738_D_17102014.lcd
Background File : DMSOd6_blanco_D_17102014.lcd
Method File : Method SCAN ACID standard azo.lcm
Report Format : DefaultLCMS.lcr
Tuning File : C:\LabSolutions\Data\Installatie NOV 2009\Tuning ESI POS + NEG JAN2010.lct
Processed by : Admin
Modified Date : 11/4/2014 12:06:14 PM



PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.849	230322	100.000

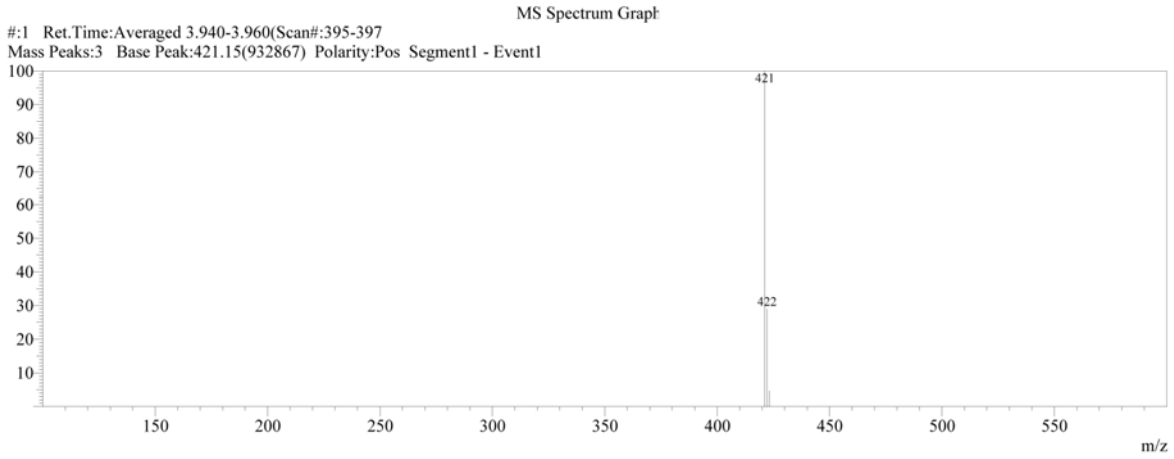


Figure S85: LC-MS chromatogram of (E)-(3-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (28)

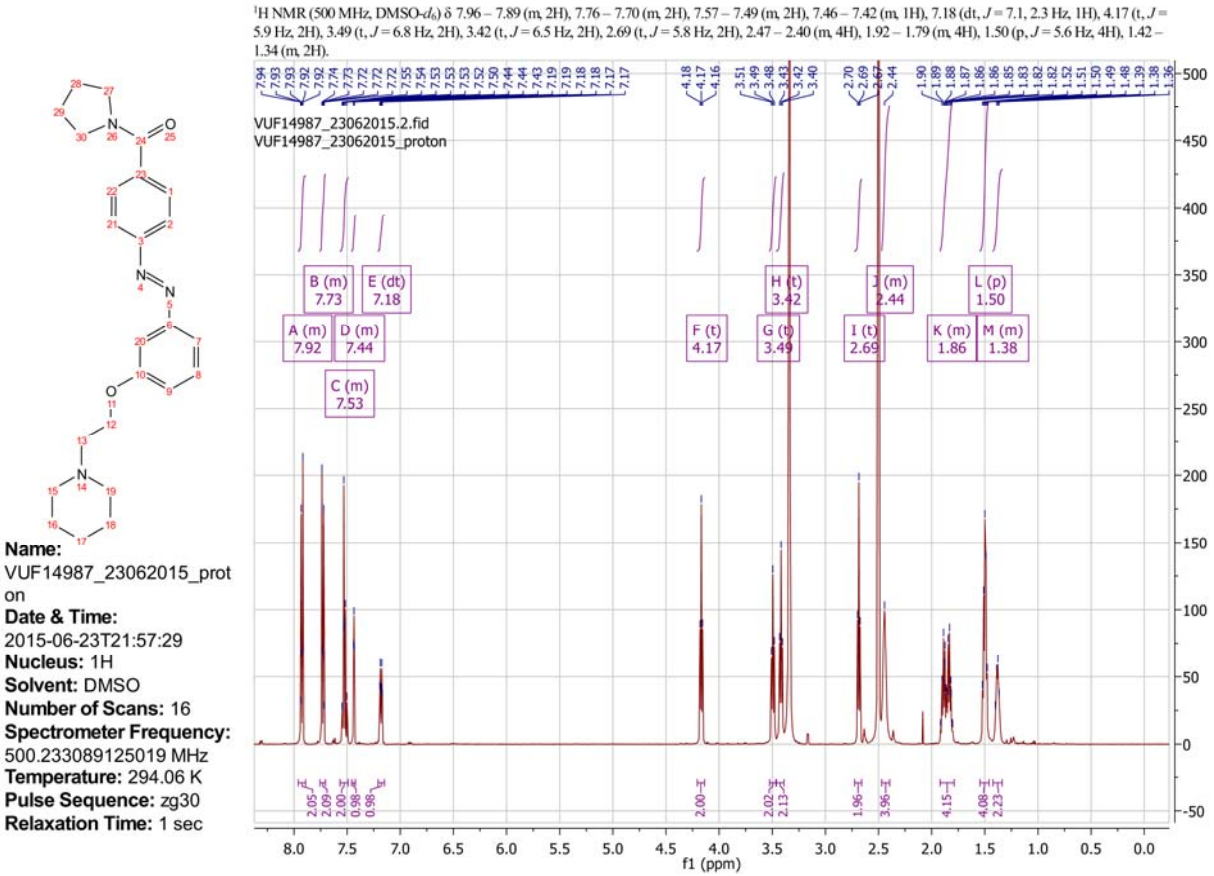


Figure S86: ^{1}H-NMR spectrum of (E)-(4-((3-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (29)

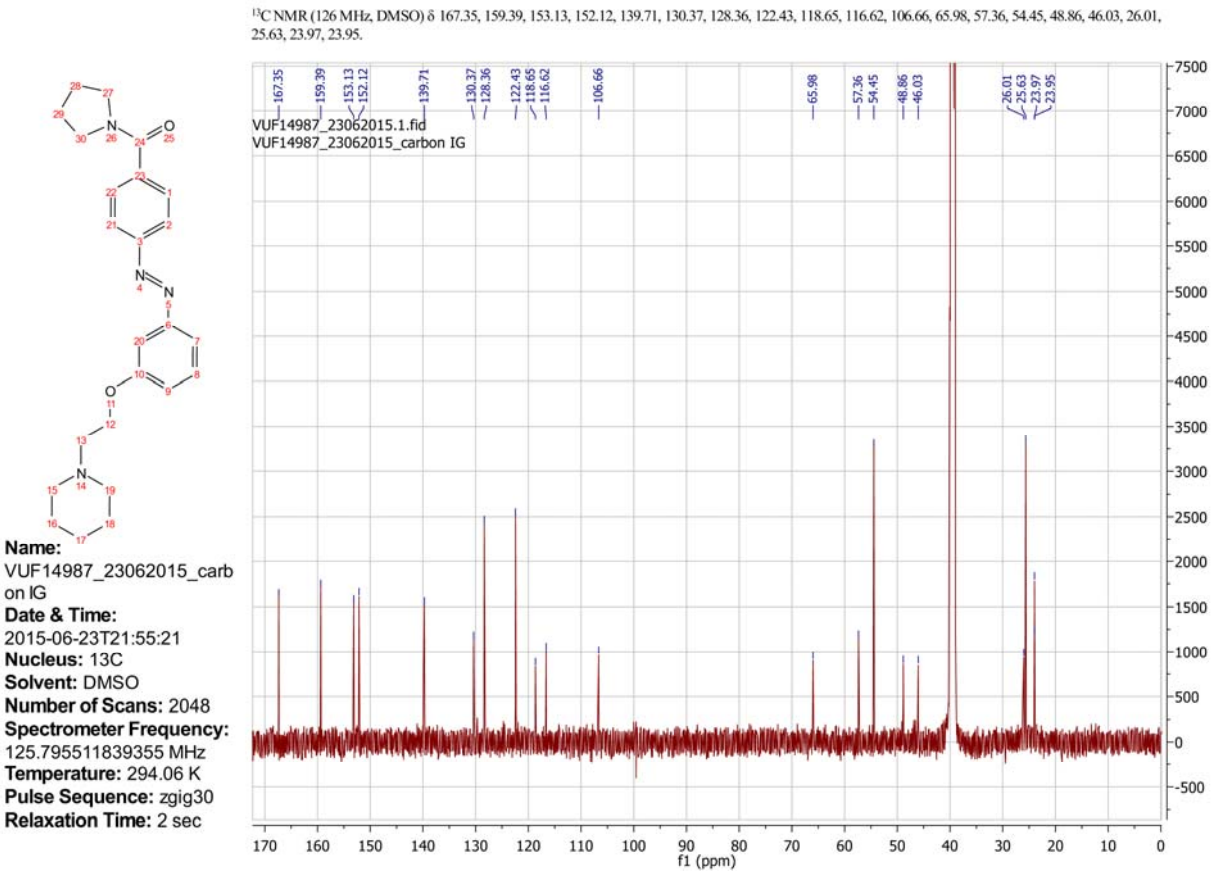
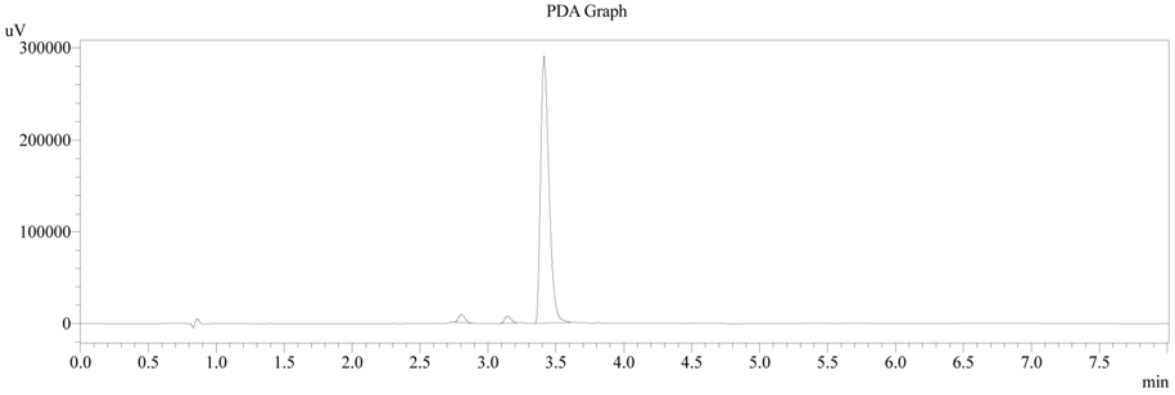


Figure S87: ^{13}C-NMR spectrum of (E)-(4-((3-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (29)

Acquired by	: Admin
Date Acquired	: 4/15/2016 12:08:45 PM
Sample Name	: NIHA_01_049_15042016
Sample ID	:
Tray#	: 1
Vial#	: 18
Injection Volume	: 5
Data File	: C:\LabSolutions\Data\2016 - wk15\NIHA_01_049_15042016.lcd
Background File	: azoblanco_13042016.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Tuning\Tuning-ESI-pos-neg01072015a.lct
Processed by	: Admin
Modified Date	: 4/15/2016 12:39:28 PM

PDA Graph

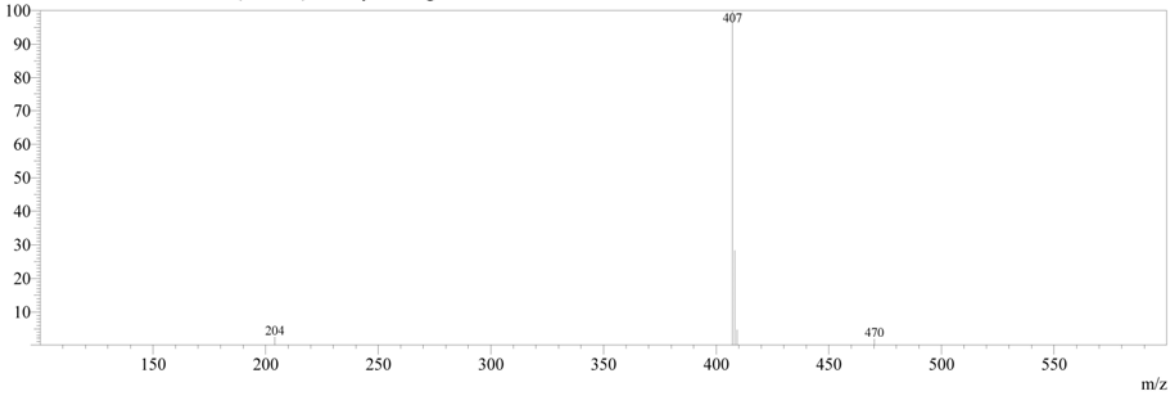


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		2.799	29629	2.263
2		3.139	26008	1.986
3		3.407	1253728	95.751

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.480-3.500(Scan#:349-351)
Mass Peaks:7 Base Peak:407.20(3867924) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.370<->3.830(338<->384)
Mass Peaks:7 Base Peak:407.20(3867924) Polarity:Pos Segment1 - Event1

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	204.05	88590	2.29				5	470.20	67753	1.75			
2	407.20	3867924	100.00				6	835.55	79392	2.05			
3	408.20	1097850	28.38				7	836.55	41247	1.07			
4	409.25	182992	4.73										

Figure S88: LC-MS chromatogram of (E)-(4-((3-(2-(Piperidin-1-yl)ethoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (29)

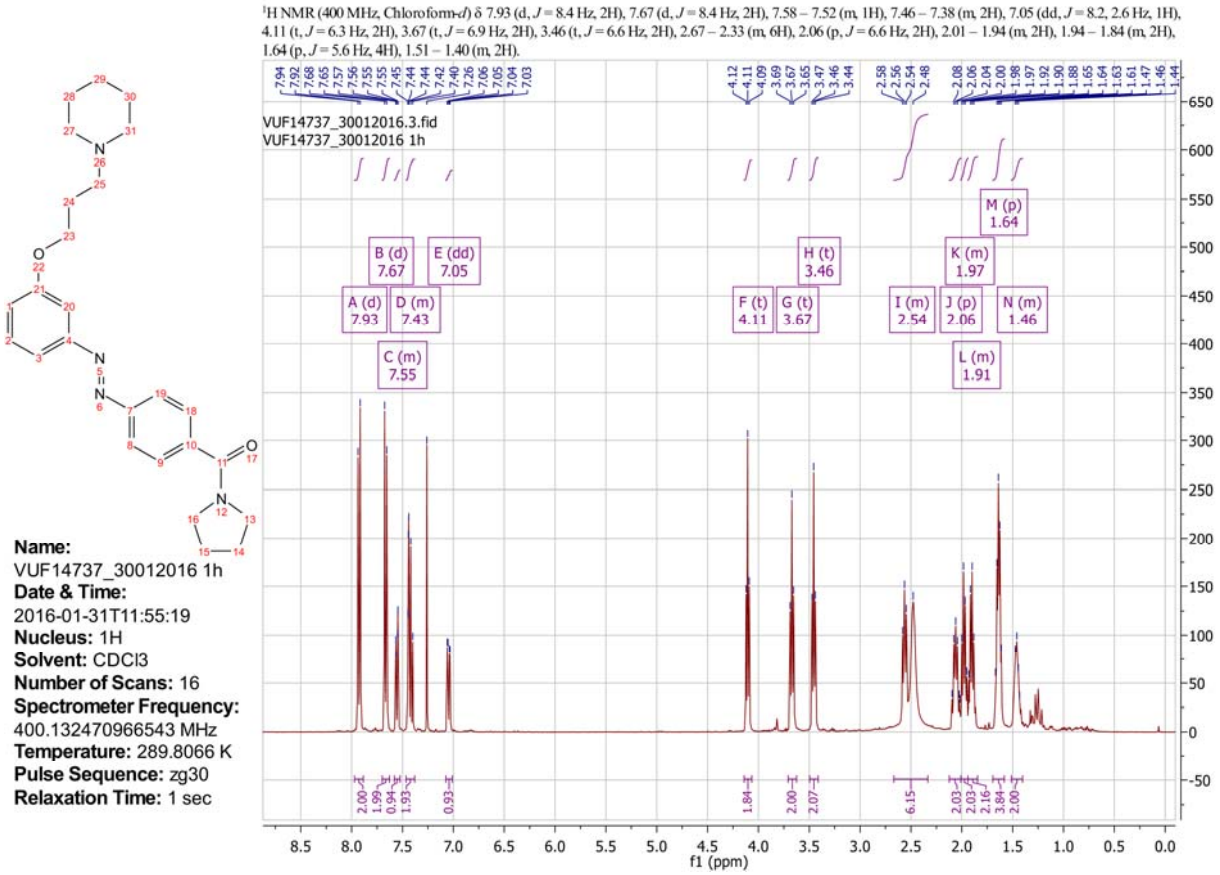


Figure S89: ^{1}H-NMR spectrum of (E)-(4-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (30)

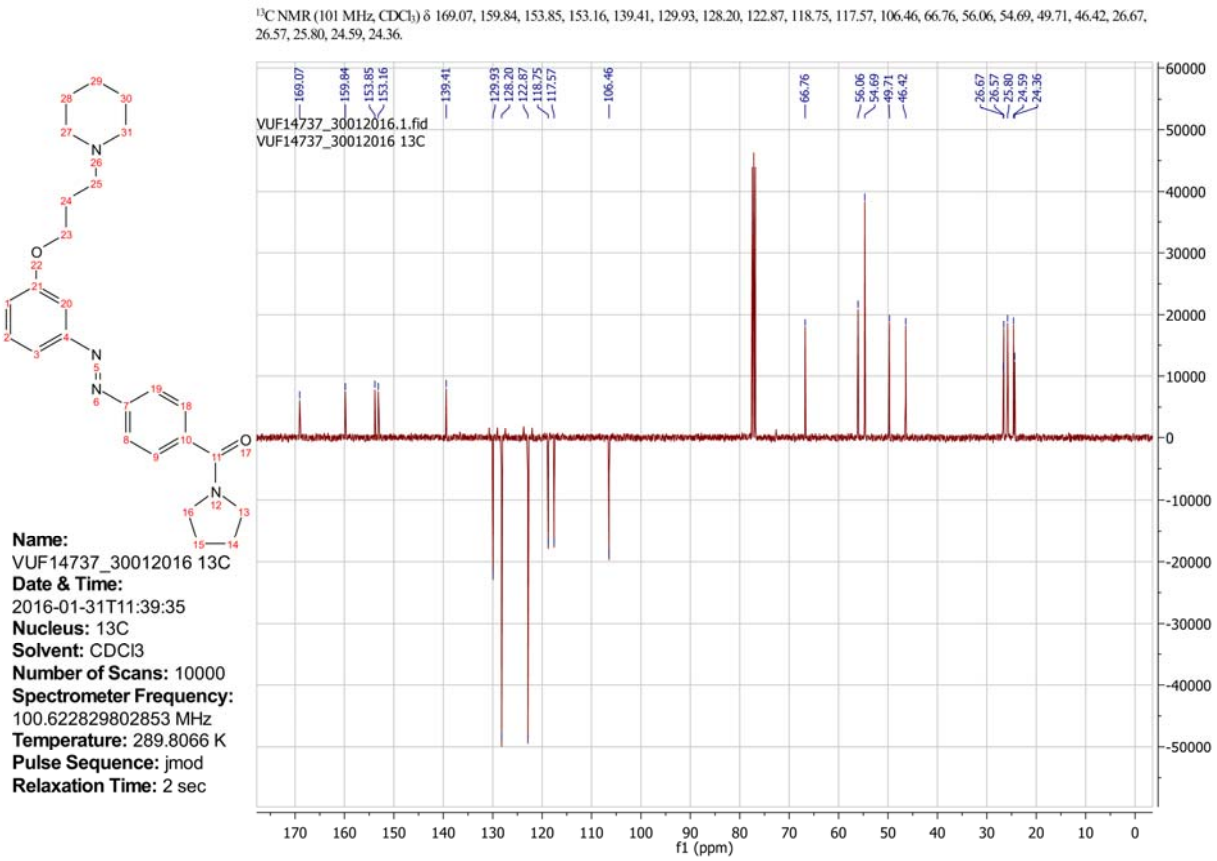
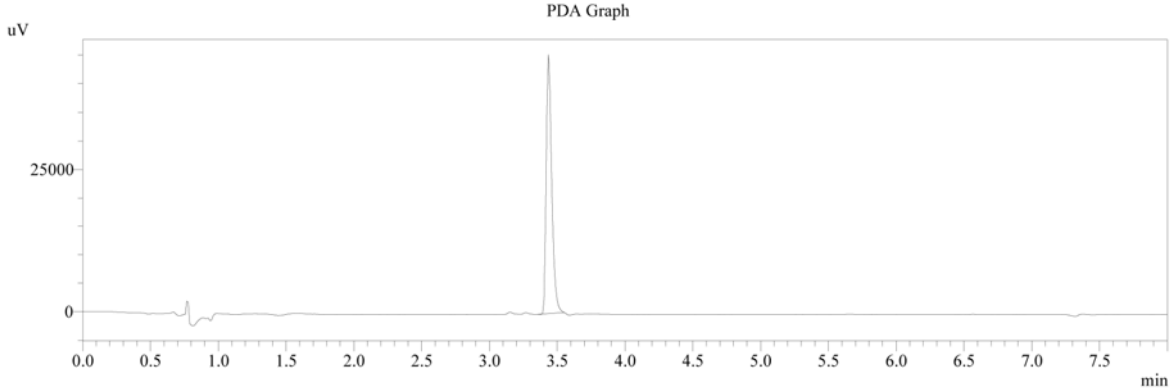


Figure S90: ^{13}C-NMR spectrum of (E)-(4-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (30)

Acquired by	: Admin
Date Acquired	: 5/13/2015 1:29:36 PM
Sample Name	: VUF14737_DARK_13052015
Sample ID	:
Tray#	: 1
Vial#	: 22
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2015\2015-WK20\VUF14737_DARK_13052015.lcd
Background File	: VUFBlanco_DARK_13052015.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Data\Installatie NOV 2009\Tuning ESI POS + NEG JAN2010.lct
Processed by	: Admin
Modified Date	: 2/2/2016 10:28:43 AM

PDA Graph

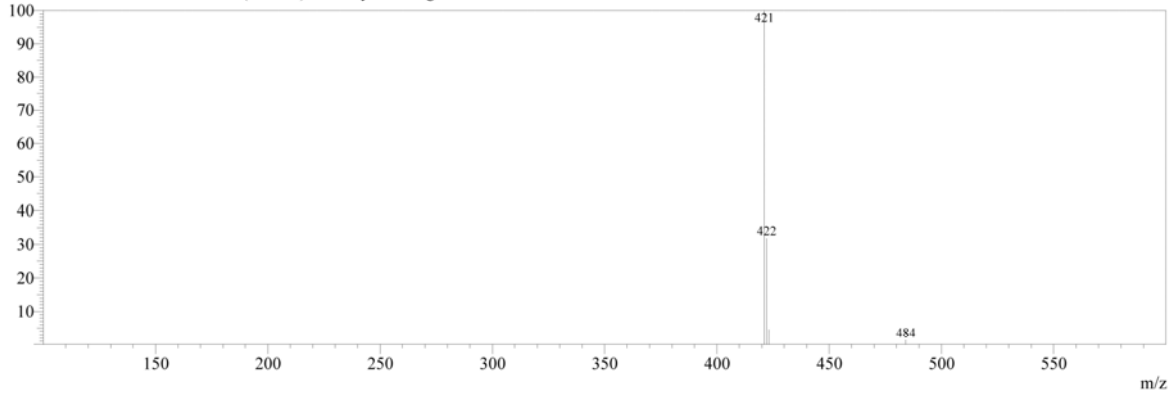


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.431	129564	100.000

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.510-3.530(Scan#:352-354)
Mass Peaks:5 Base Peak:421.05(884452) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.430<->3.720(344<->373
Mass Peaks:5 Base Peak:421.05(884452) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	421.05	884452	100.00				4	484.10	11839	1.34			
2	422.10	281682	31.85				5	863.30	9037	1.02			
3	423.10	40674	4.60										

Figure S91: LC-MS chromatogram of (E)-(4-((3-(3-(Piperidin-1-yl)propoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (30)

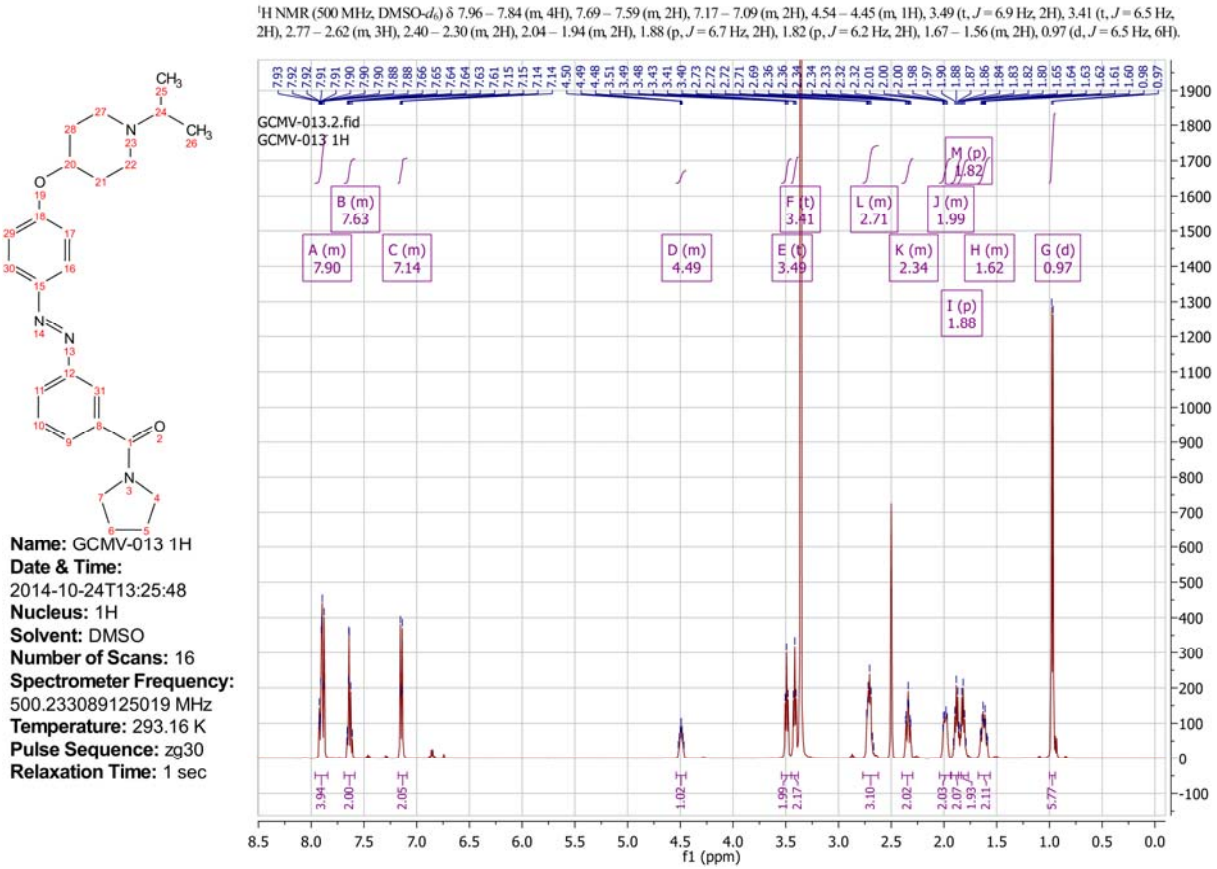


Figure S92: ^{1}H-NMR spectrum of (E)-(3-((4-((1-Isopropylpiperidin-4-yl)oxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (31)

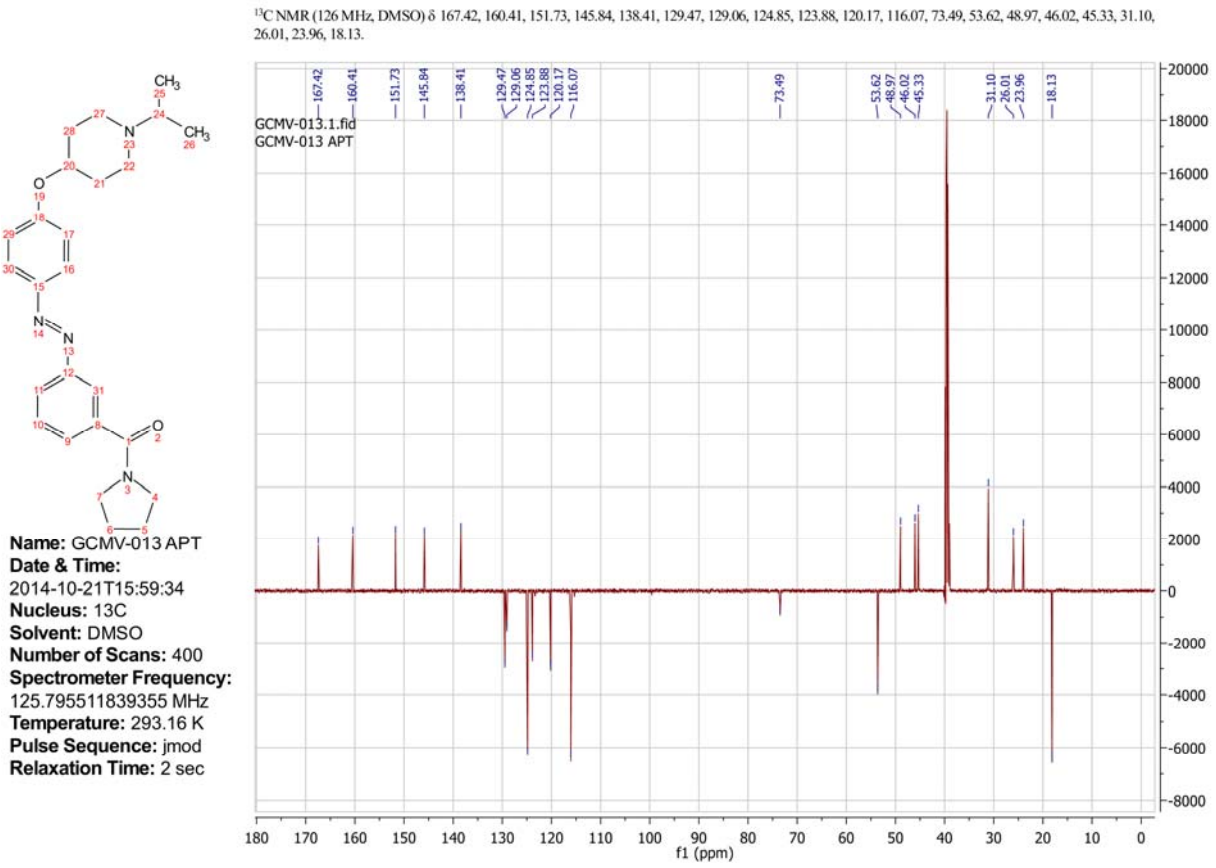
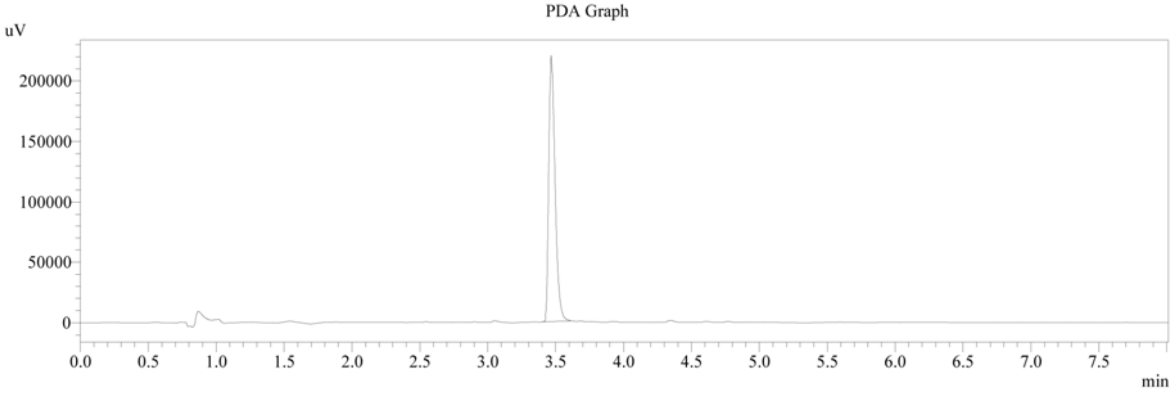


Figure S93: ^{13}C-NMR spectrum of (E)-(3-((4-((1-Isopropylpiperidin-4-yl)oxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (31)

Acquired by	: Admin
Date Acquired	: 5/21/2015 11:19:54 AM
Sample Name	: VUF14859_DARK_21052015
Sample ID	:
Tray#	: 1
Vial#	: 67
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2015\2015-wk21\VUF14859_DARK_21052015.lcd
Background File	: VUF_blanco_2_IRRA_21052015.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Data\Installatie NOV 2009\Tuning ESI POS + NEG JAN2010.lct
Processed by	: Admin
Modified Date	: 2/8/2016 1:40:38 PM

PDA Graph

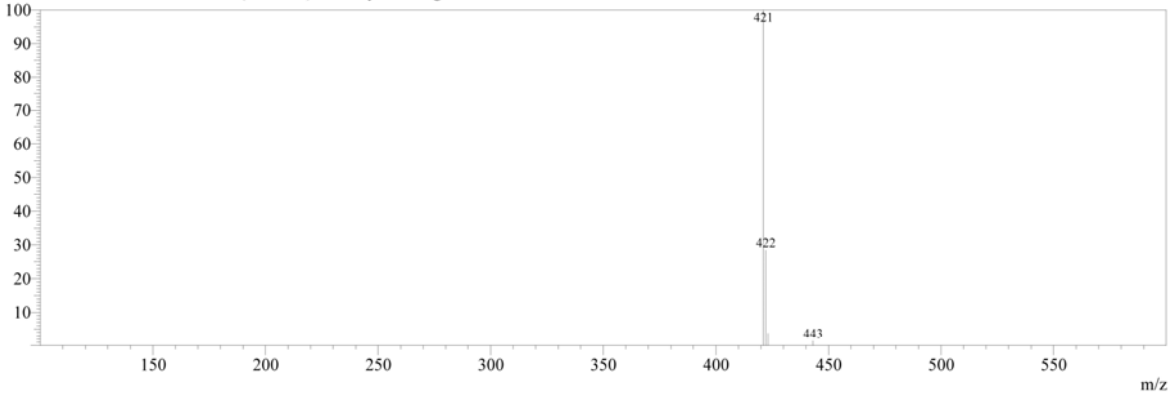


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.463	708764	100.000

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.550-3.570(Scan#:356-358)
Mass Peaks:5 Base Peak:421.05(1352873) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.450<->3.900(346<->391
Mass Peaks:5 Base Peak:421.05(1352873) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	421.05	1352873	100.00				4	443.05	19225	1.42			
2	422.05	384790	28.44				5	863.35	16527	1.22			
3	423.10	50882	3.76										

Figure S94: LC-MS chromatogram of (E)-(3-((4-((1-Isopropylpiperidin-4-yl)oxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (31)

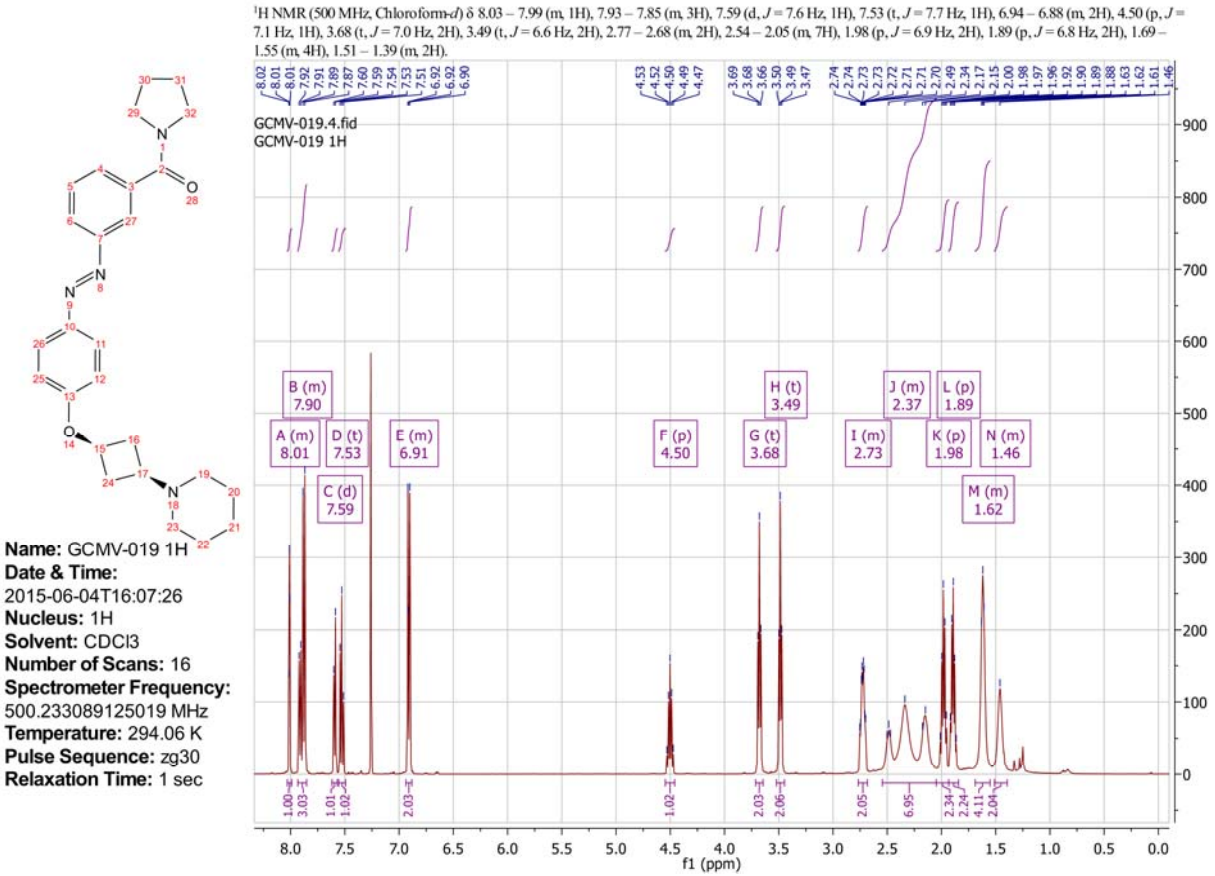


Figure S95: ^{1}H-NMR spectrum of (3-((E)-(4-((1s,3s)-3-(Piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (32)

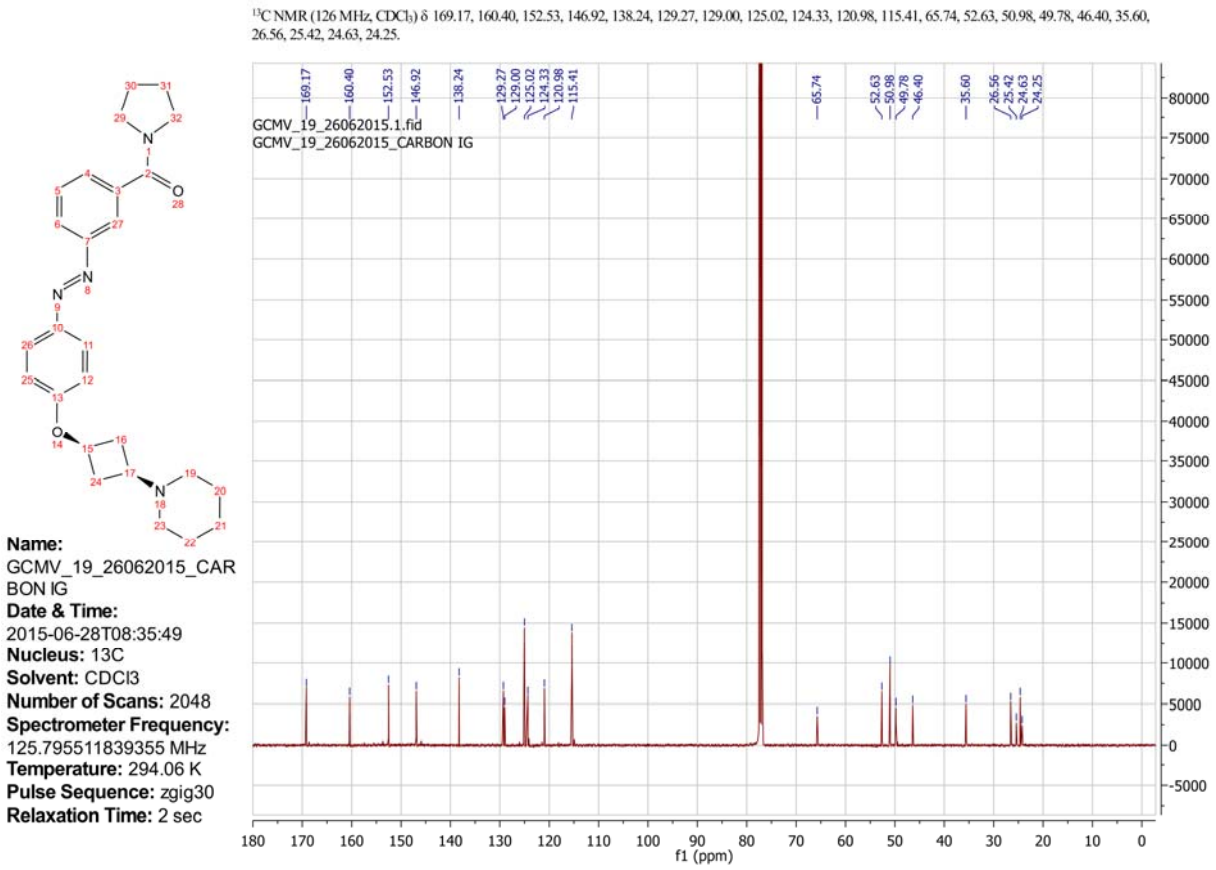
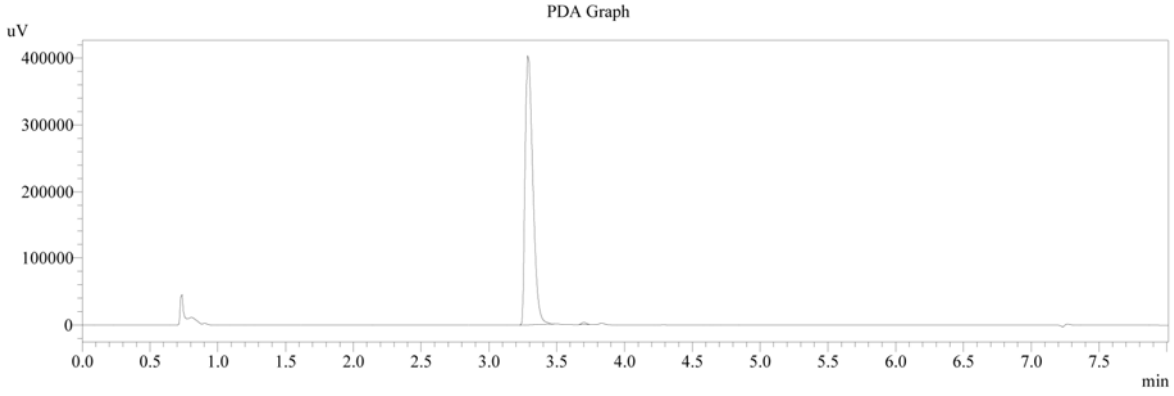


Figure S96: ^{13}C-NMR spectrum of (3-((E)-(4-((1s,3s)-3-(Piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (32)

Acquired by	: Admin
Date Acquired	: 7/17/2015 1:26:21 PM
Sample Name	: VUF15060_DARK_17072015
Sample ID	:
Tray#	: 1
Vial#	: 15
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2015\2015-wk29\VUF15060_DARK_17072015.lcd
Background File	: Blanco1_IRRA1_17072015.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Tuning File\Tuning-ESI-pos-neg01072015.lct
Processed by	: Admin
Modified Date	: 2/4/2016 1:47:38 PM

PDA Graph

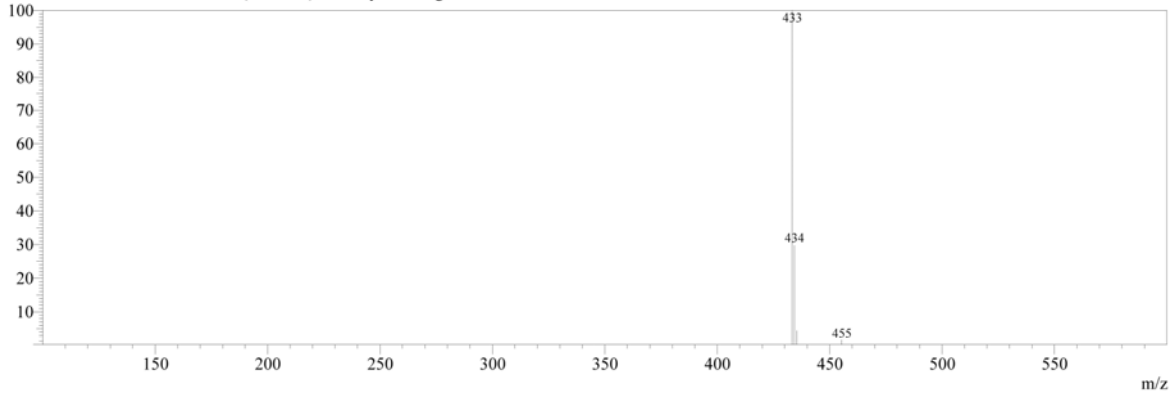


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.284	1599559	99.496
2		3.695	8108	0.504

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.370-3.390(Scan#:338-340)
Mass Peaks:7 Base Peak:433.30(5571032) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.240<->3.630(325<->364
Mass Peaks:7 Base Peak:433.30(5571032) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	433.30	5571032	100.00				5	865.60	97133	1.74			
2	434.25	1659260	29.78				6	887.65	116803	2.10			
3	435.30	248005	4.45				7	888.60	84582	1.52			
4	455.30	80395	1.44										

Figure S97: LC-MS chromatogram of (3-((E)-(4-((1s,3s)-3-(Piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (32)

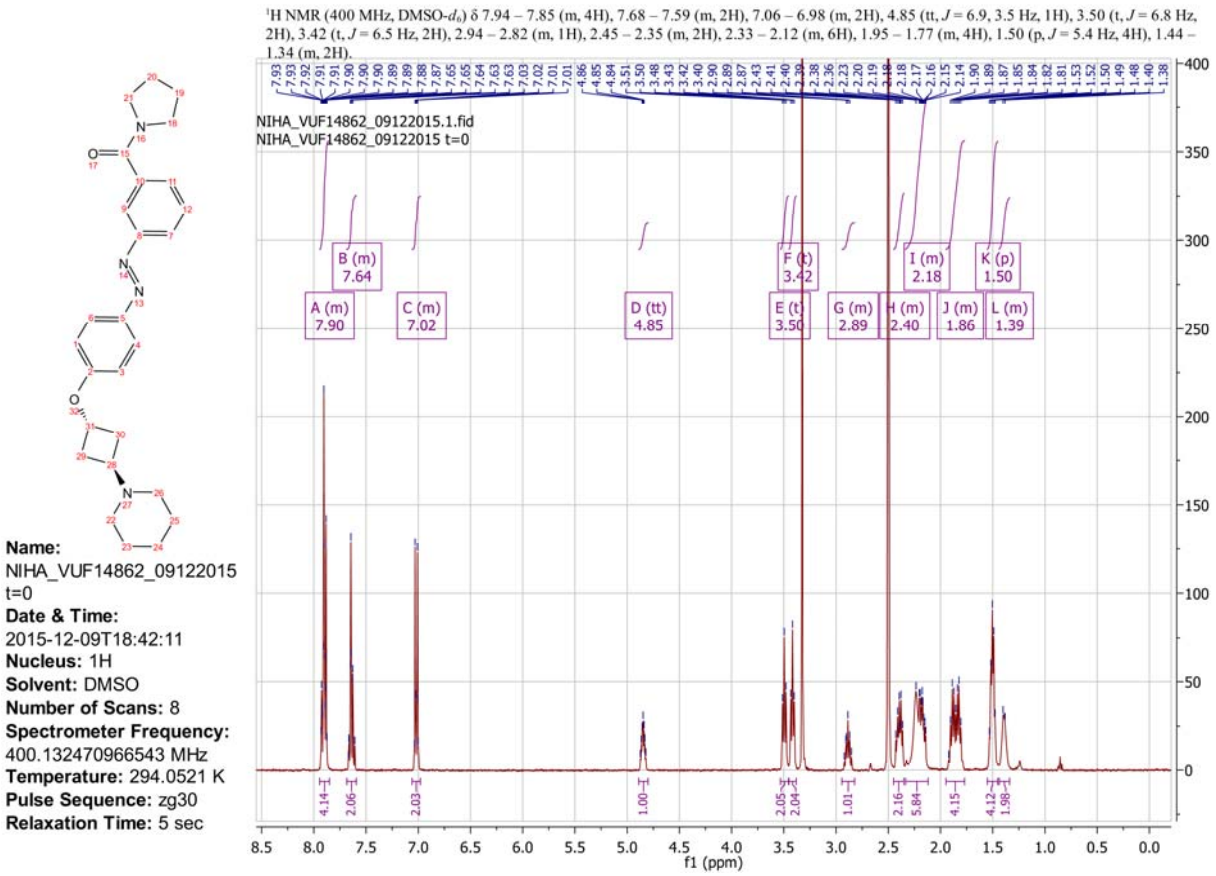


Figure S98: ^{1}H-NMR spectrum of (3-((E)-(4-((1r,3s)-3-(Piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (33)

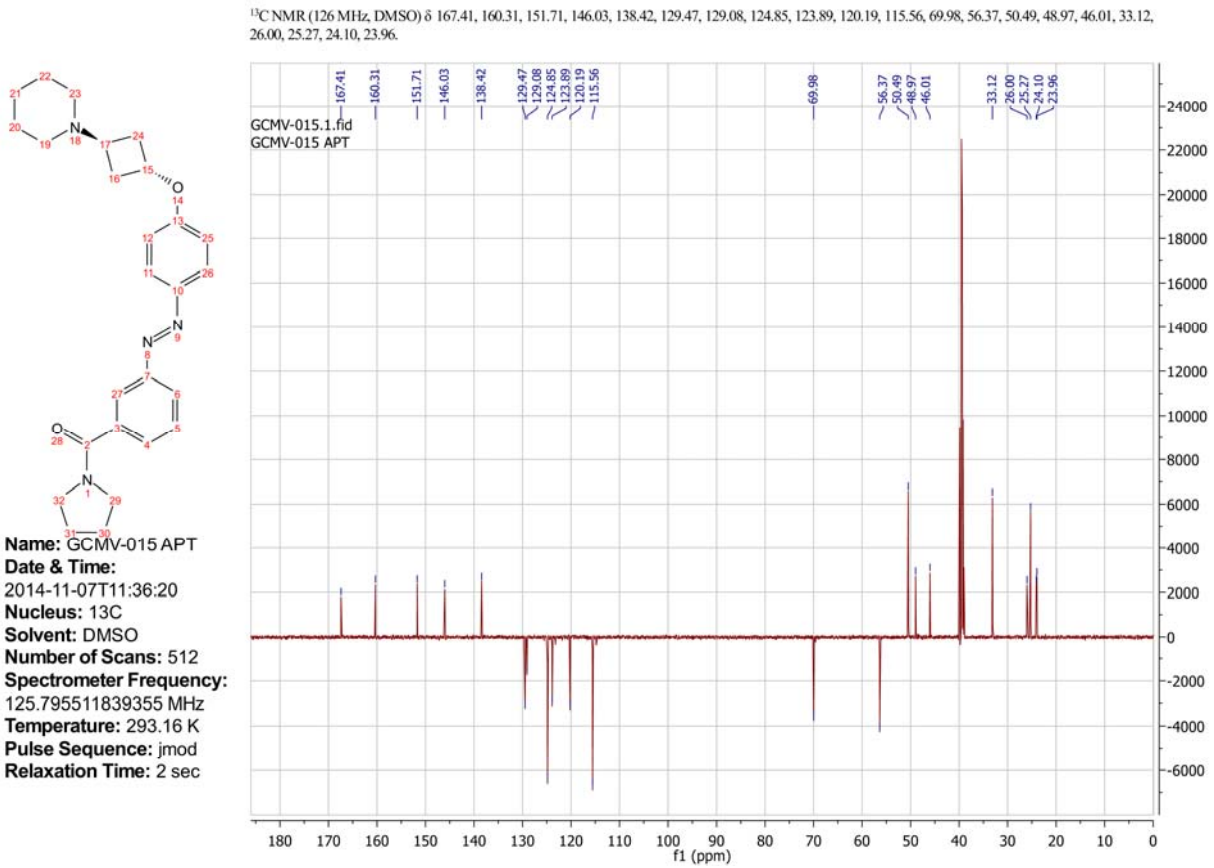
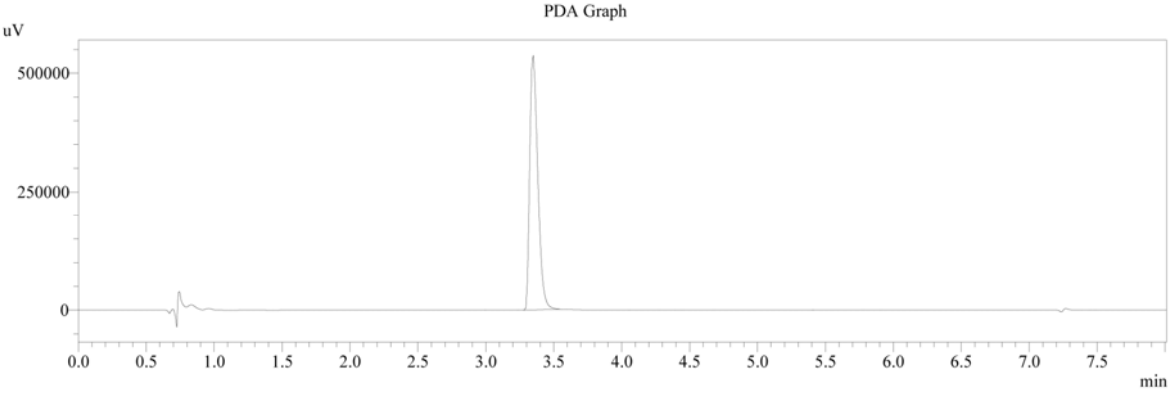


Figure S99: ^{13}C-NMR spectrum of (3-((E)-(4-((1r,3s)-3-(Piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (33)

Acquired by	: Admin
Date Acquired	: 1/22/2016 1:01:14 PM
Sample Name	: VUF14862_DARK_22012016
Sample ID	:
Tray#	: 1
Vial#	: 38
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2016\2016 - wk03\VUF14862_DARK_22012016.lcd
Background File	: Blanco_IRRA_2_22012016.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Tuning File\Tuning-ESI-pos-neg01072015.lct
Processed by	: Admin
Modified Date	: 9/9/2016 4:13:49 PM

PDA Graph

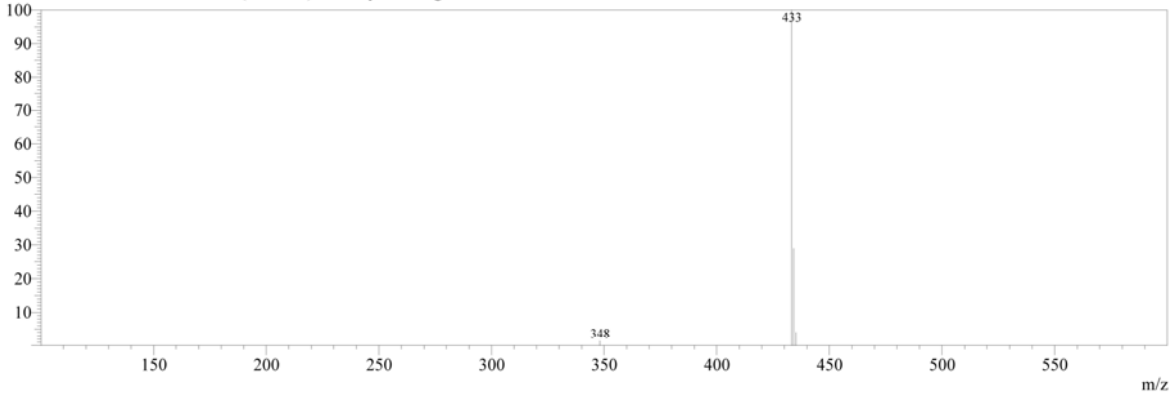


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.343	2216208	100.000

MS Spectrum Graph

#:1 Ret.Time:Averaged 3.500-3.520(Scan#:351-353)
Mass Peaks:7 Base Peak:433.25(3220618) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.370<->3.820(338<->383
Mass Peaks:7 Base Peak:433.25(3220618) Polarity:Pos Segment1 - Event

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	348.10	46254	1.44				5	865.50	40696	1.26			
2	433.25	3220618	100.00				6	865.70	42171	1.31			
3	434.20	934002	29.00				7	887.50	54099	1.68			
4	435.20	131757	4.09										

Figure S100: LC-MS chromatogram of (3-((E)-(4-((1r,3s)-3-(Piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (33)

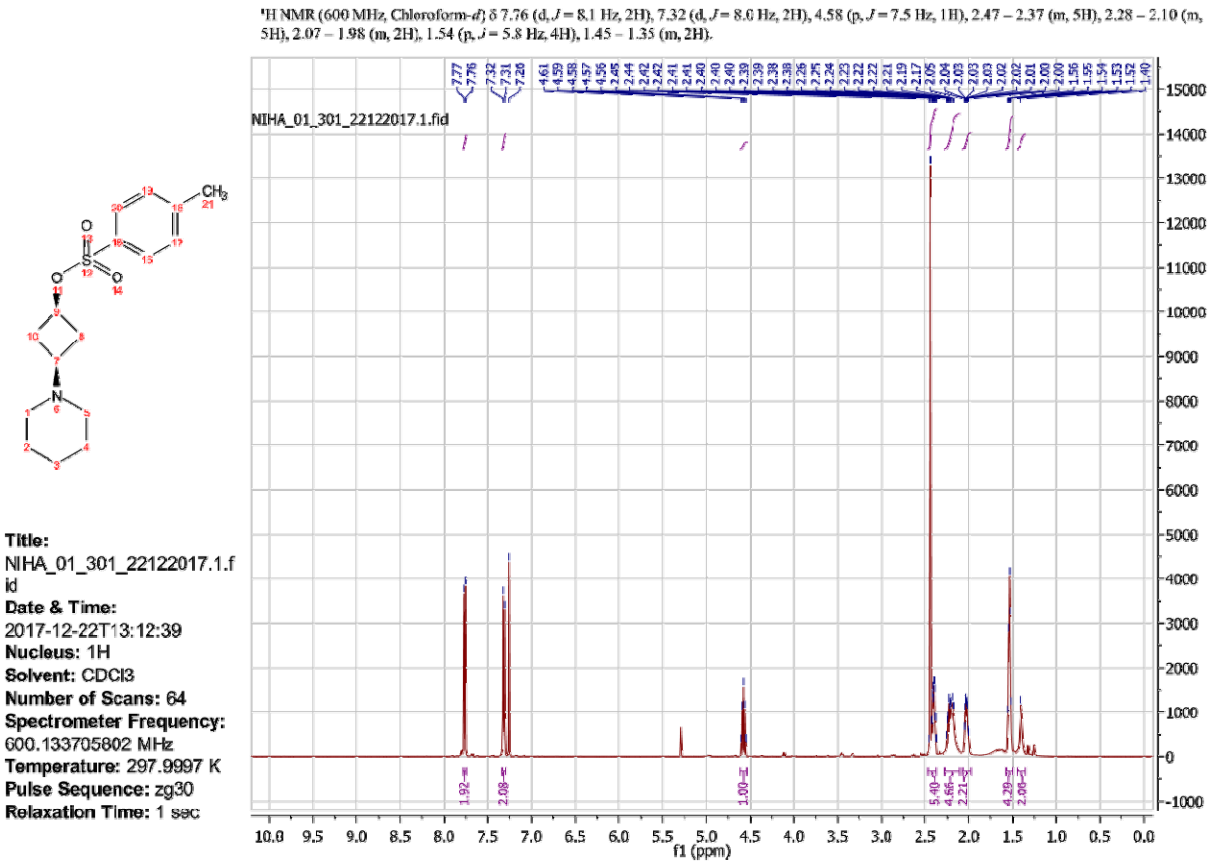


Figure S101: ^{1}H-NMR spectrum of (1s,3s)-3-(piperidin-1-yl)cyclobutyl 4-methylbenzenesulfonate (36)

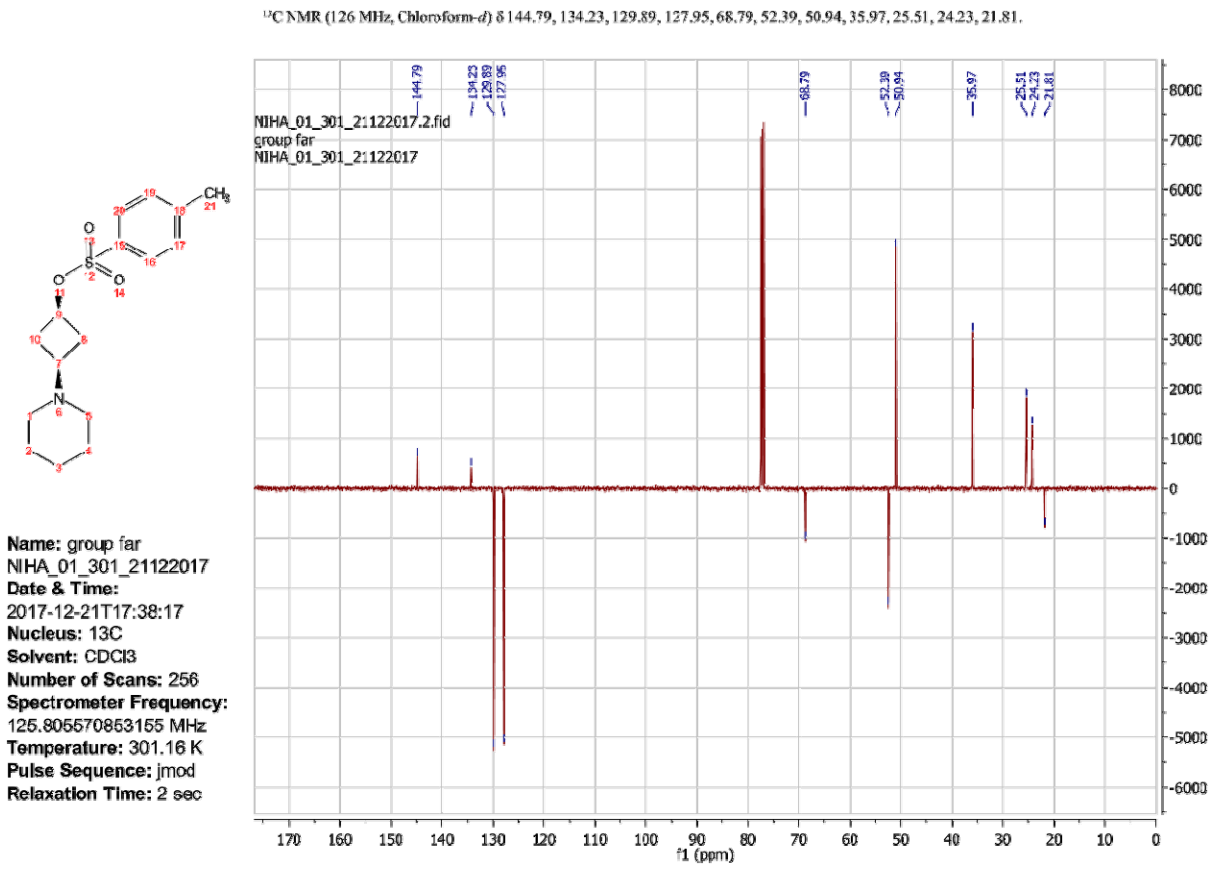
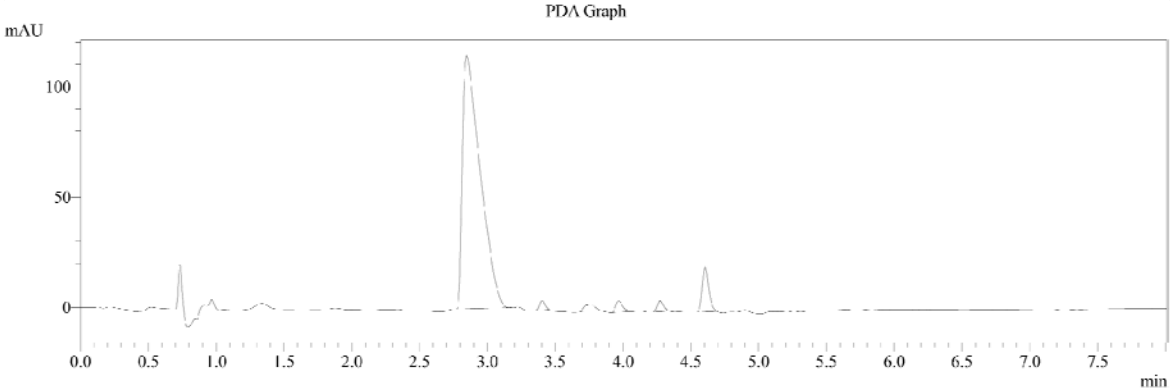


Figure S102: ^{13}C-NMR spectrum of (1s,3s)-3-(piperidin-1-yl)cyclobutyl 4-methylbenzenesulfonate (36)

Acquired by	: Admin
Date Acquired	: 16/1/2018 12:24:21 PM
Sample Name	: NIHA_01_301_16012018
Sample ID	:
Tray#	: 1
Vial#	: 8
Injection Volume	: 10
Data File	: C:\LabSolutions\Data\2018\2018-wk03\NIHA_01_301_16012018.lcd
Background File	: blanco_16012018.lcd
Method File	: Method SCAN ACID standard.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Tuning\Tuning-ESI-pos-neg01072015a.lct
Processed by	: Admin
Modified Date	: 16/1/2018 12:34:05 PM

PDA Graph

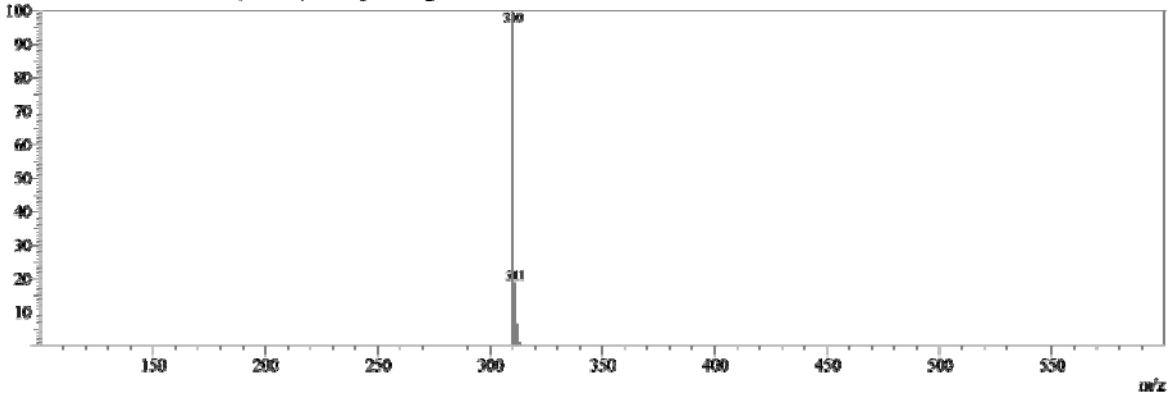


PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		2.844	1048361	88.530
2		3.399	12979	1.096
3		3.728	20020	1.691
4		3.962	18117	1.530
5		4.267	15489	1.308
6		4.600	69218	5.845

MS Spectrum Graph

#:1 Ret.Time:Averaged 2.920-2.940(Scan#:293-295)
Mass Peaks:4 Base Peak:310.15(1125675) Polarity:Pos Segment1 - Event1



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 2.780<->3.380(279<->339)
Mass Peaks:4 Base Peak:310.15(1125675) Polarity:Pos Segment1 - Event1

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	310.15	1125675	100.00				3	312.15	74205	6.59			
2	311.15	212458	18.87				4	313.15	13154	1.17			

Figure S103: LC-MS chromatogram of (1s,3s)-3-(piperidin-1-yl)cyclobutyl 4-methylbenzenesulfonate (36)

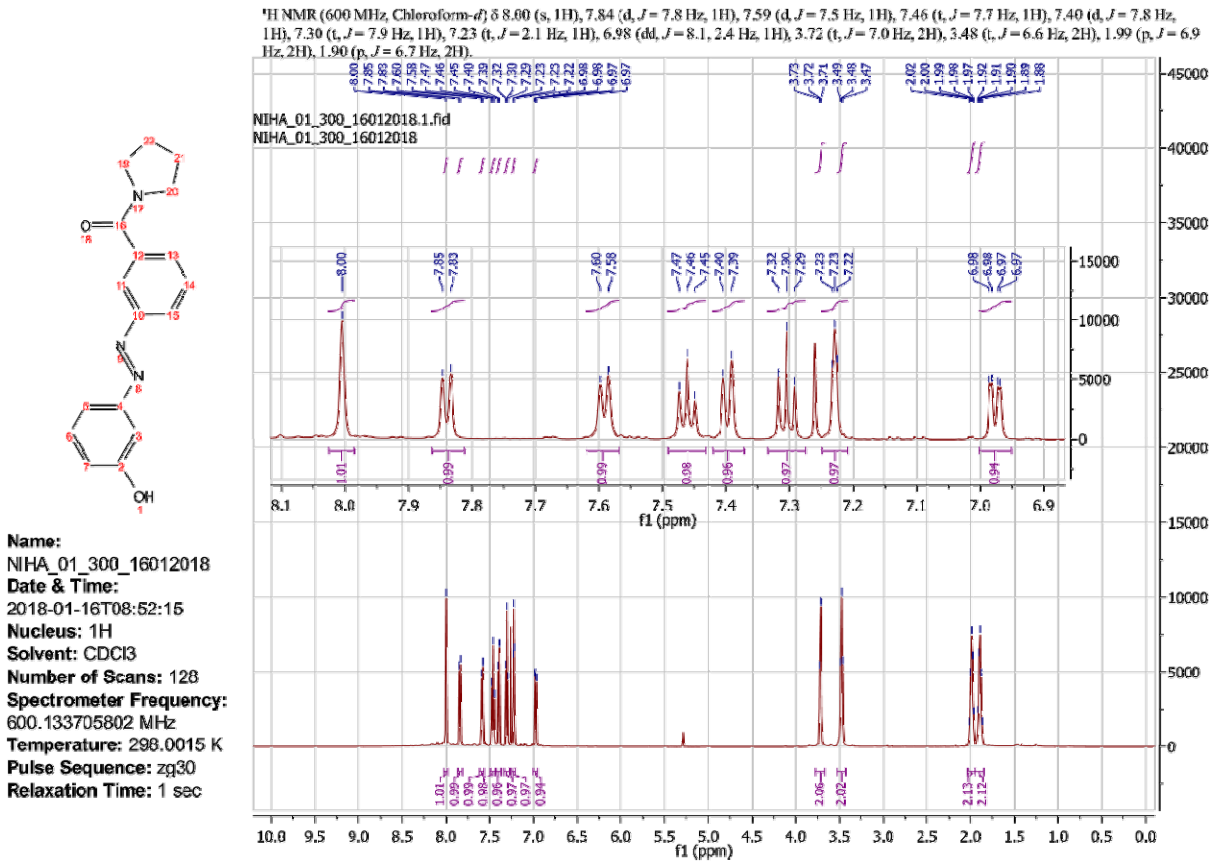


Figure S104: ^{1}H-NMR spectrum of (E)-(3-((3-hydroxyphenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (37)

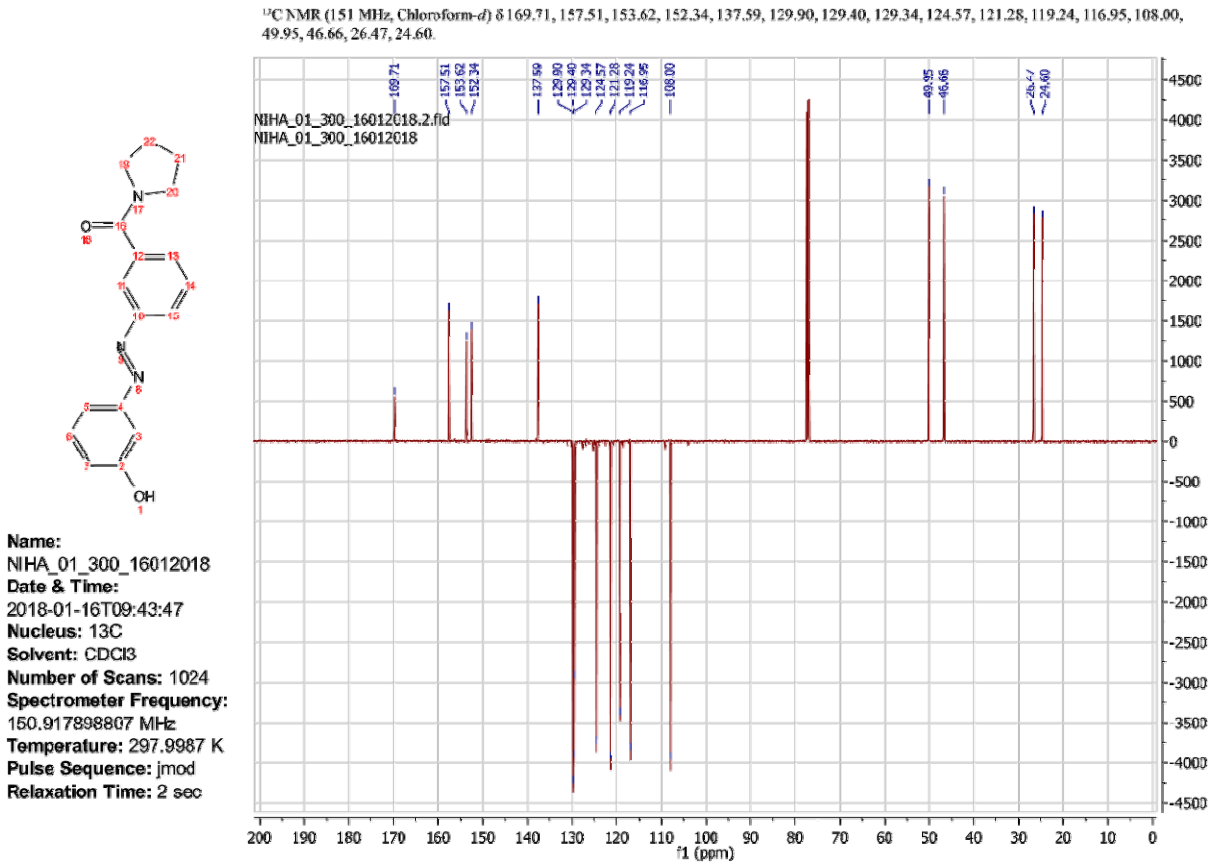
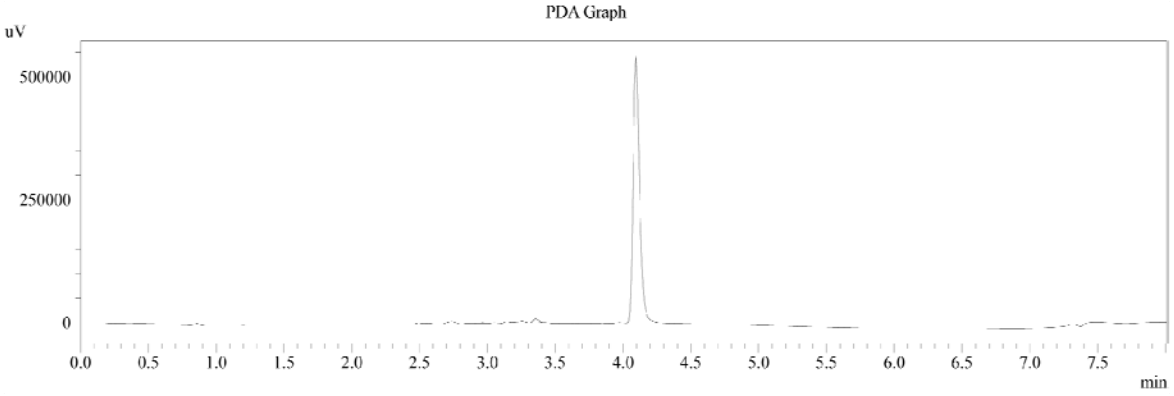


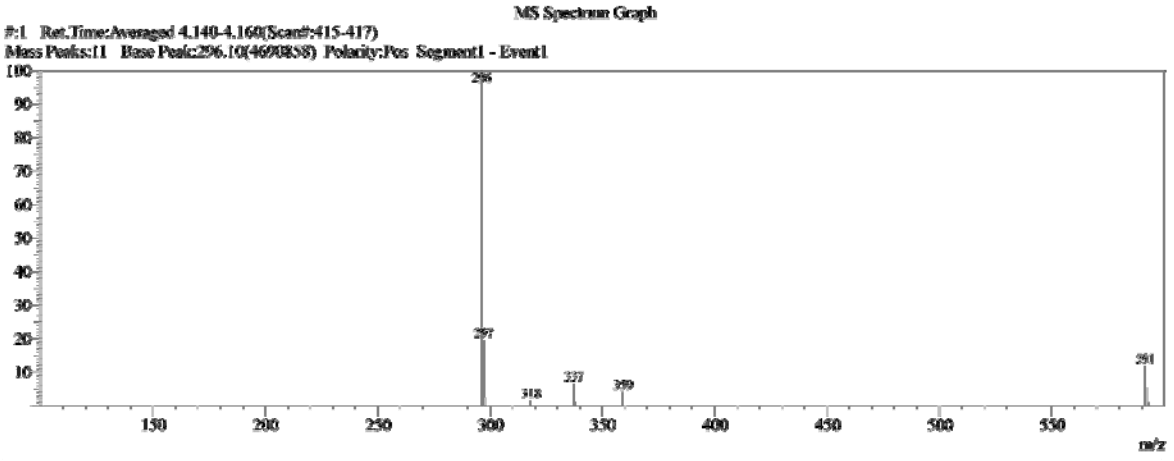
Figure S105: ^{13}C-NMR spectrum of (E)-(3-((3-hydroxyphenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (37)

Acquired by	: Admin
Date Acquired	: 21/12/2017 6:32:59 PM
Sample Name	: NIHA_01_300_f19_21122017
Sample ID	:
Tray#	: 1
Vial#	: 9
Injection Volume	: 1
Data File	: C:\LabSolutions\Data\2017\2017-wk51\NIHA_01_300_f19_21122017.lcd
Background File	: azoblanco_171222.lcd
Method File	: Method SCAN BASE standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Tuning\Tuning-ESI-pos-neg01072015a.lct
Processed by	: Admin
Modified Date	: 15/1/2018 4:16:50 PM



PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.351	21936	1.223
2		4.090	1771388	98.777



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.910<->4.770(392<->478)
Mass Peaks:11 Base Peak:296.10(4690858) Polarity:Pos Segment1 - Event1

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	296.10	4690858	100.00				7	359.05	189435	4.04			
2	297.10	917244	19.55				8	591.30	557934	11.89			
3	298.10	106124	2.26				9	592.30	248808	5.30			
4	318.10	73579	1.57				10	593.25	51650	1.10			
5	337.15	306453	6.53				11	613.30	108298	2.31			
6	338.20	60743	1.29										

Figure S106: LC-MS chromatogram of (E)-(3-((3-hydroxyphenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (37)

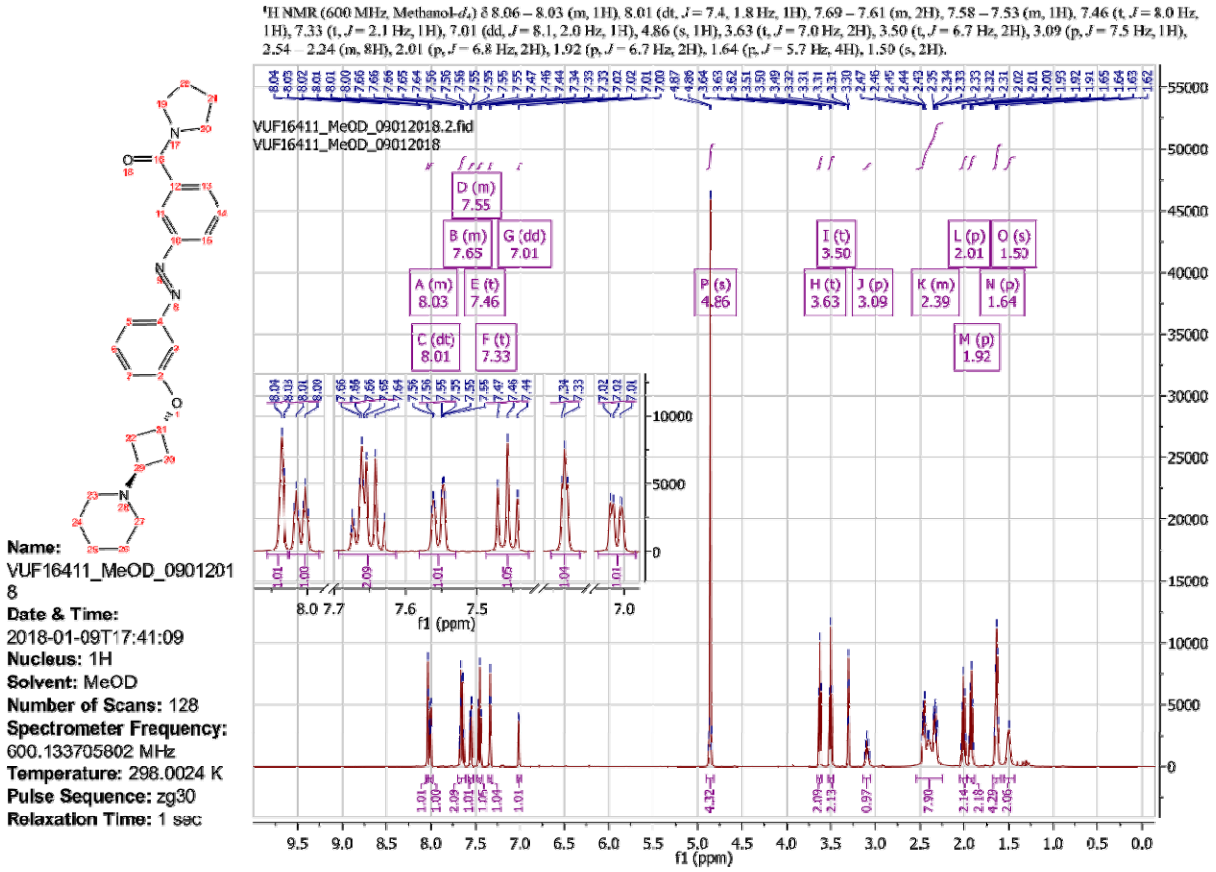


Figure S107: ^{1}H-NMR spectrum of (3-((E)-(3-((1r,3s)-3-(piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (34)

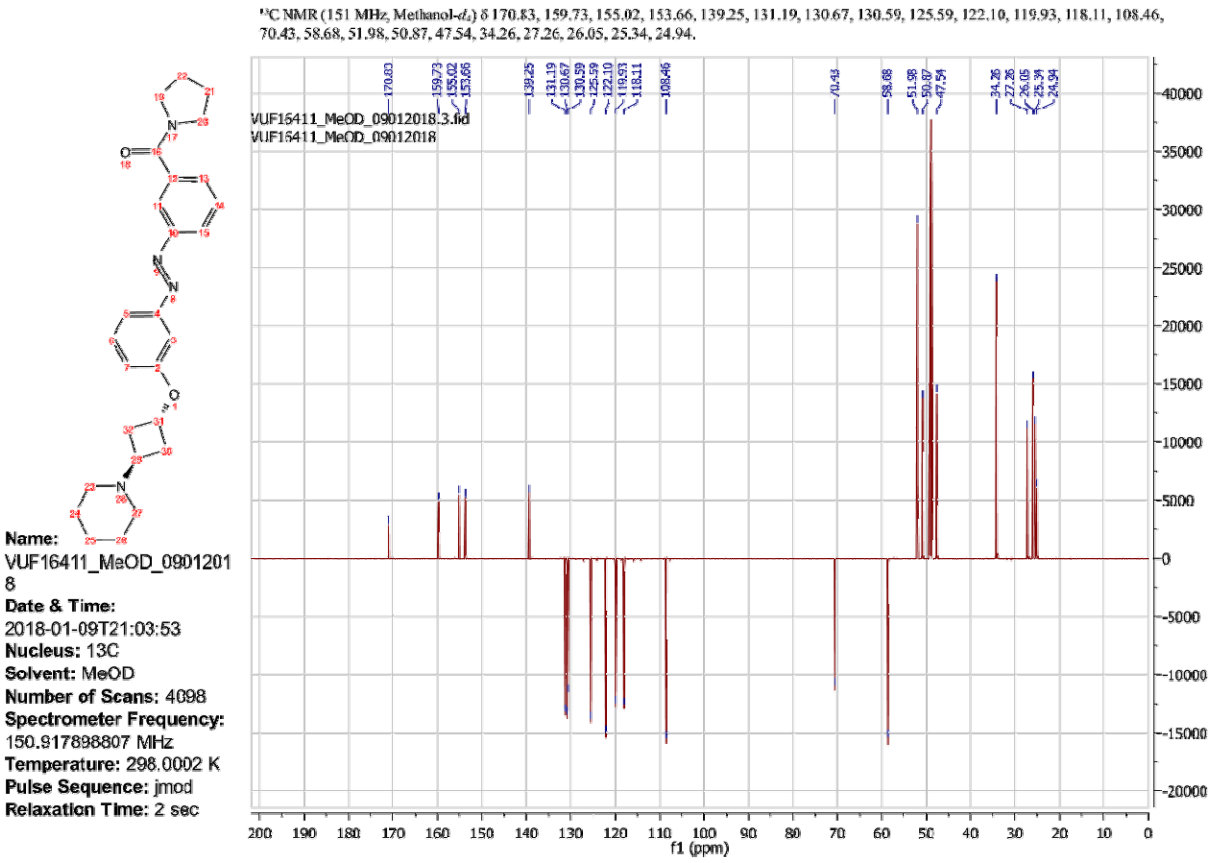
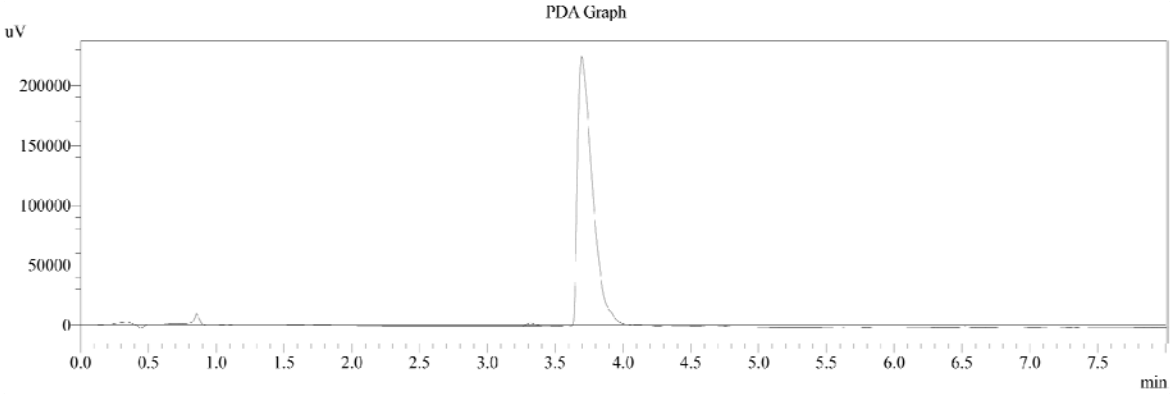


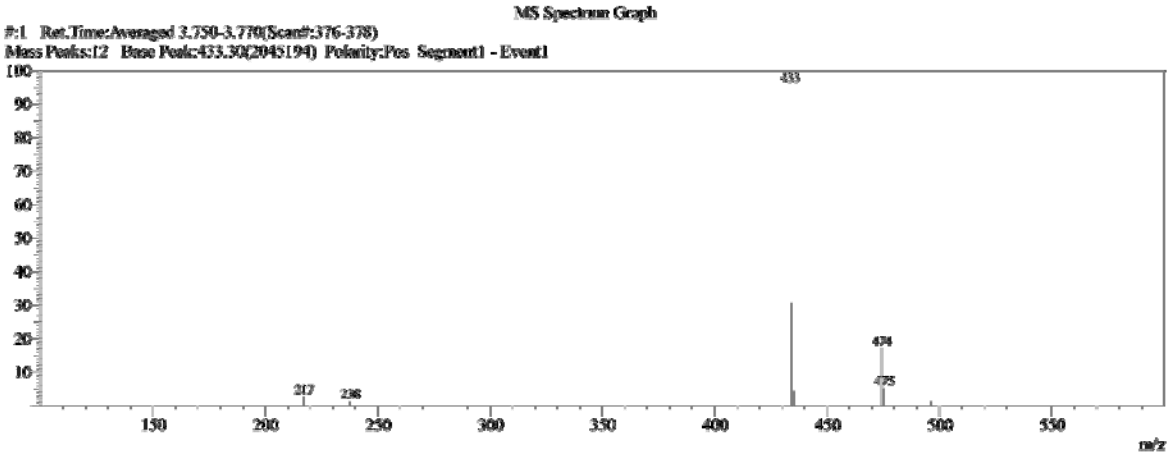
Figure S108: ^{13}C-NMR spectrum of (3-((E)-(3-((1r,3s)-3-(piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (34)

Acquired by	: Admin
Date Acquired	: 5/1/2018 9:55:22 AM
Sample Name	: NIHA_01_302_05012018
Sample ID	:
Tray#	: 1
Vial#	: 10
Injection Volume	: 1
Data File	: C:\LabSolutions\Data\2018\2018-wk01\NIHA_01_302_05012018.lcd
Background File	: blanco 05012018.lcd
Method File	: Method SCAN ACID standard azo.lcm
Report Format	: DefaultLCMS.lcr
Tuning File	: C:\LabSolutions\Tuning\Tuning-ESI-pos-neg01072015a.lct
Processed by	: Admin
Modified Date	: 15/1/2018 7:03:59 PM



PDA Ch1 254nm 4nm

Peak#	Name	Ret. Time	Area	Area %
1		3.312	12983	0.747
2		3.690	1724018	99.253



MS Spectrum Table

#:1 Ret.Time:
BG Mode:Calc 3.590<->4.210(360<->422)
Mass Peaks:12 Base Peak:433.30(2045194) Polarity:Pos Segment1 - Event1

#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic	#	m/z	Abs.Inten.	Rel.Inten.	Charge	Polarity	Monoisotopic
1	217.10	54951	2.69				7	475.35	106749	5.22			
2	237.70	27661	1.35				8	496.30	28026	1.37			
3	433.30	2045194	100.00				9	865.60	42352	2.07			
4	434.25	628264	30.72				10	866.70	22038	1.08			
5	435.25	88636	4.33				11	887.70	54281	2.65			
6	474.35	349824	17.10				12	888.75	25596	1.25			

Figure S109: LC-MS chromatogram of (3-((E)-(3-((1r,3s)-3-(piperidin-1-yl)cyclobutoxy)phenyl)diazenyl)phenyl)(pyrrolidin-1-yl)methanone (34)

References

(1) Roche, O.; Nettekoven, M.; Vifian, W.; Sarmiento, R. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4377.

(2) Wijtmans, M.; Denonne, F.; Celanire, S.; Gillard, M.; Hulscher, S.; Delaunoy, C.; Van Houtvin, N.; Bakker, R. A.; Defays, S.; Gerard, J.; Grooters, L.; Hubert, D.; Timmerman, H.; Leurs, R.; Talaga, P.; de Esch, I. J. P.; Provins, L. *MedChemComm* **2010**, *1*, 39.