Cyclic ureas as *ortho* directing substituents

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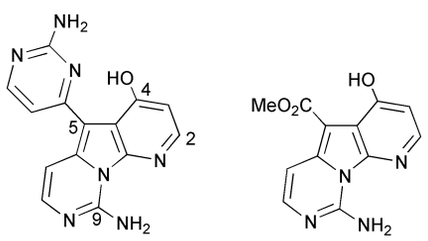
Six-membered cyclic ureas are shown to have a weak *ortho* directing ability when linked through nitrogen to benzene and pyridine rings.

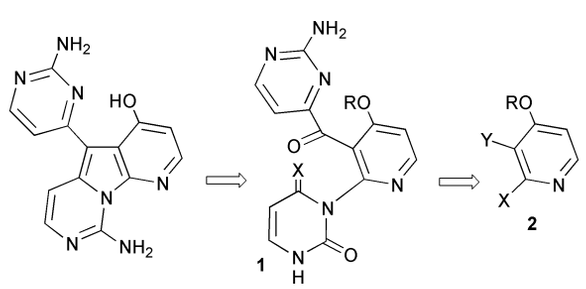
Introduction

The variolins, from the Antarctic sponge *Kirkpatrickia variolosa*, are a small group of marine heterocyclic substances[1] of which variolins B and D are typical. *In vitro* studies showed



variolin B to be the most active in tests which included assessment of antiviral activity (*Herpes simplex* Type I, *polio* Type I); variolin B is active against P388 leukemia cells.[1] Each of the variolins is based on a fused pyrimidino-7-azaindole – strictly a pyrido[3′,2′:4,5]pyrrolo[1,2-*c*]pyrimidine. Noting the presence of a heteroaryl unit located at the 3-position of the imbedded 7-azaindole, we have developed the use of palladium(0)-based methodology for the coupling of 1-protected 3-trimethylstannyl-7-azaindoles with aryl- and heteroaryl halides,[2] evolved a synthesis of the pyrrolo[1,2-*c*]pyrimidine system,[3] which is also imbedded in the variolin structures, and recently we have described a total synthesis of deoxyvariolin B using these principles.[4]

An alternative retrosynthetic analysis to that used for previous work[2,3,4] is shown in Scheme 1: here we propose that the



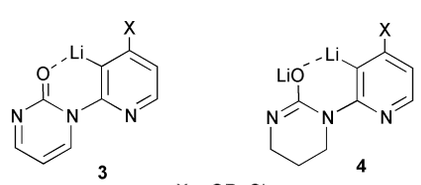
Scheme 1

pyrrole ring would be formed at a late stage from a structure such as **1** and that this would be developed from a pyridine **2** in which the two pyrimidine substituents would be introduced sequentially. A successful implementation of this route would enable the development of a library of variolin analogues, including, by alternating the order of introduction of substituents onto the pyridine, 'upside-down' variants with respect to the azaindole unit. We describe in this paper preliminary work aimed at the introduction of a pyridine-3-substituent *via* directed *ortho* metallation of a 2-substituted pyridine.

The lithiation of an aromatic or heteroaromatic molecule regioselectively *ortho* to a particular group – **D**irected **o**rtho **M**etallation (DoM) – has become an invaluable tool for the synthesis of aromatic/heteroaromatic molecules.[5] Of the many substituents which can act as *ortho* directing groups[6] little attention has been paid to ureas. We are aware of only four reports,[7–10] one of which appeared[10] during the course of the work described here: Seebach lithiated an *N*-allylurea by deprotonation of the methylene group,[7] Beak lithiated *N*-benzyl-*N*,*N*′-dimethylurea at the benzylic position,[8] Quéguiner lithiated *N*,*N*-dimethyl-*N*′-(quinolin-3-yl)urea at C-4 using LDA,[9] and finally, and most relevant to the present paper, Smith lithiated *N*,*N*-dimethyl-*N*′-(4-chlorophenyl)urea, apparently (chlorine is also an *ortho* directing substituent) *ortho* to the urea unit, using *n*-butyllithium at 0 °C. Smith also showed that *n*-butyllithium failed to lithiate *N*,*N*-dimethyl-*N*′-(4-fluorophenyl)urea, but that excess *tert*-butyllithium did effect lithiation; this stronger base also brought about ring lithiation of *N*,*N*-dimethyl-*N*′-(phenyl)urea, though accompanied by *N*-methyl deprotonation and indeed, conditions were developed to achieve efficient *N*-methyl lithiation only (two equivalents of *t*-BuLi at −20 °C).[10] There are no reports of lithiations of *N*-aryl cyclic ureas.

Results and discussion

It was our plan to utilise the carbonyl oxygen of 1-(pyridin-2-yl)pyrimidin-2(1*H*)-ones or of 1-(pyridin-2-yl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ones to assist lithiation of the pyridine at C-3, generating species such as **3** or **4** (Scheme 2), and thereby



Scheme 2

the introduction of suitable substituents. Subsequently the carbonyl oxygen, having served its *ortho* assisting purpose, was to provide the means for the introduction of an amino group at C-9 of final targets.

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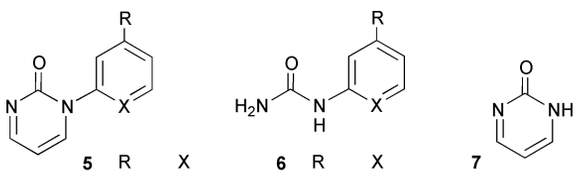
Syntheses of 1-arylpyrimidin-2(1*H*)-ones 5a and 5b

1-(3-Methoxyphenyl)pyrimidin-2(1*H*)-one **5b** was prepared[11] from *N*-(3-methoxyphenyl)urea **6a** by reaction with 1,1,3,3-tetramethoxypropane, though in only 13% yield; the urea **6a** was readily available[12] from *m*-anisidine by reaction with sodium cyanate. Although *N*-(pyridin-2-yl)urea **6b** could be prepared[13] by simply heating 2-aminopyridine with urea (19%, accompanied by *N*,*N*′-(dipyridin-2-yl)urea), or by heating with phenyl carbamate[14] (though always accompanied by *N*,*N*′-(dipyridin-2-yl)urea), a better method was based on a reported synthesis[15] involving reaction of 2-aminopyridine with *N*-chlorosulfonyl isocyanate, and the yield from this route was improved (62%, see Experimental). Unfortunately, attempts to convert *N*-(pyridin-2-yl)urea **6b** into 1-(pyridin-2-yl)pyrimidin-2(1*H*)-one **5c** by reaction with 1,1,3,3-tetramethoxypropane met with failure. Disappointing results (see later) in attempted lithiation of the 1-(aryl)pyrimidin-2(1*H*)-ones led us to set aside further attempts to prepare 1-(pyridin-2-yl)-substituted examples.



	5	R	X
	a	H	CH
	b	MeO	CH
	c	H	N

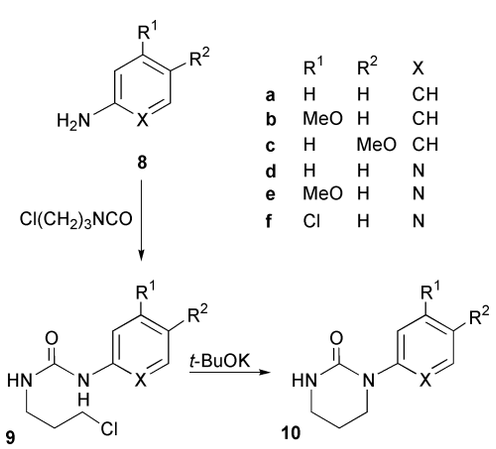
	6	R	X
	a	MeO	CH
	b	H	N

7

Looking for a better method for the synthesis of 1-(aryl)-pyrimidin-2(1*H*)-ones, we investigated the use of triarylbismuth reagents,[16,17] which had been shown to arylate simple amides and ureas.[18] As a trial, it was shown that reaction of pyridin-2-one with triphenylbismuth gave 1-phenylpyridin-2(1*H*)-one in 68% yield. Turning to pyrimidin-2(1*H*)-one **7**,[19] reactions with triphenylbismuth and tris(3-methoxyphenyl)-bismuth were successful in bringing about *N*-arylation and thus the formation of **5a** and **5b** respectively, though only in moderate yields.

Syntheses of 1-aryl/heteroaryl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-ones 10a–f

Following work by Cram,[20] the route shown in Scheme 3 was used to prepare the tetrahydropyrimidin-2(1*H*)-ones, **10a**–**f** in good yields. Thus, reaction of the aromatic/heteroaromatic amines **8** with 3-chloropropyl isocyanate led to ureas **9** from which, by base-catalysed intramolecular *N*-alkylation, the target products **10** were formed smoothly.



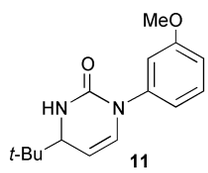
	R^1	R^2	X
a	H	H	CH
b	MeO	H	CH
c	H	MeO	CH
d	H	H	N
e	MeO	H	N
f	Cl	H	N

Scheme 3

2-Amino-4-methoxypyridine **8e** and 2-amino-4-chloropyridine **8f** were prepared from methyl 4-methoxypicolinate[21] and 4-chloropicolinic acid chloride[21] respectively, by conversion to primary amides then Hofmann degradation.

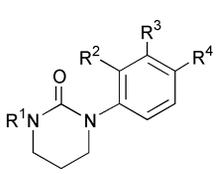
Lithiations

It was the hope that the combined effects of the methoxy substituent and the pyrimidinone carbonyl oxygen would promote ring lithiation at C-2 of the benzene ring in **5b**. However, when **5b** was treated with *n*-butyllithium at −78 °C then pivalaldehyde, an unresolvable mixture of products was produced, mass spectroscopic analysis of which suggested that it contained products of addition of the organolithium reagent to the pyrimidin-2(1*H*)-one ring. Changing to *tert*-butyllithium, again with attempted trapping using pivalaldehyde, the tendency for addition to outweigh any possible deprotonation in this system was confirmed, with the isolation of adduct **11** in 56% yield after separation from the only other component of the product mixture – unchanged starting material. Addition of Grignard nucleophiles to pyrimidin-2(1*H*)-ones has been previously described.[11]



11

It was clear that lithiation of 1-arylpyrimidin-2(1*H*)-ones was not a viable proposition – they are too susceptible to organometallic addition in the pyrimidin-2(1*H*)-one ring. Accordingly we turned to an examination of the saturated cyclic ureas **10a**–**f**. In order to determine optimum conditions, lithiation of **10b**, in which there was expected to be co-operativity between the methoxy and heterocycle in directing ability, was examined. Two mol equivalents of the base were required, the first to remove the *N*-hydrogen. At −78 °C no ring lithiation took place and thus, following quenching with excess iodomethane, only the *N*-methylated product **12a** was obtained.



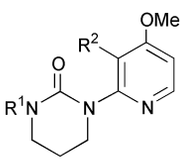
12	R^1	R^2	R^3	R^4
a	Me	H	MeO	H
b	Me	Me	MeO	H
c	H	Me_3Si	MeO	H
d	H	$Me_3CCH(OH)$	MeO	H
e	PhCO	PhCO	MeO	H
f	Me	H	H	H
g	H	Me_3Si	H	MeO
h	H	H	Me_3Si	MeO

Treatment of **10b** with 2.5 equivalents of *n*-butyllithium at the much higher temperature of 0 °C *was* successful in ring lithiation, and after quenching with iodomethane, the *N*,*C*-dimethylated product **12b** was obtained in 92% yield. Comparable trappings with trimethylsilyl chloride, pivalaldehyde and benzoyl chloride produced **12c** (68%), **12d** (56%) and **12e** (13%) respectively.

The temperature required for these lithiations is considerably higher than is typical in DoM lithiations – it was clear that the urea unit did not have a strong effect and indeed when the demethoxy-analogue **10a** was treated with *n*-butyllithium under the same conditions, no ring lithiation occurred and only the *N*-methylated product **12f** was obtained. The methoxy-compound **10c**, isomeric to **10a**, *was* lithiated however, though the products of trapping with trimethylsilyl chloride proved difficult to isolate. It was clear that the crude material contained two isomeric products, in addition to starting material; one of these, **12g**, was isolated and fully characterised. Examination of the spectroscopic data for the mixture of products made it clear that the second product was the isomer **12h** and that the two trimethylsilyl derivatives had been formed in roughly equal

proportions. Apparently a methoxy group and the cyclic urea have approximately equivalent *ortho* directing abilities.

Turning to the pyridin-2-yl urea **10d**, treatment with *n*-butyllithium, even at −78 °C, produced complex mixtures in which, by MS and NMR analysis it was clear that butyl addition had occurred, probably at pyridine C-6, though nothing could be fully characterised. With **10e** it was hoped that the co-operative effects of the two substituents would allow ring lithiation. Reaction with *n*-butyllithium at −78 °C then quenching with iodomethane led straightforwardly to the *N*-methylated derivative **13a** – there had been no ring lithiation.



13	R^1	R^2
a	Me	H
b	Me	Me
c	H	Me

14

Application of the lithiation conditions (−78⟶0 °C) which had been successful for **10b** produced a very complex mixture, analysis of which clearly showed both products from butyl addition and from butyl addition accompanied by *C*-/*N*-methylations. Operating at −40 °C did allow the isolation of the target dimethylated product **13b** but only in poor yield.

It occurred to us that intramolecular co-ordination of lithium by the pyridine nitrogen **14** might be both preventing *ortho* assistance *and* encouraging nucleophilic butyl addition. To test this idea, **10d** was treated with one equivalent of *n*-butyllithium at −78 °C, then with trimethylsilyl chloride (to form a presumed *O*-silyl derivative) and then with a further equivalent of *n*-butyllithium. Quenching with iodomethane allowed the isolation of exclusively *C*-monomethylated product **13c** in 37% yield.

Experimental

Flash column chromatography was performed using Merck Kieselgel 60 (230–400 mesh). Organic solutions were dried over anhydrous $MgSO_4$. Solid products were dried under reduced pressure using P_4O_{10} as a desiccant. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on Inova-300 Athos (300 MHz) and Unity 500 (500 MHz) spectrometers. Complex signals which 'appear' simple are described as: *e.g.* 'apparent quintet', and an average *J* value given to the nearest whole number. Carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded on an Inova-300 Athos spectrometer running at 75 MHz. All chemical shifts (δ) are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS). Signal splittings are reported as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), multiplet (m), and broad (br); *J* values are given in Hertz (Hz). UV spectra were recorded on a Hewlett Packard 8452A diode array spectrophotometer and are given in nm with ε (in $dm^3\ mol^{-1}\ s^{-1}$) in parentheses. IR spectra were recorded on an Ati Mattson Genesis Series FTIR spectrometer; only absorptions of importance to structure determination are listed; br = broad, sh = shoulder. Mass spectra were recorded on a Fisons VG Trio 2000 (EI/CI{NH_3}) (abundance relative to the base peak given in parentheses as a percentage; only fragment ions of intensity >10% of the base peak are cited) and a Concept IS (MM/FAB) spectrometer for accurate mass determinations. Melting points (°C) were recorded on a Reichart heated stage microscope and are uncorrected. Flash column chromatography was carried out according to the method of Still,[22] using Merck 9385 silica gel 60 (230–400 mesh) [or neutral alumina]. All ethers were dried over sodium wire and distilled under an atmosphere of dry argon using benzophenone as an indicator of degree of hydration. Dichloromethane (for reactions), pyridine, and triethylamine were distilled from calcium hydride. Dimethylformamide was dried over 4 Å molecular sieves. The molarities of organolithiums were determined prior to use by titration.[23*a*] All other chemicals were purified using the appropriate standard procedure as described in ref. 23*b*.

1-Phenylpyrimidin-2(1*H*)-one 5a

Method 1. 1,1,3,3-Tetramethoxypropane (24.2 ml, 147.1 mmol, 2.0 eq.) was added dropwise, over a 1 h period, to a solution of *N* phenylurea (10 g, 73.5 mmol, 1.0 eq.) in methanol (50 ml) and conc. HCl (12 M, 20 ml). The addition resulted in the formation of a white particulate suspension, which turned bright yellow on stirring at ambient temperature. Stirring was continued for a further 72 h and the reaction progress followed by TLC. After this time, the solution, which had become dark red in appearance was allowed to stand, resulting in the precipitation of a yellow semi-solid mass. The volatile components were removed under reduced pressure and the product dissolved in sat. aq. Na_2CO_3, then acidified (pH 5) with 2.5 M H_2SO_4. The resulting aqueous solution was extracted with chloroform (5 × 30 ml) (insoluble, sticky, light brown coloured material (*ca.* 8 g) was precipitated at this stage), the combined organic extracts were dried and concentrated *in vacuo*, to reveal a bright orange coloured semi-solid (13.6 g). Repeated flash column chromatography on neutral Al_2O_3 (eluting with 2–6% MeOH–CH_2Cl_2) gave **5a** as pale yellow coloured plates (2.4 g, 19%), mp 154–156 °C from EtOAc. Lit.[24] 155–156 °C; R_f 0.32 (6% MeOH–CH_2Cl_2; SiO_2) (HRMS found: M^+, 172.0635. $C_{10}H_8N_2O$ requires *M*, 172.06366) (Anal. found: C, 69.3; H, 5.2; N, 15.8%. $C_{10}H_8N_2O$ requires: C, 69.8; H, 4.7; N, 16.3%); λ_{max} (EtOH): 230, 292 nm (ε 14200, 11300); ν_{max} (film): 3054, 1669 (br), 1613 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.34 (1H, dd, *J* 7, 4, H-5), 7.33–7.45 (5H, m, C_6H_5), 7.67 (1H, dd, *J* 7, 3, H-6), 8.74 (1H, dd, *J* 4, 3, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 104.5, 126.0, 129.2, 129.6, 140.2, 148.0, 155.6, 166.9; *m*/*z* (CI): 190 (M + 18, 3%), 174 (M + 2, 18), 173 (M + 1, 100).

Method 2. A slurry of pyrimidin-2(1*H*)-one (**7**) (500 mg, 5.21 mmol, 1.0 eq.), triphenylbismuth (3.44 g, 7.82 mmol, 1.5 eq.), anhydrous $Cu(OAc)_2$ (1.42 g, 7.82 mmol, 1.5 eq.) and NEt_3 (0.73 ml, 5.21 mmol, 1.5 eq.) in anhydrous CH_2Cl_2 (8 ml) was stirred at rt in a flask equipped with a $CaCl_2$ guard tube. After a period of 20 h, the solution became gelatinous and changed from deep blue to light green, grey copper(I) salts were clearly visible. The reaction mixture was diluted with CH_2Cl_2 (10 ml), material absorbed onto silica gel and the product isolated by flash column chromatography (eluting with 6% MeOH–CH_2Cl_2). Recrystallisation from hot EtOAc afforded **5a** as white plates (256 mg, 28%), mp 155–156 °C.

N-(3-Methoxyphenyl)urea 6a

To a warm (40 °C) solution of freshly distilled *m*-anisidine (60 ml, 0.5 mol) in glacial acetic acid (140 ml) and water (260 ml) was added sodium cyanate (70 g, 1.1 mol, 2.0 eq.) in water (200 ml) with vigorous stirring. The addition caused considerable frothing and gave rise to the separation of a white precipitate. The mixture was stirred for 2 h, whilst it cooled to rt, before being left to stand overnight. The resultant solid was collected by vacuum filtration, washed with cold water (3 × 50 ml) to remove any excess AcOH and dried to leave light brown needles (89 g, 99%). Recrystallisation from hot water (800 ml) with the aid of decolourising charcoal (*ca.* 4 g), yielded **6a** as fine, white needles (75 g, 78%), mp 132–133 °C from water. Lit.[11] 134–135 °C: R_f 0.47 (10% MeOH–CH_2Cl_2; SiO_2) (HRMS found: M^+, 166.0745. $C_8H_{10}N_2O_2$ requires *M*, 166.07422) (Anal. found: C, 57.4; H, 6.3; N, 16.9%. $C_8H_{10}N_2O_2$ requires: C, 57.8; H, 6.1; N, 16.9%); λ_{max} (EtOH): 218, 242, 280 nm (ε 17049, 14378, 2868); ν_{max} (KBr): 3564–3114 (br), 1666 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO): δ 3.72 (3H, s, OCH_3), 5.85 (2H, br s, NH_2), 6.49 (1H, dd, *J* 8, 2, H-4), 6.89 (1H, dd, *J* 8, 2, H-6), 7.13

(1H, s, H-2), 7.15 (1H, apparent t, *J* 8, H-5), 8.53 (1H, br s, NH); ^{13}C-NMR (75 MHz, d_6-DMSO): δ 55.2, 103.9, 106.8, 110.5, 129.7, 142.1, 156.3, 160.0; *m*/*z* (CI): 184 (M + 18, 78%), 167 (M + 1, 100), 124 (36).

1-(3-Methoxyphenyl)pyrimidin-2(1*H*)-one 5b

Method 1. 1,1,3,3-Tetramethoxypropane (16.0 ml, 96.4 mmol, 2.0 eq.) was added to a stirred solution of *N*-(3-methoxyphenyl)urea **6a** (8.0 g, 48.2 mmol, 1.0 eq.) in methanol (30 ml) and conc. HCl (12 M, 15 ml), addition resulted in the formation of an orange particulate suspension, which gradually became homogeneous and deep red in colour on stirring at ambient temperature for 30 min. Stirring was continued for a further 72 h, then the volatile components were removed under high vacuum and the resultant solid neutralised (pH 8) by dissolving in sat. aq. $KHCO_3$. Extraction with CH_2Cl_2 (a sticky, light brown coloured material (*ca.* 6 g) was precipitated at this stage) gave the crude product as an orange coloured solid (12.3 g) which was found to contain five UV active components by TLC. This material was taken up into 3 M HCl (20 ml) and extracted with CH_2Cl_2 (3 × 20 ml portions), the aqueous layer was neutralised with solid K_2CO_3 and extracted with a further portion of CH_2Cl_2 (30 ml). The combined organic extracts were dried and concentrated *in vacuo*, to give a bright orange solid (3.87 g), containing product, still contaminated with five other compounds (TLC). It was possible to separate some of the components by flash column chromatography on neutral alumina (eluting with 5–10% MeOH–CH_2Cl_2). Only two components could be characterised, one was **5b** as pale orange coloured plates (1.3 g, 13%), mp 112–116 °C from EtOAc. Lit.[11] 114–115 °C from $CHCl_3$–hexane.

Method 2. A slurry of pyrimidin-2(1*H*)-one (**7**) (190 mg, 1.98 mmol), tris(3-methoxyphenyl)bismuth (2.10 g, 3.96 mmol, 2.0 eq.), anhydrous $Cu(OAc)_2$ (719 mg, 3.96 mmol, 2.0 eq.) and NEt_3 (0.42 ml, 2.97 mmol, 1.5 eq.) in anhydrous CH_2Cl_2 (8.0 ml) was stirred at rt in a flask equipped with a $CaCl_2$ guard tube. After a period of 24 h, the solution had changed from deep blue, to light green in colour and grey copper(I) salts could be observed. The reaction mixture was diluted with CH_2Cl_2 (10 ml) and the product isolated by flash column chromatography, following pre-absorption of the mixture onto silica gel (eluting with 1–6% MeOH–CH_2Cl_2). Recrystallisation from EtOAc afforded the title compound as off-white coloured plates (145 mg, 36%), mp 112–113 °C from EtOAc; R_f 0.32 (6% MeOH–CH_2Cl_2; SiO_2) (HRMS found: M^+, 202.0743. $C_{11}H_{10}N_2O_2$ requires *M*, 202.07422) (Anal. found: C, 63.2; H, 5.0; N, 10.9%. $C_{11}H_{10}N_2O_2$·EtOAc requires: C, 63.4; H, 5.7; N, 11.4%); λ_{max} (EtOH): 218, 274 nm (ε 14712, 8448); ν_{max} (film): 3497, 3435, 1671 (br), 1605 (br) cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.85 (3H, s, OCH_3), 6.40 (1H, dd, *J* 6.5, 4.0, H-5), 6.96 (1H, apparent s, H-2′), 6.97 (1H, ddd, *J* 8.0, 3.0, 1.0, H-4′), 7.00 (1H, dd, *J* 8.0, 1.0, H-6′), 7.42 (1H, dt, *J* 1.0, 8.0, H-5′), 7.73 (1H, dd, *J* 6.5, 3.0, H-6), 8.70 (1H, dd, *J* 4.0, 3.0, H-4); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 55.5, 103.9, 111.9, 115.0, 118.0, 130.3, 141.1, 148.0, 155.5, 160.2, 166.8; *m*/*z* (CI): 220 (M + 18, 5%), 203 (M + 1, 100), 124 (16).

Tris(3-methoxyphenyl)bismuth

A flame dried 2-necked 100 ml flask, fitted with a reflux condenser and rubber septum was charged with "bright" magnesium turnings (2.3 g, 95.15 mmol, 6.0 eq.) under a dry argon atmosphere. The turnings were covered with anhydrous Et_2O (50 ml) and 3-bromoanisole (12.0 ml, 95.15 mmol, 6.0 eq.), was added at a rate to maintain slow reflux; gentle warming was necessary to initiate the reaction which turned dark brown in colour as the magnesium was consumed. After a period of 30 min, boiling stopped, so the mixture was heated at gentle reflux for a further 30 min until all the magnesium went into solution. Anhydrous bismuth trichloride (5.0 g, 15.86 mmol, 1.0 eq.) was added slowly to the cooled mixture through a flame dried, sealed powder addition funnel under a steady stream of argon. Over this time, gentle heat was applied to ensure reflux, continued for a further hour once the addition was complete. The cold reaction mixture was poured slowly into 100 ml of ice–water, with vigorous stirring, the mixture was filtered under reduced pressure and the ether layer was retained. The residue on the filter, and the aqueous layer were extracted with ether (3 × 10 ml). Evaporation of the combined ether extracts revealed a yellow semi-solid, which crystallised as an off-white solid (4.1 g, 49%) on cooling to 0 °C. Recrystallisation from 60–80 petroleum ether afforded tris(3-methoxyphenyl)bismuth as white needles (2.9 g, 34%, mp 79–80 °C from 60–80 petroleum ether); R_f 0.92 (6% MeOH–CH_2Cl_2; SiO_2) (HRMS found: M^+, 530.1306. $C_{21}H_{21}BiO_3$ requires *M*, 530.12946) (Anal. found: C, 47.8; H, 4.0%. $C_{21}H_{21}BiO_3$ requires: C, 47.8; H, 4.0%); λ_{max} (EtOH): 206, 286 nm (ε 35614, 10013); ^{1}H-NMR (300 MHz, d_6-DMSO): δ 3.37 (9H, s, 3 × OCH_3), 6.88 (3H, dd, *J* 7, 2, 3 × H-4), 7.29 (3H, d, *J* 7, 3 × H-6), 7.35 (3H, apparent s, 3 × H-2), 7.37 (3H, apparent t, *J* 7, 3 × H-5); ^{13}C-NMR (75 MHz, d_6-DMSO): δ 55.2, 113.1, 123.6, 129.7, 131.6, 161.5; *m*/*z* (CI): 548 (M + 18, 8%), 531 (M + 1, 18), 441 (15), 440 (100), 423 (38).

N-(Pyridin-2-yl)urea 6b

Chlorosulfonyl isocyanate (0.97 ml, 10.64 mmol, 1.0 eq.) was added dropwise over a 30 min period to a stirred solution of 2-aminopyridine (1.0 g, 10.64 mmol, 1.0 eq.) in anhydrous acetonitrile (10 ml) at 0 °C. A vigorous reaction ensued, which appeared to be complete after 20 min. The mixture was warmed to rt and stirring was continued for a further 3 h. Excess aq. sat. $KHCO_3$ (10 ml) was added and the mixture was stirred at rt for 16 h. The resultant suspension was evaporated to dryness revealing an off-white solid, which was taken-up in boiling 95% EtOH (10 ml) and filtered whilst hot. The filtrate was concentrated to approximately one quarter of its volume and refrigerated overnight to afford the title compound as white plates (905 mg, 62%), mp 164–165 °C from 95% EtOH; R_f 0.47 (10% MeOH–CH_2Cl_2; SiO_2) (HRMS found: M^+, 137.0587. $C_6H_7N_3O$ requires *M*, 137.05891) (Anal. found: C, 52.4; H, 5.1; N, 30.3%. $C_6H_7N_3O$ requires: C, 52.6; H, 5.1; N, 30.6%); λ_{max} (EtOH): 234, 282 nm (ε 1073, 331); ν_{max} (KBr): 3312–2994 (br), 1708 (br), 1601 (br) cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO): δ 6.89 (1H, apparent br t, *J* 7, H-5), 6.95–7.10 (2H, br s, NH_2), 7.35 (1H, apparent d, *J* 8, H-3), 7.71 (1H, apparent t, *J* 7, H-4), 8.14 (1H, apparent d, *J* 5, H-6), 9.04 (1H, br s, NH); ^{13}C-NMR (75 MHz, d_6-DMSO): δ 112.0, 117.2, 138.4, 147.2, 153.9, 155.8; *m*/*z* (CI): 138 (M + 1, 65%), 121 (15), 95 (100).

1-Phenyl-2(1*H*)-pyridone

A slurry of pyridin-2(1*H*)-one (250 mg, 2.63 mmol, 1.0 eq.), triphenylbismuth (2.3 g, 5.26 mmol, 2.0 eq.), anhydrous $Cu(OAc)_2$ (715 mg, 3.94 mmol, 1.5 eq.) and NEt_3 (0.55 ml, 3.94 mmol, 1.5 eq.) in anhydrous CH_2Cl_2 (5.0 ml) was stirred at rt in a flask equipped with a $CaCl_2$ guard tube. After 15 min, the solution became gelatinous and changed from deep blue to light green. More $Cu(OAc)_2$ (240 mg, 1.32 mmol, 0.5 eq.) and CH_2Cl_2 (3.0 ml) were added and stirring continued for a further 48 h, after which TLC analysis indicated no further conversion. The reaction mixture was diluted with CH_2Cl_2 (10 ml) and the mixture was absorbed onto silica gel. 1-Phenyl-2-pyridone was isolated by flash column chromatography (eluting with 1–5% MeOH–CH_2Cl_2) and recrystallised from hot EtOAc, giving light brown needles (307 mg, 68%), mp 123–124 °C from EtOAc. Lit.[25] mp 123–125 °C; R_f 0.40 (6% MeOH–CH_2Cl_2; SiO_2) (HRMS found: M^+, 171.0681. $C_{11}H_9NO$ requires *M*, 171.06841) (Anal. found: C, 76.5; H, 5.5; N, 7.7%. $C_{11}H_9NO$ requires: C, 77.2; H, 5.3; N, 8.2%); λ_{max} (EtOH): 222, 310 nm

(ε 13692, 7496); ν_{max} (film): 1659 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.28 (1H, dt, *J* 2, 7, H-5), 6.70 (1H, dd, *J* 7, 2, H-3), 7.37–7.54 (7H, m, 5 × PhH, H-4 and H-6); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 105.8, 121.8, 126.5, 128.4, 129.3, 137.9, 139.8, 140.9, 162.3; *m*/*z* (CI): 172 (M + 1, 100%).

4-Methoxypicolinamide

Ammonia (*ca.* 300 ml) was condensed into a flask containing a solution of methyl 4-methoxypicolinate[21] (10.6 g, 63.5 mmol) in MeOH (300 ml), then the mixture was refluxed for 5 h. The NH_3 was allowed to evaporate, the remaining mixture concentrated to dryness, and the crude product, an off-white solid (9.0 g), recrystallised from EtOAc giving the amide as large off-white plates (8.2 g, 85%), mp 145–146 °C. Lit.[26] 149–150 °C; R_f 0.79 (6% MeOH–CH_2Cl_2 with a few drops of NEt_3; SiO_2) (HRMS found: M^+, 152.0590. $C_7H_8N_2O_2$ requires *M*, 152.05857) (Anal. found: C, 54.8; H, 5.3; N, 18.2%. $C_7H_8N_2O_2$ requires: C, 55.3; H, 5.3; N, 18.4%); λ_{max} (EtOH): 240, 248 nm (ε 9034, 14915); ν_{max} (KBr): 3411, 3189, 1687 (br) cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO): δ 3.90 (3H, s, OCH_3), 7.15 (1H, dd, *J* 5.7, 2.7, H-5), 7.57 (1H, d, *J* 2.7, H-3), 7.01 (1H, br s, NH), 8.14 (1H, br s, NH), 8.44 (1H, d, *J* 5.7, H-6); ^{13}C-NMR (75 MHz, d_6-DMSO): δ 55.9, 108.0, 112.8, 150.2, 152.7, 166.2, 166.8; *m*/*z* (CI): 153 (M + 1, 100%), 136 (14), 109 (32), 108 (10).

2-Amino-4-methoxypyridine 8e

A solution of KOH (29.9 g, 532.9 mmol, 10.0 eq.) in water (150 ml) was cooled (0–5 °C) and to this was added bromine (5.5 ml, 106.6 mmol, 2.0 eq.) dropwise with stirring, followed by 4-methoxypicolinamide (8.1 g, 53.3 mmol, 1.0 eq.) rapidly. Most of the material went into solution, however, 1,4-dioxane (50 ml) was added (slowly) in order to ensure that a homogeneous mixture was obtained. The resulting solution was stirred at rt for 30 min, then heated at 55 °C for 60 min. Heating was stopped and glacial AcOH (25 ml) was added dropwise with vigorous stirring, an exothermic reaction took place with CO_2 evolution and a cream coloured precipitate formed. The resulting suspension was heated at 55 °C for a further 30 min, causing the precipitate to dissolve. Once cool, KOH (*ca.* 18 g) was added and the resulting white suspension extracted with CH_2Cl_2 (3 × 150 ml). The combined organic extracts were dried and concentrated *in vacuo* to leave the crude product amine as a pale yellow solid (3.62 g). Recrystallisation from Et_2O furnished **8e** as off-white plates (2.97 g, 45%), mp 113–114 °C from Et_2O. Lit.[21] 116–117 °C; R_f 0.37 (2 : 2 : 1; PhMe–EtOAc–MeOH; SiO_2) (HRMS found: M^+, 124.0639. $C_6H_8N_2O$ requires *M*, 124.0637) (Anal. found: C, 57.8; H, 6.6; N, 22.5%. $C_6H_8N_2O$ requires: C, 58.1; H, 6.5; N, 22.6%); λ_{max} ($CHCl_3$): 250, 280 nm (ε 1582, 1470); ν_{max} (film): 3460, 3299, 3123, 1634, 1608 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 4.72 (2H, br s, NH_2), 6.00 (1H, d, *J* 2.2, H-3), 6.28 (1H, dd, *J* 5.9, 2.2, H-5), 7.90 (1H, d, *J* 5.9, H-6); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 54.9, 92.3, 102.5, 148.7, 160.0, 167.3; *m*/*z* (CI): 125 (M + 1, 100%), 124 (12).

4-Chloropicolinamide

A mixture of picolinic acid (10 g, 81.3 mmol), NaBr (420 mg, 4.1 mmol) and $SOCl_2$ (30 ml, 406.5 mmol) in a 500 ml, 3-necked round-bottomed flask, equipped with a reflux condenser and $CaCl_2$ drying tube was heated to reflux for 24 h (after 3 h the mixture turned black and started to solidify, a further 15 ml of $SOCl_2$ was required in order for stirring to be resumed). The excess $SOCl_2$ was evaporated and the resultant brown solid was suspended in anhydrous THF (250 ml). The flask was fitted with a dry ice condenser and vented to a mineral oil bubbler, the mixture was cooled to −78 °C and ammonia (excess) was condensed into the THF solution. Once an approximately equal volume of NH_3 to THF was achieved, the vent was closed and the dark blue suspension was stirred at −20 to −10 °C for 3 to 4 h and the mixture stirred at rt overnight allowing the ammonia to evaporate. Evaporation of the THF afforded the amide as small, light brown coloured needles, which by TLC and ^{1}H-NMR analysis were judged to be of sufficient purity for the next step (10 g, 79%); mp 143–144 °C from EtOAc. Lit.[27] 162–163 °C; R_f 0.62 (10% MeOH–CH_2Cl_2 with a few drops of NEt_3) (HRMS found: M^+, 156.0092. $C_6H_5ClN_2O$ requires *M*, 156.00904) (Anal. found: C, 44.1; H, 2.1; N, 15.4%. $C_6H_5ClN_2O{\cdot}H_2O$ requires: C, 43.5; H, 3.7; N, 16.9%); λ_{max} (EtOH): 250, 268 nm (ε 952, 1266); ν_{max} (KBr): 3366–3177 (br), 1710 (br), 1609 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO): δ 7.73 (1H, dd, *J* 5.2, 1.9, H-5), 7.85 (1H, br s, NH), 8.03 (1H, d, *J* 1.9, H-3), 8.23 (1H, br s, NH), 8.61 (1H, d, *J* 5.4, H-6); ^{13}C-NMR (75 MHz, d_6-DMSO): δ 122.4, 126.7, 144.8, 150.4, 152.4, 165.2; *m*/*z* (CI): 176 (^{37}Cl, M + 18, 26%), 174 (^{35}Cl, M + 18, 46), 159 (^{37}Cl, M + 1, 36), 157 (^{35}Cl, M + 1, 100).

2-Amino-4-chloropyridine 8f

To a solution of KOH (17.9 g, 319.5 mmol, 10.0 eq.) in water (90 ml) at 0–5 °C, bromine (3.3 ml, 63.9 mmol, 2.0 eq.) was added dropwise with stirring, followed by 4-chloropicolinamide (5.0 g, 32.0 mmol, 1.0 eq.) rapidly. Most of the material went into solution, however, 1,4-dioxane (50 ml) was added in order to ensure that a homogeneous solution was obtained. The resulting solution was stirred at rt for 30 min, then heated at 55 °C for 60 min. The mixture was cooled and glacial AcOH (10 ml) was added dropwise, when an exothermic reaction took place with CO_2 evolution and a cream coloured precipitate formed. The mixture was heated at 50–55 °C for a further 30 min, causing the precipitate to dissolve, the solution was then allowed to cool. KOH (*ca.* 7 g) was added and the resulting white suspension extracted with CH_2Cl_2 (3 × 150 ml). The combined organic extracts were dried and concentrated *in vacuo* to reveal the crude product amine as a pale yellow solid (3.1 g). Recrystallisation of this material from Et_2O–hexane (2 : 1) afforded the amine as bright white plates (2.1 g, 51%), mp 95–96 °C from Et_2O–hexane (2 : 1). Lit.[28] 130–131 °C; R_f 0.49 (10% MeOH–CH_2Cl_2; SiO_2) (HRMS found: M^+, 128.0141. $C_5H_5ClN_2$ requires *M*, 128.01412) (Anal. found: C, 46.4; H, 4.1; N, 21.3; Cl, 27.3%. $C_5H_5ClN_2$ requires: C, 46.7; H, 3.9; N, 21.8; Cl, 27.6%); λ_{max} ($CHCl_3$): 246, 294 nm (ε 1473, 1127); ν_{max}(film): 3450, 3171, 3154, 1625 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.74 (2H, br s, NH_2), 6.52 (1H, br s, H-3), 6.66 (1H, br d, *J* 5.4, H-5), 7.79 (1H, d, *J* 5.4, H-6); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 108.1, 114.4, 144.9, 149.0, 159.1; *m*/*z* (CI): 148 (^{37}Cl, M + 18, 6%), 146 (^{35}Cl, M + 18, 20%), 131 (^{37}Cl, M + 1, 30), 129 (^{35}Cl, M + 1, 100).

N-(3-Chloropropyl)-*N*′-phenylurea 9a

Aniline (2.0 g, 1.96 ml, 21.48 mmol, distilled from KOH) in anhydrous CH_2Cl_2 (20 ml) was treated with 3-chloropropyl isocyanate (3.30 ml, 32.21 mmol, 1.5 eq.) under N_2, and the resulting solution was stirred at rt for 48 h. Evaporation left a colourless oil that solidified on standing to give a sticky light brown solid, which on washing with Et_2O gave the crude product as a white powder (5.32 g). Recrystallisation from EtOAc afforded **9a** as bright white needles (3.81 g, 92%), mp 120–121 °C from EtOAc; R_f 0.68 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 212.0721. $C_{10}H_{13}ClN_2O$ requires *M*, 212.07163) (Anal. found: C, 56.1; H, 6.5; N, 13.2; Cl, 17.1%. $C_{10}H_{13}ClN_2O$ requires: C, 56.5; H, 6.2; N, 13.2; Cl, 16.7%); λ_{max} ($CHCl_3$): 254, 276 nm (ε 12487, 4209); ν_{max} (film): 3323, 2959, 2926, 1688 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO): δ 1.92 (2H, apparent quintet, *J* 6, CH_2), 3.23 (2H, apparent q, *J* 6, CH_2N), 3.69 (2H, t, *J* 6.0, CH_2Cl), 6.30 (1H, br t, *J* 5.0, alkyl NH), 6.90 (1H, dt, *J* 1.0, 7.3, ArH), 7.23 (2H, t, *J* 7.3, ArH), 7.41 (2H, d, *J* 7.3, ArH), 8.49 (1H, s, aromatic NH); ^{13}C-NMR (75 MHz, d_6-DMSO): δ 33.1, 36.9, 43.4, 118.0, 121.4, 129.0, 140.8, 155.7; *m*/*z* (CI): 232 (^{37}Cl, M + 18, 2%), 230 (^{35}Cl, M + 18, 6), 215

(^{37}Cl, M + 1, 30), 214 (15), 213 (^{35}Cl, M + 1, 100), 177 (21), 94 (16), 93 (12).

N-(3-Chloropropyl)-*N*′-(3-methoxyphenyl)urea 9b

To a solution of *m*-anisidine (2.0 g, 1.82 ml, 16.24 mmol, pre-distilled from KOH) in anhydrous CH_2Cl_2 (100 ml), under a dry nitrogen atmosphere was added 3-chloropropyl isocyanate (2.50 ml, 24.36 mmol, 1.5 eq., dropwise), the resulting solution was stirred at rt. A slight exotherm was observed and following a 15 min period the solution turned cloudy, stirring was continued for a further 72 h. Evaporation left a colourless oil that solidified on standing to give a sticky light brown solid, which on washing with Et_2O gave crude urea as a white powder (4.47 g). Recrystallisation from EtOAc gave **9b** as white needles (3.81 g, 97%), mp 92–94 °C from EtOAc; R_f 0.08 (2% MeOH–CH_2Cl_2; SiO_2) (HRMS found: M^+, 242.0819. $C_{11}H_{15}ClN_2O_2$ requires *M*, 242.0822) (Anal. found: C, 54.3; H, 6.5; N, 11.2; Cl, 15.0%. $C_{11}H_{15}ClN_2O_2$ requires: C, 54.4; H, 6.2; N, 11.5; Cl, 14.6%); λ_{max} ($CHCl_3$): 250, 282 nm (ε 14599, 5688); ν_{max} (film): 3333, 2986, 2938, 2753, 1654 (br), 1606 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.98 (2H, apparent quintet, *J* 7, CH_2), 3.39 (2H, t, *J* 6.5, CH_2N), 3.59 (2H, t, *J* 6.5, CH_2Cl), 3.78 (3H, s, OCH_3), 5.60 (1H, br s, NH), 6.64 (1H, dd, *J* 8.0, 2.0, H-4), 6.82 (1H, dd, *J* 8.0, 2.0, H-6), 7.01 (1H, t, *J* 2.0, H-2), 7.20 (1H, t, *J* 8.0, H-5), 7.26 (1H, br s, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 32.6, 37.4, 42.4, 55.1, 106.3, 109.0, 112.7, 129.8, 139.8, 156.4, 160.2; *m*/*z* (CI): 262 (^{37}Cl, M + 18, 3%), 260 (^{35}Cl, M + 18, 8), 245 (^{37}Cl, M + 1, 31), 244 (15), 243 (^{35}Cl, M + 1, 100), 207 (21), 124 (19), 123 (12).

N-(3-Chloropropyl)-*N*′-(4-methoxyphenyl)urea 9c

A solution of *p*-anisidine (1.82 g, 14.80 mmol, dried by azeotroping with anhydrous benzene) in anhydrous CH_2Cl_2 (20 ml), under a dry N_2 atmosphere, was treated with 3-chloropropyl isocyanate (2.30 ml, 22.20 mmol, 1.5 eq.), then the resulting dark brown solution was stirred at rt for 72 h, after which evaporation of the CH_2Cl_2 revealed a purple coloured oil that solidified on standing to give a sticky solid. Washing with Et_2O left a lilac powder (3.61 g). Recrystallisation from EtOAc gave **9c** as lilac needles (3.30 g, 92%), mp 120–121 °C from EtOAc; R_f 0.58 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 242.0822. $C_{11}H_{15}ClN_2O_2$ requires *M*, 242.0822) (Anal. found: C, 54.4; H, 6.5; N, 11.3; Cl, 14.7%. $C_{11}H_{15}ClN_2O_2$ requires: C, 54.4; H, 6.2; N, 11.5; Cl, 14.6%); λ_{max} (EtOH): 252, 284 nm (ε 12384, 3869); ν_{max} (film): 3307, 3049, 2961, 1628, 1607 cm^{-1}; ^{1}H-NMR (300 MHz, d_6-DMSO): δ 1.89 (2H, apparent quintet, *J* 7, CH_2), 3.21 (2H, apparent q, *J* 7, CH_2N), 3.69 (2H, apparent t, *J* 7, CH_2Cl), 3.71 (3H, s, OCH_3), 6.09 (1H, br t, *J* 6.0, alkyl NH), 6.82 (2H, dd, *J* 7.0, 2.0, H-3 and H-5), 7.30 (2H, dd, *J* 7.0, 2.0, H-2 and H-6), 8.28 (1H, s, aromatic NH); ^{13}C-NMR (75 MHz, d_6-DMSO): δ 33.2, 36.9, 43.5, 55.5, 114.2, 119.8, 134.0, 154.3, 155.9; *m*/*z* (CI): 262 (^{37}Cl, M + 18, 1%), 260 (^{35}Cl, M + 18, 3), 245 (^{37}Cl, M + 1, 28), 244 (14), 243 (^{35}Cl, M + 1, 100), 207 (12), 124 (12), 123 (11).

N-(3-Chloropropyl)-*N*′-(pyridin-2-yl)urea 9d

To a solution of 2-aminopyridine (1.1 g, 11.65 mmol) in anhydrous CH_2Cl_2 (50 ml), under dry N_2 was added 3-chloropropyl isocyanate (1.8 ml, 17.48 mmol, 1.5 eq.) then the resulting solution was stirred for 96 h. Evaporation left a pale yellow oil which solidified on standing to afford the crude product as a white powder (2.8 g). Recrystallisation from 40–60 petroleum ether provided **9d** as fine white needles (2.3 g, 93%), mp 57–58 °C from 40–60 petroleum ether; R_f 0.60 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 213.0671. $C_9H_{12}ClN_3O$ requires *M*, 213.06688) (Anal. found: C, 50.6; H, 6.1; N, 19.7%. $C_9H_{12}ClN_3O$ requires: C, 50.6; H, 5.7; N, 19.7%); λ_{max} ($CHCl_3$): 248, 284 nm (ε 1640, 1437); ν_{max} (film): 3224–2963, 3081, 2963, 1682 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.15 (2H, apparent quintet, *J* 7, CH_2), 3.60 (2H, apparent q, *J* 6, CH_2N), 3.70 (2H, t, *J* 6.5, CH_2Cl), 6.87 (1H, d, *J* 8.0, H-3), 6.92 (1H, apparent t, *J* 5, H-5), 7.62 (1H, apparent t, *J* 8, H-4), 8.21 (1H, apparent d, *J* 5, H-6), 8.64 (1H, s, NH), 9.60 (1H, br s, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 32.7, 36.9, 42.6, 111.9, 116.7, 138.2, 145.9, 153.3, 156.4; *m*/*z* (CI): 216 (^{37}Cl, M + 1, 35%), 214 (^{35}Cl, M + 1, 100%), 212 (35), 178 (20).

N-(3-Chloropropyl)-*N*′-(4-methoxypyridin-2-yl)urea 9e

To a solution of 2-amino-4-methoxypyridine **8e** (3.47 g, 27.97 mmol) in anhydrous CH_2Cl_2 (50 ml), under a dry N_2 atmosphere was added 3-chloropropyl isocyanate (4.29 ml, 41.96 mmol, 1.5 eq.), then the resulting solution was stirred at rt for 48 h. Evaporation left a pale yellow oil which solidified on standing to yield the crude product as a white powder (6.42 g), recrystallisation from EtOAc afforded **9e** as sticky white needles (5.99 g, 88%), mp 97–98 °C from EtOAc; R_f 0.63 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 243.0770. $C_{10}H_{14}ClN_3O_2$ requires *M*, 243.07745) (Anal. found: C, 48.2; H, 6.1; N, 16.2%. $C_{10}H_{14}ClN_3O_2$ requires: C, 49.3; H, 5.8; N, 17.2%); λ_{max} ($CHCl_3$): 252, 272, 314 nm (ε 1360, 1420, 108); ν_{max} (film): 3223 (br), 2901, 1686 (br), 1607 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.13 (2H, apparent quintet, *J* 7, CH_2), 3.57 (2H, apparent q, *J* 7, CH_2N), 3.69 (2H, t, *J* 6.5, CH_2Cl), 3.88 (3H, s, OCH_3), 6.33 (1H, d, *J* 2.2, H-3), 6.51 (1H, dd, 5.9, 2.2, H-5), 8.02 (1H, d, *J* 5.9, H-6), 8.35 (1H, br t, alkyl NH), 9.58 (1H, br s, aromatic NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 32.7, 37.0, 42.5, 55.2, 95.2, 105.7, 147.0, 154.9, 156.3, 167.2; *m*/*z* (CI): 246 (^{37}Cl, M + 1, 37%), 244 (^{35}Cl, M + 1, 100), 208 (14), 151 (14), 125 (18).

N-(3-Chloropropyl)-*N*′-(4-chloropyridin-2-yl)urea 9f

To a solution of 2-amino-4-chloropyridine **8f** (2.0 g, 15.56 mmol) in anhydrous CH_2Cl_2 (50 ml), under a dry nitrogen atmosphere was added 3-chloropropyl isocyanate (2.4 ml, 23.35 mmol, 1.5 eq.), then the resulting solution was stirred at rt for 48 h. Evaporation revealed a pale yellow oil which solidified on standing to yield the crude product as a white powder (4.01 g), recrystallisation from EtOAc gave **9f** as off-white needles (3.32 g, 86%), mp 114–115 °C from EtOAc; R_f 0.67 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 247.0277. $C_9H_{11}Cl_2N_3O$ requires *M*, 247.02791) (Anal. found: C, 42.7; H, 4.4; N, 16.3; Cl, 29.2%. $C_9H_{11}Cl_2N_3O$ requires: C, 43.6; H, 4.5; N, 16.9; Cl, 28.6%); λ_{max} ($CHCl_3$): 248, 286 nm (ε 9369, 5999); ν_{max} (film): 3205, 3036, 2998, 2928, 1688 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.13 (2H, apparent quintet, *J* 7, CH_2), 3.60 (2H, t, *J* 6.5, CH_2N), 3.69 (2H, t, *J* 6.5, CH_2Cl), 6.91 (1H, dd, *J* 6.0, 2.0, H-5), 7.04 (1H, d, *J* 2.0, H-3), 8.09 (1H, d, *J* 6.0, H-6), 9.40 (1H, br t, alkyl NH), 9.72 (1H, s, aromatic NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 32.6, 37.0, 42.5, 111.9, 117.3, 145.5, 146.8, 154.3, 156.3; *m*/*z* (CI): [252 (9%), 250 (60), 248 (M + 1, 100), characteristic 9 : 6 : 1 structure for 2 × Cl], 214 (25), 212 (10), 129 (10).

1-Phenyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 10a

To a stirred solution of urea **9a** (4.96 g, 23.39 mmol) in anhydrous 2-methylpropan-2-ol (50 ml) at 30 °C, *t*-BuOK (10.48 g, 93.55 mmol, 4.0 eq.) was added, and the resulting off-white suspension stirred at this temperature whilst being protected by a $CaCl_2$ drying tube. After 22 h, the pH of the solution was adjusted to 5 by careful addition of 1 M HCl (*ca.* 70 ml). The 2-methylpropan-2-ol was evaporated and the resulting off-white residue was partitioned between CH_2Cl_2 (80 ml) and water (20 ml). The aqueous layer was re-extracted with CH_2Cl_2 (3 × 10 ml) and the combined organic extracts were washed with brine (1 × 20 ml), dried and then concentrated *in vacuo* to yield a light yellow oil which solidified on

standing to reveal an off-white solid (3.32 g). Recrystallisation from EtOAc afforded **10a** as off-white needles (3.18 g, 76%), that were collected by vacuum filtration, washed with Et_2O and dried; mp 212–214 °C from EtOAc, Lit.[29] 202–203 °C; R_f 0.46 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 176.0946. $C_{10}H_{12}N_2O$ requires *M*, 176.09496) (Anal. found: C, 68.0; H, 7.1; N, 16.0%. $C_{10}H_{12}N_2O$ requires: C, 68.2; H, 6.9; N, 15.9%); λ_{max} ($CHCl_3$): 254 nm (ε 13218); ν_{max} (film): 3220 (br), 3061, 2950, 1654 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.11 (2H, apparent quintet, *J* 6, H-5), 3.44 (2H, apparent t, *J* 6, H-4), 3.72 (2H, apparent t, *J* 6, H-6), 5.45 (1H, br s, NH), 7.20 (1H, apparent tt, *J* 7, 2, ArH), 7.35 (4H, m, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.4, 40.6, 48.7, 125.3, 125.6, 128.7, 143.7, 155.7; *m*/*z* (CI): 194 (M + 18, 5%), 178 (18), 177 (M + 1, 100).

1-(3-Methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 10b

t-BuOK (6.20 g, 55.25 mmol, 4.0 eq.) was added to a stirred solution of urea **9b** (3.40 g, 14.02 mmol) in anhydrous 2-methylpropan-2-ol (200 ml) at 30 °C, then the resulting white suspension was stirred at this temperature and protected from moisture. After 16 h, the pH of the solution was adjusted to 5 by careful addition of 1 M HCl (*ca.* 45 ml), this resulted in the formation of a white precipitate (probably KCl). The 2-methylpropan-2-ol was evaporated under reduced pressure and the resulting white residue partitioned between CH_2Cl_2 (50 ml) and water (10 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 ml) and the combined organic extracts washed with brine (1 × 30 ml) and dried. Filtration, followed by evaporation yielded a light brown oil, which solidified on standing to an off-white solid (2.91 g). Slow recrystallisation of this material from EtOAc gave **10b** as large off-white needles, which were filtered, washed with Et_2O, and dried (2.28 g, 79%), mp 149–150 °C from EtOAc; R_f 0.50 (2 : 2 : 1; PhMe–EtOAc–MeOH; SiO_2) (HRMS found: M^+, 206.1058. $C_{11}H_{14}N_2O_2$ requires *M*, 206.10552) (Anal. found: C, 63.7; H, 7.0; N, 13.7%. $C_{11}H_{14}N_2O_2$ requires: C, 64.1; H, 6.8; N, 13.6%); λ_{max} ($CHCl_3$): 244, 280 nm (ε 3000, 7475); ν_{max} (film): 3302–3219 (br), 3068, 2950, 1654 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.12 (2H, apparent quintet, *J* 6, H-5), 3.45 (2H, apparent dt, *J* 2, 6, H-4), 3.71 (2H, apparent t, *J* 6, H-6), 3.83 (3H, s, OCH_3), 5.07 (1H, br s, NH), 6.77 (1H, dd, *J* 8.4, 2.6, H-4′), 6.94 (2H, m, H-2′ and H-6′), 7.30 (1H, dd, *J* 8.4, 1.8, H-5′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.4, 40.6, 48.7, 55.2, 111.2, 111.6, 117.8, 129.3, 144.8, 155.5, 159.8; *m*/*z* (CI): 207 (M + 1, 100%), (EI) 206 (M^+, 51), 136 (100), 92 (15), 77 (20), 49 (27).

1-(4-Methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 10c

To a stirred solution of urea **9c** (3.30 g, 13.61 mmol) in anhydrous 2-methylpropan-2-ol (50 ml) at 30 °C, *t*-BuOK (6.10 g, 54.43 mmol, 4.0 eq.) was added, and the resulting off-white suspension stirred at this temperature and protected from moisture. After 16 h, the pH of the solution was adjusted to 5 by careful addition of 1 M HCl (*ca.* 45 ml), the 2-methylpropan-2-ol was evaporated and the resulting off-white residue partitioned between CH_2Cl_2 (80 ml) and water (20 ml), the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml) and the combined organic extracts washed with brine (1 × 20 ml), dried and concentrated *in vacuo* to afford a purple oil which solidified on standing to yield a grey–brown solid (2.23 g). Recrystallisation from 96% EtOH furnished the title compound as off-white needles (2.03 g, 72%) which were washed with Et_2O, mp 210–211 °C from 96% EtOH; R_f 0.40 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 206.1057. $C_{11}H_{14}N_2O_2$ requires *M*, 206.10552) (Anal. found: C, 64.1; H, 6.9; N, 13.5%. $C_{11}H_{14}N_2O_2$ requires: C, 64.1; H, 6.8; N, 13.6%); λ_{max} ($CHCl_3$): 252, 282 nm (ε 13210, 5712); ν_{max} (film): 3211, 3062, 2938, 1664 (br), 1610 (sh) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.07 (2H, apparent quintet, *J* 6, H-5), 3.41 (2H, apparent dt, *J* 2, 6, H-4), 3.64 (2H, apparent t, *J* 6, H-6), 3.82 (3H, s, OCH_3), 5.77 (1H, br s, NH), 6.90 (2H, d, *J* 8.9, H-3′ and H-5′), 7.23 (2H, dd, *J* 7, 2, H-2′ and H-6′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.4, 40.6, 49.2, 55.4, 114.1, 127.2, 136.7, 156.0, 157.3; *m*/*z* (CI): 207 (M + 1, 100%) (EI) 206 (M^+, 27), 136 (100), 120 (35), 92 (15), 77 (20), 49 (27).

1-(Pyridin-2-yl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 10d

To a stirred solution of urea **9d** (2.5 g, 11.74 mmol) in anhydrous 2-methylpropan-2-ol (100 ml) at 30 °C, *t*-BuOK (5.3 g, 46.95 mmol, 4.0 eq.) was added, then the solution was stirred at this temperature and protected from moisture. After 18 h, the pH of the solution was adjusted to 5 by careful addition of 1 M HCl (*ca.* 40 ml) then the 2-methylpropan-2-ol was evaporated. The resulting off-white residue was partitioned between CH_2Cl_2 (80 ml) and water (20 ml) and the aqueous layer was extracted with additional CH_2Cl_2 (3 × 10 ml). The combined organic extracts were washed with brine (1 × 20 ml), dried and concentrated *in vacuo* to reveal a pale yellow oil which solidified on standing to yield the crude product as an off-white solid (2.1 g). Recrystallisation from EtOAc afforded **10d** as off-white plates (1.3 g, 63%) which were washed with Et_2O, mp 143–144 °C from EtOAc; R_f 0.28 (2 : 2 : 1; PhMe–EtOAc–MeOH; SiO_2) (HRMS found: M^+, 177.0901. $C_9H_{11}N_3O$ requires *M*, 177.09021) (Anal. found: C, 61.0; H, 6.4; N, 23.7%. $C_9H_{11}N_3O$ requires: C, 61.0; H, 6.3; N, 23.7%); λ_{max} ($CHCl_3$): 250, 282 nm (ε 1243, 1029); ν_{max} (film): 3233 (br), 3079, 2965, 1671 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.10 (2H, apparent quintet, *J* 6, H-5), 3.44 (2H, apparent dt, *J* 2, 6, H-4), 4.03 (2H, t, *J* 5.9, H-6), 5.39 (1H, br s, NH), 7.00 (1H, dt, *J* 1.0, 5.0, H-5′), 7.65 (1H, dt, *J* 2.0, 8.0, H-4′), 7.93 (1H, d, *J* 8.0, H-3′), 8.37 (1H, dd, *J* 5, 1, H-6′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.1, 40.7, 44.6, 118.8, 119.3, 136.6, 147.0, 154.6, 155.5; *m*/*z* (CI): 178 (M + 1, 100%) (EI) 177 (M^+, 100), 176 (15), 148 (13), 133 (16), 121 (36), 119 (99), 107 (45), 94 (24), 78 (46).

1-(4-Methoxypyridin-2-yl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 10e

To a stirred solution of urea **9e** (4.00 g, 16.49 mmol) in anhydrous 2-methylpropan-2-ol (100 ml) at 30 °C, *t*-BuOK (7.81 g, 69.57 mmol, 4.2 eq.) was added and then the mixture was stirred at this temperature whilst protected from moisture, for 24 h. The pH of the solution was adjusted to 5 by careful addition of 1 M HCl (*ca.* 60 ml) then the 2-methylpropan-2-ol was evaporated leaving an off-white residue which was partitioned between CH_2Cl_2 (80 ml) and water (20 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml), the combined organic extracts were washed with brine (1 × 20 ml), dried and concentrated *in vacuo* to reveal a pale yellow oil which solidified on standing to yield an off-white solid (1.69 g). Recrystallisation of this material from EtOAc afforded **10e** as white plates (1.35 g, 40%) that were washed with Et_2O, mp 105–106 °C from EtOAc; R_f 0.29 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 207.1005. $C_{10}H_{13}N_3O_2$ requires *M*, 207.10077) (Anal. found: C, 57.7; H, 6.3; N, 20.2%. $C_{10}H_{13}N_3O_2$ requires: C, 58.0; H, 6.3; N, 20.3%); λ_{max} ($CHCl_3$): 256, 280 nm (ε 1663, 1625); ν_{max} (film): 3233 (br), 3252, 2965, 1669 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.05 (2H, apparent quintet, *J* 6, H-5), 3.39 (2H, apparent dt, *J* 2, 6, H-4), 3.99 (2H, apparent t, *J* 6, H-6), 5.90 (1H, br s, NH), 6.56 (1H, dd, *J* 5.7, 2.4, H-5′), 7.50 (1H, d, *J* 2.4, H-3′), 8.14 (1H, d, *J* 5.7, H-6′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.1, 40.6, 44.8, 55.1, 103.7, 107.2, 147.7, 155.5, 156.2, 166.1; *m*/*z* (CI): 208 (M + 1, 100%).

1-(4-Chloropyridin-2-yl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 10f

A 1.0 M solution of *t*-BuOK in *t*-BuOH (60.0 ml, 60.0 mmol, 3.5 eq.) was added dropwise to a stirred solution of urea **9f** (4.27 g, 17.22 mmol) in anhydrous 2-methylpropan-2-ol (5.0 ml)

at 30 °C, then the mixture was stirred at this temperature whilst protected from moisture, for 24 h. The pH of the solution was adjusted to 5 by careful addition of 1 M HCl (*ca.* 45 ml), the 2-methylpropan-2-ol was evaporated and the resulting off-white residue partitioned between CH_2Cl_2 (80 ml) and water (20 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml), the combined organic extracts were washed with brine (1 × 20 ml), dried and concentrated *in vacuo* to reveal a pale yellow oil which solidified on standing to yield an off-white solid (2.98 g). Recrystallisation of this material from EtOAc afforded the title compound as off-white plates (2.26 g, 62%) that were washed with Et_2O, mp 149–150 °C; R_f 0.38 (6% MeOH–CH_2Cl_2 containing a few drops of NEt_3) (HRMS found: M^+, 211.05116. $C_9H_{10}ClN_3O$ requires *M*, 207.1077) (Anal. found: C, 50.6; H, 4.9; N, 19.5; Cl, 16.6%. $C_9H_{10}ClN_3O$ requires: C, 51.1; H, 4.8; N, 19.9; Cl, 16.8%); λ_{max} ($CHCl_3$): 246, 280 nm (ε 1136, 511); ν_{max} (film): 3317, 3240 (br), 3091, 3072, 2940, 1673 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.05 (2H, apparent quintet, *J* 6, H-5), 3.40 (2H, apparent dt, *J* 2, 6, H-4), 3.97 (2H, apparent t, *J* 6, H-6), 6.33 (1H, br s, NH), 6.97 (1H, dd, *J* 5.4, 1.8, H-5′), 8.06 (1H, d, *J* 1.8, H-3′), 8.21 (1H, d, *J* 5.4, H-6′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.0, 40.5, 44.6, 118.8, 119.0, 143.9, 147.5, 155.3, 155.4; *m*/*z* (CI): 214 (^{37}Cl, M + 1, 31%), 212 (^{35}Cl, M + 1, 100).

3,4-Dihydro-1-(3-methoxyphenyl)-4-(2,2-dimethylethyl)-pyrimidin-2(1*H*)-one 11

To a suspension of dried 1-(3-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one **10b** (314 mg, 1.56 mmol, 1.0 eq.) in anhydrous THF (6.0 ml) at −78 °C, *t*-BuLi (1.3 M, 1.2 ml, 1.56 mmol, 1.0 eq.) was added (dropwise), under a dry argon atmosphere (all glassware was flame-dried prior to use). The resulting solution was stirred at −78 °C for 60 min; during this time the 1-(3-methoxyphenyl)pyrimidin-2(1*H*)-one went into solution and an orange–red colour developed. Addition of (pre-distilled) pivalaldehyde (0.17 ml, 1.56 mmol, 1.0 eq.) caused the coloration to dissipate, suggesting that an anion had been trapped. The mixture was stirred for a further 60 min at −78 °C, before it was allowed to warm gradually to room temperature overnight. Following this, the mixture was quenched with saturated aq. NH_4Cl (*ca.* 3 ml) to remove any unreacted *t*-BuLi, water (5 ml) was added and the resulting aqueous solution extracted with CH_2Cl_2 (3 × 10 ml). The combined organic extracts were dried and concentrated *in vacuo* to reveal an off-white solid (300 mg), which was found by ^{1}H-NMR and TLC analyses to be of approximate composition 4 : 1, C-4 addition product **11** to unreacted starting material. Flash column chromatography on silica eluting with CH_2Cl_2 up to 5% MeOH–CH_2Cl_2, gave the addition product as off-white plates (228 mg); R_f 0.65 (6% MeOH–CH_2Cl_2; SiO_2) (HRMS found: M^+, 261.1607. $C_{15}H_{20}N_2O_2$ requires *M*, 261.1603); ν_{max} (film): 3246 (br), 3106, 2959, 2868, 2836, 1690 (br), 1602 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ3.80 (1H, br d, *J* 4.1, H-4), 3.84 (3H, s, OCH_3), 4.81 (1H, br s, NH), 4.95 (1H, complex m, dd, *J* 8.1, 4.1 after shaking with D_2O, H-5), 6.34 (1H, d, *J* 8.1, H-6), 6.83 (1H, br d, *J* 8.5, H-4′), 6.88 (1H, br s, H-2′), 6.90 (1H, br d, *J* 8.5, H-6′), 7.30 (1H, m, H-5′); ^{13}C-NMR (75 MHz, d_6-DMSO): δ 24.7, 36.5, 55.3, 62.0, 100.3, 112.0, 112.3, 118.3, 129.5, 129.9, 141.7, 153.2, 159.9; *m*/*z* (CI): 278 (M + 18, 4%), 262 (15), 261 (M + 1, 100), 259 (6), 203 (5).

1-(3-Methoxyphenyl)-3-methyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 12a

Tetrahydropyrimidin-2(1*H*)-one **10b** (250 mg, 1.21 mmol) was added to a 25 ml 3-necked round-bottomed flask equipped with a magnetic stirring bar, septum, stopper and a rota-flow® valve. The flask and its contents were placed under vacuum and the tetrahydropyrimidinone was carefully heated until molten, the flask was then flame-dried. Once cool, the flask was flushed with argon and anhydrous THF (5.0 ml) was added. The mixture was stirred at −78 °C and *n*-BuLi (1.56 M, 1.94 ml, 3.03 mmol, 2.5 eq.) was added dropwise (over 20 min). After 60 min, the solution became yellow and homogeneous in appearance; it was stirred for a further 7 h at this temperature then treated with dry iodomethane and the mixture allowed to warm to room temperature overnight. The resulting homogeneous mixture was quenched with saturated aq. NH_4Cl solution (3 ml), the THF was evaporated and the aqueous solution partitioned between CH_2Cl_2 (5 ml) and water (2 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml), the combined organic extracts were washed with brine (1 × 5 ml), dried and concentrated *in vacuo* to afford **12a** as an orange coloured oil (162 mg, 61%); R_f 0.60 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 220.1209. $C_{12}H_{16}N_2O_2$ requires *M*, 220.12117); λ_{max} ($CHCl_3$): 248, 280 nm (ε 12128, 4053); ν_{max} (film): 2938, 2866, 1642 (br), 1601 (sh) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.14 (2H, apparent quintet, *J* 6, H-5), 3.02 (3H, s, NCH_3), 3.40 (2H, apparent t, *J* 6, H-4), 3.71 (2H, apparent t, *J* 6, H-6), 3.82 (3H, s, OCH_3), 6.73 (1H, dd, *J* 8.0, 1.0, H-4′), 6.87 (1H, apparent d, *J* 8, H-6′), 6.89 (1H, apparent s, H-2′), 7.24 (1H, t, *J* 8.0, H-5′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.6, 35.6, 48.0, 48.7, 55.2, 110.9, 111.4, 117.6, 129.0, 145.4, 155.3, 159.7; *m*/*z* (CI): 221 (M + 1, 100%).

1-(2-Methyl-3-methoxyphenyl)-3-methyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 12b

Following a procedure similar to that described above, tetrahydropyrimidin-2(1*H*)-one **10b** (250 mg, 1.21 mmol) was treated with *n*-BuLi (1.56 M, 1.95 ml, 3.03 mmol, 2.5 eq.) initally at −78 °C and then at 0 °C for 2 h, and the solution treated with iodomethane at −78 °C giving **12b** as a pale yellow oil (284 mg, 92%); R_f 0.65 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 234.1366. $C_{13}H_{18}N_2O_2$ requires *M*, 234.13682); λ_{max} ($CHCl_3$): 242, 274 nm (ε 7214, 4878); ν_{max} (film): 2931, 2857, 1639 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.06–2.24 (5H, br s, CH_2 and $ArCH_3$), 3.02 (3H, s, NCH_3), 3.39–3.49 (3H, m), 3.56–3.65 (1H, m), 3.84 (3H, s, OCH_3), 6.79 (1H, apparent d, *J* 8, H-4′), 6.83 (1H, apparent d, *J* 8, H-6′), 7.17 (1H, t, *J* 8.1, H-5′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 10.7, 22.7, 35.5, 48.0, 49.1, 55.6, 108.7, 120.0, 125.0, 126.4, 143.7, 158.3; *m*/*z* (CI): 235 (M + 1, 100%).

1-(2-Trimethylsilyl-3-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 12c

Following a similar procedure to that described above, tetrahydropyrimidin-2(1*H*)-one **10b** (250 mg, 1.21 mmol) was treated with *n*-BuLi (1.56 M, 1.95 ml, 3.03 mmol, 2.5 eq.) initially at 0 °C and then at 0 °C for 2 h, and the resulting lithioderivative reacted with trimethylsilyl chloride (0.38 ml, 3.03 mmol, 2.5 eq.) at −78 °C giving an off-white solid (303 mg). Recrystallisation from EtOAc afforded **12c** as bright white plates (230 mg, 68%, from two crops), mp 177–178 °C from EtOAc; R_f 0.36 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M + 1, 279.1525. $C_{14}H_{22}N_2O_2Si$ requires *M* + 1, 279.1529) (Anal. found: C, 60.2; H, 8.2; N, 9.7%. $C_{14}H_{22}N_2O_2Si$ requires: C, 60.4; H, 8.0; N, 10.1%); λ_{max} ($CHCl_3$): 248, 282 nm (ε 9328, 14561); ν_{max} (film): 3224 (br), 3062, 2941, 1659 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.00 (9H, s, Me_3Si), 1.65–1.90 (2H, m, CH_2), 3.07–3.21 (3H, m), 3.24–3.33 (1H, m), 3.49 (3H, s, OCH_3), 4.79 (1H, br s, NH), 6.47 (2H, d, *J* 8.0, H-4′ and H-6′), 7.04 (1H, t, *J* 8.0, H-5′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 0.7, 22.1, 40.4, 50.2, 55.2, 108.8, 120.7, 127.1, 131.3, 149.5, 156.1, 165.1; *m*/*z* (CI): [281 (5%), 280 (22), 279 (100), M + 1, ^{30}Si, ^{29}Si and ^{28}Si respectively], 207 (15).

1-[2-(1-Hydroxy-2,2-dimethylpropyl)-3-methoxyphenyl]-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 12d

Using the typical procedure (above), 1-(3-methoxyphenyl)-

3,4,5,6-tetrahydropyrimidin-2(1*H*)-one **10b** (500 mg, 2.42 mmol) was lithiated with *n*-BuLi (1.56 M, 3.88 ml, 6.07 mmol, 2.5 eq.) at 0 °C and then at 0 °C for 2 h, and reacted at −78 °C with pivalaldehyde giving a white powder (481 mg), which was recrystallised from EtOAc, affording the title compound as opaque plates (400 mg, 56%, from two crops), mp 205–206 °C from EtOAc; R_f 0.29 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 292.1796. $C_{16}H_{24}N_2O_3$ requires *M*, 292.17868) (Anal. found: C, 65.3; H, 8.4; N, 9.6%. $C_{16}H_{24}N_2O_3$ requires: C, 65.7; H, 8.3; N, 9.6%); λ_{max} ($CHCl_3$) 250, 280 nm (ε 11153, 15246); ν_{max} (film): 3548 (br), 3312–3237 (br), 2950, 2904, 2867, 1664 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.89 (9H, s, $(CH_3)_3C$), 2.00–2.07 (1H, m), 2.11–2.20 (1H, m), 3.44–3.53 (3H, m), 3.57–3.64 (1H, m), 3.87 (3H, s, OCH_3), 4.29 (1H, d, *J* 11.8, OH), 4.49 (1H, d, *J* 11.8, CH), 5.10 (1H, br s), 6.89 (1H, d, *J* 8.0, H-4′), 6.96 (1H, d, *J* 8.0, H-6′), 7.28 (1H, apparent t, *J* 8, H-5′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.4, 27.0, 37.8, 40.8, 50.3, 55.1, 79.2, 110.1, 122.7, 126.7, 128.3, 128.4, 143.4, 156.3, 158.7; *m*/*z* (CI): 310 (M + 18, 1%), 293 (M + 1, 100), 276 (15), 275 (94), 235 (10), 207 (20).

1-(2-Benzoyl-3-methoxyphenyl)-3-benzoyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 12e

Following the usual procedure tetrahydropyrimidin-2(1*H*)-one **10a** (250 mg, 1.21 mmol) was lithiated with *n*-BuLi (1.6 M, 1.89 ml, 3.03 mmol, 2.5 eq.) at 0 °C, and the resulting species reacted at −98 °C with benzoyl chloride (0.35 ml, 3.03 mmol, 2.5 eq.), work up giving an orange semi-solid (728 mg), which was found to contain three closely running components by TLC (2 : 2 : 1; PhMe–EtOAc–MeOH; SiO_2). Repeated flash column chromatography on silica gel (eluting with CH_2Cl_2 up to 5% MeOH–CH_2Cl_2) afforded **12e** as white plates (67 mg, 13%), mp 161–162 °C from EtOAc; R_f 0.71 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 414.1573. $C_{25}H_{22}N_2O_4$ requires *M*, 414.15795) (Anal. found: C, 64.0; H, 4.4; N, 5.8%. $C_{25}H_{22}N_2O_4 \cdot 3H_2O$ requires: C, 64.1; H, 6.0; N, 6.0%); λ_{max} ($CHCl_3$): 248 nm (ε 13307); ν_{max} (film): 3064, 2965, 2893, 1677 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.15 (2H, m), 3.68 (3H, s, OCH_3), 3.75 (2H, br s, H-4), 3.86 (2H, br s, H-6), 6.93 (2H, apparent dd, *J* 8, 2, ArH), 7.00 (2H, apparent t, *J* 8, ArH), 7.11 (2H, d, *J* 8.2, ArH), 7.23–7.29 (1H, m, ArH), 7.40–7.52 (3H, m, ArH), 7.60–7.68 (1H, m, ArH), 7.86 (2H, d, *J* 8.2, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.3, 43.1, 50.8, 110.5, 120.7, 127.3, 127.4, 128.3, 128.4, 129.5, 130.0, 131.1, 133.3, 136.6, 137.3, 141.0, 152.8, 157.6, 173.0, 195.7; *m*/*z* (CI): 432 (M + 18, 3%), 415 (M + 1, 100), 105 (18).

1-Phenyl-3-methyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 12f

Following the usual drying procedure tetrahydropyrimidin-2(1*H*)-one **10a** (250 mg, 1.42 mmol) was treated with *n*-BuLi (1.23 M, 2.88 ml, 3.55 mmol, 2.5 eq.) at −78 °C and the resulting pale yellow mixture warmed to 0 °C where it was stirred for a period of 2 h. Over this time a yellow colour developed, however the mixture did not become homogeneous. Cooling to −78 °C, followed by the dropwise addition of dry iodomethane (0.22 ml, 3.55 mmol, 2.5 eq.) caused the yellow colour to fade (over 5 min) and the mixture was slowly warmed to room temperature overnight. The reaction mixture was quenched with sat. aq. NH_4Cl (2 ml), the THF was evaporated, and the aqueous mixture partitioned between CH_2Cl_2 (10 ml) and water (3 ml). The aqueous layer was re-extracted with CH_2Cl_2 (3 × 5 ml), the combined organic extracts were shaken with brine (10 ml), dried and concentrated *in vacuo* to yield the crude product as an orange coloured semi-solid (268 mg). Extensive chromatography, eluting with CH_2Cl_2 up to 1% MeOH–CH_2Cl_2 gave the major component **12f** as a colourless oil (187 mg, 69%), Lit.[30] 72 °C; R_f 0.49 (6% MeOH–CH_2Cl_2) (HRMS found: M^+, 190.1107. $C_{11}H_{14}N_2O$ requires *M*, 190.11061); λ_{max} ($CHCl_3$): 246 nm (ε 12602); ν_{max} (film): 2935, 2861, 1643 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.12 (2H, CH_2), 3.02 (3H, s, NCH_3), 3.39 (2H, m), 3.70 (2H, m), 7.11–7.21 (2H, m, ArH), 7.23–7.36 (3H, m, ArH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.6, 35.6, 48.0, 48.6, 124.8, 125.3, 128.4, 135.9, 144.3; *m*/*z* (CI): 191 (M + 1, 100%).

1-(4-Methoxy-2-trimethylsilylphenyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 12g

Following the method described above, tetrahydropyrimidin-2(1*H*)-one **10c** (298 mg, 1.45 mmol) was treated with *n*-BuLi (1.6 M, 2.26 ml, 3.62 mmol, 2.5 eq.) at −78 °C and after bringing to 0 °C for 2 h, reacted at −78 °C with trimethylsilyl chloride (0.46 ml, 3.62 mmol, 2.5 eq.) causing the orange colour to dissipate after 20 min. The solution was allowed to warm to room temperature overnight, saturated aq. NH_4Cl solution (3 ml) added, THF was evaporated and the resulting aq. mixture partitioned between CH_2Cl_2 (10 ml) and water (5 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml), the combined organic extracts were shaken with brine (10 ml), dried and concentrated *in vacuo* to leave the crude product as a light brown solid (248 mg). Attempted purification by flash silica column chromatography failed. Separation by reversed phase preparative HPLC on silica gel (eluting with 80 : 20 MeOH–H_2O at a flow rate of 15 ml min^{-1}) gave unreacted starting material (HPLC yield: 51%), then 1-(4-methoxy-2-trimethylsilylphenyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one **12g** as a glassy solid (4.7 mg, HPLC yield: 23%) (HRMS found: M + 1, 279.1532. $C_{14}H_{22}N_2O_2Si$ requires *M* + 1, 279.1529); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.00 (9H, s, Me_3Si), 1.68–1.75 (1H, m), 1.81–1.95 (1H, m), 3.12–3.19 (3H, m), 3.24–3.32 (1H, m), 3.50 (3H, s, OCH_3), 4.71 (1H, br s, NH), 6.60 (1H, dd, *J* 9, 3, H-5′), 6.76 (1H, d, *J* 3, H-3′), 6.81 (1H, d, *J* 9, H-6′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ −0.4, 22.3, 40.9, 50.4, 55.3, 115.2, 121.2, 129.1, 140.5, 141.3, 149.5, 156.8, 157.9; *m*/*z* (CI): [281 (5%), 280 (20), 279 (100), M + 1, ^{30}Si, ^{29}Si and ^{28}Si, respectively]. Finally 1-(3-trimethylsilyl-4-methoxyphenyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one **12h** (HPLC yield: 26%) was eluted contaminated with the 2-isomer **12g**.

1-(4-Methoxypyridin-2-yl)-3-methyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 13a

Following the usual drying procedure described above, a stirred solution of tetrahydropyrimidin-2(1*H*)-one **10e** (200 mg, 0.97 mmol) in anhydrous THF (5 ml), was treated with *n*-BuLi (1.6 M, 0.72 ml, 1.16 mmol, 1.2 eq. -dropwise) at −78 °C under an atmosphere of dry N_2. The resulting mixture was stirred for 60 min, where it became yellow in colour, and anhydrous iodomethane (72 μl, 1.16 mmol, 1.2 eq.) was added dropwise. Stirring was continued at −78 °C for 60 min, the reaction mixture was then warmed to rt over 3 h. The mixture was quenched with sat. aq. NH_4Cl (3 ml), the THF was evaporated and the resulting aqueous suspension partitioned between CH_2Cl_2 (10 ml) and water (2 ml). The aqueous layer was extracted with CH_2Cl_{20} (3 × 5 ml), the combined organic extracts were shaken with brine (10 ml), dried and concentrated *in vacuo* to afford **13a** as a yellow coloured oil (178 mg, 83%), no further purification was necessary; R_f 0.38 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 221.1165. $C_{11}H_{15}N_3O_2$ requires *M*, 221.11642); ν_{max} (film): 2936, 2872, 1652 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.08 (2H, apparent quintet, *J* 6, H-5), 3.03 (3H, s, NCH_3), 3.38 (2H, apparent t, *J* 6, H-4), 3.84 (3H, s, OCH_3), 3.99 (2H apparent t, *J* 6, H-6), 6.54 (1H, dd, *J* 5.8, 2.0, H-5′), 7.47 (1H, d, *J* 2.0, H-3′), 8.10 (1H, d, *J* 5.8, H-6′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.4, 35.8, 45.1, 48.2, 55.3, 102.9, 107.5, 146.7, 155.1, 156.4, 166.4; *m*/*z* (CI): 222 (M + 1, 100%).

1-(3-Methyl-4-methoxypyridin-2-yl)-3-methyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 13b

Following the usual drying procedure, a stirred solution of

tetrahydropyrimidin-2(1*H*)-one **10e** (101 mg, 0.49 mmol) in anhydrous THF (3 ml), was treated with *n*-BuLi (1.12 M, 1.1 ml, 1.22 mmol, 2.5 eq., dropwise) at −78 °C under an atmosphere of dry N_2. The resulting mixture was stirred for 25 min, then warmed to −40 °C, where it gradually became dark orange in colour. After a period of 2 h, the mixture was cooled to −78 °C and anhydrous iodomethane (76 µl, 1.22 mmol, 2.5 eq.) was added dropwise. Stirring was continued at −78 °C for 2 h, the reaction mixture was then warmed to room temperature overnight. The mixture was quenched with sat. aq. NH_4Cl (3 ml), the THF was evaporated and the resulting aqueous suspension partitioned between CH_2Cl_2 (10 ml) and water (2 ml). The aqueous layer was re-extracted with CH_2Cl_2 (3 × 5 ml), the combined organic extracts were shaken with brine (10 ml), dried and concentrated *in vacuo* to afford an orange semi-solid (134 mg). Careful resolution by flash column chromatography on silica gel (eluting with CH_2Cl_2 up to 5% MeOH–CH_2Cl_2) afforded **13b** as a yellow oil (20 mg, 16%); R_f 0.38 (2 : 2 : 1; PhMe–EtOAc–MeOH) (HRMS found: M^+, 235.1323. $C_{12}H_{17}N_3O_2$ requires *M*, 235.13207); ν_{max} (film): 2928, 2873, 1647 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.13 (3H, s, py-CH_3), 2.18–2.22 (2H, m, CH_2), 3.02 (3H, s, NCH_3), 3.38–3.66 (4H, m), 3.90 (3H, s, OCH_3), 6.72 (1H, d, *J* 5.6, H-5′), 8.25 (1H, d, *J* 5.6, H-6′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.7, 35.5, 47.0, 48.1, 55.6, 104.6, 119.8, 127.4, 147.1, 160.6, 165.2; *m*/*z* (CI): 235 (M + 1, 100%), 222 (18), 208 (10).

1-(3-Methyl-4-methoxypyridin-2-yl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one 13c

Following the usual drying procedure, a stirred solution of tetrahydropyrimidin-2(1*H*)-one (**10e**) (101 mg, 0.49 mmol) in anhydrous THF (3 ml), was treated with *n*-BuLi (1.12 M, 0.44 ml, 0.49 mmol, 1.0 eq.) dropwise at −78 °C under an atmosphere of dry N_2. The resulting mixture was stirred for 35 min, where it became yellow in colour, and anhydrous trimethylsilyl chloride (62 µl, 0.49 mmol, 1.0 eq.) was added dropwise. Stirring was continued at −78 °C for 30 min, the reaction mixture was then warmed to rt over 60 min. A white suspension formed which was cooled back to −78 °C and treated with *n*-BuLi (1.12 M, 0.44 ml, 0.49 mmol, 1.0 eq., dropwise). After stirring for 30 min the suspension was allowed to warm (slowly) to −16 °C, where it became homogeneous and yellow in colour, then finally to 0 °C where it was stirred for 2 h. After this period, the resulting dark yellow solution was cooled to −78 °C, anhydrous iodomethane (30 µl, 0.49 mmol, 1.0 eq.) was added dropwise and the mixture allowed to warm to room temperature overnight. The reaction mixture was quenched with sat. aq. NH_4Cl(aq) (3 ml), the THF was evaporated and the resulting aqueous suspension partitioned between CH_2Cl_2 (10 ml) and water (2 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 ml), the combined organic extracts were shaken with brine (10 ml), dried and concentrated *in vacuo* to yield the crude product as a dark brown foam (106 mg). TLC analysis showed this to be a complex mixture containing at least four components. The mixture was resolved by flash column chromatography on silica gel (eluting with CH_2Cl_2 up to 4% MeOH–CH_2Cl_2 containing a few drops of NEt_3). In order of elution, the following compounds were isolated: 1-(4-methoxypyridin-2-yl)-3-methyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (**13a**) (16 mg); unreacted: 1-(4-methoxypyridin-2-yl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one **10e** (20 mg); **13c** as a pale yellow coloured oil (40 mg, 37%); R_f 0.08 (HRMS found: M^+, 221.1167. $C_{11}H_{15}N_3O_2$ requires *M*, 221.11642); ν_{max} (film): 3439 (br), 2936, 2872, 1657 (br) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.81 (5H, m, CH_2 and py-CH_3), 3.08–3.18 (2H, m, H-4), 3.57 (3H, s, OCH_3), 3.62–3.72 (2H, m), 4.85 (1H, br s, NH), 6.40 (1H, d, *J* 5.6, H-5′), 7.94 (1H, d, *J* 5.6, H-6′); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 10.6, 22.4, 40.8, 46.8, 55.7, 104.9, 120.0, 147.3, 150.8, 154.8, 165.3; *m*/*z* (CI): 222 (M + 1, 100%).

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