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X=Y–ZH compounds as potential 1,3-dipoles. Part 65: atom economic cascade synthesis of highly functionalized pyrimidinylpyrrolidines☆

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ABSTRACT

The results of the reaction of aminomethyl heterocycles and 4,6-dimethyl-2-formylpyrimidine and of activated secondary amines with different aryl/heteroaryl or aliphatic aldehydes and *N*-methylmaleimide or maleimide are described. In the former case the reactions gave single diastereomers via *endo*-transition states whilst the latter gave a mixture of diastereomers, which are believed to arise from *anti*-dipoles via *endo*/*exo* transition states. The stereochemistry of the cycloadducts was determined by ^{1}H NMR and confirmed by X-ray crystallography.

1. Introduction

The pyrimidinyl nucleus occurs widely in both aromatic (e.g., thiamine pyrophosphate) and non-aromatic form (e.g., cytosine, thymine, uracil and barbiturates) and as part of a wide variety of purine derivatives (e.g., adenine and guanine). The nucleus features in an extraordinary, and growing, array of pharmaceuticals and agrochemicals (Fig. 1).[2–6] In the field of crop protection, pyrimidine derivatives span pesticidal nucleosides with a pyrimidine or purine nucleobase,[7] herbicides and fungicides.[8] Although a variety of methods for the synthesis of pyrimidinylpyrrolidines have been developed, the use of azomethine ylide cycloaddition reactions has attracted little attention.[9] These processes are attractive because a variety of strategies and catalysts are available. Furthermore there are a substantial number of bioactive synthetic and natural products containing pyrrolidine motifs.[10] The cycloaddition reactions may be carried out as two component processes with preformed imines, or as three-component cascade processes with an aldehyde, a primary or secondary amine and a dipolarophile. The latter strategy is highly atom economic (water is the only by-product), and high density functionality occupying all five positions of the pyrrolidine ring can be easily introduced.

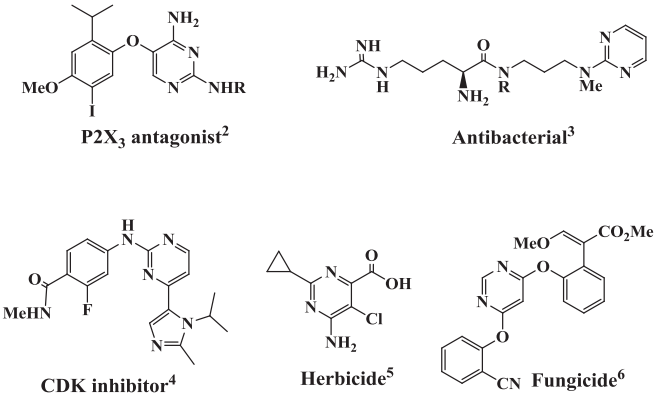

Fig. 1. Bioactive pyrimidines.

The reactions are catalyzed by a wide variety of Bronsted and Lewis acids including main group and transition metal salts and display excellent *endo*-selectivity.[11] This paper is concerned with the three component strategy.

2. Three-component cascade processes of primary amines

The concept of a thermal formal 1,2-prototropy in X=Y–ZH substrates generating 1,3-dipoles (Scheme 1) was introduced by us

☆ See Ref. 1.

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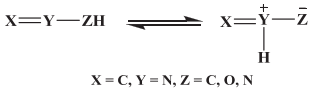
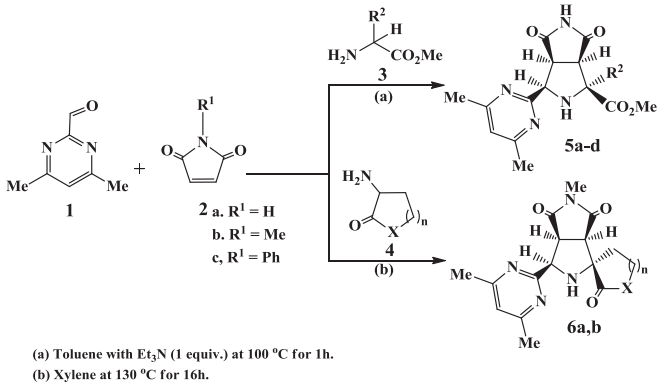


Scheme 1.

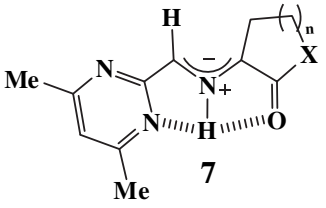
and subsequently shown to be viable for generating azomethine ylides, nitrones and azomethine imines.[12]

In the current investigation we initially employed the pyrimidine aldehyde **1** and the dipolarophiles maleimide **2a** or *N*-methylmaleimide **2b** with acyclic **3** and cyclic **4** amino esters (Scheme 2). In all cases the reaction occurred smoothly (toluene, 100 °C, oil bath) and in good yield via *endo*-transition states with precipitation of the cycloadduct from the hot toluene solution (Table 1) in the case of **5a**–**d** (Table 1, entries 1–4). Formation of spirocyclic cycloadducts **6a**,**b** (Table 1, entries 5 and 6) required more forcing conditions (xylene, 130 °C).



Scheme 2.

The proton NMR spectra (DMSO-d_6) of **5a**–**c** showed a singlet for the maleimide NH proton at δ 11.14–11.16 ppm and doublet for the pyrrolidine NH proton at δ 3.68–3.38 ppm. The corresponding signals for **5d** in $CDCl_3$ occurred at δ 8.29 and 4.14 ppm. The stereochemistry of **6a**,**b**, which was determined by NOE studies (see Experimental section), implicates the 1,3-dipoles **7**.



The reaction of **1** and **2c** with prolinamide **8** under analogous conditions afforded the tricyclic cycloadduct **10** in 89% yield via azomethine ylide **9** (Scheme 3). The stereochemistry of **10** was established by an X-ray crystal structure (Fig. 2). The high yield of **10** suggests that a series of prolinamide peptides would react similarly. The proton NMR spectrum of **10** (DMSO-d_6) clearly shows restricted rotation about the amide bond showing two signals for the NH_2 at δ 7.63 (J=2.3 Hz) and 7.32 (J=2.3 Hz).

A further small series of three-component cascades were studied in which the amino ester component of Scheme 2 was replaced by 2-aminomethyl heteroaromatic compounds **11a**,**b** and **12**.

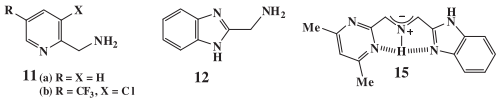
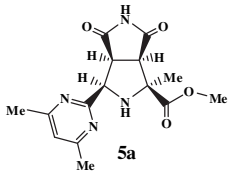
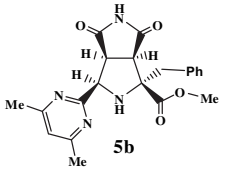
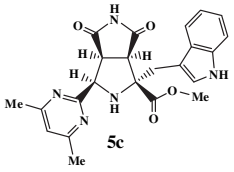
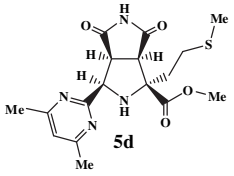
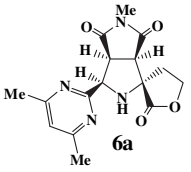
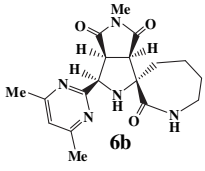
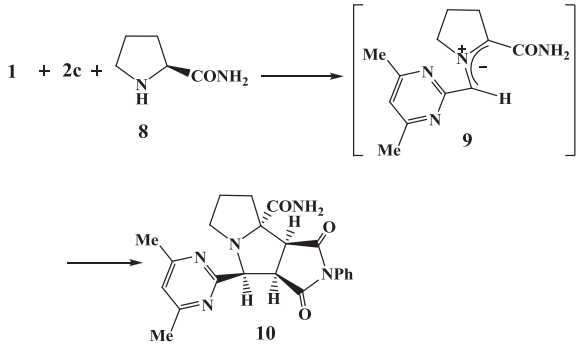


Table 1
Three-component cycloaddition cascades of **1** and **2** with **3** and **4**[a]

Entry	Amine ester HCl	Cycloadduct	Yield[b] (%)
1	Alanine	 **5a**	66
2	Phenylalanine	 **5b**	83
3	Tryptophan	 **5c**	74
4	Methionine	 **5d**	64[c]
5	**4a**	 **6a**	62[d]
6	**4b**	 **6b**	75[d]

[a] Conditions: **1** (1 mmol), amine ester hydrochloride (1 mmol), maleimide (1 mmol) and Et_3N (1 mmol) in toluene (7 mL) at 100 °C (oil bath) for 1 h.
[b] Isolated yield.
[c] Reaction (2 h).
[d] Xylene 16 h, 130 °C (oil bath), no Et_3N added.



Scheme 3.

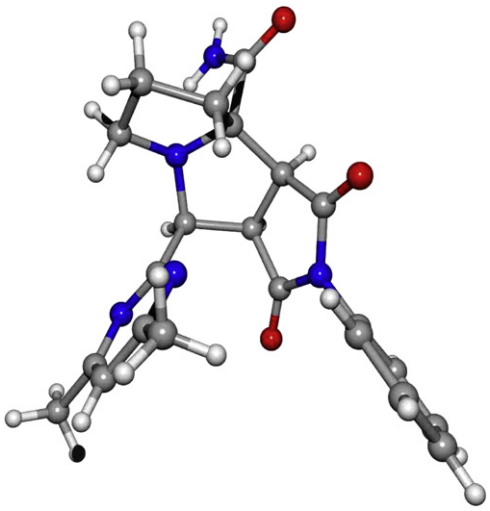
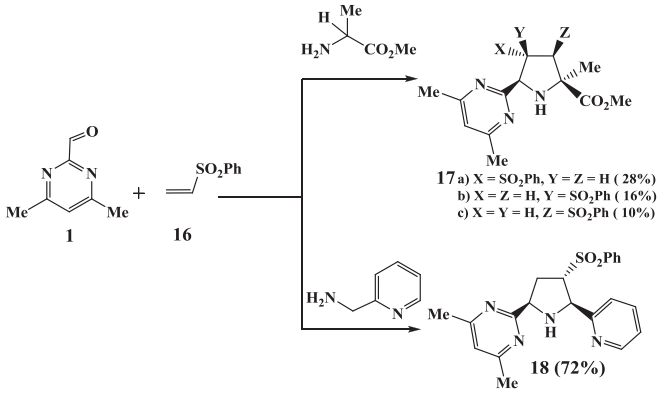


Fig. 2. X-ray crystal structure of **10**.

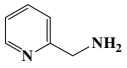
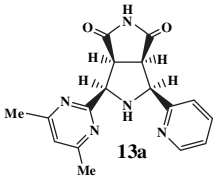
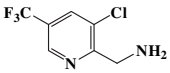
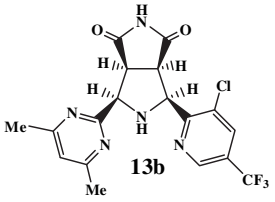
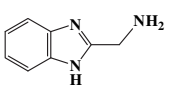
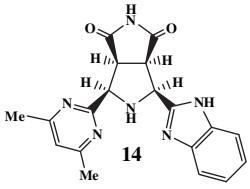
The reaction was carried out under the same conditions as those used in Scheme 2 [Et_3N, toluene, 100 °C (oil bath)] and afforded the corresponding *endo*-cycloadducts **13a**,**b** and **14** in 58–84% yield (Table 2).

The use of symmetrical maleimide dipolarophiles, required for further catalytic cascade chemistry, does not allow the regioselectivity of the cycloaddition in Tables 1 and 2 to be determined. This aspect was therefore probed using phenyl vinylsulfone **16** as the dipolarophile (Scheme 4). The reaction of **1** with alanine methyl ester and **16** occurred regioselectively to give **17a**–**c** (54%) as a 2.5:1.3:1 mixture whilst the reaction of **1** with 2-aminomethylpyridine and **16** afforded **18** (72%) stereo and regioselectively. The regio and stereoselectivity of **17a**–**c** was assigned by ^{1}H NMR and in the case of **17a** confirmed by an X-ray structure (Fig. 3). The stereo and regiochemistry of **18** was also established by X-ray crystallography (Fig. 4). The regiochemistry reflects the ability of the 1- and 3-substituents to stabilize the negative charge in the 1,3-dipole. In the case of two heterocycles, e.g., **18**, this can be predicted by the protonation pK_as of the *N*-heterocycles (pyrimidine pK_{aH}=1.3 and pyridine pK_{aH}=5.5).[13] The switch from the 'normal' *endo*-transition state product to an *exo*-transition state product in the formation of **18** reflects steric destabilization of the former by the bulky pyridyl/SO_2Ph interaction. We have noted a similar effect when a 2-pyridyl group is coordinated to Ag (I) and others have noted the ability of the SO_2Ph group to cause an *endo*→*exo* transition state switch.[14]



Scheme 4.

Table 2
Three-component cycloaddition cascades of **1** with **11** and **12**[a]

Entry	Amine	Cycloadduct	Yield[b] (%)
1		 **13a**	84
2		 **13b**	80[c]
3		 **14**	58

[a] Conditions: **1** (1 mmol), aminomethyl heterocycle (1 mmol), maleimide (1 mmol) and Et_3N (1 mmol) in toluene (7 mL) at 100 °C (oil bath) for 1.5 h.
[b] Isolated yield.
[c] Reaction completed after 10 min.

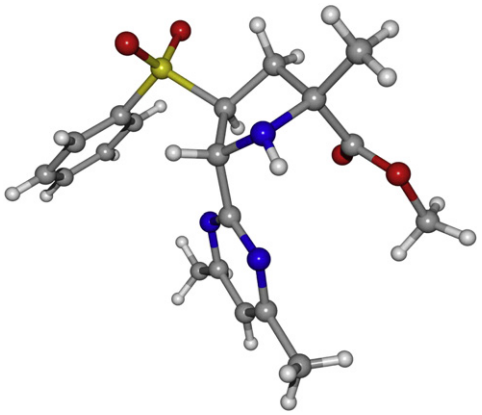


Fig. 3. X-ray crystal structure of **17a**.

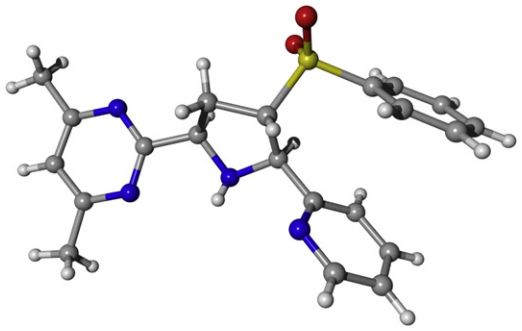
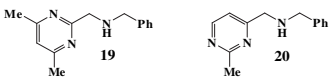
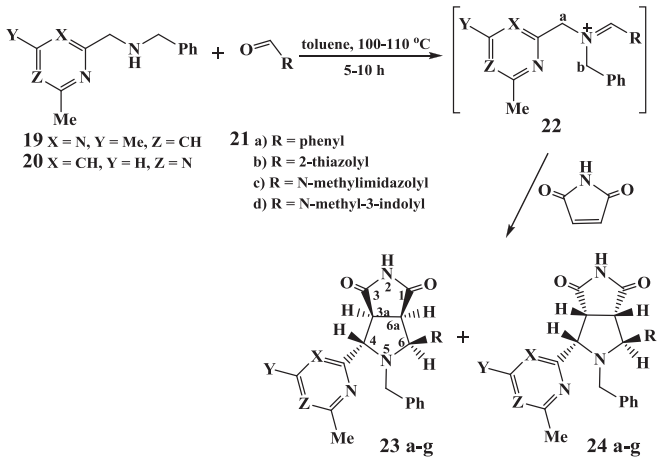


Fig. 4. X-ray crystal structure of **18**.

A second series of cycloadditions were explored using the *N*-benzylaminomethylpyrimidines **19** and **20**. These substrates, which were prepared by reductive amination of the corresponding aldehydes,[15,16] were selected to ascertain the stereoselectivity of the cycloadditions of the corresponding 1,2,3-trisubstituted azomethine ylides.[17–24]



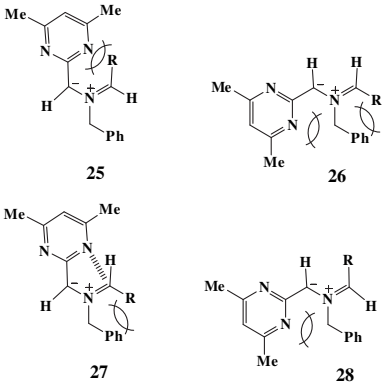
Amines **19** and **20** underwent 3-component cascade reactions with a series of aryl/heteroaryl aldehydes and maleimide or *N*-methylmaleimide (Scheme 5) in boiling toluene (Table 3). In all cases equimolar amounts of amine, aldehyde and dipolarophile were employed. The amines **19** and **20** gave rise to mixtures of two cycloadducts except in the case of Table 3, entry 7, which furnished a single cycloadduct **23g** although trace amounts of Michael adducts were observed in a number of cases. It was difficult to determine the precise cycloadduct isomer ratio from the ^{1}H NMR of the reaction mixture due to overlapping signals.



Scheme 5.

The stereochemistry of the cycloadducts was determined by comparison of the signals for their 4-H protons in the ^{1}H NMR spectra of **23** and **24**. For example in cycloadduct **23a** the 4-H proton appears as a singlet, indicating that the dihedral angle of the vicinal protons (4-H and 3a-H) is approximately 90° and consequently they are trans related, whereas the 6-H proton appears as a doublet (J=9.5 Hz) indicating that 6-H and 6a-H are cis related. In cycloadduct **24a**, however, the 4-H proton appears as a doublet (J=9.0 Hz) indicating that 4-H and 3a-H protons are cis related. The 6-H proton appears as a doublet with a small coupling constant (J=4.8 Hz) indicating that 6-H and 6a-H are trans related. These conclusions are supported by NOE studies. Irradiation of 4-H effects a 6% enhancement of the signal for 3a-H in **23b** whilst a 15% enhancement is observed in **24b**. These data indicate that 4-H and 3a-H are trans related in **23** and cis related in **24**. Similarly, irradiation of 6-H in **23c** effects a 14% enhancement of the signal for 6a-H whilst a 3% enhancement is observed in **24c**.These data suggested that 6-H and 6a-H are cis related in **23c** and trans related in **24c**. The stereochemistry of the cycloadducts was firmly established by an X-ray crystal structure of **23d** (Fig. 5). The stereochemistry of the cycloadducts **23e**–**g** and **24e**–**g** was assigned by comparison of the ^{1}H NMR spectra with those of the previously described analogues.

Two additional features of Scheme 5 merit further comment. Firstly, the intermediate **22** undergoes regioselective deprotonation solely at $(CH_2)_a$ as opposed to $(CH_2)_b$ reflecting the greater electronegativity of the pyrimidine ring versus that of the benzyl group. Secondly, there are potentially four configurations **25**–**28** of the intermediate azomethine ylide. Two *syn* (**25** and **26**) and two *anti* (**27** and **28**) dipoles are possible (with respect to the stereochemistry of the 1,3-substituens), for the *N*-substituted azomethine ylides. Their relative stability may be estimated on the grounds of steric and electronic interactions among the substituents. The U-shaped *syn*-dipole **25** and *syn*-dipole **26** are discarded because they are too sterically congested.



Both semi-empirical (AM1) and ab initio (STO-3G) calculations predict small energetic preference for *anti*-dipole **28** over the alternative *anti*-dipole **27**. Additionally the *syn*-dipoles **25** and **26** are considerably disfavoured (Table 4).

It is reported[21] that cycloaddition of dibenzylamine with benzaldehyde and *N*-methylmaleimide (toluene, reflux) gives cycloadducts derived from both *syn* and *anti*-dipole. In our case **27** and **28** are close in energy. However, the *anti*-dipole **27** has an additional potential stabilisation by 1,5-dipole interaction. No cycloadduct was obtained from *syn*-dipoles **25** or **26**. It is difficult to decide if both **27** and **28** are involved in the cycloaddition reactions because an *endo*-transition state of **27** gives the same cycloadduct as an *exo*-transition state of **28** and vice versa.

3. Conclusions

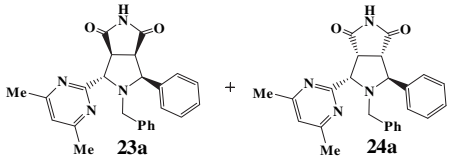
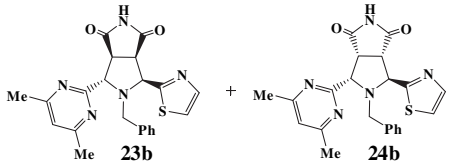
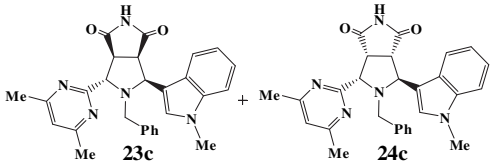
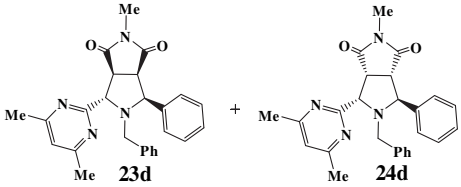
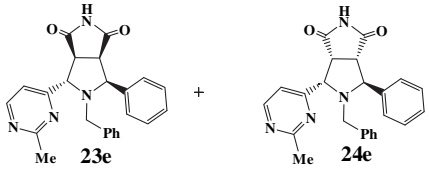
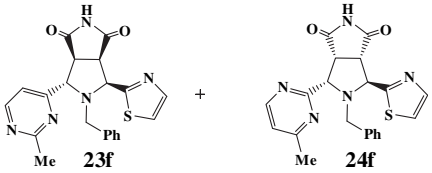
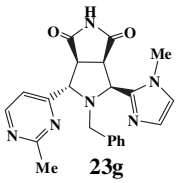
4,6-Dimethyl-2-formylpyrimidine participate in 1,3-dipolar cycloaddition with acyclic and cyclic α-amino esters and 2-aminomethyl heterocycles, with in situ dipole formation and capture by maleimides affording cycloadducts in good yields via *endo*-transition states. When the bulky phenyl vinylsulfone is used as dipolarophile *exo*-transition states predominate due to steric effects. In contrast reacting *N*-benzylaminomethylpyridines with a range of aldehydes and maleimides leads to approximately 1:1 mixture of *N*-benzyl cycloadducts via *anti*-1,3-dipoles.

4. Experimental

4.1. General

Thin layer chromatography (TLC) was carried out on a pre-coated aluminium plates with silica gel 60 F_{254} (Merck), and was visualised using ultraviolet light and/or aqueous $KMnO_4/I_2$. Flash column chromatography employed silica gel 60 (Merck, 230–400 mesh). Melting points were determined on a Kofler hot-stage apparatus or Reichert hot-stage microscope and are uncorrected. Microanalyses

Table 3
Cycloadducts from amines **19** and **20**, aldehydes **21a–d** and maleimide[a]

Entry	Aldehyde	Cycloadduct	*endo*/*exo*	Yield[b] (%)
1	**21a**	 **23a** + **24a**	1:1	68
2	**21b**	 **23b** + **24b**	1:1	63
3	**21d**	 **23c** + **24c**	1:1	63
4	**21a**	 **23d** + **24d**	1:1	74[c]
5	**21a**	 **23e** + **24e**	2.5:1	61
6	**21b**	 **23f** + **24f**	1:1.2	75
7	**21c**	 **23g**	—[d]	53

[a] Conditions: equimolar quantities of amine, aldehyde and maleimide, 100 °C, toluene, 5–10 h.
[b] Isolated yield.
[c] Dipolarophile was *N*-methylmaleimide.
[d] Single cycloadduct formed.

were performed using Flash EA (1112 series) instrument. Infrared spectra of solids were collected on a Perkin–Elmer Spectrum FT-IR spectrometer by spreading a DCM solution on sodium chloride discs and allowing evaporation. Proton magnetic resonance spectra were recorded on Bruker 300, 400 and 500 MHz instruments. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane (δ=0.00) and coupling constants are given in Hertz (Hz). The following abbreviations are used: s=singlet, br=broad, d=doublet, dd=doublet of doublets, dt=doublet of triplets, m=multiplet, t=triplet, td=triplet of doublet. ^{13}C NMR spectra were recorded at 75 MHz on a Bruker DPX300 instrument and chemical shift values are reported in parts per million (ppm). Electron impact mass spectra were obtained on a Bruker HCT-ultra (ESI$^+$) machine, and accurate masses on a Bruker Daltonics micrOTOF spectrometer.

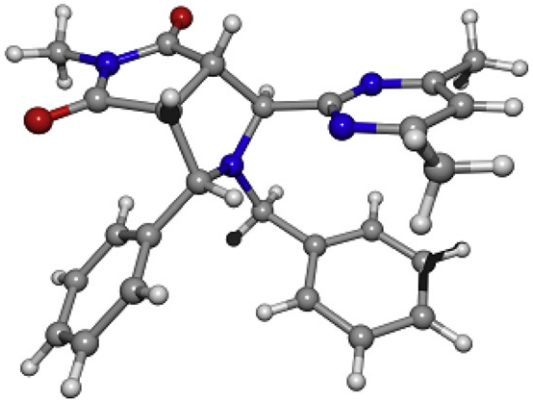


Fig. 5. X-ray crystal structure of **23d**.

Table 4
Energy calculations of 1,3-dipoles **25**–**28**

	Normalised energy[a] (Kcal/mol)			
	25	**26**	**27**	**28**
Semi-empirical (AM1)	4.65	3.74	1.12	0
ab initio (STO-3G)	4.09	3.70	1.74	0

[a] Energy calculations were performed using PC Spartan pro software. Semi-empirical calculations were run using the AM1 approximation with gradient minimization. Ab initio calculations used the STO-3G basis set with gradient minimization.

All compounds were named according to the IUPAC system using the ACD/ILAB (ACD/IUPAC v.12.0 programme) web service (http://www.acdlabs.com).

4.2. General procedure A: 1,3-dipolar cycloaddition reactions

An equimolar mixture (1 mmol) of the aldehyde **1**, amine hydrochloride, maleimide and Et_3N in toluene (7 mL) was heated at 100 °C for 10 min to 3 h with magnetic stirring. The cycloadducts precipitated out of the hot solution and were filtered off and washed with water to dissolve the Et_3NHCl. The resulting solid was crystallized.

*4.2.1. Methyl 3-(4,6-dimethylpyrimidin-2-yl)-1-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5a**).* Prepared by general procedure A from **1** (0.136 g, 1.00 mmol), D-alanine methyl ester hydrochloride (0.139 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in toluene (7 mL) at 100 °C for 1 h. The product (0.21 g, 66%) crystallized from MeOH as colourless needles, mp 258–260 °C; (Found: C, 56.65; H, 5.75; N, 17.65. $C_{15}H_{18}N_4O_4$ requires: C, 56.60; H, 5.70; N, 17.60%); δ_H (300 MHz, DMSO-d_6); 11.15 (1H, s, 5-NH), 7.16 (1H, s, pyrimidinyl–H), 4.66 (1H, dd, *J* 12.9 and 8.7, 3-H), 3.83 (1H, d, *J* 12.9, 2-NH), 3.73 (3H, s, OMe), 3.70 (1H, t, *J* 9.2, 3a-H), 3.36 (1H, d, *J* 9.6, 6a-H), 2.40 (6H, s, 2× pyrimidinyl–Me), 1.43 (3H, s, 1-Me); δ_C (75 MHz, DMSO-d_6); 177.25, 176.52, 172.38, 165.95, 164.77, 118.75, 68.14, 64.43, 58.56, 52.78, 52.27, 23.87, 23.31; ν_{max}/cm^{-1} (film); 3302, 3148, 2990, 2758, 1772, 1721, 1598, 1539, 1437, 1344, 1270; *m*/*z* (ESI^+) 341.1 (100%, MNa^+); found MNa^+, 341.1219. $C_{15}H_{18}N_4NaO_4$ requires MNa, 341.1220.

*4.2.2. Methyl 1-benzyl-3-(4,6-dimethylpyrimidin-2-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5b**).* Prepared by general procedure A from **1** (0.136 g, 1.00 mmol), L-phenylalanine methyl ester hydrochloride (0.215 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in toluene (7 mL) at 100 °C for 1 h. The product (0.32 g, 83%) crystallized from MeOH as colourless needles, mp 263–265 °C; (Found: C, 63.95; H, 5.60; N, 14.25. $C_{21}H_{22}N_4O_4$ requires: C, 63.95; H, 5.62; N, 14.20%); δ_H (300 MHz, DMSO-d_6); 11.16 (1H, s, 5-NH), 7.13–7.16 (6H, m, Ar–H), 4.84 (1H, dd, *J* 12.8 and 9.22, 3-H), 3.76 (1H, t, *J* 8.5, 3a-H), 3.71 (3H, s, OMe), 3.68 (1H, d, *J* 13.3, 2-NH), 3.54 (1H, d, *J* 7.7, 6a-H), 3.21 and 3.10 (2× 1H, 2d, *J* 13.8, CH_2Ph), 2.39 (6H, s, 2× pyrimidinyl–Me); δ_C (75 MHz, DMSO-d_6); 177.58, 176.97, 171.66, 166.49, 165.25, 137.21, 130.51, 128.03, 126.67, 119.25, 73.29, 64.49, 58.99, 53.21, 52.40, 40.74, 23.76; ν_{max}/cm^{-1} (film); 3300, 3248, 2956, 2741, 1776, 1745, 1718, 1598, 1435, 1374, 1348, 1263, 1231; *m*/*z* (ESI^+) 417.2 (100%, MNa^+); found MNa^+, 417.1534. $C_{21}H_{22}N_4NaO_4$ requires MNa, 417.1533.

*4.2.3. Methyl 3-(4,6-dimethylpyrimidin-2-yl)-1-(1H-indol-3-ylmethyl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5c**).* Prepared by general procedure A from **1** (0.136 g, 1 mmol), L-tryptophan methyl ester hydrochloride (0.254 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in toluene (7 mL) at 100 °C for 1 h. The product (0.32 g, 74%) crystallized from EtOH as colourless needles, mp 257–259 °C; (Found: C, 63.70; H, 5.40; N, 16.20. $C_{23}H_{23}N_5O_4$ requires: C, 63.73; H, 5.35; N, 16.16%); δ_H (300 MHz, DMSO-d_6); 11.14 (1H, s, 5-NH), 10.80 (1H, d, *J* 2.05, indolyl–NH), 7.53 (1H, d, *J* 7.5, indolyl–H), 7.29 (1H, d, *J* 7.8, indolyl–H), 7.15 (1H, s, pyrimidinyl–H), 7.07 (1H, d, *J* 2.1, indolyl–H), 7.00 (1H, t, *J* 7.5, indolyl–H), 6.92 (1H, t, *J* 7.4, indolyl–H), 4.86 (1H, dd, *J* 12.6 and 9.0, 3-H), 3.79 (1H, t, *J* 8.6, 3a-H), 3.74 (1H, d, *J* 13.8, 2-NH), 3.66 (3H, s, OMe), 3.58 (1H, d, *J* 7.8, 6a-H), 3.35 and 3.20 (2× 1H, 2d, *J* 14.9, CH_2–indolyl), 2.39 (6H, s, 2× pyrimidinyl–Me); δ_C (75 MHz, DMSO-d_6); 177.31, 176.59, 171.81, 165.96, 164.93, 135.38, 128.04, 124.03, 120.42, 118.74, 118.47, 118.06, 111.02, 109.43, 73.19, 64.25, 58.20, 52.84, 51.85, 31.07, 23.30; ν_{max}/cm^{-1} (film); 3390, 3054, 2890, 2763, 1772, 1716, 1594, 1544, 1434, 1348, 1205; *m*/*z* (ESI^+) 434.2 (100%, MH^+); found MH^+,434.1827. $C_{23}H_{24}N_5O_4$ requires MH, 434.1823.

*4.2.4. Methyl 3-(4,6-dimethylpyrimidin-2-yl)-1-[2-(methylthio) ethyl]-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5d**).* Prepared by general procedure A from **1** (0.136 g, 1.00 mmol), DL-methionine methyl ester hydrochloride (0.199 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.13 mL, 1.00 mmol) in toluene (7 mL) at 100 °C for 2 h. The product (0.24 g, 64%) crystallized from MeOH as colourless needles, mp 213–215 °C; (Found: C, 54.10; H, 5.90; N, 14.50; S, 8.35. $C_{17}H_{22}N_4O_4S$ requires: C, 53.95; H, 5.86; N, 14.80; S, 8.47%); δ_H (300 MHz, $CDCl_3$); 8.29 (1H, s, 5-NH), 6.94 (1H, s, pyrimidinyl–H), 4.72 (1H, dd, *J* 12.9 and 8.7, 3-H), 4.13 (1H, d, *J* 12.9, 2-NH), 3.89 (3H, s, OMe), 3.73 (1H, t, *J* 8.3, 3a-H), 3.35 (1H, d, *J* 7.8, 6a-H), 2.71–2.63 (1H, m, 1-CH_2CH_2), 2.50–2.36 (2H, m, CH_2S), 2.47 (6H, s, 2× pyrimidinyl–Me), 2.10 (3H, s, SMe), 1.96–1.88 (1H, m, 1-CH_2CH_2); δ_C (75 MHz, $CDCl_3$); 175.41, 174.94, 171.10, 166.91, 164.08, 119.41, 72.57, 65.21, 58.68, 52.98, 52.72, 36.07, 28.83, 23.88, 15.64; ν_{max}/cm^{-1} (film); 3296, 3159, 2954, 2763, 1775, 1722, 1597, 1545, 1442, 1347, 1267, 1226; *m*/*z* (ESI^+) 379.1 (100%, MH^+); found MH^+, 379.1446. $C_{17}H_{23}N_4O_4{}^{32}S$ requires MH, 279.1435.

4.3. General procedure B: spirocyclic cycloaddition

As for general procedure A except that the dipolarophiles was *N*-methylmaleimide (NMM), the solvent was xylene and the temperature was 130 °C.

*4.3.1. 3′-(4,6-Dimethylpyrimidin-2-yl)-5′-methyltetrahydro-2′H-spiro[furan-3,1′-pyrrolo[3,4-c]pyrrole]-2,4′,6′(3′H,5′H)-trione (**6a**).* A mixture of α-amino-γ-butyrolactone hydrobromide (0.3 g, 1.6 mmol), triethylamine (0.25 mL, 1.8 mmol), aldehyde **1** (0.22 g,

1.6 mmol) and *N*-methylmaleimide (0.18 g, 1.6 mmol) in xylene (10 mL) was heated at 130 °C for 16 h. Flash chromatography eluting with 9:1 v/v ethyl acetate/methanol afforded the product (0.34 g, 62%), which crystallized from dichloromethane/hexane as colourless rods, mp 210–212 °C; (Found: C, 57.90; H, 5.40; N, 17.00. $C_{16}H_{18}N_4O_4$ requires: C, 58.20; H, 5.50; N, 16.95%); δ_H (500 MHz, $CDCl_3$); 6.96 (1H, s, pyrimidinyl–H), 4.68 (1H, dd, *J* 7.9 and 13.2, 3′-H), 4.59 (1H, ddd, *J* 4.2, 5.5 and 9.5, CH_2O), 4.48 (1H, dt, *J* 7.7 and 9.3, CH_2O), 3.92 (1H, d, *J* 13.2, NH), 3.82 (1H, t, *J* 7.9, 3′a-H), 3.40 (1H, d, *J* 7.6, 6′a-H), 2.87 (3H, s, NMe), 2.47 (6H, s, 2× pyrimidinyl–Me), 2.46–2.43 (2H, m, CH_2CH_2O); ν_{max}/cm^{-1} (film); 1772, 1701, 1595, 1435, 1375, 1286.

NOE data for **6b**:

	% Enhancement			
Irradiated proton	3′-H	3′a-H+NH	6′a-H	4-H
3′-H		10.5	—	4.0
3′a-H	10.0		8.1	—

*4.3.2. 3′-(4,6-Dimethylpyrimidin-2-yl)-5′-methyldihydro-2H,2′H-spiro[azepane-3,1′-pyrrolo[3,4-c]pyrrole]-2,4′,6′(3′H,5′H)-trione (**6b**).* A mixture of 3-amino-ε-caprolactam (0.2 g, 1.5 mmol), aldehyde **1** (0.21 g, 1.5 mmol) and *N*-methylmaleimide (0.17 g, 1.5 mmol) in xylene (10 mL) was heated at 130 °C for 16 h. Flash chromatography eluting with 9:1 v/v ethyl acetate/methanol afforded the product (0.4 g, 75%), which crystallized from dichloromethane/hexane as colourless rods, mp 235–237 °C; δ_H (500 MHz, $CDCl_3$); 6.93 (1H, s, pyrimidinyl–H), 6.19 (1H, dd, *J* 2.9 and 7.6, CONH), 4.78–4.70 (2H, m, 3′-H and pyrrolidine–NH), 3.76 (1H, d, *J* 7.6, 6′a-H), 3.71 (1H, t, *J* 7.6, 3′a-H), 3.64 and 3.29 (2H, 2m, $NHCH_2$), 2.83 (3H, s, NMe), 2.45 (6H, s, 2× pyrimidinyl–Me), 1.97–1.69 (6H, m, 3× CH_2); δ_C (125 MHz, $CDCl_3$); 176.00, 175.50, 175.20, 166.50, 164.80, 118.00, 72.70, 64.20, 52.80, 50.80, 42.1, 34.70, 28.4, 25.40, 24.80, 23.80; ν_{max}/cm^{-1} (film); 1698, 1654, 1595, 1435, 1361, 1332, 1286, 1132; *m/z* (ESI^+) 358.2 (100%, MH^+); found MH^+, 358.1874. $C_{18}H_{23}N_5O_3$ requires MH, 358.1879.

NOE data for **6b**:

	% Enhancement		
Irradiated proton	3′-H	3′a-H	4-H
3′-H		10.5	4.0
3′a-H	10.0		—

*4.3.3. 4-(4,6-Dimethylpyrimidin-2-yl)-1,3-dioxo-2-phenyloctahydropyrrolo[3,4-a]pyrrolizine-8a(6H)-carboxamide (**10**).* A mixture of **1** (0.136 g, 1 mmol), L-prolinamide (0.114 g, 1 mmol), *N*-phenylmaleimide (0.173 g, 1 mmol) and Et_3N (0.13 mL, 1 mmol) was heated at 100 °C in toluene (5 mL) for 1 h. The solvent was removed under vacuum and the crude product was purified by gradient elution flash chromatography with EtOAc to 5:1 v/v EtOAc/EtOH to afford adduct. Crystallization from CH_2Cl_2 gave colourless needles (0.36, 89%), mp 219–220 °C; (Found: C, 64.90; H, 5.70; N, 17.35. $C_{22}H_{23}N_5O_3$ requires: C, 65.17; H, 5.72; N, 17.27%); δ_H (300 MHz, DMSO-d_6); 7.63 (1H, d, *J* 2.3, $CONH_2$), 7.47 (2H, t, *J* 7.5, phenyl–H), 7.38 (1H, t, *J* 7.5, phenyl–H), 7.32 (1H, d, *J* 2.3, $CONH_2$), 7.16 (1H, s, pyrimidinyl–H), 7.09 (2H, d, *J* 7.7, phenyl–H), 4.81 (1H, d, *J* 9.1, 4-H), 4.06 (1H, t, *J* 9.1, 3a-H), 3.97 (1H, d, *J* 9.1, 8b-H), 3.08–3.01 (1H, m, 6-H_A), 2.64–2.55 (2H, m, 6-H_B and 8-H_A), 2.34 (6H, s, 2× pyrimidinyl–Me), 2.13–2.03 (1H, m, 8-H_B), 1.78–1.67 (2H, m, 7-CH_2); δ_C (75 MHz, DMSO-d_6); 176.86, 175.85, 174.92, 165.82, 165.52, 132.26, 128.65, 127.95, 126.20, 118.47, 80.09, 68.30, 51.93, 49.95, 47.99, 30.16, 25.42, 23.27; ν_{max}/cm^{-1} (film); 3425, 3060, 2964, 2873, 1775, 1712, 1679, 1594, 1543, 1499, 1440, 1379; *m/z* (ESI^+) 406.2 (100%, MH^+); found MH^+,406.1864. $C_{22}H_{24}N_5O_3$ requires MH, 406.1874.

*4.3.4. 4-(4,6-Dimethylpyrimidin-2-yl)-6-(pyridin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**13a**).* A mixture of **1** (0.136 g, 1 mmol), 2-aminomethylpyridine (0.102 mL, 1 mmol), maleimide (0.097 g, 1 mmol) and Et_3N (0.13 mL, 1 mmol) was heated at 100 °C in toluene (7 mL) for 1.5 h. The solvent was removed under vacuum and the crude product was purified by flash chromatography with gradient elution from EtOAc to 1:1 v/v EtOAc/MeOH to afford the corresponding adduct **13a**, which crystallized from $CHCl_3$ as colourless needles (0.27, 84%), mp 148–150 °C; (Found: C, 63.40; H, 5.25; N, 21.75. $C_{17}H_{17}N_5O_2$ requires: C, 63.15; H, 5.30; N, 21.66%); δ_H (300 MHz, DMSO-d_6); 10.89 (1H, s, 2-NH), 8.53 (1H, d, *J* 4.6, pyridinyl–H), 7.77 (1H, dt, *J* 7.7 and 2.05, pyridinyl–H), 7.46 (1H, d, *J* 7.7, pyridinyl–H), 7.29 (1H, dd, *J* 7.7 and 4.6, pyridinyl–H), 7.16 (1H, s, pyrimidinyl–H), 4.62 (1H, dd, *J* 12.9 and 8.5, 6-H), 4.54 (1H, dd, *J* 12.9 and 7.9, 4-H), 4.03 (1H, t, *J* 12.9, 5-NH), 3.66 (1H, t, *J* 7.9, 3a-H), 3.56 (1H, t, *J* 7.9, 6a-H), 2.42 (6H, s, 2× pyrimidinyl–Me); δ_C (75 MHz, $CDCl_3$); 175.79, 175.69, 166.55, 164.64, 155.56, 149.30, 136.48, 123.06, 122.92, 119.12, 66.92, 66.29, 53.75, 53.68, 23.97; ν_{max}/cm^{-1} (film); 3467, 3285, 3164, 3054, 2762, 1774, 1715, 1596, 1546, 1475, 1442, 1350; *m/z* (ESI^+) 324.1 (100%, MH^+); found MH^+, 324.1456. $C_{17}H_{18}N_5O_2$ requires MH, 324.1455.

*4.3.5. 4-[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]-6-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**13b**).* Prepared by general procedure A from **1** (0.136 g, 1.00 mmol), 2-aminomethyl-3-chloro-5-(trifluoromethyl) pyridine hydrochloride (0.246 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.26 mL, 2.00 mmol) in toluene (7 mL) at 100 °C for 10 min. The product (0.34 g, 80%) crystallized from MeOH as colourless needles, mp 262–264 °C; (Found: C, 50.55; H, 3.50; Cl, 8.35; N, 16.45. $C_{18}H_{15}ClF_3N_5O_2$ requires: C, 50.77; H, 3.55; Cl, 8.33; N, 16.45%); δ_H (300 MHz, $CDCl_3$/MeOH-d_4); 8.77 (1H, d, *J* 1.3, pyridinyl–H), 8.00 (1H, d, *J* 1.5, pyridinyl–H), 6.99 (1H, s, pyrimidinyl–H), 5.07 (1H, d, *J* 8.0, 4-H), 4.77 (1H, d, *J* 8.0, 6-H), 3.93 (1H, t, *J* 8.0, 6a-H), 3.84 (1H, t, *J* 8.0, 3a-H), 2.82 (2H, br s, 2-NH and 5-NH), 2.51 (6H, s, 2× pyrimidinyl–Me); δ_C (75 MHz, $CDCl_3$/MeOH-d_4); 176.34, 176.07, 166.92, 164.24, 157.00, 143.72 (q, *J* 3.8), 133.89 (q, *J* 3.5), 131.34, 126.89 (q, *J* 33.7), 120.37 (q, *J* 273.6), 119.42, 66.09, 62.62, 53.74, 51.69, 23.81; ν_{max}/cm^{-1} (film); 3407, 3054, 2758, 1776, 1714, 1595, 1544, 1410, 1344, 1321; *m/z* (ESI^+) 426.1 (100%, MH^+); found MH^+, 426.0947. $C_{18}H_{16}{}^{35}ClF_3N_5O_2$ requires MH, 426.0939.

*4.3.6. 4-(1H-Benzimidazol-2-yl)-6-(4,6-dimethylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**14**).* Prepared by general procedure A from **1** (0.136 g, 1.00 mmol), 2-aminomethylbenzimidazole dihydrochloride (0.22 g, 1.00 mmol), maleimide (0.097 g, 1.00 mmol) and Et_3N (0.39 mL, 3.00 mmol) in toluene (7 mL) at 100 °C for 3 h. The product (0.21 g, 58%) was obtained as an amorphous off white powder from MeOH, mp 210–212 °C; δ_H (300 MHz, DMSO-d_6); 11.00 (1H, s, 2-NH), 7.58 (1H, d, *J* 7.2, benzimidazolyl–H), 7.51 (1H, d, *J* 7.5, benzimidazolyl–H), 7.20–7.13 (3H, m, 2× benzimidazolyl–H and pyrimidinyl–H), 4.73 (1H, dd, *J* 12.3 and 8.0, 4-H), 4.60 (1H, dd, *J* 12.3 and 8.0, 6-H), 4.02 (1H, t, *J* 12.3, 5-NH), 3.71 (1H, t, *J* 8.0, 6a-H), 3.63 (1H, t, *J* 8.0, 3a-H), 2.44 (6H, s, 2× pyrimidinyl–Me); δ_c (75 MHz, DMSO-d_6); 177.4, 177.0, 166.2, 165.4, 151.8, 121.7 (br s), 119.1, 66.3, 59.3, 53.8, 53.3, 23.9 (two symmetrical benzimidazolyl carbons could not be located due to peak overlaps); ν_{max}/cm^{-1} (film); 3478, 3297, 2950, 1868, 1761, 1713, 1599, 1542, 1485,1437, 1360, 1276; *m/z* (ESI^+) 363.2 (53%, MH^+); found MH^+, 363.1563. $C_{19}H_{19}N_6O_2$ requires MH, 363.1564.

*4.3.7. Methyl 5-(4,6-dimethylpyrimidin-2-yl)-2-methyl-4-(phenylsulfonyl)pyrrolidine-2-carboxylate (**17a**,**b**) and methyl 5-(4,6-dimethylpyrimidin-2-yl)-2-methyl-3-(phenylsulfonyl)pyrrolidine-2-carboxylate*

(***17c***). A mixture of 4,6-dimethyl-2-formylpyrimidine **1** (0.136 g, 1 mmol), D-alanine methyl ester hydrochloride (0.139 mL, 1 mmol), phenyl vinylsulfone (0.168 g, 1 mmol) and Et_3N (0.26 mL, 2 mmol) in toluene (7 mL) was heated at 100 °C for 15 min. The solvent was removed under vacuum, the residue dissolved in $CHCl_3$ and washed with water (3×10 mL), dried ($MgSO_4$) and the solvent was removed under vacuum to give crude cycloadduct. The crude product was purified by column chromatography eluting with AcOEt to separate cycloadduct **17a** and changing to EtOAc/MeOH (10:1) to separate cycloadducts **17c** then **17b**.

Compound **17a**, crystallized from $CHCl_3$ as colourless needles (0.11 g, 28%), mp 121–123 °C; δ_H (300 MHz, $CDCl_3$); 7.86 (2H, d, *J* 7.7, phenyl–H), 7.51 (1H, t, *J* 7.4, phenyl–H), 7.42 (2H, t, *J* 7.4, phenyl–H), 6.73 (1H, s, pyrimidinyl–H), 4.72 (1H, d, *J* 6.7, 5-H), 4.61 (1H, ddd, *J* 6.7, 8.5 and 15.5, 4-H), 3.55 (3H, s, CO_2Me), 3.19 (1H, br s, NH), 2.86 (1H, dd, *J* 9.4 and 13.7, 3-Ha), 2.44 (1H, dd, *J* 8.5 and 13.6, 3-Hb), 2.31 (6H, s, 2× pyrimidinyl–Me), 1.51 (3H, s, 2-Me); δ_c (75 MHz, $CDCl_3$); 175.6, 166.8, 166.6, 138.4, 133.4, 128.8 (2× C), 118.4, 67.3, 66.0, 64.9, 52.3, 37.4, 25.6, 23.8; ν_{max}/cm^{-1} (film); 3332, 2953, 1732, 1593, 1542, 1447, 1372, 1304, 1266; *m*/*z* (ESI^+) 390.2 (100%, MH^+); found MH^+, 390.1483. $C_{19}H_{24}N_3O_4{}^{32}S$ requires MH, 390.1482.

NOE data for **17a**:

	% Enhancement					
Irradiated proton	5-H	4-H	3-Ha	3-Hb	Ph	Me
5-H		—	—	—	3.9	—
4-H	—		6.4	—	4.6	—
3-Ha	—	11.6		25.5	—	—
3-Hb	3.8	—	27.4		2.8	3.8

Compound **17b**, δ_H (300 MHz, $CDCl_3$); 7.58 (2H, d, *J* 7.7, phenyl–H), 7.53 (1H, t, *J* 7.4, phenyl–H), 7.38 (2H, t, *J* 7.7, phenyl–H), 6.78 (1H, s, pyrimidinyl–H), 4.69 (1H, d, *J* 5.6, 5-H), 4.17 (1H, dt, *J* 5.6, 4-H), 3.86 (3H, s, CO_2Me), 3.38 (1H, dd, *J* 5.4 and 14.6, 3-Ha), 2.35 (6H, s, 2× pyrimidinyl–Me), 2.25 (1H, dd, *J* 7.7 and 14.3, 3-Hb), 1.51 (3H, s, 2-Me); δ_c (75 MHz, $CDCl_3$); 176.3, 166.6, 165.0, 139.6, 133.5, 129.1, 128.5, 119.3, 67.5, 66.1, 65.5, 53.0, 38.3, 29.7, 24.1; ν_{max}/cm^{-1} (film); 3330, 2927, 1736, 1593, 1543, 1446, 1371, 1305.

NOE data for **17b**:

	% Enhancement				
Irradiated proton	5-H	4-H	3-Ha	3-Hb	Ph
5-H		10.4	—	—	—
4-H	9.5		—	—	8.3
3-Ha	—	—		21.5	—
3-Hb	—	17.2	25.4		—

Compound **17c**, δ_H (300 MHz, $CDCl_3$); 7.86 (2H, d, *J* 7.2, phenyl–H), 7.63 (1H, t, *J* 7.3, phenyl–H), 7.53 (2H, t, *J* 7.4, phenyl–H), 6.90 (1H, s, pyrimidinyl–H), 4.38 (1H, dd, *J* 7.0 and 9.1, 5-H), 3.82 (3H, s, CO_2Me), 3.70 (1H, dd, *J* 7.4 and 10.2, 3-H), 2.46–2.39 (2H, m, 4-CH_2), 2.45 (6H, s, pyrimidinyl–Me), 1.25 (3H, s, 2-Me); δ_c (75 MHz, $CDCl_3$); 173.4, 167.9, 167.2, 140.4, 134.2, 129.6, 128.6, 118.9, 74.7, 67.7, 61.8, 53.4, 37.4, 27.8, 24.3; ν_{max}/cm^{-1} (film); 3296, 2952, 1737, 1593, 1545, 1447, 1373, 1308.

NOE data for **17c**:

	% Enhancement				
Irradiated proton	5-H	4-H_2	3-Ha	Ph	Me
5-H		7.9	4.1	—	—
3-H	—	5.6		5.9	4.1

*4.3.8. 4,6-Dimethyl-2-[4-(phenylsulfonyl)-5-(pyridin-2-yl)pyrrolidin-2-yl]pyrimidine (**18**).* A mixture of 4,6-dimethyl-2-formylpyrimidine **1** (0.136 g, 1 mmol), 2-aminomethylpyridine (0.103 mL, 1 mmol), phenyl vinylsulfone (0.168 g, 1 mmol) and Et_3N (0.13 mL, 1 mmol) in toluene (7 mL) was heated at 100 °C for 30 min. The solvent was removed under reduced pressure, the residue dissolved in $CHCl_3$ and washed with water (3×20 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give crude cycloadduct. The crude product was purified by column chromatography eluting with AcOEt to give the product, which crystallized from $CHCl_3$ as colourless needles (0.25 g, 64%), mp 132–134 °C; δ_H (300 MHz, $CDCl_3$); 8.50 (1H, d, *J* 4.1, pyridinyl–H), 7.83 (2H, d, *J* 7.4, phenyl–H), 7.54 (2H, dt, *J* 2.1 and 7.7, pyridinyl–H), 7.43 (2H, t, *J* 7.6, phenyl–H), 7.22 (1H, d, *J* 7.7, pyridinyl–H), 7.15 (1H, dd, *J* 5.1 and 7.2, phenyl–H), 6.90 (1H, s, pyrimidinyl–H), 4.79 (1H, d, *J* 7.2, 2-H), 4.62 (1H, dd, *J* 7.6 and 8.8, 5-H), 4.25 (1H, ddd, *J* 4.6, 7.1 and 11.3, 3-H), 3.61 (1H, br s, NH), 2.93 (1H, ddd, *J* 4.6, 7.2 and 12.0, 4-Ha), 2.44 (6H, s, 2× pyrimidinyl–Me), 2.34 (1H, ddd, *J* 9.5, 10.8 and 13.8, 4-Hb); δ_c (75 MHz, $CDCl_3$); 167.8, 166.8, 157.9, 149.4, 138.8, 136.6, 133.5, 129.1, 128.3, 123.9, 122.6, 118.6, 69.1, 65.4, 64.6, 36.2, 23.9; ν_{max}/cm^{-1} (film); 3276, 3061, 2925, 1593, 1544, 1474, 1446, 1384, 1348, 1304; *m*/*z* (ESI^+) 395.2 (100%, MH^+); found MH^+, 395.1553. $C_{21}H_{23}N_4O_2{}^{32}S$ requires MH, 395.1536.

4.4. General procedure for 19 and 20

A solution of the pyrimidine carboxaldehyde (1.5 mmol), benzylamine (1.5 mmol) and a catalytic amount of acetic acid (few drops) in dichloroethane (10 mL) was stirred for 1 h at 25 °C. Sodium triacetoxy borohydride (2.2 mmol) was then added under a nitrogen atmosphere and stirring continued for further 2 h. The reaction mixture was diluted with dichloromethane (10 mL) and washed sequentially with saturated $NaHCO_3$ solution and saturated brine. The organic layer was separated, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue afforded the amine.

*4.4.1. N-Benzyl-1-(4,6-dimethyl-2-pyrimidinyl)methanamine (**19**).* Flash chromatography of the residue eluting with 19:1 v/v ether/methanol afforded the amine (0.27 g, 81%) as a pale yellow oil. (Found: C, 73.50; H, 7.65; N, 18.50. $C_{14}H_{17}N_3$ requires: C, 73.95; H, 7.55; N, 18.50%); δ_H (250 MHz, $CDCl_3$); 7.40–7.24 (5H, m, phenyl–H), 6.88 (1H, s, pyrimidinyl–H), 3.99 (2H, s, CH_2–pyrimidinyl), 3.88 (2H, s, benzyl–CH_2), 2.42 (6H, s, 2× pyrimidinyl–Me), 2.34 (1H, br s, NH); *m*/*z* (%) 226 (M^+–1, 2), 197 (<1), 150 (2), 136 (1), 122 (100), 91 (26).

*4.4.2. N-Benzyl-1-(2-methyl-4-pyrimidinyl)methanamine (**20**).* Flash chromatography of the residue eluting with 19:1 v/v ether/methanol afforded the product (0.71 g, 81%) as pale yellow oil. (Found: C, 73.40; H, 7.20; N, 19.70. $C_{13}H_{15}N_3$ requires: C, 73.20; H, 7.10; N, 19.70%); δ_H (250 MHz, $CDCl_3$); 8.56 (1H, d, *J* 5.1, pyrimidinyl–H), 7.35–7.27 (5H, m, phenyl–H), 7.18 (1H, d, *J* 5.1, pyrimidinyl–H), 3.87 (2H, s, CH_2–pyrimidinyl), 3.84 (2H, s, benzyl–CH_2), 2.72 (3H, s, pyrimidinyl–Me), 2.15 (1H, br s, NH); *m*/*z* (%, FAB) 214 (M^++1, 100), 122 (5), 108 (17), 91 (32).

*4.4.3. 5-Benzyl-4-(4,6-dimethylpyrimidin-2-yl)-6-phenyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**23a** and **24a**).* Prepared by general procedure A from **19** (0.37 g, 1.62 mmol), benzaldehyde (0.17 mL, 1.62 mmol) and maleimide (0.16 g, 1.62 mmol) in dry toluene (12 mL) at 100 °C for 5 h. Flash chromatography (100% ether to 100% ethyl acetate gradient elution) afforded **23a** (0.23 g, 34%) followed by **24a** (0.23 g, 34%).

Compound **23a**, crystallized from dichloromethane/hexane as colourless rods, mp 205–207 °C; (Found: C, 72.60; H, 5.85; N, 13.80.

$C_{25}H_{24}O_2N_4$ requires: C, 72.80; H, 5.85; N, 13.60%); δ_H (250 MHz, $CDCl_3$); 7.90 (1H, br s, NH), 7.43–7.17(10H, m, aryl–H), 6.95 (1H, s, pyrimidinyl–H), 4.89 (1H, d, *J* 9.5, 6-H), 4.90 (1H, s, 4-H), 3.92 (1H, dd, *J* 7.9 and 9.5, 6a-H), 3.54 (1H, d, *J* 14.3, benzyl–CH_2), 3.55 (1H, d, *J* 7.9, 3a-H), 3.10 (1H, d, *J* 14.3, benzyl–CH_2), 2.48 (6H, s, 2× pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1716, 1591, 1540, 1342, 1318 and 1181; *m/z* (%, FAB) 413 (M^++1, 100), 321 (72), 250 (6), 91 (72).

Compound **24a**, crystallized from dichloromethane/hexane as colourless plates, mp 227–229 °C; (Found: C, 72.55; H, 5.85; N, 13.85. $C_{25}H_{24}O_2N_4$ requires: C, 72.80; H, 5.85; N, 13.60%); δ_H (250 MHz, $CDCl_3$); 8.04 (1H, br s, NH), 7.50–7.12 (10H, m, aryl–H), 6.89 (1H, s, pyrimidinyl–H), 4.93 (1H, d, *J* 4.8, 6-H), 4.78 (1H, d, *J* 9.0, 4-H), 3.94 (1H, t, *J* 9.3, 3a-H), 3.48 (1H, d, *J* 13.7, benzyl–CH_2), 3.46 (1H, dd, *J* 4.8 and 9.7, 6a-H), 2.91 (d, 1H, *J* 13.7, benzyl–CH_2), 2.43 (6H, s, 2× pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1716, 1593, 1542, 1453, 1370, 1346 and 1184; *m/z* (%) 412 (M^+, 2), 395 (1), 321 (100), 250 (17) 224 (7), 161 (7), 91 (44).

*4.4.4. 5-Benzyl-4-(4,6-dimethylpyrimidin-2-yl)-6-(1,3-thiazol-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**23b** and **24b**).* Prepared by general procedure A from **19** (0.18 g, 0.8 mmol), thiazole-2-carboxaldehyde (0.09 g, 0.8 mmol) and maleimide (0.077 g, 0.8 mmol) in dry toluene (12 mL) at 100 °C for 5 h. Flash chromatography eluting with ethyl acetate afforded **23b** (0.11 g, 32%) followed by **24b** (0.1 g, 31%).

Compound **23b**, crystallized from ethanol as colourless needles, mp 223–225 °C; δ_H (500 MHz, $CDCl_3$); 7.81 (1H, d, *J* 3.2, thiazolyl–H), 7.76 (1H, br s, NH), 7.33 (1H, d, *J* 3.2, thiazolyl–H), 7.29–7.18 (5H, m, phenyl–H), 6.95 (1H, s, pyrimidinyl–H), 5.53 (1H, d, *J* 9.7, 6-H), 4.88 (1H, s, 4-H), 4.13 (1H, dd, *J* 8.2 and 9.7, 6a-H), 3.75 (1H, d, *J* 14.2, benzyl–CH_2), 3.56 (1H, dd, *J* 1.0 and 8.2, 3a-H), 3.20 (1H, d, *J* 14.2, benzyl–CH_2), 2.46 (6H, s, 2× pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1718, 1594, 1540, 1345, 1202, 1184; *m/z* (ESI^+) 420.1 (100%, MH^+); found MH^+, 420.1496. $C_{22}H_{21}N_5O_2{}^{32}S$ requires MH, 420.1494.

NOE data for **23b**:

Irradiated proton	% Enhancement			
	4-H	3a-H	6a-H	6-H
4-H		6.0	—	—
3a-H	6.2		8.8	—
6a-H	—	12.6		14.3
6-H	—	—	15.8	

Compound **24b**, crystallized from ethanol as colourless plates, mp 250–252 °C; (Found: C, 62.45; H, 5.00; N, 16.95; S, 7.45. $C_{22}H_{21}O_2N_5S$ requires: C, 63.00; H, 5.05; N, 16.70; S, 7.65%); δ_H (500 MHz, $CDCl_3$); 7.83 (1H, d, *J* 3.2, thiazolyl–H), 7.72 (1H, br s, NH), 7.33 (1H, d, *J* 3.2, thiazolyl–H), 7.28–7.20 (5H, m, phenyl–H), 6.88 (1H, s, pyrimidinyl–H), 5.20 (1H, d, *J* 2.6, 6-H), 4.85 (1H, d, *J* 9.1, 4-H), 4.02 (1H, t, *J* 8.9, 3a-H), 3.66 (1H, dd, *J* 2.7 and 8.8, 6a-H), 3.58 (1H, d, *J* 14.0, benzyl–CH_2), 3.16 (1H, d, *J* 14.0, benzyl–CH_2), 2.44 (6H, s, 2× pyrimidinyl–Me); *m/z* (%, FAB) 420 (M^++1, 100), 335 (29), 314 (13), 91 (82).

NOE data for **24b**:

Irradiated proton	% Enhancement			
	4-H	3a-H	6a-H	6-H
4-H		14.8	—	—
3a-H	13.5		10.8	—
6a-H	—	9.7		5.4
6-H	—	—	4.3	

*4.4.5. 5-Benzyl-4-(4,6-dimethylpyrimidin-2-yl)-6-(1-methyl-1H-indol-3-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**23c** and **24c**).* Prepared by general procedure A from **19** (0.18 g, 0.8 mmol), *N*-methyl indole-3-carboxaldehyde (0.127 g, 0.8 mmol) and maleimide (0.077 g, 0.8 mmol) in dry toluene (12 mL) at 100 °C for 5 h. Flash chromatography eluting with ether afforded **23c** (0.126 g, 34%) followed by **24c** (0.11 g, 29%).

Compound **23c**, crystallized from ethanol as pale yellow plates, mp 235–237 °C; (Found: C, 72.05; H, 5.90; N, 15.20. $C_{28}H_{27}O_2N_5$ requires: C, 72.25; H, 5.85; N, 15.05%); δ_H (500 MHz, $CDCl_3$); 7.80 (1H, br s, NH), 7.70 (1H, br s, indolyl–H), 7.27–7.04 (9H, m, phenyl and indolyl–H), 6.94 (1H, s, pyrimidinyl–H), 5.25 (1H, d, *J* 9.4, 6-H), 4.93 (1H, s, 4-H), 3.91 (1H, t, *J* 9.0, 6a-H), 3.74 (1H, d, *J* 13.7, benzyl–CH_2), 3.72 (3H, s, NMe), 3.58 (1H, dd, *J* 0.6 and 7.9, 3a-H), 3.12 (1H, d, *J* 13.7, benzyl–CH_2), 2.48 (6H, s, 2× pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1717, 1653, 1591, 1558, 1540, 1343; *m/z* (%, FAB) 465 (M^+, 6), 374 (100), 360 (5), 335 (54), 91 (37).

NOE data for **23c**:

Irradiated proton	% Enhancement				
	4-H	3a-H	6a-H	6-H	Ar–H
4-H		5.6	—	—	3.7
3a-H	7.2		4.3	—	—
6a-H	—	9.9		11.9	—
6-H	—	—	13.7		4.1

Compound **24c**, crystallized from ethanol as pale yellow needles, mp 240–242 °C; (Found: C, 71.95; H, 5.90; N, 15.30. $C_{28}H_{27}O_2N_5$ requires: C, 72.25; H, 5.85; N, 15.05%); δ_H (500 MHz, $CDCl_3$); 7.75 (1H, dd, *J* 0.8 and 7.1, indolyl–H), 7.67 (1H, br s, NH), 7.33–7.05 (m, 9H, phenyl and indolyl–H), 6.88 (1H, s, pyrimidinyl–H), 5.21 (1H, d, *J* 4.7, 6-H), 4.77 (1H, s, 4-H), 3.98 (1H, t, *J* 9.2, 3a-H), 3.78 (3H, s, NMe), 3.74 (1H, dd, *J* 4.7 and 9.4, 6a-H), 3.56 and 2.96 (2H, 2d, *J* 13.9, benzyl–CH_2), 2.43 (6H, s, 2× pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1715, 1593, 1558, 1540, 1329, 1187; *m/z* (%, FAB); 465 (M^+, 16), 374 (91), 335 (51), 144 (48), 91 (100).

NOE data for **24c**:

Irradiated proton	% Enhancement				
	4-H	3a-H	6a-H	6-H	Ar–H
4-H		11.4	—	—	5.3
3a-H	13.2		6.7	—	3.1
6a-H	—	7.9		3.8	9.1
6-H	—	—	2.6		9.0

*4.4.6. 5-Benzyl-4-(4,6-dimethylpyrimidin-2-yl)-2-methyl-6-phenyltetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**23d** and **24d**).* Prepared by general procedure A from **19** (0.18 g, 0.8 mmol), benzaldehyde (0.1 mL, 0.8 mmol) and *N*-methylmaleimide (0.088 g, 0.8 mmol) in dry toluene (12 mL) at 110 °C for 5 h. Flash chromatography eluting with 10:1 v/v ether/hexane afforded **23d** (0.118 g, 35%) followed by **24d** (0.135 g, 39%).

Compound **23d**, crystallized from dichloromethane/hexane as colourless plates, mp 173–175 °C; (Found: C, 72.95; H, 6.10; N, 13.40. $C_{26}H_{26}O_2N_4$ requires: C, 73.20; H, 6.15; N, 13.15%); δ_H (250 MHz, $CDCl_3$); 7.35–7.11 (10H, m, aryl–H), 6.95 (1H, s, pyrimidinyl–H), 4.93 (1H, s, 4-H), 4.91 (1H, d, *J* 9.1, 6-H), 3.96 (1H, dd, *J* 7.8 and 9.5, 6a-H), 3.57 (1H, d, *J* 14.1, benzyl–CH_2), 3.45 (1H, d, *J* 7.7, 3a-H), 3.10 (1H, d, *J* 14.1, benzyl–CH_2), 2.93 (3H, s, NMe), 2.48 (6H, s, 2× pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1779, 1705, 1591, 1540, 1495, 1343, 1318, 1216; *m/z* (%, FAB) 427(M^++1, 100), 349 (7), 335 (90), 319 (7), 91 (60).

Compound **24d**, crystallized from dichloromethane/hexane as colourless needles, mp 185–187 °C; (Found: C, 73.20; H, 6.20; N, 13.40. $C_{26}H_{26}O_2N_4$ requires: C, 73.20; H, 6.15; N, 13.15%); δ_H (250 MHz,

$CDCl_3$); 7.53–7.10 (10H, m, aryl–H), 6.89 (1H, s, pyrimidinyl–H), 4.88 (1H, d, *J* 4.9, 6-H), 4.80 (1H, d, *J* 9.0, 4-H), 3.93 (1H, t, *J* 9.2, 3a-H), 3.47 (1H, d, *J* 13.0, benzyl–CH_2), 3.42 (1H, dd, *J* 4.9 and 9.4, 6a-H), 2.87 (1H, d, *J* 13.0, benzyl–CH_2), 2.85 (3H, s, NMe), 2.41 (6H, s, 2× pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1702, 1592, 1540, 1435, 1284; *m*/*z* (%, FAB) 427 (M^++1, 34), 335 (77), 250 (14), 224 (11), 91 (100).

*4.4.7. 5-Benzyl-4-(2-methylpyrimidin-4-yl)-6-phenyltetrahydropyrrolo [3,4-c]pyrrole-1,3(2H,3aH)-dione (**23e** and **24e**).* Prepared by general procedure A from **20** (0.36 g, 1.68 mmol), benzaldehyde (0.17 mL, 1.68 mmol) and maleimide (0.163 g, 1.68 mmol) in dry toluene (12 mL) at 100 °C for 10 h. Flash chromatography eluting with ether afforded **23e** followed by **24e** (combined yield, 0.163 g, 61%).

Compound **23e**, crystallized from ethanol as colourless plates, mp 225–227 °C; (Found: C, 72.25; H, 5.55; N, 14.30. $C_{24}H_{22}O_2N_4$ requires: C, 72.35; H, 5.55; N, 14.05%); δ_H (250 MHz, $CDCl_3$); 8.57 (1H, d, *J* 5.0, pyrimidinyl–H), 7.90 (1H, br s, NH), 7.47–7.18 (10H, m, aryl–H), 6.62 (1H, d, *J* 5.0, pyrimidinyl–H), 4.83 (1H, d, *J* 9.5, 2-H), 4.71 (1H, s, 5-H), 4.03 (1H, dd, *J* 7.9 and 9.6, 3-H), 3.71 (1H, d, *J* 14.5, benzyl–CH_2), 3.50 (1H, d, *J* 7.9, 4-H), 2.83 (1H, d, *J* 14.5, benzyl–CH_2), 2.8 (3H, s, pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1718, 1576, 1558, 1456, 1342; *m*/*z* (%, FAB) 399 (M^++1, 100), 307 (77), 210 (6), 91 (52).

Compound **24e**, crystallized from ethanol as colourless plates, mp 195–197 °C; (Found: C, 72.10; H, 5.50; N, 14.10. $C_{24}H_{22}O_2N_4$ requires: C, 72.35; H, 5.55; N, 14.05%); δ_H (250 MHz); 8.55 (1H, d, *J* 5.0, pyrimidinyl–H), 8.31 (1H, br s, NH), 7.46–7.12 (10H, m, aryl–H), 6.89 (1H, d, *J* 5.1, pyrimidinyl–H), 4.92 (1H, d, *J* 3.8, 6-H), 4.57 (1H, d, *J* 9.0, 4-H), 3.98 (1H, t, *J* 9.1, 3a-H), 3.59–3.52 (2H, m, 6a-H and benzyl–CH_2), 2.89 (1H, d, *J* 14.4, benzyl–CH_2), 2.73 (3H, s, pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1772, 1719, 1575, 1559, 1494, 1454, 1406, 1346; *m*/*z* (%) 498 (M^+, 1), 307 (100), 293 (7), 236 (10), 210 (10), 91 (62).

*4.4.8. 5-Benzyl-4-(4-methylpyrimidin-2-yl)-6-(1,3-thiazol-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**23f** and **24f**).* Prepared by general procedure A from **20** (0.4 g, 1.87 mmol), thiazole-2-carboxaldehyde (0.16 mL, 1.87 mmol) and maleimide (0.18 g, 1.87 mmol) in dry toluene (10 mL) at 100 °C for 5 h. Flash chromatography eluting with ethyl acetate afforded **24f** (0.34 g, 45%), followed by **23f** (0.228 g, 30%).

Compound **23f**, crystallized from ethanol as colourless rods, mp 233–235 °C; (Found: C, 62.35; H, 4.85; N, 17.40; S, 7.65. $C_{21}H_{19}O_2N_5S$ requires: C, 62.20; H, 4.70; N, 17.30; S, 7.90%); δ_H (250 MHz, $CDCl_3$); 8.60 (1H, d, *J* 5.0, pyrimidinyl–H), 8.3 (1H, br s, NH), 7.84 (1H, d, *J* 3.2, thiazolyl–H), 7.36–7.19 (6H, m, phenyl–H and thiazolyl–H), 6.67 (1H, d, *J* 5.0, pyrimidinyl–H), 5.48 (1H, d, *J* 9.7, 6-H), 4.66 (1H, s, 4-H), 4.22 (1H, dd, *J* 8.2 and 9.7, 6a-H), 3.84 (1H, d, *J* 14.3, benzyl–CH_2), 3.48 (1H, d, *J* 8.2, 3a-H), 3.97 (1H, d, *J* 14.3, benzyl–CH_2), 2.78 (3H, s, pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1720, 1575, 1558; *m*/*z* (%) 405 (M^+, 7), 314 (100), 300 (13), 269 (8), 243 (15), 217 (5), 91 (86).

Compound **24f**, crystallized from ethanol as colourless prisms, mp 255–257 °C; (Found: C, 62.00; H, 4.75; N, 17.50; S, 7.75. $C_{21}H_{19}O_2N_5S$ requires: C, 62.20; H, 4.70; N, 17.30; S, 7.90%); δ_H (250 MHz, $CDCl_3$); 8.60 (1H, d, *J* 5.0, pyrimidinyl–H), 8.0 (1H, br s, NH), 7.86 (1H, d, *J* 3.2, thiazolyl–H), 7.35–7.25 (6H, m, phenyl and thiazolyl–H), 7.18 (1H, d, *J* 5.0, pyrimidinyl–H), 5.15 (1H, d, *J* 2.6, 6-H), 4.82 (1H, d, *J* 9.1, 4-H), 4.10 (1H, t, *J* 8.9, 3a-H), 3.67 (1H, dd, *J* 2.7 and 8.8, 6a-H), 3.62 and 3.16 (2H, 2× d, *J* 14.0, benzyl–CH_2), 2.76 (3H, s, pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1718, 1576, 1559; *m*/*z* (%, ES) 406 (M^++1, 38), 315 (100).

*4.4.9. 5-Benzyl-4-(1-methyl-1H-imidazol-2-yl)-6-(4-methylpyrimidin-2-yl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione (**23g**).* Prepared by general procedure A from **20** (0.3 g, 1.4 mmol), *N*-methylimidazole-2-carboxaldehyde (0.15 g, 1.4 mmol) and maleimide (0.13 g, 1.4 mmol) in dry toluene (12 mL) at 110 °C for 10 h. Flash chromatography eluting with 9:1 v/v ethyl acetate/methanol afforded the product (0.3 g, 53%), which crystallized from ethanol as colourless plates, mp 253–255 °C; (Found: C, 65.50; H, 5.55; N, 21.05. $C_{22}H_{22}O_2N_6$ requires: C, 65.65; H, 5.50; N, 20.90%); δ_H (250 MHz, $CDCl_3$); 8.68–8.57 (2H, m, pyrimidinyl–H and NH), 7.35–7.17 (4H, m, phenyl–H and imidazolyl–H), 7.10–6.90 (3H, m, phenyl–H and imidazolyl–H), 6.73 (1H, s, pyrimidinyl–H), 5.09 (1H, br, 4-H), 4.75 (1H, br, 6-H), 3.96 (1H, m, 3a-H), 3.73–3.63 (2H, m, 6a-H and benzyl–CH_2), 3.30–3.10 (4H, m, NMe and benzyl–CH_2), 2.80 (3H, s, pyrimidinyl–Me); ν_{max}/cm^{-1} (film); 1718, 1576, 1558, 1191; *m*/*z* (%, ES) 403 (M^++1, 100).

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