Synthesis of a series of highly substituted cyclohexanols via Michael addition in an aqueous medium

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The Michael addition of active methylene compounds or nitromethane to chalcones in an aqueous medium and catalysed by tetrabutyl ammonium hydroxide (TBAOH) to afford highly substituted cyclohexanols is described. The protocol provides an efficient route for the synthesis of highly substituted cyclohexanols, with short reaction time, and a range of different substrates in the absence of toxic organic solvents.

Keywords: Michael addition, tetrabutyl ammonium hydroxide, highly substituted cyclohexanol, aqueous medium

The Michael addition is an important, highly atom-economical reaction for the formation of C–C bonds, affording complex molecules such as tri-carbonylcompounds,[1,2] nitrogen-containing ketoesters,[3,4] various heterocycle compounds,[5–8] and alkylated dicarbonyls.[9,10] Many of these products are important organic intermediates in synthetic organic chemistry.

The use of water in organic reactions offers significant environment advantages and has attracted a great deal of interest in recent years, because water is considered as a cheap, safe and 'green' solvent.[11–13] Nevertheless, the organic transformations that can be carried out in water are limited, owing to the poor solubility of organic reactants in water. In many cases, phase-transfer catalysts (PTC)[14–16] or organic co-solvents[17,18] are added to increase the reaction rate by improving the solubility of reactants in water.

As a part of our interest in reactions in aqueous medium, we have explored the Michael addition reactions of malononitrile to chalcones in aqueous medium. This has led to an efficient synthesis of a series of highly substituted cyclohexanols.

Initially, the reaction of chalcone and malononitrile was performed in water using piperidine as catalyst at 80°C for 6h. A white solid was obtained, which was identified as a highly substituted cyclohexanol **3a** on the basis of its spectroscopic and analytical data. Previously, the synthesis of highly substituted cyclohexanols has been reported from chalcones and malononitrile or nitromethane.[19–23] However, the harsh conditions or long reaction times were required, and the scope of these protocols was limited. Consequently, we sought a more efficient procedure for a wider range of different substrates.

The reaction of chalcone and malononitrile was selected as a model reaction to optimise the reaction conditions. A series of bases including piperidine, DABCO, NEt_3, NBu_3, NaOH, were screened (Table 1, entries 1–5). To improve the unsatisfactory results, tetrabutyl ammonium bromide (TBAB) as a phase-transfer catalyst (PTC) was added, and a good yield of 80% was obtained at 15min (Table 1, entry 6). No reaction occurred when the reaction was carried out in water without base (Table 1, entry 7). The above results suggested that the base was necessary in the reaction, and PTC could increase the reaction rate. Thus we decided to use tetrabutyl ammonium hydroxide (TBAOH) as catalyst, which played the role of both base and PTC in the reaction. The yield was also satisfactory (Table 1, entry 8).

With the optimised conditions in placed, various chalcones were used to reveal the generality and scope of the new protocol (Table 2, entries 1–6). The results indicated that chalcones containing electron-drawing groups or electron-donating groups could react well with malononitrile to give the desired product **3a–e** in good or moderate yields. Instead of malononitrile, ethyl cyanoacetate also gave a satisfactory yield of the desired product **3g** (Table 2, entry 7).

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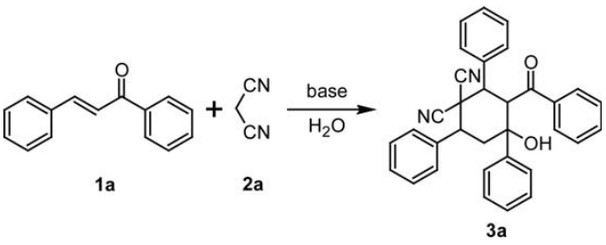
Table 1 Optimisation the reaction conditions[a]

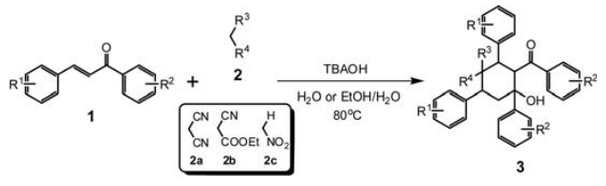


1a 2a 3a

Entry	Time	Base(10mol%)	Additive(0.1g)	Yield/%[b]
1	6h	piperidine	—	45
2	2h	DABCO[c]	—	10
3	2h	Et_3N	—	66
4	2h	Bu_3N	—	70
5	2h	NaOH	—	24
6	15min	Bu_3N	TBAB	80
7	15min	—	—	NR[d]
8	15min	TBAOH	—	86

[a] Reaction condition: 1a 1mmol, 2a 0.5mmol, H_2O 5mL, 80°C.
[b] Isolated yield of product.
[c] DABCO is 1,4-diazabicyclo[2.2.2]octane.
[d] No reaction.

Table 2 The synthesis of a series of highly substituted cyclohexanols via Micheal addition in aqueous medium[a]



1 2a 2b 2c 3

Entry	Time/h	R^1	R^2	2	Product	Yield/%[b]
1	0.25	H	H	**2a**	**3a**	86
2	0.25	4-O_2N	H	**2a**	**3b**	83
3	0.25	4-Cl	H	**2a**	**3c**	81
4	0.25	4-MeO	H	**2a**	**3d**	84
5	0.5	H	3-Cl	**2a**	**3e**	71
6	0.5	H	4-MeO	**2a**	**3f**	68
7	0.5	H	H	**2b**	**3g**	87
8[c]	3	H	H	**2c**	**3h**	72(37)[d]
9[c]	6	4-NO_2	H	**2c**	**3i**	53
10[c]	6	4-Cl	H	**2c**	**3j**	71
11[c]	6	H	4-Cl	**2c**	**3k**	55

[a] Reaction condition: **1** 1mmol, **2** 0.5mmol, H_2O or EtOH/H_2O (v/v=1:1) 5mL, TBAOH 0.05mmol, 80°C.
[b] Isolated yield of product.
[c] The solvent is EtOH/H_2O(v/v=1:1).
[d] The solvent is H_2O.

In an effort to expand the scope of the protocol, a test reaction of nitromethane and chalcone was performed under similar conditions, and a low yield (37%) of the desired product **3h** was obtained. In order to improve the reaction yield, EtOH/H_2O (v/v=1:1) was employed as a solvent. The yield of **3h** increased to 72%, due to the better solubility of the reactants and their more efficient mixing (Table 2, entry 8). Further investigation indicated that the reaction proceeded smoothly when chalcones with electron-withdrawing groups were employed (Table 2, entries 9–11). However, chalcones with electron-donating groups such as methoxyl group only gave a complex mixture.

As a consequence of these results, we also wanted to apply the protocol for more complex active methylene compounds. Therefore, 3-cyanoacetylindole which is an important intermediate for the synthesis of natural products and pharmaceuticals,[24,25] was used as active methylene compounds to react with chalcone (Scheme 1). None of the desired highly substituted cyclohexanols was obtained due to the large steric hindrance effect between chalcone and 3-cyanoacetylindole. Compound **3l** was obtaineded via Michael addition of chalcone with 3-cyanoacetyindole.

The stereostructure of the highly substituted cyclohexanols was established from the ^{1}H NMR, ^{13}C NMR and HSQC data. As a representative example, the ^{1}H NMR spectrum of **3a** shows a doublet at 5.24 for H_a, which the HSQC spectrum showed was not attached to a carbon. This hydrogen forms an intramolecular hydrogen bond with the oxygen of the carbonyl group. The doublet is due to long range coupling with H_c (J_{ac} = 2.5Hz) with a rigid W geometry. The long range W coupling also indicates the presence of a nearly perfect chair configuration. The –(C)CHCH_2– is an AMX system, and δ = 2.31, 2.97, 4.23 corresponding to H_b, H_c, H_d respectively (J_{bc} = 15.0Hz, J_{bd} = 3.0Hz, J_{cd} = 13.8Hz). The –(C)CHCH(C)– is an AB system, δ = 4.24, 4.87 assigned to H_e, H_f respectively (J_{ef} = 12.0Hz). These coupling constants correspond to the geometry in **3a**. The ^{13}C NMR data of **3a** shows a signal at δ = 204.08 characteristic of an aroyl carbonyl carbon, and there are another two signals at δ = 113.68, 113.75 due to the cyano groups. The stereostructure of **3h** is similar to **3a**, meanwhile, the chemical shift of H_g is 5.18, so C–H_g is the equatorial bond.[22] The stereostructures of **3a**, **3h** are shown in Scheme 2.

In conclusion, we have demonstrated a novel method for the synthesis of highly substituted cyclohexanols by the Michael addition of active methylene compounds or nitromethane to chalcones. Several advantages of the protocol including shorter reaction time, better tolerance to different substrates, and a simple work-up procedure make it an efficient tool for the synthesis of highly substituted cyclohexanols.

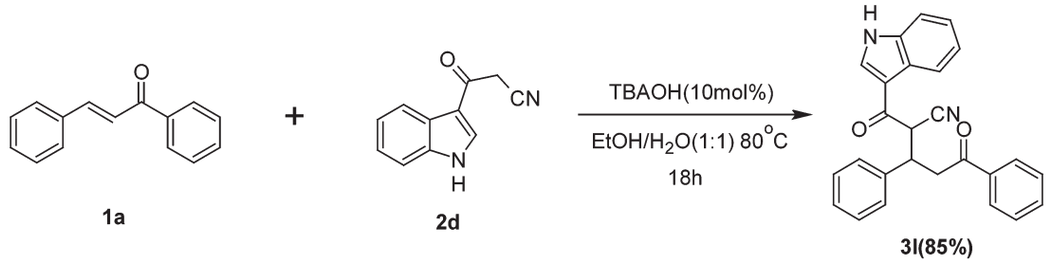
Experimental

All chalcones and 3-cyanoacetylindole were prepared according to literature methods.[24,26] All other reagents were obtained from commercial suppliers and used without further purification. ^{1}H, ^{13}C NMR and HSQC spectra were recorded at 500MHz and 125MHz respectively, in $CDCl_3$ or DMSO-d_6, and chemical shifts were reported in ppm from internal TMS (δ). All melting points are determined uncorrected. Elemental analyses were performed on a Yanagimoto MT3CHN recorder.

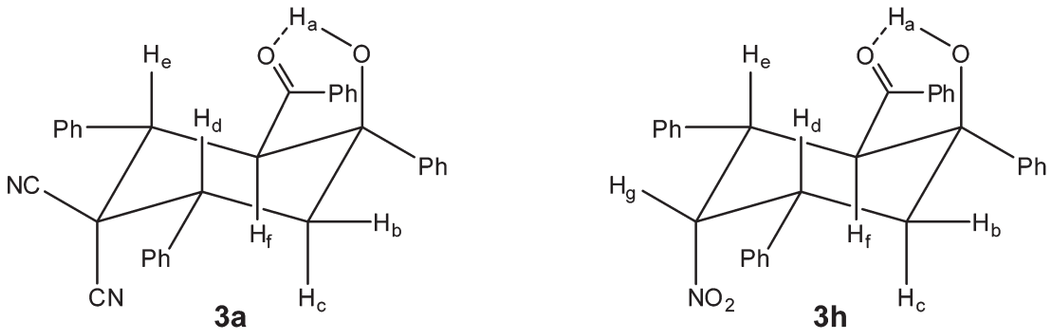
Synthesis of highly substituted cyclohexanols in aqueous medium; general procedure

A mixture of chalcone **1** (1mmol) and malononitrile **2** (0.5 mmol) in H_2O (5 ml) was stirred in 80°C for 5 min. Then, TBAOH (0.05 mmol, as a 10wt.% aqueous solution) was added dropwise, and the mixture was stirred at the same temperature for the period of time listed in Table 2, and then cooled to room temperature. The solid precipitate was collected, washed with water, dried and recrystallised by ethanol to afford the desired product **3**.

3-Benzoyl-4-hydroxy-2,4,6-triphenylcyclohexane-1,1-dicarbonitrile **3a**: White solid, m.p. 234–236°C (lit.[21]: 236–238°C). ^{1}H NMR (500MHz $CDCl_3$) δ = 2.29–2.33 (dd, 1H, H_b, J_1 = 15.0Hz, J_2 = 3.0Hz), 2.94–3.00 (dt, 1H, H_c, J_1 = 13.8Hz, J_2 = 2.5Hz), 4.22–4.25 (dd, 1H, H_d, J_1 = 12.0Hz, J_2 = 3.0Hz), 4.24 (d, 1H, H_e, J = 12.0Hz), 4.87 (d, 1H, H_f, J = 12.0Hz), 5.24 (d, 1H, H_a, J = 2.5Hz), 7.11–7.61 (m, 20H, aromatic). ^{13}C NMR (500MHz $CDCl_3$) δ = 40.69, 46.15, 48.00, 50.28, 51.59, 74.57, 113.68 (CN), 113.75 (CN), 124.63, 127.82, 128.06, 128.12, 128.59, 128.68, 128.86, 128.94, 129.13, 129.25, 133.58, 133.67, 136.38, 137.25, 143.84, 204.08 (C=O). Anal. Calcd for $C_{33}H_{26}N_2O_2$: C, 82.13; H, 5.43; N, 5.81. Found: C, 82.23; H, 5.31; N, 5.76%.



Scheme 1



Scheme 2

3-Benzoyl-4-hydroxy-2,6-bis(4-nitrophenyl)-4-phenylcyclohexane-1,1-dicarbonitrile **3b**: Light yellow solid, m.p. 216–218°C (lit.[21]: 217–219°C). ^{1}H NMR (500MHz, $CDCl_3$) δ = 2.34–2.38 (dd, 1H, H_b, J_1 = 14.5Hz, J_2 = 3.0Hz), 2.96–3.02 (dt, 1H, H_c, J_1 = 13.5Hz, J_2 = 2.5Hz), 4.39–4.15 (dd, 1H, H_d, J_1 = 11.5Hz, J_2 = 3.0Hz), 4.44 (d, 1H, H_e, J = 12.5Hz), 4.88 (d, 1H, H_f, J = 12.0Hz), 5.08 (d, 1H, H_a, J = 2.0Hz), 7.14–7.17 (m, 1H, aromatic), 7.20–7.23 (m, 2H, aromatic), 7.27–7.30 (m, 2H, aromatic), 7.40–7.44 (m, 3H, aromatic), 7.54 (d, 2H, aromatic, J = 7.5Hz), 7.67 (d, 2H, aromatic, J = 9.0Hz), 7.79 (d, 2H, aromatic, J = 9.0Hz), 8.04 (d, 2H, aromatic, J = 9.0Hz), 8.34 (d, 2H, aromatic, J = 8.5Hz). ^{13}C NMR (500MHz $CDCl_3$) δ = 40.18, 45.68, 46.69, 49.69, 51.05, 74.36, 112.79 (CN), 112.83 (CN), 123.95, 124.45, 128.10, 128.33, 128.55, 128.84, 130.01, 134.56, 136.54, 140.18, 142.63, 142.65, 148.38, 148.56, 202.68 (C=O). Anal. Calcd for $C_{33}H_{24}N_4O_6$: C, 69.22; H, 4.22; N, 9.79. Found: C, 69.23; H, 4.31; N, 9.66%.

3-Benzoyl-2,6-bis(4-chlorophenyl)-4-hydroxy-4-phenylcyclohexane-1,1-dicarbonitrile **3c**: White solid, m.p. 190–192°C. ^{1}H NMR (500MHz, $CDCl_3$) δ = 2.25–2.28 (dd, 1H, H_b, J_1 = 14.8Hz, J_2 = 2.8Hz), 2.88–2.94 (dt, 1H, H_c, J_1 = 13.8Hz, J_2 = 2.5Hz), 3.66 (s, 3H, –OCH_3), 3.83 (s, 3H, –OCH_3), 4.15–4.19 (dd, 1H, H_d, J_1 = 11.5Hz, J_2 = 3.0Hz), 4.18 (d, 1H, H_e, J = 12.0Hz) 4.82 (d, 1H, H_f, J = 12.0Hz), 5.20 (d, 1H, H_a, J = 2.5Hz), 6.65 (d, 2H, aromatic, J = 8.5Hz), 6.96 (d, 2H, aromatic, J = 9.0Hz), 7.10–7.13 (m, 1H, aromatic), 7.16–7.19 (m, 2H, aromatic), 7.24–7.27 (m, 2H, aromatic), 7.35–7.40 (m, 5H, aromatic), 7.50–7.56 (m, 4H, aromatic). ^{13}C NMR (500MHz $CDCl_3$) δ = 40.46, 45.46, 47.79, 49.52, 51.37, 74.46, 113.36 (CN), 113.42 (CN), 124.54, 128.02, 128.06, 128.32, 128.69, 129.03, 129.27, 130.15, 132.00, 134.04, 134.64, 135.48, 136.98, 143.36, 203.58 (C=O). Anal. Calcd for $C_{33}H_{24}Cl_2N_2O_2$: C, 71.87; H, 4.39; N, 5.08. Found: C, 71.56; H, 4.61; N, 4.96%.

3-Benzoyl-4-hydroxy-2,6-bis(4-methoxyphenyl)-4-phenylcyclohexane-1,1-dicarbonitrile **3d**: White solid, m.p. 200–202°C. ^{1}H NMR (500MHz, $CDCl_3$) δ = 2.25–2.29 (dd, 1H, H_b, J_1 = 14.8Hz, J_2 = 2.8Hz), 2.88–2.94 (dt, 1H, H_c, J_1 = 13.8Hz, J_2 = 2.5Hz), 3.66 (s, 3H, –OCH_3), 3.83 (s, 3H, –OCH_3), 4.15–4.19 (dd, 1H, H_d, J_1 = 11.5Hz, J_2 = 3.0Hz), 4.18 (d, 1H, H_e, J = 12.0Hz) 4.82 (d, 1H, H_f, J = 12.0Hz), 5.20 (d, 1H, H_a, J = 2.5Hz), 6.65 (d, 2H, aromatic, J = 8.5Hz), 6.96 (d, 2H, aromatic, J = 9.0Hz), 7.10–7.13 (m, 1H, aromatic), 7.16–7.19 (m, 2H, aromatic), 7.24–7.27 (m, 2H, aromatic), 7.35–7.40 (m, 5H, aromatic), 7.50–7.56 (m, 4H, aromatic). ^{13}C NMR (500MHz, $CDCl_3$) δ = 40.80, 45.37, 48.83, 49.44, 51.68, 55.11, 55.26, 74.59, 113.91 (CN), 114.01 (CN), 114.04, 114.27, 124.63, 125.65, 127.76, 128.06, 128.13, 128.56, 129.95, 133.63, 137.28, 143.93, 159.97, 160.04, 204.25 (C=O). Anal. Calcd for $C_{35}H_{30}N_2O_4$: C, 77.47; H, 5.57; N, 5.16. Found: C, 77.23; H, 5.61; N, 5.23%.

3-(3-Chlorobenzoyl)-4-(3-chlorophenyl)-4-hydroxy-2,6-diphenylcyclohexane-1,1-dicarbonitrile **3e**: White solid, m.p. 186–188°C. ^{1}H NMR (500MHz, $CDCl_3$) δ = ^{1}H NMR (500MHz $CDCl_3$) δ = 2.29–2.33 (dd, 1H, H_b, J_1 = 15.0Hz, J_2 = 2.8Hz), 2.86–2.92 (dt, 1H, H_c, J_1 = 13.8Hz, J_2 = 2.5Hz), 4.19–4.22 (dd, 1H, H_d, J_1 = 12.0Hz, J_2 = 2.8Hz), 4.20 (d, 1H, H_e, J = 12.0Hz), 4.76 (d, 1H, H_f, J = 12.0Hz), 5.02 (d, 1H, H_a, J = 2.5Hz), 7.13–7.60 (m, 18H, aromatic). ^{13}C NMR (500MHz $CDCl_3$) δ = 40.52, 46.02, 47.85, 50.04, 51.91, 74.37, 76.78, 77.03, 77.29, 113.43 (CN), 113.58 (CN), 122.78, 125.18, 126.14, 127.85, 128.20, 128.82, 128.91, 129.02, 129.28, 129.52, 129.55, 130.00, 133.29, 133.83, 134.77, 134.97, 135.99, 138.46, 145.80, 202.52 (C=O). Anal. Calcd for $C_{33}H_{24}Cl_2N_2O_2$: C, 71.87; H, 4.39; N, 5.08. Found: C, 71.75; H, 4.44; N, 5.26%.

4-Hydroxy-3-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-2,6-diphenylcyclohexane-1,1-dicarbonitrile **3f**: White solid, m.p. 194–196°C. ^{1}H NMR (500MHz $CDCl_3$) δ = 2.25–2.28 (dd, 1H, H_b, J_1 = 14.8Hz, J_2 = 3.0Hz), 2.88–2.94 (dt, 1H, H_c, J_1 = 14.0Hz, J_2 = 2.5Hz), 3.70 (s, 3H, –OCH_3), 3.77 (s, 3H, –OCH_3), 4.20–4.23 (dd, 1H, H_d, J_1 = 13.5Hz, J_2 = 3.0Hz), 4.24 (d, 1H, H_e, J = 12.0Hz), 4.79 (d, 1H, H_f, J = 12.0Hz), 5.38 (d, 1H, H_a, J = 2.0Hz), 6.65 (d, 2H, aromatic, J = 9.0Hz), 6.78 (d, 2H, aromatic, J = 9.0Hz), 7.15–7.16 (m, 3H, aromatic), 7.39–7.52 (m, 9H, aromatic), 7.59 (d, 2H, aromatic, J = 7.0Hz). ^{13}C NMR (500MHz, $CDCl_3$) δ = 41.04, 46.17, 48.02, 50.27, 50.74, 55.21, 55.44, 74.24, 113.43 (CN), 113.82 (CN), 113.86, 125.85, 128.62, 128.87, 128.91, 129.06, 129.14, 130.05, 130.87, 133.83, 136.27, 136.52, 158.89, 164.10, 201.69 (C=O). Anal. Calcd for $C_{35}H_{30}N_2O_4$: C, 77.47; H, 5.57; N, 5.16. Found: C, 77.35; H, 5.25; N, 5.32%.

Ethyl 3-benzoyl-1-cyano-4-hydroxy-2,4,6-triphenylcyclohexanecarboxylate **3g**: White solid, m.p. 202–204°C. ^{1}H NMR (500MHz, $CDCl_3$) δ = 0.72–0.75 (m, 3H, –CH_3), 2.22–2.26 (dd, 1H, H_b, J_1 = 14.5Hz, J_2 = 3.0Hz), 2.97–3.02 (dt, 1H, H_c, J_1 = 13.0Hz, J_2 = 3.0Hz), 3.73–3.79 (m, 2H, –CH_2–), 4.32–4.35 (dd, 1H, H_e, J_1 = 12.0Hz, J_2 = 3.0Hz), 4.94 (d, 1H, H_f, J = 12.5Hz), 5.36 (d, 1H, H_a, J = 2.0Hz), 7.02–7.04 (m, 3H, aromatic), 7.09–7.14 (m, 3H, aromatic), 7.23–7.37 (m, 11H, aromatic), 7.49 (d, 2H, aromatic, J = 7.5Hz), 7.62 (d, 2H, aromatic, J = 7.5Hz). ^{13}C NMR (500MHz $CDCl_3$) δ = 13.45, 41.71, 45.23, 49.34, 52.45, 59.78, 62.26, 74.99, 117.77 (CN), 124.79, 127.97, 127.98, 128.17, 128.19, 128.27, 128.41, 128.58, 133.29, 134.67, 137.94, 144.77, 166.47 (C=O), 205.37 (C=O). Anal. Calcd for $C_{35}H_{31}NO_4$: C, 79.37; H, 5.90; N, 2.64. Found: C, 79.12; H, 6.01; N, 2.78%.

(2-Hydroxy-5-nitro-2,4,6-triphenylcyclohexyl)(phenyl)methanone **3h**: White solid, m.p. 234–236°C (lit.[22]). ^{1}H NMR (500MHz, $CDCl_3$) δ = 2.14–2.17 (dd, 1H, H_b, J_1 = 13.8Hz, J_2 = 3.5Hz), 3.36–3.41 (t, 1H, H_c, J = 12.5Hz), 4.19–4.23 (m, 2H, H_d, H_e), 5.11 (d, 1H, H_a J = 1.0Hz), 5.17–5.19 (t, 1H, H_g, J = 4.0Hz), 5.50 (d, 1H, H_f, J = 12.0Hz), 7.05–7.13 (m, 3H, aromatic), 7.14–7.19 (m, 5H, aromatic), 7.26–7.37 (m, 8H, aromatic), 7.45 (d, 2H, aromatic, J = 7.5Hz), 7.67 (d, 2H, aromatic, J = 7.5Hz). ^{13}C NMR (500MHz $CDCl_3$) δ = 37.15, 41.33, 46.54, 48.73, 75.32, 93.57, 124.89, 127.33, 127.35, 127.88, 127.97, 128.14, 128.18, 128.36, 128.74, 128.93, 128.99, 133.32, 135.84, 137.68, 138.51, 145,39, 206.57 (C=O). Anal. Calcd for $C_{31}H_{27}NO_4$: C, 77.97; H, 5.70; N, 2.93. Found: C, 77.88; H, 5.61; N, 2.89%.

(2-Hydroxy-5-nitro-4,6-bis(4-nitrophenyl)-2-phenylcyclohexyl)(phenyl)methanone **3i**: Light yellow solid, m.p. 215–217°C. ^{1}H NMR (500MHz, $CDCl_3$) δ = 2.33–2.36 (dd, 1H, H_b, J_1 = 14.5Hz, J_2 = 4.0Hz), 2.44–2.47 (t, 1H, H_c, J = 13.5Hz), 4.44–4.46 (dt, 1H, H_d, J_1 = 11.5Hz, J_2 = 3.5Hz), 4.52–4.54 (m, 2H, H_e, H_f), 5.29 (s, 1H, H_a), 5.33–5.37 (m, 1H, H_g), 7.09–7.58 (m, 14H, aromatic), 7.97 (d, 2H, aromatic, J = 8.0Hz), 8.24 (d, 2H, aromatic, J = 8.0Hz). ^{13}C NMR (500MHz $CDCl_3$) δ = 43.63, 44.86, 47.75, 54.56, 74.67, 93.60, 123.99, 124.36, 124.44, 127.85, 127.92, 128.29, 128.50, 128.60, 128.94, 129.29, 134.05, 136.75, 142.37, 143.28, 145.62, 147.67, 147.79, 203.71 (C=O). Anal. Calcd for $C_{31}H_{25}N_3O_8$: C, 65.60; H, 4.44; N, 7.40. Found: C, 65.34; H, 4.21; N, 7.57%.

(4,6-Bis(4-chlorophenyl)-2-hydroxy-5-nitro-2-phenylcyclohexyl)(phenyl)methanone **3j**: White solid, m.p. 170–172°C (lit.[22]). ^{1}H NMR (500MHz, DMSO–d_6) δ = 1.90 (d, 1H, H_b, J = 11.0Hz), 2.87–2.92 (t, 1H, H_c, J = 13.0Hz), 3.94–3.99 (t, 1H, H_d, J = 11.0Hz), 4.26–4.22 (t, 1H, H_e, J = 11.5Hz), 4.95 (d, 1H, H_f, J = 11.5Hz), 5.49 (s, 1H, H_a), 5.66–5.70 (t, 1H, H_g, J = 4.0Hz), 6.91–7.54 (m, 18H, aromatic). ^{13}C NMR (500MHz, DMSO-d_6) δ = 43.59, 45.11, 46.84, 54.55, 74.60, 94.98, 125.53, 127.22, 128.00, 128.04, 128.19, 128.74, 128.93, 129.05, 129.29, 129.84, 130.81, 132.59, 132.68, 132.99, 136.96, 138.21, 139.25, 145.52, 200.73 (C=O). Anal. Calcd for $C_{31}H_{25}Cl_2NO_4$: C, 68.14; H, 4.61; N, 2.56. Found: C, 68.34; H, 4.58; N, 2.48%.

(4-Chlorophenyl)(2,4,6-tris(4-chlorophenyl)-2-hydroxy-5-nitrocyclohexyl)methanone **3k**: White solid, m.p. 222–224°C. ^{1}H NMR (500MHz, $CDCl_3$) δ = 2.10–2.14 (dd, 1H, H_b, J_1 = 14.0Hz, J_2 = 3.5Hz), 3.27–3.33 (dt, 1H, H_c, J_1 = 13.5Hz, J_2 = 2.0Hz), 4.15–4.20 (m, 2H, H_d, H_e), 5.08 (d, 1H, H_a, J = 2.0Hz), 5.16–5.18 (t, 1H, H_g, J = 4.0Hz), 5.42 (d, 1H, H_f, J = 12.5Hz), 7.08–7.39 (m, 14H, aromatic), 7.42 (d, 2H, aromatic, J = 8.5Hz), 7.59 (d, 2H, aromatic, J = 8.5Hz), 12.39 (d, 1H, aromatic, J = 2.0Hz). ^{13}C NMR (500MHz, $CDCl_3$) δ = 37.26, 41.27, 46.49, 48.53, 75.12, 93.30, 126.08, 126.37, 127.26, 127.38, 128.03, 128.13, 128.44, 128.57, 128.59, 128.91, 129.01, 129.06, 129.21, 129.49, 133.40, 135.53, 135.67, 138.19, 140.35, 144.01, 205.06 (C=O). Anal. Calcd for $C_{31}H_{25}Cl_2NO_4$: C, 68.14; H, 4.61; N, 2.56. Found: C, 68.46; H, 4.67; N, 2.89%.

2-(1H-Indole-3-carbonyl)-5-oxo-3,5-diphenylpent-3-enenitrile **3l**: White solid, m.p. 212–214°C. ^{1}H NMR (500MHz, DMSO–d_6) δ = 3.43–3.47 (m, 1H), 3.71–3.75 (m, 1H), 4.11–4.15 (m, 1H), 5.24 (d, 1H, J = 8.0Hz), 7.22–7.61 (m, 11H), 7.88 (d, 2H, J = 7.5Hz), 8.16 (d, 1H, J = 7.5Hz), 8.82 (d, 1H, J = 3.0Hz), 12.39 (d, 1H, J = 2.0Hz). ^{13}C NMR (500MHz, DMSO-d_6) δ = 42.32, 42.43, 46.77, 112.99 (CN), 115.25, 118.35, 121.74, 123.03, 124.05, 125.95, 127.81, 128.35, 128.71, 128.88, 129.13, 129.23, 133.82, 136.78, 137.33, 140.15, 185.07 (C=O), 197.82 (C=O). Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, 79.57; H, 5.14; N, 7.14. Found: C, 79.29; H, 4.99; N, 7.46%.

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