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(*E*)-3-Arylidene-4-diazopyrrolidine-2,5-diones: Preparation and Use in Rh^{II}-Catalyzed X–H Insertion Reactions towards Novel, Medicinally Important Michael Acceptors

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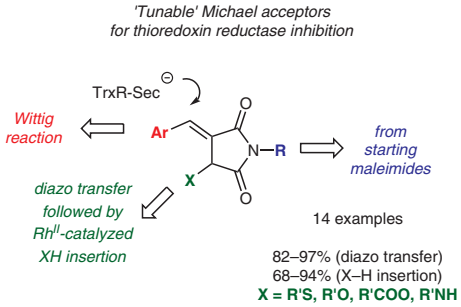

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Abstract The use of readily available 1-aryl-3-arylidenepyrrolidine-2,5-diones in high yielding direct diazo-transfer reactions and subsequent involvement of the resulting diazo compounds in Rh^{II}-catalyzed O–H, S–H, and N–H insertion reactions delivered 4-substituted 1-aryl-3-arylidenepyrrolidine-2,5-diones of defined regiochemistry and geometrical configuration. These products are intended to be studied as Michael acceptors capable of inhibiting thioredoxin reductase, a promising cancer target.

Key words Michael acceptors, pyrrolidine-2,5-diones, Wittig reaction, diazo transfer, rhodium(II) carbenes, X–H insertion, thioredoxin reductase inhibitors

Electron-deficient olefins which can react with nucleophiles via the Michael (1,4-conjugate) addition are somewhat colloquially referred to as 'Michael acceptors'. Such motifs have received certain negative stigma in the context of screening-based drug discovery as they can display potentially non-specific reactivity towards nucleophilic amino acid residues in proteins and behave as false positive hits in biological assays.[1] However, the reactivity of Michael acceptors, in particular, towards cysteine residues has been successfully exploited in the medicinal chemistry design of targeted covalent inhibitors.[2] Michael acceptor motifs are also omnipresent in natural products[3] and sometimes considered essential for the anticancer activity displayed by such compounds.[4] Michael acceptors are often selective toward cancer cells and do not perturb vital processes of normal cells. This could be due to their intrusion in the critical survival mechanisms of cancer cells (such as overactive ubiquitin proteasome[5] or upregulated thioredoxin system[6]).

Recently, our efforts have been directed at developing anticancer small-molecule inhibitors of thioredoxin reductase (TrxR), a redox defense enzyme overexpressed in cancer cells.[7] Michael acceptors incorporated into various peptidomimetic scaffolds (thus mimicking the enzyme's protein substrate thioredoxin) received particular priority in these efforts. These included the Michael acceptor DVD-445 identified as a lead compound for further development[7a,b] and α,β-unsaturated amides (so-called 'piper-amides'[8]) which were synthesized using the diazo chemistry toolbox.[9] The synthetic and medicinal chemistry development of these scaffolds was motivated by the built-in orthogonal vectors of molecular diversity. The facility in varying the periphery substituent is essential for optimizing the selectivity of TrxR inhibitors. Fine-tuning the electrophilicity of the Michael acceptor moiety from an electronic as well as a steric perspective can afford selective targeting of the catalytic selenocysteine (Sec-SeH) residue (ionized at physiological pH) of TrxR over cysteines (Cys-SH) generally abundant in proteins.[10] We reasoned that another chemotype worthy investigation in this medicinal chemistry context would be that of 1-substituted 3-arylidenepyrrolidine-2,5-diones **1**. Indeed, the scaffold comprises a Michael acceptor moiety and the two easily and independently variable periphery groups, one of which (arylidene) could potentially assume two distinct geometrical configurations. Unsurprisingly, compounds such as **1** have been explored in connection with various biological activities (e.g., anticancer,[11]

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vasorelaxant,[12] anti-HIV[13]), some of which could indeed be attributed to these compounds' Michael acceptor behavior. Moreover, the ability of these compounds to react with thiols via the conjugate addition was exploited in a recent study on bioconjugation.[14] However, compounds **1** contain an obvious additional site for further scaffold diversification, that is the fairly acidic[15] methylene group. This consideration as well as our recent involvement in the development of synthetic methodology involving diazocarbonyl compounds[16] prompted us to consider converting compounds **1** into their 4-diazo derivatives **2**. The latter are known, in principle, and have been prepared in two steps from pyrrolidine-2,3,5-trione[17] or via the thermal decomposition of 3*H*-pyrazoles fused to a succinimide moiety.[18] However, the preparation of **2** via the direct Regitz diazo transfer had not been explored. This prompted us to investigate such an approach to diazo compounds **2** as this would open access to libraries of Michael acceptors **3** (Figure 1) containing three vectors of substituent diversity one of which would be introduced via classical metal carbene X–H insertion chemistry[19] characteristic of diazo compounds in general. When this work was in progress, a report from Bhat and Laha appeared in the literature which also explored a diazo-transfer approach to compounds **2** and their use in silver-catalyzed [2+1] cycloaddition with aldehydes.[20] This prompts us to disclose our findings in this regard that can, on the one hand, provide some distinct practical convenience at the diazo-transfer stage towards **2** and, on the other hand, firmly validate the use of **2** in transition-metal-catalyzed X–H insertion reactions as the means to prepare novel Michael acceptors **3** for biological investigation.

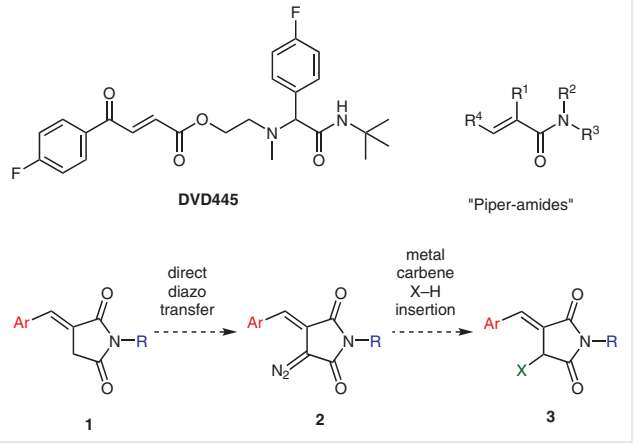
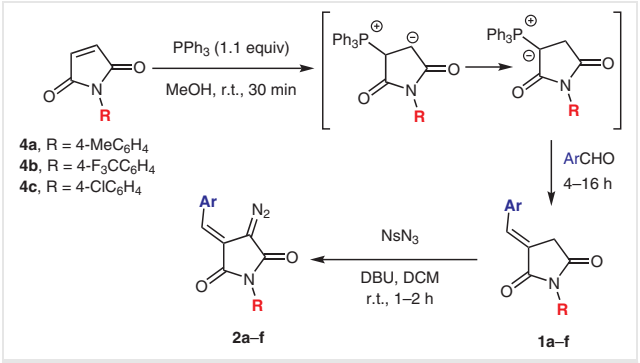


Figure 1 Michael acceptor DVD445 and piper-amides currently investigated as TrxR inhibitors and the diversification path for 1-substituted 3-arylidenepyrrolidine-2,5-diones **1** investigated in this work

Six 1-aryl-3-(hetero)arylidenepyrrolidine-2,5-diones **1a–f** (Scheme 1) were prepared from three known maleimides **4a–c** using the fairly straightforward literature approach based on conjugate addition of triphenylphosphine and subsequent Wittig reaction of the resulting phosphonium ylide with aromatic aldehydes.[21] Contrary to observations made by Kalia and co-workers,[14] the reaction proceeded very well at room temperature in methanol and afforded excellent yields of target (*E*)-configured compounds **1a–f**.[21] Further, we considered the high lipophilicity of substrates **1a–f** that would probably make them unsuitable for diazo transfer in aqueous medium which we recently performed successfully for some more hydrophilic substrates.[22,23] For this reason, we decided to perform diazo transfer in dichloromethane using 4-nitrobenzenesulfonyl azide (NsN_3) and DBU[24] for all substrates. This resulted in excellent yields of all diazo compounds **2a–f** (Table 1). A notable feature of this protocol is the redundancy of aqueous workup (in contrast to the Bhat procedure[20]), as in our case the crude reaction mixture was loaded directly onto a silica gel column for chromatographic purification. For Table 1, entry 1, we compared the yield of the diazo product to that obtained in aqueous medium using the recently developed 'sulfonyl-azide-free' (SAFE) diazo transfer.[22] Not unexpectedly, the apparent solubility issues encountered with lipophilic substrate **1a** led to a 23% drop in chemical yield of product **2a**. All diazo compounds **2a–f** were obtained with retention of the double bond configuration as confirmed by the singe-crystal X-ray analysis of compound **2d** (Figure 2).



Scheme 1 Preparation of 1-substituted 3-arylidenepyrrolidine-2,5-diones **1a–f** and their use in diazo-transfer reactions

Table 1 Structures and Chemical Yields of Compounds **1a–f** and **2a–f**

Entry	1,2	R	Ar	Yield of **1** (%)	Yield of **2** (%)
1	**a**	4-MeC_6H_4	4-ClC_6H_4	91	97[a]
2	**b**	4-$F_3CC_6H_4$	2-furyl	96	94
3	**c**	4-MeC_6H_4	2-$MeOC_6H_4$	94	96
4	**d**	4-ClC_6H_4	Ph	92	84[b]
5	**e**	4-ClC_6H_4	4-MeC_6H_4	88	92
6	**f**	4-MeC_6H_4	4-FC_6H_4	95	91

[a] SAFE protocol in aqueous medium [NaN_3 (2.0 equiv), *m*-$HO_2CC_6H_4SO_2Cl$ (2.0 equiv), K_2CO_3 (4.0 equiv), H_2O/MeCN, r.t., 1–2 h] applied to this substrate gave 74% yield.
[b] Structure of the product was confirmed by single-crystal X-ray analysis (Figure 2).

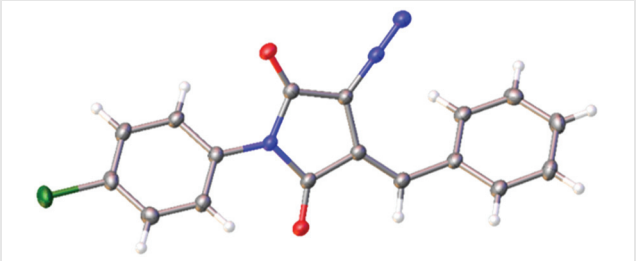


Figure 2 Single-crystal X-ray analysis of compound **2d** (CCDC 2014382, thermal ellipsoids shown at 50% probability)

Having synthesized diazo compounds **2a–f**, we proceeded to investigate their behavior in Rh^{II}-catalyzed O–H, S–H, and N–H insertion reactions.[19] Using $Rh_2(OAc)_4$ (1 mol%) provided good to excellent yields of products **3a–n** (Scheme 2). Therefore, the protocol was not optimized further. Several observations emerge from the results presented in Scheme 2. Firstly, the reaction proceeded quite well with the majority of alcohols and carboxylic acids. Secondly, the yield of the benzyl mercaptan insertion product **3h** was high and comparable to that of the benzyl alcohol insertion product **3i**. Thirdly, 2-mercaptoethanol displayed a remarkable selectivity for the O–H over S–H insertion products in **3b** and **3l**. This selectivity was unequivocally established by the characteristic appearance and chemical shift of the mercaptoethyl substituent in similar scaffolds.[25,26]

Interestingly, the similar insertion into N–H bonds did not occur with synthetically useful yields under the same protocol. However, with $Rh_2(esp)_2$ (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate)[27] as the catalyst, the reactions worked and the respective aniline **3o–r** as well as an example of a sulfamido substituted compound **3s** compound were obtained in good yields and good chemical purity (Scheme 3).

The structure of products **3a–s** was duly examined as the allylic Rh^{II} carbene **5** could, in principle, undergo a vinylogous X–H insertion[28] (Scheme 4).

The possibility of the formation of regioisomeric products **3′** (as well as of the products **3″** of isomerization of the double bond in **3**) was excluded based on the observed combination of HMBC NMR correlations and through-space correlations observed in the NOESY spectrum of **3** which would not be expected either for **3′** or for **3″** (Figure 3).

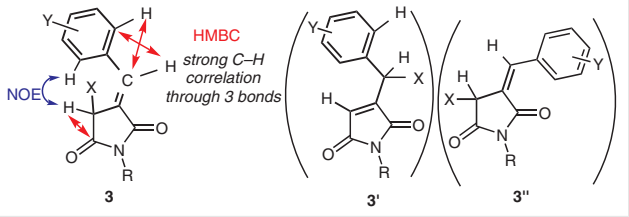
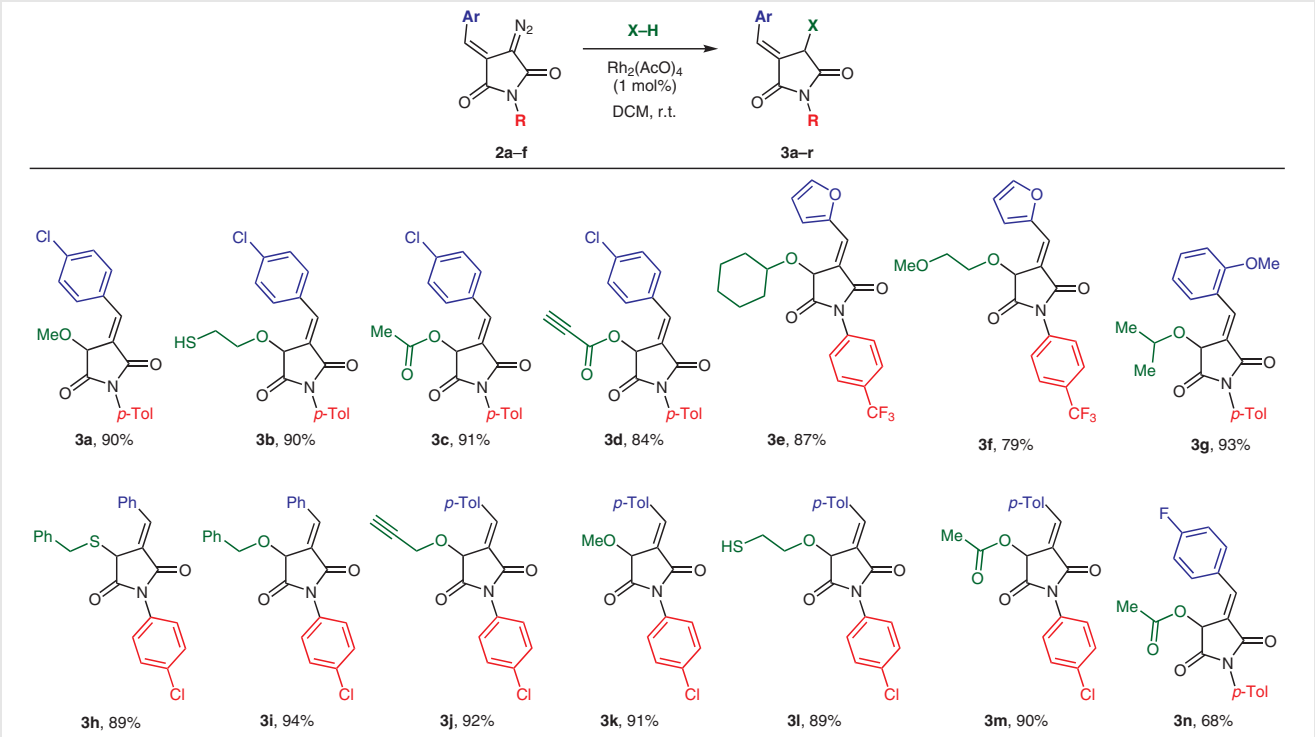
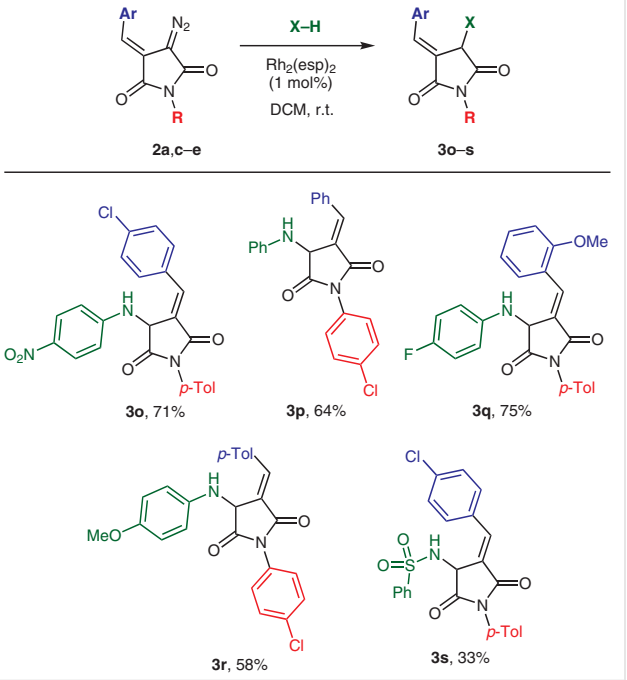


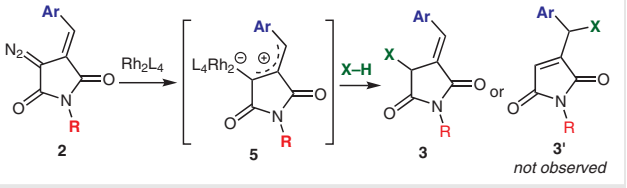
Figure 3 Structure assignment of products **3** based on HMBC and NOESY correlations



Scheme 2 Preparation and structures of products **3a–n** of insertion into O–H and S–H bonds of Rh^{II} carbenes derived from compounds **2a–f**



Scheme 3 Preparation and structures of products **3o–s** of insertion into N–H bonds of Rh^{II} carbenes derived from compounds **2a,c–e**



Scheme 4 Plausible formation of regioisomeric X–H insertion products from Rh^{II} carbenes **5**

To our delight, the above structural assignment was confirmed by the single-crystal X-ray diffraction structure of compound **3a** (Figure 4).

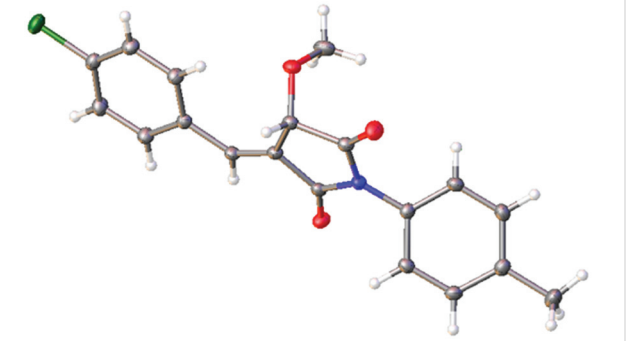


Figure 4 Single-crystal X-ray diffraction structure of compound **3a** (CCDC 20011269, thermal ellipsoids shown at 50% probability)

In summary, we described the use of readily available 1-substituted 3-arylidenepyrrolidine-2,5-diones in high yielding direct diazo-transfer reactions and the use of the resulting diazo compounds in Rh^{II}-catalyzed O–H, S–H, and N–H reactions which delivered trisubstituted succinimide **3** of defined regiochemistry and geometrical configuration which was confirmed by single-crystal X-ray analysis. These products are expected to act as Michael acceptor inhibitors of selenocysteine enzyme thioredoxin reductase, a promising cancer target. The results of the biological testing will be reported in due course.

All commercial reagents were used without purification. NMR spectra were recorded using a Bruker Avance III spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; the residual solvent peaks were used as internal standards: δ = 7.26 and 2.50 for ^{1}H in $CDCl_3$ and DMSO-d_6, respectively, δ = 39.52 and 77.16 for ^{13}C in DMSO-d_6 and $CDCl_3$, respectively). Mass spectra were recorded using a Bruker microTOF spectrometer (ionization by electrospray, positive ions detection). Melting points were determined in open capillary tubes on Stuart SMP50 Automatic Melting Point Apparatus.

CCDC 2014382 (**2d**) and 20011269 (**3a**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

1-Aryl-3-(hetero)arylidenepyrrolidine-2,5-diones 1a–f; General Procedure 1 (GP1)

To a solution of maleimide **4** (4.0 mmol) in MeOH (60 mL) was added PPh_3 (4.4 mmol) and the mixture was stirred for 30 min, followed by addition of the aldehyde (4.4 mmol). Within minutes, a precipitate started to form and the mixture was stirred at r.t. for 4–16 h. After cooling in an ice bath, the precipitate was filtered off, washed with cold MeOH (25 mL), and dried in air to afford 1-aryl-3-benzylidenepyrrolidine-2,5-diones **1**, which were used in the diazo-transfer step without further purification.

1-Aryl-3-(hetero)arylidene-4-diazopyrrolidine-2,5-diones 2a–f; General Procedure 2 (GP2)

To a stirred solution/suspension of imide **1** (2 mmol) in DCM (15 mL) were added 4-nitrobenzenesulfonyl azide (479 mg, 2.1 mmol) and DBU (313 µL, 2.1 mmol) and the mixture was stirred at r.t. for 1–2 h (TLC monitoring). The resulting mixture was loaded directly onto a silica gel column and subjected to flash chromatography (DCM or $CHCl_3$) to afford pure diazo compound **2**.

3-Acyloxy- or 3-Alkoxy-1-aryl-4-(hetero)arylidenepyrrolidine-2,5-diones 3a–n; General Procedure 3 (GP3)

Diazo compound **2** (1 mmol) was dissolved in dry DCM (5 mL) (reactions with MeOH and *i*-PrOH were performed using the alcohol as solvent), the appropriate substrate for XH-insertion (2 mmol) was added followed by addition of $Rh_2(OAc)_4$ (4.4 mg, 10 µmol, 1 mol%). The mixture was stirred at r.t. overnight, evaporated, and the crude material was purified by flash column chromatography (silica gel, *n*-hexane/acetone, gradient 9:1 to 2:1).

(*E*)-1-Aryl-3-(arylamino)-4-(hetero)arylidenepyrrolidine-2,5-diones 3o–s; General Procedure 4 (GP4)

Diazo compound **2** (1 mmol) was dissolved in dry DCM (5 mL), the appropriate partner (1 mmol) was added followed by addition of $Rh_2(esp)_2$ (4.4 mg, 10 μmol, 1 mol%). The mixture was stirred at r.t. (TLC monitoring), the crude material was filtered off and purified, if necessary, by flash column chromatography (silica gel, *n*-hexane/acetone, gradient 9:1 to 2:1).

(*E*)-3-(4-Chlorobenzylidene)-1-(*p*-tolyl)pyrrolidine-2,5-dione (1a)[29]

Following GP1 using 1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (748 mg, 4.0 mmol) and 4-chlorobenzaldehyde (618 mg, 4.4 mmol) gave **1a** as a white solid; yield: 1.13 g (91%); mp 237.5–238.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (t, *J* = 2.5 Hz, 1 H, =CH), 7.47 (s, 4 H, 4 ArH), 7.31 (d, *J* = 8.5 Hz, 2 H, 2 ArH), 7.27 (d, *J* = 8.5 Hz, 2 H, 2 ArH), 3.71 (d, *J* = 2.4 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3).

(*E*)-3-(Furan-2-ylmethylene)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-dione (1b)

Following GP1 using 1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole-2,5-dione (964 mg, 4.0 mmol) and furan-2-carbaldehyde (422 mg, 4.4 mmol) gave **1b** as a white solid; yield: 1.23 g (96%); mp 181.1–182.3 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.4 Hz, 2 H, 2 ArH), 7.68 (s, 1 H, =CH), 7.60 (d, *J* = 8.3 Hz, 2 H, 2 ArH), 7.53 (t, *J* = 4.5 Hz, 1 H, ArH), 6.81 (d, *J* = 3.5 Hz, 1 H, ArH), 6.60 (dd, *J* = 3.4, 1.8 Hz, 1 H, ArH), 3.86 (d, *J* = 2.3 Hz, 2 H, CH_2).

(*E*)-3-(2-Methoxybenzylidene)-1-(*p*-tolyl)pyrrolidine-2,5-dione (1c)

Following GP1 using 1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (748 mg, 4.0 mmol) and 2-methoxybenzaldehyde (598 mg, 4.4 mmol) gave **1c** as a white solid; yield: 1.15 g (94%); mp 135.7–136.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (t, *J* = 2.2 Hz, 1 H, =CH), 7.45 (d, *J* = 7.6 Hz, 1 H, ArH), 7.42 (d, *J* = 7.8 Hz, 1 H, ArH), 7.32 (d, *J* = 8.4 Hz, 2 H, 2 ArH), 7.28 (d, *J* = 8.3 Hz, 2 H, 2 ArH), 7.06 (t, *J* = 7.5 Hz, 1 H, ArH), 6.99 (d, *J* = 8.3 Hz, 1 H, ArH), 3.93 (s, 3 H, OCH_3), 3.70 (d, *J* = 2.3 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3).

(*E*)-3-Benzylidene-1-(4-chlorophenyl)pyrrolidine-2,5-dione (1d)[12]

Following GP1 using 1-(4-chlorophenyl)-1*H*-pyrrole-2,5-dione (828 mg, 4.0 mmol) and benzaldehyde (466 mg, 4.4 mmol) gave **1d** as a white solid; yield: 1.09 g (92%); mp 205.3–207.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (t, *J* = 2.4 Hz, 1 H, =CH), 7.56 (dd, *J* = 7.9, 1.6 Hz, 2 H, 2 ArH), 7.54–7.47 (m, 5 H, 5 ArH), 7.38 (d, *J* = 8.8 Hz, 1 H, ArH), 3.78 (d, *J* = 2.4 Hz, 2 H, CH_2).

(*E*)-1-(4-Chlorophenyl)-3-(4-methylbenzylidene)pyrrolidine-2,5-dione (1e)

Following GP1 using 1-(4-chlorophenyl)-1*H*-pyrrole-2,5-dione (828 mg, 4.0 mmol) and *p*-tolualdehyde (528 mg, 4.4 mmol) gave **1e** as a white solid; yield: 1.09 g (88%); mp 209.2–210.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (t, *J* = 2.3 Hz, 1 H, =CH), 7.49 (d, *J* = 8.8 Hz, 2 H, ArH), 7.46 (d, *J* = 8.1 Hz, 2 H, ArH), 7.38 (d, *J* = 8.8 Hz, 2 H, ArH), 7.31 (d, *J* = 8.1 Hz, 2 H, ArH), 3.77 (d, *J* = 2.3 Hz, 2 H, CH_2), 2.44 (s, 3 H, CH_3).

(*E*)-3-(4-Fluorobenzylidene)-1-(*p*-tolyl)pyrrolidine-2,5-dione (1f)

Following GP1 using 1-(*p*-tolyl)-1*H*-pyrrole-2,5-dione (748 mg, 4.0 mmol) and 4-fluorobenzaldehyde (544 mg, 4.4 mmol) gave **1f** as a white solid; yield: 1.12 g (95%); mp 164.7–165.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (t, *J* = 2.2 Hz, 1 H, =CH), 7.55 (dd, *J* = 8.7, 5.3 Hz, 2 H, 2 ArH), 7.33 (d, *J* = 8.2 Hz, 2 H, 2 ArH), 7.27 (d, *J* = 8.7 Hz, 2 H, 2 ArH), 7.20 (t, *J* = 8.6 Hz, 2 H, 2 ArH), 3.74 (d, *J* = 2.2 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3).

(*E*)-3-(4-Chlorobenzylidene)-4-diazo-1-(*p*-tolyl)pyrrolidine-2,5-dione (2a)

Following GP2 using imide **1a** (622 mg, 2.0 mmol) gave **2a** as an orange solid; yield: 656 mg (97%); mp 134.4–135.1 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (s, 1 H, =CH), 7.45 (d, *J* = 8.4 Hz, 2 H, 2 ArH), 7.36–7.27 (m, 6 H, 6 ArH), 2.42 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.0, 163.9, 138.7, 135.6, 131.8, 130.2, 129.8, 129.1, 126.4, 126.3, 117.2, 60.1 (C=N_2), 21.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{12}ClN_3NaO_2$: 360.0510; found: 360.0524.

(*E*)-3-Diazo-4-(furan-2-ylmethylene)-1-[4-(trifluoromethyl)phenyl]-pyrrolidine-2,5-dione (2b)

Following GP2 using imide **1b** (642 mg, 2.0 mmol) gave **2b** as an orange solid; yield: 652 mg (94%); mp 161.0–164.2 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.5 Hz, 2 H, 2 ArH), 7.64 (d, *J* = 8.4 Hz, 2 H, 2 ArH), 7.58 (s, 1 H, =CH), 7.40 (s, 1 H, CH), 6.81 (d, *J* = 3.4 Hz, 1 H, CH), 6.64–6.57 (m, 1 H, CH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.3, 163.9, 151.0, 146.3, 135.1, 130.1 (q, *J* = 33.0 Hz), 126.4, 126.2 (q, *J* = 3.6 Hz), 123.7 (q, *J* = 272.5 Hz), 117.6, 113.4, 113.4, 112.0, 62.1 (C=N_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_8F_3N_3NaO_3$: 370.0410; found: 370.0416.

(*E*)-3-Diazo-4-(2-methoxybenzylidene)-1-(*p*-tolyl)pyrrolidine-2,5-dione (2c)

Following GP2 using imide **1c** (614 mg, 2.0 mmol) gave **2c** as an orange solid; yield: 639 mg (96%); mp 120.2–121.1 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1 H, =CH), 7.43–7.37 (m, 1 H, ArH), 7.31 (s, 4 H, ArH), 7.27 (dd, *J* = 7.5, 1.5 Hz, 1 H, ArH), 7.04 (t, *J* = 7.5 Hz, 1 H, ArH), 6.97 (d, *J* = 8.3 Hz, 1 H, ArH), 3.91 (s, 3 H, OCH_3), 2.42 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.4, 164.2, 157.4, 138.5, 131.2, 130.0, 129.8, 129.3, 126.4, 124.5, 122.3, 120.3, 116.9, 110.9, 60.9 (C=N_2), 55.4, 21.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{15}N_3NaO_3$: 356.1006; found: 356.1003.

(*E*)-3-Benzylidene-1-(4-chlorophenyl)-4-diazopyrrolidine-2,5-dione (2d)

Following GP2 using imide **1d** (594 mg, 2.0 mmol) gave **2d** as an orange solid; yield: 542 mg (84%); mp 152.1–154.2 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (s, 1 H, =CH), 7.52–7.46 (m, 4 H, ArH), 7.45–7.40 (m, 3 H, ArH), 7.39–7.35 (m, 2 H, ArH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.9, 163.7, 134.2, 133.3, 130.3, 129.7, 129.3, 129.0, 128.8, 128.5, 127.6, 116.4, 60.3 (C=N_2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{10}ClN_3NaO_2$: 346.0354; found: 346.0348.

(*E*)-1-(4-Chlorophenyl)-3-diazo-4-(4-methylbenzylidene)pyrrolidine-2,5-dione (2e)

Following GP2 using imide **1e** (622 mg, 2.0 mmol) gave **2e** as a light orange solid; yield: 622 mg (92%); mp 129.2–130.0 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (s, 1 H, =CH), 7.48 (d, *J* = 8.9 Hz, 2 H, 2 ArH), 7.41 (d, *J* = 8.9 Hz, 2 H, 2 ArH), 7.27 (s, 4 H, 4 ArH), 2.42 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.1, 163.8, 140.2, 134.2, 130.4, 130.3, 129.6, 129.3, 129.1, 128.9, 127.6, 115.4, 60.3 (C=N_2), 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}ClN_3O_2$: 338.0691; found: 338.0697.

(*E*)-3-Diazo-4-(4-fluorobenzylidene)-1-(*p*-tolyl)pyrrolidine-2,5-dione (2f)

Following GP2 using imide **1f** (590 mg, 2.0 mmol) gave **2f** as a yellow solid; yield: 584 mg (91%); mp 129.6–130.1 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (s, 1 H, =CH), 7.37 (dd, *J* = 8.7, 5.3 Hz, 2 H, ArH), 7.31 (s, 4 H, ArH), 7.17 (t, *J* = 8.6 Hz, 2 H, ArH), 2.42 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.1, 164.0, 163.1 (d, *J* = 251.7 Hz), 138.7, 130.9 (d, *J* = 8.4 Hz), 129.8, 129.6 (d, *J* = 3.5 Hz), 129.1, 126.8, 126.3, 116.7 (d, *J* = 1.4 Hz), 116.1 (d, *J* = 22.0 Hz), 60.0 (C=N_2), 21.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}FN_3O_2$: 322.0986; found: 322.0980.

(*E*)-3-(4-Chlorobenzylidene)-4-methoxy-1-(*p*-tolyl)pyrrolidine-2,5-dione (3a)

Following GP3 using **2a** (337 mg, 1 mmol) in MeOH (5 mL) gave **3a** as a white solid; yield: 307 mg (90%); mp 211.5–212.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 1.7 Hz, 1 H, =CH), 7.70 (d, *J* = 8.5 Hz, 2 H, 2 ArH), 7.48 (d, *J* = 8.5 Hz, 2 H, 2 ArH), 7.35–7.25 (m, 4 H, 4 ArH), 5.00 (d, *J* = 1.9 Hz, 1 H, CH), 3.65 (s, 3 H, OCH_3), 2.43 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.4, 168.3, 139.6, 138.9, 137.4, 132.5, 131.5, 129.8, 129.4, 128.8, 126.1, 124.1, 73.4, 55.9, 21.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{16}ClNNaO_3$: 364.0711; found: 364.0727.

(*E*)-3-(4-Chlorobenzylidene)-4-(2-mercaptoethoxy)-1-(*p*-tolyl)-pyrrolidine-2,5-dione (3b)

Following GP3 using **2a** (337 mg, 1 mmol) and 2-mercaptoethanol (156 mg, 2 mmol) gave **3b** as a white solid; yield: 348 mg (90%); mp 174.1–175.0 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 1.8 Hz, 1 H, =CH), 7.73 (d, *J* = 8.6 Hz, 2 H, 2 ArH), 7.49 (d, *J* = 8.5 Hz, 2 H, 2 ArH), 7.35–7.28 (m, 4 H, 4 ArH), 4.82 (d, *J* = 1.9 Hz, 1 H, CH), 4.08–3.93 (m, 2 H, CH_2), 3.34 (ddd, *J* = 14.5, 7.0, 4.2 Hz, 1 H, CH*H*), 2.92 (ddd, *J* = 14.5, 6.4, 4.2 Hz, 1 H, C*H*H), 2.43 (s, 3 H, CH_3), 2.41–2.36 (m, 1 H, SH).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.5, 168.4, 138.9, 137.1, 136.8, 132.8, 131.3, 129.8, 129.3, 128.9, 126.1, 124.5, 62.4, 42.1, 34.9, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}ClNO_3S$: 388.0769; found: 388.0774; *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{18}ClNNaO_3S$: 410.0588; found: 410.0596.

(*E*)-3-Acetoxy-4-(4-chlorobenzylidene)-1-(*p*-tolyl)pyrrolidine-2,5-dione (3c)

Following GP3 using **2a** (337 mg, 1 mmol) and acetic acid (120 mg, 2 mmol) gave **3c** as a white solid; yield: 335 mg (91%); mp 123.4–124.6 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.76 (d, *J* = 8.6 Hz, 2 H, 2 ArH), 7.72 (d, *J* = 2.0 Hz, 1 H, =CH), 7.60 (d, *J* = 8.5 Hz, 2 H, 2 ArH), 7.35 (d, *J* = 8.2 Hz, 2 H, 2 ArH), 7.21 (d, *J* = 8.2 Hz, 2 H, 2 ArH), 6.40 (d, *J* = 2.1 Hz, 1 H, CH), 2.38 (s, 3 H, $COOCH_3$), 1.95 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.5, 169.5, 167.7, 138.9, 137.7, 137.3, 131.9, 130.9, 129.8, 129.4, 128.9, 126.2, 123.6, 67.9, 21.2, 20.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{16}ClNNaO_4$: 392.0660; found: 392.0658.

(*E*)-3-(4-Chlorobenzylidene)-4-(propynoyloxy)-1-(*p*-tolyl)pyrrolidine-2,5-dione (3d)

Following GP3 using **2a** (337 mg, 1 mmol) and propiolic acid (140 mg, 2 mmol) gave **3d** as a white solid; yield: 318 mg (84%); mp 141.8–143.0 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 2.0 Hz, 1 H, =CH), 7.57 (d, *J* = 8.6 Hz, 2 H, 2 ArH), 7.49 (d, *J* = 8.6 Hz, 2 H, 2 ArH), 7.34–7.31 (m, 2 H, 2 ArH), 7.29–7.27 (m, 2 H, 2 ArH), 6.16 (d, *J* = 2.1 Hz, 1 H, CH), 3.00 (s, 1 H, C≡CH), 2.43 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.4, 167.5, 150.9, 139.2, 138.9, 137.7, 132.0, 130.6, 129.9, 129.6, 128.7, 126.1, 122.1, 77.8, 72.7, 69.1, 21.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{14}ClNNaO_4$: 402.0504; found: 402.0492.

(*E*)-3-(Cyclohexyloxy)-4-(furan-2-ylmethylene)-1-[4-(trifluoromethyl)phenyl]pyrrolidine-2,5-dione (3e)

Following GP3 using **2b** (347 mg, 1 mmol) and cyclohexanol (200 mg, 2 mmol) gave **3e** as red needle crystals; yield: 364 mg (87%); mp 154.0–155.7 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.5 Hz, 2 H, 2 ArH), 7.69 (d, *J* = 1.6 Hz, 1 H, =CH), 7.66 (d, *J* = 1.7 Hz, 1 H, ArH), 7.60 (d, *J* = 8.4 Hz, 2 H, 2 ArH), 7.00 (d, *J* = 3.5 Hz, 1 H, CH), 6.63 (dd, *J* = 3.5, 1.8 Hz, 1 H, CH), 5.30 (d, *J* = 1.7 Hz, 1 H, CH), 4.17–4.09 (m, 1 H, CH), 2.22–2.12 (m, 1 H, CH), 2.06–1.96 (m, 1 H, CH), 1.89–1.72 (m, 2 H, CH_2), 1.64–1.55 (m, 1 H, CH), 1.50–1.28 (m, 4 H, 2 CH_2), 1.26–1.14 (m, 1 H, CH)

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.1, 168.0, 150.0, 146.8, 134.9, 130.3 (q, *J* = 32.9 Hz), 126.5), 126.1 (q, *J* = 3.7 Hz), 125.8, 123.7 (q, *J* = 272.3 Hz), 121.3, 119.9, 113.2, 78.6, 71.0, 33.7, 32.2, 25.5, 24.4, 24.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}F_3NO_4$: 420.1417; found: 420.1426.

(*E*)-3-(Furan-2-ylmethylene)-4-(2-methoxyethoxy)-1-[4-(trifluoromethyl)phenyl]-pyrrolidine-2,5-dione (3f)

Following GP3 using **2b** (347 mg, 1 mmol) and 2-methoxyethanol (152 mg, 2 mmol) gave **3f** as a white solid; yield: 312 mg (79%); mp 133.4–135.0 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.4 Hz, 2 H, ArH), 7.72–7.71 (m, 2 H, CH, ArH), 7.61 (d, *J* = 8.4 Hz, 2 H, ArH), 7.09 (d, *J* = 3.5 Hz, 1 H, CH_{furyl}), 6.64 (dd, *J* = 3.3, 1.6 Hz, 1 H, CH_{furyl}), 5.15 (d, *J* = 1.5 Hz, 1 H, CH), 4.37–4.31 (m, 1 H, CH), 4.06 (dt, *J* = 10.2, 4.8 Hz, 1 H, CH), 3.65–3.62 (m, 2 H, CH_2), 3.36 (s, 3 H, OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.6, 167.7, 149.9, 147.1, 134.8, 130.4 (q, *J* = 32.9 Hz), 126.6, 126.5, 126.1 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 272.4 Hz), 120.1, 119.9, 113.3, 73.7, 71.7, 70.1, 58.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}F_3NO_5$: 396.1053; found: 396.1061.

(*E*)-3-Isopropoxy-4-(2-methoxybenzylidene)-1-(*p*-tolyl)pyrrolidine-2,5-dione (3g)

Following GP3 using **2c** (333 mg, 1 mmol) in *i*-PrOH (5 mL) gave **3g** as a white solid; yield: 340 mg (93%); mp 147.3–148.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 1.7 Hz, 1 H, =CH), 7.92 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.49–7.42 (m, 1 H), 7.34–7.28 (m, 4 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 6.97 (d, *J* = 8.3 Hz, 1 H), 5.10 (d, *J* = 1.9 Hz, 1 H), 4.34 (hept, *J* = 6.1 Hz, 1 H), 3.92 (s, 3 H), 2.42 (s, 3 H), 1.26 (d, *J* = 6.1 Hz, 3 H), 1.21 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.6, 168.8, 158.7, 138.5, 135.6, 132.4, 131.2, 129.7, 129.1, 126.2, 124.7, 122.6, 120.4, 110.8, 71.4, 70.8, 55.6, 23.5, 21.7, 21.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{23}NNaO_4$: 388.1519; found: 388.1521.

(*Z*)-3-Benzylidene-4-(benzylthio)-1-(4-chlorophenyl)pyrrolidine-2,5-dione (3h)

Following GP3 using **2d** (323 mg, 1 mmol) and benzyl mercaptan (248 mg, 2 mmol) gave **3h** as a white solid; yield: 372 mg (89%); mp 200.2–202.3 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 1.9 Hz, 1 H, =CH), 7.60–7.56 (m, 2 H, 2 ArH), 7.53–7.46 (m, 4 H, 4 ArH), 7.44–7.38 (m, 4 H, 4 ArH), 7.33–7.30 (m, 4 H, 4 ArH), 4.46 (d, *J* = 13.8 Hz, 1 H, CH*H*), 4.29 (d, *J* = 1.8 Hz, 1 H, CH), 3.87 (d, *J* = 13.8 Hz, 1 H, C*H*H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.6, 168.4, 138.3, 136.6, 134.4, 132.5, 131.7, 130.8, 130.3, 129.7, 129.3, 128.7, 128.7, 127.8, 127.6, 122.9, 39.7, 35.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{18}ClNNaO_2S$: 442.0639; found: 442.0626.

(*E*)-3-Benzylidene-4-(benzyloxy)-1-(4-chlorophenyl)pyrrolidine-2,5-dione (3i)

Following GP3 using **2d** (323 mg, 1 mmol) and benzyl alcohol (216 mg, 2 mmol) gave **3i** as a white solid; yield: 378 mg (94%); mp 221.7–222.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 1.7 Hz, 1 H, =CH), 7.75–7.70 (m, 2 H, 2 ArH), 7.55–7.42 (m, 6 H, 6 ArH), 7.41–7.34 (m, 6 H, 6 ArH), 5.21 (d, *J* = 1.8 Hz, 1 H, CH), 5.07 (d, *J* = 10.8 Hz, 1 H, CH*H*), 4.86 (d, *J* = 10.8 Hz, 1 H, C*H*H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.4, 168.2, 141.5, 136.2, 134.5, 132.9, 131.4, 131.3, 130.0, 129.3, 129.0, 129.0, 128.6, 128.5, 127.5, 126.9, 123.4, 71.7, 71.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{18}ClNNaO_3$: 426.0867; found: 426.0857.

(*E*)-1-(4-Chlorophenyl)-3-(4-methylbenzylidene)-4-(prop-2-ynyloxy)pyrrolidine-2,5-dione (3j)

Following GP3 using **2e** (337 mg, 1 mmol) and propargyl alcohol (112 mg, 2 mmol) gave **3j** as a white solid; yield: 335 mg (92%); mp 118.6–119.8 °C (decomp).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 1.5 Hz, 1 H, =CH), 7.75 (d, *J* = 8.1 Hz, 2 H, 2 ArH), 7.49 (d, *J* = 8.8 Hz, 2 H, 2 ArH), 7.39 (d, *J* = 8.8 Hz, 2 H, 2 ArH), 7.32 (d, *J* = 8.0 Hz, 2 H, 2 ArH), 5.36 (d, *J* = 1.7 Hz, 1 H, CH), 4.86 (dd, *J* = 16.0, 2.3 Hz, 1 H, C*H*H), 4.62 (dd, *J* = 16.0, 2.4 Hz, 1 H, CH*H*), 2.67 (t, *J* = 2.4 Hz, 1 H, ≡CH), 2.46 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.3, 168.4, 142.4, 142.0, 134.4, 131.9, 130.0, 129.8, 129.3, 127.5, 121.5, 78.3, 70.1, 56.6, 21.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{16}ClNNaO_3$: 388.0711; found: 388.0718.

(*E*)-1-(4-Chlorophenyl)-3-methoxy-4-(4-methylbenzylidene)-pyrrolidine-2,5-dione (3k)

Following GP3 using **2e** (337 mg, 1 mmol) in MeOH (5 mL) gave **3k** as a white solid; yield: 310 mg (91%); mp 153.2–154.0 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.80 (d, *J* = 1.8 Hz, 1 H, =CH), 7.73 (d, *J* = 8.1 Hz, 2 H, 2 ArH), 7.61 (d, *J* = 8.7 Hz, 2 H, 2 ArH), 7.45 (d, *J* = 8.7 Hz, 2 H, 2 ArH), 7.35 (d, *J* = 8.0 Hz, 2 H, 2 ArH), 5.32 (d, *J* = 2.1 Hz, 1 H, CH), 3.47 (s, 3 H, OCH_3), 2.39 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.2, 168.5, 141.7, 139.4, 133.4, 131.9, 131.3, 130.6, 130.1, 129.4, 129.2, 123.7, 73.9, 55.9, 21.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{16}ClNNaO_3$: 364.0711; found: 364.0699.

(*E*)-1-(4-Chlorophenyl)-3-(2-mercaptoethoxy)-4-(4-methylbenzylidene)pyrrolidine-2,5-dione (3l)

Following GP3 using **2e** (337 mg, 1 mmol) and 2-mercaptoethanol (156 mg, 2 mmol) gave **3l** as a white solid; yield: 344 mg (89%); mp 141.0–142.7 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (s, 1 H, =CH), 7.68 (d, *J* = 8.1 Hz, 2 H, 2 ArH), 7.50 (d, *J* = 8.8 Hz, 2 H, 2 ArH), 7.40 (d, *J* = 8.8 Hz, 2 H, 2 ArH), 7.34 (d, *J* = 8.0 Hz, 2 H, 2 ArH), 4.83 (d, *J* = 1.7 Hz, 1 H, CH), 4.07–3.94 (m, 2 H, CH_2), 3.33 (ddd, *J* = 14.5, 6.7, 4.3 Hz, 1 H, C*H*H), 2.94 (ddd, *J* = 14.5, 6.5, 4.4 Hz, 1 H, CH*H*), 2.59 (dd, *J* = 7.1, 5.3 Hz, 1 H, SH), 2.45 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.4, 168.3, 142.0, 138.9, 134.5, 131.9, 130.3, 130.1, 129.8, 129.4, 127.6, 122.3, 62.2, 42.3, 35.0, 21.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{18}ClNNaO_3S$: 410.0588; found: 410.0595.

(*E*)-3-Acetoxy-1-(4-chlorophenyl)-4-(4-methylbenzylidene)pyrrolidine-2,5-dione (3m)

Following GP3 using **2e** (337 mg, 1 mmol) and acetic acid (120 mg, 2 mmol) gave **3m** as a white solid; yield: 332 mg (90%); mp 139.0–141.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 1.6 Hz, 1 H, =CH), 7.55 (d, *J* = 8.0 Hz, 2 H, 2 ArH), 7.49 (d, *J* = 8.7 Hz, 2 H, 2 ArH), 7.39 (d, *J* = 8.7 Hz, 2 H, 2 ArH), 7.31 (d, *J* = 8.0 Hz, 2 H, 2 ArH), 6.04 (d, *J* = 1.7 Hz, 1 H, CH), 2.45 (s, 3 H, CH_3), 2.06 (s, 3 H, $C(O)CH_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.6, 169.6, 167.8, 142.2, 140.0, 134.5, 131.0, 130.2, 129.6, 129.3, 127.7, 121.3, 68.3, 21.6, 20.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{16}ClNNaO_4$: 392.0660; found: 392.0667.

(*E*)-3-Acetoxy-4-(4-fluorobenzylidene)-1-(*p*-tolyl)pyrrolidine-2,5-dione (3n)

Following GP3 using **2f** (321 mg, 1 mmol) and acetic acid (120 mg, 2 mmol) gave **3n** as a white solid; yield: 240 mg (68%); mp 179.4–181.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 2.2 Hz, 1 H, =CH), 7.65 (dd, *J* = 8.9, 5.3 Hz, 2 H, ArH), 7.33 (d, *J* = 8.3 Hz, 2 H, ArH), 7.29 (d, *J* = 8.6 Hz, 2 H, ArH), 7.19 (t, *J* = 8.6 Hz, 2 H, ArH), 6.06 (d, *J* = 2.2 Hz, 1 H, CHC=O), 2.43 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3C=O).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.7, 169.6, 167.9, 164.2 (d, *J* = 254.4 Hz), 139.0, 137.9, 132.9 (d, *J* = 8.8 Hz), 129.9, 128.9, 128.8 (d, *J* = 3.4 Hz), 126.2, 122.6 (d, *J* = 2.3 Hz), 116.4 (d, *J* = 21.9 Hz), 68.1, 21.3, 20.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{16}FNNaO_4$: 376.0956; found: 376.0961.

(*E*)-3-(4-Chlorobenzylidene)-4-[(4-nitrophenyl)amino]-1-(*p*-tolyl)-pyrrolidine-2,5-dione (3o)

Following GP4 using **2a** (337 mg, 1 mmol) and 4-nitroaniline (138 mg, 1 mmol) gave **3a** as a white solid; yield: 317 mg (71%); mp 215.7–217.8 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.07 (d, *J* = 9.1 Hz, 2 H, ArH), 7.82 (d, *J* = 2.1 Hz, 1 H, =CH), 7.62 (d, *J* = 8.6 Hz, 3 H, Ar-NH), 7.40 (d, *J* = 8.5 Hz, 2 H, ArH), 7.35 (d, *J* = 8.3 Hz, 2 H, ArH), 7.26 (d, *J* = 8.3 Hz, 2 H, ArH), 6.86 (d, *J* = 8.9 Hz, 2 H, ArH), 6.03 (dd, *J* = 8.9, 2.0 Hz, 1 H, CH), 2.38 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.8, 168.6, 153.8, 138.7, 137.8, 136.0, 135.6, 133.0, 132.0, 130.0, 129.9, 129.1, 127.1, 126.9, 126.5, 112.5, 52.8, 21.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{18}ClN_3NaO_4$: 470.0878; found: 470.0879.

(*E*)-3-Benzylidene-1-(4-chlorophenyl)-4-(phenylamino)pyrrolidine-2,5-dione (3p)

Following GP4 using **2d** (323 mg, 1 mmol) and aniline (93 mg, 1 mmol) gave **3p** as a white solid; yield: 248 mg (64%); mp 205.8–207.3 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.77 (d, *J* = 2.0 Hz, 1 H, =CH), 7.72 (d, *J* = 7.2 Hz, 2 H, ArH), 7.62 (d, *J* = 8.7 Hz, 2 H, ArH), 7.42 (d, *J* = 8.7 Hz, 2 H, ArH), 7.40 (s, 1 H, NH), 7.35 (dd, *J* = 7.6, 6.9 Hz, 2 H, ArH). 7.13 (t, *J* = 7.8 Hz, 2 H, ArH), 6.77 (d, *J* = 8.0 Hz, 2 H, ArH), 6.65 (t, *J* = 7.3 Hz, 1 H, ArH), 6.35 (d, *J* = 9.3 Hz, 1 H, ArH), 5.66 (dd, *J* = 9.2, 2.0 Hz, 1 H, CH).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 174.6, 169.0, 147.4, 137.1, 133.4, 133.3, 131.9, 131.6, 130.8, 129.5, 129.4, 129.1, 129.0, 127.3, 117.7, 113.6, 53.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{18}ClN_2O_2$: 389.1051; found: 389.1054.

(*E*)-3-[(4-Fluorophenyl)amino]-4-(2-methoxybenzylidene)-1-(*p*-tolyl)-pyrrolidine-2,5-dione (3q)

Following GP4 using **2c** (333 mg, 1 mmol) and 4-fluoroaniline (111 mg, 1 mmol) gave **3q** as a white solid; yield: 312 mg (75%); mp 188.3–190.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 (d, *J* = 2.1 Hz, 1 H, =CH), 7.61 (d, *J* = 7.7 Hz, 1 H, ArH), 7.39 (t, *J* = 7.8 Hz, 1 H, ArH), 7.33 (d, *J* = 8.1 Hz, 2 H, ArH), 7.23 (d, *J* = 8.2 Hz, 2 H, ArH), 7.07 (d, *J* = 8.4 Hz, 1 H, NH), 6.94 (t, *J* = 8.9 Hz, 2 H, ArH), 6.81 (t, *J* = 7.5 Hz, 1 H, ArH), 6.69 (dd, *J* = 8.9, 4.5 Hz, 2 H, ArH), 6.16 (d, *J* = 9.1 Hz, 1 H, ArH), 5.62 (dd, *J* = 9.0, 2.0 Hz, 1 H, CH), 3.86 (s, 3 H, OCH_3), 2.37 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 175.04, 169.25, 158.73, 155.35 (d, J = 231.9 Hz), 144.22, 138.37, 132.59, 131.15, 130.76, 130.18, 129.85, 127.14, 126.84, 121.82, 120.61, 115.67 (d, *J* = 22.1 Hz), 114.50 (d, *J* = 7.5 Hz), 111.79, 56.20, 54.09, 21.22.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{22}FN_2O_3$: 417.1609; found: 417.1611.

(*E*)-1-(4-Chlorophenyl)-3-[(4-methoxyphenyl)amino]-4-(4-methylbenzylidene)pyrrolidine- 2,5-dione (3r)

Following GP4 using **2e** (337 mg, 1 mmol) and 4-methoxyaniline (123 mg, 1 mmol) gave **3r** as a white solid; yield: 250 mg (58%); mp 183.1–186.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.72 (d, *J* = 1.9 Hz, 1 H, =CH), 7.66 (d, *J* = 8.2 Hz, 2 H, ArH), 7.61 (d, *J* = 8.7 Hz, 2 H, ArH), 7.39 (d, *J* = 8.7 Hz, 2 H, ArH), 7.19 (d, *J* = 8.1 Hz, 2 H, ArH), 6.76 (d, *J* = 3.0 Hz, 4 H, ArH), 6.01 (d, *J* = 9.2 Hz, 1 H, NH), 5.48 (dd, *J* = 9.2, 1.9 Hz, 1 H, CH), 3.67 (s, 3 H, OCH_3), 2.32 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 174.7, 169.1, 152.2, 141.2, 141.1, 137.2, 133.2, 132.1, 131.7, 130.8, 129.7, 129.4, 129.1, 126.4, 115.1, 115.0, 55.7, 54.2, 21.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{21}ClN_2NaO_3$: 455.1133; found: 455.1139.

(*E*)-*N*-[4-(4-Chlorobenzylidene)-2,5-dioxo-1-(*p*-tolyl)pyrrolidin-3-yl]benzenesulfonamide (3s)

Following GP4 using **2a** (338 mg, 1 mmol) and benzenesulfonamide (157 mg, 1 mmol) gave **3s** as a white solid; yield: 154 mg (33%); mp 226.5–227.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.95 (d, *J* = 7.5 Hz, 1 H, NH), 7.52–7.44 (m, 5 H, ArH, =CH), 7.44–7.39 (m, 1 H, ArH), 7.36 (d, *J* = 8.5 Hz, 2 H, ArH), 7.35 (d, *J* = 7.9 Hz, 2 H, ArH), 7.27 (t, *J* = 7.8 Hz, 2 H), 7.18 (d, *J* = 8.3 Hz, 2 H), 5.50 (dd, *J* = 7.5, 2.3 Hz, 1 H, CHC=O), 2.38 (s, 3 H, CH_3).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.6, 168.9, 141.7, 138.6, 135.6, 135.5, 133.1, 132.5, 131.4, 130.1, 129.9, 128.81, 128.79, 127.0, 126.3, 124.7, 52.7, 21.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{19}ClN_2NaO_4S$: 489.0646; found: 489.0638.

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Supporting Information

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