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Slow interconversion of enantiomeric conformers or atropisomers of anilide and urea derivatives of 2-substituted anilines

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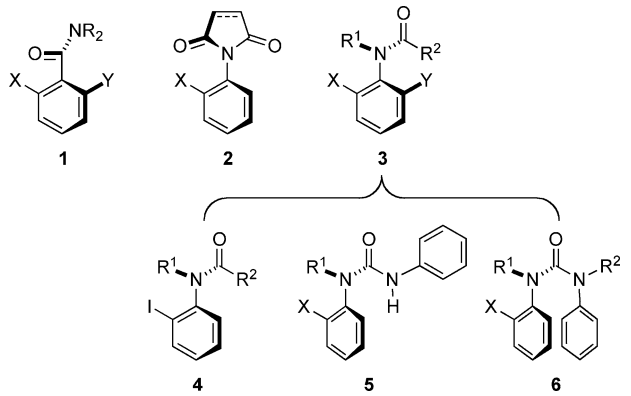
N-Acylated 2-substituted anilines undergo slow Ar–N bond rotation, allowing in some cases isolation of enantiomeric or diastereoisomeric atropisomers and in others the determination of the rate of Ar–N bond rotation by NMR. 2-Iodoanilides bearing a branched *N*-substituent demonstrate sufficient enantiomeric stability to be resolvable, either by HPLC or by formation of diastereoisomeric lactanilide derivatives. For the first time, the rates of Ar–N rotation in 2-substituted *N*,*N*′-diarylureas have been established: they mainly fall in the region of 50–70 kJ mol^{-1} with a relatively weak dependence on substituent size.

Introduction

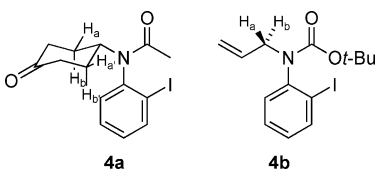
A growing interest, over the last decade, in the potential of non-biaryl atropisomers in synthesis[1,2] and in medicinal chemistry[3] has prompted investigations into the stereoselectivity of their reactions,[4–8] their enantioselective synthesis,[8–14] and their use as chiral auxiliaries[11,15,16] and chiral ligands.[9,17] Many of these studies have involved compounds such as benzamides **1**,[2,7,14,18] or maleimides, succinimides and anilides **2** and **3**.[5,6,8,11–13,16,19–21] These amide-type functional groups have featured highly because the rigidity of the amide raises the barrier to conformational interconversion and increases the likelihood that conformers may exist as separable atropisomers. In this paper we report our exploration of the rates of conformational interconversions in some subclasses of **3**: anilides **4** bearing a single 2-iodo substituent, 2-substituted *N*-alkyl-*N*,*N*′-diarylureas **5** and *N*,*N*′-dialkyl-*N*,*N*′-diarylureas **6**. We reveal that iodoanilides **4** carrying a branched *N*-alkyl substituent turn out to have a remarkably high barrier to rotation, giving rise to atropisomerism without the need for further heavy substitution. While the conformational preferences of **5** and **6** have been studied[22] their rates of racemisation have until now remained unexplored.[23,24]



In general, atropisomerism is a feature of anilides **3** only when X and Y ≠ H: in other words, only derivatives of 2,6-disubstituted anilines are usually atropisomeric,[20,25] though the interconverting conformers of mono-*ortho*substituted anilides may be detected by NMR.[26–28] † The only known exceptions to date are derivatives of 2-*tert*-butyl anilines, whose anilide derivatives are sufficiently hindered to exist as atropisomers even without a 6-substituent.[20] Mindful of the requirement for 2,6-disubstitution, recent work by Curran has employed a "dummy" 6-trimethylsilyl substituent to allow the retention of axial stereochemistry in reactions of anilides which would otherwise racemise rapidly.[25] Conformational interconversion is also possible around the N–CO bond of **3**, but when the carbonyl substituent is small (Me for example, as in acetanilides) only the N–CO conformer shown (which has Ar and the C=O group *trans*) is detectable by NMR.[20] The alternative N–CO bond rotation has been studied in some depth in a range of ureas,[23,24] and is consistently significantly faster than that in the corresponding amides.

Results and discussion

In connection with studies on the palladium-catalysed cyclisation reactions of iodoarylaminoketones,[30,31] we had made some 2-iodoanilides. Some of these compounds showed slow rotation in their NMR spectra. Both **4a** and **4b**, for example, exhibited diastereotopic protons H_a and H_b (and $H_{a'}$ and $H_{b'}$ for **4a**), indicating transient chirality which we ascribe to slow rotation (on the NMR timescale) about the ArC–N bond (Scheme 1). While anilide **4a** existed as a single conformer about its N–CO bond, simplifying its analysis by NMR,[20] **4b** was a mixture of N–CO geometrical conformers. Variable temperature NMR spectroscopy of **4b** allowed us to estimate, using the lineshape modelling program gNMR,‡ a value of



Scheme 1 Anilides exhibiting slow Ar–N rotation.

† Benzamides similarly are atropisomeric generally only when they are 2,6-disubstituted,[29a] with the exception of certain *peri*-substituted 1-naphthamides.[29b]

‡ Cherwell Scientific.

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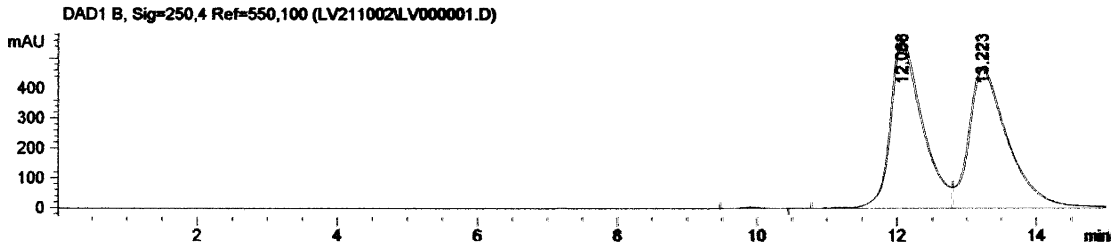
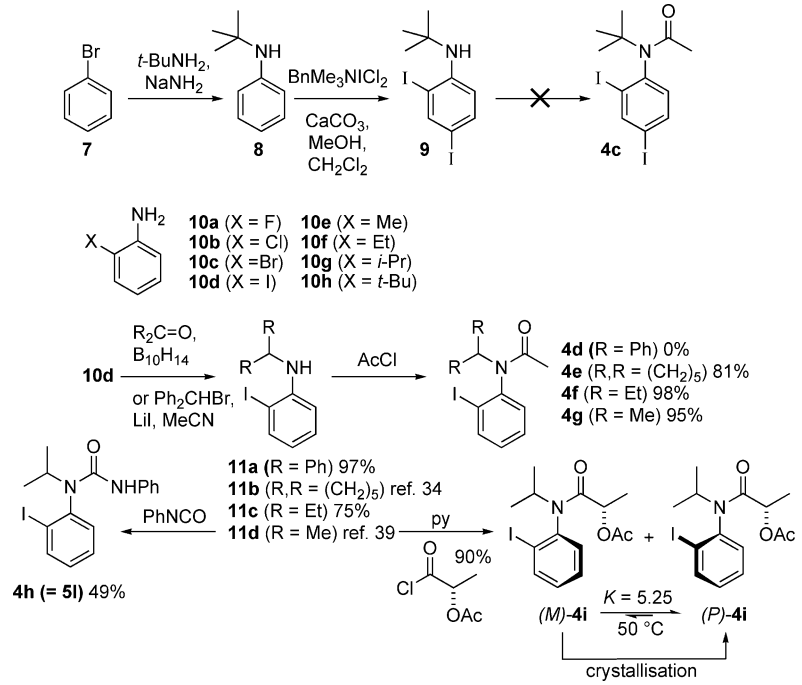


Fig. 1 HPLC trace of **4a** [chiral stationary phase: Chiralcel OT(+)].



Scheme 2 Mono-*ortho*substituted anilides.

$\Delta G^{\ddagger} = 80.5 \pm 0.5$ kJ mol^{-1} over the range 80–120 °C for the barrier to C–N rotation, corresponding to an estimated§ half-life for enantiomerisation at 25 °C of 14 s and therefore a half-life for racemisation at this temperature of just 7 s. This figure is similar to that obtained with related mono-*ortho*substituted anilides bearing unbranched *N*-substituents.[26]

With **4a** however, we were unable to attain coalescence at high temperatures but we found that the enantiomers were sufficiently stable to be separated by HPLC on a chiral stationary phase [Chiralcel OT(+)] (Fig. 1). Each resolved enantiomer was incubated at 40 °C and kinetic analysis of its first-order decay to a racemic mixture showed a half-life for racemisation of 9.2 h at this temperature, corresponding to $\Delta G^{\ddagger} = 104.9$ kJ mol^{-1}. Assuming constancy of $\Delta G^{\ddagger}$ with temperature, the estimated half-life for racemisation of **4a** at 25 °C was 36 hours.

Iodoanilide **4a** is the first anilide **3** bearing a single *ortho* substituent (other than *t*-Bu[20]) to have been shown to exhibit atropisomerism[32] at room temperature. The principal feature distinguishing it from the less stable enantiomers of **4b** and from other known achiral anilides[20,26,27] is the bulky, branched cyclohexyl substituent at *N*. We therefore decided to make a further series of anilide derivatives of 2-iodoanilines **11** bearing branched *N*-alkyl groups (Scheme 2).

We were able to synthesise the anilines **9** (by the method of Paul and Haberfield[33] from bromobenzene **7**), and **11a–d** by alkylation (for **11a**) or reductive amination from 2-iodoaniline **10d**,[34] but unfortunately both **9** and **11a** were resistant to acetylation, preventing the formation of **4c** and **4d**. However, acetylation of **11b–d** gave the anilides **4e–4g** and reaction of **11d** with phenyl isocyanate gave the urea **4h**. None of the three compounds could be resolved by HPLC, though **4e** did show two overlapping peaks in its HPLC trace. Variable temperature NMR spectroscopy of **4g** up to a temperature of 120 °C (DMSO) showed that coalescence of the diastereotopic methyl doublets occurred at a temperature higher than this and allowed us to estimate a minimum barrier to rotation about C–N of >97 kJ mol^{-1}, or an estimated half-life for racemisation at 25 °C of at least a few hours. Variable temperature NMR investigations of **4h** (modelling coalescence of the diastereotopic methyl doublets) in contrast gave a barrier to rotation of 65.7 kJ mol^{-1} at 25 °C, corresponding to a half-life for racemisation of about 3×10^{-2} seconds, indicating that *N*-phenyl ureas have significantly lower barriers to Ar–N rotation than the corresponding anilides.

With an additional stereogenic centre in the molecule the presumed stable pairs of enantiomers of **4e–g** would become pairs of diastereoisomers, allowing their more straightforward separation. Treatment of **11d** with (*S*)-*O*-acetyl lactoyl chloride gave the two atropisomeric diastereoisomers of **4i** in, initially, approximately a 1 : 1 ratio. The diastereoisomers were separated by flash chromatography. On incubating either enantiomer at 50 °C in 5 : 1 hexane–isopropanol, slow conversion (in a matter of hours) was observed, leading eventually to a ratio of atropisomeric diastereoisomers of **4i** of 5.25 : 1 *M* : *P*. Analysis of the epimerisation by the method of Siddall and Stewart[28] gave a half-life for the equilibration of 32.5 min at 50 °C. From this,

§ From the more or less constant value obtained for $\Delta G^{\ddagger}$ we assume that, in common with many other bond rotation processes, $\Delta S^{\ddagger}$ is small. The half-life for enantiomerisation at 25 °C in this instance was established by assuming $\Delta G^{\ddagger}$ is constant with temperature. The rate of racemisation is double the rate of enantiomerisation.

and the equilibrium constant, we derived barriers to rotation from (*M*)-**4i** to (*P*)-**4i** of 99.0 ± 0.5 kJ mol^{-1} at 50 °C and from (*P*)-**4i** to (*M*)-**4i** of 103.5 ± 0.5 kJ mol^{-1} at 50 °C.

When the mixture of diastereoisomers was stored at room temperature for several days, however, the enrichment of the major diastereoisomer (*P*)-**4i** increased to 100% in a process driven by the crystallisation. An X-ray crystal structure (Fig. 2) confirmed the stereochemistry of this more stable and more crystalline diastereoisomer.¶ Lactic acid derivatives of anilides have previously been used in a similar way as a means of resolution of related atropisomers.[6,11,13,21,35]

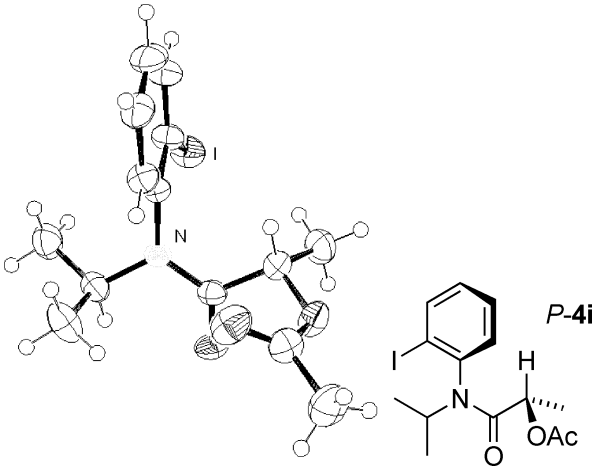


Fig. 2 X-Ray crystal structure of (*P*)-**4i**.

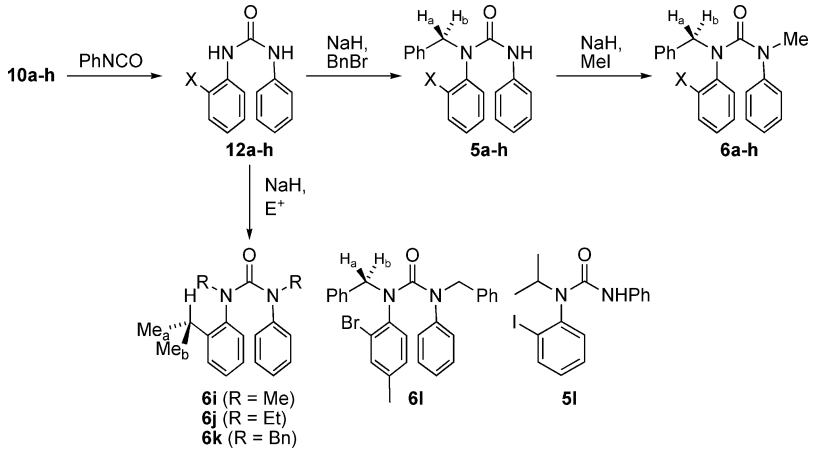
These studies were not pursued further, but indicated that *N*-*sec*-alkyl anilides bearing a 2-substituent form a new class of non-biaryl atropisomeric molecules with potential application in asymmetric synthesis or catalysis.[1]

¶ CCDC reference number 273163. See http://dx.doi.org/10.1039/b507202f for crystallographic data in CIF or other electronic format.

Just as **3** is conformationally uniform about the N–CO bond provided R^2 is small, *N*,*N*′-dialkyl-*N*,*N*′-diarylureas **6** are known to adopt a well defined conformation about the two N–CO bonds placing the two Ar rings *cis*.[22] We hoped that this would both facilitate studies of their rate of racemisation and also allow us to investigate a potential new class of atropisomeric molecules.

We therefore made a series of ureas bearing a range of sterically and electronically contrasting 2-substituents by condensation of the available anilines **10a–h** with phenylisocyanate (Scheme 3). Alkylation of the disubstituted ureas **12a–h** with benzyl bromide yielded the *N*,*N*,*N*′-trisubstituted ureas **5a–h**.[36] Interestingly, this first alkylation took place at the *more* hindered N atom, possibly because conjugation between this nitrogen anion and the ring is lessened by the impossibility of coplanarity between the urea and the ring.[36] A second alkylation with methyl iodide gave the parallel series of fully alkylated ureas **6a–h**. Barriers to Ar–CO rotation were determined by variable temperature NMR in DMSO, modelling lineshapes close to coalescence using gNMR, and the results are shown in Table 1.

The overall message from these results is that, with one or two exceptions, the size of the substituent *ortho* to the C–N bond in a monosubstituted 2-phenyl urea is of relatively small importance. Most of the "doubly alkylated" anilides **6** had barriers between around 50 and 60 kJ mol^{-1} at room temperature, corresponding to half-lives for racemisation of between 10^{-5} and 10^{-3} s while most of the "singly alkylated" anilides **5** had barriers between about 60 and 70 kJ mol^{-1}, corresponding to half-lives for racemisation approaching 0.5 s at room temperature. Alkylation of the second nitrogen of the urea leads to a decrease in rotational barrier of about 10 kJ mol^{-1}, an effect possibly attributable to a decrease in ground-state strain.[23] Two substituents provide exceptions to this general rule: fluoro, in which the barrier is so low that it could not be measured (no diastereotopic protons were seen in **5a**, even at −50 °C in $CDCl_3$) and *t*-Bu, which in **6h** gave a barrier (determinable with only poor accuracy) of around 80 kJ mol^{-1}, or a half-life for racemisation at 25 °C of somewhere between 1 and 100 s.



Scheme 3 *ortho*-Substituted *N*,*N*′-diarylureas.

Table 1 Barriers to enantiomerisation of **5** and **6**

Entry	X =	Cpd., yield (%)	$\Delta G^{\ddagger}$ (25 °C)/kJ mol^{-1}	Cpd., yield (%)	$\Delta G^{\ddagger}$ (25 °C)/kJ mol^{-1}
1	F	**5a** 56	—	**6a** 98	—
2	Cl	**5b** 42	58.8 ± 3.0	**6b** 71	50.6 ± 3.0
3	Br	**5c** 39	61.8 ± 3.0	**6c** 71	53.5 ± 2.3
4	I	**5d** 42	67.7 ± 1.5	**6d** 90	56.9 ± 2.4
5	Me	**5e** 44	64.5 ± 2.7	**6e** 47	56.7 ± 2.3
6	Et	**5f** 33	69.3 ± 4.0	**6f** 38	60.6 ± 1.5
7	i-Pr	**5g** 60	70.0 ± 4.0	**6g** 82	60.0 ± 20
8	*t*-Bu	**5h** 58	69.8 ± 7.0	**6h** 87	80.0 ± 6

Table 2 Varying *N*-alkyl groups

Entry	R =	Cpd.	$\Delta G^{\ddagger}$ (25 °C)/kJ mol^{-1}
1	Me	**6i**	58.7
2	Et	**6j**	64.8
3	Bn	**6k**	61.6
4	(Bn)	**6l**	59.2
5	(I)	**5l**	65.7

For convenience of analysis, because of the AB system which results, we studied *N*-benzyl derivatives of urea **12**, but we were also eager to establish the role of the size of this *N*-substituent on the barrier to rotation, given the evident importance of the branched substituent in **4**. We therefore made the small family of derivatives **6i–6l** and determined the barrier to Ar–N rotation for each by following the coalescence of the pair of i-Pr doublets by VT NMR. Table 2 shows the results, which indicate broadly that moving from Me to Et to Bn has little effect on the barrier to rotation at ambient temperature. A comparison between the two compounds **5d** and **5l**, both 2-iodophenylureas, but one bearing *N*-Bn and one *N*-i-Pr, confirms this view, that the *N*-substituent has little role to play in the size of the barrier in ureas.

Although the barriers to rotations in these ureas are lower than in the corresponding anilides, the Ar–N bonds seem to rotate much more slowly than the corresponding N–CO bonds of similar *N*,*N*,*N*′,*N*′-tetrasubstituted ureas, whose reported barriers to rotation are less than 35 kJ mol^{-1}.[23]

This kinetic study will lay the foundation for future synthetic and stereochemical investigations with *N*,*N*′-diaryl ureas which will be published in due course.[36]

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on a Varian XL 300 MHz Fourier Transform instrument. VT NMR studies were recorded on an Inova 300 MHz Fourier Transform instrument. NMR data are presented as follows: chemical shift δ (in ppm relative to $\delta_{TMS} = 0$), multiplicity, coupling constant *J* (quoted in hertz, Hz), integration, and assignment. IR spectra were recorded on an ATi Matson Genesis Series Fourier Transform spectrometer. Wavelengths of maximum absorbance are quoted in wavenumbers (cm^{-1}). Low resolution mass spectra (EI and CI) were recorded on a Fisons VG Trio 2000 quadrupole mass spectrometer. High resolution mass spectra were recorded on a Kratos Concept-IS mass spectrometer. Analytical TLC was carried out on Machery-Nagel pre-coated 0.2 mm silica plates with fluorescent indicator on aluminium. The drying agent used prior to purification was magnesium sulfate. Flash chromatography[37] was carried out using Fluorochem Davisil 40–63 μm 60 A silica under a positive pressure of air.

The following compounds have been published previously: 4-[*N*-acetyl-*N*-(2-iodophenyl)amino]cyclohexanone **4a**;[31] *N*-*tert*-butylaniline **8**;[33] *N*-*tert*-butyl-2,4-diiodoaniline **9**;[38] *N*-cyclohexyl-2-iodoaniline **11b**;[34] *N*-isopropyl-2-iodoaniline **11d**.[39]

***N*-Allyl-*N*-(*tert*-butoxycarbonyl)-2-iodoaniline. 4b** was made by the method of Boger and McKie.[40] ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 1.36 and 1.54 (2 s, 9H, $(CH_3)_3$, major and minor Boc rotamer respectively), 3.77 (dd, $J = 15$ and 6.8 Hz, 1H, CH_2), 4.50 (dd, $J = 15$ and 5.6 Hz, 1H, CH_2), 5.03–5.11 (m, 2H, $=CH_2$), 5.85–6.05 (m, 1H, CH=), 6.98 (ddd, $J = 7.8$, 7.4 and 1.6 Hz, 1H, H-4), 7.12 (dd, $J = 7.4$ and 1.6 Hz, 1H, H-6), 7.32 (t, $J = 7.4$ Hz, 1H, H-5), 7.86 (d, $J = 7.8$ Hz, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ Major rotamer: 28.3 (CH_3), 52.0 (CH_2), 80.3 ($C(CH_3)_3$), 100.5 (C), 117.8 (CH_2), 128.5 (CH), 128.9 (CH), 129.8 (CH), 133.5 (CH), 139.2 (CH), 144.1 (C), 153.7 (CO). Minor rotamer: 53.2 (CH_2), 117.2 (CH_2), 128.6 (CH), 130.1 (CH), 139.5 (CH).

Anal. Calcd for $C_{14}H_{18}INO_2$: C, 46.81; H, 5.05; N, 3.90. Found: C, 46.66; H, 5.05; N, 3.88.

***N*-Cyclohexyl-*N*-(2-iodophenyl)acetamide 4e.** A solution of *N*-cyclohexyl-2-iodoaniline[34] (95 mg, 0.31 mmol) in Ac_2O (5 mL) was stirred for 48 h at 85 °C. Water was added and the mixture was stirred at room temperature until only one layer was observed. The mixture was alkalinized with $Na_2CO_{3\,(s)}$ and CH_2Cl_2 was added. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2) to yield **4e** (88 mg, 81%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.76 (dd, $J =$ 3.9 and 12.3 Hz, 1H), 0.97 (tt, $J = 3.9$ and 12.3 Hz, 1H), 1.20–1.48 (m, 3H), 1.55–1.74 (m, 3H), 1.75 (s, 3H, CH_3CO), 1.96 (d, $J = 12$ Hz, 1H), 2.13 (d, $J = 12$ Hz, 1H), 4.43 (tt, $J = 3.6$ and 12 Hz, 1H, C*H*N), 7.06 (td, $J = 8.1$ and 1.5 Hz, 1H, H-4), 7.21 (dd, $J = 8.1$ and 1.5 Hz, 1H, H-6), 7.40 (td, $J = 8.1$ and 1.5 Hz, 1H, H-5), 7.94 (dd, $J = 8.1$ and 1.5 Hz, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 23.9 (*C*H_3CO), 25.5, 25.7 and 25.8 (C-3′, C-4′ and C-5′), 30.1 and 32.2 (C-2′ and C-6′), 56.1 (C-1′), 103.7 (C-2), 129.2, 129.5 and 130.3 (C-4, C-5 and C-6), 140.2 (C-3), 143.3 (C-1), 169.7 (CO).

***N*-(2-Ethylpropyl)-*N*-(2-iodophenyl)acetamide 4f.** A solution of **11c** (89 mg, 0.31 mmol) in Ac_2O (5 mL) was stirred for 48 h at 85 °C. Water was added and the mixture was stirred at room temperature until only one layer was observed. The mixture was alkalinized with $Na_2CO_{3\,(s)}$ and CH_2Cl_2 was added. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2) to yield **4f** (100 mg, 98%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.93–1.04 (m, 2H, CH_2 and CH_2'), 0.99 (t, $J = 7$ Hz, 3H, CH_3), 1.00 (t, $J = 7$ Hz, 3H, CH_3'), 1.50 (h, $J =$ 7 Hz, 1H, CH_2), 1.73–1.87 (m, 1H, CH_2'), 1.80 (s, 3H, CH_3CO), 4.49 (h, $J = 5.1$ Hz, 1H, CH), 7.04 (td, $J = 7.8$ and 1.5 Hz, 1H, H-4), 7.19 (dd, $J = 7.8$ and 1.5 Hz, 1H, H-6), 7.39 (td, $J =$ 7.8 and 1.5 Hz, 1H, H-5), 7.94 (dd, $J = 7.8$ and 1.5 Hz, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 11.1 and 11.7 (CH_3), 23.9 (CH_3CO), 24.6 and 25.9 (CH_2), 103.7 (C-2), 129.3, 129.7 and 129.9 (C-4, C-5 and C-6), 140.5 (C-3), 143.4 (C-1), 170.5 (CO).

***N*-(2-Iodophenyl)-*N*-isopropylacetamide 4g.** To a solution of *N*-isopropyl-2-iodoaniline[34] (98 mg, 0.37 mmol) and pyridine (0.1 mL, 1.16 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C was added acetyl chloride (40 μL, 0.56 mmol). The mixture was stirred for 3 h at room temperature and then water and CH_2Cl_2 were added. The aqueous phase was separated and the organic phase was washed with HCl 1N and sat. aq. $NaHCO_3$. The solution was dried, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2) to yield **4g** (107 mg, 95%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.98 (d, $J = 6.9$ Hz, 3H, CH_3), 1.27 (d, $J =$ 6.9 Hz, 3H, CH_3), 1.76 (s, 3H, CH_3CO), 4.77 (h, $J = 6.9$ Hz, 1H, -CH-), 7.07 (td, $J = 8.1$ and 1.5 Hz, 1H, H-4), 7.22 (dd, $J = 7.8$ and 1.5 Hz, 1H, H-6), 7.41 (td, $J = 7.8$ and 1.2 Hz, 1H, H-5), 7.95 (dd, $J = 8.1$ and 1.2 Hz, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 19.6 and 22.1 (CH_3), 23.9 (CH_3CO), 48.1 (CH), 103.6 (C-2), 129.3, 129.6 and 130.1 (C-4, C-5 and C-6), 140.3 (C-3), 142.9 (C-1), 169.8 (CON). IR (film) 1659 cm^{-1}.

***N*-Benzhydryl-2-iodoaniline 11a.** To a solution of 2-iodoaniline (1 g, 4.56 mmol) in CH_3CN (55 mL) was added LiI (cat.), K_2CO_3 (2.5 g, 18.1 mmol) and benzhydryl bromide (1.2 g, 4.85 mmol). The mixture was stirred at reflux temperature overnight. The solvent was evaporated under reduced pressure, and the residue was combined with CH_2Cl_2 and H_2O. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried, filtered and the solvent was removed

under reduced pressure. The crude product was purified by flash chromatography (petrol to petrol–AcOEt 95 : 5) to yield **11a** (1.7 g, 97%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.84 (bs, 1H, NH), 5.57 (s, 1H, CH), 6.43 (t, J = 7.8 Hz, 1H, H-4), 6.45 (d, J = 7.8 Hz, 1H, H-6), 7.07 (t, J = 7.8 Hz, 1H, H-5), 7.28–7.37 (m, 10H), 7.70 (d, J = 7.8 Hz, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 63.5 ($CHPh_2$), 86.2 (C-2), 112.6 (C-6), 119.5 (C-4), 127.7 (C-2′), 127.9 (C-4′), 129.3 (C-3′), 129.7 (C-5), 139.24 (C-3), 142.7 (C-1′), 146.7 (C-1). IR (film) 3387 cm^{-1}. HRMS Calcd for $C_{19}H_{16}NI$: 385.0327. Found 385.0343.

***N*-(2-Ethylpropyl)-2-iodoaniline 11c.** To a solution of 2-iodoaniline (202 mg, 0.92 mmol) and 2-pentanone (0.1 mL, 0.92 mmol) in dry MeOH (10 mL) was added decaborane (33 mg, 0.27 mmol). The solution was stirred at room temperature for 17 h. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (petrol to petrol–AcOEt 95 : 5) to yield **11c** (197 mg, 75%). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, J = 7.5 Hz, 6H, CH_3), 150–176 (m, 4H), 3.35 (q, J = 6 Hz, 1H, CH), 4.08 (bs, 1H, NH), 6.44 (ddd, J = 7.8, 7.2 and 1.5 Hz, 1H, H-4), 6.60 (d, J = 8.1 Hz, 1H, H-6), 7.23 (ddd, J = 8.1, 7.2 and 1.5 Hz, 1H, H-5), 7.71 (dd, J = 7.8 and 1.5 Hz, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 10.1 (CH_3), 26.5 (CH_2), 55.9 (CH), 85.7 (C-2), 110.9 (C-6), 117.7 (C-4), 129.2 (C-5), 139.1 (C-3), 146.9 (C-1). IR (film) 2962 cm^{-1}. HRMS Calcd for $C_{11}H_{16}NI$: 289.0327. Found 289.0322.

1-(2-Iodophenyl)-1-isopropyl-3-phenylurea 4h. 2-Iodo-*N*-isopropylaniline **11d** (1.90 g, 7.3 mmol) was dissolved in toluene (20 cm^3) and phenyl isocyanate (0.80 cm^3, 8.0 mmol) was added dropwise. The mixture was heated to reflux and maintained at this temperature for 18 h. The solvent was evaporated under reduced pressure and the residue purified by flash silica chromatography (SiO_2; 5% to 50% EtOAc in petrol) to give 1-(2-iodophenyl)-1-isopropyl-3-phenylurea **4h** (1.37 g, 49% + 20% RSM) as white blocks, mp 82–84 °C; R_f (EtOAc–petrol, 3 : 10) 0.42; ν_{max} (film)/cm^{-1} 3428 and 3339 (NH), 2979 and 2936 (CH_3), 2881 (CH) and 1670 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.04 (1 H, dd, J 8.0 and 1.5, CH-f), 7.50 (1 H, td, J 8.0 and 1.5, CH-d), 7.39 (1 H, dd, J 8.0 and 1.5, CH-c), 7.33–7.21 (4 H, m, CH-g and CH-h), 7.17 (1 H, td, J 8.0 and 1.5, CH-e), 7.03 (1 H, tt, J 7.0 and 1.2, CH-i), 5.79 (1 H, br. s, NH), 4.83 (1 H, sept, J 6.3, CH-a), 1.39 [3 H, d, J 6.3, $(CH\text{-}b)_A$] and 1.08 [3 H, d, J 6.3, $(CH\text{-}b)_B$]; ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 153.6 (C=O), 141.3 (C), 141.2 (CH), 139.0 (C), 131.5 (CH), 130.6 (CH), 130.3 (CH), 129.0 (CH), 123.5 (CH), 120.5 (CH), 104.6 (C), 49.1 (CH), 23.3 (CH_3) and 20.4 (CH_3); *m*/*z* (CI) 381 (40%, M + H$^+$) and 253 (40, M + H$^+$–I); (Found: M + H$^+$, 381.0459, $C_{16}H_{18}N_2OI$ requires M + H, 381.0458).

(*S*)-*N*-(2-Acetoxypropanoyl)-*N*-isopropyl-2-iodoaniline (*M*)-4i and (*P*)-4i. A stirred solution of *N*-isopropyl-2-iodoaniline **11d** (198, 0.76 mol), and pyridine (150 μL, 1.74 mol) in dry CH_2Cl_2 was cooled at 0 °C, and (*S*)-(−)-2-acetoxypropionylchloride (150 μL, 1.15 mmol) was added under an atmosphere of N_2. The mixture was stirred for 4 h at room temperature. Water was added and the organic phase was separated, washed with HCl 1N, $NaHCO_3$ and brine, dried, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2 to CH_2Cl_2–MeOH 2%) to yield (*P*)-**4i** (51 mg, 18%), a mixture of (*P*)-**4i** and (*M*)-**4i** (1 : 1) (107 mg) and (*M*)-**4i** (94 mg, 33%). A solution of each diastereomer was warmed at 85 °C and these were converted to the thermodynamic mixture (5.25 : 1). This thermodynamic mixture was stored at room temperature for several days and it was transformed totally to (*P*)-**4i** (89% total yield). (*P*)-**4i**: mp 149–150 °C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.09 (d, J = 6.6 Hz, 3H, CH_3), 1.37 (d, J = 6.6 Hz, 3H, CH_3), 1.40 (d, J = 6.6 Hz, 3H, CH_3), 1.99 (s, 3H, CH_3CO), 4.5 (qn, J = 6.6 Hz, 1H, C*H*(CH_3)$_2$), 4.67 (q, J = 6.6 Hz, 1H, C**H*CO), 7.09 (td, J = 7.8 and 1.8 Hz, 1H, H-4), 7.41 (td, J = 7.8 and 1.2 Hz, 1H, H-5), 7.47 (dd, J = 7.8 and 1.8 Hz, 1H, H-6), 7.96 (dd, J = 7.8 and 1.2, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 16.9 (*C*H3CHCO), 19.2, 20.7 and 21.5 (CH_3), 50.7 (CHN), 68.8 (CH3*C*HCO), 102.7 (C-2), 129.1, 130.0 and 131.4 (C4-, C-5 and C-6), 140.4 (C-3), 141.9 (C-1), 169.8 and 170.0 (CO). IR (film) 1724, 1654 cm^{-1}. Anal. Calcd for $C_{14}H_{18}INO_3$: C, 44.82; H, 4.84; N, 3.73. Found: C, 44.72; H, 4.90; N, 3.68. $[\alpha^{25}_D] = +35.3$ (c = 0.7, MeOH).

(*M*)-**4i**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.02 (d, J = 6.6 Hz, 3H, CH_3), 1.23 (d, J = 6.6 Hz, 3H, CH_3), 1.32 (d, J = 6.6 Hz, 3H, CH_3), 2.08 (s, 3H, CH_3CO), 4.73 (qn, J = 6.6 Hz, 1H, C*H*(CH_3)$_2$), 4.94 (q, J = 6.6 Hz, 1H, C**H*CO), 7.11 (t, J = 7.8 Hz, 1H, H-4), 7.21 (dd, J = 7.8 and 1.5 Hz, 1H, H-6), 7.43 (t, J = 7.8 Hz, 1H, H-5), 7.98 (d, J = 7.8, 1H, H-3). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ 17.6 (*C*H3CHCO), 19.2, 21.4 and 21.9 (CH_3), 49.3 (CHN), 68.3 (CH3*C*HCO), 103.3 (C-2), 129.0, 130.0 and 131.2 (C4-, C-5 and C-6), 140.6 (C-3), 141.0 (C-1), 169.2 and 169.7 (CO).

1-(2-Fluorophenyl)-3-phenylurea 12a. Phenyl isocyanate (5.36 g, 4.92 ml, 45.0 mmol) was dissolved in DCM (100 ml) at room temperature and 2-fluoroaniline **10a** (5.00 g, 4.34 ml, 1 eq) was added. After 1 h a white solid began to settle out. After stirring for 1 d, the white precipitate was filtered and washed with cold CH_2Cl_2 (250 ml). Drying under high vacuum gave 8.59 g (37.3 mmol, 82.9%) of the desired product, mp 176–177 °C. ^{1}H NMR (300 MHz, DMSO) δ 9.09 (s, 1H, N–H_F), 8.57 (s, 1H, N–H), 8.19 (dt, ^3J = 8.3 Hz, ^4J = 1.6 Hz, 1H, H_5), 7.48 (d, ^3J = 7.5 Hz, 2H, H_{11}, H_{15}), 7.32 (t, ^3J = 7.6 Hz, 2H, H_{12}, H_{14}), 7.24 (m_c, 1H, H_4), 7.16 (t, ^3J = 7.7 Hz, 1H, H_{13}), 7.02 (m_c, 2H, H_3, H_5). ^{13}C NMR (75 MHz, DMSO) δ 115.7 (d, 19.0 Hz), 118.81 (C_{11}, C_{15}), 121.20, 122.78, 123.1 (d, 7.5 Hz), 125.21, 125.26, 128.3 (d, 10.3 Hz), 129.6 (C_{12}, C_{14}), (N–Ar), (N–ArF), (C–F), (C=O): 140.16, 152.90, 154.28, 151.09. IR (film) 3279, 1644 cm^{-1}.

1-(2-Chlorophenyl)-3-phenylurea 12b. Phenyl isocyanate (3.20 g, 2.94 ml, 26.9 mmol) was dissolved in DCM (100 ml) at room temperature and 2-chloroaniline **10b** (3.43 g, 2.83 ml, 1 eq) was added in one portion. After 3 h a white solid settled out. The precipitate was filtered and washed with cold CH_2Cl_2 (200 ml). Drying under high vacuum afforded 4.70 g (19.0 mmol, 70.9%), mp180–182 °C. ^{1}H NMR (300 MHz, DMSO) δ 7.03 (m_c, 2H, Ar–H), 7.32 (m_c, 3H, Ar–H), 7.49 (m_c, 3H, Ar–H), 8.20 (dd, ^3J = 8.3 Hz, ^4J = 1.6 Hz, 1H, H_6), 8.34 (s, 1H, N–H), 9.44 (s, 1H, N–H_{Cl}). ^{13}C NMR (75 MHz, DMSO) δ 118.91 (C_{11}, C_{15}), 121.99 (C_6), 122.60 (Cl–Ar), 122.84 (C_{13}), 123.96 (C_4), 128.29 (C_5), 129.62 (C_{12}, C_{14}), 129.92 (C_3), 136.72 (N–ArCl), 140.18 (N–Ar), 152.85 (C=O). IR (film) 3279, 1644 cm^{-1}.

1-(2-Bromophenyl)-3-phenylurea 12c. Phenyl isocyanate (2.08 g, 1.91 ml, 17.4 mmol) was dissolved in DCM (100 ml) at room temperature and 2-bromoaniline **10c** (3.00 g, 1 eq) was added in one portion. After stirring for 4 days the reaction mixture was filtered and a white solid isolated. Washing with cold CH_2Cl_2 (200 ml) and drying under high vacuum afforded 3.56 g (12.2 mmol, 70.3%), mp 189–190 °C. ^{1}H NMR (300 MHz, DMSO) δ 7.00 (m_c, 2H, H_3, H_{13}), 7.34 (m_c, 3H, H_5, H_{12}, H_{14}), 7.50 (m_c, 2H, H_{11}, H_{15}), 7.63 (dd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, 1H, H_3), 8.10 (dd, ^3J = 8.3 Hz, ^4J = 1.6 Hz, 1H, H_6), 8.16 (s, 1H, N–H), 9.48 (s, 1H, N–H_{Br}). ^{13}C NMR (75 MHz, DMSO) δ 113.72 (C–Br), 118.92 (C_{11}, C_{15}), 122.83 (C_6), 122.92 (C_{13}), 124.75 (C_4), 128.79 (C_5), 129.61 (C_{12}, C_{14}), 133.20 (C_3), 137.81 (N–Ar), 140.21 (N–Ar_{Br}), 152.89 (C=O). IR (film) 3279, 1645 cm^{-1}.

1-(2-Iodophenyl)-3-phenylurea 12d. 2-Iodoaniline **10d** (1.63 g, 1.50 ml, 13.7 mmol) was added in one portion to a solution of phenyl isocyanate in CH_2Cl_2 (100 ml). After 72 h a brownish precipitate had been formed. The settlings were filtered and washed with cold CH_2Cl_2 (200 ml). Drying under high vacuum afforded 3.76g (11.1 mmol, 81.2%) of the desired product as a white brownish solid, mp 200–201 °C. ^{1}H NMR (300 MHz, DMSO) δ 6.86 (t, ^3J = 7.4 Hz, 1H, H_4), 7.00 (t, ^3J = 7.3 Hz, 1H,

H_{13}), 7.34 (m_c, 3H, H_5, H_{12}, H_{14}); H_3, H_6, (H_{11}, H_{15}): 7.50 (d, ^3J = 7.9 Hz, 2H), 7.86 (d, ^3J = 8.0 Hz, 2H); 7.91 (s, 1H, N–H), 9.45 (s, 1 H, N–H_1). ^{13}C NMR (75 MHz, DMSO) δ 92.08 (C–I), 118.90 (C_{11}, C_{15}), (C_6), (C_{13}): 122.73, 123.80, 125.77 (C_4), 129.30 (C_5), 129.59 (C_{12}, C_{14}), 139.66 (C_3), (Ar–N), (Ar–N_1): 140.34, 140.57; 153.10 (C = O). IR (film) 3279, 1646 cm^{-1}.

1-(2-Methylphenyl)-3-phenylurea 12e. Phenyl isocyanate (3.20 g, 2.94 ml, 26.9 mmol) was dissolved in DCM (100 ml) at room temperature and *o*-toluidine **10e** (2.88 g, 2.91 ml, 1 eq) was added in one portion. After 5 min, a white solid began to settle out. After stirring for 12 h, the white precipitate was filtered and washed with cold CH_2Cl_2 (250 ml). Drying under high vacuum afforded 5.81 g (25.7 mmol, 95.5%) of the desired product as a white solid, mp 201–202 °C. ^{1}H NMR (300 MHz, DMSO) δ 2.27 (s, 3H, CH_3); (H_4), (H_{13}), (H_3, H_5): 6.97 (m_c, 2H), 7.17 (m_c, 2H); 7.31 (m_c, 2H, H_{12}, H_{14}), 7.50 (d, ^3J = 7.5 Hz, 2H, H_{11}, H_{15}), 7.88 (d, ^3J = 8.1 Hz, 1H, H_6); (N–H_{Me}), (N–H): 7.94 (s, 1 H), 9.04 (s, 1 H). ^{13}C NMR (75 MHz, DMSO) δ 18.63 (CH_3), 118.71 (C_{11}, C_{15}), 121.72 (C_6), (C_{13}) (C_4): 122.41, 123.36; 126.88 (C_5), 128.17 (C–Me), 129.55 (C_{12}, C_{14}), 130.90 (C_3); (C–N), (C–N_{Me}): 138.14, 140.62; 153.38 (C=O). IR (film) 3276, 1636 cm^{-1}.

1-(2-Ethylphenyl)-3-phenylurea 12f. Phenyl isocyanate (3.20 g, 2.94 ml, 26.9 mmol) was dissolved in DCM (100 ml) at room temperature and 2-ethylaniline **10f** (3.26 g, 3.33 ml, 1 eq) was added in one portion. After stirring for 18 h, the white precipitate was filtered and washed with cold CH_2Cl_2 (250 ml). Drying under high vacuum afforded 6.09 g (25.5 mmol, 94.3%) of the desired product as a white solid. ^{1}H NMR (300 MHz, DMSO) δ 1.20 (t, ^3J = 7.5 Hz, 3H, CH_3), 2.63 (q, ^3J = 7.5 Hz, 2H, CH_2); (H_{13}), (H_4),(H_3, H_5): 7.0 (m_c, 2H), 7.18 (m_c, 2H); 7.30 (m_c, 2H, H_{12}, H_{14}), 7.49 (m_c, 2H, H_{11}, H_{15}), 7.82 (dd, ^3J = 7.9 Hz, ^4J = 1.2 Hz, 1H, H_6), (N–H), (N–H_{Et}): 7.92 (s, 1H), 9.03 (s, 1H). ^{13}C NMR (75 MHz, DMSO) δ 15.02 (-CH_3), 24.52 (CH_2), 118.68 (C_{11}, C_{15}), 122.39 (C_6), 122.77 (C_4 or C_{13}), 123.88 (C_{13} or C_4), 126.77 (C_5), 129.13 (C_3), 129.55 (C_{12}, C_{14}), 134.45 (C–Et); (C–N), (C–N_{Et}): 137.25, 140.65; 153.58 (C=O).

1-(2-Isopropylphenyl)-3-phenylurea 12g. Phenyl isocyanate (2.50 g, 2.29 ml, 21.0 mmol) was dissolved in DCM (100 ml) at room temperature and 2-isopropyl aniline **10g** (2.84 g, 2.97 ml, 1 eq) was added in one portion. After stirring for 18 h, the white precipitate was filtered and washed with cold CH_2Cl_2 (200 ml). Drying under high vacuum afforded 3.48 g (13.7 mmol, 65.2%) of the desired product as a white solid, mp 166–168 °C. ^{1}H NMR (300 MHz, DMSO) δ 1.22 (d, ^3J = 6.8 Hz, 6H, 2 × CH_3), 3.18 (sept, ^3J = 6.8 Hz, 1H, H_{iso}), 6.98 (m_c, 1H, H_4), 7.13 (m_c, 2H, H_{13}, H_5), 7.30 (m_c, 3H, H_{12}, H_{14}, H_3), 7.49 (m_c, 2H, H_{11}, H_{15}), 7.70 (dd, ^3J = 7.9 Hz, ^4J = 1.4 Hz, 1H, H_6). ^{13}C NMR (75 MHz, DMSO) δ 23.86 (2 × isoCH$_3$), 27.53 (CH_{iso}), 118.66 (C_{11}, C_{15}), 122.33 (C_6), (C_4) (C_{13}): 124.27, 125.96; 126.45 (C_5), 129.53 (C_{12}, C_{14}), 136.23 (C_3); (Ar–N), (Ar–$N_{isoprop}$): 140.11, 140.73; 153.86 (C=O). IR (film) 3272, 1640 cm^{-1}.

1-(2-*tert*-Butylphenyl)-3-phenylurea 12h. Phenyl isocyanate (2.38 g, 2.18 ml, 20.0 mmol) was dissolved in DCM (100 ml) at room temperature and 2-*tert*-butyl-aniline **10h** (2.98 g, 3.12 ml, 1 eq) was added in one portion. After stirring for 18 h, the white precipitate was filtered and washed with cold CH_2Cl_2 (200 ml). Drying under high vacuum afforded 4.82 g (17.9 mmol, 89.9%) of the desired product as a white solid, mp = 214–215 °C. ^{1}H NMR (300 MHz, DMSO) δ 6.96 (m_c, 1H, H_4), 7.12–7.34 (m, 5H, H_3, H_5, H_{12}, H_{13}, H_{14}), 7.39 (dd, ^3J = 7.7 Hz, ^4J = 1.8 Hz, 1H, H_6), 7.49 (m_c, 2H, H_{11}, H_{15}). ^{13}C NMR (75 MHz, DMSO) δ 31.23 (3 × CH_3), 35.25 (C_{tBu}), 118.57 (C_{11}, C_{15}), 122.19 (C_6); (C_4) (C_{13}): 126.16, 126.83; 126.90 (C_3), 129.50 (C_{12}, C_{14}), 130.86 (C_5), 136.67 (Ar–^{t}Bu), 140.97 (C–N), 144.96 (C–N_{tBu}), 152.24 (C=O). IR (film) 3280, 1640 cm^{-1}.

1-Benzyl-1-(2-fluorophenyl)-3-phenylurea 5a. A mixture of the urea **12a** (266 mg, 1.16 mmol) and sodium hydroxide (55.6 mg, 1.39 mmol, 1.2 eq) was dissolved in THF (5 ml, dry) and was stirring for 0.5 h before addition of benzyl bromide (198 mg, 0.14 ml, 1.16 mmol, 1.0 eq). After stirring for 42 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. Evaporation and drying under high vacuum gave 320 mg (crude yield) of a highly viscous oil. The crude product was purified by column chromatography using a mixture of petrol–ethyl acetate (10 : 1). The desired product was obtained as a white solid (209 mg, 56.3%), mp 108–109 °C, R_f (4 : 1 petrol (40/60)–EtOAc) = 0.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 (s, 2H, Ph–CH_AH, Ph–CHH_B), 6.19 (s, 1H, N–H), 7.06 (m_c, 1H, Ar–H), 7.16 (m_c, 2H, Ar–H), 7.32 (m_c, 11H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.65 (Ph–CH_2), 117.77 (d, J = 19.8), 117.77 (C_3), 120.04 (C_{11}, C_{15}), 123.58 (C_6), 125.56 (d, J = 4.0 Hz), 125.57 (C_5), 127.73 (C_{13}), 128.66 (C_{18}, C_{22}), 128.93 (C_{19}, C_{21}), 129.12 (C_{12}, C_{14}), 130.57 (d, J = 7.8 Hz), 130.58 (C_4), 131.50 (C_{20}); (C_{17}), (Ar–N_F), (C=O), (N–Ar), (C–F): 137.87, 138.80, 154.47, 157.26, 160.61. *m/z* (CI) 321 (100%, M + H$^+$), 202 (40%, (C_6H_5F)NH_2^+(C_7H_7)), 91 (57%, $C_7H_7^+$); *m/z* (EI) 201 (10%, (C_6H_5F)NH_2^+(C_7H_7)), 91 (100%, $C_7H_7^+$). (Found: MH$^+$, 321.1395. $C_{20}H_{18}O_1N_2F_1$ requires MH, 321.1398). IR (film): ν/cm^{-1} = 3300 (m) (N–H), 3058 (w) (Ar–H), 1659 (s) (C=O), 1597 (m), 1531 (s), 1500 (s), 1455 (w), 1442 (s).

1-Benzyl-1-(2-chlorophenyl)-3-phenylurea 5b. A mixture of the urea **12b** (250 mg, 1.01 mmol) and sodium hydroxide (48.7 mg, 1.22 mmol, 1.2 eq) was dissolved in THF (7 ml, dry) and was stirring for 0.5 h before addition of benzyl bromide (174 mg, 0.12 ml, 1.01 mmol, 1.0 eq). After stirring for 21 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. After evaporation of Et_2O and drying under high vacuum the crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as white crystals (143 mg, 0.43 mmol, 42%), mp 115–116 °C, R_f (4 : 1 petrol (40/60)–EtOAc) = 0.38. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (s, 1H, PhCH_AH), 5.56 (s, 1H, PhCHH_B), 6.03 (s, 1H, N–H), 7.07 (dd, ^3J = 7.7 Hz, ^4J = 0.9 Hz, 2H, H_{18}, H_{22}), 7.25–7.45 (m, 12H, Ar–H), 7.61 (m_c, 1H, H_6).

^{13}C NMR (75 MHz, $CDCl_3$) δ 52.18 (CH_2–Ph), 120.34 (C_{11}, C_{15}), 123.71 (C_6), 127.80 (C_{13}), 128.56 (C_4), 128.68 (C_{18}, C_{22}), 129.12 (C_{19}, C_{21}), 129.31 (C_{12}, C_{14}), 130.37 (C_{20}), 131.57 (C_5), 132.14 (C_3), 134.47 (Ar–Cl), 137.83 (N–Ar), 138.03 (C–CH_2), 138.78 (N–ArCl), 154.48 (C=O). *m/z* (CI) 337 (100%, M + H$^+$), 247 (25%, M + H$^+$-benzyl), 182 (21%, (C_6H_5)CH_2–NH^+–(C_6H_4)), 91 (18%,$C_7H_7^+$); *m/z* (EI) 336 (9%, M$^+$), 301 (19%, M$^+$–Cl), 91 (100%, $C_7H_7^+$). (Found: MH$^+$, 337.1103. $C_{20}H_{18}O_1N_2Cl_1$ requires MH, 337.1102). IR (film): ν/cm^{-1} = (N–H): 3425 (w), 3335 (w); (Ar–H): 3062 (w), 3031 (w); (alkyl C–H): 2925 (w), 2854 (w); (C=O) 1679 (s); 1523, 1441, 1313 (m), 1240 (m), 752 (m), 731 (m), 699 (m).

1-Benzyl-1-(2-bromophenyl)-3-phenylurea 5c. A mixture of the urea **12c** (350 mg, 1.21 mmol) and sodium hydroxide (57.9 mg, 1.45 mmol, 1.2 eq) was dissolved in THF (7 ml, dry) and was stirring for 0.5 h before addition of benzyl bromide (207 mg, 0.14 ml, 1.21 mmol, 1.0 eq). After stirring for 15 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. After evaporation of Et_2O and drying under high vacuum the crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as white crystals (179 mg, 0.47 mmol, 39%), mp 116–118 °C, R_f (4 : 1 petrol (40/60)–EtOAc) = 0.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, 15.0 Hz, 1H, Ph–CH_AH), 5.60 (d, 15.0 Hz, 1H, Ph–CHH_B), 5.95 (s, 1H, NH), 7.0–7.1 (m, 3H, Ar–H), 7.2–7.4 (m, 10H, Ar–H), 7.78–7.81 (m, 1H, H_6). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.13 (Ph–CH_2), 120.24 (C_{11}, C_{15}), 123.61

(C–Br), 128.67 (C_{18}, C_{22}), 129.09 (C_{19}, C_{21}), 129.19 (C_{20}), 129.42 (C_{12}, C_{14}); (C_{13}), (C_6), (C_4), (C_5), (C_3): 127.78, 129.49, 130.55, 132.35, 134.79; (C_{17}), (N–Ar), (N–ArBr): 137.86, 138.84, 139.53; 154.21 (C=O). *m/z* (CI) 383 (63%, ^{81}Br, M + H$^+$), 381 (54%, ^{79}Br, M + H$^+$), 301 (45%,M$^+$–Br), 91 (100%, $C_7H_7^+$); *m/z* (EI) 301 (17%, M$^+$–Br), 91 (100%, $C_7H_7^+$). (Found: MH$^+$, 381.0597. $C_{20}H_{18}O_1N_2Br_1$ requires MH, 381.0597). IR (film): ν/cm^{-1} = (N–H): 3424 (w), 3332 (w); (Ar–H): 3061 (w), 3029 (w); (C–H alkyl): 2959 (w), 2928 (w); 1678 (s) (C=O), 1595 (m), 1523 (s), 1499 (m), 1473 (m), 1441 (s).

1-Benzyl-1-(2-iodophenyl)-3-phenylurea 5d. A mixture of the urea **12d** (300 mg, 0.89 mmol) and sodium hydroxide (43.4 mg, 1.07 mmol, 1.2 eq) was dissolved in THF (7 ml, dry) and was stirring for 0.5 h before addition of benzyl bromide (152 mg, 0.11 ml, 0.89 mmol, 1.0 eq). After stirring for 18 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. Evaporation and drying under high vacuum gave a highly viscous yellowish oil. The crude product was purified by column chromatography using a mixture of toluene–ethyl acetate (20 : 1). The desired product was obtained as a white solid (158 mg, 0.37 mmol, 41.5%), mp 120–122 °C, R_f (10 : 1 petrol (40/60)–EtOAc) = 0.66). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (d, ^2J = 14.7 Hz, 1H, PhCH$_A$H), 5.63 (d, ^2J = 14.7 Hz, 1H, PhCHH$_B$), 5.90 (s, 1H, N–H), 6.96 (dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1H, H_6), 7.15 (m_c, 2H, Ar–H, 7.25 (m_c, 9H, Ar–H), 8.05 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, H_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.25 (Ph–CH_2), 101.46 (I–Ar); (C_6), (C_{13}), (C_4), (C_{20}), (C_5): 123.61, 127.8, 130.10, 130.65, 131.79; 120.30 (C_{11}, C_{15}); (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.69, 129.09, 129.58; (C_{17}), (N–Ar), (C_3), (N–ArI): 137.88, 138.89, 141.15, 142.83; 153.95 (C=O). *m/z* (CI) 429 (10%, M + H$^+$), 303 (100%, M + H$^+$–I). *m/z* (EI) 91 (100%, $C_7H_7^+$). (Found: MH$^+$, 429.0456. $C_{20}H_{18}O_1N_2I_1$ requires MH, 429.0458). IR (film): ν/cm^{-1} = (N–H): 3422 (m), 3321 (m); (Ar–H): 3059 (m), 3029 (m); 2927 (w) (C–H alkyl), 1676 (C=O), 1595 (s), 1523 (s), 1494 (s), 1441 (s).

1-Benzyl-1-(2-methylphenyl)-3-phenylurea 5e. A mixture of the urea **12e** (500 mg, 2.21 mmol) and sodium hydroxide (106 mg, 2.65 mmol, 1.2 eq) was dissolved in THF (8 ml, dry) and was stirring for 0.5 h before addition of benzyl bromide (378 mg, 0.26 ml, 2.21 mmol, 1.0 eq). After stirring for 60 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. Evaporation and drying under high vacuum gave 698 mg (crude yield) of a highly viscous oil. The crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as a white solid (307 mg, 1.0 mmol, 44.0%), mp 72–74 °C, R_f (4 : 1 petrol (40/60)–EtOAc) = 0.37. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H, Ar–CH_3), 4.53 (d, ^2J = 14.5 Hz, 1H, Ph–CH$_A$H), 5.27 (d, ^2J = 14.3 Hz, 1H, Ph–CHH$_B$), 6.07 (s, 1H, N–H), 7.03 (d, ^3J = 7.4 Hz, 1H, H_3), 7.3 (m_c, 13H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.76 (Ar–CH_3), 52.58 (Ph–CH_2), 119.75 (C_{11}, C_{15}); (C_6), (C_4), (C_{13}), (C_5), (C_{20}), (C_3): 123.27, 127.72, 127.97, 129.19, 130.13, 132.23; (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.63,129.10, 129.49, (C–Me), (N–ArMe), (N–Ar), (C–CH_2): 137.66, 138.22, 139.15, 139.39; 154.60 (C=O). *m/z* (CI) 317 (100%, M + H$^+$), 91 (18%, ($C_7H_7^+$)); *m/z* (EI) 316 (5%, M$^+$), 91 (100%, ($C_7H_7^+$)). (Found: MH$^+$, 317.1651. $C_{21}H_{21}O_1N_2$ requires MH, 317.1648). IR (film): ν/cm^{-1} = (N–H): 3419 (m), 3328 (m); (Ar–H): 3061 (m), 3029 (m); (alkyl–H): 2924 (m); (C=O) 1677 (s); 1594 (s), 1522 (s), 1441 (s), 1357 (s), 1311 (s), 1243 (s), 1212 (s), 753 (s), 728 (s), 700 (s).

1-Benzyl-1-(2-ethylphenyl)-3-phenylurea 5f. A mixture of the urea **12f** (500 mg, 2.08 mmol) and sodium hydroxide (100 mg, 2.50 mmol, 1.2 eq) was dissolved in THF (8 ml, dry) and was stirring for 0.5 h before addition of benzyl bromide (356 mg, 0.25 ml, 2.08 mmol, 1.0 eq). After stirring for 7 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. Evaporation and drying under high vacuum gave 0.64 g (crude yield) of a highly viscous oil. The crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as a white solid (224 mg, 0.68 mmol, 32.6%), mp 58–60 °C, R_f (4 : 1 petrol (40/60)–EtOAc) = 0.27. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, ^3J = 7.6 Hz, 3H, CH_{3Et}), 2.56 (m_c, 2H, CH_{2Et}), 4.44 (d, ^2J = 14.4 Hz, Ph–CH$_A$H), 5.33 (d, ^2J = 14.4 Hz, Ph–CHH$_B$), 6.04 (s, 1H, N–H), 7.01 (m_c, 2H, H_4?, H_{13}?), 7.26 (m_c, 10H, Ar–H), 7.35 (m_c, 2H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.64 (CH_{3Et}), 23.56 (CH_{2Et}), 53.00 (Ph–CH_2), 119.70 (C_{11}, C_{15}); (C_4), (C_6), (C_{13}), (C_5), (C_{20}), (C_3): 123.24, 127.69, 127.73, 129.42, 130.22, 130.34; (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.62, 129.09, 129.49; (C_2), (N–ArEt), (N–Ar), (C_{17}): 138.21, 138.71, 139.06, 143.32; 154.83 (C=O). *m/z* (CI) 331 (100%, M + H$^+$), 241 (23%, M + H$^+$–($C_7H_7^+$) + H$^+$), 91 (60%, ($C_7H_7^+$)); *m/z* (EI) 91 (100%, ($C_7H_7^+$)). (Found: MH$^+$, 331.1807.$C_{22}H_{23}O_1N_2$ requires MH, 331.1805). IR (film): ν/cm^{-1} = 3419 (w) (N–H); (Ar–H): 3061 (w), 3030 (w); (alkyl C–H); 2970 (w), 2932 (w), 2875 (w); 1677 (s) (C=O), 1594 (m), 1521 (s), 1501 (m), 1440(s).

1-Benzyl-1-(2-isopropylphenyl)-3-phenylurea 5g. A mixture of the urea **12g** (500 mg, 1.97 mmol) and sodium hydroxide (94.5 mg, 2.36 mmol, 1.2 eq) was dissolved in THF (8 ml, dry) and was stirring for 0.5 h before addition of benzyl bromide (404 mg, 0.28 ml, 1.16 mmol, 1.0 eq). After stirring for 18.5 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. Evaporation and drying under high vacuum gave 669 mg (crude yield) of a highly viscous oil. The crude product was purified by column chromatography using a mixture of petrol ether–diethyl ether (10 : 1). The desired product was obtained as a white solid (407 mg, 1.18 mmol, 60.0%), mp 92–94 °C, R_f (4 : 1 petrol (40/60)–Et_2O) = 0.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, ^3J = 6.9 Hz, CH_{3isoA}) 1.20 (d, ^3J = Hz, CH_{3isoB}), 3.13 (sept, ^3J = 6.8 Hz, 1H, CH_{iso}), 4.54 (d, ^2J = 14.3 Hz, Ph–CH$_A$H), 5.28 (d, ^2J = 14.3 Hz, Ph–CHH$_B$), 6.04 (s, 1H, N–H), 7.02 (m_c, 2H, H_4, H_{13}), 7.27 (m_c, 10H, Ar–H), 7.43 (m_c, 2H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.04 (CH_{3isoA}), 24.51 (CH_{3isoB}), 53.41 (Ph–CH_2), 119.62 (C_{11}, C_{15}); (C_6), (C_4), (C_{13}), (C_5), (C_3), (C_{20}): 123.24, 127.60, 127.74, 128.15, 129.72, 130.06; (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.66, 129.12, 129.58; (C–$N_{isoprop}$), (C–N), (C_2), (C_{17}): 137.71, 138.18, 139.04, 148.33; 155.01 (C=O). *m/z* (CI) 345 (100%, M + H$^+$), 91 (8%, ($C_7H_7^+$)). *m/z* (EI) 91 (100%, ($C_7H_7^+$)). (Found: MH$^+$, 345.1967. $C_{23}H_{25}O_1N_2$ requires MH, 345.1961). IR (film): ν/cm^{-1} = 3420 (w) (N–H), (Ar–H): 3061 (w), 3029 (w); (C–H alkyl): 2963 (w), 2926 (w), 2867 (w); 1677 (s) (C=O); 1594 (m), 1522 (s), 1500 (m), 1488 (m), 1440 (s).

1-Benzyl-1-(2-*tert*-butylphenyl)-3-phenylurea 5h. A mixture of the urea **12h** (500 mg, 1.87 mmol) and sodium hydroxide (89.5 mg, 2.24 mmol, 1.2 eq) was dissolved in THF (8 ml, dry) and the solution was stirring for 0.5 h before addition of benzyl bromide (319 mg, 0.22 ml, 1.87 mmol, 1.0 eq). After stirring for 18 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (5 × 10 ml) and the combined organic phases were dried over Na_2SO_4. Evaporation and drying under high vacuum gave 584 mg (crude yield) of a highly viscous oil and a waxy solid. The crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as a white solid (388 mg, 1.1 mmol, 58.0%), mp 120–122 °C, R_f (4 : 1 petrol (40/60)–EtOAc) = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H, 3 × CH_3), 3.89 (d, ^2J = 14.4 Hz, 1H, Ph–CH$_A$H), (d, ^2J = 14.4 Hz, 1H, Ph–CHH$_B$), 6.01 (s, 1H, N–H), 6.65 (dd, ^3J = 7.9 Hz, ^4J = 1.5 Hz, 1H, H_3), 7.04 (m_c, 1H), 7.13 (dt, ^3J = 7.5 Hz, ^4J = 1.6 Hz, 1H, H_4 or H_5 or H_{13} or H_{20}), 7.34 (m_c,

9H, Ar–H), 7.68 (dd, $^3J = 8.2$ Hz, $^4J = 1.5$ Hz, 1H, H_6?). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.36 (3 × CH_3), 36.59 (C_{tert}), 54.32 (Ph–CH_2), 119.70 (C_{11}, C_{15}); (C_6), (C_4), (C_{13}), (C_3), (C_5), (C_{20}): 123.26, 127.60, 127.78, 129.54, 130.58, 133.00; (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.63, 129.10, 130.02; (N–Ar^{t}Bu), (C_2), (N–Ar), (C_{17}): 138.16, 138.34, 138.98, 148.65; 155.16 (C=O). *m/z* (CI) 360 (100%, M + H^+), 301 (57%, (M–^{t}Bu)$^+$); *m/z* (EI) 301 (21%, (M–^{t}Bu)$^+$), 182 (47%, (C_7H_7)–NH^+–(C_6H_5)), 91 (100%, (C_7H_7)$^+$). (Found: MH^+, 359.2118. $C_{24}H_{27}O_1N_2$ requires MH, 359.2118). IR (film): ν/cm^{-1} = 3421 (w) (N–H), (Ar–H): 3061 (w), 3030 (w); 2962 (w) (C–H alkyl), 1678 (C=O), (C=C): 1594 (m), 1521 (s), 1500 (m), 1486 (m), 1440 (s).

1-Benzyl-1-(2-fluorophenyl)-3-methyl-3-phenylurea 6a. A mixture of the urea **5a** (dry) (99.5 mg, 0.31 mmol) and sodium hydride (62.2 mg, 1.55 mmol, 5 eq) was dissolved in DMF (5 ml, dry). Iodomethane (221 mg, 0.10 ml, 1.55 mmol, 5 eq) was added and after stirring for 18 h the excess of NaH and MeI was quenched with H_2O (3 ml). After washing the aqueous phase with Et_2O (5 × 10 ml), the combined Et_2O phases were dried over Na_2SO_4 and evaporated under high vacuum. The crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as a white solid (102 mg, 0.305 mmol, 98%), mp 80–82 °C, R_f (4 : 1 petrol (40/60)–EtOAc) = 0.34. ^1H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H, N–Me), 4.80 (s, 2H, Ph–CH_AH_B), 6.60 (dt, $^3J = 7.6$ Hz, $^4J = 1.9$ Hz, 1H, H_4 or H_5 or H_{13} or H_{20}), 6.73 (m_c, 2H, Ar–H), 6.82 (m_c, 2H, Ar–H), 6.94 (m_c, 2H, Ar–H), 7.07 (m_c, 2H, Ar–H), 7.30 (m_c, 5H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.96 (N–Me), 54.37 (Ph–CH_2); (C_2), (C_3), (C_6), (C_{13}), (C_5), (C_4), (C_{20}), 116.0 (d, $J = 20.4$ Hz), 124.07 (d, $J = 3.8$ Hz), 125.38, 127.50 (d, $J = 3.0$ Hz), 127.62, 129.88 (d, $J = 1.4$ Hz); 125.93 (C_{11}, C_{15}); (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.42, 128.96, 129.18; (N–Ar), (C_{17}), (C–NArF), (C=O), (C–F): 138.20, 145.48, 156.32, 159.63, 160.92. *m/z* (CI) 335 (100%, M + H^+), 91 (30%, (C_7H_7)$^+$); *m/z* (EI) 91 (100%, (C_7H_7)$^+$). (Found: MH^+,335.1556. $C_{21}H_{20}O_1N_2F_1$ requires MH, 335.1554). IR (film): ν/cm^{-1} = (Ar–H): 3063 (w), 3031 (w); 2935 (w) (C–H alkyl), 1660 (s) (C=O), 1596 (s), 1585 (m), 1499 (s), 1456 (m), 1436 (m), 1421 (m).

1-Benzyl-1-(2-chlorophenyl)-3-methyl-3-phenylurea 6b. A mixture of the urea **5b** (138 mg, 0.41 mmol) and sodium hydroxide (19.7 mg, 0.49 mmol, 1.2 eq) was dissolved in THF (5 ml, dry) and the solution was stirring for 0.5 h before addition of iodomethane (87.5 mg, 0.04 ml, 0.62 mmol, 1.5 eq). After stirring for 18 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. Evaporation and drying under high vacuum gave 140 mg (crude yield) of a highly viscous oil and a waxy solid. The crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as a white solid (102 mg, 0.29 mmol, 70.8%), mp 94–96 °C, R_f (4 : 1 petrol (40/60)–EtOAc) = 0.44. ^1H NMR (300 MHz, $CDCl_3$) δ 3.25 (s, 3H, N–CH_3), 4.82 (s, 2H, Ph–CH_AH_B), 6.39 (dd, $^3J = 8.0$ Hz, $^4J = 1.6$ Hz, 1H, H_3), 6.76 (m_c, 2H, Ar–H), 6.89 (dt, $^3J = 7.7$ Hz, $^4J = 1.6$ Hz, 1H, H_4), 7.02 (m_c, 3H, Ar–H), 7.13 (dd, $^3J = 8.1$ Hz, $^4J = 1.5$ Hz, 1H, H_6), 7.3 (m_c, 6H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.20 (N–Me), 54.18 (Ph–CH_2), 126.22 (C_{11}, C_{15}); (C_6), (C_{13}), (C_4), (C_{20}), (C_5), (C_3), (Ar–Cl): 120.10, 125.58, 126.96, 127.25, 127.51, 129.99, 130.98; (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.40, 129.02, 129.44; (Ph–C), (N–ArCl), (N–Ar), 138.14, 140.88, 145.49; 160.75 (C=O). *m/z* (CI) 351 (100%, M + H^+), 91 (18%, (C_7H_7)$^+$); *m/z* (EI) 350 (4%, M^+), 91 (100%, (C_7H_7)$^+$). (Found: MH^+, 351.1254. $C_{24}H_{17}O_1N_2Cl_1$ requires MH, 351.1254). IR (film): ν/cm^{-1} = (Ar–H): 3061 (w), 3029 (w); 2928 (w) (C–H alkyl), 1657 (C=O), 1595 (m), 1523 (m), 1494 (s), 1479 (s) 1454 (w), 1439 (m).

1-Benzyl-1-(2-bromophenyl)-3-methyl-3-phenylurea 6c. A mixture of the urea **5c** (149.5 mg, 0.39 mmol) and sodium hydroxide (18.8 mg, 0.47 mmol, 1.2 eq) was dissolved in THF (6 ml, dry) and the solution was stirring for 0.5 h before addition of iodomethane (83.6 mg, 0.04 ml, 0.59 mmol, 1.5 eq). After stirring for 18 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. Evaporation and drying under high vacuum gave 140 mg (crude yield) of a highly viscous oil and a waxy solid. The crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as a white solid (147 mg, 0.28 mmol, 70.8%), mp 101–102 °C, R_f (4 : 1 petrol (40/60)–EtOAc) = 0.45. ^1H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 3H, N–CH_3), 4.82 (s, 2H, PhCH_AH, PhCHH_B), 6.32 (dd, $^3J = 7.7$ Hz, $^4J = 1.8$ Hz, 1H, H_3), 6.78 (m_c, 3H, Ar–H), 7.02 (m_c, 3H, Ar–H), 7.32 (m_c, 7H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.37 (N–CH_3), 54.35 (Ph–CH_2), 123.60 (C–Br); (C_6), (C_{13}), (C_4), (C_{20}), (C_5), (C_3): 125.65, 126.36, 127.45, 127.54, 127.55, 133.28; (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{14}, C_{12}): 128.43, 129.08, 129.51; (Ar–N), (C–CH_2), (N–ArBr): 138.11, 142.33, 145.57; 160.56 (C=O). *m/z* (CI) 395 (100%, M + H^+, ^{79}Br), 397 (97%, M + H^+, ^{81}Br), 315 (50%, (M–^{79}Br)$^+$), 91 (72%, $C_7H_7^+$); *m/z* (EI) (10%, (M–^{79}Br)$^+$), 91 (100%, $C_7H_7^+$), 77 (36%, $C_6H_5^+$). (Found: MH^+, 395.0754. $C_{21}H_{20}O_1N_2Br_1$ requires MH, 395.0754). IR (film): ν/cm^{-1} = (Ar–H): 3061 (w), 3029 (w); 2928 (w) (C–H alkyl), 1659 (s) (C=O), 1595 (m), 1584 (m), 1522 (m), 1494 (m), 1474 (m), 1454 (m), 1440 (m).

1-Benzyl-1-(2-iodophenyl)-3-methyl-3-phenylurea 6d. A mixture of the urea **5d** (dry) (128 mg, 0.30 mmol) and sodium hydride (35.9 mg, 1.5 mmol, 5 eq) was dissolved in DMF (5 ml, dry). Iodomethane (212 mg, 0.09 ml, 1.5 mmol, 5 eq) was added and after stirring for 19 h the excess of NaH and MeI was quenched with H_2O (3 ml). After washing the aqueous phase with Et_2O (5 × 10 ml), the combined Et_2O phases were dried over Na_2SO_4 and evaporated under high vacuum. The crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as white crystals (119 mg, 0.27 mmol, 90%), mp 89–90 °C, R_f (4 : 1 petrol (40/60)–EtOAc) = 0.13. ^1H NMR (300 MHz, $CDCl_3$) δ 3.25 (s, 3H, N–CH_3), 5.23 (s, 2H, Ph–CH_AH_B), 6.21 (dd, $^3J = 7.8$ Hz, $^4J = 1.6$ Hz, 1H, H_6), 6.65 (dt, $^3J = 7.7$ Hz, $^4J = 1.8$ Hz, 1H, H_4), 6.75 (m_c, 2H, Ar–H), 7.00 (m_c, 4H, Ar–H), 7.30 (m_c, 5H, Ar–H), 7.65 (dd, $^3J = 7.9$ Hz, $^4J = 1.5$ Hz, 1H, H_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.72 (N–CH_3), 54.63 (Ph–CH_2), 99.64 (Ar–I); (C_6), (C_{13}), (C_4), (C_{20}), (C_5), (C_3): 125.74, 127.50, 127.58, 128.35, 131.22, 139.81; 126.56 (C_{11}, C_{15}); (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.47, 129.15, 129.62; (C_{17}), (N–Ar), (N–ArI); 138.02, 145.50, 145.69; 160.18 (C=O). *m/z* (CI) 443 (15%, M + H^+), 315 (49%, M + H^+–I), 108 (100%, $MeNH_2^+$–(C_6H_5)), 91 (37%, $C_7H_7^+$); *m/z* (EI) 442 (5%, M^+), 315 (28%, M + H^+–I), 91 (100%, $C_7H_7^+$). (Found: MH^+, 443.0616. $C_{21}H_{20}O_1N_2I_1$ requires MH, 443.0615). IR (film): ν/cm^{-1} = (Ar–H); 3061 (m), 3029 (m); (alkyl–H): 2963 (w), 2929 (m); (C=O) 1656 (s); 1596 (s), 1495 (s), 1377 (s), 1019 (m), 750 (s), 722 (s), 697 (s).

1-Benzyl-1-(2-methylphenyl)-3-methyl-3-phenylurea 6e. A mixture of the urea **5e** (204 mg, 0.65 mmol) and sodium hydroxide (31.0 mg, 0.77 mmol, 1.2 eq) was dissolved in THF (5 ml, dry) and the solution was stirring for 0.5 h before addition of iodomethane (137 mg, 0.06 ml, 0.97 mmol, 1.5 eq). After stirring for 20 h, the same quantity of iodomethane (137 mg, 0.06 ml, 0.97 mmol, 1.5 eq) was added again and the reaction mixture was stirred for the following 20 h. Then Et_2O (5 ml) and distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. Evaporation and drying under high vacuum gave 220 mg (crude yield) of a highly viscous yellowish oil. The crude product was purified by column chromatography

using a mixture of petrol–diethyl ether (10 : 1). The desired product was obtained as a white solid (100 mg, 0.30 mmol, 47%), mp 86–87 °C, R_f (4 : 1 petrol (40/60)–Et_2O) = 0.15. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 3H, Ar–CH_3), 3.20 (s, 3H, N–CH_3), 6.35 (d, ^2J = 7.7 Hz, 1H, H_3), 6.59 (m_c, 1H, Ar–H), 6.72 (m_c, 2H, Ar–H), 6.96 (m_c, 5H, Ar–H), 7.28 (m_c, 5H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.96 (Ar–CH_3), 40.42 (N–CH_3), 55.02 (Ph–CH_2); (C_6), (C_4), (C_{13}), (C_5), (C_{20}), (C_3): 125.64, 126.27, 126.32, 127.46, 129.33, 130.63; 126.41 (C_{11}, C_{15}); (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.38, 128.93, 129.52; (C_2), (N–ArMe), (N–Ar), (C_{17}): 135.95, 138.32, 142.39, 146.01; 161.52 (C=O). *m/z* (CI) 331 (100%, M + H^+), 108 (44%, $MeNH_2^+$–(C_6H_5)), 91 (71%, $C_7H_7^+$); *m/z* (EI) 91 (100%, $C_7H_7^+$). (Found: MH^+, 331.1800. $C_{22}H_{23}O_1N_2$ requires MH, 331.1805). IR (film): ν/cm^{-1} = (Ar–H): 3062 (m), 3029 (m); (alkyl–H) 2927 (m); (C=O) 1655 (s); 1596 (s), 1495 (s), 1378 (s), 1328 (s), 753 (s), 723 (s), 700 (s).

1-Benzyl-1-(2-ethylphenyl)-3-methyl-3-phenylurea 6f. A mixture of the urea **5f** (131 mg, 0.40 mmol) and sodium hydroxide (19.1 mg, 0.48 mmol, 1.2 eq) was dissolved in THF (5 ml, dry) and the solution was stirring for 0.5 h before addition of iodomethane (84.3 mg, 0.04 ml, 0.60 mmol, 1.5 eq). After stirring for 60 h, first Et_2O (5 ml) and then distilled H_2O (1 ml) were added. The aqueous phase was washed with Et_2O (3 × 10 ml) and the combined organic phases were dried over Na_2SO_4. Evaporation and drying under high vacuum gave 137 mg (crude yield) of a highly viscous oil. The crude product was purified by column chromatography using a mixture of toluene–ethyl acetate (20 : 1). The desired product was obtained as a white solid (52 mg, 0.15 mmol, 37.8%), R_f (4 : 1 petrol (40/60)–Et_2O) = 0.15. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, ^3J = 7.6 Hz, 3H, CH_3), 2.29 (q, ^3J = 7.6 Hz, 2H, CH_2), 3.17 (s, 3H, N–CH_3), 4.55 (bs, 1H, Ph–CH_AH), 4.92 (bs, 1H, Ph–CHH_B), 6.29 (dd, ^3J = Hz, ^4J = Hz, 1H, H_3), 6.78 (m_c, 3H, Ar–H), 7.00 (m_c, 5H, Ar–H), 7.29 (m_c, 5H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.98 (CH_{3Et}), 23.10 (CH_{2Et}), 40.52 (N–CH_3), 55.39 (Ph–CH_2); (C_6), (C_4), (C_{13}), (C_5), (C_{20}), (C_3): 125.57, 125.99, 126.46, 127.44, 128.26, 129.43; 126.53 (C_{11}, C_{15}); (C_{22}, C_{18}), (C_{19}, C_{21}), (C_{12}, C_{14}); 128.39, 128.94, 129.51; (C_2), (N–Ar), (C_{17}), (N–Ar^{t}Bu): 138.32, 141.40, 141.78, 146.08; 161.79 (C=O). *m/z* (CI) 345 (100%, M + H^+), 108 (11%, $MeNH_2^+$–(C_6H_5)), 91 (10%, $C_7H_7^+$); *m/z* (EI) 91 (81%, $C_7H_7^+$). IR (film): ν/cm^{-1} = (Ar–H): 3061 (w), 3029 (w); (C–H alkyl): 2966 (w), 2932 (w), 2875 (w); 1652 (C=O), 1596 (s), 1584 (m), 1494 (s), 1452 (m), 1433 (m), 1421 (m). (Found: MH^+, 345.1966. $C_{23}H_{25}O_1N_2$ requires MH, 345.1961).

1-Benzyl-1-(2-isopropylphenyl)-3-methyl-3-phenylurea 6g. A mixture of the urea **5g** (dry) (200 mg, 0.581 mmol) and sodium hydride (69.8 mg, 2.91 mmol, 5 eq) was dissolved in DMF (5 ml, dry). Iodomethane (413 mg, 0.18 ml, 2.91 mmol, 5 eq) was added and after stirring for 21 h the excess of NaH and MeI was quenched with H_2O (3 ml). After washing the aqueous phase with Et_2O (5 × 10 ml), the combined Et_2O phases were dried over Na_2SO_4 and evaporated under high vacuum. The crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as white crystals (171 mg, 0.48 mmol, 82%), mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (bs, 3H, Me_A), 1.25 (bs, 3H, Me_B), 2.84 (sept, ^3J = 6.8 Hz, 1H, iso-H), 3.15 (s, 3H, N–CH_3), 4.61 (d, ^2J = 13.5 Hz, 1H, Ph–CH_AH), 4.94 (d, ^2J = 13.8 Hz, 1H, Ph–CHH_B), 6.11 (dd, ^3J = 8.1 Hz, ^4J = 1.3 Hz, 1H, H_3), 6.56 (dt, ^3J = 7.6, ^4J = 1.6 Hz, 1H, H_4), 6.68 (m, 2H, Ar–H), 6.94–7.14 (m, 5H, Ar–H), 7.22–7.36 (m, 5H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.18 (iso-Me_A), 24.94 (iso-Me_B), 27.63 (iso-CH), 40.67 (N–Me), 55.81 (Ph–CH_2), (C_6), (C_4), (C_{13}), (C_5), (C_3), (C_{20}): 125.61, 125.71, 126.48, 126.68, 127.54, 129.34; 126.51 (C_{11}, C_{15}); (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.52, 129.08, 129.67; (C_{17}), (C_2), (N–$Ar_{isoprop}$), (N–Ar): 138.40, 140.71, 146.53, 146.56; 162.32 (C=O). *m/z* (CI) 359 (77%, M + H^+), 108 (82%, $MeNH_2^+$–(C_6H_5)), 91 (100%, $C_7H_7^+$); *m/z* (EI) 358 (3%, M^+), 107 (77%, $MeNH^+$–(C_6H_5)), 91 (100%, $C_7H_7^+$). (Found: MH^+, 359.2118. $C_{24}H_{27}O_1N_2$ requires MH^+, 359.2118). IR (film): ν/cm^{-1} = (Ar–H): 3061 (w), 3034 (w); (alkyl–H): 2982 (m), 2962 (s), 2926 (m), 2913 (m), 2868 (m); (C=O) 1645 (s); 1595 (s), 1493 (s), 1448 (s), 1420 (s), 1381 (s), 757 (s), 741 (s), 701 (s).

1-Benzyl-1-(2-*tert*-butylphenyl)-3-methyl-3-phenylurea 6h. A mixture of the urea **5h** (dry) (102 mg, 0.285 mmol) and sodium hydride (34.2 mg, 1.43 mmol, 5 eq) was dissolved in DMF (5 ml, dry). Iodomethane (202 mg, 0.09 ml, 1.43 mmol, 5 eq) was added and after stirring for 16 h the excess of NaH and MeI was quenched with H_2O (3 ml). After washing the aqueous phase with Et_2O (5 × 10 ml), the combined Et_2O phases were dried over Na_2SO_4 and evaporated under high vacuum. The crude product was purified by column chromatography using a mixture of petrol ether–ethyl acetate (10 : 1). The desired product was obtained as a waxy white mass (92 mg, 0.25 mmol, 87%), R_f (4 : 1 petrol (40/60)–EtOAc) = 0.34. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H, 3 × CH_3), 3.10 (s, 3H, N–CH_3), 3.82 (d, ^2J = 14.5 Hz, 1H, Ph–CH_AH), 5.71 (d, ^2J = 14.5 Hz, 1H, Ph–CHH_B), 5.81 (dd, ^3J = 8.0 Hz, ^4J = 1.3 Hz, 1H, H_3), 6.36 (dt, ^3J = 8.0 Hz, ^4J = 1.5 Hz, H_4), 6.57 (m_c, 2H, Ar–H), 6.94 (m_c, 6H, Ar–H), 7.39 (m_c, 4H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.49 (3 × CH_3), 36.35 (C_{tertBu}), 41.44 (N–CH_3), 56.82 (Ph–CH_2); (C_6), (C_4), (C_{13}), (C_3), (C_5), (C_{20}): 125.54, 125.80, 126.72, 127.63, 129.17, 133.08; 126.98 (C_{11}, C_{15}); (C_{18}, C_{22}), (C_{19}, C_{21}), (C_{12}, C_{14}): 128.63, 129.13, 129.50; (Ar–C_{tBu}), (C_{17}), (N–Ar^{t}Bu), (N–Ar): 139.15, 141.17, 146.32, 146.80; 161.55 (C = O). *m/z* (CI) 373 (100%, M + H^+), 315 (18%, M + H^+–^{t}Bu), 108 (72%, $MeNH_2^+$–(C_6H_5)), 91 (63%, $C_7H_7^+$); *m/z* (EI) 315 (27%, M + H^+–^{t}Bu), 91 (100%, $C_7H_7^+$). (Found: MH^+, 373.2284. $C_{25}H_{29}O_1N_2$ requires MH, 373.2274). IR (film): ν/cm^{-1} = 2960 (alkyl–H) (m); 1649 (C=O) (s); 1595 (m), 1494 (m), 1380 (m), 756 (m), 696 (m).

1-(2-Isopropylphenyl)-1,3-dimethyl-3-phenylurea 6i. Sodium hydroxide (1.40 g, 35 mmol), potassium carbonate (1.00 g, 7.0 mmol), tetrabutylammonium hydrogen sulfate (0.05 g, 1.4 mmol) and 1-(2-isopropylphenyl)-3-phenylurea **10g** (1.80 g, 7.0 mmol) were suspended in toluene (50 cm^3) and the mixture heated to reflux for 1 h. Dimethyl sulfate (2.00 g, 15 mmol) was added dropwise and reflux continued for 18 h. After cooling to room temperature, the mixture was filtered, the filtrate washed with 1 N hydrochloric acid (3 × 50 cm^3) and water (2 × 150 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; EtOAc–petrol, 15 : 85) to give 1-(2-isopropylphenyl)-1,3-dimethyl-3-phenylurea **6i** (1.80 g, 91%), as colourless cubes, mp 82–84 °C (from EtOAc–petrol); R_f (EtOAc–petrol, 1 : 4) 0.25; ν_{max} (film)/cm^{-1} 1710 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52–7.20 (m, 2H, CH-a) 7.17 (dd, 1H, J = 8.0 and 2.0, CH-d), 7.11–6.78 (m, 3H, CH-c, CH-e and CH-f), 6.76–6.69 (m, 2H, CH-b), 6.4 (dd, 1H, J = 8.0 and 1.0, CH-g), 3.18 [s, 3H, $(NCH_3)_A$], 3.13 [s, 3H, $(NCH_3)_B$], 2.95 (sept, 1H, J = 7.0, CH-h), 1.22 [m, 6H, $(CH_3)_A$ and $(CH_3)_B$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (C=O), 146.5 (C), 146.1 (C), 142.4 (C), 129.1 (CH), 129.0 (CH), 128.9 (CH), 126.8 (CH), 126.4 (CH), 126.2 (CH), 125.6 (CH), 40.6 $(NCH_3)_A$, 40.1 $(NCH_3)_B$, 27.9 (CH) and 24.5 (CH_3); *m/z* (CI) 283 (100%, M + H^+); (Found: M + H^+, 283.1803, $C_{18}H_{23}N_2O$ requires M + H, 283.1805).

1,3-Diethyl-1-(2-isopropylphenyl)-3-phenylurea 6j. Sodium hydroxide (1.60 g, 40 mmol), potassium carbonate (1.12 g, 7.9 mmol), tetrabutylammonium hydrogen sulfate (0.06 g, 0.16 mmol) and 1-(2-isopropylphenyl)-3-phenylurea **10g** (2.0 g, 7.9 mmol) were suspended in toluene (50 cm^3) and the mixture heated to reflux for 1 h. Ethyl iodide (0.63 cm^3, 17 mmol) was added dropwise and reflux continued for 18 h. After cooling to room temperature, the mixture was filtered, the filtrate was washed with 1 N hydrochloric acid (3 × 30 cm^3) and water

(2×25 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a mixture of products as analysed by NMR. The residue (1.45 g) was dissolved in THF (50 cm^3) and sodium hydride (0.28 g, 7.0 mmol in mineral oil) was added before being stirred at room temperature for 2 h. Ethyl iodide (0.56 cm^3, 11 mmol) was added and the mixture stirred at room temperature for 18 h. Water (30 cm^3) was added and extracted with EtOAc (3×30 cm^3) and the combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2; EtOAc–petrol, 1 : 9) to give 1,3-diethyl-1-(2-isopropylphenyl)-3-phenylurea **6j** (1.35 g, 55%), as a colourless oil, R_f (EtOAc–petrol, 1 : 4) 0.50; ν_{max} (film)/cm^{-1} 2958 and 2912 (CH_3), 2880 (CH) and 1710 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, 1H, J = 8.0 and 2.0, CH-d), 7.10–6.96 (m, 4H, CH-a and CH-b), 6.71–6.60 (m, 3H, CH-c, CH-e and CH-f), 6.28 (dd, 1H, J = 8.1 and 1.0, CH-g), 3.75 [br., 2H, $(NCH_2CH_3)_A$], 3.40 [br., 2H, $(NCH_2CH_3)_B$], 3.00 (sept, 1H, J = 7.0, CH-h), 1.22 [br. m, 6H, $(CH_3)_A$ and $(CH_3)_B$], 1.18 [t, 3H, J = 7.0, $(NCH_2CH_3)_A$], 1.10 [t, 3H, J = 7.0, $(NCH_2CH_3)_B$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (C=O), 146.4 (C), 144.2 (C), 141.1 (C), 129.4 (CH), 128.8 (CH), 127.7 (CH), 126.5 (CH), 126.4 (CH), 125.8 (CH), 125.5 (CH), 47.1 $(NCH_2CH_3)_A$, 46.7 $(NCH_2CH_3)_B$, 27.4 (CH), 24.4 $(CH_3)_A$, 22.4 $(CH_3)_B$, 14.0 $(NCH_2CH_3)_A$ and 13.3 $(NCH_2CH_3)_A$; m/z (CI) 311 (100%, M + H$^+$); (Found: M + H$^+$, 311.2116, $C_{20}H_{27}N_2O$ requires M + H, 311.2118).

1,3-Dibenzyl-1-(2-isopropylphenyl)-3-phenylurea 6k. Sodium hydroxide (1.60 g, 40 mmol), potassium carbonate (1.12 g, 7.9 mmol), tetrabutylammonium hydrogen sulfate (0.06 g, 0.16 mmol) and 1-(2-isopropylphenyl)-3-phenylurea **10g** (2.0 g, 7.9 mmol) were suspended in toluene (50 cm^3) and the mixture heated to reflux for 1 h. Benzyl bromide (0.93 cm^3, 17 mmol) was added dropwise and reflux continued for 18 h. After cooling to room temperature, the mixture was filtered, the filtrate washed with 1 N hydrochloric acid (3×30 cm^3) and water (2×25 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a mixture of products as analysed by NMR. The residue (1.26 g) was dissolved in THF (50 cm^3), sodium hydride (0.14 g, 4.0 mmol in mineral oil) was added and stirred at room temperature for 2 h. Benzyl bromide (0.35 cm^3, 6 mmol) was added dropwise and the mixture stirred at room temperature for 18 h before water (30 cm^3) and EtOAc (30 cm^3) were added. The aqueous layer was extracted with EtOAc (3×30 cm^3) and the combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash silica chromatography (SiO_2; EtOAc–petrol, 1 : 9) to give 1,3-dibenzyl-1-(2-isopropylphenyl)-3-phenylurea **95** (1.30 g, 40%), as colourless cubes, mp 112–114 °C (from EtOAc–petrol); R_f (EtOAc–petrol, 1 : 4) 0.63; ν_{max} (film)/cm^{-1} 2967 and 2932 (CH_3), 2884 (CH) and 1710 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.20 [m, 10H, $(NCH_2Ar)_A$ and $(NCH_2Ar)_B$], 7.16 (dd, 1H, J = 8.0 and 1.0, CH-d), 7.01–6.93 (m, 4H, CH-a and CH-b), 6.61–6.50 (m, 3H, CH-c, CH-e and CH-f), 6.08 (d, 1H, J = 8.0, CH-g), 5.05 [br., 2H, $(NCH_2Ar)_A$], 4.58 [m, 2H, $(NCH_2Ar)_B$], 2.95 (sept, 1H, J = 7.0, CH-h), 1.25 [br., 3H, $(CH_3)_A$], [br., 3H, $(CH_3)_B$]. ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (C=O), 146.4 (C), 144.0 (C), 140.8 (C), 138.5 (C), 138.1 (C), 129.8 (CH), 129.6 (CH), 128.6 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 127.4 (CH), 126.7 (CH), 126.4 (CH), 125.7 (CH), 56.2 $(NCH_2Ar)_A$, 56.0 $(NCH_2Ar)_B$, 27.6 (CH), 25.2 $(CH_3)_A$ and 23.3 $(CH_3)_B$; m/z (CI) 435 (25%, M + H$^+$); (Found: M + H$^+$, 435.2447, $C_{30}H_{31}N_2O$ requires M + H, 435.2431).

1,3-Dibenzyl-1-(2-bromo-4-methylphenyl)-3-phenylurea 6l. Sodium hydroxide (0.39 g, 10 mmol), potassium carbonate (0.28 g, 1.9 mmol), tetrabutylammonium hydrogen sulfate (0.01 g, 0.04 mmol) and 1-(2-bromo-4-methylphenyl)-3-phenylurea (0.60 g, 1.9 mmol) were suspended in toluene (20 cm^3) and the mixture heated at reflux for 1 h. Benzyl bromide (0.54 cm^3, 4.2 mmol) was added dropwise and reflux continued for 18 h. After cooling to room temperature, the mixture was filtered, the filtrate washed with 1 N hydrochloric acid (3×30 cm^3) and water (2×25 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO2; EtOAc–petrol, 1 : 9) to give 1,3-dibenzyl-1-(2-bromo-4-methylphenyl)-3-phenylurea **6l** (0.66 g, 73%), as white needles, mp 111–113 °C (from EtOAc–petrol); R_f (EtOAc–petrol, 1 : 4) 0.43; ν_{max} (film)/cm^{-1} 1711 (C=O) and 734 (C–Br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.20 [m, 10H, $(NCH_2Ar)_A$ and $(NCH_2Ar)_B$], 7.16 (d, 1H, J = 1.0, CH-f), 6.99–6.92 (m, 3H, CH-a and CH-c), 6.67–6.59 (m, 2H, CH-b), 6.51 (ddq, 1H, J = 8.1, 2.0, 1.0, CH-e), 6.13 (d, 1H, J = 8.1, CH-d), 5.45–4.30 [m, 4H, $(NCH_2Ar)_A$ and $(NCH_2Ar)_B$], 2.18 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6 (C=O), 143.5 (C), 139.4 (C), 138.4 (C), 138.2 (C), 137.7 (C), 133.5 (CH), 131.2 (CH), 129.6 (CH), 129.5 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.7 (CH), 127.5 (CH), 127.3 (CH), 125.8 (CH), 123.2 (C), 56.1 $(NCH_2Ar)_A$, 54.4 $(NCH_2Ar)_B$ and 20.8 (CH_3); m/z (CI) 485 (25%, M + H$^+$), 281 (30, M + H$^+$–Br) and 318 (65, M + H$^+$–Br–C_7H_7); (Found: M$^+$, 484.1134, $C_{28}H_{25}N_2OBr$ requires M, 484.1145).

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