Diaryl- and Triaryl-pyrrole derivatives: inhibitors of the MDM2-p53 and MDMX-p53 protein-protein interactions.

Tim J. Blackburn¹, Shafiq Ahmed², Christopher R. Coxon¹, Junfeng Liu², Xiaohong Lu², Bernard T. Golding¹, Roger J. Griffin¹, Claire Hutton², David R. Newell², Stephen Ojo¹, Anna F. Watson¹, Andrey Zaytzev¹, Yan Zhao², John Lunec²⁎, Ian R. Hardcastle¹⁎

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

SUPPORTING INFORMATION

EXPERIMENTAL

Determination of inhibition of the MDM2-p53 and MDMX-p53 interactions using binding assays (ELISA).

Assays for MDM2-p53 inhibition were carried out as described previously.¹ Assays for MDMX-p53 inhibition were conducted using a similar method. A pCMV-XL5-MDMX cDNA construct (OriGene Technologies) was used for the in vitro coupled T7 transcription and rabbit reticulocyte lysate translation of MDMX, and a rabbit anti-MDMX antigen affinity-purified polyclonal antibody (Bethyl Laboratories Inc, via UK supplier Cambridge Bioscience, UK, Cat No. A300-287 A) was used for the ELISA.

Western blot analysis for p53 activation in intact cells

Western blot analysis of p53, MDM2, p21WAF1 and actin proteins in cells treated with the MDM2-p53 antagonists was carried out as described previously.¹ Detection of α-tubulin on western blots with the Clone DM1A monoclonal antibody (Sigma-Aldrich, Dorset, UK) at 1:2000 dilution was used as an additional protein loading control.

Molecular modelling

PDB coordinates and electron density maps for 3LBK (MDM2) and 3LBK (MDM2) were imported into COOT (v0.7).² The ligands, 1b in 3LBK (MDM2) and 1a in 3LBJ (MDMX), respectively, were converted using the CCP4 ‘cprodrg’ function.³ Experimental ligands 4c, 11c and 11d were built in 2D using the ligand builder function. Ligand 4c was superimposed onto both 4a and 4b, using a graph map function, followed by minimisation in situ using the ‘Sphere Refine’ tool. The original ligand was deleted from the model and new coordinates for the modeled complex generated. Coordinates for ligands 11c and 11d were generated by their superimposition onto the model of 4c using the same method.
General Synthetic 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, obtained either by distillation 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 60F254; 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). Proton (1H) and carbon (13C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Spectrospin AC 300E (1H at 300 MHz, 13C at 75 MHz), a Jeol JNM-LA500 spectrometer (1H at 500 MHz, 13C at 125 MHz), or a Bruker Avance II 500 (1H at 500 MHz, 13C at 125 MHz) employing the solvent as internal standard. IR spectra were recorded on a Bio-Rad FTS 3000MX diamond ATR. 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) with 5 or 12 min gradient elution with 0.05% formic acid in methanol (10-90%), final compounds were ≥ 95% purity. Elemental analyses were performed by The School of Pharmacy, Analytical Facility, University of London, WC1N 1AX. Accurate masses were measured using a Finnigan MAR 95 XP or a Finnigan MAR 900 XLT at the EPSRC National Mass Spectrometry Service Centre (Chemistry Department, University of Wales, Swansea, Wales, SA2 8PP).

Synthesis

General Procedure A

To a mixture of the appropriate aniline (1.1 eq unless otherwise stated) of 1,2-dibenzoylethane (1.0 eq) and 2,2,2,-trifluoroethanol in a sealed microwave vial of appropriate capacity, was added trifluoroacetic acid (2.0 eq), drop-wise, under N₂ and then heated by microwave for 20 min at 150 °C. The resulting suspension was basified by addition of aqueous sodium hydroxide (1M) with stirring, filtered, and the solid washed with ethanol. The crude product 5 was dried in vacuo.

General Procedure B

To an appropriate capacity microwave vial was added the appropriate pyrrole 5 (1.0 eq) and anhydrus DMF and the vial was sealed. The mixture was cooled to -5 °C in an ice-salt bath, phosphorus oxychloride (3.0 eq) was added dropwise, under N₂ and heated by microwave 10 min at 70 °C. The mixture was poured over ice, basified with sodium hydroxide (1M), and heated to reflux for 1 h, then cooled to 0 °C and ethyl acetate (50
mL) added. The organic layer was washed with HCl (10%, 2 x 50 mL), water (2 x 50 mL), dried (sodium sulfate), and evaporated. Crude 6 was washed with ethanol and dried in vacuo.

**General Procedure C**

A mixture of 1-(4-halophenyl)-2,5-diphenyl-1H-pyrrole-3-carbaldehyde 6 (1 mol. eq.) and the appropriate barbituric acid (1.1 mol. eq.) in anhydrous EtOH was stirred at room temperature for 16 h, then concentrated in vacuo. Chromatography gave 4 as an orange solid.

**General Procedure D**

A mixture of 1-(4-halophenyl)-2,5-diphenyl-1H-pyrrole-3-carbaldehyde 6 (1 mol. eq.), the appropriate barbituric acid (1.1 mol. eq.) and glacial acetic acid (11 mL/mmol) was heated to 120 °C for 2 h, then filtered hot. The solid was washed with acetic acid (2 x 5 mL) and water (2 x 10 mL), and dried in vacuo, to give 4 as an orange solid.

**General Procedure E**

A solution of 1-(4-chlorophenyl)-2,5-diphenyl-1H-pyrrole-3-carbaldehyde 6a (1 eq), the appropriate dicarbonyl compound (1.25 eq), piperidine (3 µL) and acetic acid (7 µL) in toluene (1.24 mL) was heated to reflux for 5 h. The precipitate was filtered. Chromatography (silica; ethyl acetate, methanol) gave 7 or 10 as a yellow solid.

**General Procedure F**

To dry DCM (8 mL per mmol 15) at room temperature under nitrogen was added diethylzinc (4.1 eq, 1 M in hexanes). Diiodomethane (4.1 eq) was added dropwise at 0 °C and stirring continued for 10 minutes and a white suspension formed. The appropriate β-ketoester 15 (1 eq) was added dropwise and stirring was continued 30 min, then the appropriate aldehyde (1.05 eq) was added and the resulting pale yellow solution was stirred for 1 h, and quenched with sat. aqueous ammonium chloride and the organic phase was separated. The aqueous phase was extracted with Et₂O (2 x 20 mL), and the combined organic phases were washed with brine and dried (Na₂SO₄), and concentrated in vacuo.

The crude product (1 eq.) was dissolved in DCM (1.4 mL per mmol 19) and pyridinium chlorochromate (PCC, 2.1 eq) was added at rt and the mixture stirred 18 h. In some cases additional PCC (1.05 eq.) was added. The mixture was filtered through a short pad of silica gel and the filtrate was concentrated in vacuo to give 16.

**General Procedure G**
A mixture of 1,4-dicarbonyl compound 12 (1 eq.), aniline (1.2 eq.), p-toluene sulfonic acid (PTSA, 0.05 eq.) and toluene (0.94 mL per mmol 12) was heated to reflux for 18 h. The mixture was cooled to rt, then filtered and washed with toluene through Celite™. The filtrate was concentrated in vacuo. Chromatography (silica; EtOAc, hexane) gave 13.

**General Procedure H**

To a solution of pyrrole ester 18 (1 eq.) in dry DCM (14 mL per mmol 18) at -78°C under nitrogen was added di-isopropylaluminium hydride (DIBAL-H, 3 eq., 1 M solution in hexane) and the resulting solution allowed to stir for 2 hours. The mixture was quenched by the dropwise addition of methanol and allowed to warm to room temperature, diluted with aqueous Rochelle’s salt and stirred vigorously for 30 min, then was extracted with EtOAc (x 4). The combined organic phases were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. Chromatography (silica; EtOAc, hexane) gave 19.

**General Procedure I**

To a suspension of pyrrole alcohol 19 (1 eq.) and 4 Å molecular sieves (500 mg per mmol 19) in dry DCM (2 mL per mmol 19) was added N-methylmorpholine-N-oxide (NMO, 2 eq.) and the mixture stirred for 10 min. Tetrapropylammonium perruthenate (TPAP, 0.1 eq.) was added and the mixture stirred until TLC indicated the complete consumption of the starting material (ca. 30 min). The mixture was diluted with DCM and filtered and washed with ether thorough Celite™. The organic phase was washed with aq. sodium metabisulfite and brine. The aqueous layer was extracted with Et₂O (x 3). The combined organic extracts were dried (MgSO₄) and concentrated in vacuo. Chromatography (silica; EtOAc, hexane) gave 17.

**General Procedure J**

A mixture of 1-(4-halophenyl)-2,5-disubstituted-1H-pyrrole-3-carbaldehyde 17 (1 mol. eq.), the appropriate barbituric acid (1.1 mol. eq.) and glacial acetic acid (11 mL/mmol) was heated to 120 °C for 2 h, then filtered hot. The solid was washed with acetic acid (2 x 5 mL) and water (2 x 10 mL), and dried in vacuo, to give 11 as an orange solid.

1-(4-Chlorophenyl)-2,5-diphenyl-1H-pyrrole (5a)

**General Procedure A:** 4-chloroaniline (0.24 g, 1.90 mmol), 1,2-dibenzylethane (0.41 g, 1.72 mmol) and TFA (0.26 ml, 3.44 mmol) in TFE (20 mL) gave 5a as a white solid (0.45 g, 79%). mp 224-226 °C; IR (cm⁻¹) 3026, 3031, 1676, 1593, 1487; ¹H NMR (300 MHz, CDCl₃) δ 6.49 (s, 2H, pyrrole-H), 6.96 (d, J = 8.7 Hz, 2H, -CH₂C₆H₄H₂C(Cl)), 7.04-7.12 (m, 4H, Ar-H), 7.18-7.22 (m, 6H, ArH), 7.23 (m, 2H, ArH); ¹³C NMR (75 MHz, CDCl₃) δ 110.6, 126.8, 128.3, 129.2, 130.5, 133.6, 136.4. LCMS (ES⁺) m/z = 330 [M+H]⁺.
1-(4-Bromophenyl)-2,5-diphenyl-1H-pyrrole (5b)

General Procedure A: 4-bromoaniline (0.33 g, 1.90 mmol), 1,2-dibenzylethane (0.41 g, 1.72 mmol) and TFA (0.26 ml, 3.44 mmol) in trifluoroethanol (20 mL) gave 5b as a white solid (0.53 g, 83%). mp: 218-219 °C; IR (cm⁻¹): 3055, 1595, 1484, 1396; ¹H NMR (300 MHz, CDCl₃) δ 6.49 (s, 2H, pyrrole-H), 6.91 (d AB, J = 8.7 Hz, 2H, -C₂H₂C₂H₂C(Br)), 7.05-7.10 (m, 4H, ArH), 7.18-7.23 (m, 6H, ArH), 7.37 (d, J = 8.7 Hz, 2H, -C₂H₂C₂H₂C(Br)). ¹³C NMR (75 MHz, CDCl₃) δ 99.9, 110.5, 126.7, 128.2, 129.1, 130.7, 132.1, 133.4, 136.2. LCMS (ES⁺) m/z = 374, 376 [M+H]⁺.

4-(2,5-Diphenyl-1H-pyrrol-1-yl)benzonitrile (5c)

General Procedure A: 4-aminobenzonitrile (0.054 g, 0.46 mmol), 1,2-dibenzoylethane (0.1 g, 0.42 mmol), and TFA (0.96 g, 0.84 mmol) in TFE gave 5c as a white solid. (0.049 g, 37%). mp 247-249 °C; ¹H NMR (300 MHz, d₆-DMSO) δ 7.81 (d, J = 8.5 Hz, 2 H, Ar-H), 7.03 (d, J = 8.10 Hz, 2 H, Ar-H), 7.22 (s, 10 H, Ar-H), 6.51 (s, 2 H, pyrrole).

1-(4-(t-Butyl)phenyl)-2,5-diphenyl-1H-pyrrole (5d)

General Procedure A: 4-t-butylaniline (0.051 g, 0.46 mmol), 1,2-dibenzoylethane (0.1 g, 0.42 mmol), TFA (0.96 g, 0.84 mmol) gave 5d as a white solid. (124 mg ; 85%): mp 246-248 °C; ¹H NMR (300 MHz, d₆-DMSO) δ 7.33 (d, J = 8.5 Hz, 2 H, Ar-H), 7.01 (d, J = 8.5 Hz, 2 H, Ar-H), 7.13 (m, 10 H, Ar-H), 6.46 (s, 2 H, pyrrole), 3.33 (d, J = 7.1 Hz, 9 H, t-Butyl); LCMS (ES⁺) m/z = 368.3 [M+H]⁺.

1-(4-Nitrophenyl)-2,5-diphenyl-1H-pyrrole (5e)

General Procedure A: 4-nitroaniline (0.064 g, 0.46 mmol), 1,2-dibenzoylethane (0.1 g, 0.42 mmol), TFA (0.96 g, 0.84 mmol) in TFE gave 5e as a white solid (39 mg, 27%): mp 244-246 °C; ¹H NMR (300 MHz, d₆-DMSO) δ 8.2 (d, J = 8.9, 2 H, Ar-H), 7.3 (d, J = 8.9, 2 H, Ar-H), 7.5 (m, 10 H, Ar-H), 6.54 (s, 2 H, pyrrole).

1-(4-Methoxyphenyl)-2,5-diphenyl-1H-pyrrole (5f)

General Procedure A: 4-methoxyaniline (0.057 g, 0.46 mmol), 1,2-dibenzoylethane (0.1 g, 0.42 mmol), TFA (0.96 g, 0.84 mmol) in TFE gave 5f as a white solid (117 mg, 86%). mp 227-229 °C.

Methyl 1-(4-bromophenyl)-5-(t-tert-buty)l-2-phenyl-1H-pyrrole-3-carboxylate (19b)

General Procedure A: 16c (0.20 g, 0.72 mmol), 4-bromoaniline (0.622 g, 3.6 mmol), and TFA (0.1 ml, 1.44mmol) gave 19b as white flaky solid (889 mg; 60%). IR (cm⁻¹) 2967, 2943, 1715, 1483; ¹H NMR (300 MHz) δ 1.12 (s, 9H, t-Bu), 3.58 (s, 3H, CH₃), 6.51 (s, 1H, 4-H), 6.95-7.05 (m, 4H, Ar-H), 7.08-7.12 (m, 3H, Ar-H), 7.24-
7.31 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz) δ 31.5, 33.2, 50.9, 107.7, 113.0, 122.8, 127.6, 128.0, 131.5, 131.6, 132.3, 132.7, 139.3, 141.1, 144.2, 165.5; LCMS (ES$^+$) m/z = 412.00 [M+H]$^+$.

**Methyl 5-(tert-butyl)-1-(4-chlorophenyl)-2-phenyl-1H-pyrrole-3-carboxylate (19c)**

General Procedure A: 16c (0.150 g, 0.54 mmol), 4-chloroaniline (0.138g, 1.08mmol), and TFA (0.08 ml, 1.08mmol) gave 19c as a white flaky solid (0.105 g, 52%): IR (cm$^{-1}$) 2965, 1709, 1487, 1229; $^1$H NMR (300 MHz) δ 1.19 (s, 9H, t-Bu), 3.68 (s, 3H, CH$_3$), 6.61 (s, 1H, 4-H), 7.08-7.24 (m, 9H, Ar-H); $^{13}$C (100 MHz) δ 31.5, 33.2, 127.6, 127.9, 128.6, 131.5, 132.4, 144.2; LCMS (ES$^+$) m/z = 367 [M+H]$^+$;

**1-(4-Chlorophenyl)-2,5-diphenyl-1H-pyrrole-3-carbaldehyde (6a)**

General Procedure B: 5a (0.20 g, 0.6 mmol), phosphorous oxychloride (0.16 mL, 1.8 mmol) in DMF (8 mL) gave 6a as a white solid (0.18 g, 84%). mp 222-223 ºC; IR (cm$^{-1}$) 3099, 3073, 3049, 2833, 2749, 1649, 1601. $^1$H NMR (300 MHz, CDCl$_3$) δ 6.91 (d, $J = 8.7$ Hz, 2H, Ar-H), 6.99 (s, 1H, pyrrole-H), 7.06-7.14 (m, 2H, Ar-H), 7.17-7.23 (m, 4H, Ar-H), 7.30-7.38 (m, 6H, Ar-H), 9.72 (s, 1H, CHO); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 98.1, 105.3, 112.9, 116.4, 119.6, 122.5, 123.8, 125.4, 126.0, 127.1, 128.3, 128.6, 129.3, 130.3, 131.6, 136.4, 194.8. LCMS (ES$^+$) m/z = 358 [M+H]$^+$.

**1-(4-Bromophenyl)-2,5-diphenyl-1H-pyrrole-3-carbaldehyde (6b)**

General Procedure B: 1-(4-bromophenyl)-2,5-diphenyl-1H-pyrrole 5b (0.225 g, 0.6 mmol), phosphorous oxychloride (0.16 mL, 1.8 mmol) in DMF (8 mL) gave 6b as a cream solid (0.16 g, 67%). mp 193-194 ºC; IR (cm$^{-1}$) 3066, 3037, 2826, 2743, 1739, 1651; $^1$H NMR (300 MHz, CDCl$_3$) δ 6.84 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.98 (s, 1H, pyrrole-H), 7.09-7.14 (m, 2H, Ar-H), 7.18-7.27 (m, 4H, Ar-H), 7.32-7.36 (m, 2H, Ar-H), 9.72 (s, 1H, CHO); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 100.0, 118.9, 119.3, 119.6, 128.5, 128.6, 129.1, 129.3, 130.5, 131.5, 132.4, 134.6, 135.4, 140.9, 145.1, 148.5, 191.9. LCMS (ES$^+$) m/z = 402, 404 [M+H]$^+$.

**4-(3-Formyl-2,5-diphenyl-1H-pyrrol-1-yl)benzonitrile (6c)**

General Procedure B: 5c (0.096 g, 0.3 mmol), phosphorus oxychloride (0.08 mL, 0.9 mmol) in DMF (4 mL) gave 6c as a cream solid (0.084 g, 80%). mp 259-261 ºC; 1H NMR (300 MHz, d$_6$-DMSO) δ 9.57 (s, 1H, CHO), 6.90 (s, 1H, pyrrole), 7.80 (d, $J = 8.6$, 2H, Ar-H), 7.34 (d, $J = 8.5$, 2H, Ar-H), 7.24 (m, 10H, Ar-H).

**1-(4-(t-Butyl)phenyl)-2,5-diphenyl-1H-pyrrole-3-carbaldehyde (6d)**

General Procedure B: 5d (0.11 g, 0.3 mmol,) and phosphorus oxychloride (0.08 mL, 0.9 mmol) in DMF (4 mL) gave 6d as a cream solid (0.051 mg, 48%). mp 174-176 ºC; $^1$H NMR (300 MHz, d$_6$-DMSO) δ 9.53 (s, 1H, CHO), 6.84 (s, 1H, Pyrrole-H), 7.08 (d, $J = 8.8$ Hz, 2H, Ar-H), 6.81 (d, $J = 8.9$ Hz, 2H, Ar-H), 7.24 (m, 10H, Ar-H), 3.34 (s, 9H, t-Butyl).
1-(4-Nitrophenyl)-2,5-diphenyl-1H-pyrrole-3-carbaldehyde (6e)

General Procedure B: 5e (0.1 g, 0.3 mmol), phosphorus oxychloride (0.08 mL, 0.9 mmol), in DMF (4 mL) gave 6e as a cream solid. (24.3 mg, 22%). mp 208-209 °C; \( ^1\)H NMR (300 MHz, d₆-DMSO) δ 6.92 (s, 1H, pyrrole-H), 7.31 (m, 10H, Ar-H), 7.41 (d, \( J = 8.9 \) Hz, 2H, Ar-H), 8.13 (d, \( J = 8.9 \) Hz, 2H, Ar-H), 9.58 (s, 1H, CHO).

1-(4-Methoxyphenyl)-2,5-diphenyl-1H-pyrrole-3-carbaldehyde (6f)

General Procedure B: 5f (0.098 g, 0.3 mmol), phosphorus oxychloride (0.08 mL, 0.9 mmol) in DMF (4 mL) gave 6f as a white solid. (90 mg, 79%). mp 180-181 °C; \( ^1\)H NMR (300 MHz, d₆-DMSO) δ 3.68 (s, 3H, OCH₃), 6.81 (d, \( J = 8.9 \) Hz, 2H, N-Ar), 7.08 (d, \( J = 8.9 \) Hz, 2H, N-Ar), 7.25 (m, 10H, Ph), 9.53 (s, 1H, CHO). LCMS (ES⁺) m/z = 353.2 [M+H]+.

5-((1-(4-Chlorophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (4c)

General Procedure C: 6a (100 mg, 0.28 mmol), thiobarbituric acid (44.7 mg, 0.31 mmol), EtOH (3 mL) gave 4c (127 mg, 95%). mp 250-251 °C; \( ^1\)H NMR (300 MHz, d₆-DMSO) 12.2 (s, 1 H, NH), 12.1 (s, 1 H, NH) 8.01 (s, 1 H, vinyl), 7.32 (d, \( J = 8.7 \) Hz, 2 H, Ar-H), 7.18 (d, \( J = 8.7 \) Hz, 2 H, Ar-H), 7.27 (m, 11 H, Ar-H).

5-((1-(4-Chlorophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (4m)

General Procedure D: 6a (100 mg, 0.28 mmol), barbituric acid (42 mg, 0.26 mmol), glacial acetic acid (3 mL) gave 4m (98.7 mg, 75%). mp 364-366 °C; \( ^1\)H NMR (300 MHz, d₆-DMSO) 11.1 (s, 1 H, NH), 11.0 (s, 1 H, NH), 8.01 (s, 1 H, vinyl), 7.29 (m, 11 H, Ar-H), 7.19 (d, \( J = 8.7 \) Hz, 2 H, Ar-H), 7.34 (d, \( J = 8.7 \) Hz, 2 H, Ar-H); LCMS (ES⁺) m/z = 468.20 [M+H]+.

5-((1-(4-Bromophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (4n)

General Procedure D: 6b (100 mg, 0.24 mmol), barbituric acid (36 mg, 0.26 mmol), glacial acetic acid (3 mL) gave 4n (102 mg, 87%). mp 366-368 °C; \( ^1\)H NMR (300 MHz, d₆-DMSO) δ 7.12 (d, \( J = 8.7 \), 2H, Ar-H), 7.47 (d, \( J = 8.7 \), 2H, Ar-H), 7.27 (s, 1H, pyrrole), 7.31 (m, 10H, Ar-H), 8.01 (s, 1H, vinyl), 11.01 (s, 1H), 11.06 (s, 1H, NH); LCMS (ES⁺) m/z = 512 [M+H]+.

5-((1-(4-Methoxyphenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (4o)

General Procedure D: 1-(4-methoxyphenyl)-2,5-diphenyl-1H-pyrrole-3-carbaldehyde 6f (100 mg, 0.26 mmol), barbituric acid (41.5 mg, 0.29 mmol, 1.1 eq), glacial acetic acid (3 mL) gave 4o as a bright yellow solid (74 mg, 74%). mp 347-349 °C; \( ^1\)H NMR (300 MHz, d₆-DMSO) δ 1.18 (s, 3 H, OMe), 7.19 (m, 10 H, phenyl), 7.06 (d, \( J = 8.7 \), 2H, Ar-H), 7.27 (s, 1H, pyrrole), 7.31 (m, 10H, Ar-H), 8.01 (s, 1H, vinyl), 11.01 (s, 1H), 11.06 (s, 1H, NH); LCMS (ES⁺) m/z = 512 [M+H]+.
7.63, 2 H, N-Ar), 7.29 (s, 1 H, pyrrole), 7.36 (d, J = 7.63, 2 H, N-Ar), 8.01 (s, 1 H, vinyl), 11.03 (s, 1 H, NH), 11.08 (s, 1 H, NH);

5-((1-(4-((t-Butyl)phenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (4p)

General Procedure D: 6d (100 mg, 0.26 mmol), barbituric acid (42 mg, 0.31 mmol), glacial acetic acid (3 mL) gave 4p as bright yellow solid (16.2 mg, 13%). mp >320 °C; 1H NMR (300 MHz, d6-DMSO) δ 3.34 (s, 9 H, t-butyl), 7.25 (m, 11 H, Ar-H & pyrrole), 7.06 (d, J = 8.54, 2 H, Ar-H), 7.36 (d, J = 7.71, 2 H, Ar-H), 8.01 (s, 1 H, vinyl), 11.03 (s, 1 H, NH), 11.08 (s, 1 H, NH); LCMS (ES+) m/z = 490 [M+H]+; CHN C, 76.05; H, 5.56; N, 8.58; found C 75.53, H 5.52, N 8.84;

4-(2,5-Diphenyl-3-((2,4,6-trioxotetrahydropyrimidin-5(2H)-ylidene)methyl)-1H-pyrrol-1-yl)benzonitrile (4q)

General Procedure D: 6c (100 mg, 0.29 mmol), barbituric acid (42 mg, 0.31 mmol), glacial acetic acid (3 mL) gave 4q as bright yellow solid (94.0 mg, 70%). mp 368 -370 °C; 1H NMR (300 MHz, d6-DMSO) δ 7.23 (m, 11 H, Ar-H, pyrrole), 7.39 (d, J = 8.96, 2 H, Ar-H), 7.79 (d, J = 8.48, 2 H, Ar-H), 8.01 (s, 1 H, vinyl), 11.08 (s, 1 H, NH), 11.12 (s, 1 H, NH); LCMS (ES-) m/z = 457 [M-H]-.

4-(2,5-Diphenyl-3-((2-thioxodihydropyrimidine-4,6(1H,5H)-dione)methyl)-1H-pyrrol-1-yl)benzonitrile (4r)

General Procedure D: 6c (100 mg, 0.29 mmol), thiobarbituric acid (46 mg, 0.32 mmol), glacial acetic acid (3 mL) gave 4r as bright yellow solid (119 mg, 86%). mp 334-336 °C (dec); 1H NMR (300 MHz, d6-DMSO) δ 7.14 (dd, J = 6.51, 3.00 Hz, 3H), 7.28 (ddd, J = 9.33, 6.48, 1.62 Hz, 5H), 7.42 (dd, J = 9.32, 3.79 Hz, 3H), 7.39 (d, J = 8.46 Hz, 2H, Ar-N), 7.80 (d, J = 8.56 Hz, 2H, Ar-CN), 8.04 (s, 1H), 8.06 (s, 1H, vinyl), 12.22 (s, 1H, NH ex), 12.24 (s, 1H, NH ex); LCMS (ES+) m/z = 475.4 [M+H]+.

5-((1-(4-Nitrophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)pyrimidine-2,4,6(1H,3H,5H)-trione (4s)

General Procedure D: 6e (100 mg, 0.29 mmol), barbituric acid (42 mg, 0.31 mmol), glacial acetic acid (3 mL) gave 4s as bright yellow solid (94 mg, 70%). mp 368 -370 °C; 1H NMR (300 MHz, d6-DMSO) δ 7.23 (m, 11 H, Ar-H, pyrrole), 7.39 (d, J = 8.96, 2 H, Ar-H), 7.79 (d, J = 8.48, 2 H, Ar-H), 8.01 (s, 1 H, vinyl), 11.08 (s, 1 H, NH), 11.12 (s, 1 H, NH); LCMS (ES-) m/z = 457 [M-H]-.

5-((1-(4-Nitrophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (4t)

General Procedure D: 6e (100 mg, 0.29 mmol), thiobarbituric acid (43 mg, 0.30 mmol), glacial acetic acid (3 mL) gave 4t as bright yellow solid (107 mg, 79%). mp 333-334 °C; 1H NMR (300 MHz, d6-DMSO) δ 7.16 (dd, J = 6.53, 2.94 Hz, 3H, phenyl), 7.29 (m, 5H, phenyl, Ar-N), 7.44 (dd, J = 13.77, 8.10 Hz, 5H, phenyl), 8.06 (d, J =
11.70 Hz, 2H, Ar-NO2), 8.13 (s, 1H), 8.16 (s, 1H, vinyl), 12.24 (s, 1H, NH ex), 12.25 (s, 1H, NH ex); LCMS (ES+) m/z = 495.3 [M+H]+. Anal. Calcd. for C27H18N4O4S: req.uires C, 65.58; H, 3.67; N, 11.32%; found: C, 65.56; H, 3.60; N, 11.41%

5-((1-(4-Chlorophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-1,3-diethyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (4u)

General Procedure C: 6a (0.195 g, 0.54 mmol), 1,3-diethyl-2-thiobarbituric acid (0.12 g, 0.6 mmol), EtOH (6 mL). Chromatography (silica; DCM) gave 4u as an orange solid (0.26 g, 89%). mp 272-273 °C. IR (cm⁻¹) 3171, 3082, 2927, 2162, 2029, 1694, 1661; ¹H NMR (300 MHz, CDCl₃) δ 1.32 (t, J = 7.0 Hz, 6H, CH₃), 4.58 (q, J = 7.0 Hz, 4H, 2 x CH₂), 6.89 (d, J = 8.7 Hz, 2H, -C₂H₂C₂H₂C(Cl)), 7.13-7.22 (m, 6H, Ar-H), 7.25-7.27 (d, J = 8.7 Hz, 2H, -C₂H₂C₂H₂C(Cl)), 7.34-7.41 (m, 4H , Ar -H), 8.09 (s, 1H, pyrrole), 8.40 (s, 1H, -C=CH-). ¹³C NMR (75 MHz, CDCl₃) δ 12.7, 12.9, 43.6, 44.1, 112.3, 114.4, 121.2, 128.1, 128.6, 128.7, 129.5, 129.6, 129.7, 129.9, 131.7, 132.0, 134.6, 136.8, 149.9, 152.9, 159.7, 162.2, 179.6; HRMS (EI): C₃₁H₂₆ClN₃O₂S calcd. m/z 540.1507 [M]+; found m/z 540.1507 [M]+.

5-((1-(4-Bromophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-1,3-diethylpyrimidine-2,4,6(1H,3H,5H)-trione (4v)

General Procedure C: 6b (0.07 g, 0.174 mmol) and N,N-diethylbarbituric acid (0.035 g, 0.191 mmol) in anhydrous EtOH (2 mL). Chromatography (silica; 75-100% DCM, petrol) gave 4v as a yellow solid (0.051 g, 52%); mp 285-286 °C. λ max (CH₃OH)/nm = 406. IR: 3167, 3083, 2924, 2851, 1722, 1657, 1542 cm⁻¹; ¹H NMR: (300 MHz, CDCl₃) δ 1.25 (t, J = 7.1 Hz, 6H, CH₃), 4.04 (q, J = 7.1 Hz, 4H, CH₂), 6.83 (d AB, J = 8.7 Hz, 2H, -C₂H₂C₂H₂C(Br)), 7.13-7.16 (m, 4H, ArH), 7.24-7.27 (m, 4H, ArH), 7.32-7.40 (m, 4H, ArH), 8.07 (s, 1H, pyrrole H), 8.39 (s, 1H, C=CH-). ¹³C NMR: (75 MHz, CDCl₃) δ 16.94, 27.38, 103.76, 107.26, 118.91, 123.17, 124.89, 128.19, 128.62, 131.95, 134.81, 136.21, 150.21, 152.11, 158.75, 165.38. HRMS (EI): C₃₁H₂₆BrN₃O₃ Calcd.m/z = 567.1158 [M]+, obsd m/z = 567.1178 [M]+. Anal. Calcd. for C₃₁H₂₆BrN₃O₃: C, 65.49; H, 4.57; N, 7.39%. Found: C, 65.87; H, 4.39; N, 7.35%.

5-((1-(4-Bromophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-1,3-diethyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (4w)

General Procedure C: 6b (0.20 g, 0.497 mmol), 1,3-diethyl-2-thiobarbituric acid (0.11 g, 0.547 mmol), EtOH (6 mL). Chromatography (silica; DCM) gave 4w as an orange solid (0.238 g, 82%). mp 271-272 °C. IR (cm⁻¹) 3171, 3082, 2978, 2928, 2160, 1693, 1660, 1533; ¹H NMR (300 MHz, CDCl₃) δ 1.32 (t, J = 6.9 Hz, 6H, CH₃), 4.58 (q, J = 6.9 Hz, 4H, 2 x CH₂), 6.85 (d, J = 8.7 Hz, 2H, -C₂H₂C₂H₂C(Br)), 7.13-7.17 (m, 4H, Ar-H), 7.25-7.27 (m, 2H, Ar-H), 7.34-7.41 (m, 6H, Ar-H), 8.09 (s, 1H, pyrrole proton), 8.40 (s, 1H, -C=CH-). ¹³C NMR (75 MHz, CDCl₃) δ 12.7, 12.9, 43.6, 44.1, 112.3, 114.5, 121.2, 128.1, 128.6, 128.7, 129.6, 129.7, 132.0, 130.2, 131.7, 132.0,
132.5, 137.1, 137.9, 149.8, 152.9, 159.7, 162.1, 179.7. HRMS (El): C_{31}H_{26}^{79}BrN_{3}O_{2}S calcd. m/z 584.1002 [M]^+; found: m/z 584.0998 [M]^+. CHN

5-((1-(4-Chlorophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-3-methyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (4x)

General Procedure D: 6a (0.086 g, 0.24 mmol), 4,6-dihydroxy-1-methylpyrimidine-2(1H)-thione (0.042 g, 0.26 mmol), glacial acetic acid (3 mL). Chromatography (silica; DCM) gave a mixture of regioisomers 4x as an orange solid (0.065 g, 53%). mp: 316-317 °C; IR (cm⁻¹) 3141, 3078, 2920, 2850, 2031, 2011, 1977, 1693, 1649. ¹H NMR (300 MHz, d₆-DMSO) δ 3.50 & 3.59 (2s, 2x3H, CH₃), 7.16-7.20 (d, J = 8.7, 2H, -C₂H₂C₂H₂C(Cl)), 7.22-7.34 (m, 6H, Ar-H), 7.35-7.39 (m, 3H, Ar-H), 7.40-7.45 (m, 3H, Ar-H), 8.04-8.07 (2 x s, 1H, C=CH -), 8.08 (s, 1H, pyrrole H), 12.38 (s, 1H, NH). ¹³C NMR (75 MHz, d₆-DMSO) δ 35.1, 99.5, 111.8, 115.1, 121.7, 123.5, 124.7, 127.9, 127.5, 128.7, 129.1, 130.8, 132.0, 132.9, 138.3, 149.5, 156.5, 157.3, 185.8; LCMS m/z = 498 (ES⁺). Anal. Calcd. for C₂₈H₂₀ClN₃O₂S + 0.2 H₂O: C, 67.05; H, 4.10; N, 8.38%. Found: C, 67.45; H, 4.35; N, 7.99%.

5-((1-(4-Bromophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-1-methylpyrimidine-2,4,6(1H,3H,5H)-trione (4y)

General Procedure C: 6b (0.07 g, 0.174 mmol), N-methylbarbituric acid (0.025 g, 0.191 mmol), EtOH (2 mL). Chromatography (silica; DCM - 1% MeOH/DCM) gave a mixture of regioisomers 4y as a yellow solid (0.06 g, 60%). R_f = 0.34 and 0.41 (5:95 MeOH:DCM); IR (cm⁻¹) 695, 755, 790, 839, 961, 1028, 1068, 1138, 1189, 1306, 1371, 1443, 1483, 1538, 1654, 1684, 2850, 2920, 3065, 3167; ¹H NMR (300 MHz, CDCl₃) δ 3.34 and 3.40 (s, 3H, CH₃), 6.90 (d, J = 8.5, 2H, -C₂H₂C₂H₂C(Br)), 7.12-7.16 (m, 4H, Ar -H), 7.25-7.27 (m, 2H, ArH), 7.33-7.41 (m, 6H, Ar-H), 7.85 (s, 1H, NH), 8.09 (s, 1H, pyrrole H), 8.36 and 8.41 (s, 1H, C=CH). ¹³C NMR (75 MHz, CDCl₃) δ 28.3, 100.4, 110.5, 118.7, 121.1, 123.7, 126.4, 127.8, 128.6, 128.7, 129.5, 129.6, 129.7, 130.5, 130.5, 130.9, 131.1, 130.2, 131.6, 131.6, 132.0, 132.5, 137.8, 141.8, 149.3, 149.7, 150.6, 159.4; LCMS (ES⁺)m/z = 526, 528. HRMS (El): m/z Calcd. for ion: 525.0688 [M]^+. Found: 525.0685 [M]^+. CHN.

5-((1-(4-Bromophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-3-methyl-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (4z)

General Procedure D: 6b (0.10 g, 0.25 mmol) and 4,6- dihydroxy-1-methylpyrimidine-2(1H)-thione (0.043 g, 0.27 mmol), glacial acetic acid (3 mL) gave 4z as an orange solid (0.108 g, 81%). IR (cm⁻¹) 3138, 3076, 2928, 2164, 2069, 1976, 1695, 1649; ¹H NMR (300 MHz, DMSO) δ 3.50 and 3.59 (2 x s, 3H, CH₃), 7.18 (d, J = 8.6, 2H, C₂H₂C₂H₂C(Br)), 7.30-7.31 (m, 6H, Ar-H), 7.42-7.43 (m, 3H, Ar-H), 7.49-7.52 (m, 3H, Ar-H), 8.04 (1H, C=CH-), 8.08 (s, 1H, pyrrole H), 12.37 (br s, 1H, NH); ¹³C NMR (75 MHz, DMSO) δ 32.3, 99.4, 110.5, 118.7, 121.1, 123.7, 126.4, 127.8, 128.6, 128.6, 129.1, 131.1, 131.6, 132.1, 132.3, 132.8, 143.2, 150.1, 155.2, 158.8, 181.3. LCMS (ES⁺) m/z = 542, 544. CHN.
5-((1-(4-Bromophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-2,2-dimethyl-1,3-dioxiane-4,6-dione. (7)

General Procedure E: 6b (100 mg, 0.248mmol), Meldrum’s acid 8 (44.7 mg, 0.31 mmol). The reaction mixture was diluted with EtOAc (20 mL) and washed with saturated NaHCO₃ (2 x 10 mL), dried (Na₂SO₄) and concentrated in vacuo. Chromatography (5-40% EtOAc, hexane) gave 7 as a yellow solid (93 mg, 49%). mp 220 ºC, IR (cm⁻¹) 2958, 1712, 1608, 1545; ¹H NMR (500 MHz, CDCl₃) δ 1.69 (6H, s, (CH₃)₂), 6.70-6.74 (2H, m, Ar-H), 7.05-7.06 (4H, m, Ar-H), 7.16-7.17 (2H, m, Ar-H), 7.26-7.45 (5H, m, Ar-H), 7.77 (1H, s, 4-H), 8.18 (1H, s, 3-CH); ¹³C NMR (125MHz, CDCl₃) δ 14.1, 21.1, 22.6, 27.4, 29.7, 31.6, 60.4, 103.6, 106.8, 113.0, 119.1, 122.2, 127.7, 128.2, 128.5, 128.7, 129.0, 129.3, 129.8, 131.0, 132.2, 136.4, 137.5, 131.4, 148.5, 150.9, 161.1, 164.4, 171.1. LCMS (ES+) m/z = 472 [M+H]+;

5-((1-(4-Bromophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione. (9)

To a suspension of 7 (50 mg; 0.095 mmol) in MeOH (0.6 mL) at 0 ºC was added NaBH₄ (3.6 mg; 0.19mmol), and mixture was allowed to warm to rt with stirring for 30 minutes. HCl (1M; 0.5mL) was added and the precipitate filtered, and washed with water giving 9 as a white solid (30 mg; 60%); mp 159 ºC; IR (cm⁻¹) 2023, 1748, 1490; ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.28 (6H, m, Ar-H), 7.11-7.21 (4H, m, Ar-H), 6.97 (2H, d, J = 7.9 Hz, Ar-H), 6.77 (2H, d, J = 8.6 Hz, Ar-H), 6.42 (1H, s, 4-H), 3.62 (1H, t, J = 5.1 Hz, CH), 3.32 (2H, d, J = 5.1 Hz, 3-CH₂), 1.61 (3H, s, CH₃), 1.60 (3H, s, CH₃): δC (75MHz, CDCl₃) 24.2, 27.4, 28.9, 29.9, 47.8, 105.1, 110.7, 118.9, 121.0, 126.8, 127.7, 128.3, 128.9, 130.6, 131.5, 131.9, 132.4, 133.2, 134.2, 134.9, 138.5, 165.6. LCMS (ES+) m/z = 364.

Dimethyl 2-((1-(4-chlorophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)malonate (10a)

General Procedure E: 6a (50 mg, 0.140 mmol), dimethyl malonate (20 µl, 0.18 mmol). Chromatography (30% EtOAc, Petrol) gave 10a as a white solid (47 mg, 71%); mp 228.6 ºC; IR (cm⁻¹) 3060, 2950, 2361, 1731; ¹H NMR (500MHz, CDCl₃) δ 3.76 (s, 3H, O-CH₃), 3.93 (s, 3H, O-CH₃), 6.54 (s, 1H, Pyrrole), 6.83-6.80 (m, 2H, Ar-H), 7.09-7.02 (m, 3H, Phenyl), 7.14-7.19 (m, 2H, Ar-H), 7.23-7.20 (m, 3H, Ar-H), 7.32-7.27 (m, 3H, Ph), 7.60 (s, 1H, 3-CH); ¹³C NMR (125MHz, d₈-THF) δ 52.12, 52.40, 109.17, 118.22, 121.98, 128.18, 129.12, 129.14, 129.26, 129.89, 131.31, 131.47, 132.42, 133.14, 133.39, 134.17, 137.74, 138.00, 141.90, 165.59, 168.23; LCMS (ES+) m/z = 472.18 [M+H⁺]; HRMS: C₂₈H₂₂O₄NClNa [M+Na]+ Calculated: 494.1130, Found: 494.1121

2-((1-(4-Chlorophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)malonic acid (10b) and (E)-3-(1-(4-chlorophenyl)-2,5-diphenyl-1H-pyrrol-3-yl) acrylic acid (10f)

General Procedure E: 6a (50 mg, 0.140 mmol), malonic acid (18 mg, 0.175 mmol). Chromatography (30% EtOAc, petrol then 1% MeOH, EtOAc) gave 10b as a white solid (30 mg, 48%). mp 302 ºC (dec); IR (cm⁻¹)
3058, 2923, 2183, 1493; LCMS (ES⁻) m/z = 444 [M+H]⁺; HRMS: C₂₆H₁₇NO₄ClNa [M-H]⁻ Calculated: 442.0852, Found: 442.0857.

and 10f (17 mg, 30%) mp 302 °C (dec) IR (cm⁻¹) 3054, 2361, 1676, 1594, 1496; ¹H NMR (500MHz, DMSO) δ 6.30 (d, J = 15.5, 1H, HC=C), 7.03 (s, 1H, pyrrole), 7.14 (d, J = 13.5, 2H, Ar-H), 7.20-7.16 (m, J = 21, 4H), 7.41-7.24 (m, J = 83.5, 10H), 11.89 (s br, 1H, COOH); LCMS (ES⁻) m/z = 400 [M+H⁺]; HRMS: C₂₅H₁₇NO₂Cl [M-H]⁻ Calculated: 398.0953, Found: 398.0950.

2-((1-(4-Chlorophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)malonamide (10c)

General Procedure E: 6a (50 mg, 0.140 mmol), malonamide (18 mg, 0.175 mmol). Chromatography (EtOAc) and recrystallisation (MeOH) gave 10c as white crystals (38 mg, 61%). mp 301.6 °C; IR (cm⁻¹) 3349, 3174, 2938, 2833, 1649, 1566; ¹H NMR (500MHz, d₆-DMSO) δ 6.90-6.79 (m, 2H, N'H' and 4-H), 7.11-7.04 (m, 6H, N'H and Ar-H), 7.16-7.13 (m, 2H, Ar-H), 7.29-7.20 (m, 4H, Ar-H), 7.29-7.24 (m, 10H, NH' and Ar-H), 7.58 (s, 1H, 3-CH), 7.97 (s, 1H, NH); ¹³C NMR (125MHz, d₈-THF) δ 26.5, 30.8, 110.2, 119.1, 127.9, 128.8, 129.0, 129.7, 129.9, 131.1, 131.4, 131.9, 132.4, 133.6, 134.0, 136.7, 141.0, 166.4, 172.1. LCMS (ES⁺) m/z = 442.15 [M+H⁺]; HRMS: C₂₆H₂₁O₂N₃Cl [M+H] Calculated: 442.1317, Found: 442.1316

2-((1-(4-Chlorophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-N₁,N₃-dimethylmalonamide (10d)

General Procedure E: 6a (50 mg, 0.14 mmol), N,N'-dimethylmalondiamide (23mg, 0.175 mmol). Chromatography (5% MeOH, EtOAc) gave 10d as a white solid (47 mg, 71%). mp 259.4 °C; IR (cm⁻¹) 3232, 3068, 2927, 1638, 1534. ¹H NMR (500MHz, CDCl₃) δ 2.84 (d, J = 5, 3H, NCH₃), 2.94 (d, J = 5, 3H, CH₃), 6.76-6.72 (m, 1H, NH), 6.54 (s, 1H, pyrrole), 6.84-6.82 (m, 2H, Ar-H), 7.07-7.02 (m, 4H, Ar-H), 7.16-7.12 (m, 2H, Ar-H), 7.22-7.19 (m, 3H, Ar-H), 7.28-7.25 (m, 3H, Ar-H), 7.35-7.30 (m, 1H, NH), 7.65 (s, 1H, 3-CH); ¹³C NMR (125MHz, THF) δ 26.5, 30.8, 110.2, 119.1, 127.9, 128.8, 129.0, 129.1, 129.3, 129.7, 129.9, 131.1, 131.4, 131.9, 132.3, 133.5, 134.1, 136.8, 138.4, 140.2, 165.5, 170.2; LCMS m/z = 470.21 [M+H⁺]; HRMS: C₂₈H₂₅O₂N₃Cl [M+H] Calculated: 470.1630, Found: 470.1633.

2-((1-(4-Chlorophenyl)-2,5-diphenyl-1H-pyrrol-3-yl)methylene)-N₁,N₃-bis(2-hydroxyethyl)malonamide (10e)

General Procedure E: 6a (50 mg, 0.140 mmol), N₁,N₃-bis(2-hydroxyethyl)malonamide (33mg, 0.175mmol). Recrystallisation (EtOH, H₂O) gave 10e as a yellow solid (36 mg, 49%). mp 246.3°C; IR (cm⁻¹) 3275; 2872 , 1637, 1598, 1525; ¹H NMR (500MHz, d₆-DMSO) δ 3.27-3.22 (m, 2H, CH₂), 3.41-3.37 (m, 2H, CH₃), 3.49-3.43 (m, 2H, CH₂), 3.63-3.56 (m, 2H, CH₂), 4.74 (t, 1H, J = 5 Hz, OH), 4.84 (t, 1H, J = 5 Hz, OH), 6.70 (s, 1H, pyrrole), 7.16-7.10 (m, 4H, Ar-H), 7.24-7.18 (m, 3H, Ar-H), 7.35-7.25 (m, 3H, Ar-H), 7.45-7.36 (m, 6H, Ar-H & 2NH), 8.51 (m, 1H, 3-CH). LCMS: m/z = 530.23 [M+H⁺] HRMS: C₃₀H₂₉O₄N₃Cl [M+H] Calculated: 530.1841, Found: 530.1839.
Ethyl 2-(cyclopropanecarbonyl)-4-oxo-4-phenylbutanoate (16a)

General Procedure F: ethyl 3-oxo-3-phenylpropanoate 15a (4 g, 20.8 mmol), diethyl zinc (85 mL, 85 mmol), diiodomethane (6.7 mL, 85 mmol), cyclopropyl aldehyde (1.7 mL, 22.89 mmol), DCM (171 mL) and PCC (9.42 g, 40.3 mmol) gave 16a as a clear viscous oil (2.04 g, 36%). IR (cm$^{-1}$) 1734, 1685, 1449, 1384; $^1$H NMR (300 MHz) $\delta$ 0.94-1.20 (m, 4H, H$_2$ and H$_2'$), 1.34 (t, 7.0, CH$_3$), 2.25-2.41 (m, 1H, 2-(CO)CH), 3.5-3.78 (m, 2H, 3-H$_2$), 4.28 (q, 2H, H$_2$), 4.39-4.50, (m, 2H, 2-H), 7.40-7.65 (m, 3H, Ar-H), 7.92-8.80 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz) $\delta$ 11.8, 14.3, 20.9, 37.4, 54.9, 61.8, 128.4, 128.9, 133.5, 137.1, 169.4, 197.3, 204.2; LCMS (ES$^+$) m/z = 274.3 [M+H$^+$]

Ethyl 2-benzoyl-4-cyclopropyl-4-oxobutanoate (16b)

General Procedure F: ethyl 3-cyclopropyl-3-oxopropanoate 15b (3.5 g, 22.5 mmol), diethyl zinc (92 mL, 92.1 mmol), diiodomethane (7.42 mL, 92.1 mmol), benzaldehyde (2.5 mL, 24.7 mmol), PCC (12.11 g, 56.2 mmol) gave 16b as a clear viscous oil (2.93 g, 48%). $^1$H NMR (400 MHz) $\delta$ 0.88-0.93 (m, 2H, H$_2$), 1.01-1.05 (m, 2H, H$_2'$), 1.14 (t, J = 7.1, 3H, CH$_3$), 1.99 (tt, J = 4.6 and 7.8, 1H, 4-CH), 3.28 (dd, J = 6.2 and 18.0, 1H, 3-H), 3.37 (dd, J = 7.5 and 18.0, 1H, 3-H'), 4.11 (q, J = 7.1, 2H, H$_2$), 4.91 (dd, J = 6.2 and 7.5, 1H, 2-H), 7.40-7.99 (m, 2H, Ar-H), 7.54-7.59 (m, 1H, Ar-H), 7.99-8.03 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz) $\delta$ 11.0, 13.9, 20.6, 41.9, 48.6, 61.6, 128.6, 128.8, 133.5, 136.1, 169.1, 194.7.

Methyl 2-benzoyl-5,5-dimethyl-4-oxohexanoate (16c)

General Procedure F: 4,4-dimethyl-3-oxopentanoate 15c (1 g, 6.3 mmol), diethyl zinc (25.9 mL, 25.9 mmol), diiodomethane (2.08 mL, 25.9 mmol), benzaldehyde (0.67 mL, 6.8 mmol), PCC (3.25 g, 15.1 mmol) gave 16c as a clear viscous oil (1.71 g, 98%). IR (cm$^{-1}$) 2958, 2872, 2019, 1738, 1684; $^1$H NMR (300 MHz) $\delta$ 1.20 (s, 9H, t-Bu), 3.24 (dd, J = 9, 18, 1H, 3-H), 3.35 (dd, J = 6, 18, 1H, 3-H'), 3.69 (s, 3H, CH$_3$), 4.94 (dd, J = 6, 9, 1H, 2-H), 7.48-7.54 (m, 2H, Ar-H), 7.59-7.65 (m, 1H, Ar-H), 8.00-8.80 (m, 2-H, Ar-H); $^{13}$C (100 MHz) $\delta$ 26.8, 37.0, 44.3, 49.0, 52.8, 129.0, 129.2, 133.7, 136.7, 170.2, 195.1, 213.0

Ethyl 1-(4-chlorophenyl)-2-cyclopropyl-5-phenyl-1H-pyrrole-3-carboxylate (18d)

General Procedure G: 16a (500 mg, 1.8 mmol), 4-chloroaniline (697 mg, 5.4 mmol), PTSA (17 mg, 0.09 mmol) in toluene (1.7 mL). Chromatography (4% EtOAc, hexane) gave 18d (582 mg, 88%). $^1$H NMR (400 MHz) $\delta$ 0.39-0.43 (m, 2H, H$_2$), 0.70-0.75 (m, 2H, H$_2'$), 1.37 (t, J = 7.1, 3H, CH$_3$), 1.79 (tt, J = 5.5 and 8.5, 1H, 2-CH), 4.32 (q, J = 7.1, 2H, H$_2$), 6.73 (s, 1H, 4-H), 7.00-7.04 (m, 2H, Ar-H), 7.07-7.10 (m, 2H, Ar-H), 7.13-7.19 (m, 3H, Ar-H), 7.29-7.34 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz) $\delta$ 7.9, 8.4, 14.5, 59.7, 110.7, 115.1, 126.8, 128.1, 128.4, 129.0, 129.6, 132.1, 133.6, 164.8.

Ethyl 1-(4-bromophenyl)-2-cyclopropyl-5-phenyl-1H-pyrrole-3-carboxylate (18e)
General Procedure G: 16a (500 mg, 1.8 mmol), 4-bromoaniline (940 mg, 5.4 mmol), PTSA (17 mg, 0.09 mmol). Chromatography (4% EtOAc, hexane) gave 18e (609 mg, 82%). IR (cm⁻¹) 3668, 2978, 2901, 1701, 1490, 1410; ¹H NMR (400 MHz) δ 0.39-0.44 (m, 2H, m, CH₂), 0.70-0.76 (m, 2H, H₂'), 1.36 (t, J = 7, 3H, CH₃), 1.79 (tt, J = 5.7, 8.4, 1H, 2-CH), 4.32 (q, J = 7, 2H, H₂), 6.72 (s, 1H, 4-H), 6.99-7.05 (m, 4H, Ar-H), 7.13-7.20 (m, 3H, Ar-H), 7.45-7.49 (m, 2H, Ar-H). ¹³C NMR (75 MHz) δ 8.5, 8.7, 14.8, 60.0, 111.4, 115.7, 122.0, 127.2, 128.5, 130.0, 130.5, 132.4, 134.0, 138.5, 141.2, 165.1. LCMS (ES⁺) m/z = 412.2 [M+H]⁺

Ethyl 1-(4-chlorophenyl)-5-cyclopropyl-2-phenyl-1H-pyrrole-3-carboxylate (18f)

General Procedure G: 16b (500 mg, 1.8 mmol), 4-chloroaniline (697 mg, 5.4 mmol), PTSA (17 mg, 0.09 mmol). Chromatography (4% EtOAc, hexane) gave 18f (582 mg, 88%). ¹H NMR (400 MHz) δ 0.79-0.84 (m, 2H, H₂), 0.85-0.91 (m, 2H, H₂'), 1.30 (t, J = 7.2, 3H, CH₃), 1.54-1.62 (m, 1H, 5-CH), 4.28 (q, J = 7.2, 2H, H₂), 6.53 (s, 1H, 4-H), 7.19-7.23 (m, 2H, H₂), 7.27-7.31 (m, 2H, Ar-H), 7.27-7.31 (m, 2H, Ar-H), 7.31-7.35 (m, 3H, Ar-H), 7.38-7.42 (m, 2H, Ar-H); ¹³C NMR (75 MHz) δ 7.6, 8.2, 14.4, 59.7, 106.8, 114.0, 127.37, 127.9, 129.2, 130.3, 131.5, 132.2, 134.1, 137.5, 138.9, 165.0.

Methyl 1-(4-bromophenyl)-5-cyclopropyl-2-phenyl-1H-pyrrole-3-carboxylate (18g)

General Procedure g: 16b (500 mg, 1.8 mmol), 4-bromoaniline (941 mg, 5.4 mmol), PTSA (17 mg, 0.09 mmol). Chromatography (4% EtOAc, hexane) gave 18g (582 mg, 88%). ¹H NMR (400 MHz) δ 0.63-0.68 (m, 2H, CH₂), 0.69-0.75 (m, 2H, H₂), 1.14 (t, J = 7.2, 3H, CH₃), 1.38-1.46 (m, 2H, 5-CH), 4.12 (q, J = 7.2, 2H, CH₂), 6.37 (s, 1H, 4-H), 6.97-7.01 (m, 2H, Ar-H), 7.11-7.16 (m, 2H, Ar-H), 7.17-7.21 (m, 3H, Ar-H), 7.38-7.42 (m, 2H, Ar-H); ¹³C NMR (100 MHz) δ 7.4, 7.9, 14.2, 59.5, 106.3, 113.2, 121.6, 127.4, 127.7, 130.2, 131.1, 131.4, 131.9, 137.0, 137.2, 138.6, 164.7.

(1-(4-Bromophenyl)-5-(tert-butyl)-2-phenyl-1H-pyrrol-3-yl)methanol (19b)

General Procedure H: 18b (100 mg, 0.24 mmol), DIBAL-H (0.61 mL, 0.61 mmol). Chromatography (30% EtOAc, hexane) gave 19b (75 mg, 80%). IR (cm⁻¹) 3430, 2961, 2920, 2866, 1485; ¹H NMR (300 MHz) δ 1.10 (s, 9H, t-Bu), 1.51 (br. s, 1H, OH) 4.40 (s, 2H, 3-CH₂), 6.18 (s, 1H, 4-H), 6.98-7.12 (m, 7H, Ar-H), 7.28-7.35 (m, 2H, Ar-H); ¹³C NMR (100 MHz) δ 31.8, 33.2, 58.6, 106.7, 121.0, 122.3, 127.3, 128.1, 131.3, 131.6, 132.3, 132.9, 134.9, 140.4, 144.4.

(5-(tert-Butyl)-1-(4-chlorophenyl)-2-phenyl-1H-pyrrol-3-yl)methanol (19c)

General Procedure H: 18c (50 mg, 0.14 mmol), DIBAL-H (0.34 mL, 0.34 mmol). Chromatography (30% EtOAc, hexane) gave 19c (42 mg, 91%). IR (cm⁻¹) 2957, 2925, 1491; ¹H NMR (300 MHz) δ 1.10 (s, 9H, t-Bu), 1.46 (br. s, 1H, OH), 4.39 (s, 2H, 3-CH₂), 6.18 (s, 1H, 4-H), 6.93-7.01 (m, 2H, Ar-H), 7.05-7.18 (m, 7H, Ar-H); ¹³C (100 MHz) δ 31.8, 33.2, 58.6, 106.6, 127.3, 128.0, 128.5, 131.3, 132.6, 134.3, 135.0, 144.4
(1-(4-Chlorophenyl)-2-cyclopropyl-5-phenyl-1H-pyrrol-3-yl)methanol (19d)

General Procedure H: 18d (300 mg, 0.71 mmol), DIBAL-H (2.2 mL, 2.2 mmol). Chromatography (30% EtOAc, hexane) gave 19d (250 mg, 91%). $^1$H NMR (400 MHz) $\delta$ 0.44-0.50 (m, 2H, H$_2$), 0.62-0.68 (m, 2H, H$_2'$), 1.51 (br. s, 1H, OH), 1.58-1.67 (m, 1H, 2-CH), 4.69 (s, 2H, 3-CH$_2$), 6.36 (s, 1H, 4-H), 7.01-7.05 (m, 2H, Ar-H), 7.08-7.19 (m, 5, Ar-H), 7.28-7.33 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz) 6.3, 6.6, 38.3, 57.7, 109.7, 122.4, 126.3, 128.3, 129.0, 129.8, 132.8, 133.0, 133.9.

(1-(4-Bromophenyl)-2-cyclopropyl-5-phenyl-1H-pyrrol-3-yl)methanol (19e)

General Procedure H: 18e (304 mg, 0.74 mmol), DIBAL-H (2.2 mL, 2.2 mmol). Chromatography (30% EtOAc, hexane) gave 19e (250 mg, 91%). $^1$H NMR (400 MHz) $\delta$ 0.44-0.49 (m, 2H, H$_2$), 0.63-0.68 (m, 2H, H$_2'$), 1.48 (br. s, 1H, OH), 1.59-1.66 (m, 1H, 2-CH), 4.69 (s, 2H, 3-CH$_2$), 6.36 (s, 1H, 4-H), 7.00-7.06 (m, 4H, Ar-H), 7.09-7.19 (m, 3H, Ar-H), 7.43-7.48 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz) 6.4, 6.6, 57.7, 109.7, 120.9, 122.3, 126.2, 128.1, 130.0, 131.8, 132.7, 133.4, 133.7, 138.7.

(1-(4-Chlorophenyl)-5-cyclopropyl-2-phenyl-1H-pyrrol-3-yl)methanol (19f)

General Procedure H: 18f (291 mg, 0.79 mmol), DIBAL-H (2.4 mL, 2.39 mmol). Chromatography (30% EtOAc, hexane) gave 19f (233 mg, 90%). $^1$H NMR (300 MHz) $\delta$ 0.52-0.61 (m, 2H, H$_2$), 0.63-0.70 (m, 2H, H$_2'$), 1.38-1.49 (m, 1H, 5-CH), 1.58 (br. s, 1H, OH), 4.43 (s, 2H, 3-CH$_2$), 5.97 (s, 1H, 4-H), 6.98-7.08 (m, 5H, Ar-H), 7.10-7.14 (m, 2H, Ar-H), 7.16-7.23 (m, 2H, Ar-H); $^{13}$C NMR (100 MHz) 7.7, 8.5, 58.5, 105.8, 122.1, 127.1, 128.1, 128.3, 129.1, 130.2, 130.6, 132.5, 132.6, 133.1, 133.2, 133.4, 137.7, 138.3.

(1-(4-Bromophenyl)-5-cyclopropyl-2-phenyl-1H-pyrrol-3-yl)methanol (19g)

General Procedure H: 18g (300 mg, 0.73 mmol), DIBAL-H (2.2 mL, 2.2 mmol). Chromatography (30% EtOAc, hexane) gave 19g (229 mg, 85%). $^1$H NMR (300 MHz) $\delta$ 0.65-0.70 (m, 2H, H$_2$), 0.71-0.80 (m, 2H, H$_2'$), 1.44-1.59 (m, 2H, 5-H), 1.64 (br. s, 1H, OH), 4.53 (s, 2H, 3-CH$_2$), 6.07 (s, 1H, 4-H), 7.03-7.12 (m, 4H, Ar-H), 7.19-7.30 (m, 3H, Ar-H), 7.40-7.47 (m, 2H, Ar-H); $^{13}$C NMR (75 MHz) $\delta$ 7.8, 8.5, 58.5, 105.9, 121.3, 122.2, 127.1, 128.3, 130.5, 130.6, 132.2, 132.2, 132.6, 137.7, 138.8.

(1-(4-Bromophenyl)-5-((tert-butyl)-2-phenyl-1H-pyrrole-3-carbaldehyde (17b)

General Procedure I: 19b (75 mg, 0.20 mmol), TPAP (7 mg, 0.19 mmol), NMO (46 mg, 0.4 mmol) and 4 Å molecular sieves (100 mg). Chromatography (5-10% EtOAc, hexane) gave 17b (62mg, 83%). $^1$H NMR (300 MHz) 1.09 (s, 9H, t-Bu), 6.58 (s, 1H, 4-H), 7.00-7.08 (m, 4H, Ar-H), 7.11-7.17 (m, 3H, Ar-H), 7.31-7.39 (m, 2H, Ar-H), 9.43 (s, 1H, CHO); $^{13}$C NMR (100 MHz) 31.4, 33.3, 104.5, 123.2, 123.6, 128.2, 128.8, 131.7, 131.9, 132.6, 138.7, 146.3, 186.9.
5-(tert-Butyl)-1-(4-chlorophenyl)-2-phenyl-1H-pyrrole-3-carbaldehyde (17c)

General Procedure I. 19c (42 mg, 0.12 mmol), TPAP (4 mg, 0.12 mmol), NMO (28 mg, 0.25 mmol) and 4 Å molecular sieves (61 mg). Chromatography (5-10% EtOAc, hexane) gave 17c (21 mg, 50%). IR (cm⁻¹) 698, 746, 1090, 1217, 1431, 1486, 1661, 2928, 2963; ¹H NMR (300 MHz) δ 1.10 (s, 9H, t-Bu), 6.59 (s, 1H, 4-H), 7.04-7.21 (m, 9H, Ar-H), 9.44 (s, 1H, CHO); ¹³C NMR (100 MHz) δ 31.4, 33.3, 104.5, 123.7, 128.2, 128.7, 128.9, 130.0, 131.7, 132.2, 135.2, 138.2, 145.8, 146.3, 186.9; LCMS (ES⁺) m/z = 337.84 [M+H]⁺;

1-(4-Bromophenyl)-2-cyclopropyl-5-phenyl-1H-pyrrole-3-carbaldehyde (17e)

General Procedure I: 19e (196 mg, 0.53 mmol), TPAP (18 mg, 0.53 mmol), NMO (114 mg; 1.06 mmol) and 4Å MS (266 mg). Chromatography (10-20% EtOAc, hexane) gave 17e (168 mg, 86%). ¹H NMR (400 MHz) δ 0.54-0.59 (m, 2H, H₂), 0.78-0.84 (m, 2H, H₂'), 1.77-1.84 (m, 1H, 2-CH), 6.74 (s, 1H, 4-H), 6.99-7.07 (m, 4H, Ar-H), 7.15-7.21 (m, 3H, Ar-H), 7.48-7.53 (m, 2H, Ar-H), 10.2 (s, 1H, CHO); ¹³C NMR (100 MHz) δ 6.8, 7.3, 53.4, 107.4, 122.1, 124.3, 127.2, 128.3, 128.4, 129.7, 131.5, 132.2, 135.5, 137.4, 186.2;

1-(4-Chlorophenyl)-2-cyclopropyl-5-phenyl-1H-pyrrole-3-carbaldehyde (17d)

General Procedure I: 19d (176 mg, 0.48 mmol), TPAP (17 mg, 0.47 mmol), NMO (112 mg; 0.95 mmol). Chromatography (10-20% EtOAc, hexane) gave 17d (146 mg; 98%). ¹H NMR (400MHz) δ 0.54-0.59 (m, 2H, H₂), 0.77-0.84 (m, 2H, H₂'), 1.77-1.84 (m, 1H, 2-CH), 6.74 (s, 1H, 4-H), 7.00-7.05 (m, 2H, Ar-H), 7.09-7.13 (m, 2H, Ar-H), 7.15-7.20 (m, 3H, Ar-H), 7.32-7.37 (m, 2H, Ar-H), 1.20 (m, 1H, CHO), ¹³C NMR (100 MHz) δ 6.8, 7.3, 29.7, 107.4, 124.4, 127.3, 128.3, 128.6, 129.3, 129.6, 131.6, 134.1, 135.7, 137.0, 144.7, 186.9;

1-(4-Chlorophenyl)-5-cyclopropyl-2-phenyl-1H-pyrrole-3-carbaldehyde (17f)

General Procedure I: 19f (176 mg, 0.48 mmol), TPAP (17 mg, 0.47 mmol), NMO (112 mg; 0.95 mmol) and 4Å MS (238 mg) in DCM (1.1 mL). Chromatography (10- 20% EtOAc, hexane) gave 17f (146 mg, 95%). ¹H NMR (300 MHz) δ 0.59-0.65 (m, 2H, H₂), 1.32-1.43 (m, 1H, 5- CH), 6.36 (s, 1H, 4-H), 6.97-7.02 (m, 2H, Ar-H), 7.03-7.11 (m, 4H, Ar-H), 7.15-7.28 (m, 5H, Ar-H), 9.54 (s, 1H, CHO); ¹³C (100 MHz) δ 7.8, 8.2, 30.0, 103.4, 124.2, 128.5, 128.8, 129.6, 130.2, 131.3, 134.6, 136.7, 139.7, 143.5, 186.7.

1-(4-Bromophenyl)-5-cyclopropyl-2-phenyl-1H-pyrrole-3-carbaldehyde (17g)

General Procedure I. 19g (200 mg, 0.54 mmol), TPAP (19 mg, 0.054 mmol), NMO (127 mg, 1.08 mmol) and 4Å molecular sieves (271 mg). Chromatography (5-10% EtOAc, hexane) gave 17g (152 mg, 76%). ¹H NMR (300 MHz) δ 0.57-0.65 (m, 2H, H₂), 1.32-1.43 (m, 1H, 5-CH), 6.36 (s, 1H, 4-H), 6.97-7.02 (m, 2H, Ar-H), 7.03-7.12 (m, 2H, Ar-H), 7.18-7.25 (m, 3H, Ar-H), 7.37-7.42 (m, 2H, Ar-H), 9.55 (s, 1H, CHO); ¹³C NMR (75 MHz) δ 7.9, 8.2, 103.4, 122.5, 124.2, 128.5, 128.8, 129.9, 130.5, 131.3, 132.5, 137.2, 139.7, 143.4, 186.7.
5-((1-(4-Bromophenyl)-5-(tert-butyl)-2-phenyl-1H-pyrrol-3-yl)methylene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (11b)

General Procedure J: 17b (67 mg, 0.20 mmol) and thiobarbituric acid (31 mg, 0.22 mmol) to give 24b as bright yellow solid (46 mg, 50%). LCMS 508.43; 309.0 – 309.8 °C; IR (cm⁻¹) 3155, 3064, 2967, 2869, 1694, 1645, 1516, 1484; ¹H NMR (300 MHz, THF d⁸) δ 11.28 (1H, br s, NH), 11.22 (1H, br s, NH), 8.11 (1H, s, 3-C), 7.99 (1H, s, 4-H), 7.49-7.51 (2H, m, Ar - H), 7.25-7.31 (5H, m, Ar - H), 7.13-7.16 (2H, m, Ar - H), 1.22 (9H, s, 5-(CH₃)₃); LCMS (ES⁺) m/z = 508.43 [M+H⁺]; HRMS: C₂₅H₂₂BrN₃O₂S [M+H⁺] Calculated: 508.4301, Found: 508.0869.

5-((5-(tert-Butyl)-1-(4-chlorophenyl)-2-phenyl-1H-pyrrol-3-yl)methylene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (11c)

General Procedure I: 17c (21 mg, 0.06 mmol) and thiobarbituric acid (10 mg, 0.067 mmol) gave 11c as bright yellow solid (13 mg, 47%). mp: 308.9 -309.2 °C; IR (cm⁻¹) 3064, 2968, 2870, 1694, 1642, 1516, 1487; ¹H NMR (300 MHz, THF d⁸) δ 11.28 (1H, br s, NH), 11.21 (1H, br s, NH), 8.11(1H, s, 3-CH), 7.99 (1H, s, 4 - H), 7.35 (4H, s, Ar - H) 7.14-7.16 (2H, m, Ar - H), 1.22 (9H, s, 5-(CH₃)₃); HRMS: C₂₅H₂₃ClN₃O₂S [M+H⁺] Calculated: 464.1194, Found: 464.1195.

5-((1-(4-Chlorophenyl)-2-cyclopropyl-5-phenyl-1H-pyrrol-3-yl)methylene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (11d)

General Procedure J: 17d (115 mg, 0.357 mmol), thiobarbituric acid (56 mg, 0.393 mmol) to give 11d as a bright orange solid (119 mg, 74%). mp 298 °C; IR (cm⁻¹) 3134, 1696, 1636, 1516, 1487, 1441. ¹H NMR (400 MHz, THF d⁸) δ 0.48-0.52 (2H, m, H₂), 0.86-0.91 (2H, m, H₂'), 1.95 (1H, tt, J = 8.4, 5.5, 2-CH), 7.10-7.11 (2H, m, Ar - H), 7.16-7.22 (3H, m, Ar - H), 7.27-7.31 (2H, m, Ar - H), 7.42-7.46 (2H, m, Ar - H), 8.04 (1H, s, 4-H), 9.04 (1H, s, 3-CH), 11.27 (1H, br s, NH), 11.38 (1H, br s, NH); LCMS (ES⁺) m/z = 447.9 [M+H⁺]; HRMS: C₂₄H₂₃ClN₃O₂S [M+H⁺] Calculated: 448.0881, Found: 448.0881.

5-((1-(4-Bromophenyl)-2-cyclopropyl-5-phenyl-1H-pyrrol-3-yl)methylene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (11e)

General Procedure J: 17e (111 mg, 0.30 mmol) and thiobarbituric acid (48 mg, 0.33 mmol) to give 11e as a bright orange solid (103 mg, 70%). mp 304-305 °C; IR (cm⁻¹) 3133, 3059, 2892, 1665, 1635, 1510, 1485; ¹H NMR (400 MHz, THF d⁸) δ 0.48-0.52 (2H, m, H₂), 0.86-0.91 (2H, m, H₂'), 1.95 (1H, tt, J = 8.4, 5.6, 2-CH), 7.09-7.11 (2H, m, Ar - H), 7.16-7.20 (3H, m, Ar - H), 7.21-7.24 (2H, m, Ar - H), 7.53-7.60 ( 2H, m, Ar - H), 8.03 (1H, s, 4-H), 9.03 (1H, s, 3-CH), 11.27 (1H, br s, NH), 11.38 (1H, br s, NH); LCMS (ES⁺) m/z = 494.2 [M+H⁺]; HRMS: C₂₄H₁₈BrN₃O₂S [M+H⁺] Calculated: 492.0376, Found: 492.0367.
5-((1-(4-Chlorophenyl)-5-cyclopropyl-2-phenyl-1H-pyrrol-3-yl)methylene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (11f)

General Procedure J: 17f (115 mg, 0.36 mmol), thiobarbituric acid (56 mg, 0.39 mmol) gave 11f as a bright orange solid (119 mg, 74%). mp 300 °C; IR (cm⁻¹) 3671, 2984, 2901, 1692, 1636, 1518, 1485, 1439; ¹H NMR (300 MHz, THF d₈) 0.68-0.79 (4H, m, H₂ and H₂’), 1.47-1.56 (1H, m, 5-CH), 7.15-7.19 (2H, m, Ar-H), 7.26-7.35 (5H, m, Ar-H), 7.37-7.42 (2H, s, Ar-H), 7.73 (1H, s, 4-H), 8.21 (1H, s, 3-CH), 11.21 (1H, br s, NH), 11.28 (1H, br s, NH); LCMS (ES⁺) m/z = 448.27 [M+H]⁺; HRMS: C₂₄H₁₈BrN₃O₂S [M+H]⁺ Calculated: 448.0881, Found: 448.0880.

5-((1-(4-Bromophenyl)-5-cyclopropyl-2-phenyl-1H-pyrrol-3-yl)methylene)-2-thioxodihydropyrimidine-4,6(1H,5H)-dione (11g)

General Procedure J: 17g (200 mg, 0.54 mmol), thiobarbituric acid (78 mg, 0.54 mmol). Chromatography (10-20% EtOAc, hexane) gave 11g (152 mg, 76%). mp 312 °C; IR (cm⁻¹) 3662, 2984, 2901, 1692, 1636, 1516, 1481; ¹H NMR (300 MHz, THF d₈) δ 0.68-0.79 (4H, m, H₂ and H₂’), 1.47-1.57 (1H, m, 5-CH), 7.14-7.17 (2H, m, Ar-H), 7.19-7.24 (2H, m, Ar-H), 7.29-7.34 (3H, m, Ar-H), 7.52-7.56 (2H, m, Ar-H), 7.73 (1H, s, 4-H), 8.20 (1H, s, 3-CH), 11.21 (1H, br s, NH), 11.27 (1H, br s, NH); LCMS (ES⁺) m/z = 492.20 [M+H]⁺; HRMS: C₂₄H₁₈BrN₃O₂S [M+H]⁺ Calculated: 492.0376, Found: 492.0368.

Combustion Analysis Data

| Paper # | Mol Form. | Requires | Found |
|---------|-----------|----------|-------|
|         |           | C(H%)  | H (%) | N (%) | C(H%)  | H (%) | N (%) |
| 4w      | C₂₁H₂₆BrN₃O₂S | 63.70  | 4.48  | 7.19  | 64.02  | 4.53  | 7.10  |
| 4y      | C₂₈H₂₀BrN₂O₃ | 63.89  | 3.83  | 7.98  | 63.65  | 3.95  | 7.61  |
| 4z      | C₂₈H₂₀BrN₂O₂S | 62.01  | 3.72  | 7.75  | 62.31  | 3.70  | 7.87  |
Table S1: MDM2 structure-activity relationships for commercial pyrroles 4a-I.

![Diagram of MDM2 structure-activity relationships for commercial pyrroles 4a-I.]

| Compound | R<sup>1</sup>   | R<sup>2</sup> | R<sup>3</sup> | R<sup>4</sup> | MDM2 IC<sub>50</sub> (nM) |
|----------|-----------------|--------------|--------------|--------------|-----------------------------|
| 4a       | 4-CIPh          | Me           | H            | H            | 720 ± 100                   |
| 4b       | 4-CIPh          | Me           | H            | Ph           | 3300 ± 700                  |
| 4c       | 4-CIPh          | Ph           | H            | H            | 120 ± 20                    |
| 4d       | 4-CIPh          | Ph           | H            | Ph           | 230 ± 44                    |
| 4e       | 4-CIPh          | Ph           | H            | 3-CIPh       | 163 ± 17                    |
| 4f       | 4-CIPh          | Ph           | 3,4-diMePh   | Ph           | 256 ± 39                    |
| 4g       | 4-CIPh          | Ph           | Me           | Me           | Insol.                      |
| 4h       | 4-BrPh          | Me           | Ph           | H            | 199 ± 16                    |
| 4i       | 4-MePh          | Me           | Ph           | H            | 8400 ± 900                  |
| 4j       | 4-MePh          | Me           | H            | H            | 4700 ± 200                  |
| 4k       | 4-EtO<sub>2</sub>CPh | Ph | H | H | 700 ± 20 |
Table S2: Structures of additional commercial analogues with MDM2-p53 IC₅₀ values

| R¹   | R²   | R³   | R⁴   | IC₅₀ (µM) |
|------|------|------|------|-----------|
| 4-BrPh | Me   | H    | H    | >10       |
| 4-BrPh | Me   | Ph   | Ph   | 0.20 ± 0.02 |
| Ph    | Me   | H    | H    | >10       |
| 3,5-diMePh | Me   | H    | H    | >10       |
| 3,5-diMePh | Me   | Ph   | Ph   | >10       |
| 3,5-diMePh | Me   | H    | Ph   | >10       |
| 3,5-diMePh | Me   | H    | 4-BrPh | >10       |
| 3,5-diMePh | Me   | H    | 3-ClPh | >10       |
| 3,5-diMePh | Me   | H    | 2-FPh | >10       |
| 4-AcOPh | Me   | H    | 4-BrPh | >10       |
| 3-NO₂Ph | Me   | H    | H    | >10       |
| 3-NO₂Ph | Me   | Ph   | Ph   | >10       |
| 3-NO₂Ph | Me   | H    | Ph   | >10       |
| 3-NO₂Ph | Me   | H    | 4-BrPh | >10       |
| 3-NO₂Ph | Me   | H    | 3-ClPh | >10       |
| 4-EtO₂CPh | Me   | H    | H    | >10       |
| 4-EtO₂CPh | Me   | Ph   | Ph   | >10       |
| 4-EtO₂CPh | Me   | H    | Ph   | >10       |
| 4-EtO₂CPh | Me   | H    | 4-BrPh | >10       |
| 4-EtO₂CPh | Me   | H    | 3-EtOPh | >10       |
| 4-EtO₂CPh | Me   | Me   | Me   | >10       |
| 3,4-diMePh | Ph   | H    | 4-EtO₂CPh | >10       |
| 3,4-diMePh | Ph   | Me   | Me   | Insol.    |
| 4-CIPh  | Ph   | H    | H    | 0.70 ± 0.02 |
| 4-CIPh  | Ph   | H    | Ph   | 0.23 ± 0.04 |
| 4-CIPh  | Ph   | H    | 4-BrPh | >10       |
| 4-CIPh  | Ph   | H    | 3-CIPh | 0.16 ± 0.02 |
| 3,4-diMePh | Ph   | 3,4-diMePh | Ph   | 0.26 ± 0.04 |
| 4-CIPh  | Ph   | Me   | Me   | 4.7 ± 0.2  |
| $R^1$ | $R^2$ | $R^3$ | $R^4$ | IC$_{50}$ (µM) |
|-------|-------|-------|-------|---------------|
| 4-MePh | Me | H | Ph | 8.4 ± 0.9 |
| 4-ClPh | Me | H | H | 0.72 ± 0.10 |
| 4-ClPh | Me | H | Ph | 3.3 ± 0.7 |
| 4-ClPh | Me | Me | Me | >10 |
| 3,4-diMePh | Me | H | 3-EtOPh | >10 |
| 4-Me$_2$NPh | Me | H | 3-EtOPh | >10 |
| 4-Me$_2$NPh | Me | H | 4-BrPh | >10 |
| 4-(4-NO$_2$PhS) Ph | Me | H | 4-MePh | >10 |
| $C_6$H$_{11}$ | Me | H | H | >10 |
| $C_5$H$_{11}$ | Me | H | 4-BrPh | >10 |
| $C_6$H$_{11}$ | Me | H | 4-EtPh | >10 |
| $C_6$H$_{11}$ | Me | H | Ph | >10 |
| 4-BrPh | Me | H | 4-EtOPh | >10 |
| 4-HO$_2$CPh | Me | H | 4-EtPh | >10 |
| 3-HO$_2$CPh | Me | H | 4-EtPh | >10 |
| 3-Me-4-IPh | Me | H | 4-MeOPh | >10 |
| 4-t-BuPh | Me | H | 2,3-diClPh | >10 |
| 4-Me$_2$CPh | Me | H | H | >10 |
| 3,5-di(HO$_2$C)Ph | Me | H | 2-FPh | >10 |
| 2-Et-5-MePh | Me | H | H | >10 |
| 2-Et-5-MePh | Me | H | 4-MeOPh | >10 |
| 2-Et-5-MePh | Me | H | 2-F-Ph | >10 |
| 2-F-Ph | Me | H | 2-F-Ph | >10 |
| 4-F-Ph | Me | H | 2-F-Ph | >10 |
| 3-(HO$_2$C)-4-ClPh | Me | H | 2-F-Ph | >10 |
| 2-Me-3-(HO$_2$C) Ph | Me | H | 2-F-Ph | >10 |
| 4-EtPh | Me | H | 4-F-Ph | >10 |
| Ph | Me | Me | Me | >10 |
| 4-NO$_2$Ph | Me | Me | Me | >10 |
| 4-MePh | Me | Me | Me | >10 |
| 3-NO$_2$Ph | Me | Me | Me | >10 |
| 2-MePh | Me | Me | Me | >10 |
| 3-HO$_2$CPh | Me | Me | Me | >10 |
| 4-HO$_2$CPh | Me | H | Me | >10 |
| 4-HO$_2$CPh | Me | H | Et | >10 |
| 4-HOPh | Me | Me | Me | >10 |
| 2,6-diMePh | Me | Me | Me | >10 |
| 4-PhPh | Me | H | H | >10 |
| 2-Et-Ph | Me | H | H | >10 |
| 3-AcOPh | Me | H | H | >10 |
| Me | Me | 3-MeOPh | H | >10 |
| 3,5-(HO$_2$C)$_2$Ph | Me | H | H | >10 |
| 4-(4-NO$_2$PhS)-Ph | Me | 2-ClPh | H | >10 |
| 4-(4-Br8n)-OPh | Me | H | 3-MePh | >10 |
| 4-Py | Me | Me | Me | >10 |
| 3-Py | Me | Me | Me | >10 |
| 3-Py | Me | H | CH$_2$CH=CH$_2$ | >10 |
| 3-Py | Me | H | 3-FPh | >10 |
| 2-Py | Me | Me | Me | >10 |
| 2-Py | Me | H | CH$_2$CH=CH$_2$ | >10 |
Table S3: Growth inhibitory activity of selected purchased pyrroles in a panel of cell lines with defined MDM2 and p53 status.

| R¹  | R²  | R³  | R⁴  | IC₅₀ (µM) |
|-----|-----|-----|-----|-----------|
| MeOCH₂CH₂ | Me | Me | Me | >10 |
| MeOCH₂CH₂ | Me | H | CH₂CH=CH₂ | >10 |
| 3,4-(OCH₃)Ph | Me | H | 4-BrPh | >10 |
| W | Me | H | 4-EtPh | >10 |
| W | Me | Ph | Ph | >10 |
| W | Me | H | 4-ClPh | >10 |
| X | Me | H | Me | >10 |
| Y | Me | H | Ph | >10 |
| Z | Me | H | H | >10 |
| Z | Me | H | 3,5-diMePh | >10 |
| Z | Me | H | 4-MeOPh | >10 |
| Z | Me | H | 4-BrPh | >10 |
| A | - | - | - | >10 |

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**Figure 1:** Modeled binding mode of **11d** (green) overlayed with MDMX (pink).
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