Variation in sites of lithiation of substituted *N*-benzylpivalamides and *N'*-benzyl-*N,N*-dimethylureas: application in synthesis

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Abstract

Directed lithiation of various substituted benzylamines takes different courses depending on the substituents at nitrogen and on the aryl ring and/or the nature of the alkyllithiums. Lithiation of *N*-benzylpivalamide with *t*-BuLi gives a mixture of ring (2-position) and side-chain lithiated species, but the 2-lithiated isomer can be obtained cleanly *via* bromine-lithium exchange of *N*-(2-bromobenzyl)pivalamide. *N'*-Benzyl-*N,N*-dimethylurea, *N'*-(4-substituted benzyl)-*N,N*-dimethylureas and *N*-(4-substituted benzyl)pivalamides give 2-lithiated derivatives directly with *t*-BuLi at -78 °C. By contrast, lithiation of *N*-(2-methoxybenzyl)pivalamide occurs at the 6-position, *ortho*- to the methoxy group, while lithiation of *N'*-(2-methoxybenzyl)-*N,N*-dimethylurea gives a mixture of 2- and 6-lithiated species. All organolithiums are converted in high yields to their corresponding substitution products on reactions with various electrophiles.

Keywords: Directed *ortho*-lithiation, electrophilic substitution, substituted benzylamines, synthesis, side-chain lithiation

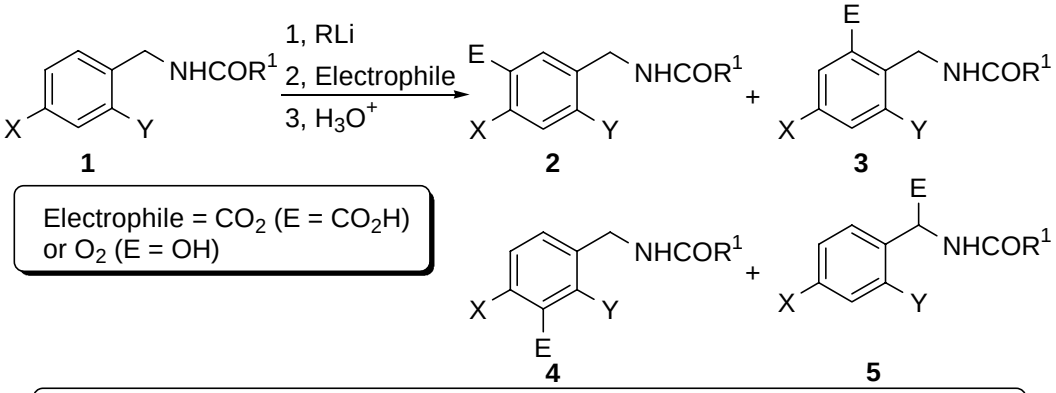
Introduction

Regioselective synthesis of substituted aromatics is one of the classical problems in synthetic chemistry. Simple electrophilic substitution often leads to various isomers and polysubstituted aromatics and usually takes place under forcing conditions in the presence of a catalyst. In recent years, many efforts have been made to develop more regioselective processes for production of specific products and it is well recognized that organolithium reagents[1,2] can play an important role in such cases. In particular, lithiation of aromatic compounds often occurs proximal to substituents that possess hetero atoms.[3] As a result, lithiation of aromatics or heterocycles followed by treatment with an electrophile is one of the most efficient approaches for synthesis of substituted and/or modified derivatives.[4,5]

For example, we have developed several efficient lithiation procedures for preparation of various substituted aromatics and heteroaromatics that might be difficult to prepare by other

means.[6] As part of such studies we became interested in directed lithiation of benzylamine derivatives. Lithiation of pivaloyl, *tert*-butoxycarbonyl and dimethylaminocarbonyl derivatives has been reported by Schlosser and shows interesting variations in the site(s) of lithiation depending on both the *N*-substituent and on any group present on the aromatic ring.[7,8] Notably, in several cases mixtures resulting from different sites of lithiation were obtained. It was of interest to try to overcome such difficulties and to develop protocols for high yield syntheses of specific products.

Some of Schlosser's results are summarized in Figure 1, which illustrates that there are four possible sites of lithiation for compounds of type **1**, in which the lithium is introduced adjacent to a *para*-substituent (product **2**), adjacent to the substituted aminomethyl group **3**, adjacent to an *ortho*-substituent **4** or on the substituted aminomethyl group **5**.



Product	Lithium reagent, T (°C)	R^1	X	Y	Yield (%)
2	LIC-KOR, -50 to -75	^{t}BuO	F, OMe	H	*ca*. 63
3	*sec*-BuLi, -50	Me_2N	F, OMe	H	*ca*. 85
3	*t*-BuLi, -100 or *sec*-BuLi, -50	Me_2N	H	H, F	*ca*. 81
3	*n*-BuLi, 0	^{t}Bu	Cl, OMe	H	*ca*. 50
4	*sec*-BuLi, -50 or LIC-KOR, -75	^{t}BuO	H	F, OMe	*ca*. 50
5	*sec*-BuLi, -50	^{t}BuO	H	H	79
3 and **4**	unspecified reagent and temp.	Me_2N	H	OMe	--------
3 and **5**	*n*-BuLi, 0	^{t}Bu	H	H, OMe	24 and 56

Figure 1. Lithiation and substitution of compounds of type **1** reported by Schlosser.[7,8]

Clearly the situation is rather complicated and it is difficult to draw general conclusions when the reagents and conditions used were different for different substrates. We therefore decided to undertake a comparative study of the lithiation of various compounds of type **1** (R^1 = ^{t}Bu or Me_2N; X = H, Me, OMe, Cl, F; Y = H, OMe) under a limited range of conditions in order to understand better the various influences. As a result, we have been able to define conditions that allow almost quantitative conversion of **1** (R^1 = ^{t}Bu or Me_2N; X = H, Me, OMe, Cl, F; Y = H)

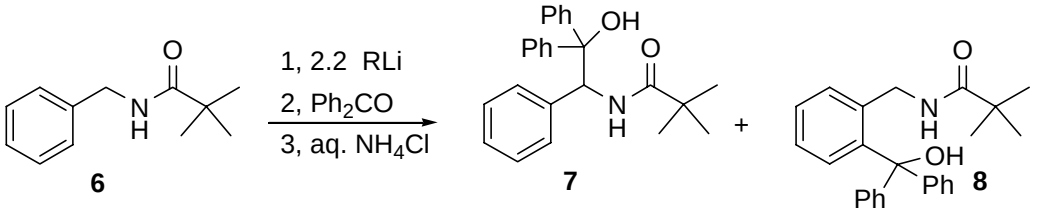
into products **3**, and for quantitative conversion of **1** (R^1 = ^{t}Bu; X = H; Y = OMe) into compounds **4**.

In a preliminary communication we reported that directed lithiation of *N*-(2-methoxybenzyl)pivalamide (**1**; R^1 = ^{t}Bu; X = H; Y = OMe) with two mole equivalents of *t*-BuLi in anhydrous THF at -78 °C followed by reactions with various electrophiles gave ring substitution,[9] but *ortho*- to the methoxy group, which was unexpected in view of earlier results reported with *n*-BuLi at 0 °C.[7] We now report the full details of that work and the successful lithiation and substitution of various other substituted benzylamines using a simple, general and efficient lithiation procedure using *t*-BuLi in THF at low temperatures.

Results and Discussion

Substituted *N*-benzylpivalamides and *N'*-benzyl-*N*,*N*-dimethylureas were prepared in high yields from the corresponding substituted benzylamines using standard procedures.[10]

Initially, *N*-benzylpivalamide **6** in THF was treated with *n*-BuLi (2.2 mole equivalents) at -78 °C and the reddish solution obtained was stirred for 4 h at -78 °C. Benzophenone in THF was added and the mixture was stirred for another 2 h. After warming to room temperature and work-up, the product mixture was separated by column chromatography (silica gel; Et_2O–hexane, 1:3) to give **7** and **8** (Scheme 1) in 4 and 7% yields, respectively, along with **6** (81%) and benzophenone.



Scheme 1. Lithiation of **6** followed by reaction with benzophenone.

The low yields of **7** and **8** were presumably because lithiation of **6** with *n*-BuLi at - 78 °C was slow. Use of *sec*-BuLi gave results that were similar to those with *n*-BuLi. However, use of *t*-BuLi under similar conditions gave **7** and **8** in somewhat better yields (6 and 10%, respectively) along with **6** (69%). Therefore, we carried out lithiation with this reagent at different temperatures. The results obtained are recorded in Table 1.

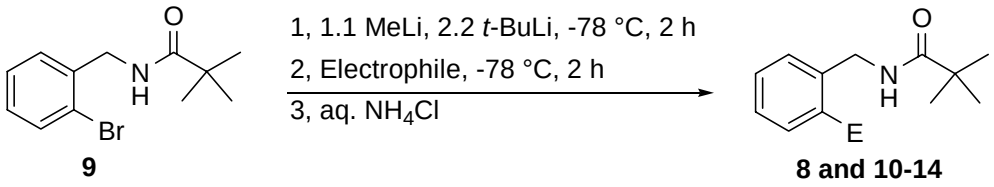
Table 1. Yields of **7** and **8** from lithiation of **6** using *t*-BuLi (2.2 mole equivalents) for 4 h at the appropriate temperature, followed by reaction with benzophenone according to Scheme 1

		Yield (%)[a]			
Entry	T (°C)	**6**	**7**	**8**	Total of **7** and **8**
1	-78	69	6	10	16
2	0	20	37	34	71
3	20	30	42	17	59

[a] Yield of isolated product after purification by column chromatography.

The overall yield was improved at higher temperatures, but was highest at 0 °C (Table 1; entry 2) and somewhat lower at 20 °C (entry 3), presumably because of some loss of the *t*-BuLi by reaction with the solvent.[11] However, the yield of **7** was actually higher at 20 °C than at 0 °C, all of the loss having arisen from a reduction in the yield of **8**. Indeed, there was a significant change in selectivity, from favouring **8** at low temperature to favouring **7** at higher temperature. Presumably, the dilithium reagent leading to **8** is not very stable in THF at 20 °C and either converts back to the starting material **6** (by reaction with the solvent) or isomerises to a more stable dilithium reagent (presumably the one that leads to **7**). To test these possibilities, generation of the ring-lithiated material was attempted *via* bromine-lithium exchange of *N*-(2-bromobenzyl)pivalamide **9**.

Bromine-lithium exchange of **9** took place smoothly with MeLi (to deprotonate the nitrogen) and then *t*-BuLi (bromine-lithium exchange) at -78 °C in THF (Scheme 2). The mixture was stirred for 2 h at -78 °C and the dilithium reagent thus obtained was allowed to react with a range of electrophiles at -78 °C in THF for 2 h (Scheme 2). Following work-up, the crude products obtained were crystallized from EtOAc–Et_2O (1:3) to give the corresponding *N*-(2-substituted benzyl)pivalamides **8** and **10-14** (Scheme 2) in high yields (Table 2).



9 **8 and 10-14**

Scheme 2. Synthesis of *N*-(2-substituted benzyl)pivalamides **8** and **10-14** *via* bromine-lithium exchange of **9** followed by reaction with various electrophiles.

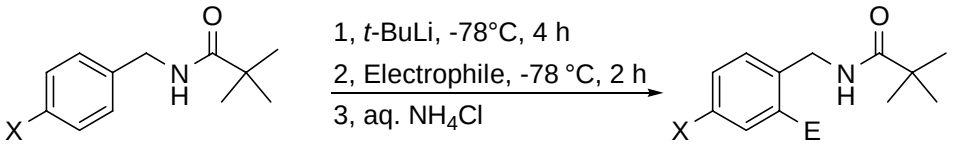
Table 2. Synthesis of various *N*-(2-substituted benzyl)pivalamides according to Scheme 2

Product	Electrophile	E	Yield (%)[a]
8	Ph_2CO	$Ph_2C(OH)$	90
10	$(CH_2)_5C=O$	$(CH_2)_5C(OH)$	90
11	PhCHO	PhCH(OH)	86
12	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	87
13	D_2O	D	91
14	MeI	Me	85

[a] Yield of isolated product after crystallization.

As Table 2 shows, the yields of products were high in all cases. The ^{1}H NMR spectra of compounds **11** and **12** showed the expected diastereotopicity for the hydrogens of the CH_2 group at position 1. Clearly bromine-lithium exchange of **9** had occurred smoothly and rapidly at –78 °C. Therefore, to test the possibility that the dilithium intermediate might be unstable, a solution was prepared as above at –78 °C and then allowed to warm to room temperature (20 °C) and stirred for 30 minutes at that temperature before addition of benzophenone. The reaction mixture was stirred for 2 h at room temperature and then worked-up. The yield of **8** obtained was significantly reduced (to 78%) and the loss was accounted for by the production of **6** (*ca*. 15%), but no other product was obtained. This implies that the low yield of **8** following lithiation of **6** at 20 °C results from reaction of the intermediate with solvent to give back **6**, rather than isomerisation.

Attention was next turned to investigate lithiation of *N*-(4-substituted benzyl)pivalamides **15-18** using *t*-BuLi as the lithium reagent. Two mole equivalents of *t*-BuLi were used at -78 °C in THF. The mixtures were stirred for 4 h at -78 °C in an attempt to ensure complete lithiation and the solutions obtained were then treated with various electrophiles. Each reaction was conducted under identical conditions and then warmed to room temperature and quenched by the addition of aq. NH_4Cl. The crude products were purified by column chromatography to give the corresponding 2-substituted derivatives **19-43** (Scheme 3) in good yields (Table 3).



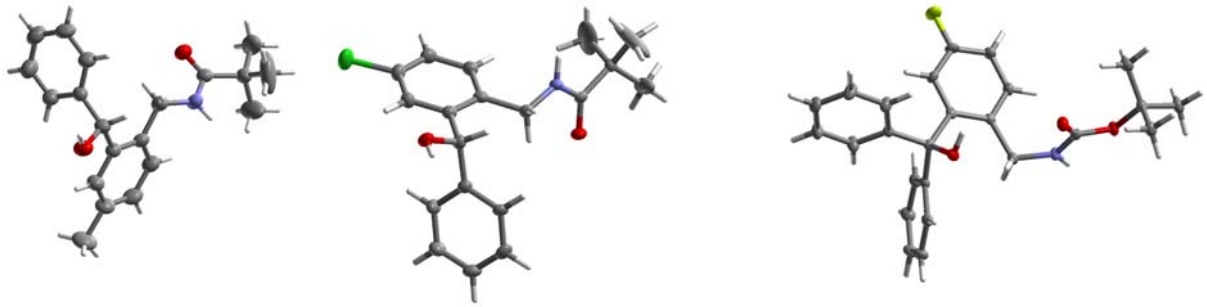
15 X = Me
16 X = OMe
17 X = Cl
18 X = F

19-43

Scheme 3. Synthesis of various substituted *N*-benzylpivalamides **19-43** *via* directed lithiations of **15-18** followed by reactions with electrophiles.

From the results in Table 3 it is clear that for all four substrates lithiation was rapid at -78 °C and that substitution took place almost exclusively at the position *ortho*- to the $CH_2NHCOBu^t$

group. This was somewhat surprising in view of the low yield and the mixture of products obtained on direct lithiation of the unsubstituted *N*-benzylpivalamide **6**. It would appear that the presence of a substituent in the 4-position inhibits deprotonation of the CH_2 group while promoting deprotonation at the 2-position. Given the different natures of the substituents and the relatively small effects those substituents have on ^1H and ^{13}C chemical shifts at positions *meta* to them, it not obvious why this should be. However, the results are unequivocal. The structures of **20**, **33** and **40** were confirmed by X-ray crystallography (Figure 2), while the ^1H NMR spectra of compounds obtained *via* reactions with aldehydes and unsymmetrical ketones showed that the signals of the two hydrogens of the CH_2 group appear separately, as two separated double doublets that converted to two doublets after addition of D_2O, indicating that they are diastereotopic.



20 **33** **40**

Figure 2. X-Ray crystal structures of compounds **20**, **33** and **40.**

Table 3. Synthesis of various substituted *N*-benzylpivalamides **19-43** according to Scheme 3

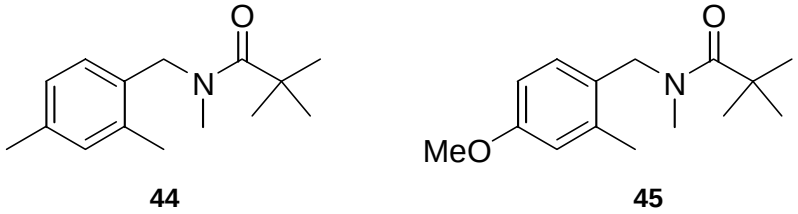
Product	X	Electrophile	E	Yield (%)[a]
19	Me	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	81
20	Me	PhCHO	PhCH(OH)	79
21	Me	Ph_2CO	$Ph_2C(OH)$	81
22	Me	$(CH_2)_5C=O$	$(CH_2)_5C(OH)$	82
23	Me	D_2O	D	88
24	Me	MeI	Me	80[b]
25	Me	EtI	Et	81
26	OMe	MeI	Me	81[c]
27	OMe	Ph_2CO	$Ph_2C(OH)$	80
28	OMe	$(CH_2)_5C=O$	$(CH_2)_5C(OH)$	77
29	OMe	MeCOBu	MeC(OH)Bu	78
30	OMe	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	82

Table 3. Continued

Product	X	Electrophile	E	Yield (%)a
31	OMe	D_2O	D	88
32	Cl	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	83
33	Cl	PhCHO	PhCH(OH)	82
34	Cl	Ph_2CO	$Ph_2C(OH)$	79
35	Cl	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	73
36	Cl	EtI	Et	79
37	Cl	D_2O	D	88
38	F	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	78
39	F	PhCHO	PhCH(OH)	79
40	F	Ph_2CO	$Ph_2C(OH)$	76
41	F	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	82
42	F	EtI	Et	82
43	F	D_2O	D	85

[a] Yield of isolated product after purification by column chromatography.
[b] Compound **44** (Figure 3) was obtained in 2% yield as a side product and in 88% yield when the reaction was repeated with 2.2 equivalents of MeI.
[c] Compound **45** (Figure 3) was produced in 5% yield as a side product and in 87% yield when the reaction was repeated with 2.2 equivalents of MeI.

Reactions involving MeI as electrophile gave small amounts of *N*-methylated compounds (**44** and **45**, Figure 3) as by-products. These could be obtained in high yields by use of excess MeI.

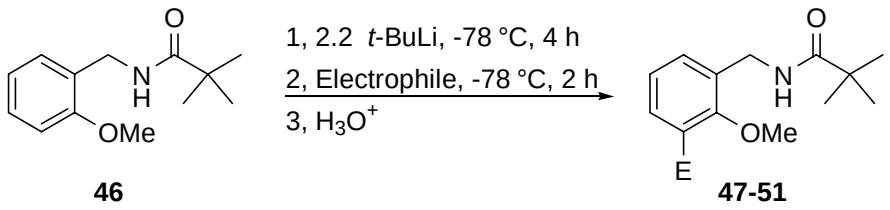


44 **45**

Figure 3. Structures of compounds **44** and **45**.

We next turned our attention to *N*-(2-methoxybenzyl)pivalamide **46**. Double lithiation **46** took place smoothly with *t*-BuLi (2 equivalents) under the general conditions used previously with other substrates. The dilithium reagent produced was allowed to react with various electrophiles at -78 °C for 2 h. The reaction mixtures were warmed to room temperature and quenched by the addition of aq. NH_4Cl. The crude products were purified by column chromatography or direct crystallization from ethyl acetate to give the corresponding

N-(3-substituted 2-methoxybenzyl)pivalamides **47-51** (Scheme 4) in high yields (Table 4). Small quantities of by-products were also obtained in some cases (Table 4 and Figure 4).



Scheme 4. Synthesis of *N*-(3-substituted 2-methoxybenzyl)pivalamides *via* lithiation of **46**.

Table 4. Synthesis of *N*-(3-substituted 2-methoxybenzyl)pivalamides **47-51** *via* lithiation and substitution of **46** according to Scheme 4

Product	Electrophile	E	Yield (%)[a]
47	CO_2	CO_2H	80[b,c]
48	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	76[d]
49	PhCHO	PhCH(OH)	75
50	Ph_2CO	$Ph_2C(OH)$	73[e]
51	D_2O	D	86

[a] Yield of isolated product after purification by column chromatography unless otherwise indicated.
[b] Compound **47** was purified by crystallization from ethyl acetate.
[c] The mother liquor showed the presence of **52** (Figure 4) and additional **47** in nearly equal proportions along with traces of **46**.
[d] Compound **53** (Figure 4) was obtained as a by-product in 2% yield.
[e] Compound **54** (Figure 4) was obtained as a by-product in 3% yield.

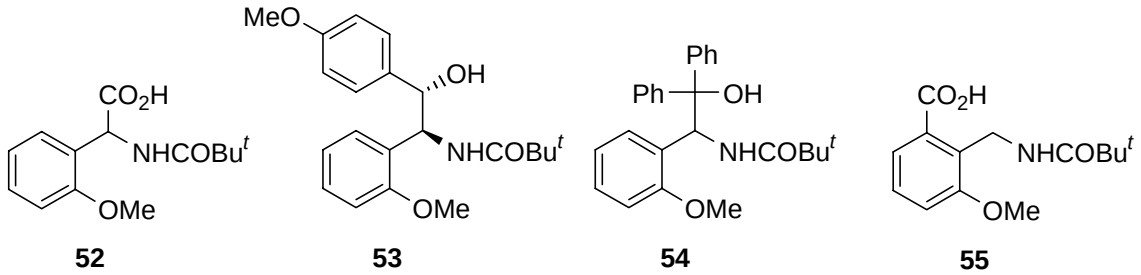
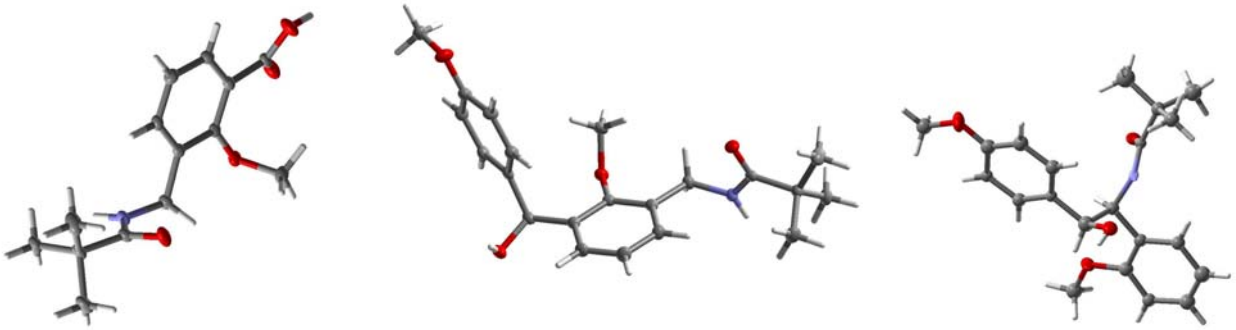


Figure 4. Structures of compounds **52-55**, by-products from reactions according to Scheme 4.

The ^1H NMR spectra of **48** and **49** showed the CH_2 hydrogens as two separated double doublets, indicating that they are diastereotopic. By-product **53** from the reaction with 4-anisaldehyde was expected to be formed as a mixture of diastereoisomers but its NMR spectra

showed what appeared to be single sets of signals, indicating that the isolated product was probably a single diastereoisomer. However, since it was isolated in only 2% yield, it is possible that a small amount of the other diastereoisomer was formed but not isolated. The structures of compounds **47**, **48** and **53** were confirmed by X-ray crystallography (Figure 5).



47 **48** **53**

Figure 5. X-ray crystal structures of compounds **47**, **48** and **53**.

The results in Table 4 clearly showed that compound **46** undergoes lithiation with *t*-BuLi at -78 °C mainly at the position *ortho*- to the methoxy group, with only a small extent of lithiation on the side chain and no evidence for lithiation at the ring position adjacent to the $CH_2NHCOBu^t$ group. This was not expected based on the early results reported by Schlosser[8] using *n*-BuLi at 0 °C, or based on the results we saw with **16**, where lithiation took place next to $CH_2NHCOBu^t$.

In order to understand the situation better, lithiation of compound **46** was attempted using different lithium reagents (*t*-BuLi, *sec*-BuLi and *n*-BuLi) under different reaction conditions. Compound **46** was treated with RLi (2.2 mole equivalents) at -78 or 0 °C and the mixture was stirred for 2 h at 0 °C or 4 h at -78 °C. Solid carbon dioxide was added and the reaction mixture was stirred for 30 minutes. The mixture was diluted with ethyl acetate and quenched with dilute HCl. The crude product was crystallized from ethyl acetate to give the pure products and inspection of the ^{1}H NMR spectra of the residual mother liquors allowed the overall yields of all components obtained in the reactions to be estimated. The results are presented in Table 5.

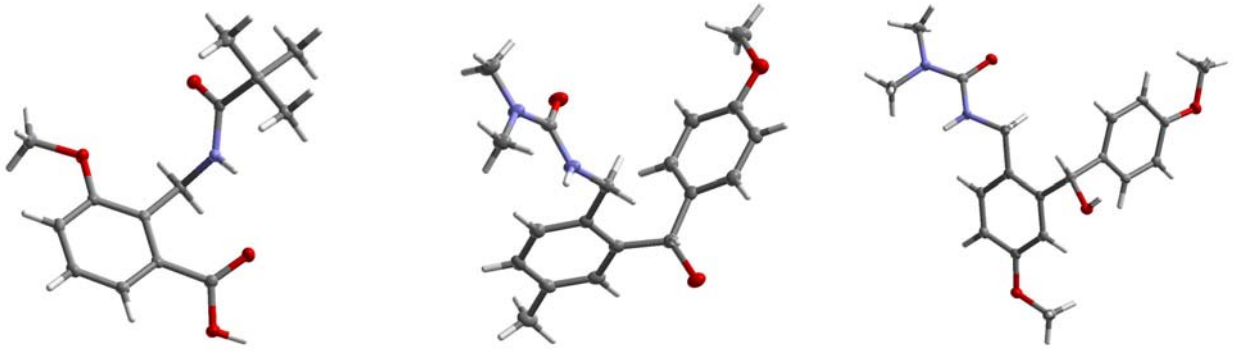
The results showed interesting variations in both rates and product proportions. The extent of lithiation at -78 °C ranged from virtually quantitative with *t*-BuLi to virtually zero with *n*-BuLi, while all three reagents brought about substantial lithiation at 0 °C. Both *n*-BuLi and *sec*-BuLi gave mixtures indicative of lithiation on the side chain and at the 6-position, as reported by Schlosser with *n*-BuLi.[8] There was very little lithiation at the 3-position with these reagents, whereas this was predominant with *t*-BuLi at 0 °C and almost exclusive at -78 °C. It is not clear why lithiation of **46** with *t*-BuLi in THF at -78 °C occurs *ortho*- to the methoxy group while *n*-BuLi and *sec*-BuLi give mixtures involving lithiation at two other sites, but it could relate to the way the reagents aggregate, their ability to chelate the two substituents, their basicity, or the

relative bulk of the alkyl groups. Whatever the explanation, the procedure outlined in Scheme 4 represents a simple and high yielding route for substitution of **46** *ortho*- to the methoxy group.

Table 5. Products from lithiation of **46** with RLi and then reaction with carbon dioxide

		Approximate yields of the components of the total product (%)[a]			
RLi	T (°C)	**46**	**47**	**52**[b]	**55**[c]
t-BuLi	-78	2	87	7	—
t-BuLi	0	—	49	26	19
sec-BuLi	-78	22	—	34	36
sec-BuLi	0	9	—	38	48
n-BuLi	-78	97	—	—	—
n-BuLi	0	17	8	40	30

[a] By combination of weights of the crystallised materials and the quantities estimated by ^{1}H NMR to be present in the mother liquors.
[b] No attempt was made to isolate a pure sample of **52**.
[c] The structure of **55** was confirmed by X-ray crystallography (Figure 6).



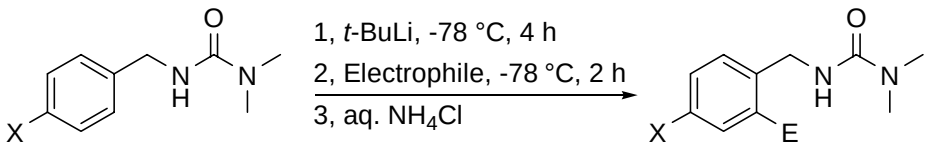
55 **66** **71**

Figure 6. X-Ray crystal structures of compounds **55**, **66** and **71**.

Attention was next turned to investigate lithiation of various *N'*-benzyl-*N*,*N*-dimethylureas **56-60** under the general conditions used previously with *N*-benzylpivalamides **15-18**. The mixtures were stirred with *t*-BuLi for 4 h at -78 °C in an attempt to ensure complete lithiation and then treated with various electrophiles, warmed to room temperature and quenched by the addition of aq. NH_4Cl. The crude products were purified by column chromatography to give the corresponding 2-substituted derivatives **61-82** (Scheme 5) in good yields (Table 6).

From the results in Table 6 it is clear that for all substrates, including the unsubstituted one, substitution took place almost exclusively at the position *ortho*- to the urea-containing group. The ^{1}H NMR spectra of compounds obtained *via* reactions with aldehydes and unsymmetrical ketones showed that the signals of the two hydrogens of the CH_2 group appear separately, as two

separated double doublets that converted to two doublets after addition of D_2O, indicating that they are diastereotopic. The structures of **66** and **71** were confirmed by X-ray crystallography (Figure 6).



56 X = H
57 X = Me
58 X = OMe
59 X = Cl
60 X = F

61-82

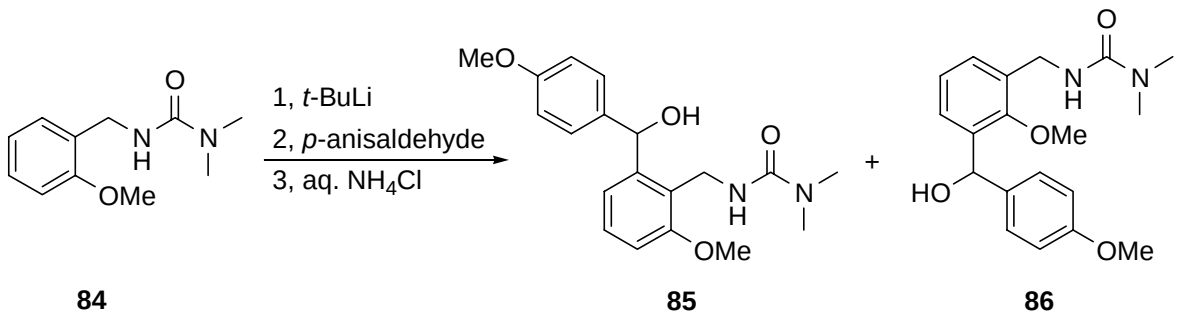
Scheme 5. Synthesis of various substituted *N'*-benzyl-*N*,*N*-dimethylureas **61-82**.

Table 6. Synthesis of substituted *N'*-benzyl-*N*,*N*-dimethylureas **61-82** according to Scheme 5

Product	X	Electrophile	E	Yield (%)[a]
61	H	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	86
62	H	PhCHO	PhCH(OH)	82
63	H	Ph_2CO	$Ph_2C(OH)$	84
64	H	MeI	Me	80
65	H	D_2O	D	89
66	Me	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	76
67	Me	PhCHO	PhCH(OH)	70
68	Me	Ph_2CO	$Ph_2C(OH)$	72
69	Me	EtI	Et	80
70	Me	D_2O	D	86
71	OMe	4-$MeOC_4H_6CHO$	4-$MeOC_4H_6CH(OH)$	85
72	OMe	PhCHO	PhCH(OH)	89
73	OMe	Ph_2CO	$Ph_2C(OH)$	84
74	OMe	D_2O	D	86
75	OMe	EtI	Et	88[b]
76	Cl	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	79
77	Cl	PhCHO	PhCH(OH)	79
78	Cl	EtI	Et	78
79	Cl	D_2O	D	79
80	F	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	83
81	F	PhCHO	PhCH(OH)	83
82	F	D_2O	D	86

[a] Yield of isolated product after purification by column chromatography.
[b] *N'*-Ethyl-*N'*-(2-ethyl-4-methoxybenzyl)-*N*,*N*-dimethylurea **83** was obtained in 3% yield, as a side-product and in 90% yield when the reaction was repeated with 2.2 equivalents of EtI.

In contrast to the situation with the corresponding pivalamide, lithiation of *N'*-(2-methoxybenzyl)-*N*,*N*-dimethylurea (**84**, Scheme 6) under the above conditions, and then reaction with 4-anisaldehyde and separation by column chromatography, gave *N'*-(2-(hydroxy(4-methoxyphenyl)methyl)-6-methoxybenzyl)-*N*,*N*-dimethylurea (**85**; 29%) and *N'*-(3-(hydroxy-(4-methoxyphenyl)methyl)-2-methoxybenzyl)-*N*,*N*-dimethylurea (**86**; 26%), along with **84** (39%). The sites of lithiation were the ones expected based on Schlosser's findings with an unspecified reagent, but in the earlier work no pure products were separated from the reaction mixture.[7] It was of interest to see if the reaction would proceed in the same manner under different conditions. Therefore, a more detailed study was conducted using *t*-BuLi with different reaction times and temperatures (Scheme 6). The results obtained are recorded in Table 7.



Scheme 6. Lithiation of **84** followed by reaction with 4-anisaldehyde.

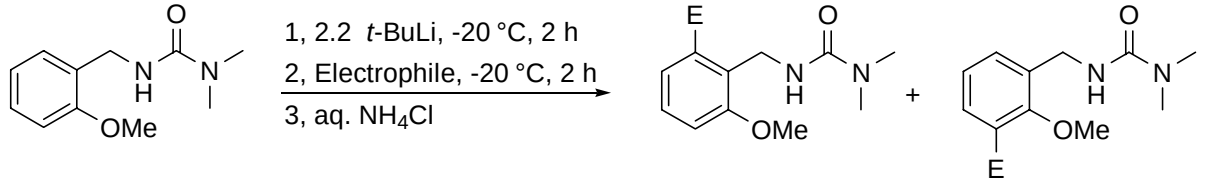
Table 7. Yields from reaction according to Scheme 6 under various conditions

Entry	T (°C)	Time (h) Lithiation	Yield (%)[a]		
			84	**85**	**86**
1	–78	2	39	29	26
2	–78	4	34	31	27
3	–50	2	13	35	33
4	–50	4	13	36	34
5	–20	2	—	49	40

[a] Yield of isolated products after purification.

It was found that at higher temperatures the yields of **85** and **86** were higher than at -78 °C while less of **84** was recovered. At -20 °C no starting material remained and the total yield was good, but there was no significant change in selectivity. Clearly, direct lithiation of **84** on the ring *ortho* to the urea containing group without lithiation *ortho* to the methoxy group was not a realistic hope. Both substitution sites were attacked competitively. It was nevertheless of interest to see if the reaction of **84** would be general and useful. Therefore, lithiation of **84** using *t*-BuLi at –20 °C in THF for 2 h was followed by reactions with various electrophiles for 2 h at -20 °C. The mixtures were separated by column chromatography to give *N'*-(2-substituted

6-methoxybenzyl)-*N*,*N*-dimethylureas, **85**, **87**, **89**, **91** and **93**, and *N*′-(3-substituted 2-methoxybenzyl)-*N*,*N*-dimethylureas, **86**, **88**, **90**, **92** and **94** (Scheme 7), in high overall yields (Table 8).



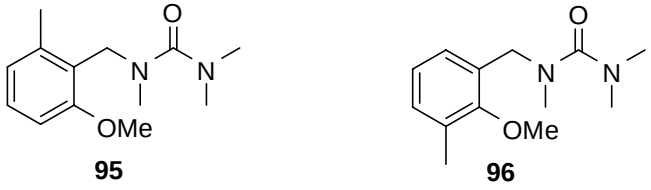
84 **85, 87, 89, 91 and 93** **86, 88, 90, 92 and 94**

Scheme 7. Synthesis of *N*′-(substituted methoxybenzyl)-*N*,*N*-dimethylureas **85-94** *via* lithiation and substitution of **84**.

Table 8. Synthesis of **85-94** according to Scheme 7

Electrophile	E	Product (Yield %)[a]		Overall yield (%)
		2-Substituted-	6-Substituted-	
4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	**85** (49)	**86** (40)	89
PhCHO	PhCH(OH)	**87** (51)	**88** (38)	89
Ph_2CO	$Ph_2C(OH)$	**89** (47)	**90** (30)	77
MeI[b]	Me	**91** (51)	**92** (40)	91
EtI	Et	**93** (51)	**94** (38)	89

[a] Yield of isolated products after purification by column chromatography.
[b] A mixture of **95** and **96** (Figure 7), which was difficult to separate, was also obtained, in 5% yield.



95 **96**

Figure 7. Structures of by-products **95** and **96**.

From the results recorded in Table 8 it is clear that different electrophiles give the corresponding products in comparable yields. The ^{1}H NMR spectra of compounds **85-88** showed two separate double doublets for the diastereotopic hydrogens of the CH_2 groups.

Conclusions

A simple, efficient and high yielding lithiation procedure that allows electrophilic substitution of various substituted benzylamines has been demonstrated. Lithiation of *N*-benzylpivalamide with *t*-BuLi gave a mixture derived from lithiation at ring position 2 (*ortho*-substitution) and on the side-chain CH_2 group (α-substitution). Exclusive ring substitution could be achieved *via* bromine-lithium exchange of *N*-(2-bromobenzyl)pivalamide and subsequent reactions with electrophiles to give the corresponding *N*-(2-substituted benzyl)pivalamides in high yields.

Lithiation of *N*-(4-substituted benzyl)pivalamides, unsubstituted *N'*-benzyl-*N*,*N*-dimethylurea and *N'*-(4-substituted benzyl)-*N*,*N*-dimethylureas with *t*-BuLi in THF at -78 °C followed by reactions with a variety of electrophiles gave high yields of products involving substitution at the 2-position. Unexpectedly, *N*-(2-methoxybenzyl)pivalamide undergoes lithiation *ortho*- to the methoxy group with *t*-BuLi at -78 °C, while use of *n*-BuLi or *sec*-BuLi under similar conditions gives almost no lithiation at this position, leading instead to competitive lithiation on the side-chain (pivaloylaminomethyl group) and *ortho*- to the pivaloylaminomethyl group. By contrast, lithiation of *N'*-(2-methoxybenzyl)-*N*,*N*-dimethylurea with *t*-BuLi at -20 °C in THF followed by reactions with a range of electrophiles gives mixtures of products involving ring substitution both next to the methoxy group (*o'*-substitution) and next to the urea containing group (*o*-substitution).

Clearly, all factors can be significant in determining the position of substitution in such systems and the right choice of lithiating agent, substituent group and reaction conditions are necessary in order to ensure that the desired product is obtained.

Experimental Section

General. Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 or AV500 spectrometer operating at 400 or 500 MHz for ^{1}H or 100 and 125 MHz for ^{13}C measurements. Chemical shifts δ are reported in parts per million (ppm) relative to TMS and coupling constants *J* are in Hz and have been rounded to the nearest whole number. ^{13}C multiplicities were revealed by DEPT signals. Assignments of signals are based on integration values, coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. Low-resolution mass spectra (see supplementary information) were recorded on a Quattro II spectrometer, electron impact (EI) at 70 eV and chemical ionization (CI) at 50 eV by the use of NH_3 as ionization gas. Atmospheric pressure chemical ionization mass spectra (APCI) were performed on a Waters LCT Premier XE instrument. Electrospray (ES) analyses were performed on a ZQ4000 spectrometer in positive and negative ionisation modes. Accurate mass data were obtained on a MAT900 instrument. IR spectra (see supplementary information) were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer or a Perkin Elmer 1600 series FT-IR

Spectrometer. Microanalyses were performed by Warwick analytical service at the University of Warwick. The X-ray single-crystal diffraction data were collected on a Nonius Kappa CCD diffractometer using graphite-monochromated Mo-K_α, (λ = 0.710 73 Å) radiation. Crystal and structure refinement data are shown in the supplementary information. The structures were solved by direct methods using SHELXS-96[12] and refined with all data on F^2 full-matrix least squares using SHELXL-97.[13] Non-hydrogen atoms were generally refined anisotropically. Hydrogen atom positions were located from difference Fourier maps and a riding model with atomic displacement parameters 1.2 times (1.5 times for methyl groups) those of the atom to which they are bonded was used for subsequent refinements. Despite the poor quality of the crystals of **53** the structural results obtained are good enough to support the conclusions reached in the discussion. Full crystallographic data have been deposited with the CCDC, reference numbers 736581-736588 and 736920, and can be obtained free of charge *via* http://www.ccdc.ac.uk/data_request/cif. Column chromatography was carried out using Fischer Scientific silica 60A (35-70 micron). Alkyllithiums were obtained from Aldrich Chemical Company and were estimated prior to use by the method of Watson and Eastham.[14] Other chemicals were obtained from Aldrich Chemical Company and used without further purification. THF was distilled from sodium benzophenone ketyl. Other solvents were purified by standard procedures.[15]

General procedure for the lithiation and substitution of *N*-benzylpivalamide (6)

A solution of *t*-BuLi in pentane (2.6 mL, 1.7 M, 4.4 mmol) was added to a stirred solution of **6** (0.38 g, 2.0 mmol) at the appropriate temperature (–78, 0 or 20 °C) in THF (20 mL) under N_2. The mixture was stirred at the appropriate temperature for 2–4 h and a solution of benzophenone (0.40 g, 2.2 mmol) in THF (8 mL) was added. The reaction mixture was stirred for 2 h at the appropriate temperature, and then allowed to warm to room temperature if the reaction was carried out at low temperature. It was then diluted with EtOAc (20 mL) and quenched with aq. sat. NH_4Cl (20 mL). Following work-up, the residue obtained was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure products **7** and **8**. The yields obtained of **7** and **8** under various reaction conditions are recorded in Table 1.

***N*-(2-Hydroxy-1,2,2-triphenylethyl)pivalamide (7).** 44 mg–0.31 g (0.12–0.83 mmol, 6–42%). Mp 229–230 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58 (d, *J* = 9 Hz, exch., 1 H, NH), 7.55–7.02 (m, 15 H, 3 Ph), 6.21 (br, exch., 1 H, OH), 5.88 (d, *J* = 9 Hz, 1 H, CH), 0.92 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.0 (C=O), 147.5 (C-1 of Ph), 145.9 (C-1 of Ph), 140.6 (C-1), 129.9 (C-3/C-5), 128.6, 128.2 (C-3/C-5 of 2 Ph), 127.6 (C-2/C-6), 127.4 (C-4), 127.1, 126.7 (C-2/C-6 of 2 Ph), 127.0, 126.9 (C-4 of 2 Ph), 80.7 (C-OH), 59.9 (CH), 38.8 [*C*$(CH_3)_3$], 27.9 [C(*C*$H_3)_3$]. HRMS (CI): *m/z* calcd for $C_{25}H_{28}NO_2$ $[MH]^+$: 374.2115; found: 374.2114. Anal. Calcd for $C_{25}H_{27}NO_2$: C, 80.40; H, 7.29; N, 3.75. Found: C, 80.41; H, 7.27; N, 3.76.

***N*-(2-(Hydroxydiphenylmethyl)benzyl)pivalamide (8).** 74 mg–0.25 g (0.20–0.67 mmol, 10–34%). Mp 218–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.85 (t, *J* = 6 Hz, exch., 1 H, NH),

7.35–7.32 (m, 5 H, H-4 and H-3/H-5 of 2 Ph), 7.28–7.23 (m, 7 H, H-6 and H-2/H-6 and H-4 of 2 Ph), 7.08–7.04 (m, 2 H, H-5 and OH), 6.53 (d, J = 8 Hz, 1 H, H-3), 4.02 (d, J = 6 Hz, 2 H, CH_2), 1.08 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.5 (C=O), 148.5 (C-1 of 2 Ph), 145.3 (C-1), 140.2 (C-2), 129.7 (C-3), 129.4 (C-6), 128.6 (C-3/C-5 of 2 Ph), 128.4 (C-4), 128.3 (C-2/C-6 of 2 Ph), 127.6 (C-4 of 2 Ph), 126.4 (C-5), 82.3 (C-OH), 41.9 (CH_2), 38.8 [$C(CH_3)_3$], 28.2 [$C(CH_3)_3$]. HRMS (EI): *m/z* calcd for $C_{25}H_{27}NO_2$ $[M]^+$: 373.2036; found: 373.2043.

_N_-(2-Substituted benzyl)pivalamides 8 and 10-14

To a cooled solution (–78 °C) of *N*-(2-bromobenzyl)pivalamide (**9**; 0.54 g, 2.0 mmol) in anhydrous THF (20 mL) under a nitrogen atmosphere was added a solution of MeLi in Et_2O (2.2 mL, 1.0 M, 2.2 mmol), in order to deprotonate the nitrogen. The mixture was stirred for 10 min at –78 °C. Bromine-lithium exchange was then effected by the addition of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol). The mixture was stirred at -78 °C for 2 h, to ensure the complete formation of the dilithium reagent, after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at -78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. Following work-up, the crude product obtained was purified by crystallization from EtOAc–Et_2O (1:3) to give a white solid. The yields obtained are recorded in Table 2.

***N*-(2-(Hydroxydiphenylmethyl)benzyl)pivalamide (8).** 0.67 g (1.80 mmol, 90%). Mp 218–219 °C. The material produced was found to be identical in all respects with the one produced from ring lithiation of **6** followed by reaction with benzophenone.

***N*-(2-(1-Hydroxycyclohexyl)benzyl)pivalamide (10).** Yield: 0.52 g (1.80 mmol, 90%). Mp 127–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.35 (m, 2 H, H-3 and H-5), 7.28–7.19 (m, 2 H, H-4 and H-6), 6.67 (br, exch., 1 H, NH), 4.73 (d, J = 5 Hz, 2 H, CH_2N), 2.89 (s, exch., 1 H, OH), 2.00-1.68 [m, 10 H, $(CH_2)_5$], 1.16 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.5 (C=O), 146.7 (C-2), 137.7 (C-1), 132.5 (C-6), 127.7 (C-3), 127.6 (C-4), 126.0 (C-5), 75.0 (C-1 of cyclohexyl), 43.2 (CH_2NH), 39.2 (C-2/C-6 of cyclohexyl), 38.9 [$C(CH_3)_3$], 27.9 [$C(CH_3)_3$], 25.7 (C-4 of cyclohexyl), 22.4 (C-3/C-5 of cyclohexyl). HRMS (CI): *m/z* calcd for $C_{18}H_{28}NO_2$ $[MH]^+$: 290.2115; found: 290.2116.

***N*-(2-(Hydroxyphenylmethyl)benzyl)pivalamide (11).** 0.51 g (1.72 mmol, 86%). Mp 138–139 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (app. t, J = 6 Hz, exch., 1 H, NH), 7.45 (dd, J = 2, 8 Hz, 1 H, H-6), 7.33–7.14 (m, 8 H, H-3, H-4, H-5 and Ph), 5.95 (d, J = 5 Hz, exch., 1 H, OH), 5.91 (d, J = 5 Hz, 1 H, CH), 4.34 (dd, J = 6, 16 Hz, 1 H, CH_aH_b), 4.17 (dd, J = 6, 16 Hz, 1 H, CH_aH_b), 1.13 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.1 (C=O), 145.2 (C-1 of Ph), 143.1 (C-1), 137.4 (C-2), 128.9 (C-3/C-5 of Ph), 127.8 (C-2/C-6 of Ph), 127.7 (C-4 of Ph), 127.6 (C-3), 127.5 (C-4), 127.4 (C-5), 127.3 (C-6), 71.7 (CH), 40.2 (CH_2), 38.9 [$C(CH_3)_3$], 28.3 [$C(CH_3)_3$]. HRMS: *m/z* calcd for $C_{19}H_{24}NO_2$ $[MH]^+$: 298.1802; found: 298.1805.

***N*-(2-(Hydroxy-(4-methoxyphenyl)methyl)benzyl)pivalamide (12).** 0.57 g (1.74 mmol, 87%). Mp 164–166 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.87 (app. t, J = 5 Hz, exch., 1 H, NH), 7.48 (dd, J = 2, 8 Hz, 1 H, H-6), 7.27–7.20 (m, 4 H, H-4, H-5 and H-2/H-6 of 4-methoxyphenyl),

7.13 (d, *J* = 8 Hz, 1 H, H-3), 6.89 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.88 (d, *J* = 4 Hz, exch., 1 H, OH), 5.79 (d, *J* = 4 Hz, 1 H, CH), 4.33 (dd, *J* = 5, 16 Hz, 1 H, C$H_a$$H_b$), 4.10 (dd, *J* = 5, 16 Hz, 1 H, C$H_a$$H_b$), 3.73 (s, 3 H, OCH_3), 1.13 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 177.6 (C=O), 158.5 (C-4 of 4-methoxyphenyl), 142.8 (C-1), 142.7 (C-2), 136.7 (C-1 of 4-methoxyphenyl), 128.6 (C-2/C-6 of 4-methoxyphenyl), 127.0 (C-3), 126.9 (C-6), 126.8 (C-4), 126.7 (C-5), 114.1 (C-3/C-5 of 4-methoxyphenyl), 70.8 (CH), 55.4 (OCH_3), 39.8 (CH_2), 38.4 [*C*$(CH_3)_3$], 27.8 [C(*C*$H_3)_3$]. HRMS (CI): *m/z* calcd for $C_{20}H_{25}NO_3$ $[MH]^+$: 328.1907; found: 328.1908. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.71; N, 4.22. Found: C, 73.37; H, 7.70; N, 4.28.

***N*-(2-(Deuteriobenzyl)pivalamide (13).** 0.35 g (1.82 mmol, 91%). Mp 81–82 °C (Mp of undeuteriated analogue 79–78 °C[16]). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.23 (m, 2 H, H-3 and H-5), 7.21–7.17 (m, 2 H, H-4 and H-6), 5.92 (br, exch., 1 H, NH), 4.35 (d, *J* = 4 Hz, 2 H, CH_2), 1.15 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (C=O), 139.0 (C-1), 129.1 (C-4), 129.0 (C-6), 128.0 (C-3), 127.8 (C-5), 127.5 (seen as three lines, 1:1:1, because of coupling to D, C-2), 43.8 (CH_2), 39.1 [*C*$(CH_3)_3$], 28.0 [C(*C*$H_3)_3$]. HRMS (CI): *m/z* calcd for $C_{12}H_{17}DNO$ $[MH]^+$: 193.1446; found: 193.1445.

***N*-(2-Methylbenzyl)pivalamide (14).** 0.35 g, (1.70 mmol, 85%). Mp 108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07–7.02 (m, 4 H, H-3, H-4, H-5 and H-6), 5.65 (br, exch., 1 H, NH), 4.29 (d, *J* = 5 Hz, 2 H, CH_2), 2.17 (s, 3 H, CH_3), 1.09 [s, 9 H, $C(CH_3)_3$].^{13}C NMR (400 MHz, $CDCl_3$): δ = 178.5 (C=O), 136.9 (C-1), 136.6 (C-2), 130.9 (C-3), 128.8 (C-6), 128.1 (C-4), 126.6 (C-5), 42.3 (CH_2), 39.2 [*C*$(CH_3)_3$], 28.0 [C(*C*$H_3)_3$], 19.3 (CH_3). HRMS (CI): *m/z* calcd for $C_{13}H_{20}NO$ $[MH]^+$: 206.1539; found: 206.1542.

General procedure for the lithiation of substituted *N*-benzylpivalamides and *N'*-benzyl-*N*,*N*-dimethylureas and subsequent reactions with electrophiles

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-78 °C), stirred solution of the appropriate substituted benzylamine (2.0 mmol) in anhydrous THF (20 mL) under N_2. Formation of the dilithium reagent was observed as a brownish solution. The mixture was stirred at –78 °C for 4 h, to ensure the complete formation of the dilithium reagent, after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at –78 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was diluted with Et_2O (10 mL) and quenched with aq. sat. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the corresponding pure products. In the case of carbon dioxide as electrophile the procedure was slightly different – see specific cases (**47** and **55**) for details.

***N*-(2-(Hydroxy-(4-methoxyphenyl)methyl)-4-methylbenzyl)pivalamide (19).** 0.55 g (1.61 mmol, 81%). Mp 184–186 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.55 (app. t, *J* = 6 Hz, exch., 1 H, NH), 7.05 (s, 1 H, H-3), 6.96 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 6.78 (br, 2

H, H-5 and H-6), 6.62 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.60 (d, *J* = 4 Hz, 1 H, CH), 5.51 (d, *J* = 4 Hz, exch., 1 H, OH), 4.02 (dd, *J* = 6, 15 Hz, 1 H, C$H_a$$H_b$), 3.79 (dd, *J* = 6, 15 Hz, 1 H, C$H_a$$H_b$), 3.48 (s, 3 H, OCH_3), 2.03 (s, 3 H, CH_3), 0.86 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.0 (C=O), 158.9 (C-4 of 4-methoxyphenyl), 143.2 (C-2), 137.3 (C-1), 136.1 (C-4), 134.2 (C-1 of 4-methoxyphenyl), 129.0 (C-2/C-6 of 4-methoxyphenyl), 128.1 (C-3), 128.0 (C-6), 127.7 (C-5), 114.2 (C-3/C-5 of 4-methoxyphenyl), 71.3 (CH), 55.9 (OCH_3), 40.0 (CH_2), 38.9 [*C*$(CH_3)_3$], 28.3 [C(*C*$H_3)_3$], 21.8 (CH_3). HRMS (ES^-): *m/z* calcd for $C_{21}H_{26}NO_3$ $[M - 1]^-$: 340.1918; found: 340.1908.

***N*-(2-(Hydroxyphenymethyl)-4-methylbenzyl)pivalamide (20).** 0.49 g (1.58 mmol, 79%). Mp 150–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.06 (m, 7 H, Ph, H-3 and H-6), 7.00 (dd, *J* = 2, 8 Hz, 1 H, H-5), 5.99 (br t, exch., 1 H, NH), 5.92 (br, 1 H, CH), 4.29 (dd, *J* = 5, 14 Hz, 1 H, C$H_a$$H_b$), 4.16 (dd, *J* = 5, 14 Hz, 1 H, C$H_a$$H_b$), 3.40 (br, exch., 1 H, OH), 2.23 (s, 3 H, CH_3), 0.97 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7 (C=O), 143.9 (C-1 of Ph), 141.8 (C-2), 137.9 (C-1), 133.7 (C-4), 130.7 (C-3), 129.4 (C-6), 129.3 (C-5), 128.9 (C-3/C-5 of Ph), 127.8 (C-4 of Ph), 127.1 (C-2/C-6 of Ph), 74.1 (CH), 41.1 (CH_2), 38.9 [*C*$(CH_3)_3$], 27.8 [C(*C*$H_3)_3$], 21.6 (CH_3). HRMS (ES^+): *m/z* calcd for $C_{20}H_{26}NO_2$ $[MH]^+$: 312.1958; found: 312.1960. Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.23; H, 8.14; N, 4.45.

***N*-(2-(Hydroxydiphenylmethyl)-4-methylbenzyl)pivalamide (21).** 0.63 g (1.63 mmol, 81%). Mp 244–246 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.81 (br t, exch., 1 H, NH), 7.34–7.24 (m, 10 H, 2 Ph), 7.17 (d, *J* = 8 Hz, 1 H, H-6), 7.08 (d, *J* = 8 Hz, 1 H, H-5), 7.05 (s, 1 H, H-3), 6.36 (s, exch., 1 H, OH), 3.93 (d, *J* = 5 Hz, 2 H, CH_2), 2.08 (s, 3 H, CH_3), 1.07 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.4 (C=O), 148.6 (C-1 of 2 Ph), 145.3 (C-2), 137.1 (C-1), 135.2 (C-4), 130.4 (C-3), 129.7 (C-6), 129.0 (C-5), 128.6 (C-3/C-5 of 2 Ph), 128.3 (C-2/C-6 of 2 Ph), 127.5 (C-4 of 2 Ph), 82.2 (C-OH), 41.7 (CH_2), 38.7 [*C*$(CH_3)_3$], 28.2 [C(*C*$H_3)_3$], 21.8 (CH_3). HRMS (CI): *m/z* calcd for $C_{26}H_{30}NO_2$ $[MH]^+$: 388.2271; found: 388.2266.

***N*-(2-(1-Hydroxycyclohexyl)-4-methylbenzyl)pivalamide (22).** 0.50 g (1.65 mmol, 82%). Mp 127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8 Hz, 1 H, H-6), 7.08 (s, 1 H, H-3), 6.93 (d, *J* = 8 Hz, 1 H, H-5), 6.57 (br t, exch., 1 H, NH), 4.59 (d, *J* = 5 Hz, 2 H, CH_2N), 2.85 (br s, exch., 1 H, OH), 2.24 (s, 3 H, CH_3), 1.89–1.59 [m, 10 H, $(CH_2)_5$], 1.06 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (C=O), 146.6 (C-2), 137.1 (C-1), 134.6 (C-4), 132.6 (C-3), 128.3 (C-6), 126.8 (C-5), 75.0 (C-1 of cyclohexyl), 43.0 (CH_2NH), 39.2 (C-2/C-6 of cyclohexyl), 38.9 [*C*$(CH_3)_3$], 27.9 [C(*C*$H_3)_3$], 25.8 (C-4 of cyclohexyl), 22.4 (C-3/C-5 of cyclohexyl), 21.7 (CH_3). HRMS (CI): *m/z* calcd for $C_{19}H_{30}NO_2$ $[MH]^+$: 304.2271; found: 304.2275.

***N*-(2-Deuterio-4-methylbenzyl)pivalamide (23).** 0.39 g (1.76 mmol, 88%). Mp 96–97 °C (Mp of undeuteriated analogue 94–96 °C[17]). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.05 (m, 3 H, H-3, H-5 and H-6), 5.84 (br, exch., 1 H, NH), 4.03 (d, *J* = 5 Hz, 2 H, CH_2), 2.26 (s, 3 H, CH_3), 1.14 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6 (C=O), 137.5 (C-1), 135.9 (C-4), 129.8 (C-3), 129.7 (C-5), 128.1 (C-6), 127.8 (seen as three lines, 1:1:1, because of coupling to D, C-2), 43.7 (CH_2), 39.1 [*C*$(CH_3)_3$], 28.0 [C(*C*$H_3)_3$], 21.5 (CH_3). HRMS (CI): *m/z* calcd for $C_{13}H_{19}DNO$ $[MH]^+$: 207.1602; found: 207.1598.

***N*-(2,4-Dimethylbenzyl)pivalamide (24).** 0.35 g (1.60 mmol, 80%). Mp 95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8 Hz, 1 H, H-6), 6.93 (s, 1 H, H-3), 6.90 (d, *J* = 8 Hz, 1 H, H-5), 5.63 (br, exch., 1 H, NH), 4.30 (d, *J* = 5 Hz, 2 H, CH_2), 2.23 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3), 1.13 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (C=O), 137.8 (C-1), 136.9 (C-2), 133.5 (C-4), 131.8 (C-3), 129.1 (C-6), 127.2 (C-5), 42.2 (CH_2), 39.1 [*C*$(CH_3)_3$], 28.1 [C(*C*$H_3)_3$], 21.4 (CH_3), 19.3 (CH_3). HRMS (CI): *m/z* calcd for $C_{14}H_{22}NO$ $[MH]^+$: 220.1696; found: 220.1693.

***N*-(2-Ethyl-4-methylbenzyl)pivalamide (25).** 0.38 g (1.63 mmol, 81%). Mp 88–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8 Hz, 1 H, H-6), 6.97 (s, 1 H, H-3), 6.92 (d, *J* = 8 Hz, 1 H, H-5), 5.60 (br, exch., 1 H, NH), 4.33 (d, *J* = 5 Hz, 2 H, CH_2N), 2.54 (q, *J* = 7 Hz, 2 H, C*H*$_2$CH$_3$), 2.26 (s, 3 H, CH_3), 1.13 [s, 9 H, $C(CH_3)_3$], 1.11 (t, *J* = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (C=O), 143.0 (C-1), 138.1 (C-2), 132.8 (C-4), 130.1 (C-3), 129.5 (C-6), 126.8 (C-5), 41.6 (CH_2), 39.1 [*C*$(CH_3)_3$], 28.0 [C(*C*$H_3)_3$], 25.7 (*C*H_2CH_3), 21.5 (CH_3), 16.0 (CH_2*C*H_3). HRMS (CI): *m/z* calcd for $C_{15}H_{24}NO$ $[MH]^+$: 234.1852; found: 234.1854.

***N*-(4-Methoxy-2-methylbenzyl)pivalamide (26).** 0.38 g (1.62 mmol, 81%). Mp 93–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (d, *J* = 8 Hz, 1 H, H-6), 6.66 (d, *J* = 2 Hz, 1 H, H-3), 6.62 (dd, *J* = 2, 8 Hz, 1 H, H-5), 5.64 (br, exch., 1 H, NH), 4.27 (d, *J* = 5 Hz, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 2.20 (s, 3 H, CH_3), 1.12 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (C=O), 159.5 (C-4), 138.5 (C-2), 130.4 (C-6), 128.7 (C-1), 116.7 (C-3), 115.5 (C-5), 55.6 (OCH_3), 41.9 (CH_2), 39.1 [*C*$(CH_3)_3$], 28.0 [C(*C*$H_3)_3$], 19.6 (CH_3). HRMS (CI): *m/z* calcd for $C_{14}H_{22}NO_2$ $[MH]^+$: 236.1645; found: 236.1646.

***N*-(2-(Hydroxydiphenylmethyl)-4-methoxybenzyl)pivalamide (27).** 0.64 g (1.60 mmol, 80%). Mp 205–207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 11 H, H-6 and 2 Ph), 6.79 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.41 (t, *J* = 6 Hz, exch., 1 H, NH), 6.26 (d, *J* = 2 Hz, 1 H, H-3), 5.22 (s, exch., 1 H, OH), 4.08 (d, *J* = 6 Hz, 2 H, CH_2), 3.63 (s, 3 H, OCH_3), 1.05 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8 (C=O), 158.1 (C-4), 147.7 (C-1 of 2 Ph), 146.7 (C-2), 132.8 (C-6), 131.1 (C-1), 128.4 (C-3/C-5 of 2 Ph), 128.2 (C-2/C-6 of 2 Ph), 127.6 (C-4 of 2 Ph), 117.1 (C-3), 112.8 (C-5), 82.9 (C-OH), 55.4 (OCH_3), 41.9 (CH_2), 38.8 [*C*$(CH_3)_3$], 27.8 [C(*C*$H_3)_3$]. HRMS (ES^+): *m/z* calcd for $C_{26}H_{29}NO_3Na$ $[M + Na]^+$: 426.2040; found: 426.2041.

***N*-(2-(1-Hydroxycyclohexyl)-4-methoxybenzyl)pivalamide (28).** 0.49 g (1.54 mmol, 77%). Mp: 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8 Hz, 1 H, H-6), 6.83 (d, *J* = 2 Hz, 1 H, H-3), 6.64 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.56 (br t, exch., 1 H, NH), 4.55 (d, *J* = 6 Hz, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 2.72 (s, exch., 1 H, OH), 1.89–1.61 [m, 10 H, $(CH_2)_5$], 1.06 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (C=O), 158.9 (C-4), 148.4 (C-2), 133.8 (C-6), 129.8 (C-1), 113.1 (C-3), 111.5 (C-5), 74.9 (C-1 of cyclohexyl), 55.6 (OCH_3), 42.7 (CH_2NH), 39.1 (C-2/C-6 of cyclohexyl), 38.9 [*C*$(CH_3)_3$], 27.9 [C(*C*$H_3)_3$], 25.7 (C-4 of cyclohexyl), 22.4 (C-3/C-5 of cyclohexyl). HRMS (CI): *m/z* calcd for $C_{19}H_{30}NO_3$ $[MH]^+$: 320.2220; found: 320.2225.

***N*-(2-(2-Hydroxyhexan-2-yl)-4-methoxybenzyl)pivalamide (29).** 0.50 g (1.56 mmol, 78%). Mp 102–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (d, *J* = 8 Hz, 1 H, H-6), 6.72 (d, *J* = 2

Hz, 1 H, H-3), 6.68 (br, exch., 1 H, NH), 6.64 (dd, *J* = 2, 8 Hz, 1 H, H-5), 4.54 (dd, *J* = 6, 14 Hz, 1 H, C*H*$_a$H$_b$NH), 4.50 (dd, *J* = 5, 14 Hz, 1 H, CH$_a$*H*$_b$NH), 3.71 (s, 3 H, OCH$_3$), 2.83 (s, exch., 1 H, OH), 1.85 (m, 1 H, C*H*$_c$H$_d$COH), 1.74 (m, 1 H, CH$_c$*H*$_d$COH), 1.55 (s, 3 H, C*H*$_3$COH), 1.25–1.11 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 1.05 [s, 9 H, C(CH$_3$)$_3$], 0.78 (app. t, *J* = 7 Hz, 3 H, C*H*$_3$CH$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 178.3 (C=O), 158.7 (C-4), 146.9 (C-2), 134.1 (C-6), 129.5 (C-1), 114.1 (C-3), 111.3 (C-5), 77.0 (C-OH), 55.6 (OCH$_3$), 44.7 (*C*H$_2$CH$_2$CH$_2$CH$_3$), 42.9 (CH$_2$NH), 38.9 [*C*(CH$_3$)$_3$], 31.5 (*C*H$_3$COH), 27.9 [C(*C*H$_3$)$_3$], 26.9 (*C*H$_2$CH$_2$CH$_3$), 23.5 (*C*H$_2$CH$_3$), 14.4 (CH$_2$*C*H$_3$). HRMS (CI): *m/z* calcd for C$_{19}$H$_{32}$NO$_3$ [MH]$^+$: 322.2377; found: 322.2379.

***N*-(2-(Hydroxy-(4-methoxyphenyl)methyl)-4-methoxybenzyl)pivalamide (30).** 0.58 g (1.64 mmol, 82%). Mp 130–132 °C. ^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 7.76 (app. t, *J* = 6 Hz, exch., 1 H, NH), 7.22 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.08 (d, *J* = 2 Hz, 1 H, H-3), 7.07 (d, *J* = 8 Hz, 1 H, H-6), 6.88 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.80 (dd, *J* = 2, 8 Hz, 1 H, H-5), 5.86 (s, 1 H, CH), 5.81 (s, exch., 1 H, OH), 4.26 (dd, *J* = 6, 15 Hz, 1 H, C*H*$_a$CH$_b$), 3.98 (dd, *J* = 6, 15 Hz, 1 H, CH$_a$*H*$_b$), 3.74 (s, 3 H, OCH$_3$), 3.73 (s, 3 H, OCH$_3$), 1.11 [s, 9 H, C(CH$_3$)$_3$]. ^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 177.5 (C=O), 158.5 (C-4), 158.4 (C-4 of 4-methoxyphenyl), 144.3 (C-2), 136.6 (C-1 of 4-methoxyphenyl), 136.5 (C-1), 128.7 (C-6), 128.6 (C-2/C-6 of 4-methoxyphenyl), 113.8 (C-3/C-5 of 4-methoxyphenyl), 112.8 (C-3), 111.9 (C-5), 70.8 (CH), 55.4 (OCH$_3$), 55.3 (OCH$_3$), 39.2 [*C*(CH$_3$)$_3$], 39.4 (CH$_2$), 27.8 [C(*C*H$_3$)$_3$]. HRMS (ES$^+$): *m/z* calcd for C$_{21}$H$_{27}$NO$_4$Na [M + Na]$^+$: 380.1832; found: 380.1832. Anal. Calcd for C$_{21}$H$_{27}$NO$_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.63; H, 7.64; N, 3.89.

***N*-(2-Deuterio-4-methoxybenzyl)pivalamide (31).** 0.39 g (1.76 mmol, 88%). Mp 90–91 °C (Mp of undeuteriated analogue 88–90 °C[17]). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.18 (d, *J* = 8 Hz, 1 H, H-6), 6.88–6.76 (m, 2 H, H-3 and H-5), 5.96 (br t, exch., 1 H, NH), 4.34 (d, *J* = 6 Hz, 2 H, CH$_2$), 3.79 (s, 3 H, OCH$_3$), 1.21 [s, 9 H, C(CH$_3$)$_3$]. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 178.6 (C=O), 159.3 (C-4), 131.1 (C-1), 129.4 (C-6), 129.1 (seen as three lines, 1:1:1, because of coupling to D, C-2), 114.5 (C-3), 114.4 (C-5), 55.7 (OCH$_3$), 43.4 (CH$_2$), 39.1 [*C*(CH$_3$)$_3$], 28.0 [C(*C*H$_3$)$_3$]. HRMS (CI): *m/z* calcd for C$_{13}$H$_{19}$DNO$_2$ [MH]$^+$: 223.1551; found: 223.1553.

***N*-(4-Chloro-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)pivalamide (32).** 0.60 g (1.66 mmol, 83%). Mp 212–214 ºC. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 7.93 (br, exch., 1 H, NH), 7.50 (s, 1 H, H-3), 7.30 (d, *J* = 8 Hz, 1 H, H-5), 7.20 (d, 2 H, *J* = 9 Hz, H-2/H-6 of 4-methoxyphenyl), 7.12 (d, *J* = 8 Hz, 1 H, H-6), 6.88 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.93 (d, *J* = 3 Hz, exch., 1 H, OH), 5.89 (d, *J* = 3 Hz, 1 H, CH), 4.30 (dd, *J* = 6, 14 Hz, 1 H, C*H*$_a$H$_b$), 3.95 (dd, *J* = 6, 14 Hz, 1 H, CH$_a$*H*$_b$), 3.70 (s, 3 H, OCH$_3$), 1.10 [s, 9H, C(CH$_3$)$_3$]. ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ = 177.9 (C=O), 158.8 (C-4 of 4-methoxyphenyl), 145.3 (C-1), 136.0 (C-1 of 4-methoxyphenyl), 135.8 (C-2), 131.6 (C-4), 129.0 (C-6), 128.8 (C-2/C-6 of 4-methoxyphenyl), 127.0 (C-3), 126.5 (C-5), 114.1 (C-3/C-5 of 4-methoxyphenyl), 70.4 (CH), 55.5 (OCH$_3$), 40.0 [*C*(CH$_3$)$_3$], 38.5 (CH$_2$), 27.9 [C(*C*H$_3$)$_3$]. HRMS (EI): *m/z* calcd for C$_{20}$H$_{24}$NO$_3$^{35}Cl [M]$^+$: 361.1445; found: 361.1447.

***N*-(4-Chloro-2-(hydroxyphenylmethylbenzyl)pivalamide (33).** 0.54 g (1.63 mmol, 82%). Mp 180–182 ºC. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 7.90 (app. t, *J* = 6 Hz, exch., 1 H, NH), 7.85-

7.70 (m, 5 H, Ph), 7.70 (s, 1 H, H-3), 7.67 (d, *J* = 8 Hz, 1 H, H-5), 7.62 (d, *J* = 8 Hz, 1 H, H-6), 6.60 (s, exch., 1 H, OH), 5.85 (s, 1 H, CH), 4.90 (dd, *J* = 6, 14 Hz, 1 H, C*H*$_a$H$_b$), 4.65 (dd, *J* = 6, 14 Hz, 1 H, CH$_a$*H*$_b$), 1.50 [s, 9 H, C(CH$_3$)$_3$]. ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ = 177.9 (C=O), 158.8 (C-2), 145.3 (C-1), 136.0 (C-4), 135.8 (C-1 of Ph), 130.7 (C-4 of Ph), 128.7 (C-3/C-5 of Ph), 127.7 (C-6), 127.6 (C-5), 127.5 (C-3), 127.4 (C-2/C-6 of Ph), 72.1 (CH), 39.9 (CH$_2$), 38.7 [*C*(CH$_3$)$_3$], 27.4 [C(*C*H$_3$)$_3$]. HRMS (EI): *m/z* calcd for C$_{19}$H$_{22}$NO$_2$^{35}Cl [M]$^+$: 331.1339; found: 331.1345.

***N*-(4-Chloro-2-(hydroxydiphenylmethyl)benzyl)pivalamide (34).** 0.64 g (1.57 mmol, 79%). Mp 240–242 ºC. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 7.83 (br, exch., 1 H, NH), 7.38-7.36 (m, 10 H, 2 Ph), 7.30 (d, *J* = 8 Hz, 1 H, H-5), 7.20 (d, *J* = 8 Hz, 1 H, H-6), 7.10 (s, exch., 1 H, OH), 6.50 (s, 1 H, H-3), 3.90 (d, *J* = 6 Hz, 2 H, CH$_2$), 1.07 [s, 9 H, C(CH$_3$)$_3$]. ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ = 178.2 (*C*=O), 147.3 (C-1 of 2 Ph), 147.2 (C-2), 138.9 (C-1), 132.3 (C-4), 130.6 (C-6), 128.9 (C-3), 128.4 (C-3/C-5 of 2 Ph), 127.8 (C-2/C-6 of 2 Ph), 127.5 (C-4 of 2 Ph), 127.5 (C-5), 81.6 (C-OH), 41.0 (CH$_2$), 38.4 [*C*(CH$_3$)$_3$], 27.8 [C(*C*H$_3$)$_3$]. HRMS (APCI): *m/z* calcd for C$_{25}$H$_{26}$NO$_2$^{35}ClK [M + K]$^+$: 446.1289; found: 446.1304.

***N*-(4-Chloro-2-(1-hydroxycyclohexyl)benzyl)pivalamide (35).** 0.47 g (1.45 mmol, 73%). Mp 166–168 ºC. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 7.91 (s, 1 H, H-3), 7.83 (t, *J* = 6 Hz, 1 H, NH), 7.80 (d, *J* = 8 Hz, 1 H, H-5), 7.63 (d, *J* = 8 Hz, 1 H, H-6), 5.22 (s, exch., 1 H, OH), 5.20 (d, *J* = 6 Hz, 2 H, CH$_2$N), 2.40–2.05 [m, 10 H, (CH$_2$)$_5$], 1. 60 [s, 9 H, C(CH$_3$)$_3$]. ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ = 177.8 (C=O), 150.2 (C-2), 138.4 (C-1), 132.4 (C-4), 132.4 (C-6), 126.8 (C-3), 126.0 (C-5), 73.9 (C-OH), 41.7 (CH$_2$NH), 38.8 (C-2/C-6 of cyclohexyl), 29.7 [*C*(CH$_3$)$_3$], 27.4 [C(*C*H$_3$)$_3$], 25.8 (C-4 of cyclohexyl), 22.2 (C-3/C-5 of cyclohexyl). HRMS (EI): *m/z* calcd for C$_{18}$H$_{26}$NO$_2$^{35}Cl [M]$^+$: 323.1652; found: 323.1656.

***N*-(4-Chloro-2-ethylbenzyl)pivalamide (36).** 0.40 g (1.58 mmol, 79%). Mp 117–119 ºC. ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.30 (s, 1 H, H-3), 7.20 (d, *J* = 8 Hz, 1 H, H-5), 7.15 (d, *J* = 8 Hz, 1 H, H-6), 5.80 (br, exch., 1 H, NH), 4.40 (d, *J* = 6 Hz, 2 H, CH$_2$N), 2.65 (q, *J* = 7 Hz, 2 H, C*H*$_2$CH$_3$), 1.20 (t, *J* = 7 Hz, 3 H, CH$_2$C*H*$_3$), 1.20 [s, 9 H, C(CH$_3$)$_3$]. ^{13}C NMR (125 MHZ, CDCl$_3$): δ = 178.1 (C=O), 144.3 (C-2), 134.1 (C-1), 133.5 (C-4), 130.0 (C-6), 128.7 (C-3), 126.2 (C-5), 40.7 (CH$_2$NH), 38.7 [*C*(CH$_3$)$_3$], 27.6 [C(*C*H$_3$)$_3$], 25.2 (*C*H$_2$CH$_3$), 15.5 (CH$_2$*C*H$_3$). HRMS (EI): *m/z* calcd for C$_{14}$H$_{20}$NO^{35}Cl [M]$^+$: 253.1233; found: 253.1234.

***N*-(4-Chloro-2-deuteriobenzyl)pivalamide (37).** 0.40 g (1.76 mmol, 88%). Mp 114–116 ºC (Mp of undeuteriated analogue 114–116 °C[10]). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.30 (d, *J* = 8 Hz, 1 H, H-5), 7.20 (s, 1 H, H-3), 7.18 (d, *J* = 8 Hz, 1 H, H-6), 6.09 (br t, exch., 1 H, NH), 4.40 (d, *J* = 6 Hz, 2 H, CH$_2$), 1.22 [s, 9 H, C(CH$_3$)$_3$]. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 178.4 (C=O), 137.2 (C-1), 133.1 (C-4), 128.9 (C-3), 128.8 (C-5), 128.7 (C-6), 128.6 (seen as three lines, 1:1:1, because of coupling to D, C-2), 42.8 (CH$_2$), 38.7 [*C*(CH$_3$)$_3$], 27.6 [C(*C*H$_3$)$_3$]. HRMS (APCI): *m/z* calcd for C$_{12}$H$_{16}$DNO^{35}Cl [MH]$^+$: 227.1061; found: 227.1059.

***N*-(4-Fluoro-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)pivalamide (38).** 0.54 g (1.56 mmol, 78%). Mp 200–202 ºC. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 7.93 (app. t, *J* = 6 Hz, exch., 1 H, NH), 7.30 (m, 1 H, H-6), 7.20 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.12 (m, 1

H, H-5), 7.05 (m, 1 H, H-3), 6.89 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.93 (s, exch., 1 H, OH), 5.89 (s, 1 H, CH), 4.30 (dd, *J* = 6, 14 Hz, 1 H, C*H*$_a$H$_b$), 3.95 (dd, *J* = 6, 14 Hz, 1 H, CH$_a$*H*$_b$), 3.71 (s, 3 H, OCH$_3$), 1.10 [s, 9H, C(CH$_3$)$_3$]. ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ = 177.8 (C=O), 161.6 (seen as two lines because of coupling to F, *J* = 241 Hz, C-4), 158.8 (C-4 of 4-methoxyphenyl), 145.7 (seen as two lines because of coupling to F, *J* = 8 Hz, C-2), 136.2 (C-1 of 4-methoxyphenyl), 132.7 (seen as two lines because of coupling to F, *J* = 2 Hz, C-1), 129.1 (seen as two lines because of coupling to F, *J* = 8 Hz, C-6), 128.8 (C-2/C-6 of 4-methoxyphenyl), 114.0 (C-3/C-5 of 4-methoxyphenyl), 113.6 (seen as two lines because of coupling to F, *J* = 21 Hz, C-3), 113.3 (seen as two lines because of coupling to F, *J* = 21 Hz, C-5), 70.4 (CH), 55.5 (OCH$_3$), 40.0 [*C*(CH$_3$)$_3$], 38.5 (CH$_2$), 27.9 [C(*C*H$_3$)$_3$]. HRMS (ES$^+$): *m/z* calcd for C$_{20}$H$_{25}$NO$_3$F [MH]$^+$: 346.1818; found: 346.1830.

***N*-(4-Fluoro-2-(hydroxyphenylmethylbenzyl)pivalamide (39).** 0.50 g (1.58 mmol, 79%). Mp 157–159 ºC. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 7.93 (app. t, *J* = 6 Hz, exch., 1H, NH), 7.32-7.23 (m, 6 H, Ph and H-6), 7.15 (m, 1 H, H-5), 7.05 (m, 1 H, H-3), 6.05 (s, exch., 1 H, OH), 5.95 (s, 1 H, CH), 4.30 (dd, *J* = 6, 14 Hz, 1 H, C*H*$_a$H$_b$), 4.02 (dd, *J* = 6, 14 Hz, 1 H, CH$_a$*H*$_b$), 1.10 [s, 9 H, C(CH$_3$)$_3$]. ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ = 161.6 (seen as two lines because of coupling to F, *J* = 241 Hz, C-4), 158.5 (C=O), 145.4 (seen as two lines because of coupling to F, *J* = 8 Hz, C-2), 144.1 (C-1 of Ph), 132.9 (seen as two lines because of coupling to F, *J* = 3 Hz, C-1), 132.9 (C-4 of Ph), 129.3 (seen as two lines because of coupling to F, *J* = 8 Hz, C-6), 128.6 (C-3/C-5 of Ph), 127.5 (C-2/C-6 of Ph), 113.8 (seen as two lines because of coupling to F, *J* = 22 Hz, C-3), 113.6 (seen as two lines because of coupling to F, *J* = 22 Hz, C-5), 70.8 (CH), 40.0 [*C*(CH$_3$)$_3$], 38.5 (CH$_2$), 27.9 [C(*C*H$_3$)$_3$]. HRMS (ES$^+$): *m/z* calcd for C$_{19}$H$_{23}$NO$_2$F [MH]$^+$: 316.1713; found: 316.1715.

***N*-(4-Fluoro-2-(hydroxydiphenylmethyl)benzyl)pivalamide (40).** 0.60 g (1.53 mmol, 76%). Mp 216–218 ºC. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 7.85 (t, *J* = 6 Hz, exch., 1 H, NH), 7.29-7.22 (m, 11 H, 2 Ph and H-6), 7.13-710 (m, 2 H, H-3 and H-5), 6.22 (s, exch., 1 H, OH), 4.95 (d, *J* = 6 Hz, 2 H, CH$_2$), 1.10 [s, 9 H, C(CH$_3$)$_3$]. ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ = 178.1 (C=O), 160.3 (seen as two lines because of coupling to F, *J* = 240 Hz, C-4), 147.4 (seen as two lines because of coupling to F, *J* = 7 Hz, C-2), 135.8 (C-1 of 2 Ph), 132.9 (seen as two lines because of coupling to F, *J* = 3 Hz, C-1), 130.8 (seen as two lines because of coupling to F, *J* = 7 Hz, C-6), 128.4 (C-3/C-5 of 2 Ph), 127.8 (C-2/C-6 of 2 Ph), 127.5 (C-4 of 2 Ph), 116.1 (seen as two lines because of coupling to F, *J* = 22 Hz, C-3), 114.4 (seen as two lines because of coupling to F, *J* = 22 Hz, C-5), 81.6 (C-OH), 40.2 (CH$_2$), 38.4 [*C*(CH$_3$)$_3$], 27.8 [C(*C*H$_3$)$_3$]. HRMS (CI): *m/z* calcd for C$_{25}$H$_{25}$NOF [MH – H$_2$O]$^+$: 374.1920; found: 374.1925.

***N*-(4-Fluoro-2-(1-hydroxycyclohexylbenzyl)pivalamide (41).** 0.50 g (1.63 mmol, 82%). Mp 140–142 ºC. ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ = 7.88 (br, exch., 1 H, NH), 7.22-6.98 (m, 3 H, H-3, H-5 and H-6), 5.0 (s, exch., 1 H, OH), 4.55 (d, *J* = 6 Hz, 2 H, CH$_2$N), 1.93–1.50 [m, 10 H, (CH$_2$)$_5$], 1.10 [s, 9 H, C(CH$_3$)$_3$]. ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ = 177.8 (C=O), 162.2 (seen as two lines because of coupling to F, *J* = 240 Hz, C-4), 150.4 (seen as two lines because of coupling to F, *J* = 8 Hz, C-2), 134.8 (seen as two lines because of coupling to F, *J* = 2 Hz, C-1),

129.9 (seen as two lines because of coupling to F, J = 8 Hz, C-6), 113.1 (seen as two lines because of coupling to F, J = 20 Hz, C-3), 112.5 (seen as two lines because of coupling to F, J = 20 Hz, C-5), 73.0 (C-OH), 41.2 (CH_2NH), 38.5 [$C(CH_3)_3$], 37.7 (C-2/C-6 of cyclohexyl), 27.9 [$C(CH_3)_3$], 25.6 (C-4 of cyclohexyl), 22.3 (C-3/C-5 of cyclohexyl). HRMS (ES^+): *m/z* calcd for $C_{18}H_{27}NO_2F$ $[MH]^+$: 308.2026; found: 308.2039.

***N*-(4-Fluoro-2-ethylbenzyl)pivalamide (42).** 0.39 g (1.64 mmol, 82%). Oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.05 (m, 1 H, H-6), 6.72-6.61 (m, 2 H, H-3 and H-5), 6.49 (br, exch., 1 H, NH), 4.20 (d, J = 6 Hz, 2 H, CH_2N), 2.49 (q, J = 7 Hz, 2 H, CH_2CH_3), 1.10 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.10 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.3 (C=O), 162.1 (seen as two lines because of coupling to F, J = 246 Hz, C-4), 144.3 (seen as two lines because of coupling to F, J = 7 Hz, C-2), 131.6 (seen as two lines because of coupling to F, J = 2 Hz, C-1), 129.6 (seen as two lines because of coupling to F, J = 7 Hz, C-6), 114.9 (seen as two lines because of coupling to F, J = 21 Hz, C-3), 112.4 (seen as two lines because of coupling to F, J = 21 Hz, C-5), 40.3 (CH_2N), 38.5 [$C(CH_3)_3$], 27.4 [$C(CH_3)_3$], 25.1 (CH_2), 14.6 (CH_3). HRMS (EI): *m/z* calcd for $C_{14}H_{20}NOF$ $[M]^+$: 237.1529; found: 237.1522.

***N*-(2-Deuterio-4-fluorobenzyl)pivalamide (43).** 0.36 g (1.71 mmol, 85%). Mp 97–99 ºC (Mp of undeuteriated analogue 97–99 °C[10]). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.12 (m, 1 H, H-6), 6.93-6.89 (m, 2 H, H-3 and H-5), 6.10 (br, exch., 1 H, NH), 4.29 (d, J = 6 Hz, 2 H, CH_2), 1.15 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4 (C=O), 162.1 (seen as two lines because of coupling to F, J = 244 Hz, C-4), 134.5 (seen as two lines because of coupling to F, J = 3 Hz, C-1), 129.2 (seen as two lines because of coupling to F, J = 8 Hz, C-6), 128.9 (seen as six lines, because of coupling to F and D, J = 8, 25 Hz, C-2), 115.5 (seen as two lines because of coupling to F, J = 12 Hz, C-3), 115.3 (seen as two lines because of coupling to F, J = 12 Hz, C-5), 42.7 (CH_2), 38.7 [$C(CH_3)_3$], 27.6 [$C(CH_3)_3$]. HRMS (ES^+): *m/z* calcd for $C_{12}H_{15}DNOF$ $[M]^+$: 210.1279; found: 210.1279.

***N*-(2,4-Dimethylbenzyl)-*N*-methylpivalamide (44).** The procedure was identical with the general one except that excess iodomethane (0.63 g, 4.4 mmol) was used as an electrophile. The reaction mixture was worked-up and purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give **44** as a colourless oil. 0.41 g (1.76 mmol, 88%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.04–6.85 (m, 3 H, H-3, H-5 and H-6), 4.49 (s, 2 H, CH_2), 2.86 (s, 3 H, NCH_3), 2.18 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 1.21 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0 (C=O), 137.0 (C-2), 136.2 (C-4), 133.5 (C-1), 131.6 (C-3), 129.7 (C-6), 127.1 (C-5), 51.1 (CH_2), 39.4 (NCH_3), 36.6 [$C(CH_3)_3$], 28.8 [$C(CH_3)_3$], 21.3 (CH_3), 19.3 (CH_3). HRMS (CI): *m/z* calcd for $C_{15}H_{24}NO$ $[MH]^+$: 234.1852; found: 234.1853.

***N*-(4-Methoxy-2-methylbenzyl)-*N*-methylpivalamide (45).** The procedure was identical with the general one except that excess iodomethane (0.63 g, 4.4 mmol) was used. The reaction mixture was worked-up and purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give **45** (0.43 g, 1.74 mmol, 87%) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.87 (d, J = 8 Hz, 1 H, H-6), 6.61-6.59 (m, 2 H, H-3 and H-5), 4.47 (s, 2 H, CH_2), 3.66 (s, 3 H, OCH_3), 2.85 (s, 3 H, NCH_3), 2.14 (s, 3 H, CH_3), 1.21 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 178.9 (C=O), 159.0 (C-4), 137.8 (C-2), 128.8 (C-1), 127.6 (C-6), 116.6 (C-3), 111.4 (C-5), 55.6 (OCH_3), 50.7 (CH_2), 39.5 [*C*$(CH_3)_3$], 36.4 (NCH_3), 28.8 [C(*C*$H_3)_3$], 19.6 (CH_3). HRMS (CI): *m/z* calcd for $C_{15}H_{24}NO_2$ $[MH]^+$: 250.1802; found: 250.1804.

2-Methoxy-3-(pivaloylaminomethyl)benzoic acid (47). In this case, after formation of the dianion at low temperature, the cooling bath was removed before solid carbon dioxide was added and the mixture was then stirred for 30 minutes while the temperature rose to room temperature and then quenched with HCl (2 M; 5 mL). The crude product was purified by fractional crystallisation using ethyl acetate. 0.42 g (1.59 mmol, 80%). Mp 156–157 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.03 (t, *J* = 6 Hz, exch., 1 H, NH), 7.57 (dd, *J* = 2, 8 Hz, 1 H, H-6), 7.32 (dd, *J* = 2, 8 Hz, 1 H, H-4), 7.16 (app. t, *J* = 8 Hz, 1 H, H-5), 4.32 (d, *J* = 6 Hz, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 1.15 [s, 9 H, C$(CH_3)_3$] (the CO_2H signal was not seen due to exchange with water in the DMSO). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 178.1 (C=O), 167.8 (CO_2H), 157.1 (C-2), 134.6 (C-3), 131.5 (C-4), 129.6 (C-6), 126.1 (C-1), 123.9 (C-5), 62.1 (OCH_3), 38.6 [*C*$(CH_3)_3$], 37.3 (CH_2), 27.9 [C(*C*$H_3)_3$]. HRMS (ES^+): *m/z* calcd for $C_{14}H_{20}NO_4$ $[MH]^+$: 266.1392; found: 266.1386.

***N*-(3-(Hydroxy(4-methoxyphenyl)methyl)-2-methoxybenzyl)pivalamide (48).** 0.54 g (1.52 mmol; 76%). Mp 144–145 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.04 (app. t, *J* = 6 Hz, exch., 1 H, NH), 7.39 (dd, *J* = 2, 8 Hz, 1 H, H-4), 7.28 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.13 (app. t, *J* = 8 Hz, 1 H, H-5), 7.08 (dd, *J* = 2, 8 Hz, 1 H, H-6), 6.89 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.98 (d, *J* = 4 Hz, exch., 1 H, OH), 5.72 (d, *J* = 4 Hz, 1 H, CH), 4.40 (dd, *J* = 6, 16 Hz, 1 H, C*H*$_a$H$_b$), 4.28 (dd, *J* = 6, 16 Hz, 1 H, CH$_a$*H*$_b$), 3.75 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 1.19 [s, 9 H, C$(CH_3)_3$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.4 (C=O), 158.9 (C-2), 154.9 (C-4 of 4-methoxyphenyl), 139.4 (C-1 of 4-methoxyphenyl), 138.3 (C-1), 133.5 (C-3), 128.5 (C-2/C-6 of 4-methoxyphenyl), 127.0 (C-4), 126.8 (C-6), 124.7 (C-5) 114.1 (C-3/C-5 of 4-methoxyphenyl), 68.7 (CH), 61.9 (OCH_3), 55.9 (OCH_3), 38.9 [*C*$(CH_3)_3$], 37.5 (CH_2), 28.3 [C(*C*$H_3)_3$]. HRMS (CI): *m/z* calcd for $C_{21}H_{28}NO_4$ $[MH]^+$: 358.2013; found: 358.2014. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.56; H, 7.64; N, 4.09.

***N*-(3-(Hydroxyphenylmethyl)-2-methoxybenzyl)pivalamide (49).** 0.49 g (1.50 mmol, 75%). Mp 133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7 Hz, 2 H, H-3/H-5 of Ph), 7.36–7.32 (m, 3 H, H-2/H-4/H-6 of Ph), 7.27 (dd, *J* = 2, 8 Hz, 1 H, H-4), 7.19 (dd, *J* = 2, 8 Hz, 1 H, H-6), 7.13 (app. t, *J* = 8 Hz, 1 H, H-5), 6.12 (br app. t, exch., 1 H, NH), 6.10 (s, 1 H, CH), 4.51 (dd, *J* = 6, 15 Hz, 1 H, *H*$_a$H$_b$), 4.44 (dd, *J* = 5, 15 Hz, 1 H, CH$_a$*H*$_b$), 3.59 (s, 3 H, OCH_3), 2.97 (br, exch., 1 H, OH), 1.21 [s, 9 H, C$(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9 (C=O), 156.1 (C-2), 144.1 (C-1 of Ph), 137.8 (C-1), 132.0 (C-3), 129.2 (C-4), 128.8 (C-3/C-5 of Ph), 128.1 (C-4 of Ph), 127.8 (C-6), 126.9 (C-2/C-6 of Ph), 125.2 (C-5), 71.8 (CH), 62.1 (OCH_3), 39.1 (CH_2), 39.0 [*C*$(CH_3)_3$], 28.0 [C(*C*$H_3)_3$]. HRMS (ES^+): *m/z* calcd for $C_{20}H_{26}NO_3$ $[MH]^+$: 328.1907; found: 328.1905. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.39; H, 7.72; N, 4.26.

***N*-(3-(Hydroxydiphenylmethyl)-2-methoxybenzyl)pivalamide (50).** 0.59 g (1.46 mmol, 73%). Mp: 173–174 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.80 (t, *J* = 6 Hz, exch., 1 H, NH), 7.10–

7.01 (m, 10 H, 2 Ph), 6.90 (d, *J* = 8 Hz, 1 H, H-4), 6.76 (app. t, *J* = 8 Hz, 1 H, H-5), 6.48 (dd, *J* = 2, 8 Hz, 1 H, H-6), 5.74 (s, exch., 1 H, OH), 4.04 (d, *J* = 6 Hz, 2 H, CH_2), 3.12 (s, 3 H, OCH_3), 0.92 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.5 (C=O), 156.4 (C-2), 147.9 (C-1 of 2 Ph), 141.2 (C-1), 134.5 (C-3), 128.4 (C-2/C-6 and C-3/C-5 of 2 Ph), 128.4 (C-4), 128.3 (C-6), 127.7 (C-4 of 2 Ph), 123.7 (C-5), 81.5 (C-OH), 61.2 (OCH_3), 40.0 [*C*$(CH_3)_3$], 37.8 (CH_2), 28.3 [C(*C*$H_3)_3$]. HRMS (ES^+): *m/z* calcd for $C_{26}H_{30}NO_3$ $[MH]^+$: 404.2220; found: 404.2219.

***N*-(3-Deuterio-2-methoxybenzyl)pivalamide (51).** 0.38 g (1.72 mmol, 86%). Mp: 103–104 °C (Mp of undeuteriated analogue, 103–104 °C[10]). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.15 (m, 2 H, H-5 and H-6), 6.83 (m, 1 H, H-4), 6.14 (br, exch., 1 H, NH), 4.36 (d, *J* = 6 Hz, 2 H, CH_2), 3.78 (s, 3 H, OCH_3), 1.11 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (C=O), 158.0 (C-2), 130.1 (C-6), 129.1 (C-4), 129.0 (C-1), 121.1 (C-5), 110.5 (seen as three lines, 1:1:1, because of coupling to D, C-3), 55.7 (OCH_3), 40.0 (CH_2), 39.1 [*C*$(CH_3)_3$], 28.0 [C(*C*$H_3)_3$]. HRMS (CI): *m/z* calcd for $C_{13}H_{19}DNO_2$ $[MH]^+$: 223.1551; found: 223.1550.

***N*-(2-Hydroxy-1-(2-methoxyphenyl)-2-(4-methoxyphenyl)ethyl)pivalamide (53).** 14 mg (0.04 mmol, 2%). Mp 203–205 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.25 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.23–7.19 (m, 3 H, NH, H-4 and H-6), 6.96 (d, *J* = 8 Hz, 1 H, H-3), 6.91 (app. t, *J* = 8 Hz, 1 H, H-5), 6.86 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.52 (d, *J* = 4 Hz, exch., 1 H, OH), 5.24 (dd, *J* = 3, 6 Hz, 1 H, C*H*NH), 4.78 (dd, *J* = 4, 3 Hz, 1 H, C*H*OH), 3.83 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 1.05 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.5 (C=O), 158.4 (C-4 of 4-methoxyphenyl), 156.5 (s, C-2), 136.2 (s, C-1 of 4-methoxyphenyl), 130.3 (s, C-1), 128.1 (C-6), 127.6 (C-4), 127.2 (C-2/C-6 of 4-methoxyphenyl), 120.3 (C-5), 113.3 (C-3/C-5 of 4-methoxyphenyl), 110.9 (C-3), 73.1 (CHOH), 55.8 (OCH_3), 55.3 (OCH_3), 53.8 (CHNH), 38.5 [*C*$(CH_3)_3$], 27.6 [C(*C*$H_3)_3$]. HRMS (CI): *m/z* calcd for $C_{21}H_{28}NO_4$ $[MH]^+$: 358.2013; found: 358.2012.

***N*-(2-Hydroxy-1-(2-methoxyphenyl)-2,2-diphenylethyl)pivalamide (54).** 24 mg (0.06 mmol, 3%). Mp: 203–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.54–6.99 (m, 13 H, 2 Ph, H-4, H-6 and NH), 6.86 (app. t, *J* = 8 Hz, 1 H, H-5), 6.54 (d, *J* = 8 Hz, 1 H, H-3), 6.34 (d, *J* = 9 Hz, 1 H, CH), 6.15 (s, exch., 1 H, OH), 3.14 (s, 3 H, OCH_3), 0.91 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.6 (C=O), 157.0 (C-2), 147.5, 145.3 (C-1 of 2 Ph), 130.8 (C-6), 128.9 (C-1), 128.52, 128.49 (C-3/C-5 of 2 Ph), 127.51, 127.41 (C-2/C-6 of 2 Ph), 127.4, 127.1 (C-4 of 2 Ph), 126.6 (C-4), 120.1 (C-5), 110.4 (C-3), 80.9 (C-OH), 55.4 (OCH_3), 52.1 (CH), 38.7 [*C*$(CH_3)_3$], 27.9 [C(*C*$H_3)_3$]. HRMS (CI): *m/z* calcd for $C_{26}H_{30}NO_3$ $[MH]^+$: 404.2220; found: 404.2221.

3-Methoxy-2-(pivaloylaminomethyl)benzoic acid (55). The procedure used for isolation of **55** was different than the general procedure. A solution of *sec*-BuLi in cyclohexane (3.2 mL, 1.4 M, 4.4 mmol) was added to a cold (0 °C), stirred solution of **46** (0.44 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. The brownish solution obtained was stirred at 0 °C for 2 h, after which the cooling bath was removed. Solid carbon dioxide was added and the mixture was stirred for 30 minutes while the mixture was allowed to warm to room temperature. It was then diluted with ethyl acetate (10 mL) and quenched with HCl (2 M; 5 mL). The organic layer was separated, washed with H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The

residue obtained was treated with diethyl ether and on standing overnight gave **55** (0.13 g, 0.49 mmol, 25%) as white crystals. Mp 170-171 °C (lit.[8] 168–169 °C). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.43 (t, *J* = 6 Hz, exch., 1 H, NH), 7.34 (app. t, *J* = 8 Hz, 1 H, H-5), 7.27 (dd, *J* = 2, 8 Hz, 1 H, H-6), 7.19 (br d, *J* = 8 Hz, 1 H, H-4), 4.47 (d, *J* = 6 Hz, 2 H, CH_2), 3.82 (s, 3 H, OCH_3), 1.05 [s, 9 H, $C(CH_3)_3$] (the CO_2H signal was not seen due to exchange with water in the DMSO). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.5 (C=O), 169.7 (CO_2H), 158.4 (C-3), 134.3 (C-2), 128.7 (C-5), 126.7 (C-1), 121.6 (C-6), 114.6 (C-4), 56.5 (OCH_3), 38.4 [$C(CH_3)_3$], 35.7 (CH_2), 27.8 [$C(CH_3)_3$]. HRMS (ES^+): *m/z* calcd for $C_{14}H_{20}NO_4$ $[MH]^+$: 266.1392; found: 266.1392.

***N'*-(2-(Hydroxy-(4-methoxyphenyl)methyl)benzyl)-*N*,*N*-dimethylurea (61).** 0.54 g (1.72 mmol, 86%). Mp 185–186 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.44 (app. dt, *J* = 2, 8 Hz, 1 H, H-4), 7.27-7.21 (m, 5 H, H-3, H-5, H-6 and H-2/H-6 of 4-methoxyphenyl), 6.87 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.66 (t, *J* = 6 Hz, exch., 1 H, NH), 5.92 (d, *J* = 4 Hz, 1 H, CH), 5.80 (d, *J* = 4 Hz, exch., 1 H, OH), 4.30 (dd, *J* = 6, 16 Hz, 1 H, CH_aH$_b$), 4.09 (dd, *J* = 6, 16 Hz, 1 H, CH$_a$$H_b$), 3.73 (s, 3 H, OCH_3), 2.79 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0 (C=O), 158.9 (C-4 of 4-methoxyphenyl), 143.3 (C-1), 138.3 (C-2), 137.4 (C-1 of 4-methoxyphenyl), 129.0 (C-2/C-6 of 4-methoxyphenyl), 128.1 (C-3), 127.4 (C-6), 127.3 (C-4), 127.1 (C-5) 114.2 (C-3/C-5 of 4-methoxyphenyl), 71.2 (CH), 55.9 (OCH_3), 44.4 (CH_2), 36.7 [$N(CH_3)_2$]. HRMS (ES^+): *m/z* calcd for $C_{18}H_{23}N_2O_3$ $[MH]^+$: 315.1703; found: 315.1700. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.55; H, 7.14; N, 8.84.

***N'*-(2-(Hydroxyphenylmethyl)benzyl)-*N*,*N*-dimethylurea (62).** 0.47 g (1.65 mmol, 82%). Mp 138–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.23 (m, 9 H, ArH), 6.05 (d, *J* = 4 Hz, 1 H, CH), 5.00 (t, *J* = 6 Hz, exch., 1 H, NH), 4.71 (d, *J* = 4 Hz, exch., 1 H, OH), 4.38 (dd, *J* = 6, 14 Hz, 1 H, CH_aH$_b$), 4.27 (dd, *J* = 6, 14 Hz, 1 H, CH$_a$$H_b$), 2.71 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (C=O), 144.1 (C-1 of Ph), 142.2 (C-1), 137.8 (C-2), 130.6 (C-3), 128.9 (C-6), 128.7 (C-3/C-5 of Ph), 128.4 (C-4), 128.0 (C-5), 127.6 (C-4 of Ph), 127.1 (C-2/C-6 of Ph), 73.8 (CH), 42.6 (CH_2), 36.4 [$N(CH_3)_2$]. HRMS (ES^+): *m/z* calcd for $C_{17}H_{21}N_2O_2$ $[MH]^+$: 285.1598; found: 285.1600.

***N'*-(2-(Hydroxydiphenylmethyl)benzyl)-*N*,*N*-dimethylurea (63).** 0.61 g (1.69 mmol, 84%). Mp 235–236 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.43-7.23 (m, 13 H, 2 Ph, H-4, H-6 and OH), 7.04 (dt, *J* = 2, 8 Hz, 1 H, H-5), 6.80 (t, *J* = 6 Hz, exch., 1 H, NH), 6.49 (dd, *J* = 2, 8 Hz, 1 H, H-3), 3.86 (d, *J* = 6 Hz, 2 H, CH_2), 2.76 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3 (C=O), 149.0 (C-1 of 2 Ph), 145.3 (C-1), 141.2 (C-2), 130.5 (C-3), 129.5 (C-6), 128.9 (C-3/C-5 of 2 Ph), 128.6 (C-5), 128.4 (C-2/C-6 of 2 Ph), 127.4 (C-4 of 2 Ph), 126.3 (C-4), 82.0 (C-OH), 43.0 (CH_2), 36.7 [$N(CH_3)_2$]. HRMS (ES^+): *m/z* calcd for $C_{23}H_{24}N_2O_2Na$ $[M + Na]^+$: 383.1730; found: 383.1731.

***N'*-(2-Methylbenzyl)-*N*,*N*-dimethylurea (64).** 0.31 g (1.61 mmol, 80%). Mp 82–83 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.19–7.01 (m, 4 H, H-3, H-4, H-5 and H-6), 4.48 (br, exch., 1 H, NH), 4.31 (br, 2 H, CH_2), 2.82 [s, 6 H, $N(CH_3)_2$], 2.26 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.7 (C=O), 137.5 (C-1), 136.8 (C-2), 130.8 (C-3), 128.8 (C-6), 127.9 (C-4),

126.5 (C-5), 43.6 (CH_2), 36.7 [$N(CH_3)_2$], 19.45 (CH_3). HRMS (CI): *m/z* calcd for $C_{11}H_{17}N_2O$ $[MH]^+$: 193.1335; found: 193.1335.

***N'*-(2-Deuteriobenzyl)-*N*,*N*-dimethylurea (65).** 0.32 g (1.78 mmol, 89%). Mp 76–77 °C (Mp of undeuteriated analogue lit.[18] 77 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 4 H, H-3, H-4, H-5 and H-6), 4.84 (br, exch., 1 H, NH), 4.41 (br, 2 H, CH_2), 2.91 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 140.2 (C-1), 128.9 (C-3), 128.8 (seen as three lines, 1:1:1, because of coupling to D, C-2), 128.1 (C-5), 127.8 (C-6), 127.6 (C-4), 45.4 (CH_2), 36.6 [$N(CH_3)_2$]. HRMS (CI): *m/z* calcd for $C_{10}H_{14}DN_2O$ $[MH]^+$: 180.1242; found: 180.1243.

***N'*-(2-(Hydroxy-(4-methoxyphenyl)methyl)-4-methylbenzyl)-*N*,*N*-dimethylurea (66).** 0.50 g (1.52 mmol, 76%). Mp 174–175 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.26 (s, 1 H, H-3), 7.21 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.11 (d, *J* = 8 Hz, 1 H, H-6), 7.01 (d, *J* = 8 Hz, 1 H, H-5), 6.86 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.58 (t, *J* = 6 Hz, exch., 1 H, NH), 5.89 (d, *J* = 5 Hz, 1 H, CH), 5.78 (d, *J* = 5 Hz, exch., 1 H, OH), 4.25 (dd, *J* = 6, 16 Hz, 1 H, CH_aH$_b$), 4.03 (dd, *J* = 6, 16 Hz, 1 H, CH$_a$$H_b$), 3.72 (s, 3 H, OCH_3), 2.78 [s, 6 H, $N(CH_3)_2$], 2.58 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0 (C=O), 158.9 (s, C-4 of 4-methoxyphenyl), 143.2 (C-2), 137.5 (C-1), 136.0 (C-4), 135.3 (C-1 of 4-methoxyphenyl), 128.9 (C-2/C-6 of 4-methoxyphenyl), 128.5 (C-3), 128.0 (C-6), 127.8 (C-5) 114.2 (C-3/C-5 of 4-methoxyphenyl), 71.2 (CH), 55.9 (OCH_3), 41.4 (CH_2), 36.7 [$N(CH_3)_2$], 21.8 (CH_3). HRMS (CI): *m/z* calcd for $C_{19}H_{25}N_2O_3$ $[MH]^+$: 329.1860; found: 329.1852. Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.44; H, 7.40; N, 8.58.

***N'*-(2-(Hydroxyphenylmethyl)-4-methylbenzyl)-*N*,*N*-dimethylurea (67).** 0.41 g (1.39 mmol, 70%). Mp 135–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.13 (m, 10 H, ArH, NH and OH), 5.97 (br s, 1 H, CH), 4.27 (d, *J* = 14 Hz, 1 H, CH_aH$_b$), 4.17 (d, *J* = 14 Hz, 1 H, CH$_a$$H_b$), 2.64 [s, 6 H, $N(CH_3)_2$], 2.21 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (C=O), 144.2 (C-1 of Ph), 142.2 (C-2), 138.5 (C-1), 134.7 (C-4), 130.8 (C-3), 129.6 (C-6), 129.1(C-5), 128.9 (C-3/C-5 of Ph), 127.7 (C-4 of Ph), 127.1 (C-2/C-6 of Ph), 73.9 (CH), 42.4 (CH_2), 36.5 [$N(CH_3)_2$], 21.6 (CH_3). HRMS (CI): *m/z* calcd for $C_{18}H_{23}N_2O_2$ $[MH]^+$: 299.1754; found: 299.1753.

***N'*-(2-(Hydroxydiphenylmethyl)-4-methylbenzyl)-*N*,*N*-dimethylurea (68).** 0.54 g (1.44 mmol, 72%). Mp 225–227 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.40 (s, exch., 1 H, OH), 7.34–7.22 (m, 11 H, 2 Ph and H-6), 7.09 (dd, *J* = 1, 8 Hz, 1 H, H-5), 6.76 (t, *J* = 6 Hz, exch., 1 H, NH), 6.31 (d, *J* = 1 Hz, 1 H, H-3), 3.79 (d, *J* = 6 Hz, 2 H, CH_2), 2.75 [s, 6 H, $N(CH_3)_2$], 2.08 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3 (C=O), 149.1 (C-1 of 2 Ph), 145.3 (C-2), 138.2 (C-1), 135.1 (C-4), 130.7 (C-3), 130.2 (C-6), 129.4 (C-5), 128.9 (C-3/C-5 of 2 Ph), 128.5 (C-2/C-6 of 2 Ph), 127.4 (C-4 of 2 Ph), 81.9 (C-OH), 42.8 (CH_2), 36.7 [$N(CH_3)_2$], 21.8 (CH_3). HRMS (ES^+): *m/z* calcd for $C_{24}H_{27}N_2O_2$ $[MH]^+$: 375.2067; found: 375.2072.

***N'*-(2-Ethyl-4-methylbenzyl)-*N*,*N*-dimethylurea (69).** 0.35 g (1.59 mmol, 80%). Mp 60–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 8 Hz, 1 H, H-6), 6.95 (s, 1 H, H-3), 6.91 (d, *J* = 8 Hz, 1 H, H-5), 4.38 (br, exch., 1 H, NH), 4.31 (br, 2 H, CH_2N), 2.58 (q, *J* = 7 Hz, 2 H, CH_2CH$_3$), 2.25 [s, 6 H, $N(CH_3)_2$], 2.25 (s, 3 H, CH_3), 1.14 (t, *J* = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100

MHz, $CDCl_3$): δ = 158.6 (C=O), 142.9 (C-1), 137.8 (C-2), 133.7 (C-4), 130.0 (C-3), 129.5 (C-6), 127.2 (C-5), 42.9 (CH_2NH), 36.6 [$N(CH_3)_2$], 25.8 (CH_2CH_3), 21.5 (CH_3), 16.0 (CH_2CH_3). HRMS (CI): *m/z* calcd for $C_{13}H_{21}N_2O$ $[MH]^+$: 221.1648; found: 221.1649.

***N'*-(2-Deuterio-4-methylbenzyl)-*N*,*N*-dimethylurea (70).** 0.33 g (1.71 mmol, 86%). Mp 97–98 °C (Mp of undeuteriated analogue 93 °C [19]). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.14 (m, 3 H, H-3, H-5 and H-6), 4.73 (br, exch., 1 H, NH), 4.38 (br, 2 H, CH_2), 2.92 [s, 6 H, $N(CH_3)_2$], 2.35 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 137.3 (C-1), 137.0 (C-4), 129.6 (C-3), 129.5 (C-5), 128.2 (C-6), 127.9 (seen as three lines, 1:1:1, because of coupling to D, C-2), 45.2 (CH_2), 36.7 [$N(CH_3)_2$], 21.5 (CH_3). HRMS (CI): *m/z* calcd for $C_{11}H_{16}DN_2O$ $[MH]^+$: 194.1398; found: 194.1398.

***N'*-(2-(Hydroxy-(4-methoxyphenyl)methyl)-4-methoxybenzyl)-*N*,*N*-dimethylurea (71).** 0.59 g (1.71 mmol; 85%). Mp 137–138 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.21 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.14 (d, *J* = 8 Hz, 1 H, H-6), 7.03 (d, *J* = 2 Hz, 1 H, H-3), 6.86 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.78 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.53 (app. t, *J* = 6 Hz, exch., 1 H, NH), 5.88 (d, *J* = 5 Hz, 1 H, CH), 5.81 (d, *J* = 5 Hz, exch., 1 H, OH), 4.21 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 3.96 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 3.73 (app. s, 6 H, 2 OCH_3), 2.77 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.0 (C=O), 158.9 (C-4), 158.8 (C-4 of 4-methoxyphenyl), 144.8 (C-2), 137.3 (C-1 of 4-methoxyphenyl), 130.3 (C-1), 129.9 (C-6), 129.0 (C-2/C-6 of 4-methoxyphenyl), 114.2 (C-3/C-5 of 4-methoxyphenyl), 113.2 (C-3), 112.4 (C-5), 71.2 (CH), 55.9 (OCH_3), 55.8 (OCH_3), 41.2 (CH_2), 36.7 [$N(CH_3)_2$]. HRMS (ES^+): *m/z* calcd for $C_{19}H_{25}N_2O_4$ $[MH]^+$: 345.1809; found: 345.1811. Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.23; H, 7.04; N, 8.05.

***N'*-(2-(Hydroxyphenylmethyl)-4-methoxybenzyl)-*N*,*N*-dimethylurea (72).** 0.56 g (1.78 mmol, 89%). Colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.12 (m, 6 H, Ph and H-6), 6.81 (d, *J* = 2 Hz, 1 H, H-3), 6.66 (dd, *J* = 2, 8 Hz, 1 H, H-5), 5.89 (d, *J* = 4 Hz, 1 H, CH), 4.80 (app. t, *J* = 6 Hz, exch., 1 H, NH), 4.68 (d, *J* = 4 Hz, exch., 1 H, OH), 4.21 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 4.08 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 3.64 (s, 3 H, OCH_3), 2.58 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (C=O), 158.7 (C-4), 144.0 (C-1 of Ph), 143.8 (C-2), 132.1 (C-6), 129.8 (C-1), 128.7 (C-3/C-5 of Ph), 127.6 (C-4 of Ph), 127.2 (C-2/C-6 of Ph), 114.6 (C-5), 113.3 (C-3), 73.7 (CH), 55.6 (OCH_3), 42.1 (CH_2), 36.4 [$N(CH_3)_2$]. HRMS (CI): *m/z* calcd for $C_{18}H_{23}N_2O_3$ $[MH]^+$: 315.3869; found: 315.3866.

***N'*-(2-(Hydroxydiphenylmethyl)-4-methoxybenzyl)-*N*,*N*-dimethylurea (73).** 0.66 g (1.69 mmol, 84%). Mp 223–224 °C. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.48 (s, exch., 1 H, OH), 7.36–7.18 (m, 11 H, H-6 and 2 Ph), 6.78 (dd, *J* = 2, 8 Hz, 1 H, H-5), 6.64 (t, *J* = 6 Hz, exch., 1 H, NH), 6.01 (d, *J* = 2 Hz, 1 H, H-3), 3.75 (d, *J* = 6 Hz, 2 H, CH_2), 3.54 (s, 3 H, OCH_3), 2.76 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.3 (C=O), 157.6 (C-4), 148.9 (C-1 of 2 Ph), 146.9 (C-2), 132.8 (C-1), 132.4 (C-6), 128.3 (C-3/C-5 of 2 Ph), 128.1 (C-2/C-6 of 2 Ph), 127.2 (C-4 of 2 Ph), 116.8 (C-3), 112.3 (C-5), 81.8 (C-OH), 55.4 (OCH_3), 42.5 (CH_2), 36.6 [$N(CH_3)_2$]. HRMS (ES^+): *m/z* calcd for $C_{24}H_{26}N_2O_3Na$ $[M + Na]^+$: 413.1836; found: 413.1837.

***N'*-(2-Deuterio-4-methoxybenzyl)-*N*,*N*-dimethylurea (74).** 0.36 g (1.72 mmol, 86%). Mp 81–82 °C (Mp of undeuteriated analogue 81-82 °C[19]). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8 Hz, 1 H, H-6), 6.80–6.77 (m, 2 H, H-3 and H-5), 4.30 (br t, exch., 1 H, NH), 4.28 (d, *J* = 6 Hz, 2 H, CH_2), 3.72 (s, 3 H, OCH_3), 2.83 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (C=O), 158.7 (C-4), 132.0 (C-1), 29.5 (C-6), 129.2 (seen as three lines, 1:1:1, because of coupling to D, C-2), 114.4 (C-3), 114.3 (C-5), 55.7 (OCH_3), 44.9 (CH_2), 36.7 [$N(CH_3)_2$]. HRMS (CI): *m/z* calcd for $C_{11}H_{16}DN_2O_2$ $[MH]^+$: 210.1347; found: 210.1349.

***N'*-(2-Ethyl-4-methoxybenzyl)-*N*,*N*-dimethylurea (75).** 0.42 g (1.77 mmol, 88%). Mp 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8 Hz, 1 H, H-6), 6.78 (d, *J* = 2 Hz, 1 H, H-3), 6.73 (dd, *J* = 2, 8 Hz, 1 H, H-5), 4.38 (br, 3 H, CH_2N and NH), 3.81 (s, 3 H, OCH_3), 2.91 [s, 6 H, $N(CH_3)_2$], 2.68 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 1.24 (t, *J* = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (C=O), 158.6 (C-4), 144.7 (C-2), 130.9 (C-6), 129.0 (C-1), 115.0 (C-3), 111.3 (C-5), 55.6 (OCH_3), 42.7 (CH_2NH), 36.6 [$N(CH_3)_2$], 26.0 (CH_2CH_3), 15.8 (CH_2CH_3). HRMS (CI): *m/z* calcd for $C_{13}H_{21}N_2O_2$ $[MH]^+$: 237.1598; found: 237.1599.

***N'*-(4-Chloro-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)-*N*,*N*-dimethylurea (76).** 0.55 g (1.58 mmol, 79%). Mp 186–188 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.50 (s, 1 H, H-3), 7.30 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.25 (d, *J* = 8 Hz, 1 H, H-5), 7.22 (d, *J* = 8 Hz, 1 H, H-6), 6.90 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.65 (app. t, *J* = 6 Hz, exch., 1 H, NH), 5.95 (s, exch., 1 H, OH), 5.90 (s, 1 H, CH), 4.30 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 4.00 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 3.75 (s, 3 H, OCH_3), 2.80 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.8 (C=O), 158.5 (C-4 of 4-methoxyphenyl), 145.3 (C-1), 137.0 (C-1 of 4-methoxyphenyl), 136.3 (C-2), 131.5 (C-4), 129.8 (C-5), 128.6 (C-2/C-6 of 4-methoxyphenyl), 126.7 (C-3), 126.5 (C-6), 113.8 (C-3/C-5 of 4-methoxyphenyl), 70.4 (CH), 55.3 (OCH_3), 36.1 (CH_2), 29.5 [$N(CH_3)_2$]. HRMS (ES^+): *m/z* calcd for $C_{18}H_{22}N_2O_3{}^{35}Cl$ $[MH]^+$: 349.1319; found: 349.1334.

***N'*-(4-Chloro-2-(hydroxyphenylmethyl)benzyl)-*N*,*N*-dimethylurea (77).** 0.50 g (1.57 mmol, 79%). Mp 190–192 ºC. ^{1}H NMR (500MHz, DMSO-d_6): δ = 7.45 (s, 1 H, H-3), 7.35-7.28 (m, 5 H, Ph), 7.22 (d, *J* = 8 Hz, 1 H, H-5), 7.20 (d, *J* = 8 Hz, 1 H, H-6), 6.72 (app. t, *J* = 6 Hz, exch., 1 H, NH), 6.05 (s, exch., 1 H, OH), 5.95 (s, 1 H, CH), 4.30 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 4.05 (dd, *J* = 6, 14 Hz, 1 H, CH_aH_b), 2.79 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.5 (C=O), 145.0 (C-1 of Ph), 144.2 (C-1), 137.1 (C-2), 131.5 (C-4), 129.8 (C-6), 128.6 (C-3/C-5 of Ph), 127.5 (C-2/C-6 of Ph), 127.4 (C-3), 127.0 (C-4 of Ph), 126.7 (C-5), 70.7 (CH), 40.8 (CH_2), 36.3 [$N(CH_3)_2$]. HRMS (ES^+): *m/z* calcd for $C_{17}H_{17}N_2O^{35}Cl$ $[M - H_2O]^+$: 300.1029; found: 300.1026.

***N'*-(4-Chloro-2-ethylbenzyl)-*N*,*N*-dimethylurea (78).** 0.37 g (1.53 mmol, 78%). Mp 102–104 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.25 (s, 1 H, H-3), 7.20 (d, *J* = 8 Hz, 1 H, H-5), 7.18 (d, *J* = 8 Hz, 1 H, H-6), 6.80 (t, *J* = 6 Hz, exch., 1 H, NH), 4.22 (d, *J* = 6 Hz, 2 H, CH_2N), 2.82 [s, 6 H, $N(CH_3)_2$], 2.62 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 1.15 (t, *J* = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 158.6 (C=O), 144.0 (C-2), 137.8 (C-1), 131.4 (C-4), 129.7 (C-6), 128.0

(C-3), 125.8 (C-5), 40.8 (CH_2NH), 36.4 [$N(CH_3)_2$], 24.9 (CH_2CH_3), 15.1 (CH_2CH_3). HRMS (APCI): *m/z* calcd for $C_{12}H_{18}N_2O^{35}Cl$ $[MH]^+$: 241.1108; found: 241.1106.

***N'*-(4-Chloro-2-deuteriobenzyl)-*N*,*N*-dimethylurea (79).** 0.38 g (1.58 mmol, 79%). Mp 133-135 ºC (Mp of undeuteriated analogue 133-135 °C[10]). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8 Hz, 1 H, H-5), 7.20 (s, 1 H, H-3), 7.17 (d, *J* = 8 Hz, 1 H, H-6), 4.92 (br, exch., 1 H, NH), 4.35 (d, *J* = 6 Hz, 2 H, CH_2), 2.90 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (C=O), 138.4 (C-1), 132.8 (C-4), 128.9 (seen as three lines, 1:1:1, because of coupling to D, C-2), 128.7 (C-3), 128.6 (C-5), 128.5 (C-6), 44.2 (CH_2), 36.2 [$N(CH_3)_2$]. HRMS (APCI): *m/z* calcd for $C_{10}H_{13}DN_2O^{35}Cl$ $[MH]^+$: 241.0857; found: 214.0851.

***N'*-(4-Fluoro-2-(hydroxy-(4-methoxyphenyl)methyl)benzyl)-*N*,*N*-dimethylurea (80).** 0.55 g (1.65 mmol, 83%). Mp 197–199 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.20-7.10 (m, 3 H, H-3, H-5 and H-6), 7.10 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.05 (app. t, *J* = 6 Hz, exch., 1 H, NH), 6.85 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 6.65 (s, exch., 1 H, OH), 5.91 (s, 1 H, CH), 4.29 (dd, *J* = 6, 16 Hz, 1 H, CH_aH$_b$), 3.95 (dd, *J* = 6, 16 Hz, 1 H, CH$_a$$H_b$), 3.72 (s, 3 H, OCH_3), 2.80 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.6 (seen as two lines because of coupling to F, *J* = 241 Hz, C-4), 158.8 (C=O), 158.5 (C-4 of 4-methoxyphenyl), 145.7 (seen as two lines because of coupling to F, *J* = 3 Hz, C-1), 136.3 (C-1 of 4-methoxyphenyl), 133.8 (seen as two lines because of coupling to F, *J* = 7 Hz, C-2), 129.8 (seen as two lines because of coupling to F, *J* = 7 Hz, C-6), 128.8 (C-2/C-6 of 4-methoxyphenyl), 114.0 (C-3/C-5 of 4-methoxyphenyl), 113.5 (seen as two lines because of coupling to F, *J* = 22 Hz, C-3), 113.2 (seen as two lines because of coupling to F, *J* = 22 Hz, C-5), 70.3 (CH), 55.5 (OCH_3), 40.2 (CH_2), 36.3 [$N(CH_3)_2$]. HRMS (ES^+): *m/z* calcd for $C_{18}H_{22}N_2O_3F$ $[MH]^+$: 333.1614; found: 333.1601.

***N'*-(4-Fluoro-2-(hydroxyphenylmethyl)benzyl)-*N*,*N*-dimethylurea (81).** 0.50 g (1.65 mmol, 83%). Mp 165–167 ºC. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.38-7.21 (m, 7 H, Ph, H-5 and H-6), 7.05 (m, 1 H, H-3), 6.7 (app. t, *J* = 6 Hz, exch., 1 H, NH), 6.05 (d, *J* = 4 Hz, exch., 1 H, OH), 6.0 (d, *J* = 4 Hz, 1 H, CH), 4.30 (dd, *J* = 6, 14 Hz, 1 H, CH_aH$_b$), 4.05 (dd, *J* = 6, 14 Hz, 1 H, CH$_a$$H_b$), 2.80 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.6 (seen as two lines because of coupling to F, *J* = 247 Hz, C-4), 158.5 (C=O), 145.4 (seen as two lines because of coupling to F, *J* = 3 Hz, C-1), 144.3 (C-1 of Ph), 134.0 (seen as two lines because of coupling to F, *J* = 8 Hz, C-2), 130.0 (seen as two lines because of coupling to F, *J* = 8 Hz, C-6), 130.0 (C-4 of Ph), 128.6 (C-3/C-5 of Ph), 127.5 (C-2/C-6 of Ph), 113.7 (seen as two lines because of coupling to F, *J* = 22 Hz, C-3), 113.4 (seen as two lines because of coupling to F, *J* = 22 Hz, C-5), 70.7 (CH), 40.2 (CH_2), 36.3 [$N(CH_3)_2$]. HRMS (APCI): *m/z* calcd for $C_{17}H_{20}N_2O_2F$ $[MH]^+$: 303.1509; found: 303.1497.

***N'*-(2-Deuterio-4-fluorobenzyl)-*N*,*N*-dimethylurea (82).** 0.34 g (1.72 mmol, 86%). Mp 112–114 ºC (Mp of undeuteriated analogue 112–114 °C[10]). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 (m, 1 H, H-6), 6.90-6.85 (m, 2 H, H-3 and H-5), 5.05 (s, exch., 1 H, NH), 4.25 (d, *J* = 6 Hz, 2 H, CH_2), 2.80 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.9 (seen as two lines because of coupling to F, *J* = 246 Hz, C-4), 158.4 (C=O), 135.7 (seen as two lines because of coupling to

F, *J* = 3 Hz, C-1), 129.1 (seen as two lines because of coupling to F, *J* = 8 Hz, C-6), 128.8 (seen as six lines because of coupling to F and D, *J* = 8, 24 Hz, C-2), 115.2 (seen as two lines because of coupling to F, *J* = 12 Hz, C-3), 115.0 (seen as two lines because of coupling to F, *J* = 12 Hz, C-5), 44.1 (CH_2), 36.2 [$N(CH_3)_2$]. HRMS (APCI): *m/z* calcd for $C_{10}H_{13}DN_2OF$ $[MH]^+$: 198.1153; found: 198.1147.

***N'*-Ethyl-*N'*-(2-ethyl-4-methoxybenzyl)-*N*,*N*-dimethylurea (83).** The procedure was identical with the general one except that iodoethane (0.69 g, 4.4 mmol) was used as an electrophile. The reaction mixture was worked-up and the product mixture was purified by column chromatography (silica gel; Et_2O–hexane, 1:3) to give **83** as a colourless oil. 0.48 g (1.81 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8 Hz, 1 H, H-6), 6.68 (d, *J* = 2 Hz, 1 H, H-3), 6.63 (dd, *J* = 2, 8 Hz, 1 H, H-5), 4.24 (s, 2 H, CH_2N), 3.71 (s, 3 H, OCH_3), 3.04 (q, *J* = 7 Hz, 2 H, NCH_2CH_3), 2.74 [s, 6 H, $N(CH_3)_2$], 2.52 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 1.31 (t, *J* = 7 Hz, 3 H, NCH_2CH_3), 1.02 (t, *J* = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8 (C=O), 159.2 (C-4), 144.0 (C-2), 129.4 (C-6), 127.9 (C-1), 114.9 (C-3), 110.9 (C-5), 55.6 (OCH_3), 48.6 (NCH_2), 42.8 (NCH_2CH_3), 39.1 [$N(CH_3)_2$], 25.7 (CH_2CH_3), 15.0 (CH_3), 13.0 (CH_3). HRMS (CI): *m/z* calcd for $C_{15}H_{25}N_2O_2$ $[MH]^+$: 265.3713; found: 265.3713.

Synthesis of substituted *N'*-benzyl-*N*,*N*-dimethylureas 85-94 *via* lithiation of *N'*-(2-methoxybenzyl)-*N*,*N*-dimethylurea (84) at –20 °C

A solution of *t*-BuLi in heptane (2.6 mL, 1.7 M, 4.4 mmol) was added to a cold (-20 °C), stirred solution of **84** (0.42 g, 2.0 mmol) in anhydrous THF (20 mL) under N_2. The mixture was stirred at –20 °C for 2 h after which an electrophile (2.2 mmol), in anhydrous THF (8 mL) if solid, otherwise neat, was added. The mixture was stirred for 2 h at -20 °C then the cooling bath was removed and the mixture allowed to warm to room temperature. It was then diluted with Et_2O (10 mL) and quenched with aq. sat. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The product mixture was separated by column chromatography (silica gel; Et_2O–hexane, 1:3) to give the pure product.

***N'*-(2-(Hydroxy-(4-methoxyphenyl)methyl)-6-methoxybenzyl)-*N*,*N*-dimethylurea (85).** 0.34 g (0.99 mmol, 49%). Mp: 139–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.10 (app. t, *J* = 8 Hz, 1 H, H-4), 6.78–6.72 (m, 4 H, H-3, H-5 and H-3/H-5 of 4-methoxyphenyl), 6.12 (d, *J* = 6 Hz, exch., 1 H, OH), 6.02 (d, *J* = 6 Hz, 1 H, CH), 5.23 (app. t, *J* = 6 Hz, exch., 1 H, NH), 4.30 (dd, *J* = 6, 16 Hz, 1 H, CH_aH_b), 4.22 (dd, *J* = 6, 16 Hz, 1 H, CH_aH_b), 3.78 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 2.72 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (C=O), 158.9 (C-6), 158.7 (C-4 of 4-methoxyphenyl), 144.6 (C-2), 137.1 (C-1 of 4-methoxyphenyl), 128.8 (C-4), 127.8 (C-2/C-6 of 4-methoxyphenyl), 126.1 (C-1), 122.4 (C-3), 113.8 (C-3/C-5 of 4-methoxyphenyl), 110.2 (C-5), 73.3 (CH), 56.0 (OCH_3), 55.6 (OCH_3), 37.2 (CH_2), 36.5 [$N(CH_3)_2$]. HRMS (ES^+): *m/z* calcd for $C_{19}H_{25}N_2O_4$ $[MH]^+$: 345.1809; found: 345.1807.

***N'*-(3-(Hydroxy-(4-methoxyphenyl)methyl)-2-methoxybenzyl)-*N*,*N*-dimethylurea (86).** 0.28 g (0.81 mmol, 40%). Mp: 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 2, 8 Hz, 1 H, H-4), 7.19 (d, *J* = 9 Hz, 2 H, H-2/H-6 of 4-methoxyphenyl), 7.16 (br d, *J* = 8 Hz, 1 H, H-6), 7.01 (app. t, *J* = 8 Hz, 1 H, H-5), 6.75 (d, *J* = 9 Hz, 2 H, H-3/H-5 of 4-methoxyphenyl), 5.96 (s, 1 H, CH), 5.44 (s, exch., 1 H, OH), 4.81 (app. t, *J* = 6 Hz, exch., 1 H, NH), 4.36 (dd, *J* = 6, 16 Hz, 1 H, C*H*$_a$H$_b$), 4.32 (dd, *J* = 6, 16 Hz, 1 H, CH$_a$*H*$_b$), 3.69 (s, 3 H, OCH_3), 3.49 (s, 3 H, OCH_3), 2.78 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3 (C=O), 158.9 (C-2), 156.0 (C-4 of 4-methoxyphenyl), 137.8 (C-1 of 4-methoxyphenyl), 136.4 (C-1), 133.0 (C-3), 129.3 (C-4), 128.3 (C-2/C-6 of 4-methoxyphenyl), 127.6 (C-6), 125.0 (C-5), 114.1 (C-3/C-5 of 4-methoxyphenyl), 71.2 (CH), 62.1 (OCH_3), 55.6 (OCH_3), 40.3 (CH_2), 36.6 [$N(CH_3)_2$]. HRMS (CI): *m/z* calcd for $C_{19}H_{25}N_2O_4$ $[MH]^+$: 345.1809; found: 345.1813.

***N'*-(2-(Hydroxyphenylmethyl)-6-methoxybenzyl)-*N*,*N*-dimethylurea (87).** 0.32 g (1.02 mmol, 51%). Mp: 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8 Hz, 2 H, H-2/H-6 of Ph), 7.34 (app. t, *J* = 8 Hz, 2 H, H-3/H-5 of Ph), 7.32–7.20 (m, 2 H, H-4 and H-4 of Ph), 6.86 (dd, *J* = 1, 8 Hz, 1 H, H-3), 6.82 (dd, *J* = 1, 8 Hz, 1 H, H-5), 6.41 (d, *J* = 6 Hz, exch., 1 H, OH), 6.18 (d, *J* = 6 Hz, 1 H, CH), 5.36 (app. t, *J* = 6 Hz, exch., 1 H, NH), 4.41 (dd, *J* = 6, 16 Hz, 1 H, C*H*$_a$H$_b$), 4.32 (dd, *J* = 6, 16 Hz, 1 H, CH$_a$*H*$_b$), 3.90 (s, 3 H, OCH_3), 2.85 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2 (C=O), 159.0 (C-6), 144.9 (C-1 of Ph), 144.5 (C-2), 128.8 (C-4), 128.4 (C-3/C-5 of Ph), 126.9 (C-4 of Ph), 126.7 (C-2/C-6 of Ph), 126.3 (C-1), 122.8 (C-3), 110.3 (C-5), 73.7 (CH), 56.0 (OCH_3), 37.3 (CH_2), 36.5 [$N(CH_3)_2$]. HRMS (CI): *m/z* calcd for $C_{18}H_{23}N_2O_3$ $[MH]^+$: 315.1703; found: 315.1702.

***N'*-(3-Hydroxyphenylmethyl)-2-methoxybenzyl)-*N*,*N*-dimethylurea (88).** 0.24 g (0.76 mmol, 38%). Mp: 146–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8 Hz, 2 H, H-2/H-6 of Ph), 7.26 (app. t, *J* = 8 Hz, 2 H, H-3/H-5 of Ph), 7.21–7.15 (m, 4 H, H-4, H-5, H-6 and OH), 7.01 (t, *J* = 8 Hz, 1 H, H-4 of Ph), 6.00 (s, 1 H, CH), 4.75 (app. t, *J* = 6 Hz, exch., 1 H, NH), 4.37 (dd, *J* = 6, 16 Hz, 1 H, C*H*$_a$H$_b$), 4.34 (dd, *J* = 6, 16 Hz, 1 H, CH$_a$*H*$_b$), 3.51 (s, 3 H, OCH_3), 2.80 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 156.1 (C-2), 144.2 (C-1 of Ph), 137.6 (C-1), 133.1 (C-3), 129.5 (C-4), 128.7 (C-3/C-5 of Ph), 127.9 (C-4 of Ph), 127.8 (C-6), 127.0 (C-2/C-6 of Ph), 125.1 (C-5), 71.8 (CH), 62.2 (OCH_3), 40.4 (CH_2), 36.6 [$N(CH_3)_2$]. HRMS (CI): *m/z* calcd for $C_{18}H_{23}N_2O_3$ $[MH]^+$: 315.1703; found: 315.1700. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.74; H, 7.06; N, 8.90.

***N'*-(2-(Hydroxydiphenylmethyl)-6-methoxybenzyl)-*N*,*N*-dimethylurea (89).** 0.37 g (0.95 mmol, 47%). Mp: 218–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.98 (s, exch., 1 H, OH), 7.64 (d, *J* = 8 Hz, 4 H, H-2/H-6 of 2 Ph), 7.31 (t, *J* = 8 Hz, 4 H, H-3/H-5 of 2 Ph), 7.21 (t, *J* = 8 Hz, 2 H, H-4 of 2 Ph), 7.07 (app. t, *J* = 8 Hz, 1 H, H-4), 6.88 (br d, *J* = 8 Hz, 1 H, H-3), 6.31 (dd, *J* = 2, 8 Hz, 1 H, H-5), 5.48 (br t, exch., 1 H, NH), 4.04 (d, *J* = 6 Hz, 2 H, CH_2), 3.91 (s, 3 H, OCH_3), 2.85 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.8 (C=O), 159.4 (C-6), 149.2 (C-1 of 2 Ph), 147.9 (C-2), 128.2 (C-3/C-5 of 2 Ph), 128.0 (C-2/C-6 of 2 Ph), 127.7 (C-4), 126.9 (C-1), 126.8 (C-4 of 2 Ph), 123.5 (C-3), 110.6 (C-5), 81.4 (C-OH), 56.1 (OCH_3), 39.5

(CH_2), 36.5 [$N(CH_3)_2$]. HRMS (CI): *m/z* calcd for $C_{24}H_{27}N_2O_3$ $[MH]^+$: 391.2016; found: 391.2013.

***N'*-(3-(Hydroxydiphenylmethyl)-2-methoxybenzyl)-*N*,*N*-dimethylurea (90).** 0.24 g (0.62 mmol, 30%). Mp: 207–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27-6.81 (m, 13 H, 2 Ph, OH, H-4 and H-5), 6.42 (dd, *J* = 2, 8 Hz, 1 H, H-6), 4.88 (br, exch., 1 H, NH), 4.40 (d, *J* = 6 Hz, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 2.86 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 158.0 (C-2), 147.0 (C-1 of 2 Ph), 133.5 (C-1), 128.7 (C-3), 128.4 (C-3/C-5 of 2 Ph), 128.3 (C-2/C-6 of 2 Ph), 128.2 (C-4), 128.1 (C-4 of 2 Ph), 127.7 (C-6), 124.0 (C-5), 82.6 (C-OH), 61.6 (OCH_3), 40.4 (CH_2), 36.7 [$N(CH_3)_2$]. HRMS (CI): *m/z* calcd for $C_{24}H_{27}N_2O_3$ $[MH]^+$: 391.2016; found: 391.2015.

***N'*-(2-Methoxy-6-methylbenzyl)-*N*,*N*-dimethylurea (91).** 0.23 g (1.03 mmol, 51%). Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (app. t, *J* = 8 Hz, 1 H, H-4), 6.72 (d, *J* = 8 Hz, 1 H, H-5), 6.66 (d, *J* = 8 Hz, 1 H, H-3), 4.81 (br, exch., 1 H, NH), 4.38 (d, *J* = 6 Hz, 2 H, CH_2), 3.77 (s, 3 H, OCH_3), 2.78 [s, 6 H, $N(CH_3)_2$], 2.37 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 158.7 (C-2), 138.9 (C-6), 128.4 (C-4), 126.4 (C-1), 124.8 (C-5), 108.5 (C-3), 55.9 (OCH_3), 37.3 (CH_2), 36.6 [$N(CH_3)_2$], 20.2 (CH_3). HRMS (CI): *m/z* calcd for $C_{12}H_{19}N_2O_2$ $[MH]^+$: 223.1441; found: 223.1441.

***N'*-(2-Methoxy-3-methylbenzyl)-*N*,*N*-dimethylurea (92).** 0.18 g (0.81 mmol, 40%). Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (dd, *J* = 1, 8 Hz, 1 H, H-4), 7.02 (br d, *J* = 8 Hz, 1 H, H-6), 6.91 (app. t, *J* = 8 Hz, 1 H, H-5), 4.84 (br, exch., 1 H, NH), 4.37 (d, *J* = 6 Hz, 2 H, CH_2), 3.69 (s, 3 H, OCH_3), 2.82 [s, 6 H, $N(CH_3)_2$], 2.22 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 157.2 (C-2), 132.7 (C-1), 131.5 (C-3), 131.0 (C-4), 127.8 (C-6), 124.7 (C-5), 60.8 (OCH_3), 40.9 (CH_2), 36.6 [$N(CH_3)_2$], 16.4 (CH_3). HRMS (CI): *m/z* calcd for $C_{12}H_{19}N_2O_2$ $[MH]^+$: 223.1441; found: 223.1443.

***N'*-(2-Ethyl-6-methoxybenzyl)-*N*,*N*-dimethylurea (93).** 0.24 g (1.02 mmol, 51%). Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.14 (m, 2 H, H-4 and NH), 6.86 (d, *J* = 8 Hz, 1 H, H-3), 6.68 (d, *J* = 8 Hz, 1 H, H-5), 4.30 (br, 2 H, CH_2N), 3.74 (s, 3 H, OCH_3), 3.07 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 2.72 [s, 6 H, $N(CH_3)_2$], 1.06 (t, *J* = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5 (C=O), 156.3 (C-6), 126.9 (C-4), 126.8 (C-2), 125.4 (C-1), 119.4 (C-3), 109.0 (C-5), 54.2 (OCH_3), 45.4 (CH_2NH), 41.5 (CH_2CH_3), 37.7 [$N(CH_3)_2$], 11.8 (CH_2CH_3). HRMS (CI): *m/z* calcd for $C_{13}H_{21}N_2O_2$ $[MH]^+$: 237.1598; found: 237.1598.

***N'*-(3-Ethyl-2-methoxybenzyl)-*N*,*N*-dimethylurea (94).** 0.18 g (0.76 mmol, 38%). Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (app. t, *J* = 8 Hz, 1 H, H-5), 6.75 (d, *J* = 8 Hz, 1 H, H-6), 6.67 (d, *J* = 8 Hz, 1 H, H-4), 4.84 (br, exch., 1 H, NH), 3.89 (d, *J* = 6 Hz, 2 H, CH_2N), 3.78 (s, 3 H, OCH_3), 2.77 [s, 6 H, $N(CH_3)_2$], 2.73 (q, *J* = 7 Hz, 2 H, CH_2CH_3), 1.12 (t, *J* = 7 Hz, 3 H, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (C=O), 158.7 (C-2), 130.7 (C-1), 130.7 (C-4), 127.7 (C-3), 124.7 (C-6), 121.9 (C-5), 55.9 (OCH_3), 36.9 (CH_2NH), 36.6 [$N(CH_3)_2$], 26.6 (CH_2CH_3), 16.5 (CH_2CH_3). HRMS (CI): *m/z* calcd for $C_{13}H_{21}N_2O_2$ $[MH]^+$: 237.1598; found: 237.1599.

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