Isoindolinone inhibitors of the MDM2-p53 protein-protein interaction: structure-activity studies leading to improved potency.

Ian R. Hardcastle*[1], Junfeng Liu[2], Eric Valeur[1], Anna Watson[1], Shafiq U. Ahmed[2], Timothy J. Blackburn[1], Karim Bennaceur[2], William Clegg[1], Catherine Drummond[2], Jane A. Endicott[3], Bernard T. Golding[1], Roger J. Griffin[1], Jan Gruber[3], Karen Haggerty[1], Ross Harrington[1], Claire Hutton[2], Stuart Kemp[1], Xiaohong Lu[2], James M. McDonnell[3], David R. Newell[2], Martin E.M. Noble[3], Sara L. Payne[1], Charlotte H. Revill[1], Christiane Riedinger[3], Qing Xu[2], and John Lunec*[2].

1 Newcastle Cancer Centre, Northern Institute for Cancer Research and School of Chemistry, Bedson Building, Newcastle University, Newcastle, NE1 7RU, UK

2 Newcastle Cancer Centre, Northern Institute for Cancer Research, Paul O'Gorman Building, Medical School, Framlington Place, Newcastle University, Newcastle, NE2 4HH, UK

3 Laboratory of Molecular Biophysics, Department of Biochemistry, University of Oxford, South Parks Road, Oxford, OX1 3QU, U.K.

CONTENTS

Synthesis
- General methods
- Compounds: 103-105,
- General Procedure A
- Compounds: 10-13, 15-19, 21, 24, 26-29, 32-39, 43, 45, 46a, 47
- General Procedure B
- Compounds: 48, 50, 51, 53-57, 61-65, 67-69, 71-72, 78-88, 92-96, 101, 102
- General Procedure C
- Compounds: 40-42, 98-100
- General Procedure D
- Compounds: 34, 85, 86, 89, 99, 102
- References

Table 1. Crystal data and structure refinement for **74b**
Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å^2) for **74b**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.
Table 3. Bond lengths [Å] and angles [°] for **74b**.
Table 4. Anisotropic displacement parameters (Å^2) for **74b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$
Table 5. Hydrogen coordinates and isotropic displacement parameters (Å^2) for **74b**.
Table 6. Torsion angles [°] for **74b**.
Table 7. Hydrogen bonds for **74b** [Å and °].

Figure S1: X-ray structure of **74b**.
Figure S2: Western blot analysis with Nutlin-3, **7, 47** and **49** in SJSA cells at time points of 1, 2 and 4 hours.
Figure S3: Western Blotting analysis with **53**, **54**, **50** and **55** in SJSA cells. Concentrations 1, 5 and 10µM, time point 4 hours.
Figure S4: Western Blotting analysis with Nutlin-3 and **50** in SJSA cells at 48 hrs showing the dose response for gene expression.
Figure S5: SRB Growth Inhibition Assay in Response to Drug Exposure in MDM2 Amplified Cell Lines with **74**, **74a** and **74b**.

SYNTHESIS

General Methods

Reagents were purchased from fine chemicals vendors, and used as received unless otherwise stated. Solvents were purified and stored according to standard procedures. Petrol refers to that fraction in the boiling range 40-60 °C. THF refers to anhydrous tetrahydrofuran, either by distillaton from sodium benzophenone, or from commercial sources. Melting points were obtained on a Stuart Scientific Smp3 apparatus and are uncorrected. Thin layer chromatography was performed using silica gel plates (Kieselgel $60F_{254}$; 0.2 mm), and visualized with UV light or potassium permanganate. Chromatography was conducted under medium pressure in glass columns or using a Biotage SP4 instrument in prepacked columns (FLASH+ Silica columns (40-63 µm, 60 Å), NH FLASH+ cartridges (40-75 µm, 100 Å) and C18 FLASH+ cartridges (40-63 µm, 90 Å)). Semi-preparative HPLC was conducted using using a Varian Prostar instrument equipped with a Waters XTerra column (RP_{18} OBD 10 µm, 150 x 30 mm) , at a flow rate of 15 mL/min, monitoring by UV at $\lambda = 270$ nm. Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Spectrospin AC 300E (^1H at 300 MHz, ^{13}C at 75 MHz), a Jeol JNM-LA500 spectrometer (^1H at 500 MHz, ^{13}C at 125 MHz), or a Bruker Avance II 500 (^1H at 500 MHz, ^{13}C at 125 MHz) employing the solvent as internal standard. NH signals appeared as broad singlets (br s) exchangeable with D_2O. Mass spectra were determined on a Micromass Autospec M spectrometer in electron impact (EI) mode. Liquid Chromatography-Mass Spectrometry (LCMS) was carried out on a Micromass Platform instrument operating in positive and negative ion electrospray mode, employing a 50 x 4.6 mm C18 column (Waters Symmetry or Waters Atlantis) 5 or 12 min gradient elution with 0.05% formic acid in methanol (10-90%). IR spectra were recorded on a Bio-Rad FTS 3000MX diamond ATR. Elemental analyses were performed by Butterworth Laboratories, Middlesex, UK. Accurate mass analyses were measured using a Finnigan MAR 95 XP or a Finnigan MAR 900 XLT at Swansea EPSRC National Mass Spectrometry Service Centre (EPSRC, Chemistry Department, University of Wales Swansea, Wales, SA2 8PP).

Dimethylaminomethylene-N,N-dimethylformohydrazonamide (103).[1]

To DMF (75 mL) at 5°C was added thionyl chloride (14.3 mL, 196 mmol) and the resulting pale yellow solution was warmed to room temperature and stirred overnight. The solution was cooled to 5°C before the dropwise addition of a solution of hydrazine hydrate (1.52 mL, 49 mmol) in DMF (10 mL). The resulting white suspension was warmed to room temperature and stirred for 5 days, then filtered. The resulting white solid was washed with DMF followed by Et_2O and allowed to air dry on a suction filter giving **103** (5.61g, 53%) which was used without further purification.

4-(4*H*-1,2,4-Triazol-4-yl)benzonitrile (104).[1]

To a vigorously stirred suspension of dimethylaminomethylene-N,N-dimethylformohydrazonamide (1.5g; 6.9 mmol) in toluene (18.5 mL) at 60°C was added 4-aminobenzonitrile (823mg, 6.9 mmol). The resulting mixture was heated to reflux and stirred overnight. The hot reaction mixture was vacuum filtered and the solid washed with toluene (2 mL). Water (3 mL) was added and the suspension stirred then filtered. The solid was then stirred with Et_2O (3 mL), filtered, and to give **104** as a beige solid. (1.16g, 98%). δ_H (500 MHz, $CDCl_3$) 9.3 (2H, s, Ar-H), 8.09 (2H, d, J = 8.7, Ar-H), 7.99 (2H, d, J = 8.7, Ar-H). δ_C (125 MHz, $CDCl_3$) 141.1, 137.3, 134.3, 121.5, 118.1, 110.4. HRMS Found; 171.061 [M + H]; $C_9H_7N_4$, requires 171.0665.

4-(4-(Ammoniomethyl)phenyl)-4H-1,2,4-triazol-4-ium chloride (105).

To a suspension of 4-(4H-1,2,4-triazol-4-yl)benzonitrile (200mg, 1.17 mmol) was added concentrated HCl (0.8 mL) and the resulting pale yellow solution stirred. 10% palladium on carbon (60mg) was added and stirring continued for 2.5 h under H_2 (1 atm). The reaction was filtered through Celite® and the pad washed with portions of MeOH. The filtrate was concentrated *in vacuo* to give **105** as a fine yellow powder which

was dried in a vacuum oven (50°C) for 3 h to give the title compound as a sandy brown solid (245 mg, 84%). mpt 276-277 °C; δ_H (500 MHz, $CDCl_3$) 9.68 (2H, s, Ar-*H*), 9.03 (1H, br s, N-*H*), 8.78 (3H, br s, N-H_3), 7.84 (2H, d, J = 8.4, Ar-*H*), 7.7 (2H, d, J = 8.4, Ar-*H*), 4.06 (2H, m, H_2). δ_C (125 MHz, $CDCl_3$) 141.6, 134.9, 133.1, 130.6, 121.5, 34.0. HRMS Found; 174.090416 [M]; $C_9H_{10}N_4$, requires 174.090546.

4-((Trifluoromethyl)sulfonyl)benzylamine hydrochloride

To 4-((trifluoromethyl)sulfonyl)benzonitrile (400 mg, 1.70 mmol) in THF was added 1M BH_3.THF complex in THF (13.6 mL, 13.60 mmol). The mixture was stirred at rt for 1 h, then heated to reflux for 4 days, and allowed to cooling to rt. A mixture of water (5 mL) and acetic acid (5 mL) was added slowly and the mixture was stirred for 15 min, then concentrated *in vacuo* and the resulting white solid suspended in water (10 mL) and cooled to 0 °C. Saturated aqueous sodium bicarbonate solution was added to pH ~8 and the residue extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated *in vacuo*. Chromatography (Biotage SP4; silica; 3-20 % MeOH, EtOAc) gave a yellow oil which was redissolved in the minimum amount of methanol and 1M HCl (5 mL) added then evaporated *in vacuo* to give the title compound as a white solid, (240 mg, 51 %) which was dried over P_2O_5 before further use. mp 278.1-278.8 °C; UV λ_{max} (EtOH) = 271.0 nm; IR (cm^{-1}) 2860, 2162,1361; ^{1}H NMR (500 MHz, d_6-DMSO) δ 4.26 (2H, s, CH_2), 7.97 (2H, d, *J* = 8.5 Hz, 2 x Ar-H), 8.24 (2H, d, *J* = 8.5 Hz, 2 x Ar-H), 8.68 (3H, s, NH_3); ^{13}C NMR (125 MHz d_6-DMSO) δ 41.2 (CH_2), 120.7, 129.2, 130.9, 131.0, 144.6; ^{19}F NMR (470 MHz d_6-DMSO) δ -78.4393; MS (ESI+) *m/z* 240.0 $[M]^+$.

General Procedure A: 3-Hydroxy compounds

To a solution of the appropriate benzoic acid (1 equiv.) in THF (10 mL), under N_2, was added thionyl chloride (2 equiv.) and 3 drops of anhydrous DMF and the resulting mixture was stirred for 4h at rt, then concentrated *in vacuo*. The residue was diluted with THF (10 mL) and the required amine (1.1 equiv.) and DIPEA (1.1 equiv.) were added, under N_2, the resulting mixture was stirred overnight at rt, then concentrated *in vacuo*. The residue was diluted with EtOAc (50 mL), filtered and the filtrate washed with water (3 x 25 mL) and brine (1 x 25 mL). The organic layer was dried ($MgSO_4$ or Na_2SO_4), concentrated *in vacuo* to afford the required 3-hydroxysioindolinone as a solid which was recrystallised (EtOAc, petrol) or purified by chromatography.

3-(4-Chlorophenyl)-3-hydroxy-2-propylisoindolin-1-one (10)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (1 g, 3.8 mmol), thionyl chloride (0.55 mL, 7.6 mmol), then triethylamine (398.9 mg, 0.549 mL, 3.94 mmol) and n-propylamine (159.8 mg, 0.22 mL, 1.792 mmol). Recrysallisation (ethyl acetate, petrol) gave **10** as a white crystalline solid (425 mg, 77%). Mp 201.5-201.7 °C. IR: 3157, 2968, 1664, 1608, 1466 cm^{-1}. ^{1}H NMR: (300 Hz, $CDCl_3$) δ ppm 0.76 (t, 3H, *J* = 7.4 Hz, CH_2-CH_2-CH_3), 1.45 (m, 2H, N-CH_2-CH_2), 2.86 (m, 2H, N-CH_2), 3.36 (m, 2H, N-CH_2), 7.16 (d, 1H, ArH), 7.38 (dd, 4H, ArH, 7.45 (m, 2H, ArH), 7.70 (d, 1H, ArH). ^{13}C NMR: (75 Hz, DMSO); δ 11.8, 21.9, 40.6, 90.5, 122.7, 122.9, 128.2, 128.7, 129.5, 131.0, 131.2, 132.7, 133.1, 139.9, 149.6, 167.0.

2-Benzyl-3-(4-chlorophenyl)-3-hydroxy-2,3-dihydroisoindolin-1-one (11)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (1.0 g, 3.8 mmol), thionyl chloride (0.55 mL, 7.6 mmol), by triethylamine (1.06 mL, 7.7 mmol) and benzylamine (0.79 mL, 5.8 mmol) Recrystallisation (ethyl acetate, petrol) gave **11** as a white crystalline solid (1.04 g, 77% yield). IR: 3285, 2936, 1664, 1463, cm^{-1}. ^{1}H NMR: (300 Hz, $CDCl_3$) δ ppm 4.33 (d, 2H, *J* = 15.48 Hz, N-CH_2), 7.16 (m, 5H, ArH), 7.25 (m, 5H, ArH), 7.56 (m, 2H, ArH), 7.75 (d, 1H, ArH). ^{13}C NMR: (75 Hz, DMSO); δ 42.80, 90.60, 122.95, 123.18, 126.78, 128.07, 128.35, 128.41, 128.51, 129.70, 130.81, 132.97, 133.07, 138.42, 139.46, 149.59, 167.20.

3-(4-Chlorophenyl)-2-(4-fluorobenzyl)-3-hydroxy-2,3-dihydroisoindol-1-one (12)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (2.24 g, 8.59 mmol) and 4-fluorobenzylamine (1.08 mL, 9.44 mmol). Recrystallisation (EtOAc, petrol), and chromatography (Biotage SP4; silica; 10-30%

EtOAc, petrol) gave **12** as white crystals (1.57 g, 50%), mp 149-150 ^{o}C, HPLC purity (as area %): > 98. UV (in EtOH): λ max = 254 nm; IR: 3301, 2925, 2851, 2021, 1664, 1602, 1506, 1466 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40-4.53 (dd AB, J = 15.2 Hz, 2H, N-CH_2), 4.58 (s, 1H, OH), 6.80-6.89 (m, 2H, $CC_2H_2C_2H_2C$(F)), 7.14-7.29 (m, 7H, ArH), 7.50-7.60 (m, 2H, ArH), 7.80-7.86 (m, 1H, -C*H*-C(C=O)); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 43.58, 92.63, 115.85, 116.13, 124.37, 124.52, 129.65, 129.82, 131.12, 131.91, 132.02, 134.55, 135.57, 135.70, 139.95, 151.19, 165.35, 170.25; HRMS ($C_{21}H_{15}ClFNO_2$+H) calcd 368.0854 , obsd 368.0846.

3-(4-Chlorophenyl)-3-hydroxy-2-(4-chlorobenzyl)isoindolin-1-one (13)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (1 g, 3.8 mmol), thionyl chloride (0.55 mL, 7.6 mmol), then THF (25 mL), triethylamine (1.178 mL, 8.45 mmol) and 4-chlorobenzylamine (0.467 mL, 3.84 mmol). recrystallisation (EtOAc, petrol) gave **13** as a fine white crystalline solid (1.2 g, 83%): (40:60 EtOAc:hexane); mp 156–157 ºC; IR (cm^{-1}) 1661, 1467; ^{1}H NMR, (300 MHz, DMSO-d_6) δ 4.23 (d, 1H , *J* = 15.6 Hz , N-CH) 4.45 (d, 1H, *J* = 15.6 Hz, N-CH') 7.25 (m, 9H, Ar-H) 7.56 (m, 2H, Ar-H) 7.76 (m, 1H, C(O)=C=CH); ^{13}C NMR (75 Hz, DMSO-d_6) δ 42.1, 90.5, 123.0, 123.2, 128.0, 128.4, 128.6, 129.8, 130.2, 130.7, 131.6, 133.1, 133.2, 137.4, 139.3, 149.5, 167.2 (C=O); HRMS ($C_{21}H_{15}Cl_2NO_2$) calcd 384.0558, obsd 384.0555.

3-(4-Chlorophenyl)-3-hydroxy-2-(4-iodobenzyl)-2,3-dihydroisoindol-1-one (15)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (1.76 g, 6.75 mmol) and 4-iodobenzylamine hydrochloride (2 g, 7.42 mmol). Recrystallisation (EtOAc, petrol) followed by chromatography (silica; 6% - 50% EtOAc, petrol) gave **15** as a white solid (1.72 g, 52%), mp 184 – 185 ^{o}C, HPLC purity (as area %): > 99. λ max (EtOH)= 231 nm; IR: 3178, 3175, 2912, 1659, 1467, 1412 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37 (s, 1H, OH), 4.17-4.46 (dd AB, J = 15.6 Hz, 2H, N-CH_2), 6.98-7.01 (d AB, J = 7.8 Hz, 2H, $CC_2H_2C_2H_2C$(I)), 7.23-7.32 (m, 5H, ArH), 7.50-7.62 (m, 4H, ArH), 7.75-7.78 (m, 1H, -C*H*-C(C=O)); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 167.15, 149.54, 139.34, 138.32, 136.90, 133.21, 133.03, 130.80, 130.70, 129.73, 128.57, 128.38, 123.18, 122.98, 92.38, 90.59, 42.32; HRMS ($C_{21}H_{15}ClINO_2$+H) calcd 475.9914, obsd 475.9905.

3-(4-Chlorophenyl)-3-hydroxy-2-(4-methylbenzyl)isoindolin-1-one (16)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (2.0 g, 7.6 mmol), thionyl chloride (1.1 mL, 15.3 mmol), then THF (8.5 mL), diisopropylethylamine (1.5 mL, 8.4 mmol) and (4-methylbenzylamine (1.1 mL, 8.4 mmol). Chromatography (Biotage SP4 silica; 10-80% EtOAc/hexane) gave **16** as a white solid (2.0 g, 72%). mp 160 – 162 ^{o}C; IR (cm^{-1}) 3669, 3150, 2901, 1661; ^{1}H NMR, (500 MHz, $CDCl_3$) δ 2.22 (s, 3H, CH_3), 4.20 (d,1H, *J* = 15.4 Hz, N-CH), 4.41 (d,1H, *J* = 15.4 Hz, N-CH'), 6.96 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.05 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.24-7.26 (m, 2H, Ar-H), 7.28-7.31, (m, 3H, Ar-H), 7.53-7.59 (m, 2H, Ar-H), 7.74-7.77 (m, 1H, C(O)=C=CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 42.1, 90.2, 122.6, 122.8, 127.9, 128.0, 128.2, 128.3, 129.4, 130.3, 132.6, 132.7, 135.0, 135.5, 139.0, 149.1, 166.7; HRMS ($C_{22}H_{19}NO_2Cl$+H) calcd 364.1099, obsd 364.1101.

2-(4-(Aminomethyl)benzonitrile)-3-(4-chlorophenyl)-3-hydroxyisoindolin-1-one (17)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (1 g, 3.8 mmol), thionyl chloride (0.55 mL, 7.6 mmol), then triethylamine (1.1 mL, 7.7 mmol) and 4-(aminomethyl)benzonitrile (508mg, 3.8 mmol). Recrystallisation (ethyl acetate, petrol) gave the **17** as a fine pale yellow crystalline solid (665 mg, 50 %): mp 136-137 ^{o}C; IR (cm^{-1}) 2227, 1655, 1397; ^{1}H NMR, (300 MHz, DMSO-d_6) δ 4.31 (d, 1H, *J* = 16.1 Hz, N-CH_2), 4.55 (d, 1H, *J* = 16.1 Hz, N-CH_2), 7.26 (m, 5H, Ar-H), 7.37 (m, 3H, OH and Ar-H), 7.58 (m, 2H, Ar-H), 7.64 (d, 2H, *J* = 8.3 Hz, Ar-H), 7.77 (1H, m, C(O)=C=CH); ^{13}C NMR, (75 Hz, DMSO-d_6) δ 42.5 (N-*C*H_2), 60.02 (CN) 90.6 (O-C-N), 109.8, 119.1, 123.1, 123.3, 128.4, 128.6, 129.1, 129.8, 130.5, 132.1, 133.2, 133.3, 133.5, 139.2, 144.2, 149.5, 167.2; MS (ESI+) m/z 375.18 [M+H]$^{+}$; CHN.

3-Hydroxy-2-(4-nitrobenzyl)-3-phenyl-2,3-dihydroisoindol-1-one (18)

General Procedure A: 2-benzoylbenzoic acid (0.5 g, 2.2 mmol) and 4-nitrobenzylamine hydrochloride (0.46 g, 2.4 mmol). Recrystallisation (EtOAc, petrol) gave **18** as a yellow solid (0.56 g, 70%). mp 190 – 191 ^{o}C; HPLC purity (as area %) > 99; IR (cm^{-1}) 3181, 3083, 1605, 1514, 1468; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.35 (s, 1H, OH), 4.28 (d, 1H, J = 15.3 Hz, N-CH), 4.68 (d, 1H, J = 15.3 Hz, N-CH'), 7.22-7.34 (m, 8H, Ar-H), 7.48-7.57 (m, 2H, Ar-H), 7.81-7.84 (m, 1H, C(O)=C=CH), 7.96-8.01 (d, 2H, J = 8.8 Hz, Ar-H); ^{13}C NMR, (75 MHz, $CDCl_3$), δ 41.0, 91.1, 123.7, 124.1, 125.6, 126.7, 127.6, 128.9, 129.1, 129.8, 133.5, 138.1, 138.3, 142.3, 145.8, 148.6, 168.3; HRMS ($C_{21}H_{16}N_2O$+H) calcd 361.1183, obsd 361.1186.

3-(4-Fluorophenyl)-3-hydroxy-2-(4-nitrobenzyl)-2,3-dihydroisoindol-1-one (19)

General Procedure A: 2-(4-fluorobenzoyl)benzoic acid (2.10 g, 8.60 mmol) and 4-nitrobenzylamine hydrochloride (1.78 g, 9.46 mmol), thionyl chloride (1.24 mL, 17.2 mmol) diisopropylethylamine (3.1 mL, 17.2 mmol). Recrystallisation (EtOAc, petrol), and chromatography (Biotage SP4; silica; 10-40% EtOAc, petrol) gave **19** as a yellow solid (1.0 g, 31%). mp 183–185 ^{o}C; HPLC purity (as area %) > 95; IR (cm^{-1}) 3282, 3078, 1668, 1601, 1509, 1468, 1395 cm^{-1}; ^{1}H NMR, (500 MHz, $CDCl_3$) δ 4.16-4.23 (m, 2H, OH & N-CH), 4.53 (d, 1H, J = 15.4 Hz, N-CH'), 6.85 (ap. t, 2H, J = 17.4 Hz, Ar-H), 7.19-7.24 (m, 5H, Ar-H), 7.41 (td, J = 7.4, 1.1 Hz, Ar-H), 7.46 (td, 1H, J = 7.4, 1.2 Hz, Ar-H), 7.66-7.68 (m, 1H, C(O)=C=CH), 7.88-7.90 (m, 2H, Ar-H); ^{13}C NMR, (125 MHz, $CDCl_3$) δ 42.2, 91.1, 115.3, 115.5, 122.9, 123.3, 123.5, 128.3, 128.4, 129.4, 129.9, 133.3, 133.8, 145.3, 146.9, 148.7, 167.9; HRMS ($C_{21}H_{15}FN_2O_4$+H) calcd 379.1089, obsd 379.1084.

3-(4-Bromophenyl)-3-hydroxy-2-(4-nitrobenzyl)isoindolin-1-one (21)

General Procedure A: 2-(4-bromobenzoyl)benzoic acid (2.6 g, 8.6 mmol) and 4-nitrobenzylamine hydrochloride (1.8 g, 9.4 mmol), thionyl chloride (1.24 mL, 17.2 mmol) diisopropylethylamine (3.1 mL, 17.2 mmol). Recrystallisation (EtOAc, petrol) gave **21** as a cream solid (3.1 g, 81%): mp 194-195 ^{o}C; IR (cm^{-1}) 3232, 1676, 1605, 1516, 1467; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 4.24 (d, 1H, J = 15.3 Hz, N-CH) 4.64 (d, 1H, J = 15.3 Hz, N-CH'), 7.15-7.20 (m, 2 H, Ar-H), 7.27-7.34 (m, 3 H, Ar-H), 7.36-7.40 (m, 2H, Ar-H), 7.48-7.58 (m, 2H, Ar-H), 7.76-7.79 (m, 1H, C(O)=C=CH), 7.97-8.02 (m, 2H, Ar-H); ^{13}C NMR, (75 MHz, $CDCl_3$), δ 42.8, 100.0, 121.3, 123.1, 123.7, 124.1, 128.5, 129.8, 130.5, 131.4, 132.2, 134.9, 141.7, 145.6, 147.7, 148.7, 167.9; MS (ESI+) m/z = 440 $[M+H]^+$, CHN.

3-(4-Chlorophenyl)-3-hydroxy-2-[2-(4-nitrophenyl)ethyl]-2,3-dihydroisoindol-1-one (24)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (5 g, 19.2 mmol), thionyl chloride (3.0 mL, 38.3 mmol,) then THF (20 mL), 2-(4-nitrophenyl)ethylamine hydrochloride (4.3 g, 21.1 mmol,) and diisopropylethylamine (3.49 mL, 21.1 mmol,). Recrystallisation (EtOAc, petrol) gave **24** as a cream solid (4.5 g, 57%): mp: 206-208 ºC (EtOAc). IR (cm^{-1}) 3240, 1166, 1520, 1338; ^{1}H NMR, (300 MHz, DMSO-d_6) δ 2.89-2.96 (m, 2H, N-CH_2-C$\underline{H_2}$), 3.19-3.28 (m, 1H, N-CH), 3.57-3.69 (m, 1H, N-CH'), 7.40-7.26 (m, 8H, OH & Ar-H), 7.51-7.60 (m, 2H, Ar-H), 7.74 (d, 1H, J = 6.6 Hz, C(O)=C=CH), 8.09 (d, 1H, J = 8.4 Hz, Ar-H); ^{13}C NMR, (75 MHz, DMSO-d_6), 122.1, 122.4, 122.9, 127.5, 128.1, 129.0, 129.3, 130.1, 132.2, 132.6, 138.8, 145.9, 147.1, 148.8, 166.4; (ES) *m/z* 409 ($[M+H]^+$).

3-(4-Chlorophenyl)-3-hydroxy-2-naphthalen-1-ylmethyl-2,3-dihydroisoindol-1-one (26)

General Procedure A: 2-(4-chlorobenzoyl)-benzoic acid (2.24 g, 8.6 mmol) and 1-naphthylmethylamine (1.36 mL, 9.4 mmol). Chromatography (silica; 6-50% EtOAc, petrol) gave **26** as yellow crystals (0.35 g, 10%), mp 75 – 76 ^{o}C, HPLC purity (as area %): > 92. λmax (EtOH) = 223 nm; IR: 3331, 3270, 3053, 2967, 2873, 2070, 1674, 1599, 1468 cm^{-1}; ^{1}H NMR (300 MHz, MeOD) δ 4.90 (s, 1H, OH), 4.90 (d, J = 15.2 Hz, 1H, N-CH_2), 5.27 (d, J = 15.2 Hz, 1H, N-CH_2), 6.75-6.79 (m, 2H, ArH), 6.95-6.98 (m, 2H, ArH), 7.13-7.27 (m, 3H, ArH), 7.35-7.61 (m, 5H, ArH), 7.72-7.75 (m, 1H, -CH-C(C=O)), 7.86-7.89 (m, 1H, ArH), 8.17-8.19 (m, 1H, ArH); ^{13}C NMR (MeOD, 75 MHz), δ 41.9, 92.8, 124.3, 124.6, 125.2, 126.4, 126.89, 127.4, 129.0, 129.1, 129.3, 129.4, 127.0, 131.1, 132.0, 133.4, 134.0, 134.6, 135.0, 135.5, 139.7, 151.6, 170.3; HRMS (ESI) calculated mass of ion 400.1099 $[M+H]^+$, measured mass of ion 400.1099 $[M+H]^+$.

2-(3-Bromobenzyl)-3-(4-chlorophenyl)-3-hydroxy-2,3-dihydroisoindol-1-one (27)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (2.24 g, 8.6 mmol) and 3-bromobenzylamine hydrochloride (2.10 g, 9.4 mmol). Recrystallisation (EtOAc, petrol) gave **27** as orange crystals (2.12 g, 58%) mp 167 – 170 ^{o}C, HPLC purity (as area %): > 98. λ max (EtOH) = 254 nm; IR: 3246, 3016, 2932, 2875, 1668, 1600, 1468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (d, J = 15.0 Hz, 1H, N-CH_2), 4.33 (d, J = 15.0 Hz, 1H, N-CH_2), 4.54 (br s, 1H, OH), 6.93-7.04 (m, 2H, C_6H_4Br), 7.08-7.10 (m, 1H, ArH), 7.12-7.19 (m, 4H, -C_6H_4Cl), 7.20-7.29 (m, 2H, ArH), 7.41-7.53 (m, 2H, ArH), 7.64-7.69 (m, 1H, =CH-C-C(=O)); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 42.7, 91.4, 122.5, 122.6, 123.1, 124.0, 127.8, 128.3, 128.9, 130.0, 130.2, 130.5, 132.2, 133.4, 135.1, 137.2, 140.4, 149.1, 168.1; HRMS (ESI) calculated mass of ion 428.0047 [M+H]$^{+}$, measured mass of ion 428.0041 [M+H]$^{+}$

3-(4-Chlorophenyl)-3-hydroxy-2-(4-(methylthio)benzyl)isoindolin-1-one (28)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (2.24 g, 8.6 mmol), 4-methylsulfanylbenzylamine (1.45 g, 9.4 mmol). Chromatography (Biotage SP4; silica; 50-100% DCM, petrol) gave **28** as a yellow oil (1.52 g, 45%). UV (in EtOH): λ max = 260 nm; IR: 2915, 2847, 1695, 1597, 1489 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (d,1H, J = 15.0 Hz, N-CH_2), 4.56 (d,1H, J = 15.0 Hz, N-CH_2), 7.05-7.13 (m, 3H, Ar-H), 7.17-7.25 (m, 6H, Ar-H), 7.44-7.51 (m, 2H, Ar-H), 7.87-7.93 (m, 1H, C(O)-C=CH-); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 15.6, 42.4, 95.2, 123.4, 126.4, 128.5, 128.7, 129.7, 130.5, 133.4, 133.5, 134.45, 137.2, 137.9, 144.8, 167.6; HRMS (ESI): $C_{22}H_{18}ClNO_2S$ calculated [M+H]$^{+}$ 396.0820 [M+H]$^{+}$, measured 396.0823; CHN.

3-(4-Chlorophenyl)-3-hydroxy-2-(4-(methylsulfinyl)benzyl)isoindolin-1-one (29)

To a solution of **28** (500 mg, 1.3 mmol) in DCM (25 mL) was added m-chloroperbenzoic acid (240 mg, 1.4 mmol) at 0 ^{o}C. The mixture was stirred at 0 ^{o}C for 20 mins, a second portion of mCPBA (240 mg, 1.4 mmol) was added and stirring continued at rt for 20 mins. The mixture was diluted with DCM (30 mL), washed with brine (30 mL), saturated $NaHCO_3$ solution (30 mL), water (30 mL) and brine (2 x 30 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography (silica; 0-1% MeOH, DCM) gave **29** as pale brown crystals (324 mg, 62%). mp 117–118 ^{o}C. HPLC purity (as area %) > 95. UV (in EtOH): λ max = 224 nm; IR: 2925, 1699, 1598, 1467 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3H, -S(=O)-CH_3), 2.91 (br s, 1H, OH)), 4.30 (d, 1H, J = 14.9 Hz, N-CH_2-), 4.47 (d, 1H, J = 14.9 Hz, N-CH_2-),7.02-7.12 (m, 5H, Ar-H), 7.31-7.33 (d, J = 8.3 Hz, 2H, C_6H_4SOMe), 7.41-7.46 (m, 2H, Ar-H), 7.62-7.65 (d, J = 8.3 Hz, 2H, C_6H_4SOMe), 7.85-7.94 (m, 1H, C(O)-C=CH-); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 42.7, 44.8, 95.5, 123.5, 124.1, 127.4, 128. 4, 128.8, 130.4, 132.1, 133.3, 134.8, 137.6, 140.1, 143.9, 145.1, 168.5; HRMS (ESI) $C_{22}H_{18}ClNO_3S$ calculated [M+H]$^{+}$ 410.0612, measured 410.0609.

3-(4-Chlorophenyl)-3-hydroxy-2-(4-(trifluoromethyl)benzyl)isoindolin-1-one (32)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (2.24 g, 8.6 mmol), 4-(trifluoromethyl)benzylamine (1.35 mL, 9.4 mmol). Chromatography (Biotage SP4; silica; 10-20% EtOAc, petrol) gave **32** as a white solid (2.07 g, 58%). mp 178 – 179 ^{o}C. UV (in EtOH): λ max = 252 nm; IR: 3185, 2922, 1659, 1600, 1470 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 4.36 (d,1H, J = 15.0 Hz, N-CH_2), 4.54 (d,1H, J = 15.0 Hz, N-CH_2), 7.22-7.30 (m, 5H, Ar-H), 7.37-7.40 (m, 3H, Ar-H), 7.50-7.63 (m, 4H, Ar-H), 7.77-7.80 (m, 1H, C(O)-C=CH-); ^{13}C NMR (DMSO, 75 MHz), δ 42.3, 90.5, 123.0, 123.2, 124.9, 123.0, 128.4, 128.5, 129.0, 129.8, 130.6, 133.2, 139.2, 143.2, 149.4, 167.2; HRMS (ESI) $C_{22}H_{15}ClF_3NO_2$ calculated [M+H]$^{+}$ 418.0816; measured 418.0814. HPLC purity (as area %): > 97.

Methyl 4-((1-(4-chlorophenyl)-1-hydroxy-3-oxoisoindolin-2-yl)methyl)benzoate (33)

General Procedure A: 4-(carboxylic acid methyl ester)benzylamine hydrochloride (4.3 g, 21.1 mmol), thionyl chloride (3.0 mL, 38.3 mmol), THF (20 mL), 2-(4-nitrophenyl)ethylamine hydrochloride (4.3 g, 21.1 mmol) and diisopropylethylamine (3.5 mL, 21.1 mmol). Recrystallisation gave **33** as a white solid (EtOAc, Petrol) (6.2 g, 79%): mp 157-158 ºC; IR (cm^{-1}) 1703; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 3.82 (s, 3H, CH_3),

4.16 (d, 1H, J = 16.2 Hz, N-CH'), 4.33 (d, 1H, J = 16.2 Hz, N-CH'), 7.24-7.37 (m, 8H, OH & Ar-H), 7.54-7.61 (m, 2H, Ar-H), 7.76-7.80 (m, 3H, C(O)=C=CH and Ar-H); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 42.5, 52.2, 90.6, 123.1, 123.2, 128.4, 128.5, 128.6, 129.1, 129.8, 130.7, 133.1, 133.2, 139.3, 144.0, 149.6, 166.5, 167.2; MS (ESI+) m/z = 408 $[M+H]^+$. CHN.

4-((1-(4-Chlorophenyl)-1-hydroxy-3-oxoisoindolin-2-yl)methyl)benzoic acid (34)

To a solution of **33** (0.50 g, 1.2 mmol) was added potassium trimethylsilanolate (0.36 g, 2.7 mmol) in THF (20 mL) in two portions over 24 hrs. The mixture was concentrated *in vacuo*. Chromatography (Biotage SP4; silica; 50% EtOAc, petrol to 10% MeOH, EtOAc) gave **34** as a white solid (0.42 g, 86%). mp 209-210°C. UV (in EtOH): λ max = 228 nm; IR: 3249, 2982, 2927, 2560, 1736, 1680, 1609, 1469 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 4.26 (d, 2H, J = 16.0Hz, NCH_2), 4.56 (d, 2H, J = 16.0Hz, NCH_2), 7.24-7.32 (m, 7H, Ar-H), 7.35 (br s, 1H, OH), 7.53-7.63 (m, 2H, Ar-H), 7.73-7.79 (m, 3H, Ar-H); ^{13}C NMR (DMSO 75 MHz), δ 42.9, 90.8, 122.8, 123.2, 126.9, 128.5, 128.9, 129.5, 130.9, 132.8, 133.0, 138.3, 139.9, 140.2, 149.8, 167.3, 169.8 ppm; HRMS (ESI) $C_{22}H_{16}ClNO_4$ calculated mass $[M+NH_4]^+$ 411.1106, measured 411.1110

2-(4-Acetylbenzyl)-3-(4-chlorophenyl)-3-hydroxy-2,3-dihydroisoindol-1-one (35)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (687 mg, 2.6 mmol) and 4-acetylbenzylammonium trifluoroacetate (630 mg, 2.4 mmol). Chromatography (silica; 10-50% EtOAc, petrol) gave **35** as white crystals (552 mg, 54%) mp 147 – 150 ^{o}C, HPLC purity (as area %): > 98. λmax (EtOH) = 254 nm; IR: 3140, 3007, 2934, 2846, 2055, 1666, 1603, 1468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3H, CH_3), 4.10 (d, J = 15.1 Hz, 1H, N-CH_2), 4.60 (d, J = 15.1 Hz, 1H, N-CH_2), 5.03 (s, 1H, OH), 7.15-7.21 (m, 4H, ArH), 7.24-7.28 (m, 3H, ArH), 7.40-7.52 (m, 2H, ArH), 7.57-7.60 (d AB, J = 8.2 Hz, 2H, ArH), 7.65-7.69 (m, 1H, -CH-C(C=O)); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 26.3, 43.0, 91.4, 123.0, 123.6, 128.2, 128.3, 128.8, 129.14, 129.8, 130.6, 133.0, 134.7, 136.2, 138.0, 143.7, 149.3, 168.1, 198.0; HRMS (ESI) calculated mass of ion 392.1048 $[M+H]^+$, measured mass of ion 392.1051 $[M+H]^+$.

2-(4-Benzoylbenzyl)-3-(4-chlorophenyl)-3-hydroxy-2,3-dihydroisoindol-1-one (36)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (791 mg, 3.0 mmol) and 4-acetylbenzylammonium trifluoroacetate (640 mg, 2.0 mmol). Chromatography (silica; 10-30% EtOAc, petrol) gave **36** as white crystals (414 mg, 46%) mp 163 – 164 ^{o}C, HPLC purity (as area %): > 97. λmax (EtOH)= 259 nm; IR: 3179, 3065, 2931, 2157, 1655, 1597, 1468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (d, J = 15.1 Hz, 2H, N-CH_2), 4.56 (d, J = 15.1 Hz, 1H, N-CH_2), 6.01 (s, 1H, OH), 7.14-7.20 (m, 4H, ArH), 7.21-7.28 (m, 3H, ArH), 7.31-7.43 (m, 6H, ArH), 7.50-7.53 (m, 1H, -CH-C(C=O)), 7.56-7.62 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 43.0, 91.5, 123.1, 123.7, 128.4, 128.6, 128.8, 129.0, 129.9, 130.2, 130.3, 130.6, 132.7, 133.2, 134.8, 136.5, 137.9, 138.0, 143.1, 149.3, 168.2, 196.7; HRMS (ESI) calculated mass of ion 454.1204 $[M+H]^+$, measured mass of ion 454.1206 $[M+H]^+$.

3-(4-Chlorophenyl)-3-hydroxy-2-(pyridin-4-ylmethyl)isoindolin-1-one (37)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (2.24 g, 8.6 mmol) and 4-(aminomethyl)pyridine (0.96 mL, 9.4 mmol). Chromatography (Biotage SP4; silica; EtOAc) gave **37** as a cream solid (1.07 g, 36%). mp 224 – 225°C; UV (in EtOH): λ max = 252 nm; IR: 3083, 3040, 2917, 2845, 2648, 2635, 2328, 2185, 2166, 2098, 2015, 1701, 1607, 1567 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (d,1H, J = 15.0 Hz, N-CH_2), 4.65 (d,1H, J = 15.0 Hz, N-CH_2), 7.05-7.07 (m, 2H, Ar-H), 7.26-7.42 (m, 5H, Ar-H), 7.42-7.52 (m, 2H, Ar-H), 7.57-7.59 (m, 2H, -CH=N-CH-), 7.37-7.76 (m, 1H, Ar-H), 7.93 (m, 1H, C(O)-C=CH-). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 42.5, 91.6, 123.1, 123.8, 124.2, 128.2, 129.1, 129.9, 130.5, 133.3, 135.0, 138.1, 148.0, 148.7, 149.6, 168.0 HRMS (ESI): $C_{20}H_{15}ClN_2O_2$ calculated for $[M+H]^+$ 351.0895 $[M+H]^+$, measured 351.0901. CHN.

3-(4-Chlorophenyl)-3-hydroxy-2-(pyridin-3-ylmethyl)isoindolin-1-one (38)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (2.24 g, 8.6 mmol) and 3-(aminomethyl)pyridine (0.96 mL, 9.4 mmol). Chromatography (Biotage SP4; silica; 40-70% EtOAc, petrol) gave **38** as a white solid

(0.76 g, 25%). mp 183 – 184°C. UV (in EtOH): λ max = 256 nm; IR: 3064, 2808, 1695, 1424 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (d, J = 15.4 Hz, 1H, N-CH_2-), 4.65 (d, J = 15.4 Hz, 1H, N-CH_2-), 6.85-6.89 (dd, J = 4.9, 7.7 Hz, 1H, Py-H), 7.21-7.31 (m, 6H, Ar-H), 7.38-7.52 (m, 3H, Ar-H), 7.67-7.70 (dd, J = 1.4, 7.4 Hz, 1H, Py-H), 8.18 (dd, J = 1.8 Hz, 1H, Py-H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 41.0, 91.6 123.1, 123.7, 128.2, 129.0, 129.8, 133.2, 134.5, 134.8, 137.3, 137.4, 138.2, 147.1, 147.2, 149.3, 149.8, 168.0; HRMS (ESI) $C_{20}H_{15}ClN_2O_2$ calculated $[M+H]^+$ 351.0895, measured 351.0897.

3-(4-Chlorophenyl)-3-hydroxy-2-(pyridin-2-ylmethyl)isoindolin-1-one (39)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (2.24 g, 8.6 mmol), 2-(aminomethyl)pyridine (0.97 mL, 9.4 mmol). Chromatography (Biotage SP4; silica; 25-50% EtOAc, petrol) gave **39** as a yellow solid (2.37 g, 79%). mp 133 – 134°C. UV (in EtOH): λ max = 256 nm; IR: 3259, 2921, 1673, 1591, 1469 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.00 (d, 1H, J = 15.0 Hz, N-CH_2), 4.82 (d, 1H, J = 15.0 Hz, N-CH_2), 6.93-6.97 (dd, J = 5.4, 6.7 Hz, 1H, Py-H), 7.12-7.16 (m, 3H, Ar-H), 7.19-7.23 (m, 2H, Ar-H), 7.26-7.33 (m, 3H, Ar-H), 7.40-7.45 (dt, J = 1.7, 7.7 Hz, 1H, Py-H), 7.59-7.61 (dd, J = 1.7, 7.4 Hz, 1H, -C(O)-C-CH-), 8.15-8.16 (dd, J = 2.1, 5.0 Hz, 1H, Py-H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 45.1, 90.6, 122.8, 123.0, 123.6, 128.3, 129.0, 129.3, 130.0, 133.1, 134.5, 137.8, 139.6, 148.4, 150.7, 157.0, 168.1 ; HRMS (ESI) $C_{20}H_{15}ClN_2O_2$ calculated $[M+H]^+$ 351.0895, measured 351.0896 $[M+H]^+$.

2-(4-(4H-1,2,4-Triazol-4-yl)benzyl)-3-(4-chlorophenyl)-3-hydroxyisoindolin-1-one (43).

General Procedure A: 2-(4-chlorobenzoyl)-benzoic acid (2.0 g, 7.6 mmol) and 4-(4H-1,2,4-triazol-4-yl)benzonitrile (235 mgs, 0.954 mmol). Chromatography (silica; 2-10% MeOH, DCM) gave **43** as a white solid (168 mg, 46%). δ_H (500 MHz, $CDCl_3$) 4.19 (1H, d, J = 15.1, 2-CH'), 4.58 (1H, d, J = 15.1, 2-CH), 5.73 (1H, br s, OH), 6.96-6.99 (2H, m, Ar-H), 7.51-7.17 (2H, m, Ar-H),7.93 (2H, s, Ar-*H*), 7.69-7.11 (1H, m, Ar-*H*), 7.22-7.25 (3H, m, 4 & Ar-H), 7.32-7.35 (2H, m, Ar-*H*), 7.38 (1H, ddd, *J* = 8.6, 7.5, 1.1, 6-*H*), 7.44 (1H, ddd, *J* = 8.6, 7.3, 1.3, 5-*H*). δ_C (125 MHz, $CDCl_3$) 167.9, 148.9, 150.0, 139.6, 137.4, 134.5, 133.1, 132.3, 131.0, 130.1, 129.7, 128.7, 127.9, 123.4, 122.9, 121.6, 91.2, 42.41; MS (ESI+) m/z = 417.19 [M+H].

3-(4-Chlorophenyl)-3-hydroxy-2-(4-((trifluoromethyl)sulfonyl)benzyl)isoindolin-1-one (45)

General procedure A: 2-(4-Chloro-benzoyl)-benzoic acid (56 mg, 0.21 mmol), THF (2 mL), thionyl chloride (31 µL, 0.43 mmol) and catalytic DMF (4 drops) . Then diisopropylethylamine (0.09 mL, 0.70 mmol) and 4-((trifluoromethyl)sulfonyl)benzylamine hydrochloride (65 mg, 0.24 mmol). Chromatography (Biotage SP4, silica, 15-100% EtOAc, petrol) to give **45** as a white solid (88 mg, 87 %). Mp = 208.8-209.2 °C; HPLC purity (as area %): > 99%. UV (nm) λ_{max} (CH_3CH_2OH)/nm 340.5; IR: 2393, 1655, 1598, 1365 cm^{-1} ^1H NMR (500 MHz d_6-DMSO) δ 4.52 (1H, d, *J* = 16.4 Hz, NCH_2), 4.63 (1H, d, *J* = 16.4 Hz, NCH_2), 7.23-7.27 (4H, m, Ar-H), 7.31 (1H, d, *J* = 7.2 Hz, Ar-H), 7.41 (1H, s, OH), 7.57-7.64 (4H, m, Ar-H), 7.81 (1H, dd, *J* = 0.7 and 6.8 Hz, Ar-H), 7.93 (2H, d, *J* = 8.4 Hz, Ar-H); ^{13}C NMR (125 MHz d_6-DMSO) δ 41.8 (NCH_2), 90.0, 122.8, 122.9, 127.4, 128.0, 128.2, 129.6, 129.8, 129.9, 130.4, 132.8, 133.1, 138.5, 148.9, 149.0, 166.9 (carbonyl); ^{19}F NMR (470 MHz, d_6-DMSO) -78.6307; LCMS (ESI+) *m/z* = 482.11 $[M+H]^+$

(*S*)-3-(4-Chlorophenyl)-2-[1-(4-chlorophenyl)ethyl]-3-hydroxy-2,3-dihydroisoindol-1-one (46a)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (5 g, 19.2 mmol) , thionyl chloride (3.0 mL, 38.3 mmol), then THF (20 mL), and (*S*)-4-chloro-α-methylbenzylamine (2.4 g, 15.6 mmol) and diisopropylethylamine (3.5 mL, 21.1 mmol). Recrystallisation (EtOAc, Petrol) gave **46a** as a mixture of diastereoisomers as a white crystalline powder (3.1 g, 55%). IR (cm^{-1}) 3119, 1667; ^1H NMR, (300 MHz, DMSO-d_6), δ 1.69 and 1.56 (d, *J* = 7.0 Hz, 3H, CH_3), 4.18 and 4.11 (br s, 1H, OH), 4.58 and 4.43 (q, 1H, *J* = 7.0 Hz, CH), 6.90 (d, 1H and 1H, *J* = 8.7 Hz, Ar-H), 7.26-7.02 (m, 5H and 5H, Ar-H), 7.46-7.30 (m, 5H and 5H, Ar-H), 7.64-7.61 (m, 1H and 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6), δ 18.4, 19.8, 52.0, 52.1, 91.5, 91.9, 122.5, 123.4, 123.4, 128.0, 128.2, 128.3, 128.4, 128.7, 128.8, 129.4, 129.5, 129.8, 131.2, 131.3, 132.7, 132.8, 132.9, 133.0, 134.7, 134.7, 137.3, 137.4, 140.5, 141.1, 148.3, 148.3, 167.3, 167.3; MS (ESI+) m/z = 398 $[M+H]^+$.

3-(4-Chlorophenyl)-3-hydroxy-2-(4-methoxybenzyl)isoindolin-1-one (47)

General Procedure A: 2-(4-chlorobenzoyl)benzoic acid (1.0 g, 3.8 mmol), 4-methoxybenzylamine (0.542 mL, 4.18 mmol) and THF (8.5 mL). Then THF (8.5mL), thionyl chloride (0.554 mL, 7.6 mmol) and diisopropylethylamine (1.3 mL; 7.6 mmol) Chromatography (Biotage SP4, silica; 10-80% EtOAc, hexane) gave **47** as a white solid (0.830 g, 57%). ^{1}H NMR, (500 MHz, $CDCl_3$) δ 3.72 (s, 3H, CH_3), 4.26 (d, 1H, J = 15.2, N-CH), 4.40 (d, 1H, J = 15.2, N-CH'), 6.73-6.76 (m, 2H, Ar-H), 7.10-7.13 (m, 2H, Ar-H), 7.25-7.27 (m, 2H, Ar-H), 7.29-7.33 (m, 3H, Ar-H), 7.57-7.61 (m, 2H, Ar-H), 7.78-7.80 (m,1H, C(O)=C=CH); ^{13}C NMR, (125 MHz, $CDCl_3$) 41.7; 55.0, 90.1, 166.7, 113.1, 122.5, 122.8, 128.0, 128.2, 129.3, 129.4, 130.0, 130.3, 132.5, 132.6 139.0, 149.1, 157.9; HRMS ($C_{22}H_{19}NO_3Cl$+H) calcd 380.1048, obsd 380.1055.

General Procedure B*: 3-Alkoxy isoindolinones*

To solution of the appropriate isoindolinone (1 equiv.) in THF (10 mL) under N_2, was added thionyl chloride (2 equiv.) and a catalytic amount of DMF (1-3 drops), and the resulting mixture was stirred for 4 h at rt, then concentrated *in vacuo*. The residue was diluted with THF (10 mL) and the required alcohol (2 equiv.) and potassium carbonate (2 equiv.) or DIPEA (1.1 eq) were added, and the resulting mixture was stirred overnight at rt, then concentrated *in vacuo*. The residue diluted with EtOAc (50 mL) and washed with water (3 x 25 mL) and brine (1 x 25 mL). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to afford an oil which was purified by chromatography (silica; EtOAc/petrol).

3-(4-Fluorophenyl)-3-(3-hydroxycyclopentyloxy)-2-propyl-2,3-dihydroisoindol-1-one (48)

General Procedure B: 3-(4-fluorophenyl)-3-hydroxy-2-propyl-2,3-dihydroisoindol-1-one (200 mg, 0.7 mmol), thionyl chloride (0.06 mL, 0.84 mmol) and DMF (Cat.). Then 1,3-cyclopentanediol (0.65 mL, 6.9 mmol) and K_2CO_3 (193 mg; 1.4 mmol). HPLC (C18; H_2O, MeOH) gave **48** as a clear glass (126 mg, 49%): IR (cm^{-1}) 3387, 2936, 1683, 1604, 1505, 1366; ^{1}H NMR, (300 MHz, MeOH-d_4) δ 0.77 (t, 3H, J = 7.4 Hz, $CH_2CH_2CH_3$), 1.15 (m, 1H, NCH_2CH), 1.32 (m, 1H, NCH_2CH'), 1.40-2.05 (m, 6H, cyclopentane), 3.12 (m, 1H, N-CH), 3.29 (m, 1H, N-CH'), 3.90 (m, 1H, cyclopentane), 4.31 (m, 1H, cyclopentane), 7.07 (ap.t, 2H, J = 9 Hz, Ar-H), 7.23 (m, 1H, Ar-H), 7.39 (m, 2H, Ar-H), 7.60 (m, 2H, Ar-H), 7.87 (m, 1H, Ar-H); ^{13}C NMR, (125 MHz, MeOH-d_4) δ 12.2, 22.9, 32.7, 33.1, 34.2, 43.1, 44.3, 44.8, 72.8, 73, 75.7, 96.5, 116.3, 116.6, 124.3, 125.7, 130, 130.1, 131.6, 133.6, 134.1, 137.1, 148.1, 166.2, 170.7; LCMS (ESI+) m/z = 370.3 $[M+H]^+$, 392.3 $[M+Na]^+$; HRMS ($C_{22}H_{24}FNO_3$) calcd 369.1740, obsd 369.1737.

2-Benzyl-3-(4-chlorophenyl)-3-(3-hydroxycyclopentoxy)-2,3-dihydroisoindol-1-one (50)

General Procedure B: **11** (225 mg, 0.57 mmol), 1,3-cyclopentanediol (0.26 mL, 2.85 mmol). HPLC (C18; H_2O, MeOH) gave **50** as an inseparable mixture of diastereoisomers as a clear glass (128 mg, 69%). IR (cm^{-1}) 3362, 2934, 1683, 1489, 1464, 1388. ^{1}H NMR, (300 MHz, DMSO-d_6) δ 1.09 (m, 1H, cyclopentane), 1.24 (m, 2H, cyclopentane), 1.49 (m, 2H, cyclopentane), 1.80 (m, 1H, cyclopentane), 3.71 (m, 1H, cyclopentane), 4.18 (m, 1H, cyclopentane), 4.18 (m, 1H, N-CH), 4.38 (d, 1H, J = 14.8 Hz, N-CH'), 7.06 (m, 10H, Ar-H), 7.14 (m, 2H, Ar-H), 7.39 (m, 2H, Ar-H), 7.42 (m, 2H, Ar-H), 7.81 (m, 1H, Ar-H). ^{13}C NMR, (75 MHz, DMSO-d_6) δ 30.7, 31.0, 31.1, 32.0, 32.1, 32.8, 33.5, 33.7, 33.9, 34.3, 42.9, 43.3, 43.4, 44.1, 45.6, 71.9, 72.6, 72.8, 73, 73.2, 73.3, 73.4, 74, 74.1, 77, 77.4, 77.8, 91.5, 95.1, 123, 123.8, 123.9, 124.3, 124.4, 127.4, 127.5, 128.2, 128.5, 128.6, 128.7, 128.9, 129.1, 129.3, 129.4, 130.1, 130.2, 131.8, 132.7, 132.7, 133.2, 134.5, 137.8, 138, 146.4, 146.5, 146.6, 149, 168, 168.8, 168.9. LCMS m/z 434.1 $[M+H]^+$; Anal. requires $C_{26}H_{24}ClNO_3$: C, 71.97; H, 5.57; N, 3.23%. Found C, 71.39; H, 5.40; N, 3.46%. HRMS ($C_{26}H_{24}ClNO_3$) calcd 433.1444, obsd 433.1436.

3-(4-Chlorophenyl)-3-(3-hydroxycyclopentoxy)-2-(4-nitrobenzyl)-2,3-dihydroisoindol-1-one (51)

General Procedure B: **20** (146 mg, 0.37 mmol), 1,3-cyclopentanediol (0.17 mL, 1.89 mmol). HPLC (C18; H_2O, MeOH) gave **51** as an inseparable mixture of diastereoisomers as a clear glass (94 mg, 52%). IR (cm^{-1})

3377, 2941, 4693, 1519, 1340, 1094; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.19 (m, 1H, cyclopentane), 1.35 (m, 2H, cyclopentane), 1.62 (m, 2H, cyclopentane), 1.89 (m, 1H, cyclopentane), 3.75 (m, 1H, cyclopentane), 4.26 (m, 1H, cyclopentane), 4.31 (m, 1H, N-CH_2), 4.50 (d, 1H, J = 15.2 Hz, N-CH_2), 7.04 (m, 5H, Ar-H), 7.16 (m, 2H, Ar-H), 7.45 (m, 2H, Ar-H), 7.83 (m, 1H, Ar-H), 7.90 (m, 2H, Ar-H). ^{13}C NMR, (75 MHz, $CDCl_3$) δ 29.8, 31.1, 31.2, 31.4, 32, 32.1, 33.6, 33.7, 33.9, 34.3, 42.5, 42.7, 43.1, 44, 45.6, 53.8, 72, 72.5, 72.7, 73, 73.3, 73.4, 74.1, 74.2, 74.4, 91.4, 94.8, 123.6, 123.7, 124, 124.1, 124.1, 124.4, 124.4, 128.3, 128.4, 128.7, 128.8, 129.1, 129.8, 130, 130.1, 130.3, 130.5, 130.5, 131.5, 133.2, 135, 137.4, 145.3, 145.3, 146.2, 147.2, 168.1, 168.7, 168.8, 168.9. LCMS (ESI+) *m/z* = 479.2 $[M+H]^+$; CHN requires $C_{26}H_{23}ClN_2O_5$: C, 64.72; H, 4.89; N, 5.81%; found C, 64.49; H, 4.90; N, 5.95%. HRMS ($C_{26}H_{23}ClN_2O_5$) calcd 478.1295, obsd 478.1286.

***cis*-4-((1-(4-Chlorophenyl)-1-(4-hydroxycyclopent-2-enyloxy)-3-oxoisoindolin-2-yl)methyl)benzonitrile (53)**

General Procedure B: **17** (400 mg, 1.1 mmol), THF (10 mL), thionyl chloride (0.18 mL, 2.4 mmol) and DMF (Cat.). Then THF (6 mL) *cis*-cyclopentene diol (275 mg, 2.8 mmol) and K_2CO_3 (380 mg, 2.8 mmol). Chromatography (silica; 40% EtOAc, petrol) gave **53** as a yellow oily solid (105 mg, 21 %): mp 126-127 °C; IR (cm^{-1}) 3061, 2229, 1609, 1382; ^{1}H NMR, (300 MHz, DMSO) δ 1.31 (m, 1H, O-CHC*H*$_2$CHOH-), 1.73, 2.11 (m, 1H, O-CHC*H*$_2$CHOH-), 3.89 (br s, 1H, OH), 4.22 (m, 1H, O-CHCH$_2$C*H*OH), 4.42 (d, 1H, J = 7.10 Hz, NCH$_2$), 4.52 (d, 1H J = 7.03 Hz, NCH$_2$), 4.98-5.04 (dd, 1H, O-CHC*H*=C*H*), 5.01-5.27 (dd, 1H, O-CHC*H*=C*H*), 5.75 (m, 1H, O-C*H*), 7.24 (m, 7H, ArH) 7.62 (m, 4H, ArH), 7.87 (d, 1H, ArH). HRMS ($C_{27}H_{21}ClN_2O_3$+Na) calcd 479.1138, obsd 479.1134.

***cis*-2-Benzyl-3-(4-chlorophenyl)-3-(4-hydroxycyclopent-2-enyloxy) isoindolin-1-one (54)**

General Procedure B: **11** (400 mg, 1.1 mmol), THF (25 mL), thionyl chloride (0.2 mL, 2.5 mmol.), then THF (25 mL), *cis*-cyclopentene diol (572 mg, 5.7 mmol) and K_2CO_3 (793 mg, 5.7 mmol). Chromatography (silica; 40% EtOAc, petrol) gave **54** as a cream solid (278 mg, 56 % yield), mp 63.4-63.9 ºC. IR (cm^{-1}) 3379, 3061, 1683, 1489; ^{1}H NMR, (300 Hz, $CDCl_3$) δ 0.84, 1.66 (m, 1H, O-CHC*H*$_2$CHOH) 1.26 (m, 1H, O-CHC*H*$_2$CHOH) 3.85 (m, 1H, O-CHCH$_2$C*H*OH) 3.36 (m, 1H, O-C*H*) 4.15 (d, 1H, J=15.27 Hz, NCH$_2$), 4.62 (d, 1H, J=15.31 Hz, NCH$_2$), 4.68-5.73 (dd, 1H, O-CHC*H*=C*H*), 5.21-5.64 (dd, 1H, O-CHC*H*=C*H*), 7.18 (m,10H, ArH), 7.62 (m, 2H, ArH), 7.83 (d, 1H, ArH).

***cis*-3-(4-Chlorophenyl)-3-(4-hydroxycyclopent-2-enyloxy)-2-(4-chlorobenzyl) isoindolin-1-one (55)**

General Procedure B: **13** (200 mg, 0.50 mmol), THF (10 mL), thionyl chloride (0.1 mL, 1.2 mmol) and DMF (Cat.). Then THF (3 mL) *cis*-cyclopentene diol (135 mg, 1.4 mmol) in THF (3 mL) and K_2CO_3 (187mg, 1.4 mmol). Chromatography (silica; 40% EtOAc, petrol) gave **55** as a yellow viscous oil (104 mg, 43 %). IR (cm^{-1}) 3397, 2926, 1683, 1467; ^{1}H NMR, (300 MHz, DMSO-d_6) δ 1.27 (m, 1H, O-CHC*H*$_2$CHOH-), 1.41, 1.68 (m, 1H, O-CHC*H*$_2$CHOH-) 3.86 (m, 1H, O-CHCH$_2$C*H*OH), 4.16 (m, 1H, O-C*H*) 4.31 (d, 1H, J = 15.49 Hz, NCH$_2$) 4.50 (d, 1H, J = 15.48 Hz, NCH$_2$) 4.93-5.75 (dd, 1H, O-CHC*H*=C*H*) 5.25-5.70 (dd, 1H, O-CHC*H*=C*H*), 7.21 (m, 9H, ArH) 7.63 (m, 2H, ArH) 7.85 (d, 1H, ArH).

***cis*-3-(4-Chlorophenyl)-3-(4-hydroxycyclopent-2-enyloxy)-2-(4-methylbenzyl)isoindolin-1-one (56)**

General Procedure B: **16** (400 mg, 1.1 mmol), THF (10 mL), thionyl chloride (0.2 mL, 2.5 mmol) and DMF (Cat.). Then THF (3 mL) *cis*-cyclopentene diol (285 mg, 2.9 mmol) in THF (3 mL) and K_2CO_3 (390. mg, 2.9 mmol). Chromatography (silica; 40% EtOAc, petrol) gave **56** as a colorless viscous oil (242. mg, 50 %). IR (cm^{-1}) 2922, 1699, 1467; ^{1}H NMR, (300 MHz, DMSO-d_6) δ 1.19 (m, 1H, O-CHC*H*$_2$CHOH-), 1.67, 2.05 (m, 1H, O-CHC*H*$_2$CHOH-) 2.21 (s, 3H, CH$_3$), 3.85 (m, 1H, O-CHCH$_2$C*H*OH), 4.06 (d, 1H, J = 15.21 Hz, NCH$_2$), 4.32 (m, 1H, O-C*H*) 4.53 (d, 1H, J = 15.21 Hz, NCH$_2$), 4.81-5.74, (dd, 1H, O-CHC*H*=C*H*) 5.20-5.66 (dd, 1H, O-CHC*H*=C*H*), 6.95 (m, 4H, ArH), 7.25 (m, 5H, ArH), 7.65 (m, 2H, ArH) 7.74 (d, 1H, ArH). HRMS ($C_{27}H_{24}ClNO_3$+H) calcd 446.1523, found 446.1517.

***cis*-3-(4-Chlorophenyl)-3-(4-hydroxycyclopent-2-enyloxy)-2-(4-nitrobenzyl) isoindolin-1-one (57)**

General Procedure B: **20** (200 mg, 0.52 mmol), THF (10 mL), thionyl chloride (0.1 mL, 1.2), then THF (3 mL), *cis*-cyclopentene diol (260 mg, 2.6 mmol) in THF (3 mL) and K_2CO_3 (359 mg, 2.6 mmol). Chromatography (silica; 40% EtOAc, petrol) to give **57** yellow viscous oil. (211 mg, 85 %). ^{1}H NMR, (300 MHz, DMSO-d_6) δ 1.34, (m, 1H, O-CHCH_2CHOH) 1.74-2.2 (m, 1H, O-CHCH_2CHOH) 4.22 (m, 1H, O-CHCH_2CHOH) 4.40 (d, 1H, J=15.99 Hz, NCH_2), 4.63 (d, 1H, J=16.02 Hz, NCH_2), 4.93-4.98, (dd, 1H, O-CHCH=CH), 5.15-5.29 (dd, 1H, O-CHCH=CH), 5.76 (m, 1H, O-CH) 7.26 (m, 7H, ArH), 7.66 (m, 2H, ArH), 7.88 (d, 1H, ArH), 8.00 (m, 2H, ArH).

4-[1-(4-Chlorophenyl)-1-(4-hydroxybutoxy)-3-oxo-1,3-dihydroisoindol-2-ylmethyl]benzonitrile (61)

General Procedure B: **17** (513 mg, 1.4 mmol), thionyl chloride (214 µL, 2.75 mmol) and 1,4-butanediol (616 mg, 6.9 mmol), K_2CO_3 (526 mg, 5.0 mmol) gave **61** as a white solid (302 mg, 67%). ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.16-1.53 (m, 4H, $(CH_2)_2$), 2.74-2.79 (m, 2H, OCH_2), 3.54-3.58 (m, 2H, HOCH_2), 4.23 (d, 1H, J = 15.0 Hz, N-CH), 4.60 (d, 1H, J = 15.0 Hz, N-CH'), 7.10-7.13 (m, 1H, Ar-H), 7.19 (s, 4H, Ar-H), 7.33 (d, 4H, J = 8.4 Hz, Ar-H), 7.47 (d, 4H, J = 8.4 Hz, Ar-H), 7.55-7.52 (m, 2H, Ar-H), 7.94-7.91 (m, 1H, C(O)=C=CH); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 25.7, 29.4, 42.7, 62.3, 62.8, 94.8, 111.3, 118.4, 123.1,123.8, 128.0, 128.6, 129.85, 130.0, 131.5, 131.9, 132.9, 134.8, 137.2, 142.9, 145.3, 168.2; CHN.

(*S*)-3-(4-Chlorophenyl)-2-[1-(4-chlorophenyl)ethyl]-3-(4-hydroxybutoxy)-2,3-dihydroisoindol-1-one (62)

General Procedure B: **46a** (498 mg, 1.4 mmol), thionyl chloride (214 µL, 2.75 mmol) and 1,4-butanediol (616 mg, 6.9 mmol), K_2CO_3 (526 mg, 5.0 mmol) gave **62** as a pale yellow oil (242 mg, 51%). IR (cm-1) 3401, 2937, 2877, 1681, 1596, 1490, 1467; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.77-1.81(m, 5H, OH & $(CH_2)_2$), 1.86 (d, 3H, J = 7.2 Hz, CH_3), 3.25-3.29 (m, 2H, OCH), 2.95-3.01 (m, 2H, OCH'), 3.68-3.75 (m, 2H, HOC$\underline{H_2}$), 4.41 (q, J = 7.2 Hz, 1H, N-CH), 7.07-7.03 (m, 9H, Ar-H), 7.53-7.46 (m, 2H, Ar-H), 7.87-7.83 (m, 1H, C(O)=C=CH); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 20.1, 26.5, 30.0, 52.5, 62.9, 63.4, 95.4, 123.3, 123.7, 128.3, 128.4, 128.8, 129.7, 130.2, 132.8, 133.1, 133.2, 134.8, 141.5, 137.8, 145.3, 168.3. m/z (ES) 470 ($[M+H]^+$); CHN.

(*R*)-3-(4-Chlorophenyl)-2-[1-(4-chlorophenyl)ethyl]-3-(4-hydroxybutoxy)-2,3-dihydroisoindol-1-one (63)

General Procedure B: **46b** (498 mg, 1.4 mmol), thionyl chloride (214 µL, 2.75 mmol) and 1,4-butanediol (616 mg, 6.9 mmol), K_2CO_3 (526 mg, 5.0 mmol) gave **63** as a clear oil (242 mg, 51%). IR (cm^{-1}) 3428, 2938, 2873, 2160, 2021, 1682, 1597, 1490, 1468, 1400; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.76-1.66 (m, 4H, CH_2), 1.86 (d, J = 7.2 Hz, 3H, CH_3), 3.31-3.24 and 3.02-2.95 (m, 2H, OCH_2), 3.70 (m, 2H, HO-CH_2), 4.41 (q, J = 7.2 Hz, 1H, N-CH), 7.07-7.00 (m, 9H, Ar-H), 7.53-7.46 (m, 2H, Ar-H), 7.87-7.84 (m, 1H, C(O)=C=CH),; ^{13}C NMR, (75 MHz, $CDCl_3$) δ 20.08, 26.48, 29.96, 52.49, 62.88, 63.36, 95.45, 123.27, 123.72, 128.41, 128.74, 129.67, 130.20, 132.84, 133.06, 133.15, 134.80, 137.77, 141.48, 145.27, 168.32. MS (ESI+) m/z = 470 $[M+H]^+$; CHN.

3-(4-Chlorophenyl)-3-(4-hydroxybutoxy)-2-[2-(4-nitrophenyl)ethyl]-2,3-dihydroisoindol-1-one (64)

General Procedure B: **24** (562 mg, 1.4 mmol), thionyl chloride (214 µL, 2.75 mmol) and 1,4-butanediol (616 mg, 6.9 mmol), K_2CO_3 (526 mg, 5.0 mmol) gave **64** as a white solid (306 mg, 63%): mp 124-126 ^oC; IR (cm-1) 3451, 2939, 2872, 1685, 1599, 1509, 1470, 1405; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.75-1.63 (m, 5H, CH_2 and OH), 2.66-2.73 (1H, m, Ar-CH), 2.88-3.00 (m, 2H, Ar-CH' & N-CH) 3.11-3.18 (m, 1H, N-CH'), 3.40-.51 (m, 2H, HO-CH_2), 3.66 (m, 2H, N-CH_2), 7.30-7.14 (m, 7H, Ar-H), 7.55-7.53 (m, 2H, Ar-H), 7.91-7.88 (m, 1H, C(O)=C=CH), 8.11-8.08 (m, 2H, O_2N-C-CH); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 26.1, 29.6, 34.2, 40.5, 62.4, 62.8, 94.5, 123.1, 123.5, 123.7, 127.9, 128.7, 129.5, 123.0, 132.0, 132.7, 134.8, 137.7, 145.3, 146.6, 147.0, 168.2; CHN.

3-(4-Bromophenyl)-3-(3-hydroxypropoxy)-2-(4-nitrobenzyl)isoindolin-1-one (65)

General Procedure B: **21** (0.50 g, 1.1 mmol), thionyl chloride (214 μL, 2.75 mmol) and 1,3-propanediol (0.16 mL, 2.3 mmol), K_2CO_3 (526 mg, 5.0 mmol). Chromatography (Biotage SP4, silica; 10-50% EtOAc, petrol) gave **65** as a pale yellow oil (0.40 g, 70%): IR (cm-1) 3409, 2925, 2879, 1688, 1603, 1518, 1467; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.46-1.61 (m, 2H, CH_2), 2.90-2.94 (m, 2H, OCH_2), 3.60 (t, 2H, J = 6.1 Hz, HOCH_2), 4.34 (d, 1H, J = 15.1 Hz, N-CH), 4.60 (d, 1H, J = 15.1 Hz, N-CH'), 6.95-6.99 (m, 1H, Ar-H), 7.10-7.17 (m, 2H, Ar-H), 7.27-7.39 (m, 4H, Ar-H), 7.50-7.55 (m, 2H, Ar-H), 7.89-7.92 (m, 1H, C(O)=C=CH), 7.97-8.04 (m, 2H, Ar-H); ^{13}C NMR, (75 MHz, $CDCl_3$), δ 32.5, 42.7, 60.2, 60.8, 95.2, 123.3, 123.5, 123.6, 124.2, 128.6, 130.2, 130.5, 131.8, 132.0, 133.4, 138.0, 145.1, 145.4, 147.6, 168.6; CHN.

3-(4-Chlorophenyl)-3-(4-hydroxymethylbenzyloxy)-2-(4-nitrobenzyl)-2,3-dihydroisoindol-1-one (67)

General Procedure B: **20** (541 mg, 1.4 mmol), thionyl chloride (214 μL, 2.75 mmol) and 1,4-benzenedimethanol (946 mg, 6.9 mmol), K_2CO_3 (526 mg, 5.0 mmol) gave **67** as a white solid (405 mg, 78%). mp 159-162 ^{o}C; IR (cm^{-1}) 3436, 2927, 1681, 1606, 1519, 1468, 1423; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 2.12 (t, 1H, J = 6.0 Hz, OH), 3.68 (d, 1H, J = 11.7 Hz, OCH), 3.90 (d, 1H, J = 11.7 Hz, OCH'), 4.12 (d, 1H, J = 15.0 Hz, 1H, N-CH), 4.66 (d, 2H, J = 5.7 Hz, CH_2OH), 4.85 (d, 1H, J = 15.0 Hz, N-CH'), 6.93 (d, 2H, J = 7.8 Hz, Ar-H), 7.18-7.37 (m, 9H, Ar-H), 7.61-7.53 (m, 2H, Ar-H), 7.85-7.88 (m, 2H, Ar-H) 7.98-8.01 (m, 1H, C(O)=C=CH); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 42.9, 65.1, 65.3, 95.5, 123.7, 124.3, 127.1, 127.3, 128.4, 129.2, 130.3, 130.6, 131.7, 133.4, 135.4, 136.4, 137.3, 144.9, 141.2, 145.4, 147.6, 168.5; MS (ESI+) m/z = 515 $[M+H]^+$. CHN.

3-(4-Chlorophenyl)-3-(4-hydroxymethylcyclohexylmethoxy)-2-(4-nitrobenzyl)-2,3-dihydroisoindol-1-one (68)

General Procedure B: **20** (400 mg, 1.0 mmol), thionyl chloride (214 μL, 2.75 mmol) and *trans*-cyclohexane-1,4-dimethanol (728 mg, 5.0 mmol) K_2CO_3 (526 mg, 5.0 mmol) gave **68** as a yellow oil (374 mg, 71%). IR (cm^{-1}) 3450, 2919, 2852, 2161, 1699, 1606, 1519, 1490, 1467; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 0.79-0.93 (m, 5H, Cy-H.), 1.08-1.21 (m, 1H, Cy-H), 1.32-1.44 (m, 2H, Cy-H.), 1.74-1.81 (m, 3H, OH and Cy-H), 2.53-2.65 (m, 2H, OCH_2), 3.44 (d, 2H, J = 6.3 Hz, , HOCH_2), 4.35 (d, 1H, J = 15.0 Hz, N-CH), 4.59 (d, 1H, J = 15.0 Hz, N-CH'), 7.08-7.14 (m, 1H, Ar-H), 7.17-7.24 (m, 4H, Ar-H), 7.35-7.40 (m, 2H, Ar-H), 7.53-7.56 (m, 2H, Ar-H), 7.92-8.05 (m, 3H, Ar-H & C(O)=C=CH); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 28.9, 29.3, 29.7, 38.0, 40.6, 42.4, 68.3, 68.4, 94.7, 123.2, 123.2, 123.8, 128.0, 128.6, 130.0, 132.9, 134.8, 137.4, 144.8, 145.4, 168.3; (ES) m/z = 521 $[M+H]^+$. CHN.

3-(4-Chlorophenyl)-3-(3-hydroxymethylbenzyloxy)-2-(4-nitrobenzyl)-2,3-dihydroisoindol-1-one (69)

General Procedure B: **20** (541 mg, 1.4 mmol), thionyl chloride (214 μL, 2.75 mmol) and 1,3-benzenedimethanol (946 mg, 6.9 mmol), K_2CO_3 (526 mg, 5.0 mmol) gave **69** as a white solid (390 mg, 75%): mp 183-185 ^{o}C; IR (cm^{-1}) 3459, 3375, 2159, 2032, 1672, 1605, 1517, 1468, 1427; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 1.95 (t, 1H, J = 5.4 Hz, OH), 3.73 (d, 1H, J = 11.4 Hz, OCH), 3.93 (d, 1H, J = 11.4 Hz, OCH'), 4.13 (d, 1H, J = 15.0 Hz, N-CH), 4.64 (d, 2H, J = 5.1 Hz, C$\underline{H_2}$OH), 4.80 (d, 1H, J = 15.0 Hz, N-CH') 6.91-6.95 (m, 2H, Ar-H), 7.17-7.39 (m, 9H, Ar-H), 7.53- 7.62 (m, 2H, Ar-H), 7.90-7.93 (m, 2H, Ar-H), 7.98-8.01 (m, 1H, C(O)=C=CH); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 42.9, 65.4, 65.4, 95.6, 123.7, 124.3, 125.8, 126.5, 126.6, 128.4, 128.8, 129.2, 130.3, 130.6, 131.79, 133.4, 135.4, 137.5, 141.6, 144.9, 145.4, 168.5, MS (ESI+) m/z = 515 $[M+H]^+$; CHN.

3-(4-Chlorophenyl)-3-(4-hydroxybut-2-ynyloxy)-2-(4-nitrobenzyl)-2,3-dihydroisoindol-1-one (71)

General Procedure B: **20** (400 mg, 1.0 mmol) thionyl chloride (214 μL, 2.75 mmol) and butynediol (435 mg, 5.0 mmol), K_2CO_3 (526 mg, 5.0 mmol) gave **71** as a yellow solid (271 mg, 58%): mp 119-123 ^{o}C, IR (cm^{-1}) 3457, 3053, 1693, 1605, 1516, 1469, 1426; ^{1}H NMR, (300 MHz, $CDCl_3$) δ 2.4 (t, 1H, J = 6.0 Hz, OH), 3.5 (dt, 1H, J = 15.3, 1.8 Hz, OCH), 3.83 (dt, 1H, J = 15.3, 1.8 Hz, OCH'), 4.18-4.20 (m, 2H, HOCH_2), 4.52 (d, 1H, J = 15.0 Hz, N-CH), 4.60 (d, 1H, J = 15.0 Hz, N-CH'), 7.16-7.24 (m, 5H, Ar-H), 7.33-7.36 (m, 2H, Ar-H), 7.54-7.61 (m, 2H, Ar-H), 7.93-8.05 (m, Ar-H and C(O)=C=CH); ^{13}C NMR, (75

MHz, $CDCl_3$) δ 43.6, 51.6, 53.0, 54.0, 81.3, 86.0, 95.9, 124.1, 124.4, 124.8, 128.8, 129.4, 130.8, 131.3, 132.5, 133.8, 135.9, 137.2, 145.2, 148.2, 169.2; m/z (ES) 463 ($[M+H]^+$); CHN.

3-(4-Chlorophenyl)-3-(2-hydroxymethylcyclohexylmethoxy)-2-(4-nitrobenzyl)-2,3-dihydroisoindol-1-one (72)

General Procedure B: **20** (400 mg, 1.0 mmol), thionyl chloride (214 µL, 2.75 mmol) and K_2CO_3 (526 mg, 5.0 mmol) *cis*-cyclohexane-1,2-dimethanol (728 mg, 5.0 mmol) gave **72** as a mixture of diastereoisomers as a yellow solid (337 mg, 64%). Mp 98-100 ^oC; IR (cm^{-1}) 3441, 3082, 2926, 2858, 2160, 2034, 1693, 1606, 1519, 1490, 1467; ^1H NMR, (300 MHz, $CDCl_3$) δ 1.09-1.87 (m, 20H, Cy-H) 2.61- 2.87 (m, 2H, OCH_2), 3.53-3.24 (m, 2H, HO-CH_2), and 4.59 and 4.36 (d: *AB*, *J* = 15.0 Hz, 2H, N-CH_2), 4.61 and 4.25 (d: *AB*, *J* = 15.0 Hz, 2H, N-CH_2) 7.23-7.11 (m, 5H, Ar-H), 7.43-7.36 (m, 2H, Ar-H), 7.58-7.54 (m, 2H, Ar-H), 8.08-7.93 (m, 3H, Ar-H & C(O)=C=CH);. ^{13}C NMR, (75 MHz, $CDCl_3$) δ 168.25, 147.42, 145.37, 145.20, 144.84, 144.76, 137.28, 137.12, 134.97, 134.88, 133.03, 131.55, 131.41, 130.15, 130.10, 129.98, 129.94, 128.81, 128.69, 127.98, 127.92, 123.91, 123.81, 123.33, 123.30, 123.10, 123.06, 95.07, 94.97, 63.91, 63.57, 63.44, 63.31, 42.50, 42.43, 40.77, 39.99, 37.18, 27.40, 27.09, 26.21, 26.16, 23.77, 23.44, 23.29. CHN.

4-((1-(4-Chlorophenyl)-1-((1-(hydroxymethyl)cyclopropyl)methoxy)-3-oxoisoindolin-2-yl)methyl)benzonitrile (78)

General Procedure B: **47** (379 mg, 1.0 mmol), thionyl chloride (214 µL, 2.75 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.2 mL, 2.0 mmol), K_2CO_3 (526 mg, 5.0 mmol). Chromatography (Biotage SP4, silica; 20-50% EtOAc, petrol) gave **78** as white crystals (221 mg, 51%). mp 136–137 ^oC; HPLC purity (as area %) > 98; IR (cm^{-1}) 3408, 2926, 2854, 2228, 1680, 1605, 1491, 1468; ^1H NMR, (300 MHz, $CDCl_3$) δ 0.01-0.19 (m, 2H, CH_2), 0.34-0.42 (m, 2H, CH_2), 1.96 (s, 1H, OH), 2.72-2.79 (m, 2H, OCH_2), 3.41 (d, 1H, *J* = 11.4 Hz, C*H*OH), 3.49 (d, 1H, *J* = 11.4 Hz, C*H*'OH), 4.40 (s, 2H, N-CH_2), 7.05-7.12 (m, 5H, Ar-H), 7.18-7.21 (m, 1H, Ar-H), 7.35-7.37 (m, 1H, Ar-H), 7.45-7.50 (m, 2H, Ar-H), 7.82-7.85 (m, 1H, C(O)C=CH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 8.9, 22.6, 43.0, 67.4, 67.6, 94.9, 111.5, 118.7, 123.5, 124.1, 128.3, 128.9, 130.1, 130.5, 131.8, 132.2, 133.4, 135.1, 137.5, 143.1, 145.5, 168.6; HRMS ($C_{27}H_{23}ClN_2O_3$+H) calcd 459.1470, obsd 459.1471; CHN.

3-(4-Chlorophenyl)-2-(4-fluorobenzyl)-3-(1-hydroxymethylcyclopropylmethoxy)-2,3-dihydroisoindol-1-one (79)

General Procedure B: **12** (372 mg, 1.01 mmol), thionyl chloride (156 µL, 2.0 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.19 mL, 2.03 mmol), K_2CO_3 (210 mg, 2.0 mmol). Chromatography (silica; 10-40% EtOAc, petrol) gave **79** as yellow crystals (238 mg, 52%): mp 130 – 132 ^oC; HPLC purity (as area %) > 96; IR (cm^{-1}) 3396, 3080, 3005, 2929, 2848, 1674, 1602, 1508, 1468; ^1H NMR, (300 MHz, $CDCl_3$) δ 0.01-0.04 (m, 2H, CH_2), 0.29-0.34 (m, 2H, CH_2), 2.01 (s, 1H, OH), 2.55 (d, 1H, *J* = 9.4 Hz, OCH), 2.69 (d, 1H, *J* = 9.4 Hz, OCH'), 3.28 (d, 1H, *J* = 11.3 Hz, C*H*OH) 3.4 (d, 1H, *J* = 11.3 Hz, C*H*'OH) 4.10 (d, 1H, *J* = 14.8 Hz, N-CH), 4.39 (d, 1H, *J* = 14.8 Hz, N-CH'), 6.70 (ap. t, 2H, J = 9 Hz, Ar-H), 6.98-7.10 (m, 7H, Ar-H), 7.31-7.40 (m, 2H, Ar-H), 7.78-7.80 (m, 1H, C(O)=C=CH); ^{13}C NMR, ($CDCl_3$, 75 MHz) δ 8.8, 21.1, 42.7, 67.8, 95.1, 115.1, 123.3, 124.0, 128.3, 128.9, 130.3, 131.2, 131.3, 133.2, 133.7, 134.9, 137.8, 145.8, 164.1, 168.5; HRMS ($C_{26}H_{23}ClFNO_3$+H) calcd 452.1423, obsd 452.1419.

2-(4-Chlorobenzyl)-3-(4-chlorophenyl)-3-((1-(hydroxymethyl)cyclopropyl)methoxy)isoindolin-1-one (80)

General Procedure B: **16** (200 mg, 0.5 mmol), thionyl chloride (78 µL, 1 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.1 mL, 1.0 mmol), K_2CO_3 (105 mg, 1 mmol). Chromatography (Biotage SP4, silica; 20-40% EtOAc, petrol) gave **80** as white crystals (192 mg, 79%). mp 118–119 ^oC HPLC purity (as area %) > 99; IR (cm^{-1}) 3489, 2927, 2882, 1609, 1487, 1425; ^1H NMR, (300 MHz, $CDCl_3$) δ 0.05-0.12 (m, 2H, CH_2), 0.34-0.39 (m, 2H, CH_2), 1.97 (s, 1H, OH), 2.64 (d, 1H, *J* = 9.6 Hz, OCH), 2.77 (d, 1H, *J* = 9.6 Hz, OCH'), 3.35 (d, 1H, *J* = 11.3 Hz, C*H*OH), 3.48 (d, 1H, *J* = 11.3 Hz, C*H*'OH) 4.20 (d, 1H, *J* = 14.9 Hz,

N-CH), 4.48 (d, 1H, *J* = 14.9 Hz, N-CH'), 7.07-7.09 (m, 4H, Ar-H), 7.10-7.14 (m, 5H, Ar-H), 7.44-7.47 (m, 2H, Ar-H), 7.83-7.86 (m, 1H, C(O)C=CH); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 8.8, 22.6, 42.8, 60.6, 67.7, 95.1, 123.3, 124.0, 128.3, 128.6, 128.9, 130.3, 130.9, 132.0, 133.2, 133.6, 134.9, 136.3, 137.7, 145.7, 168.5; HRMS ($C_{26}H_{23}Cl_2NO_3$+H) calcd 468.1128, obsd 468.1128.

2-(4-Bromobenzyl)-3-(4-chlorophenyl)-3-((1-(hydroxymethyl)cyclopropyl)methoxy)isoindolin-1-one (81)

General Procedure B: **14** (433 mg, 1.0 mmol), thionyl chloride (156 µL, 2 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.2 mL, 2.0 mmol), K_2CO_3 (210 mg, 2 mmol). Chromatography (Biotage SP4, silica; 20-40% EtOAc, petrol) gave **81** as white crystals (333 mg, 64%) mp 161–162 ^{o}C; HPLC purity (as area %)> 99; IR (cm^{-1}) 3499, 2944, 2884, 2586, 1692, 1612, 1471, 1420; ^{1}H NMR, (300 MHz, DMSO-d_6) δ -0.09-0.05 (m, 2H, CH_2), 0.19-0.28 (m, 2H, CH_2), 2.55 (d, 1H, *J* = 9.0 Hz, OCH), 2.74 (d, 1H, *J* = 9.0 Hz, OCH'), 3.08-3.22 (m, 1H, C*H*OH), 3.32-3.42 (m, 1H, C*H'*OH) 4.18 (d, 1H, *J* = 15.4 Hz, N-CH), 4.33 (d, 1H, *J* = 15.4 Hz, N-CH'), 4.40 (s, 1H, OH), 6.94-7.03 (m, 1H, Ar-H), 7.11-7.20 (m, 3H, Ar-H), 7.22-7.33 (m, 4H, Ar-H), 7.50-7.61 (m, 2H, Ar-H), 7.76-7.83 (m, 1H, C(O)C=CH); ^{13}C NMR (75 MHz, DMSO-d_6), δ 7.9, 22.2, 41.0, 67.0, 73.0, 94.2, 120.4, 123.4, 123.6, 123.8, 128.5, 128.7, 131.0, 131.1, 131.4, 131.8, 133.5, 137.1, 138.1, 143.5, 167.6; HRMS ($C_{26}H_{23}BrClNO_3$+H) calcd 512.0623 , obsd 512.0627; CHN.

3-(4-Chlorophenyl)-3-(1-hydroxymethylcyclopropylmethoxy)-2-(4-iodobenzyl)-2,3-dihydroisoindol-1-one (82)

General Procedure B: **15** (499 mg, 1.0 mmol), thionyl chloride (156 µL, 2.0 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.2 mL, 2.0 mmol), K_2CO_3 (210 mg, 2.0 mmol). Chromatography (silica; 10-40% EtOAc, petrol) gave **82** as white crystals (487 mg, 83%), mp 164 – 165 ^{o}C HPLC purity (as area %) > 98; IR (cm^{-1}) 3508, 3063, 3005, 2943, 2880, 2817, 1769, 1684, 1611, 1471, 1418 cm^{-1}; ^{1}H NMR (500MHz, $CDCl_3$) δ 0.10-0.16 (m, 2H, CH_2), 0.38-0.43 (m, 2H, CH_2), 1.57-1.61 (s, 1H, OH), 2.66 (d, 1H, *J* = 9 Hz, OCH), 2.79 (d, 1H, *J* = 9 Hz, OCH'), 3.36 (dd, 1H, *J* = 11.4, 4.2 Hz, C*H*OH), 3.47 (dd, 1H, *J* = 11.4, 4.2 Hz, C*H'*OH), 4.14 (d, 1H, *J* = 14.9 Hz, 1H, N-CH), 4.5 (d, 1H, *J* = 14.9 Hz, 1H, N-CH'), 6.94 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.11-7.14 (m, 1H, Ar-H), 7.16-7.21 (m, 4H, Ar-H), 7.48-7.53 (m, 4H, Ar-H), 7.88-7.91 (m, 1H, C(O)=C=CH); ^{13}C NMR (75 MHz, $CDCl_3$), δ 8.9, 22.6, 42.9, 67.8, 67.9, 94.7, 95.1, 123.3, 124.0, 128.3, 128.9, 130.3, 131.5, 133.2, 135.0, 137.5, 137.5, 137.6, 144.9, 145.6, 168.4; HRMS ($C_{26}H_{23}ClINO_3$+H) calcd 560.0484, obsd 560.0472.

3-(4-Chlorophenyl)-3-(1-hydroxy-2-cyclopropyl-3-methoxy)-2-(4-methylbenzyl)isoindolin-1-one (83)

General Procedure B: **16** (300 mg, 0.83 mmol), thionyl chloride (2 eq.) and 1,1-bis(hydroxymethyl)cyclopropane (0.16 mL, 1.67 mmol), K_2CO_3 (2 eq.). Chromatography (Biotage SP4, silica; 10-80% EtOAc, *n*-hexane) gave **83** as a glassy solid (187 mg, 54%), mp 98-99 ºC. HPLC purity (as area %) > 98; IR (cm^{-1}) 3414, 3077, 2921, 2853, 1686, 1605, 1518, 1466; ^{1}H NMR, (500 MHz, $CDCl_3$) δ -0.02-0.03 (m, 2H, CH_2), 0.27-0.30 (m, 2H, CH_2), 1.54 (br s, 1H, OH), 2.21 (s, 3H, CH_3), 2.55 (d, 1H, *J* = 9.5, OCH), 2.64 (d, 1H, *J* = 9.5, OCH'), 3.25 (d, 1H, *J* = 11.3, C<u>H</u>OH), 3.31 (d, 1H, *J* = 11.3, C<u>H</u>'OH), 3.95 (d, 1H, *J* = 14.8, N-CH), 4.60 (d, 1H, *J* = 14.8, 2-CH'), 7.82-7.84 (m, 1H, Ar-H), 6.93 (d, 2H, *J* = 7.8, Ar-*H*), 7.04-7.07 (m, 3H, Ar-*H*), 7.15 (s, 4H, Ar-*H*), 7.41-7.45 (m, 2H, Ar-H); ^{13}C NMR, (125 MHz, $CDCl_3$) δ 8.6, 21.0, 22.1, 29.7, 42.9, 67.7, 68.0, 95.0, 122.8, 123.7, 127.9, 128.7, 128.9, 129.2, 129.9, 131.7, 132.8, 134.4, 134.5, 137.1, 137.3, 145.3,168.2; HRMS ($C_{27}H_{27}NO_3Cl$+H) calcd 448.1674, obsd 448.1673 .

3-(4-Chlorophenyl)-3-(1-hydroxymethylcyclopropylmethoxy)-2-(4-methoxybenzyl)isoindolin-1-one (84)

General Procedure B: **47** (300 mg, 0.79 mmol), thionyl chloride (2 eq.) and 1,1-bis(hydroxymethyl)cyclopropane (0.12 mL, 1.58 mmol), K_2CO_3 (2 eq.). Chromatography (Biotage SP4, silica; 10-80% EtOAc, *n*-hexane) gave **84** as a glassy solid (181mg, 53%). mp 114-115 ºC; IR (cm^{-1}) 2988, 2900, 1684, 1511; ^{1}H NMR, (500 MHz, $CDCl_3$) δ -0.02-0.02 (m, 2H, CH_2), 0.23-0.28 (m, 2H, CH_2), 1.53

(br s, 1H, OH), 2.53 (d, 1H, *J* = 9.4, OCH), 2.62 (d, 1H, *J* = 9.4, COCH'), 3.22 (d, 1H, *J* = 11.3, C*H*OH), 3.32 (d, 1H, *J* = 11.3, C*H*'OH), 3.62 (s, 3H, CH_3), 3.97 (d, 1H, *J* = 14.8, N-CH), 4.45 (d, 1H, *J* = 14.8, N-CH'), 6.57-6.60 (m, 2H, Ar-H), 6.99-7.02 (m, 3H, Ar-*H*), 7.08 (m, 4H, Ar-H), 7.35-7.39 (m, 2H, Ar-H), 7.75-7.86 (m, 1H, C(O)=C=CH); ^{13}C NMR, (125 MHz, $CDCl_3$) δ 8.6. 8.7, 22.1, 42.5, 55.3, 67.7, 68.0, 94.9, 113.6, 122.7, 123.6, 127.9, 128.6, 129.8, 129.9, 130.5, 131.7, 132.8, 134.4, 137.2, 145.3, 158.9, 168.1, HRMS ($C_{27}H_{27}NO_3Cl$+H) calcd 464.1623, obsd 464.1619.

3-(4-Chlorophenyl)-3-(1-hydroxymethylcyclopropylmethoxy)-2-naphthalen-1-ylmethyl-2,3-dihydroisoindol-1-one (85)

General Procedure B: **26** (270 mg, 0.69 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.13 mL, 1.38 mmol). Chromatography (Biotage SP4, silica; 6-25% EtOAc, petrol) gave **85** as cream crystals (153 mg, 47%) mp 82 – 84 ^{o}C, HPLC purity (as area %): > 95. λ max (EtOH) = 223 nm; IR: 3395, 3051, 3004, 2923, 2874, 1685, 1598, 1487 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.35-0.15 (m, 2H, cyclopropane CH), 0.12-0.25 (m, 2H, cyclopropane CH), 1.80 (br s, 1H, OH), 2.38-2.70 (dd AB, J = 9.4 Hz, 2H, CH_2O-C), 3.18-3.31 (dd AB, J = 11.1 Hz, 2H, CH_2OH), 4.63-5.27 (dd AB, J = 14.9 Hz, 2H, N-CH_2), 7.02-7.07 (m, 5H, C_6H_4Cl and ArH)), 7.15-7.30 (m, 2H, ArH), 7.43-7.48 (m, 4H, ArH), 7.68-7.71 (m, 1H, napthylH), 7.76-7.79 (m, 1H, -CH-C(C=O)), 7.93-7.97 (m, 1H, napthylH), 8.29-8.32 (m, 1H, napthylH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 8.58, 8.61, 22.36, 41.25, 67.68, 67.78, 95.41, 123.17, 124.09, 124.54, 125.35, 126.02, 126.70, 128.05, 128.50, 128.68, 128.85, 129.09, 130.15, 131.92, 132.40, 132.91, 133.19, 134.03, 134.49, 137.55, 146.16, 168.32. HRMS (ESI) calculated mass of ion 484.1674 [M+H]$^{+}$, measured mass of ion 484.1673 [M+H]$^{+}$.

2-(3-Bromobenzyl)-3-(4-chlorophenyl)-3-(1-hydroxymethylcyclopropylmethoxy)-2,3-dihydroisoindol-1-one (86)

General Procedure B: **27** (292 mg, 0.68 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.13 mL, 1.35 mmol). Chromatography (Biotage SP4, silica; 6-50% EtOAc, petrol) gave **86** as a pale yellow oil (253 mg, 73%), HPLC purity (as area %): > 98. λmax (EtOH) = 203 nm; IR: 3429, 3065, 3001, 2920, 2874, 1686, 1595, 1571, 1467 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.05-0.05 (m, 2H, cyclopropane CH), 0.22-0.31 (m, 2H, cyclopropane CH), 2.33 (br s, 1H, OH), 2.54 (d, J = 9.3 Hz, 1H, CH_2O-C), 2.73 (d, J = 9.3 Hz, 1H, CH_2O-C), 3.26 (d, J = 11.0 Hz, 1H, C*H*$_2$OH), 3.32 (d, J = 11.0 Hz, 1H, C*H*$_2$OH), 4.10-4.31 (dd AB, J = 14.9 Hz, 2H, N-CH_2), 6.81-6.87 (m, 1H, C_6H_4Br), 6.95-7.05 (m, 7H, ArH), 7.09-7.11 (m, 1H, ArH), 7.33-7.35 (m, 2H, ArH), 7.71-7.74 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 8.8, 8.8, 22.6, 42.8, 67.5, 67.6, 95.0, 122.5, 123.4, 124.0, 128.2, 128.3, 128.9, 130.0, 130.3, 130.6, 132.0, 132.6, 133.3, 135.0, 137.6, 140.0, 145.7, 168.4; HRMS (ESI) calculated mass of ion 512.0623 [M+H]$^{+}$, measured mass of ion 512.0620 [M+H]$^{+}$.

3-(4-Chlorophenyl)-3-{[1-(hydroxymethyl)cyclopropyl]methoxy}-2-[4-(trifluoromethyl)benzyl]isoindolin-1-one (87)

General Procedure B: **32** (422 mg, 1.0 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.19 mL, 2.0 mmol). Chromatography (Biotage SP4; 20-40% EtOAc,petrol) gave **87** as yellow crystals (396 mg, 78%), mp 80 – 81°C, HPLC purity (as area %) > 97. λ max (EtOH) = 254 nm; IR: 3412, 2925, 2877, 1687, 1616, 1468 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.06-0.03 (m, 2H, cyclopropane CH_2), 0.24-0.27 (m, 2H, cyclopropane CH_2), 1.96 (br s, 1H, OH), 2.55-2.72 (m, 2H, C-O-CH_2-), 3.25-3.39 (m, 2H, CH_2OH)), 4.23 (d, J = 14.9 Hz, 1H, N-CH_2-), 4.43 (d, J = 14.9 Hz, 1H, N-CH_2-), 6.98-7.04 (m, 5H, Ar-H), 7.12-7.15 (m, 2H, Ar-H), 7.24-7.27 (m, 2H, Ar-H), 7.34-7.39 (m, 2H, Ar-H), 7.75-7.78 (m, 1H, C(O)-C=CH-); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 8.7, 8.8, 21.1, 42.9, 67.7, 95.0, 122.6, 123.4, 124.1, 125.3, 125.4, 126.2, 128.3, 128.9, 129.8, 129.9, 129.9, 130.2, 130.2, 130.2, 130.3, 130.4, 131.9, 131.9, 132.0, 133.3, 135.0, 137.5, 137.6, 141.9, 145.5, 145.6, 168.5; HRMS (ESI) calculated mass of ion 502.1391 [M+H]$^{+}$, measured mass of ion 502.1400 [M+H]$^{+}$; CHN.

3-(4-Chlorophenyl)-3-((1-(hydroxymethyl)cyclopropyl)methoxy)-2-(4-(methylthio)benzyl)isoindolin-1-one (88)

General Procedure B: **28** (400 mg, 1.0 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.19 mL, 2.0 mmol). Chromatography (silica; 20-40% EtOAc, petrol) gave **88** as a pale yellow oil (100 mg, 21%) HPLC purity (as area %) > 95. λmax (EtOH) = 259 nm; IR: 3408, 2920, 2871, 1686, 1599, 1489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.01-0.01 (m, 2H, cyclopropane CH_2), 0.25-0.29 (m, 2H, cyclopropane CH_2), 1.92 (s, 3H, -S-CH_3), 2.31 (br s, 1H, OH), 2.52 (d, J = 9.5 Hz, 1H, C-O-CH_2-), 2.67 (d, J = 9.5 Hz, 1H, C-O-CH_2-), 3.21 (d, J = 11.3 Hz, 1H, CH_2OH), 3.36 (d, J = 11.3 Hz, 1H, CH_2OH), 3.99 (d, J = 14.8 Hz, 1H, N-CH_2), 4.47 (d, J = 14.8 Hz, 1H, N-CH_2), 6.84-7.02 (m, 6H, Ar-H), 7.05-7.10 (m, 3H, Ar-H), 7.35-7.40 (m, 2H, Ar-H), 7.76-7.79 (m, 1H, C(O)-C=CH-); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 8.9, 9.0, 16.6, 22.6, 43.0, 67.9, 68.1, 94.9, 123.3, 124.0, 127.3, 128.3, 128.8, 128.9, 129.9, 130.1, 130.3, 132.1, 133.1, 134.8, 137.8, 145.8, 168.4; HRMS (ESI) calculated mass of ion 480.1395 $[M+H]^+$, measured mass of ion 480.1395 $[M+H]^+$.

3-(4-Chlorophenyl)-3-(1-hydroxymethylcyclopropylmethoxy)-2-(4-carboxamidebenzyl)isoindolin-1-one (92)

To a solution of **44** (200mg, 0.436mmol) in *t*-BuOH (8.48mL) at 50°C was added finely powdered KOH (647mg) and the resulting suspension was stirred 3 h at 50°C. The hot reaction mixture was filtered through Celite® and the pad rinsed with THF (3 x 5mL). The filtrate was partitioned between EtOAc (10 mL) and H_2O (10 mL) the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Chromatography (silica; 2-10% MeOH, DCM) gave **92** as a glassy solid (62 mg, 30%). δ_H (500 MHz, $CDCl_3$) 7.77-7.80 (1H, m, 7-*H*), 7.51 (2H, d, *J* = 8.2, Ar-*H*), 7.38-7.42 (2H, m, 5 & 6-*H*), 7.13-7.15 (2H, m, Ar-*H*), 7.06 (4H, m, Ar-*H*), 7.00-7.02 (1H, m, 4-*H*), 6.11, (1H, br s, N-H), 5.71 (1H, br s, N-*H*'), 4.48 (1H, d, *J* = 15.0, 2-C*H*), 4.16 (1H, d, *J* = 15.0, 2-C*H*'), 3.31 (1H, d, *J* = 10, 1'-*H*), 3.25 (1H, d, *J* = 10, 1'-*H'*), 2.62 (2H, s, 3'-H_2), 1.66 (1H, br s, 1'-O*H*) 0.24-0.34 (2H, m, H_2), -0.01-0.04 (2H, m, H_2).

δ_C (125 MHz, $CDCl_3$) 169.2, 168.3, 145.1, 141.5, 137.0, 134.6, 133.1, 132.3, 131.4, 130.1, 129.3, 128.7, 127.9, 127.3, 123.8, 123.0, 94.8, 67.6, 67.4, 50.8, 42.7, 22.2, 8.6. HRMS Found; 499.1395 [M+Na]; $C_{27}H_{25}N_2O_4ClNa$, requires 499.1395.

2-(4-Acetylbenzyl)-3-(4-chlorophenyl)-3-(1-hydroxymethylcyclopropylmethoxy)-2,3-dihydroisoindol-1-one (93)

General Procedure B: **35** (270 mg, 0.69 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.13 mL, 1.4 mmol). Chromatography (silica; 20-70% EtOAc, petrol) gave **93** as a yellow oil (108 mg, 33%), HPLC purity (as area %): > 97. λmax (EtOH) = 251 nm; IR: 3402, 3368, 3001, 2922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.05-0.03 (m, 2H, cyclopropane CH_2), 0.20-0.31 (m, 2H, cyclopropane CH_2), 1.76 (br s, 1H, OH), 2.42 (s, 3H, CH_3) 2.58 (d, J = 9.4 Hz, 1H, O-CH_2), 2.70 (d, J = 9.4 Hz, 1H, O-CH_2), 3.23 (d, J = 11.3 Hz, 1H, CH_2OH), 3.37 (d, J = 11.3 Hz, 1H, CH_2OH) 4.20 (d, J = 15.0 Hz, 1H, N-CH_2), 4.44 (d, J = 15.0 Hz, 1H, N-CH_2), 6.95-7.10 (m, 5H, -ArH), 7.11-7.16 (m, 2H, ArH), 7.38-7.41 (m, 2H, ArH), 7.59-7.64 (m, 2H, ArH), 7.76-7.80 (m, 1H, -CH-C(C=O)); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 8.8, 21.1, 26.6, 43.1, 67.9, 69.4, 95.1, 123.4, 124.1, 128.3, 128.5, 128.9, 129.6, 130.4, 132.0, 133.3, 135.0, 136.8, 137.6, 143.0, 145.7, 168.5, 197.6; HRMS (ESI) calculated mass of ion 476.1623 $[M+H]^+$, measured mass of ion 476.618 $[M+H]^+$.

2-(4-Benzoylbenzyl)-3-(4-chlorophenyl)-3-(1-hydroxymethylcyclopropylmethoxy)-2,3-dihydroisoindol-1-one (94)

General Procedure B: **36** (142 mg, 0.31 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.06 mL, 0.63 mmol). Chromatography (silica; 10-50% EtOAc, petrol) gave **94** as yellow crystals (124 mg, 74%), mp 69 – 71 °C, HPLC purity (as area %): > 94. λ max (EtOH) = 261 nm; IR: 3411, 3063, 2921, 2877, 1690, 1656, 1605, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ -0.08-0.03 (m, 2H, cyclopropane CH_2), 0.25-0.30 (m, 2H, cyclopropane CH_2), 1.94 (br s, 1H, OH), 2.60 (d, J = 9.4 Hz, 1H, O-CH_2), 2.69 (d, J = 9.4 Hz, 1H, O-CH_2),

3.23 (d, J = 11.3 Hz, 2H, C*H*$_2$OH), 3.37 (d, J = 11.3 Hz, 2H, C*H*$_2$OH), 4.22 (d, J = 15.0 Hz, 1H, N-CH$_2$), 4.42 (d, J = 15.0 Hz, 1H, N-CH$_2$), 6.96-7.05 (m, 5H, -C$_6$*H*$_4$CCl and PyH), 7.09-7.12 (d AB, J = 8.1 Hz, 2H, ArH), 7.25-7.42 (m, 7H, ArH), 7.53-7.56 (d AB, J = 8.1 Hz, 2H, ArH), 7.73-7.76 (m, 1H, -CH-C(C=O)); ^{13}C NMR (CDCl$_3$, 75 MHz), δ 8.9, 22.7, 43.1, 67.7, 69.3, 95.1, 123.4, 124.1, 128.4, 128.6, 128.9, 129.1, 129.3, 130.2, 130.4, 132.0, 132.6, 133.3, 135.0, 137.1, 137.7, 138.2, 142.3, 145.7, 168.5, 196.3; HRMS (ESI) calculated mass of ion 560.1599 [M+Na]$^+$, measured mass of ion 560.1601 [M+Na]$^+$.

3-(4-Chlorophenyl)-3-{[1-(hydroxymethyl)cyclopropyl]methoxy}-2-(pyridin-4-ylmethyl)isoindolin-1-one (95)

General Procedure B: **37** (354 mg, 1.0 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.19 mL, 2.0 mmol). Chromatography (silica; EtOAc) gave **95** as pink crystals (278 mg, 63%) mp 72 – 73°C,
HPLC purity (as area %) > 93. λ max (EtOH) = 257 nm; IR: 3382, 2921, 2853, 1699, 1602, 1467 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.07-0.21 (m, 2H, cyclopropane CH$_2$), 0.35-0.46 (m, 2H, cyclopropane CH$_2$), 2.64 (br s, 1H, OH), 2.75-2.83 (m, 2H, C-O-CH$_2$-), 3.38 (d, J = 11.3 Hz, 1H, CH$_2$OH), 3.50 (d, J = 11.3 Hz, 1H, CH$_2$OH), 4.27 (d, J = 15.3 Hz, 1H, N-CH$_2$), 4.46 (d, J = 15.3 Hz, 1H, N-CH$_2$), 7.06-7.07 (m, 2H, Ar-H), 7.12-7.18 (m, 5H, Ar-H), 7.49-7.52 (m, 2H, Ar-H), 7.87-7.90 (m, 1H, C(O)-C=CH-), 8.30-8.40 (m, 2H, PyH); ^{13}C NMR (CDCl$_3$, 75 MHz), δ 8.9, 8.9, 22.6, 42.4, 67.9, 95.0, 123.5, 124.2, 127.1, 128.3, 129.0, 130.5, 131.9, 133.4, 135.3, 139.4, 145.6, 146.9, 150, 165.2; HRMS (ESI) calculated mass of ion 435.1470 [M+H]$^+$, measured mass of ion 435.1469 [M+H]$^+$; CHN.

3-(4-Chlorophenyl)-3-((1-(hydroxymethyl)cyclopropyl)methoxy)-2-(pyridin-3-ylmethyl)isoindolin-1-one (96)

General Procedure B: **38** (354 mg, 1.01 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.19 mL, 2.03 mmol). Chromatography (Biotage SP4, silica; 50-100% EtOAc, petrol) gave **96** as a pale yellow oil (321 mg, 73%) mp 58 – 60°C, HPLC purity (as area %): > 93. λ max (EtOH) = 259 nm; IR: 3391, 2921, 2853, 1695, 1650, 1596, 1466 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.02-0.10 (m, 2H, cyclopropane CH$_2$), 0.28-0.38 (m, 2H, cyclopropane CH$_2$), 2.67-2.75 (m, 2H, C-O-CH$_2$), 3.32 (s, 1H, OH), 3.37-3.47 (m, 2H, CH$_2$OH), 4.37-4.42 (m, 2H, N-CH$_2$), 6.96-7.00 (dd, J = 4.9, 7.8 Hz, 1H, Ar-H), 7.03-7.12 (m, 5H,Ar-H), 7.39-7.42 (m, 2H, Ar-H), 7.44-7.48 (m, 1H, Ar-H), 7.78-7.81 (dd, J = 1.6, 6.9 Hz, 1H, -C(O)-C=CH-), 8.23-8.26 (m, 2H, PyH); ^{13}C NMR (CDCl$_3$, 75 MHz), δ 8.7, 8.8, 22.6, 40.8, 67.1, 67.4, 94.9, 123.3, 123.4, 124.0, 128.3, 128.9, 130.3, 131.8, 133.3, 133.4, 134.9, 137.1, 137.6, 145.6, 148.7, 150.5, 168.5; HRMS (ESI) calculated mass of ion 435.1470 [M+H]$^+$, measured mass of ion 435.1476 [M+H]$^+$.

2-(4-(4H-1,2,4-triazol-4-yl)benzyl)-3-(4-chlorophenyl)-3-((1'-hydrox-2-cyclopropyl-3-methoxy)isoindolin-1-one (101).

General Procedure B: **43** (150 mg, 0.36 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.09 mL, 0.9 mmol). Chromatography (silica; 10% MeOH, DCM) gave **101** as a glassy solid (86mg, 47%). δ_H (500 MHz, CDCl$_3$) 8.17 (1H, s, Ar-*H*), 7.69-7.72 (1H, m, 7-*H*), 7.31-7.35 (1H, m, 5-*H* & 6-*H*), 7.08-7.10 (2H, m, Ar-*H*), 6.92-6.97 (7H, m, Ar-*H*), 4.32 (1H, d, *J* = 15.0, 2-C*H*), 4.25 (1H, d, *J* = 15.0, 2-C*H*'), 3.29 (2H, m, 1'-*H*$_2$), 2.67 (1H, d, *J* = 9.4, 3'-*H*), 2.58 (1H, d, *J* = 9.4, 3'-*H*'), 1.62 (1H, m, 1'-O*H*), 0.23-0.28 (2H, m, *H*$_2$), -0.02-0.046 (2H, m, *H*$_2$); δ_C (125 MHz, CDCl$_3$) 168.2, 145.01, 141.5, 138.8, 137.1, 134.5, 133.2, 132.8, 131.4, 131.0, 130.7, 130.2, 128.5, 128.0, 123.8, 123.0, 122.0, 94.4, 67.6, 67.4, 42.2, 22.3, 8.7.
LRMS (ESI+) m/z = 501.2 [M+H]$^+$.

3-(4-Chlorophenyl)-3-(1-((hydromethyl)cyclopropyl)methoxy)-2-(((trifluoromethyl) sulfonyl)benzyl)isoindolin-1-one (102)

To a solution of **46** (209 mg, 0.43 mmol) in DCM (3 mL) was added BF$_3$.OEt$_2$ (134 µL, 1.09 mmol) at 0 ^{o}C the solution stirred at 0 ^{o}C for 15 min. A solution of 1,1-bis(hydroxymethyl)cyclopropane (0.27 mL, 4.34 mmol) in DCM (0.5 mL) was added dropwise and the resulting solution was stirred for 1.5 h at 0 ^{o}C and 1 h at rt. The solution was then diluted with sat. aqueous NH$_4$Cl solution (10 mL) and the extracted with DCM

(3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Chromatography (Biotage SP4, silica; 15-100 % EtOAc, petrol) gave **102** as a colourless oil (151 mg, 62 %). HPLC purity (as area %) > 98%. λ_{max} (EtOH) 203.0 nm; IR 3408, 2159, 1698, 1597, 1364, 1216, 1191 cm^{-1}; ^1H NMR (500 MHz d_3-MeCN) δ 0.15-0.18 (1H, m, cyclopropyl), 0.20-0.23 (1H, cyclopropyl), 0.36-0.38 (2H, m, cyclopropyl), 2.56 (1H, t, *J* = 5.7 Hz, OH), 2.82 (1H, d, *J* = 9.3 Hz, O*CH*$_2$-cyclopropyl), 2.87 (1H, d, *J* = 9.3 Hz, O*CH*$_2$-cyclopropyl), 3.41 (1H, dd, *J* = 6.2 and 11.2 Hz, cyclopropyl-*CH*$_2$-OH), 3.47 (1H, dd, *J* = 6.2 Hz and 11.2 Hz, cyclopropyl-*CH*$_2$-OH), 4.43 (1H, d, *J* = 15.8 Hz, NCH_2), 4.72 ((1H, d, *J* = 15.8 Hz, NCH_2), 7.10 (2H, d, *J* = 8.9 Hz, Ar-H), 7.18-7.20 (3H, m, Ar-H), 7.46 (2H, d, *J* = 8.6 Hz, Ar-H), 7.59-7.61 (2H, m, Ar-H), 7.79 (2H, d, *J* = 8.4 Hz, Ar-H), 7.86-7.88 (1H, m, *CH*CCO); ^{13}C NMR (125 MHz d_3-MeCN) δ 7.3 , 21.6, 41.4 (NCH_2), 64.9, 65.7, 93.5, 122.9, 123.0, 127.8, 128.0, 128.5, 129.9, 130.1, 133.5, 137.3, 144.8, 148.0, 167.5; ^{19}F NMR (470 MHz d_3-MeCN) δ -79.8; HRMS (ESI+) $C_{27}H_{23}ClF_3NO_5S.NH_4$ Calculated: 583.1261 Found: 583.1276 $[M+NH_4]^+$

General Procedure C – *pyridine N-oxides*

To a solution of the corresponding isoindolinone (1 equiv.) in anhydrous DCM (5 mL) was added mCPBA (1.1 equiv.). The reaction mixture was stirred at 30°C for 4 h and then diluted with DCM (30 mL), washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford an oil which was purified by flash chromatography (Biotage SP4).

4-((1-(4-Chlorophenyl)-1-hydroxy-3-oxoisoindolin-2-yl)methyl)pyridine-1-oxide (40)

General Procedure C: **37** (200 mg, 0.57 mmol). Chromatography (Biotage SP4; silica; 0-10% MeOH, EtOAc) gave **40** as cream crystals (159 mg, 76%). mp 140-141°C. UV (in EtOH): λ max = 269 nm; IR: 3059, 2784, 1693, 1483 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (d, J = 15.7 Hz, 1H, N-CH_2-), 4.62 (d, J = 15.7 Hz, 1H, N-CH_2-), 7.10-7.12 (d, J = 6.8 Hz, 2H, Ar-H), 7.19-7.30 (m, 5H, Ar-H), 7.39-7.47 (m, 4H, Ar-H), 7.67-7.70 (m, 1H, -C(O)-C=CH-), 7.88 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 41.7, 91.7, 123.2, 123.6, 126.8, 128.1, 129.2, 129.7, 130.2, 133.4, 134.9, 138.3, 138.4, 139.7, 149.7, 168.2; HRMS (ESI) $C_{20}H_{15}ClN_2O_3$ calculated $[M+H]^+$ 367.0844, measured 367.0849 $[M+H]^+$; HPLC purity (as area %): > 98; CHN:

3-((1-(4-Chlorophenyl)-1-hydroxy-3-oxoisoindolin-2-yl)methyl)pyridine 1-oxide (41)

General Procedure C: **38** (200 mg, 0.57 mmol). Chromatography (Biotage SP4; silica; 0-15% MeOH, EtOAc) gave **41** as a white solid (200 mg, 96%). mp 136-137°C. HPLC purity (as area %): > 97. UV (in EtOH): λ max = 265 nm; IR: 3037, 2923, 2770, 1689, 1603, 1487 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 1H, OH), 4.03 and 4.59 (d, J = 15.6 Hz, 2H, N-CH_2), 6.98-7.02 (m, 1H, PyH), 7.20-7.23 (dd, J = 1.6, 8.1 Hz, 1H, PyH), 7.26-7.39 (m, 5H, Ar-H), 7.41-7.50 (m, 2H, Ar-H), 7.50-7.56 (m, 1H, CH-C-C(=O)), 7.64-7.67 (d, J = 1.0, 7.4 Hz, 1H, PyH), 8.03-8.04 (m, 1H PyH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 40.3, 91.5, 123.1, 123.5, 125.4, 128.2, 128.4, 129.1, 129.7, 130.2, 130.2, 133.3, 134.9, 137.5, 138.3, 139.7, 149.7, 168.1. HRMS (ESI) $C_{20}H_{15}ClN_2O_3$ calculated $[M+H]^+$ 367.0844, measured 367.0846;

2-((1-(4-Chlorophenyl)-1-hydroxy-3-oxoisoindolin-2-yl)methyl)pyridine-1-oxide (42)

General Procedure C: **39** (200 mg, 0.57 mmol). Chromatography (Biotage SP4; silica; 0-5% MeOH, EtOAc) gave **42** as a white solid (134 mg, 65%). mp 222 – 224 °C. UV (in EtOH): λ max = 261 nm; IR: 3130, 3066, 2925, 2783, 1699, 1609, 1489, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 and 4.84 (d, J = 14.5 Hz, 2H, N-CH_2-), 7.21-7.27 (m, 2H, ArH), 7.29-7.33 (m, 2H, Ar-H), 7.35-7.45 (m, 5H, Ar-H), 7.71-7.74 (dd, J = 1.6, 7.5 Hz, 1H, PyH), 7.87-7.90 (dd, J = 1.9, 7.8 Hz, 1H, -C(O)-C=CH-), 8.22-8.24 (dd, J = 1.2, 6.4 Hz, 1H, PyH), 8.91 (br s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz), δ 38.4, 90.5, 123.2, 123.6, 126.0, 128.3, 129.3, 129.4, 129.8, 133.3, 134.8, 139.4, 139.5, 140.0, 147.9, 149.5, 149.51 168.9 ppm;

HRMS (ESI) $C_{20}H_{15}ClN_2O_3$ calculated $[M+H]^+$ 367.0844, measured 367.0843; HPLC purity (as area %): > 98

4-((1-(4-Chlorophenyl)-1-((1-(hydroxymethyl)cyclopropyl)methoxy)-3-oxoisoindolin-2-yl)methyl)pyridine 1-oxide (98)

General Procedure C: **95** (80 mg, 0.18 mmol). Chromatography (Biotage SP4, silica; 0-20% MeOH, EtOAc) gave **n** as a pale yellow oil (42 mg, 52%) HPLC purity (as area %): > 99. λmax (EtOH) = 271 nm; IR: 696, 725, 762, 808, 847, 918, 951, 1005, 1039, 1065, 1094, 1169, 1201, 1233, 1288, 1317, 1352, 1383, 1401, 1469, 1609, 1696, 2852, 2922, 3292 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.22-0.28 (m, 2H, cyclopropane CH_2), 0.44-0.46 (m, 2H, cyclopropane CH_2), 2.65 and 3.00 (d, J = 9.4 Hz, 2H, C-O-CH_2), 3.43 (s, 1H, OH), 3.40 and 3.54 (d, J = 11.3 Hz, 2H, CH_2OH), 4.34 (s, 2H, N-CH_2-), 7.05-7.07 (d, J = 6.8 Hz, 2H, Ar-H), 7.11-7.14 (m, 1H,Ar-H), 7.19-7.22 (m, 4H, Ar-H), 7.51-7.54 (m, 2H, Ar-H), 7.86-7.89 (m, 1H, -C(O)-C=CH-), 7.95-7.98 (d, J = 6.5 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 22.7, 41.5, 67.5, 67.6, 94.8, 123.5, 124.2, 126.9, 128.3, 129.1, 130.5, 131.7, 133.6, 135.4, 136.9, 137.4, 139.0, 145.4, 168.6; HRMS (ESI) calculated mass of ion 451.1419 $[M+H]^+$, measured mass of ion 451.1426 $[M+H]^+$.

3-((1-(4-Chlorophenyl)-1-((1-(hydroxymethyl)cyclopropyl)methoxy)-3-oxoisoindolin-2-yl)methyl)pyridine 1-oxide (99)

General Procedure C: **96** (80 mg, 0.18 mmol). Chromatography (Biotage SP4, silica; 0-15% MeOH, EtOAc) gave **99** as white crystals (49 mg, 60%) mp 122-124 °C, HPLC purity (as area %): > 98. λmax (EtOH) = 266 nm; IR: 3372, 3078, 2922, 2872, 1698, 1605, 1437 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.22-0.30 (m, 2H, cyclopropane CH_2), 0.42-0.48 (m, 2H, cyclopropane CH_2), 2.58 and 3.14 (dd, J = 9.5 Hz, 2H, CH_2O-), 3.48 (br s, 1H OH), 3.34 and 3.65 (dd, J = 11.4 Hz, 2H, CH_2OH), 4.10 and 4.59 (dd, J = 15.2 Hz, 2H, N-CH_2), 7.12-7.16 (m, 2H, Ar-H), 7.18-7.29 (m, 5H, Ar-H), 7.51-7.58 (m, 2H, Ar-H), 7.89-7.92 (m, 1H, -CH-C-C(=O)), 8.06-8.08 (dd, J= 6.4, 2.0 Hz, 1H, PyH), 8.19 (d, J = 2.0 Hz, 1H, PyH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 8.8, 8.8, 22.8, 40.5, 67.0, 67.3, 95.0, 123.5, 124.3, 125.8, 128.2, 129.2, 130.5, 133.5, 135.3, 135.4, 137.2, 138.4, 140.2, 145.5, 168.4; HRMS (ESI) calculated mass of ion 451.1419 $[M+H]^+$, measured mass of ion 451.1417 $[M+H]^+$.

2-((1-(4-Chlorophenyl)-1-((1-(hydroxymethyl)cyclopropyl)methoxy)-3-oxoisoindolin-2-yl)methyl)pyridine-1-oxide (100)

General Procedure C: **97** (80 mg, 0.18 mmol). Chromatography (Biotage SP4, silica; 0-10% MeOH, EtOAc) gave **100** as pale brown crystals (54 mg, 67%) mp 196-197 °C, HPLC purity (as area %): > 99. λmax (EtOH)= 262 nm; IR: 3284, 3077, 2921, 2884, 1699, 1609, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.27-0.31 (m, 2H, cyclopropane CH_2), 0.43-0.51 (m, 2H, cyclopropane CH_2), 2.57 and 3.29 (dd, J = 9.3 Hz, 2H, CH_2O-), 3.46 (br s, 1H OH), 3.28 and 3.85 (dd, J = 11.4 Hz, 2H, CH_2OH), 4.68-4.86 (dd, J = 16.7 Hz, 2H, N-CH_2), 7.04-7.11 (m, 2H, Ar-H), 7.12-7.17 (m, 2H, Ar-H), 7.23-7.30 (m, 4H, Ar-H), 7.53-7.62 (m, 2H, Ar-H), 7.90-7.92 (m, 1H, -CH-C-C(=O)), 8.09-8.11 (m, 1H, PyH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 9.0, 9.1, 22.8, 37.6, 67.4, 67.8, 94.6, 123.7, 124.0, 124.6, 125.4, 126.8, 128.2, 128.8, 130.5, 132.1, 133.5, 135.0, 137.6, 139.6, 145.6, 147.6, 168.7; HRMS (ESI) calculated mass of ion 451.1419 $[M+H]^+$, measured mass of ion 451.1414 $[M+H]^+$.

General Procedure D

To a solution of the corresponding ester (1 mol. equiv.) in dry THF was added under a nitrogen atmosphere potassium trimethylsilanolate (1.1 mol. equiv.). The reaction mixture was stirred at room temperature overnight and monitored by TLC. Further potassium trimethylsilanolate (1.1 mol. equiv.) was added and the mixture was again stirred at room temperature overnight. On completion the solvent was concentrated in vacuo to afford a solid which was purified by chromatography.

Synthesis of 4-((1-(4-chlorophenyl)-1-(4-hydroxybutoxy)-3-oxoisoindolin-2-yl)methyl)benzoic acid (34)

General Procedure D: **33** (0.35 g, 0.73 mmol) and potassium trimethylsilanolate (206 mg, 1.60 mmol) in dry THF (15 mL). Chromatography (Biotage SP4; 50% EtOAc/petrol then 10% MeOH/EtOAc) gave **34** as an off-white solid (0.31 g, 92%) mp 148 – 149 ^{o}C. UV (in EtOH): λ max = 227 nm; IR: 2922, 2852, 1977, 1685, 1609, 1466 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ 1.14-1.27 (m, 4H, CH_2), 2.64-2.68 (m, 2H, CH_2), 3.19-3.23 (m, 2H, CH_2), 4.05 and 4.64 (d, J = 15.2 , 2H, NCH_2), 7.19-7.28 (m, 5H, Ar-H), 7.34-7.37 (m, 2H, Ar-H), 7.60-7.63 (m, 2H, Ar-H), 7.74-7.77 (m, 2H, Ar-H), 7.84-7.87 (m, 1H, Ar-H); ^{13}C NMR ($DMSO_3$, 75 MHz), δ 25.7, 29.4, 42.6, 60.9, 62.8, 94.7, 123.6, 128.5, 128.6, 128.8, 129.3, 130.5, 131.3, 131.5, 133.4, 133.6, 138.2, 138.7, 141.7, 145.4, 167.6, 168.5. HRMS (ESI) Found m/z = 483.1690; calculated $C_{26}H_{24}ClNO_5.NH_4$ 483.1681.

3-(4-Chlorophenyl)-2-((R)-1-(4-chlorophenyl)ethyl)-3-((1-(hydroxymethyl)cyclopropyl)methoxy)isoindolin-1-one (85)

General Procedure B: **46b** (401 mg, 1.0 mmol), thionyl chloride (156 μL, 2.0 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.2 mL, 2.0 mmol), K_2CO_3 (210 mg, 2.0 mmol). Chromatography (Biotage SP4, silica; 20-40% EtOAc, petrol) gave **85** as a pale yellow oil (146 mg, 30%). HPLC purity (as area %) > 97; IR (cm^{-1}) 3389, 2930, 2876, 1682, 1597, 1489, 1467; ^{1}H NMR, (300 MHz, $CDCl_3$) *δ* 0.36-0.59 (m, 4H, $(CH_2)_2$), 1.88 (d, 3H, *J* = 7.3 Hz, CH_3), 2.30 (br s, 1H, OH), 2.90 (d, 1H, *J* = 9.5 Hz, OCH), 3.28 (d, 1H, *J* = 9.5 Hz, OCH'), 3.58-3.67 (m, 2H, C*H*$_2$OH)), 4.35 (q, 1H, *J* = 7.3 Hz, N-CH), 6.96-7.01 (m, 8H, Ar-H), 7.04-7.07 (m, 1H, Ar-H), 7.43-7.47 (m, 2H, Ar-H), 7.80-7.83 (m, 1H, C(O)C=CH); ^{13}C NMR, (75 MHz, $CDCl_3$) *δ* 9.0, 9.0, 20.4, 22.9, 52.8, 60.6, 67.8, 95.3, 123.3, 123.8, 128.3, 128.4, 128.7, 129.6, 130.3, 133.1, 133.1, 134.8, 137.6, 141.7, 145.0, 168.3; HRMS ($C_{27}H_{25}Cl_2NO_3$+H) calcd 482.1284, obsd 482.1279 .

3-(4-Chlorophenyl)-2-((*S*)-1-(4-chlorophenyl)ethyl)-3-((1-(hydroxymethyl)cyclopropyl)methoxy)isoindolin-1-one (86)

General Procedure B: **46a** (401 mg, 1.0 mmol), thionyl chloride (156 μL, 2.0 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.2 mL, 2.0 mmol), K_2CO_3 (210 mg, 2.0 mmol). Chromatography (Biotage SP4, silica; 10-30% EtOAc, petrol) gave **86** as a pale yellow oil (60 mg, 12%). HPLC purity (as area %) > 98; IR (cm^{-1}) 3415, 2923, 2876, 1695, 1583, 1487; ^{1}H NMR, (300 MHz, $CDCl_3$) *δ* 0.36-0.59 (m, 4H, $(CH_2)_2$), 1.88 (d, 3H, *J* = 7.3 Hz, CH_3), 2.30 (br s, 1H, OH), 2.91 (d, 1H, *J* = 9.5 Hz, OCH), 3.28 (d, 1H, *J* = 9.5 Hz, OCH'), 3.58-3.67 (m, 2H, C*H*$_2$OH)), 4.34 (q, 1H, *J* = 7.2, N-CH), 6.96-7.01 (m, 8H, Ar-H), 7.04-7.07 (m, 1H, Ar-H), 7.43-7.47 (m, 2H, Ar-H), 7.80-7.83 (m, 1H, C(O)C=CH); ^{13}C NMR, ($CDCl_3$, 75 MHz), *δ* 9.0, 9.0, 20.4, 22.9, 52.8, 60.6, 67.8, 95.2, 123.3, 123.8, 128.3, 128.4, 128.7, 129.6, 130.3, 133.09, 133.08, 134.8, 137.6, 141.8, 145.0, 168.3; HRMS ($C_{27}H_{25}Cl_2NO_3$+H) calcd 482.1284, obsd 482.1285.

Synthesis of 4-((1-(4-chlorophenyl)-1-((1-(hydroxymethyl)cyclopropyl)methoxy)-3-oxoisoindolin-2-yl)methyl)benzoic acid (89)

General Procedure E: **90** (0.23 g, 0.47 mmol). Chromatography (Biotage SP4, silica; 0-10% MeOH, EtOAc) gave **89** as a white solid (0.21 g, 92%), mp 170 – 171°C. UV (in EtOH): λ max = 223 nm; IR: 2921, 2871, 2036, 1682, 1609, 1557, 1468 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ -0.03-0.09 (m, 2H, CH_2), 0.28-0.35 (m, 2H, CH_2), 2.63-2.86 (dd, J = 9.0, 60.5 Hz, 2H, OCH_2), 3.22 and 3.50 (d, J = 11.1, 2H, CH_2OH), 4.30 and 4.57 (d, J = 15.6, 2H, NCH_2), 4.50 (s, 1H, OH), 7.21-7.24 (m, 2H, Ar-H), 7.26-7.32 (m, 3H, Ar-H), 7.34-7.37 (m, 2H, Ar-H), 7.63-7.71 (m, 2H, Ar-H), 7.77-7.79 (m, 2H, Ar-H), 7.89-7.91 (m, 1H, Ar-H); ^{13}C NMR (DMSO, 75 MHz), δ 7.9, 22.2, 42.5, 64.4, 66.2, 94.3, 123.4, 123.6, 128.5, 128.5, 128.6, 128.9, 129.1, 129.3, 130.45, 131.5, 133.5, 138.2, 141.7, 145.7, 166.0, 167.7. HRMS (ESI) measured m/z = 495.1688; calculated $C_{27}H_{24}ClNO_5$. NH_4 m/z = 495.1681.

3-(4-Chlorophenyl)-3-((1-(hydroxymethyl)cyclopropyl)methoxy)-2-(pyridin-2-ylmethyl)isoindolin-1-one (99)

General Procedure B: **39** (354 mg, 1.0 mmol), thionyl chloride (156 µL, 2.0 mmol) and 1,1-bis(hydroxymethyl)cyclopropane (0.2 mL, 2.0 mmol), K_2CO_3 (210 mg, 2.0 mmol). Chromatography (Biotage SP4, silica; 50-100% EtOAc, petrol) gave **99** as yellow crystals (383 mg, 87%). mp 123-125 ^oC; HPLC purity (as area %) > 97; IR (cm^{-1}) 3277, 2909, 2854, 1695, 1595, 1469, 1421; ^1H NMR, (300 MHz, $CDCl_3$) δ 0.04-0.17 (m, 2H, CH_2), 0.30-0.37 (m, 2H, CH_2), 2.58 (d, 1H, *J* = 9.3 Hz, OCH), 3.16 (d, 1H, *J* = 9.3 Hz, COCH'), 3.28 (dd, 1H, *J* = 11.1, 5.1 Hz, C*H*OH), 3.51 (dd, 1H, *J* = 11.1, 3 Hz, , C*H*'OH), 4.10 (m, 1H OH), 4.38 (d, 1H, *J* = 15.3 Hz, N-CH), 4.45 (d, 1H, *J* = 15.3 Hz, N-CH'), 6.94-7.02 (m, 3H, Ar-H), 7.04-7.07 (m, 1H, Ar-H), 7.10-7.15 (m, 2H, Ar-H), 7.19-7.22 (m, H, Ar-H), 7.35-7.42 (m, 3H, Ar-H), 7.76-7.79 (m, 1H, C(O)=C=CH), 8.22-8.23 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.8, 8.9, 22.6, 45.6, 67.1, 67.6, 94.8, 122.3, 123.4, 123.9, 124.1, 128.3, 128.7, 130.2, 132.1, 133.1, 134.6, 136.5, 137.9, 145.7, 149.0, 157.1, 168.4; HRMS ($C_{25}H_{23}ClN_2O_3$+H) calcd 435.1470, obsd 435.1471.

3-(4-Chlorophenyl)-3-(1-((hydromethyl)cyclopropyl)methoxy)-2-(((trifluoromethyl) sulfonyl)benzyl)isoindolin-1-one (102)

To a solution of **46** (209 mg, 0.43 mmol) in DCM (3 mL) was added $BF_3.OEt_2$ (134 µL, 1.09 mmol) at 0 ^oC the solution stirred at 0 ^oC for 15 min. A solution of 1,1-bis(hydroxymethyl)cyclopropane (0.27 mL, 4.34 mmol) in DCM (0.5 mL) was added dropwise and the resulting solution was stirred for 1.5 h at 0 ^oC and 1 h at rt. The solution was then diluted with sat. aqueous NH_4Cl solution (10 mL) and the extracted with DCM (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. Chromatography (Biotage SP4, silica; 15-100 % EtOAc, petrol) gave **102** as a colourless oil (151 mg, 62 %). HPLC purity (as area %) > 98%. λ_{max} (EtOH) 203.0 nm; IR 3408, 2159, 1698, 1597, 1364, 1216, 1191 cm^{-1}; ^1H NMR (500 MHz d_3-MeCN) δ 0.15-0.18 (1H, m, cyclopropyl), 0.20-0.23 (1H, cyclopropyl), 0.36-0.38 (2H, m, cyclopropyl), 2.56 (1H, t, *J* = 5.7 Hz, OH), 2.82 (1H, d, *J* = 9.3 Hz, OCH_2-cyclopropyl), 2.87 (1H, d, *J* = 9.3 Hz, OCH_2-cyclopropyl), 3.41 (1H, dd, *J* = 6.2 and 11.2 Hz, cyclopropyl-CH_2-OH), 3.47 (1H, dd, *J* = 6.2 Hz and 11.2 Hz, cyclopropyl-CH_2-OH), 4.43 (1H, d, *J* = 15.8 Hz, NCH_2), 4.72 ((1H, d, *J* = 15.8 Hz, NCH_2), 7.10 (2H, d, *J* = 8.9 Hz, Ar-H), 7.18-7.20 (3H, m, Ar-H), 7.46 (2H, d, *J* = 8.6 Hz, Ar-H), 7.59-7.61 (2H, m, Ar-H), 7.79 (2H, d, *J* = 8.4 Hz, Ar-H), 7.86-7.88 (1H, m, *CH*CCO); ^{13}C NMR (125 MHz d_3-MeCN) δ 7.3 , 21.6, 41.4 (NCH_2), 64.9, 65.7, 93.5, 122.9, 123.0, 127.8, 128.0, 128.5, 129.9, 130.1, 133.5, 137.3, 144.8, 148.0, 167.5; ^{19}F NMR (470 MHz d_3-MeCN) δ -79.8; HRMS (ESI+) $C_{27}H_{23}ClF_3NO_5S.NH_4$ Calculated: 583.1261 Found: 583.1276 $[M+NH_4]^+$

References

1. Naik, A. D.; Marchand-Brynaert, J.; Garcia, Y. A Simplified Approach to N- and N,Nâ€²-Linked 1,2,4-Triazoles by Transamination. *Synthesis* **2008,** 2008, 149-154.

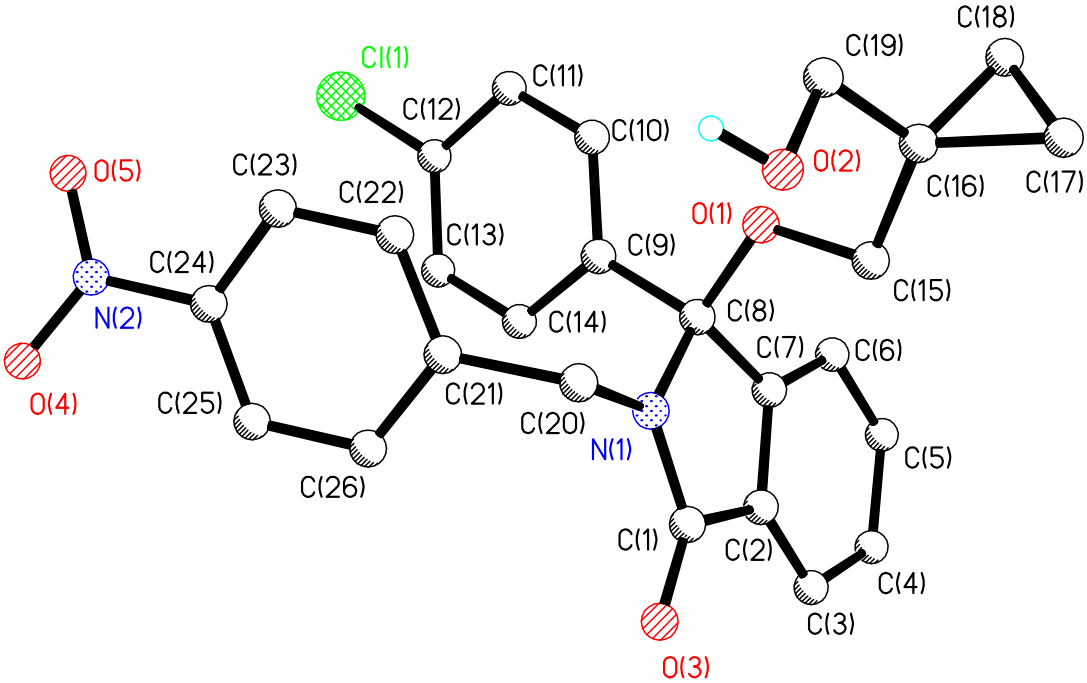

Figure S1: X-ray structure of NU8354B.

Table 1. Crystal data and structure refinement for NU8354B.

Identification code	NU8354B	
Chemical formula (moiety)	$C_{26}H_{23}ClN_2O_5$	
Chemical formula (total)	$C_{26}H_{23}ClN_2O_5$	
Formula weight	478.91	
Temperature	150(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	orthorhombic, $P2_12_12_1$	
Unit cell parameters	a = 8.9393(2) Å	α = 90°
	b = 11.2873(4) Å	β = 90°
	c = 23.1245(7) Å	γ = 90°
Cell volume	2333.27(12) $Å^3$	
Z	4	
Calculated density	1.363 g/cm^3	
Absorption coefficient μ	0.205 mm^{-1}	
F(000)	1000	
Crystal colour and size	colourless, 0.45 × 0.40 × 0.40 mm^3	
Reflections for cell refinement	8039 (θ range 2.9 to 29.6°)	
Data collection method	Oxford Diffraction Gemini A Ultra diffractometer thin-slice ω scans	
θ range for data collection	2.9 to 29.6°	
Index ranges	h −11 to 8, k −15 to 15, l −23 to 31	
Completeness to θ = 26.0°	99.7 %	
Reflections collected	16257	
Independent reflections	5686 (R_{int} = 0.0467)	
Reflections with $F^2>2\sigma$	4371	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.9136 and 0.9227	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0630, 0.0000	
Data / restraints / parameters	5686 / 0 / 312	
Final R indices [$F^2>2\sigma$]	R1 = 0.0525, wR2 = 0.1070	
R indices (all data)	R1 = 0.0717, wR2 = 0.1116	
Goodness-of-fit on F^2	0.998	
Absolute structure parameter	−0.01(7)	
Extinction coefficient	0.0014(9)	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.50 and −0.34 e $Å^{-3}$	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (Å^2) for NU8354B. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Cl(1)	0.25867(7)	1.00036(7)	0.04402(3)	0.0430(2)
O(1)	0.17442(16)	0.67360(13)	–0.18847(6)	0.0189(3)
O(2)	0.2444(2)	0.77093(17)	–0.32528(8)	0.0342(4)
O(3)	0.62253(16)	0.49406(16)	–0.18475(7)	0.0286(4)
O(4)	0.8635(2)	1.08153(18)	–0.04852(9)	0.0452(5)
O(5)	0.6545(2)	1.17538(16)	–0.05601(7)	0.0384(5)
N(1)	0.43268(19)	0.62950(16)	–0.17420(8)	0.0194(4)
N(2)	0.7354(2)	1.09183(19)	–0.06727(8)	0.0292(5)
C(1)	0.4982(2)	0.5216(2)	–0.16638(9)	0.0201(5)
C(2)	0.3910(2)	0.4492(2)	–0.13300(9)	0.0197(5)
C(3)	0.4058(3)	0.3356(2)	–0.11253(10)	0.0290(6)
C(4)	0.2845(3)	0.2867(2)	–0.08345(11)	0.0312(6)
C(5)	0.1541(3)	0.3517(2)	–0.07584(10)	0.0298(6)
C(6)	0.1414(3)	0.4669(2)	–0.09532(9)	0.0232(5)
C(7)	0.2634(2)	0.51541(19)	–0.12390(9)	0.0172(4)
C(8)	0.2825(2)	0.63860(19)	–0.14775(9)	0.0170(5)
C(9)	0.2783(2)	0.7322(2)	–0.09989(9)	0.0174(5)
C(10)	0.1686(2)	0.8185(2)	–0.09863(10)	0.0208(5)
C(11)	0.1628(2)	0.9011(2)	–0.05489(10)	0.0240(5)
C(12)	0.2686(3)	0.8973(2)	–0.01159(10)	0.0246(5)
C(13)	0.3798(3)	0.8120(2)	–0.01170(10)	0.0275(5)
C(14)	0.3830(3)	0.7289(2)	–0.05557(10)	0.0251(5)
C(15)	0.1547(2)	0.5971(2)	–0.23760(9)	0.0214(5)
C(16)	0.0520(2)	0.6610(2)	–0.27833(9)	0.0198(5)
C(17)	–0.0345(3)	0.5855(2)	–0.31976(10)	0.0314(6)
C(18)	–0.1135(3)	0.6449(3)	–0.27058(11)	0.0348(6)
C(19)	0.1028(3)	0.7813(2)	–0.29734(10)	0.0242(5)
C(20)	0.4967(3)	0.72282(19)	–0.20988(10)	0.0211(5)
C(21)	0.5637(2)	0.8222(2)	–0.17455(10)	0.0218(5)
C(22)	0.4977(3)	0.9321(2)	–0.17319(10)	0.0272(5)
C(23)	0.5518(3)	1.0206(2)	–0.13821(10)	0.0294(6)
C(24)	0.6777(2)	0.9987(2)	–0.10513(9)	0.0215(5)
C(25)	0.7480(3)	0.8908(2)	–0.10637(11)	0.0297(5)
C(26)	0.6912(3)	0.8019(2)	–0.14109(12)	0.0312(6)

Table 3. Bond lengths [Å] and angles [°] for NU8354B.

Cl(1)–C(12)	1.736(2)	O(1)–C(8)	1.406(2)
O(1)–C(15)	1.438(3)	O(2)–H(2)	0.86(3)
O(2)–C(19)	1.426(3)	O(3)–C(1)	1.230(3)
O(4)–N(2)	1.230(3)	O(5)–N(2)	1.217(3)
N(1)–C(1)	1.363(3)	N(1)–C(8)	1.478(3)
N(1)–C(20)	1.455(3)	N(2)–C(24)	1.462(3)
C(1)–C(2)	1.477(3)	C(2)–C(3)	1.373(3)
C(2)–C(7)	1.380(3)	C(3)–H(3A)	0.950
C(3)–C(4)	1.390(4)	C(4)–H(4A)	0.950
C(4)–C(5)	1.389(4)	C(5)–H(5A)	0.950
C(5)–C(6)	1.381(3)	C(6)–H(6A)	0.950
C(6)–C(7)	1.388(3)	C(7)–C(8)	1.506(3)
C(8)–C(9)	1.531(3)	C(9)–C(10)	1.382(3)
C(9)–C(14)	1.389(3)	C(10)–H(10A)	0.950
C(10)–C(11)	1.376(3)	C(11)–H(11A)	0.950
C(11)–C(12)	1.378(3)	C(12)–C(13)	1.384(3)
C(13)–H(13A)	0.950	C(13)–C(14)	1.382(3)
C(14)–H(14A)	0.950	C(15)–H(15A)	0.990
C(15)–H(15B)	0.990	C(15)–C(16)	1.500(3)
C(16)–C(17)	1.498(3)	C(16)–C(18)	1.501(3)
C(16)–C(19)	1.498(3)	C(17)–H(17A)	0.990
C(17)–H(17B)	0.990	C(17)–C(18)	1.497(4)
C(18)–H(18A)	0.990	C(18)–H(18B)	0.990
C(19)–H(19A)	0.990	C(19)–H(19B)	0.990
C(20)–H(20A)	0.990	C(20)–H(20B)	0.990
C(20)–C(21)	1.512(3)	C(21)–C(22)	1.374(3)
C(21)–C(26)	1.397(3)	C(22)–H(22A)	0.950
C(22)–C(23)	1.373(3)	C(23)–H(23A)	0.950
C(23)–C(24)	1.383(3)	C(24)–C(25)	1.372(3)
C(25)–H(25A)	0.950	C(25)–C(26)	1.382(4)
C(26)–H(26A)	0.950		

C(8)–O(1)–C(15)	116.41(15)	H(2)–O(2)–C(19)	100.2(19)
C(1)–N(1)–C(8)	113.40(17)	C(1)–N(1)–C(20)	123.57(18)
C(8)–N(1)–C(20)	122.75(17)	O(4)–N(2)–O(5)	123.5(2)
O(4)–N(2)–C(24)	118.16(19)	O(5)–N(2)–C(24)	118.4(2)
O(3)–C(1)–N(1)	124.6(2)	O(3)–C(1)–C(2)	128.8(2)
N(1)–C(1)–C(2)	106.57(18)	C(1)–C(2)–C(3)	129.4(2)
C(1)–C(2)–C(7)	108.42(19)	C(3)–C(2)–C(7)	122.2(2)
C(2)–C(3)–H(3A)	121.2	C(2)–C(3)–C(4)	117.6(2)
H(3A)–C(3)–C(4)	121.2	C(3)–C(4)–H(4A)	119.8
C(3)–C(4)–C(5)	120.4(2)	H(4A)–C(4)–C(5)	119.8
C(4)–C(5)–H(5A)	119.2	C(4)–C(5)–C(6)	121.7(2)
H(5A)–C(5)–C(6)	119.2	C(5)–C(6)–H(6A)	121.2
C(5)–C(6)–C(7)	117.5(2)	H(6A)–C(6)–C(7)	121.2
C(2)–C(7)–C(6)	120.6(2)	C(2)–C(7)–C(8)	110.51(18)
C(6)–C(7)–C(8)	128.90(19)	O(1)–C(8)–N(1)	111.50(16)
O(1)–C(8)–C(7)	115.26(17)	O(1)–C(8)–C(9)	105.84(16)
N(1)–C(8)–C(7)	100.98(16)	N(1)–C(8)–C(9)	111.70(16)
C(7)–C(8)–C(9)	111.71(17)	C(8)–C(9)–C(10)	121.31(19)
C(8)–C(9)–C(14)	119.88(19)	C(10)–C(9)–C(14)	118.8(2)
C(9)–C(10)–H(10A)	119.3	C(9)–C(10)–C(11)	121.3(2)
H(10A)–C(10)–C(11)	119.3	C(10)–C(11)–H(11A)	120.4
C(10)–C(11)–C(12)	119.2(2)	H(11A)–C(11)–C(12)	120.4
Cl(1)–C(12)–C(11)	118.85(18)	Cl(1)–C(12)–C(13)	120.28(18)
C(11)–C(12)–C(13)	120.9(2)	C(12)–C(13)–H(13A)	120.4

C(12)–C(13)–C(14)	119.3(2)	H(13A)–C(13)–C(14)	120.4
C(9)–C(14)–C(13)	120.6(2)	C(9)–C(14)–H(14A)	119.7
C(13)–C(14)–H(14A)	119.7	O(1)–C(15)–H(15A)	110.4
O(1)–C(15)–H(15B)	110.4	O(1)–C(15)–C(16)	106.40(17)
H(15A)–C(15)–H(15B)	108.6	H(15A)–C(15)–C(16)	110.4
H(15B)–C(15)–C(16)	110.4	C(15)–C(16)–C(17)	116.3(2)
C(15)–C(16)–C(18)	118.0(2)	C(15)–C(16)–C(19)	115.78(19)
C(17)–C(16)–C(18)	59.89(16)	C(17)–C(16)–C(19)	119.0(2)
C(18)–C(16)–C(19)	116.4(2)	C(16)–C(17)–H(17A)	117.8
C(16)–C(17)–H(17B)	117.8	C(16)–C(17)–C(18)	60.16(15)
H(17A)–C(17)–H(17B)	114.9	H(17A)–C(17)–C(18)	117.8
H(17B)–C(17)–C(18)	117.8	C(16)–C(18)–C(17)	59.95(15)
C(16)–C(18)–H(18A)	117.8	C(16)–C(18)–H(18B)	117.8
C(17)–C(18)–H(18A)	117.8	C(17)–C(18)–H(18B)	117.8
H(18A)–C(18)–H(18B)	114.9	O(2)–C(19)–C(16)	109.11(19)
O(2)–C(19)–H(19A)	109.9	O(2)–C(19)–H(19B)	109.9
C(16)–C(19)–H(19A)	109.9	C(16)–C(19)–H(19B)	109.9
H(19A)–C(19)–H(19B)	108.3	N(1)–C(20)–H(20A)	109.0
N(1)–C(20)–H(20B)	109.0	N(1)–C(20)–C(21)	112.73(18)
H(20A)–C(20)–H(20B)	107.8	H(20A)–C(20)–C(21)	109.0
H(20B)–C(20)–C(21)	109.0	C(20)–C(21)–C(22)	120.8(2)
C(20)–C(21)–C(26)	120.1(2)	C(22)–C(21)–C(26)	119.1(2)
C(21)–C(22)–H(22A)	119.4	C(21)–C(22)–C(23)	121.3(2)
H(22A)–C(22)–C(23)	119.4	C(22)–C(23)–H(23A)	120.6
C(22)–C(23)–C(24)	118.9(2)	H(23A)–C(23)–C(24)	120.6
N(2)–C(24)–C(23)	119.3(2)	N(2)–C(24)–C(25)	119.3(2)
C(23)–C(24)–C(25)	121.4(2)	C(24)–C(25)–H(25A)	120.4
C(24)–C(25)–C(26)	119.3(2)	H(25A)–C(25)–C(26)	120.4
C(21)–C(26)–C(25)	120.1(2)	C(21)–C(26)–H(26A)	119.9
C(25)–C(26)–H(26A)	119.9		

Table 4. Anisotropic displacement parameters (Å^2) for NU8354B. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	0.0286(3)	0.0548(4)	0.0457(4)	–0.0303(4)	–0.0069(3)	0.0096(3)
O(1)	0.0140(7)	0.0205(8)	0.0222(8)	–0.0008(6)	–0.0036(6)	0.0057(6)
O(2)	0.0285(10)	0.0251(10)	0.0491(11)	0.0024(9)	0.0112(9)	–0.0065(8)
O(3)	0.0155(8)	0.0329(9)	0.0373(9)	–0.0048(8)	0.0021(7)	0.0075(7)
O(4)	0.0247(10)	0.0539(13)	0.0571(11)	–0.0241(11)	–0.0064(9)	0.0032(9)
O(5)	0.0521(12)	0.0307(11)	0.0325(9)	–0.0072(8)	–0.0070(9)	0.0165(9)
N(1)	0.0121(9)	0.0177(10)	0.0283(10)	0.0011(8)	0.0019(8)	0.0007(7)
N(2)	0.0308(12)	0.0301(12)	0.0268(11)	–0.0019(9)	0.0035(9)	0.0048(10)
C(1)	0.0164(10)	0.0221(13)	0.0218(11)	–0.0056(10)	–0.0024(9)	0.0026(9)
C(2)	0.0199(11)	0.0168(12)	0.0226(11)	–0.0014(9)	–0.0040(10)	0.0014(9)
C(3)	0.0311(13)	0.0228(13)	0.0332(13)	–0.0009(11)	–0.0078(11)	0.0028(11)
C(4)	0.0453(17)	0.0186(13)	0.0297(13)	0.0065(10)	–0.0064(12)	–0.0031(11)
C(5)	0.0337(14)	0.0317(14)	0.0241(11)	0.0030(11)	–0.0019(11)	–0.0133(12)
C(6)	0.0211(11)	0.0261(13)	0.0224(11)	–0.0008(10)	–0.0007(9)	–0.0038(10)
C(7)	0.0167(10)	0.0151(11)	0.0198(10)	–0.0016(9)	–0.0040(9)	–0.0006(9)
C(8)	0.0108(10)	0.0175(11)	0.0227(11)	0.0008(9)	–0.0014(8)	0.0014(8)
C(9)	0.0128(10)	0.0169(11)	0.0227(11)	0.0026(9)	0.0003(9)	0.0016(8)
C(10)	0.0130(10)	0.0223(13)	0.0271(12)	–0.0001(10)	–0.0027(9)	0.0042(9)
C(11)	0.0152(11)	0.0250(13)	0.0317(12)	–0.0037(11)	–0.0016(10)	0.0070(9)
C(12)	0.0199(12)	0.0263(13)	0.0276(12)	–0.0085(10)	0.0016(10)	–0.0014(10)
C(13)	0.0207(12)	0.0314(14)	0.0303(13)	–0.0042(11)	–0.0079(10)	0.0051(10)

C(14)	0.0198(12)	0.0236(12)	0.0319(13)	–0.0002(11)	–0.0057(11)	0.0092(10)
C(15)	0.0178(11)	0.0233(12)	0.0232(11)	–0.0023(10)	0.0009(9)	0.0000(10)
C(16)	0.0179(11)	0.0217(12)	0.0198(11)	–0.0019(10)	0.0012(9)	0.0013(9)
C(17)	0.0291(13)	0.0345(15)	0.0305(13)	–0.0038(12)	–0.0081(11)	–0.0093(11)
C(18)	0.0171(12)	0.0516(18)	0.0356(13)	0.0066(13)	–0.0013(11)	–0.0059(12)
C(19)	0.0188(11)	0.0274(13)	0.0263(12)	0.0001(11)	–0.0017(10)	0.0007(10)
C(20)	0.0183(11)	0.0175(11)	0.0275(12)	0.0011(10)	0.0029(10)	0.0001(9)
C(21)	0.0160(11)	0.0217(12)	0.0276(12)	0.0040(11)	0.0041(9)	–0.0032(9)
C(22)	0.0253(12)	0.0256(13)	0.0306(12)	0.0052(11)	–0.0036(11)	0.0024(10)
C(23)	0.0296(13)	0.0257(14)	0.0330(13)	0.0049(11)	0.0012(11)	0.0087(11)
C(24)	0.0212(11)	0.0178(12)	0.0254(11)	–0.0005(10)	0.0048(9)	–0.0002(10)
C(25)	0.0169(11)	0.0258(13)	0.0465(14)	–0.0030(11)	–0.0038(12)	0.0014(10)
C(26)	0.0193(12)	0.0195(13)	0.0548(17)	–0.0048(12)	–0.0027(11)	0.0074(10)

Table 5. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for NU8354B.

	x	y	z	U
H(2)	0.271(3)	0.844(3)	–0.3258(12)	0.042(8)
H(3A)	0.4956	0.2921	–0.1180	0.035
H(4A)	0.2909	0.2083	–0.0687	0.037
H(5A)	0.0715	0.3159	–0.0567	0.036
H(6A)	0.0524	0.5113	–0.0894	0.028
H(10A)	0.0959	0.8210	–0.1286	0.025
H(11A)	0.0868	0.9599	–0.0546	0.029
H(13A)	0.4530	0.8106	0.0180	0.033
H(14A)	0.4575	0.6689	–0.0554	0.030
H(15A)	0.1101	0.5207	–0.2255	0.026
H(15B)	0.2521	0.5811	–0.2564	0.026
H(17A)	–0.0518	0.6168	–0.3592	0.038
H(17B)	–0.0204	0.4986	–0.3176	0.038
H(18A)	–0.1478	0.5947	–0.2381	0.042
H(18B)	–0.1793	0.7129	–0.2797	0.042
H(19A)	0.0288	0.8159	–0.3244	0.029
H(19B)	0.1114	0.8344	–0.2634	0.029
H(20A)	0.4177	0.7556	–0.2353	0.025
H(20B)	0.5753	0.6884	–0.2349	0.025
H(22A)	0.4130	0.9472	–0.1969	0.033
H(23A)	0.5037	1.0956	–0.1368	0.035
H(25A)	0.8349	0.8773	–0.0836	0.036
H(26A)	0.7390	0.7267	–0.1422	0.037

Table 6. Torsion angles [°] for NU8354B.

C(8)–N(1)–C(1)–O(3)	179.8(2)	C(8)–N(1)–C(1)–C(2)	0.2(2)
C(20)–N(1)–C(1)–O(3)	5.7(3)	C(20)–N(1)–C(1)–C(2)	−173.96(18)
O(3)–C(1)–C(2)–C(3)	2.7(4)	O(3)–C(1)–C(2)–C(7)	−177.6(2)
N(1)–C(1)–C(2)–C(3)	−177.7(2)	N(1)–C(1)–C(2)–C(7)	2.0(2)
C(1)–C(2)–C(3)–C(4)	−178.2(2)	C(7)–C(2)–C(3)–C(4)	2.1(3)
C(2)–C(3)–C(4)–C(5)	0.0(4)	C(3)–C(4)–C(5)–C(6)	−1.6(4)
C(4)–C(5)–C(6)–C(7)	1.1(3)	C(1)–C(2)–C(7)–C(6)	177.53(19)
C(1)–C(2)–C(7)–C(8)	−3.4(2)	C(3)–C(2)–C(7)–C(6)	−2.7(3)
C(3)–C(2)–C(7)–C(8)	176.4(2)	C(5)–C(6)–C(7)–C(2)	1.0(3)
C(5)–C(6)–C(7)–C(8)	−177.8(2)	C(15)–O(1)–C(8)–N(1)	59.7(2)
C(15)–O(1)–C(8)–C(7)	−54.6(2)	C(15)–O(1)–C(8)–C(9)	−178.62(16)
C(1)–N(1)–C(8)–O(1)	−124.98(19)	C(1)–N(1)–C(8)–C(7)	−2.0(2)
C(1)–N(1)–C(8)–C(9)	116.8(2)	C(20)–N(1)–C(8)–O(1)	49.2(3)
C(20)–N(1)–C(8)–C(7)	172.13(18)	C(20)–N(1)–C(8)–C(9)	−69.0(2)
C(2)–C(7)–C(8)–O(1)	123.60(19)	C(2)–C(7)–C(8)–N(1)	3.3(2)
C(2)–C(7)–C(8)–C(9)	−115.55(19)	C(6)–C(7)–C(8)–O(1)	−57.5(3)
C(6)–C(7)–C(8)–N(1)	−177.7(2)	C(6)–C(7)–C(8)–C(9)	63.4(3)
O(1)–C(8)–C(9)–C(10)	8.4(3)	O(1)–C(8)–C(9)–C(14)	−173.8(2)
N(1)–C(8)–C(9)–C(10)	129.9(2)	N(1)–C(8)–C(9)–C(14)	−52.3(3)
C(7)–C(8)–C(9)–C(10)	−117.8(2)	C(7)–C(8)–C(9)–C(14)	60.0(3)
C(8)–C(9)–C(10)–C(11)	178.5(2)	C(14)–C(9)–C(10)–C(11)	0.7(3)
C(9)–C(10)–C(11)–C(12)	0.0(3)	C(10)–C(11)–C(12)–Cl(1)	−179.03(18)
C(10)–C(11)–C(12)–C(13)	0.0(4)	Cl(1)–C(12)–C(13)–C(14)	178.25(19)
C(11)–C(12)–C(13)–C(14)	−0.8(4)	C(12)–C(13)–C(14)–C(9)	1.5(4)
C(8)–C(9)–C(14)–C(13)	−179.3(2)	C(10)–C(9)–C(14)–C(13)	−1.5(3)
C(8)–O(1)–C(15)–C(16)	−171.92(16)	O(1)–C(15)–C(16)–C(17)	−155.99(18)
O(1)–C(15)–C(16)–C(18)	−87.7(2)	O(1)–C(15)–C(16)–C(19)	56.8(2)
C(15)–C(16)–C(17)–C(18)	108.6(2)	C(19)–C(16)–C(17)–C(18)	−105.4(2)
C(15)–C(16)–C(18)–C(17)	−105.8(2)	C(19)–C(16)–C(18)–C(17)	109.8(2)
C(15)–C(16)–C(19)–O(2)	58.8(2)	C(17)–C(16)–C(19)–O(2)	−87.4(2)
C(18)–C(16)–C(19)–O(2)	−156.0(2)	C(1)–N(1)–C(20)–C(21)	−105.7(2)
C(8)–N(1)–C(20)–C(21)	80.8(2)	N(1)–C(20)–C(21)–C(22)	−110.2(2)
N(1)–C(20)–C(21)–C(26)	67.5(3)	C(20)–C(21)–C(22)–C(23)	175.6(2)
C(26)–C(21)–C(22)–C(23)	−2.2(3)	C(21)–C(22)–C(23)–C(24)	1.8(3)
C(22)–C(23)–C(24)–N(2)	−179.4(2)	C(22)–C(23)–C(24)–C(25)	−0.5(3)
O(4)–N(2)–C(24)–C(23)	−163.8(2)	O(4)–N(2)–C(24)–C(25)	17.2(3)
O(5)–N(2)–C(24)–C(23)	16.1(3)	O(5)–N(2)–C(24)–C(25)	−162.8(2)
N(2)–C(24)–C(25)–C(26)	178.4(2)	C(23)–C(24)–C(25)–C(26)	−0.5(4)
C(24)–C(25)–C(26)–C(21)	0.1(4)	C(20)–C(21)–C(26)–C(25)	−176.6(2)
C(22)–C(21)–C(26)–C(25)	1.2(3)		

Table 7. Hydrogen bonds for NU8354B [Å and °].

D–H...A	d(D–H)	d(H...A)	d(D...A)	<(DHA)
O(2)–H(2)...O(3A)	0.86(3)	1.96(3)	2.795(3)	165(3)

Symmetry operations for equivalent atoms
A −x+1,y+1/2,−z−1/2

Figure S2: Western blot analysis with Nutlin-3, **7, 47**, and, **49** in SJSA cells at time points of 1, 2 and 4 hours.

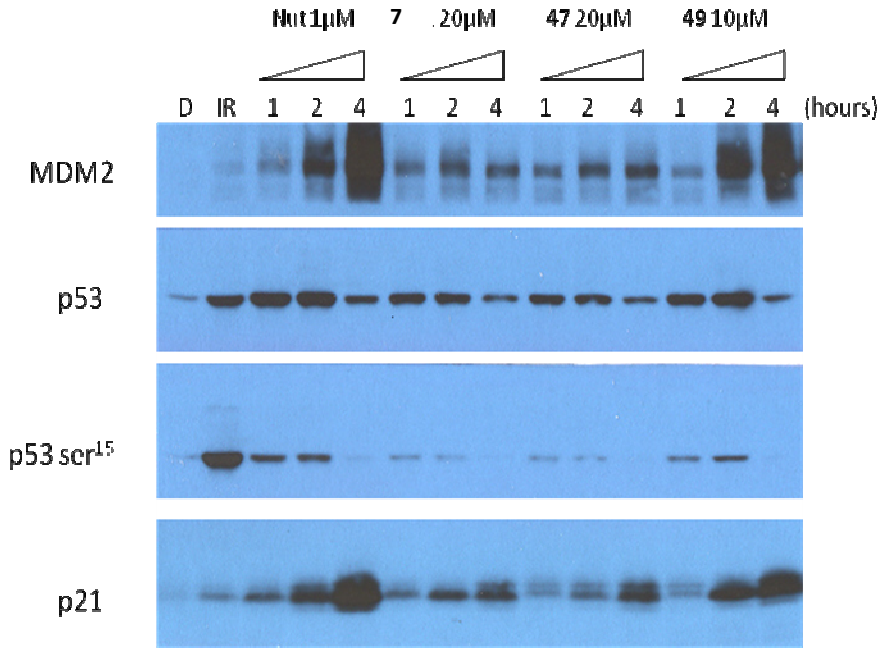

Figure S3: Western Blotting analysis with **53**, **54**, **50** and **55** in SJSA cells. Concentrations 1, 5 and 10µM, time point 4 hours.

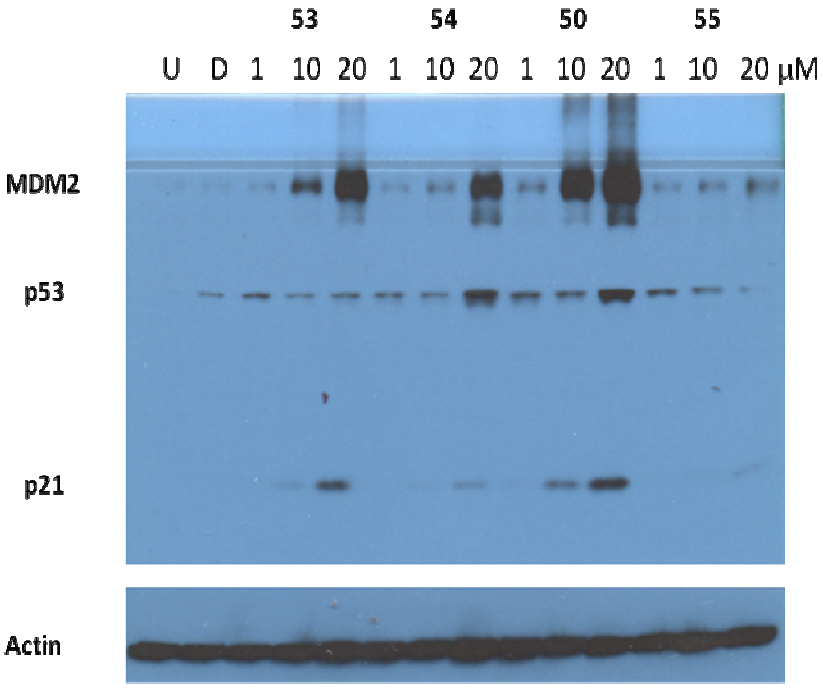

Figure S4: Western Blotting analysis with Nutlin-3 and **50** in SJSA cells at 48 hrs showing the dose response for gene expression.

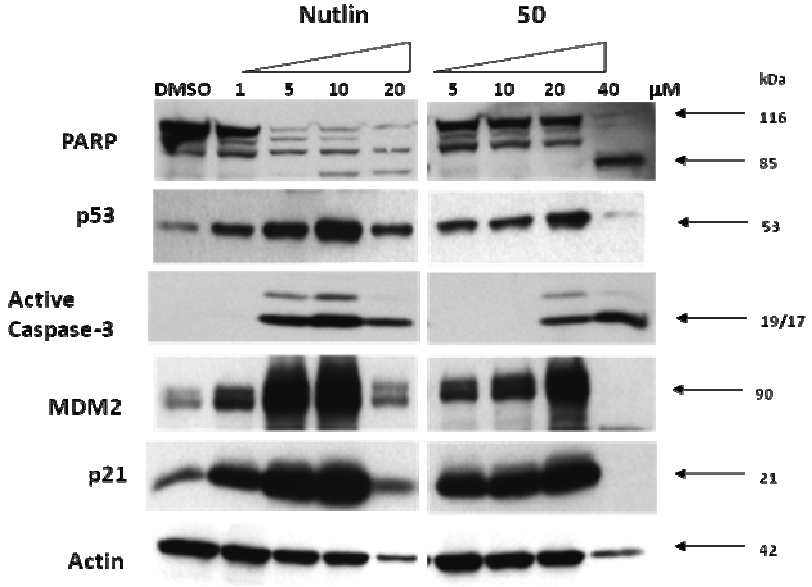
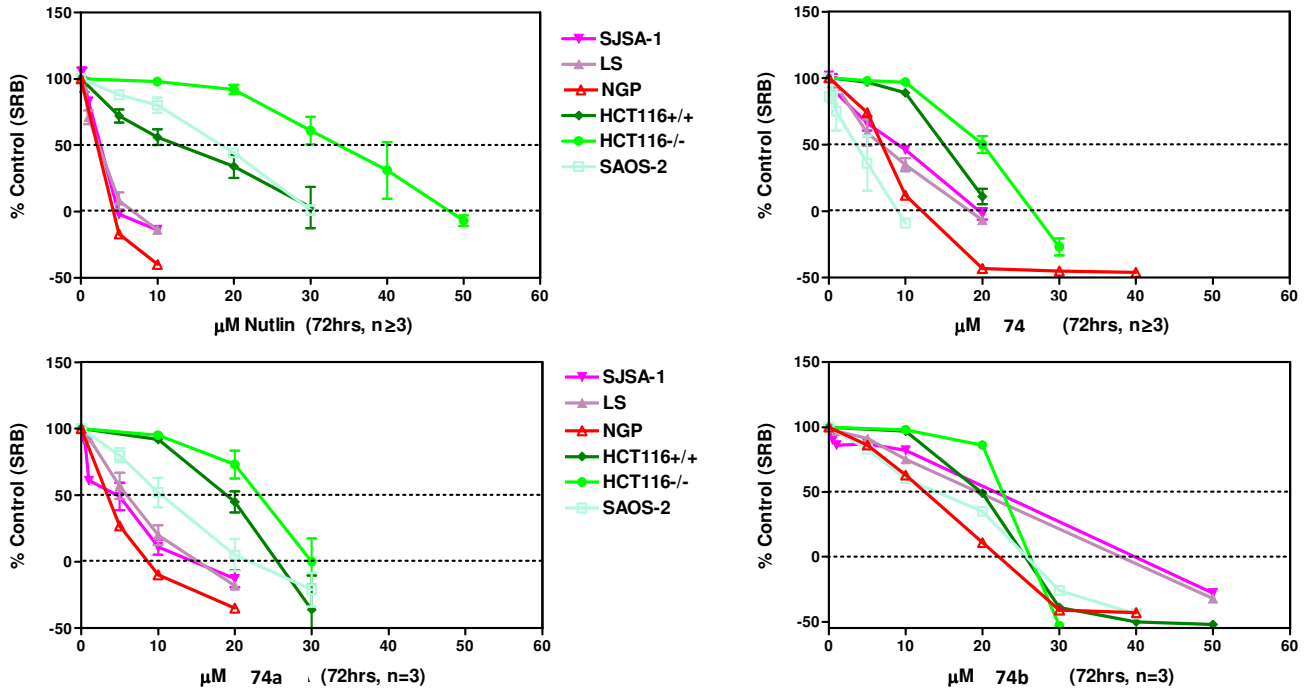
Figure S5: SRB Growth Inhibition Assay in Response to Drug Exposure in MDM2 Amplified Cell Lines with **74**, **74a** and **74b**.