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Acyclic Amides as Estrogen Receptor Ligands: Synthesis, Binding, Activity and Receptor Interaction

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Abstract—We have prepared a series of bisphenolic amides that mimic bibenzyl and homobibenzyl motifs commonly found as substructures in ligands for the estrogen receptor (ER). Representative members were prepared from three classes: *N*-phenyl benzamides, *N*-phenyl acetamides, and *N*-benzyl benzamides; in some cases the corresponding thiocarboxamides and sulfonamides were also prepared. Of these three classes, the *N*-phenyl benzamides had the highest affinity for ER, the *N*-phenyl acetamides had lower, and the *N*-benzyl benzamides were prone to fragmentation via a quinone methide intermediate. In the *N*-phenyl benzamide series, the highest affinity analogues had bulky *N*-substituents; a CF_3 group, in particular, conferred high affinity. The thiocarboxamides bound better than the corresponding carboxamides and these bound better than the corresponding sulfonamides. Binding affinity comparisons suggest that the *p*-hydroxy group on the benzoate ring, which contributes most to the binding, is playing the role of the phenolic hydroxyl of estradiol. Computational studies and NMR and X-ray crystallographic analysis indicate that the two anilide systems studied have a strong preference for the *s-cis* or *exo* amide conformation, which places the two aromatic rings in a *syn* orientation. We used this structural template, together with the X-ray structure of the ER ligand binding domain, to elaborate an additional hydrogen bonding site on a benzamide system that elevated receptor binding further. When assayed on the individual ER subtypes, ERα and ERβ, these compounds show modest binding affinity preference for ERα. In a reporter gene transfection assay of transcriptional activity, the amides generally have full to nearly full agonist character on ERα, but have moderate to full antagonist character on ERβ. One high affinity carboxamide is 500-fold more potent as an agonist on ERα than on ERβ. This work illustrates that ER ligands having simple amide core structures can be readily prepared, but that high affinity binding requires an appropriate distribution of bulk, polarity, and functionality. The strong conformational preference of the core anilide function in all of these ligands defines a rather rigid geometry for further structural and functional expansion of these series.

Introduction

Recent advances in nuclear hormone receptor pharmacology and mechanism of action have redefined the classification of estrogen receptor (ER) ligands.[1] The selective estrogen receptor modulator class, or SERMs, are considered to be very important because of the potential of SERMs for maintaining bone mineral density and cardiovascular health, and for treating and preventing breast cancer and other hormone-dependent disorders, without adverse stimulation of the uterus and breast.[2] SERMs comprise several structurally diverse classes, including the triarylethylenes, triarylnaphthalenes, benzo[b]furans, benzopyrans, and various other tetracyclic manifestations of these core structures.[3] Collectively, SERMs display a wide range of tissue-selective agonist and antagonist activities, but major efforts continue to be directed toward optimizing ER ligand structure in order to obtain desired tissue-specific properties with minimal side-effects, which is an important concern in maintaining efficacy and patient compliance.[4]

In connection with our interests in novel templates for ER ligands, especially ones that might be suitable for

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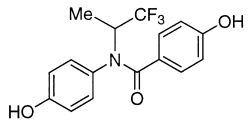
combinatorial development,[5] we wondered whether acyclic tertiary amides might be developed as mimics of common structural motifs found at the core of many ER ligands and thus support a combinatorial approach to SERM discovery and optimization. In this report, we describe the design and synthesis of three types of amide-core ER ligands, and we investigate their molecular structure, their structure binding–affinity relationships, and their activity in ERα and ERβ transactivation assays. A number of interesting trends and high affinity amides were discovered during this investigation. One high affinity amide in particular (**16g**) was found to be an ERα-potency selective agonist.



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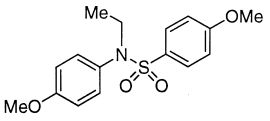

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Results and Discussion

Rationale and design

To the best of our knowledge, only two examples of ER ligands containing, either partially or exclusively, an amide core structure are known in the public literature. Hartmann and co-workers studied a small series of bis-phenolic carboxamides[6,7] containing an invariant *N*-(1,1,1-trifluoro-2-propyl) substituent (e.g., **1**) and found them to be anti-estrogens with weak to moderate potency. An early example of an *N*-ethyl benzene sulfonamide (**2**)[8] was also reported and shown to be weakly estrogenic in vivo. Neglecting amide bond stereoisomers for the moment, these ligands represent potential mimics (**I**) for either the *anti*- or *syn*-bibenzyl motifs **A** and **B**, respectively (Fig. 1, right), that are found in many common ER ligands (Fig. 1, left). In addition to the bibenzyl structural template of these leads, we envisioned two homologues (**II** and **III**, Fig. 2, right) which mimic the *homo*-bibenzyl motif **C** (Fig. 2, **II**–**III**), a structural element that is also well represented in high affinity ligands for the ER (Fig. 2, left).

From this analysis, model *para*-substituted bis-phenolic carboxamides, sulfonamides and thioamides containing *N*-alkyl and trifluoroalkyl substituents (R and R′) were considered as potential templates for combinatorial development (Fig. 3). Preparation for many of these compounds is straightforward and thus not unreasonable for adaptation to combinatorial library synthesis.

Chemical syntheses

***N*-Phenyl benzamides and benzene sulfonamides.** To synthesize simple *N*-alkyl amide analogues in an expeditious manner, we used catalytic phase transfer conditions (Scheme 1). Thus, *N*-alkylation of the known secondary benzene sulfonamide **3**[8] proceeded under mild conditions using n-Bu_4NSO_4H, NaOH, and excess alkyl halide in CH_2Cl_2/H_2O.[9] The target *N*-alkylated sulfonamides **5a**–**c** were then obtained after deprotection. The less acidic carboxamide **6** was alkylated using a solid–liquid two-phase system, consisting of powdered NaOH and cat. n-Bu_4NBr in refluxing benzene, to afford the tertiary amides **9a**–**e** in good yield.[9,10] Carboxamides **9f** and **9g** were conveniently prepared from the secondary anilines **7** and **8**. Aniline **7** was prepared via reductive alkylation of the corresponding aldimine using a modified literature procedure.[11] Aniline **8** was obtained by reductive amination, using $NaBH(OAc)_3$, *p*-anisidine, and 3-methyl-2-butanone. Thioamides were prepared in relatively good yield by treating the carboxamide (**9a**–**g**) with Lawesson's reagent.[12] Deprotection with BBr_3 or

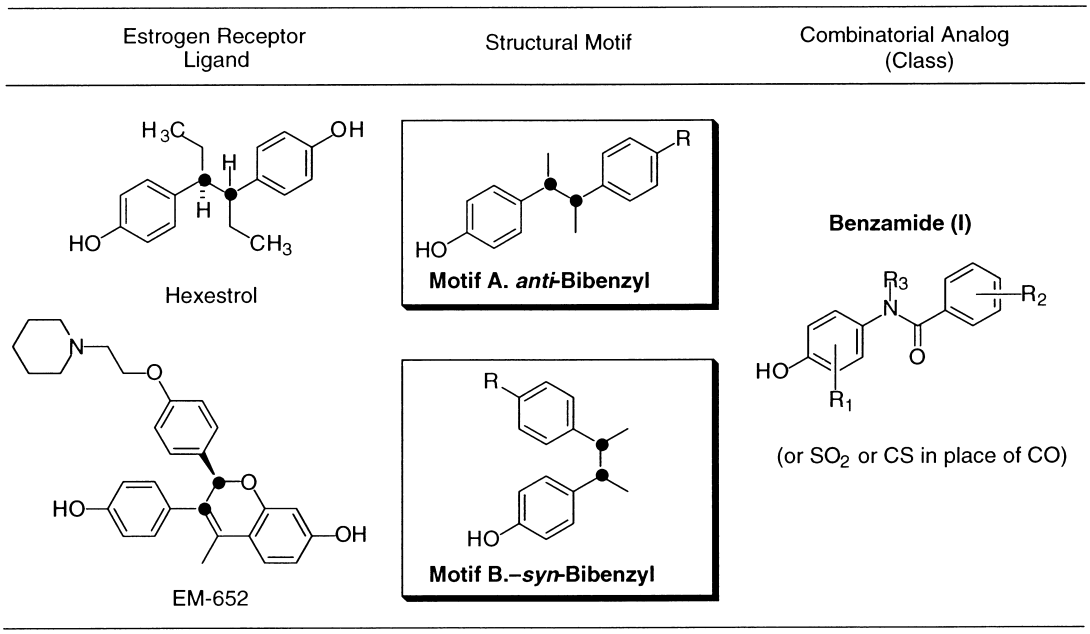


Figure 1. *Syn* and *anti*-bibenzyl motifs and proposed acyclic amide analogues.

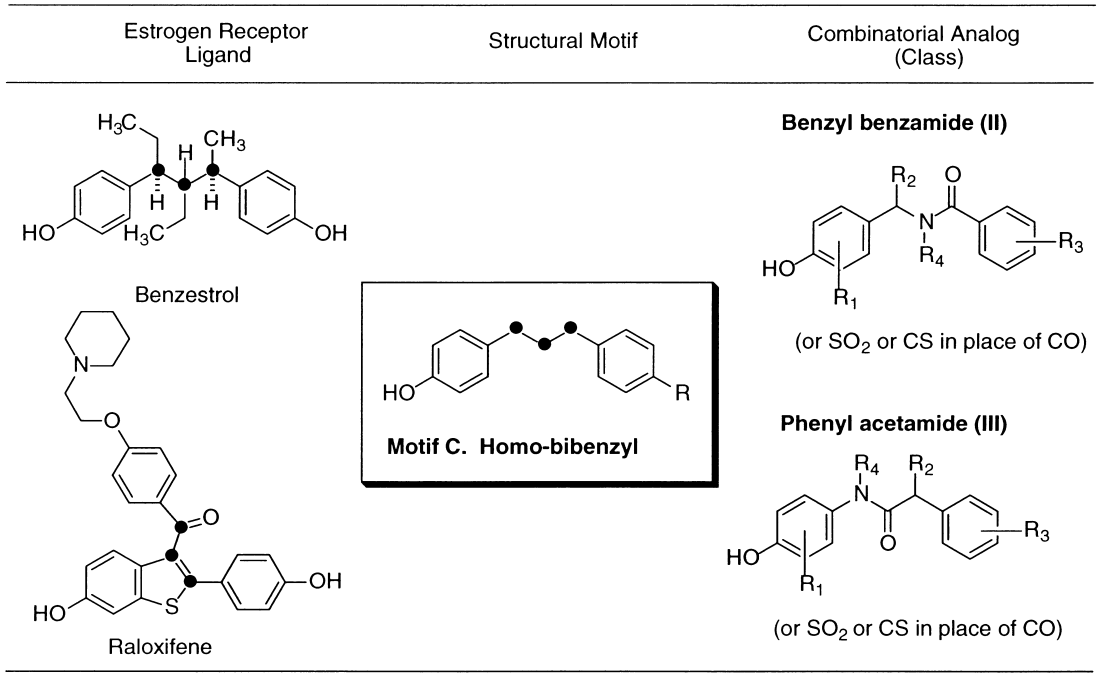


Figure 2. *Homo*-bibenzyl motif and proposed acylic amide analogues.

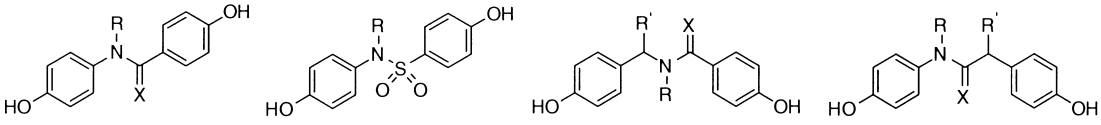
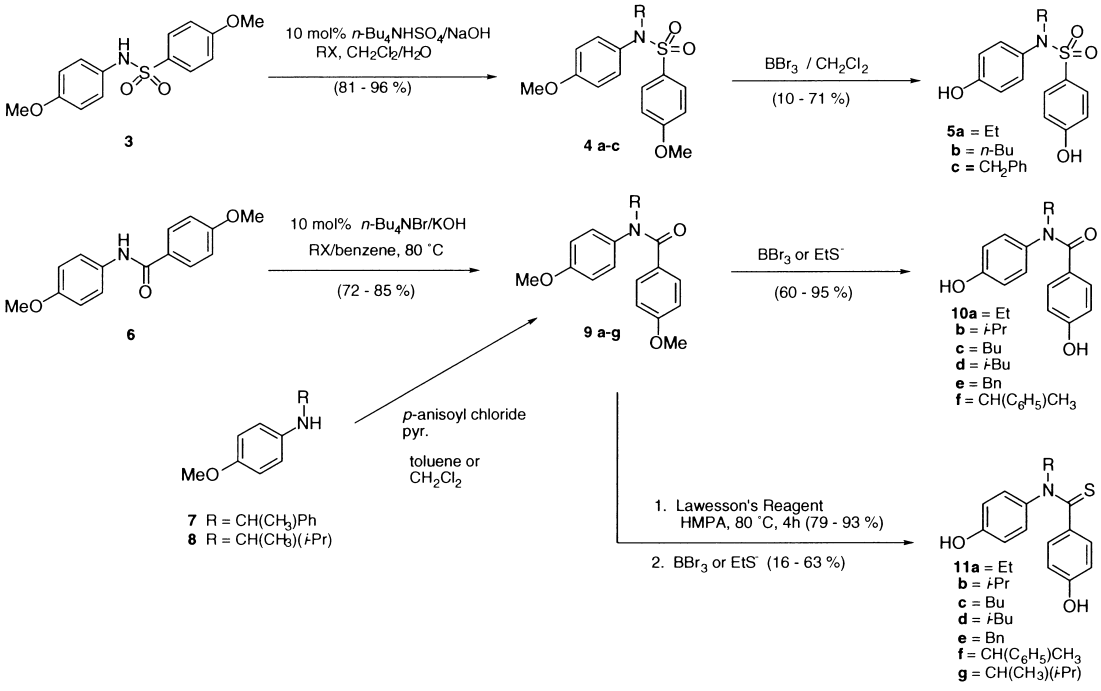


Figure 3. Potential amide ER ligand scaffolds for combinatorial chemistry (X = O, S).

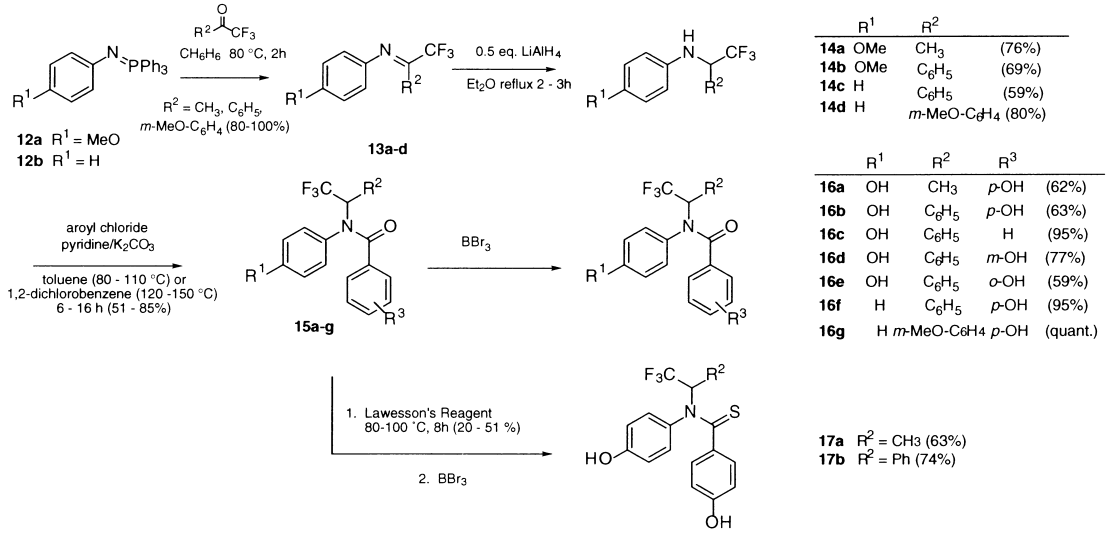


Scheme 1. Synthesis of *N*-phenyl benzamides.

ethanethiolate afforded the target benzamides **10a–f** and thiobenzamides **11a–g**.

CF_3-containing *N*-phenyl benzamides. To further explore the effect that a trifluoromethyl group would have on receptor binding affinity, we prepared several carboxamide and thioamide analogues related to the weak antiestrogen (**1**) reported by Hartmann and co-workers.[6] The synthetic route to CF_3-amide analogues, depicted in Scheme 2, was adapted from that reported by Hartmann and required introduction of the CF_3-alkyl substituent at the aniline stage in two steps starting from the corresponding iminophosphoranes. The starting trifluoromethylketones were commercially available, with the exception of 2,2,2-trifluoro-l-(3-methoxyphenyl)ethanone, which was prepared from 3-bromoanisole according to the procedures described by Hatanaka et al. and references therein.[13] Ylides **12a** and **12b** were readily obtained by treatment of the corresponding azides with Ph_3P.[14,15] Subsequent Staudinger reaction to afford the CF_3-substituted imines **13a–d**, followed by LAH reduction, furnished the desired secondary anilines **14a–d** in good overall yield. Amidation in warm toluene proceeded satisfactorily to provide carboxamides **15a–e**; however, unactivated anilines **14c** and **14d** required 1,2-dichlorobenzene as solvent and higher temperatures to afford benzamides **15f** and **15g** in satisfactory yields. Subsequent deprotection using BBr_3 afforded the desired phenols **16a–g** as before. Thionation of the protected, CF_3-substituted carboxamides proceeded in significantly lower yield (20–51%) than did those with simple *N*-alkyl substitution (>79%). Alternative thionation conditions, such as P_2S_5 and $POCl_3/(TMS)_2S$, did not give improved yields. Nevertheless, the two thioamides **17a** and **17b** could be obtained after deprotection with BBr_3.

***N*-Phenyl acetamides and *N*-benzyl benzamides.** Acetamides were attractive because they offer an additional site for structural diversity that is not available in benzamides (Scheme 3). *N*-Ethylation of amide **18** using PTC conditions as before afforded **19** in excellent yield. Subsequent α-alkylation using LDA at −78 °C then afforded the disubstituted carboxamides **20a–b** in high yield. Thionation and/or deprotection as before furnished

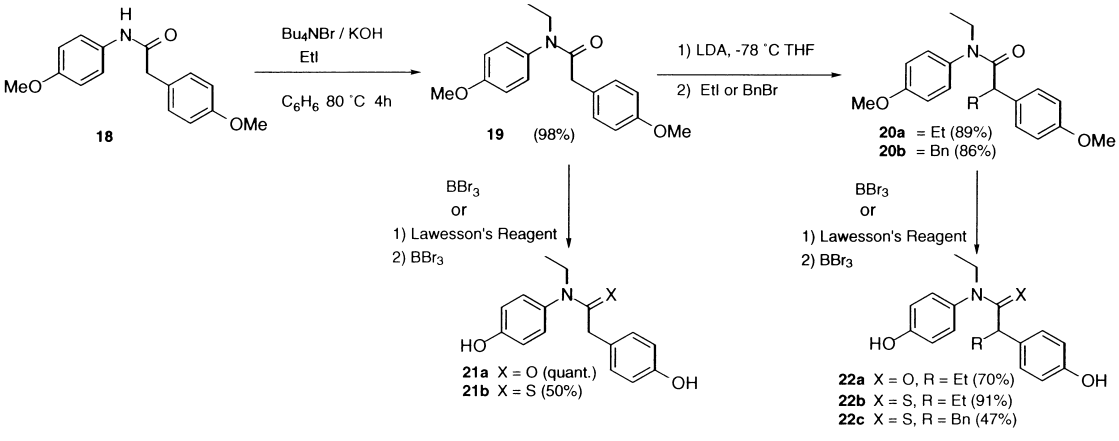


	R^1	R^2	
14a	OMe	CH_3	(76%)
14b	OMe	C_6H_5	(69%)
14c	H	C_6H_5	(59%)
14d	H	*m*-MeO-C_6H_4	(80%)

	R^1	R^2	R^3	
16a	OH	CH_3	*p*-OH	(62%)
16b	OH	C_6H_5	*p*-OH	(63%)
16c	OH	C_6H_5	H	(95%)
16d	OH	C_6H_5	*m*-OH	(77%)
16e	OH	C_6H_5	*o*-OH	(59%)
16f	H	C_6H_5	*p*-OH	(95%)
16g	H	*m*-MeO-C_6H_4	*p*-OH	(quant.)

17a R^2 = CH_3 (63%)
17b R^2 = Ph (74%)

Scheme 2. Synthesis of CF_3-containing *N*-phenyl benzamides.



Scheme 3. Synthesis of *N*-phenyl-acetamides.

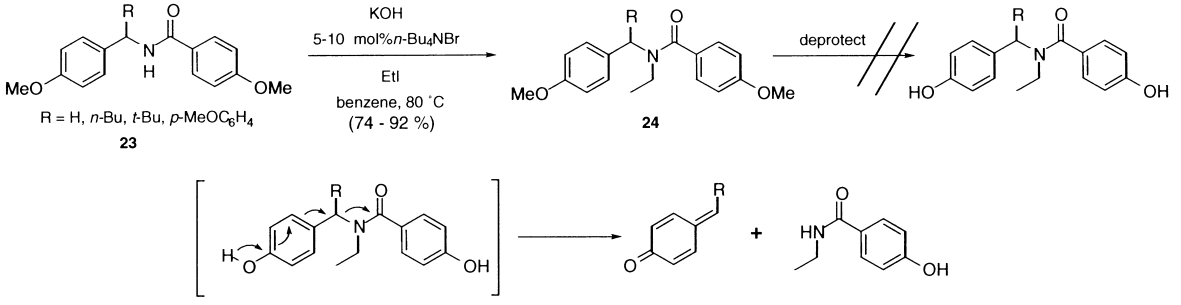
the desired bis-phenolic amides **21a–b** and **22a–c** without complication.

The *N*-benzyl-*N*-alkylbenzamides **24** (Scheme 4), which are essentially amide isomers of the acetamide class, and related benzenesulfonamides (not shown), were also investigated. These *N*-benzyl amides, protected as methyl ethers, could be prepared by routes that are analogous to those used in Schemes 1–3. However, these systems proved to be unstable to various deprotection conditions: BBr_3, ethanethiolate, HBr/AcOH and TMSI all led to decomposition. The only isolatable products were the corresponding secondary amides, presumed to result from an elimination of the 4-hydroxy-*N*-benzyl substituent via a quinone-methide intermediate (Scheme 4). Due to their propensity for elimination, additional efforts were not made to prepare members of the *N*-benzyl benzamide class.

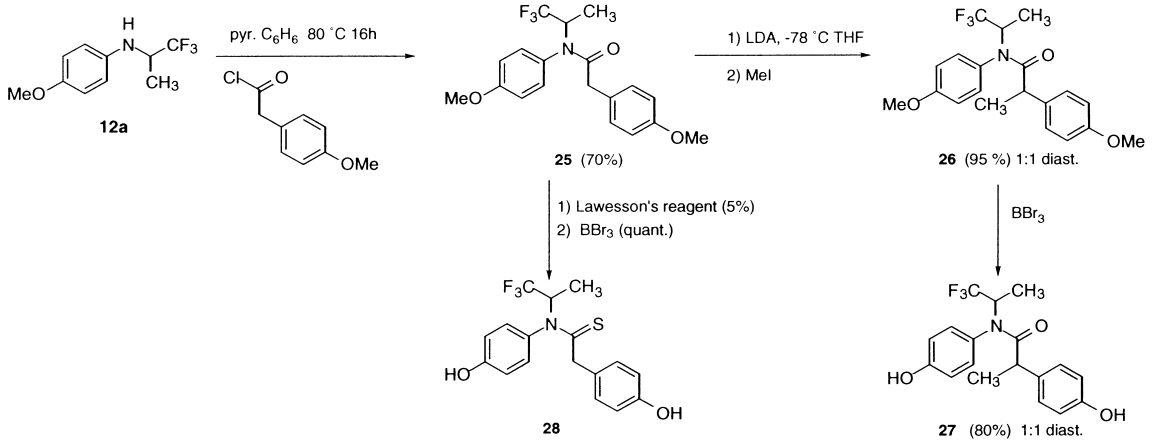
CF_3-containing *N*-phenyl acetamides. Incorporation of the CF_3-group was also explored in the acetamide series, and the synthesis of α-substituted acetamides containing an *N*-(1,1,1-trifluoro-2-propyl) substituent is shown in Scheme 5. Thus, the *N*-(1,1,1-trifluoro-2-propyl) substituted aniline **12a** was treated with 4-methoxyphenylacetyl chloride to afford carboxamide **25**. α-Alkylation as before using LDA at −78 °C and MeI proceeded in excellent yield to give **26** as a ~1:1 mixture of diastereomers as indicated by ^{1}H NMR and HPLC analysis. Demethylation then afforded the di-substituted phenylacetamide **27** in good yield. Unfortunately, attempts to thionate **26** with Lawesson's reagent failed; however, treatment of the unsubstituted phenylacetamide **25** with Lawesson's reagent did give thioamide **28**, in albeit low yield. Repeated attempts using other reagents (P_2S_5 and $POC_{13}/(TMS)_2S$) or higher temperatures failed to provide thioamide **26** or to improve the yield of **28**. Increased steric hindrance about the C=O bond is thought to be responsible for the lack of reactivity of the CF_3-substituted *N*-phenyl acetamides towards O–S replacement, as lower yields for thionation were also observed for the CF_3-containing benzamides (Scheme 2).

Molecular conformation

As was noted in Figure 1, bibenzyl motifs in ER ligands are well represented as both *syn* and *anti* conformations. Since *N*-aryl-benzamides share a similar bibenzyl-like two-atom connection between two aromatic rings, we were interested in their conformational preference to establish which structural motif they might be mimicking. From early ^{1}H NMR studies of *N*-substituted anilides, there is known to be a surprisingly strong preference for the *exo*-isomer (*N*-phenyl group *trans* to carbonyl oxygen).[16] Even simple *N*-methyl and *N*-ethylformanilides, where steric considerations would place the bulkier alkyl group next to the formyl hydrogen in an *endo* preference, have a 95% *exo* preference in solution.[17] This so-called '*exo*-rule' is quite general, and it has been stated that for *N*-substituted anilides other than formyl, the *exo*-isomer dominates to the exclusion

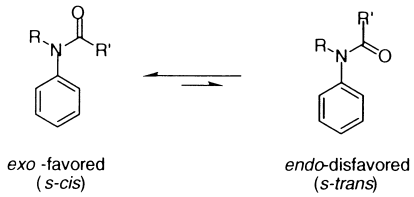


Scheme 4. Attempted synthesis of *N*-benzyl-benzamides.



Scheme 5. Synthesis of CF_3-containing *N*-alkyl-phenylacetamides.

of the *endo*-isomer.[16] The *endo*-isomer is detectable only when large *ortho* substituents are present on the *N*-phenyl ring or when R′=H.



Molecular modeling studies on both carboxamide **16a** and thiocarboxamide **17a** that we have performed using molecular mechanics (MM2) were in agreement with the reported NMR observations, and indicated the *exo* or *s-cis* conformer as being energetically more favorable (Fig. 4). In the case of carboxamide **16a**, a substantial ΔH of 5.3 kcal/mol between the global minimum energy *cis* and *trans* isomers was found, the major energetic difference being due to additional electrostatic contributions in the *s-trans* conformation. Thiocarboxamide **17a** has a smaller ΔH of 0.9 kcal/mol between the global minimum energy *cis* and *trans* isomers (not shown). This result is in accord with destabilization of the *s-cis* (*exo*) thioamide conformer relative to the *s-trans* (*endo*) conformer because of additional steric repulsions between sulfur and the *N*-alkyl substituent that arise from the larger covalent radii of sulfur versus oxygen (1.4 Å for sulfur, 0.74 Å for oxygen) and its longer bond length (C=S 1.64 Å; C=0 1.24 Å).

Direct structural studies of *N*-substituted thioanilides, let alone hindered systems containing a CF_3-substituent, have not been reported, as far as we have found. For this reason and because of the relatively small energy difference found from molecular modeling for **17a**, we obtained an X-ray crystallographic structure of the methyl ether derivative of **17a** to firmly establish its preferred stereochemistry about the amide bond. In addition, for comparison, a crystallographic structure was determined on the less hindered *N*-(*i*-propyl)-carboxamide **10b**. ORTEP representations of these molecules are shown in Figure 5.

As can be seen in Figure 5, both the *i*-propyl carboxamide and CF_3-substituted thioamide were found to crystallize in the lower energy *s-cis* conformation. Prominent torsion angles are indicated in Table 1. Comparison of the amide torsional bonds (torsion **A**) reveals greater deviation of the *N*-aryl ring from the amide plane in thiocarboxamide **17a** compared to **10b** (18° versus 9.7°), consistent with the greater steric hindrance anticipated in the amide plane of the thioamide system. The greater distortion in the thioamide bond planarity is also evident from its improper torsion (torsion **E**) and its *N*-alkyl torsion **B**. Both structures also show a twisting of the phenyl rings out of the amide plane (**C** and **D**), with the thioamide being more planar. This difference appears in part to be due to additional nearby nonbonding interactions with the CF_3-group in thioamide **17a**.

Solution VT ^{1}H NMR experiments (Fig. 6) were also conducted, and the results were found to be consistent with a single amide conformer. Shown in Figure 6 is the ^{1}H NMR spectrum of the aromatic region for thioamide **17a** at −60, +23, and +55 °C in MeOD. The spectra at −60 °C and room temperature are very similar. Interestingly, there is a slow rotation about the N–C bond of the *N*-phenyl group, which results in distinct signals for the *ortho* and *meta* ring protons of the *N*-phenyl ring. Assignments are based on COSY cross couplings. Upon heating to +55 °C, no new signals are observed for either the CH_3 group (not shown), which remains a doublet at all three temperatures, or the aroyl protons. However, the *ortho* and *meta* signals of the *N*-phenyl ring coalesce. This type of slow N–C rotation is well known in *N*-phenyl carboxamides and is analogous to hindered bi-phenyl rotations.[16] The lack of

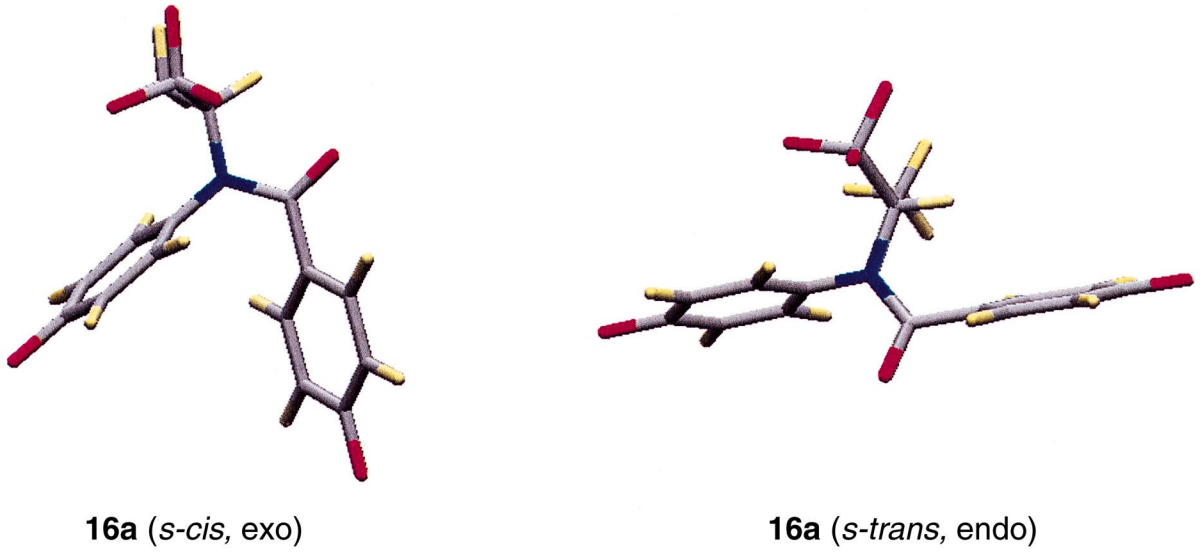


Figure 4. Capped-stick models of lowest energy *c-cis* and *s-trans* conformers of caboxamide **16a**. This *s-cis* conformer (left) has lower energy (ΔH = 5.3 kcal/mol).

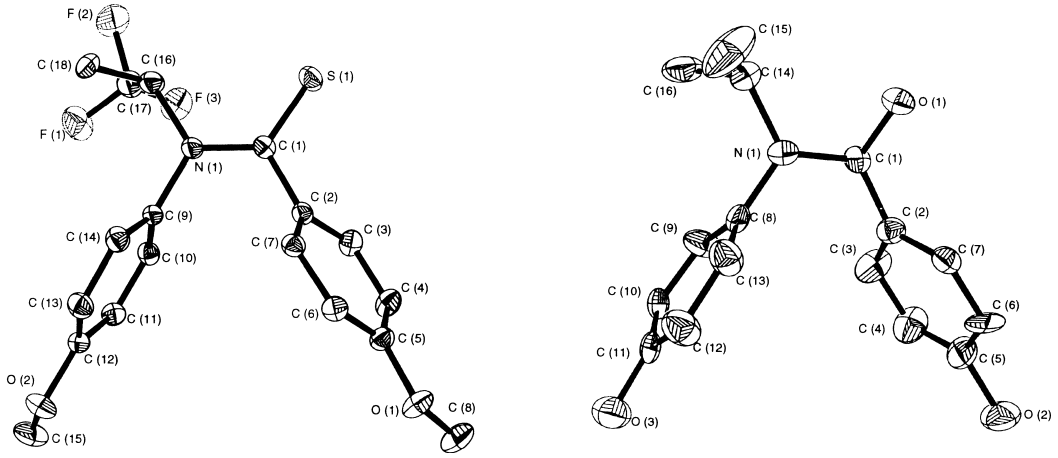


Figure 5. Molecular structures for thiocarboxamide **17a** (left) and carboxamide **10b** (right) (ORTEP; ellipsoids drawn at the 35% probability level).

Table 1. Prominent torsion angles found in carboxamide **10b** and thiocarboxamide **17a**

Torsion	Compound **17a** thioamide 1–4 atoms	Angle	Compound **10b** carboxamide 1–4 atoms	Angle
A	C(2)–C(9)	18°	C(2)–C(8)	9.7°
B	C(16)–S(1)	7.8°	C(14)–O(1)	3.2°
C	C(1)–C(10)	76°	C(1)–C(9)	80°
D	C(3)–N(1)	50°	C(3)–N(1)	62°
E	*N*-improper torsion	5.4°	*N*-improper torsion	4.6°

additional signals indicates that there is a single amide conformer in solution, which we presume, on the basis of the computational and X-ray structures, to be the *s-cis*. Furthermore, for thioamides, it is worthy to note that the barner for *cis–trans* inter-conversion is generally 2–5 kcal greater than it is for the analogous carboxamides. The traditional 'resonance model' used to rationalize the origin of the higher *cis–trans* barriers in thioamides has recently been challenged[18] and is currently under debate.[19–22] Nevertheless, from these studies we believe that it is reasonable to conclude that sterically hindered *N*-aryl ***thio***benzamides also have a strongly preferred *s-cis* conformation, similar to *N*-substituted ***oxo***anilides. Therefore, these systems can be considered as mimics of the *syn*-bibenzyl substructural motif.

Receptor binding affinities and structure–binding affinity relationships

Binding affinities for the estrogen receptor and octanol–water partition coefficients (Log $P^{o/w}$) determinations of the benzamides we have prepared are shown in Table 2 and are organized according to the substituent on the amide nitrogen (either *N*-alkyl/aryl or *N*-CF_3 containing alkyl/aryl). Binding affinities and Log $P^{o/w}$ determinations for phenylacetamides are presented in Table 3. Binding affinities were obtained from a competitive radiometric binding assay, using [^{3}H]estradiol as tracer and lamb uterine cytosol as a source of ER, and they are expressed as relative binding affinities (RBA), with estradiol having an affinity of 100%. Additional binding

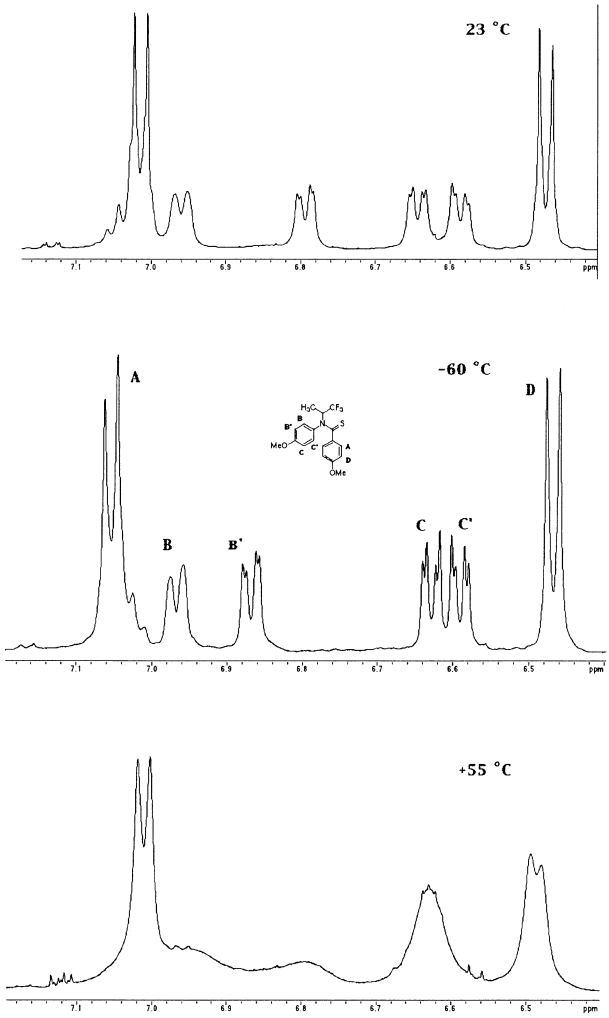
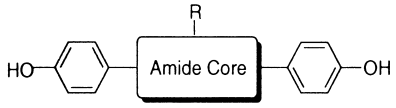


Figure 6. VT-^{1}H NMR for **17a**, aromatic region.

assays of select compounds for receptor subtypes ERα and ERβ, as well as ERα and ERβ transcriptional activation profiles in human endometrial cancer (HEC-1) cells using an estrogen-responsive reporter gene construct, are also shown in Table 4. Log $P^{o/w}$ determinations were obtained according to the method of Minick,

Table 2. Estrogen receptor relative binding affinity RBA (estradiol = 100) and log octanol–water partition coefficient (log $P^{o/w}$) data for *N*-phenyl-benzamides



Compound	Core structure	R group	RBA[a]	Log $P^{o/w}$
5a	-CSO_2R-	Et	0.23	2.76
5b		*n*-Bu	0.13	3.66
5c		Bn	0.053	4.62
10a	-CONR-	Et	0.062	2.40
10b		*i*-Pr	0.009	2.31
10c		*n*-Bu	0.042	—
10d		*i*-Bu	0.020	3.15
10e		CH_2Ph	0.089	—
10f		$CH(C_6H_5)CH_3$	0.45	3.96
11a	-CSNR-	Et	0.62	2.80
11b		*i*-Pr	0.83	2.97
11c		*n*-Bu	1.3	3.99
11d		*i*-Bu	1.5	—
11e		CH_2Ph	0.15	—
11f		$CH(C_6H_5)CH_3$	2.5	3.98
11g		$CH(CH_3)$(*i*-Pr)	4.6	4.31

[a]Relative binding affinities are the average of duplicate determinations (CV 0.3), measured in lamb uterine cytosol. For estradiol, RBA = 100. For details, see Experimental.

Table 3. Estrogen receptor relative binding affinity RBA (estradiol = 100) and log octanol–water partition coefficient (log $P^{o/w}$) data for *N*-CF_3-substituted benzamides

Compound	X	R^1	R^2	R^3	RBA[a]	Log $P^{o/w}$
16a	O	HO	CH_3	*p*-HO	0.49	3.29
16b	O	HO	C_6H_5	*p*-HO	9.0	4.51
16c	O	HO	C_6H_5	H	0.063	4.46
16d	O	HO	C_6H_5	*m*-HO	0.45	—
16e	O	HO	C_6H_5	*o*-HO	0.068	—
16f	O	H	C_6H_5	*p*-HO	8.9	4.97
16g	O	H	*m*-HOC_6H_4	*p*-HO	15	4.63
17a	S	HO	CH_3	*p*-HO	7.5	3.99
17b	S	HO	C_6H_5	*p*-HO	14	5.40

[a]Relative binding affinities are the average of duplicate determinations (CV 0.3), measured in lamb uterine cytosol. For estradiol, RBA = 100. For details, see Experimental.

using a standardized Chromegabond MC8 reverse phase HPLC system.[23]

Binding affinity of *N*-phenyl benzamides. The receptor binding affinities for *N*-phenyl benzamides are shown in Table 2. The sulfonamides and carboxamides all have rather low affinity, the highest being carboxamide **10f**. Within the carboxamide series (**10a**–**f**), it is interesting to compare the effect of branching near the amide core. For example, the ethyl (**10a**) and benzyl (**10e**) compounds have similarly low affinities, and likewise the branched *i*-propyl amide **10b** has very low affinity. However, amide **10f**, which contains both an α-phenyl and methyl substituent, shows a significant, 5- to 7-fold increase in affinity compared to either monosubstituted amide **10a** or **10e**. Overall, the analogous *N*-alkyl

Table 4. Estrogen receptor relative binding affinity RBA (estradiol = 100) and log octanol–water partition coefficient (log $P^{o/w}$) data for *N*-phenyl phenylacetamides

Compound	X	R^1	R^2	RBA[a]	Log $P^{o/w}$
21a	O	CH_2CH_3	H	0.006	2.68
22a	O	CH_2CH_3	CH_2CH_3	0.004	3.52
27	O	$CH(CH_3)(CF_3)$	CH_3	0.010	—
28	S	$CH(CH_3)(CF_3)$	H	0.66	—
21b	S	CH_2CH_3	H	0.20	3.40
22b	S	CH_2CH_3	CH_2CH_3	0.089	4.27
22c	S	CH_2CH_3	CH_2Ph	0.34	—

[a]Relative binding affinities are the average of duplicate determinations (CV 0.3), measured in lamb uterine cytosol. For estradiol, RBA = 100. For details, see Experimental.

thioamides (**11a**–**g**) bind with affinity 2- to 90-fold greater than their carboxamide counterparts, which is presumably due to their greater hydrophobic character, although there are not great differences in the Log $P^{o/w}$ values, where comparisons can be made. A related trend is also observed in other non-steroidal ligands containing heteroatoms, such as benzo[b]furans and benzo[b]thiophenes, with benzo[b]thiophenes displaying higher affinity than benzo[b]furans.[24,25]

The beneficial effect of placing more sterically encumbered groups near the amide core on receptor affinity is also evident in the thioamide series, because the same relative affinity increases which occurred for carboxamides (**10a** < **10e** < **10f**) are also reflected in the thioamides (**11e** < **11a** < **11f**). Replacement of the phenyl substituent in **11f** with an *i*-propyl group to afford thioamide **11g** results in even greater crowding near the amide plane, enhancing the relative affinity to 4.6%, the highest observed for any simple *N*-phenyl benzamide.

Binding affinity of CF_3-containing *N*-phenyl benzamides. The RBA data for the CF_3-containing benzamides are presented in Table 3. Immediately apparent is the relatively high binding affinity for thioamide **17b** and carboxamide **16g**, and to a lesser extent amides **16b, 16f** and **17a**. Compound **16a**, reported by Hartmann and coworkers, is included for comparison.[6] In general, all the CF_3-substituted benzamides show affinity enhancements relative to their non-fluorinated amide counterparts (Table 2).

Shown in Figure 7 are four direct comparisons of RBA and Log $P^{o/w}$ data for benzamides from Tables 2 and 3. These four pairs of compounds clearly show the relationship between core structure (*O* and *S* substitution) and peripheral group presentation (methyl to phenyl, and methyl to trifluoromethyl) and how these components alter ER affinity.

Comparison of the relative RBAs for these four pairs of amides, starting from the *i*-propyl pair (upper left) to the CF_3-containing phenethyl pair (lower right), shows a diminishing effect of sulfur–oxygen replacement as binding affinity increases and as larger substituents are added near the amide core. The sulfur–oxygen

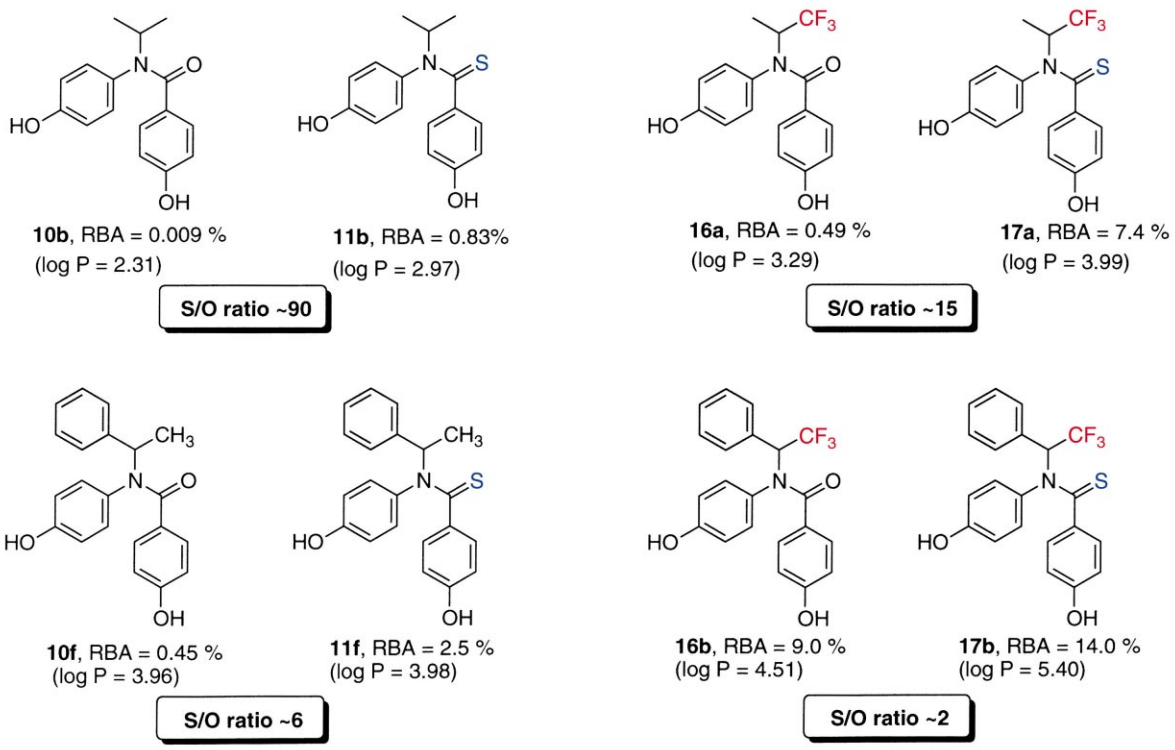


Figure 7. Comparison of the relative binding affinities of the principal carboxamides and thiocarboxamides.

enhancement is greatest in the parent *i*-propyl system (**10b** versus **11b**), where the overall affinity is lowest, and is least when the substituents are phenyl and trifluoromethyl (**16b** versus **17b**), where the overall affinity is highest. In addition, there is a general increase in binding affinity with increasing lipophilicity. The observed parallel affinity–lipophilicity increase within the series is not too surprising in light of what is known about the hydrophobic character of the ER ligand binding pocket.[26]

CF_3 effect: lipophilic, steric or electrostatic effects? The effect of adding a CF_3 group in place of methyl on the RBA may be the result of several factors, including lipophilic, steric and/or electrostatic effects. In terms of steric effects, a recent review by O'Hagan and Rzepa[27] cites several studies which place an upper size limit of a CF_3-group being close to that of *i*-propyl. The greatest increases in RBA for CH_3 to CF_3 substitution are found in the carboxamide class (20- to 50-fold, versus 5- to 8-fold for thioamide), with the highest being the *i*-propyl compounds (Fig. 7, **16a** versus **10b**). In order to test whether or not RBA increases associated with CF_3-replacement are the result of its steric or its electronic property, the branched $CH(CH_3)$(*i*-Pr) thioamide **11g** was prepared to compare with the CF_3 analogue **17a**. Based on the above-mentioned studies, if steric effects alone operate, compound **11g** would be expected to have an RBA close to that of the CF_3-substituted thioamide **17a** (7.5%). The observed RBA, however, for compound **11g** was only 4.6%. This indicates that an additional effect may be contributing to the binding energy, either lipophilic or electrostatic. The fact that the Log $P^{o/w}$ values for **11g** and **17a** are quite similar, with **11g** being somewhat higher, suggests that the difference in binding affinity is probably not due to a lipophilic component. Thus, based on this data it would seem that the additional component has, in addition to its steric effect, an electronic effect as well.

Optimization of binding orientation and hydroxylation pattern. For unsymmetrical non-steroidal ER ligands, a common approach to determining which phenol is imitating the crucial A-ring phenol of estradiol is to prepare and test the corresponding mono-phenolic derivatives.[28] The highest affinity mono-phenolic analogue is then presumed to be the A-ring mimic, because the hydroxyl substituent at this position is known to be very important in binding to the ER. Many non-steroidal ER ligands benefit from a second hydroxyl hydrogen bonding partner and appear to do so in an *anti*-bibenzyl motif, which places the hydroxyl oxygen–oxygen interatomic distances approx. 10–12 Å. Thus, it was apparent to us that the rigid *s-cis* benzamide conformation (*syn*-bibenzyl motif) in our amides was likely not benefiting from a second hydrogen bonding interaction, because its hydroxyl oxygen–oxygen interatomic distance was only 7.4 Å. The importance for this second hydrogen bond is evident in the recent non-steroidal diethylstilbestrol and raloxifene ERα LBD crystal structures.[26,29] Both of these complexes have an expected A-ring phenol mimic and a second phenol imitating the D-ring 17β-hydroxyl group of estradiol. In both cases, the second phenol uses the same hydrogen bond interaction with His_{524} as does the 17β-hydroxy1 group of estradiol.

To obtain an optimal hydroxylation pattern and discern which ring phenol was imitating the A-ring phenol of estradiol, we prepared benzamides **16c**–**g**. The results of these studies (Table 3) clearly show a pattern indicative of a preferred A-ring phenol mimic. For example, removal of the 4-hydroxyl phenol on the benzamide ring and retention of the 4-hydroxyl of the *N*-phenyl in compound **16c** lead to a nearly complete loss in binding affinity compared to the parent di-hydroxy compound **16b** (RBA = 0.063% versus 9.0%). In contrast, removal of *N*-phenyl hydroxyl and retention of the benzamide 4-hydroxyl result in an analogue **16f**, which retains a binding affinity equivalent to that of the parent compound. These findings clearly implicate the benzoyl ring phenol as the A-ring mimic of estradiol. In addition, as might be expected, positioning the hydroxyls elsewhere on the benzoyl ring is not well tolerated, as both the *ortho*- and *meta*-hydroxy analogues **16d** and **16e** have little or no affinity for the receptor.

Having discerned which phenol in the benzamide system was important for binding, we wished to explore alternative positions for a second hydroxyl group in order to benefit from the second hydrogen bonding interaction which is found in the raloxifene and DES ER binding pockets. Depicted in Figure 8 is a schematic representation of the predicted binding mode and phenol interactions for benzamide **16f** in the binding pocket of ER. This rudimentary model was derived from the interactions that were described to be present in the estradiol (E_2) X-ray crystal structure in the ERα LBD, the coordinates of which, at the time of our consideration, were not released.[26] Based on this view, we proposed that a hydroxyl substituent on the phenethyl ring might be positioned in the binding subpocket near His_{524}.

The choice of positioning the second OH at the *meta* position on the phenethyl substituent seemed somewhat obvious, since modeling showed that alternative OH substitution on the *N*-phenyl ring fails to provide O·O interatomic distances much greater than in the *para*-substituted system **16b**. Furthermore, the binding mode depicted in Figure 8 actually places the *N*-phenyl group more closely in the 11β subpocket of the ligand binding site, rather than the D-ring subpocket. In choosing the ring-substitution for the hydroxyl on the phenethyl ring, we considered both the *para* and *meta* isomers. However, in light of the problems encountered with quinone methide elimination in the *N*-benzyl benzamide series bearing a *para*-methoxy protecting group, we opted not to prepare the *para*-hydroxy analogue of **16f**, since the electron withdrawing CF_3 group would presumably exacerbate quinone methide elimination.

With the recent release of the E_2 ERα LBD crystal structure coordinates, we performed molecular docking studies of the proposed *meta*-hydroxybenzamide (**16g**) using TRIPOS' Flexidock routine (see Experimental), to see whether or not the proposed binding mode in Figure 8 was reasonable and whether a *meta*-hydroxy derivative could participate in a hydrogen bonding interaction with His_{524}.

The final docked and minimized model, using the *S*-enantiomer of **16g**, is depicted in crossed-stereo in Figure 9. The *R*-enantiomer (not shown) was also modeled in the same manner but resulted in a higher energy complex. The final *S*-enantiomer model converged to an RMS of < 0.05 kcal/mol·Å with a reasonably favorable binding energy. In this conformation, the benzoyl phenol is comfortably accommodated in the A-ring pocket, and the *N*-phenyl group projects into what

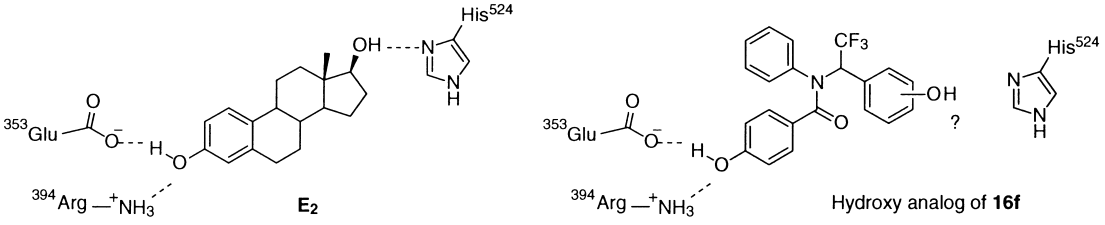


Figure 8. Putative binding mode for *N*-phenyl benzamide template with A-ring mimic interactions and a proposed site for second HO-group.

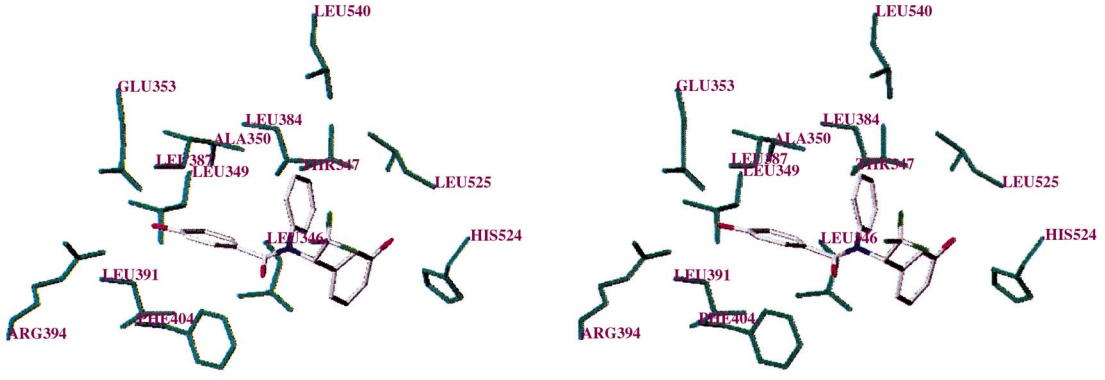


Figure 9. Crossed-stereo view of **16g** docked and minimized in ERα LBD binding pocket showing select residues within 3 Å of the benzamide.

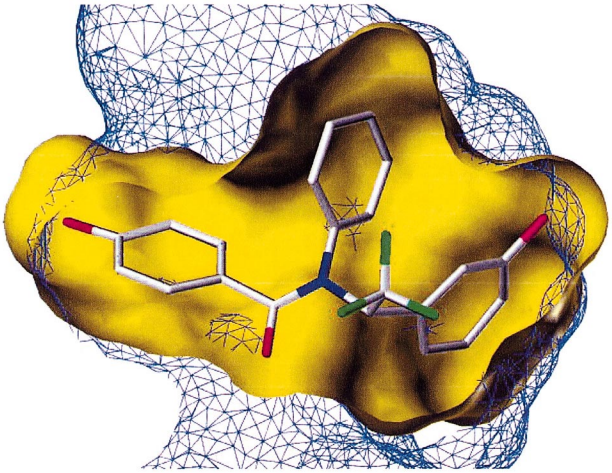


Figure 10. Depiction of solvent accessible surfaces for **16g** in ERα binding pocket.

would resemble the 11β pocket of the ERα-E_2 structure. Interestingly, the amide bond occupies a region of the binding pocket similar to that of the isosteric ethylene unit of DES in the recently solved ERα-DES crystal structure.[29]

Using the above model, we generated Connolly solvent accessible surfaces for the ligand and binding pocket to visualize close contacts (Fig. 10). This view reveals mostly favorable interactions within acceptable van der Waals radii. The ligand itself has a volume of 296 $Å^3$, which is 51 $Å^3$ greater than E_2, but is well under the total volume of 450 $Å^3$ for the binding pocket as reported in the ERα-E_2 crystal structure.[26]

We were grateful to find that the bis-(phenolic) benzamide **16g** had an RBA of 15%, the highest of any carboxamide ER ligand. This value represents a 1.6-fold increase over the affinity of the corresponding monophenolic benzamide **16f** and is close to what one might expect: in E_2 and other non-steroidal ER ligand systems, removal of the 17β hydroxyl, as in E_2, or the second D-ring hydroxyl mimic, as in raloxifene, result in a 0.6 kcal/mol reduction in binding energy, which corresponds to a 3-fold drop in affinity.[30] The fact that the addition of the second hydroxyl does not give a full 3-fold increase may be due to a somewhat unfavorable hydrogen bond trajectory in the binding pocket. From our model, the distance between the *m*-hydroxyl substituent and His_{524} (3.69 Å) is sufficiently close for some hydrogen bonding interaction, but is not ideal either in terms of distance or geometry. A second more likely explanation may have to do with stereochemical issues: This compound (**l6g**) was tested as a racemate, so only one enantiomer is likely to be able to benefit from the second hydrogen bonding interaction. The ERα and ERβ RBAs and the transcriptional activation profile for *rac*-**16g** in HEC-l cells are discussed below.

***N*-Phenyl acetamides as ER ligands.** The RBA and Log $P^{o/w}$ data for *N*-alkyl- and CF_3-containing acetamides are shown in Table 4. Disappointingly, none of these compounds were found to show appreciable affinity for the ER. Several direct comparisons can be made to other series in this investigation, which suggest that acetamides may not provide viable scaffolds for further combinatorial consideration, despite their potential to support greater structural diversity than the benzamides. Even the CF_3-containing acetamide **27** and thioacetamide **28** have affinities less that 1%, which are 50- and 11-fold lower, respectively, than their benzamide counterparts **16a** and **17a**.

One possible explanation for the low affinity in the acetamide class may lie in their conformation. Monte Carlo conformational studies of compound **27** and the unsubstituted analogue **27b**, using molecular mechanics methods, show a distinct preference for a *syn* conformation, as shown in Figure 11. The *syn*-conformer for **27** is predicted to be 5 kcal/mol lower in energy than the *anti*-conformer; even without the α-methyl substituent, which eliminates possible alkyl-*N*-phenyl steric repulsions, the *syn*-conformer is predicted to be favored by 2.5 kcal/mol (not shown). It is also noted that the barrier to rotation about the acetyl bond was estimated

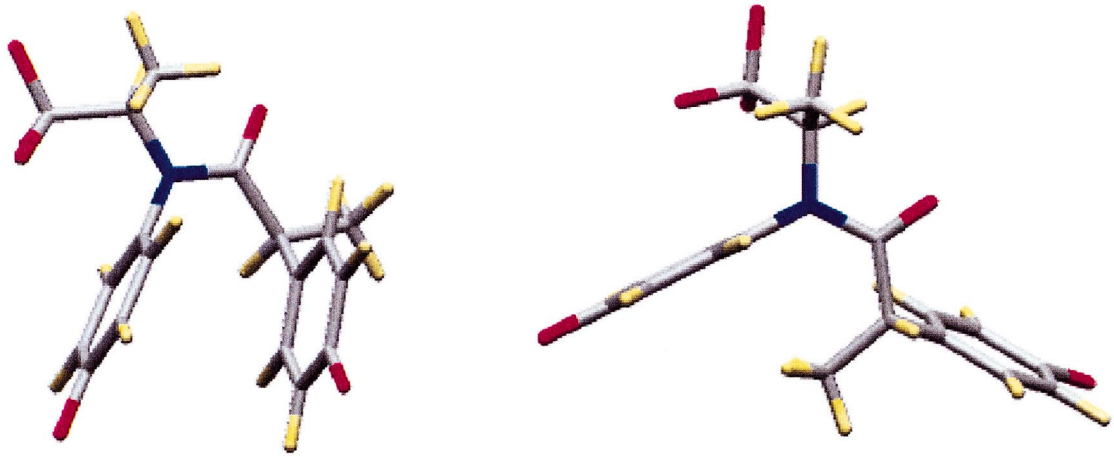


Figure 11. Conformational analysis of *N*-penyl-penylacetamide **27**.

to be between 4 and 5 kcal/mol for **27**, based on MM2 dihedral drive calculations.

As in the benzamides, in the acetyl conformations of **27** the *exo*-rule is upheld; this places the *N*-phenyl group *exo* with respect to the amide C=O, making the amide configuration *s-cis*. This *exo*-effect may also be operative for the α-phenyl substituent as well, since it also prefers to be essentially *exo* to the amide C=O rather than *endo*. Since the hydroxyl O·O interatomic distances for many estrogens requires a minimum of approximately 10.5 Å, the *syn*-conformation is excluded as a structure that is likely to fit in the ER binding pocket. Based on these studies and the RBA data available at this time, further investigations of the acetamide series did not appear to be warranted.

ERα/ERβ binding affinity, transcriptional activity and enantioselectivity

Shown in Table 5 are the RBA values of select benzamides for purified ERα and ERβ, along with their transcriptional activity in HEC-1 cells using an estrogen-responsive reporter gene construct ($(ERE)_3$-pS2-CAT) with expression vectors for either ERα or ERβ and benzamide at 10^{-6} M. It is apparent that binding affinities show selectivity for ERα, mostly in the range of 2- to 8-fold; compound **16g** has the highest selectivity for ERα of 21-fold (27% versus 1.3%). The enantiomers of **17b**, which were separated using chiral HPLC (ChiralPak AD column), also showed interesting RBA differences between the two receptor subtypes. For example, enantiomer *ent*$_2$-**17b** was found to have greater selectivity for ERα than enantiomer *ent*$_1$-**17b** by more than 5-fold, indicating that the individual binding pockets for ERα and ERβ are uniquely sensitive to subtle changes in ligand shape.

In the transcription assays,[31] agonism is measured with 1 μM of compound alone and is expressed as the percent of transcriptional activity with 1 nM E_2 (high values indicate agonist activity); antagonism is measured with 1 μM compound together with 1 nM E_2 (low values indicate antagonist activity). All of the benzamides tested were full or nearly full agonists through ERα, whereas some were effective partial antagonists through ERβ. Compound **16g** was a full agonist on ERα and ERβ.

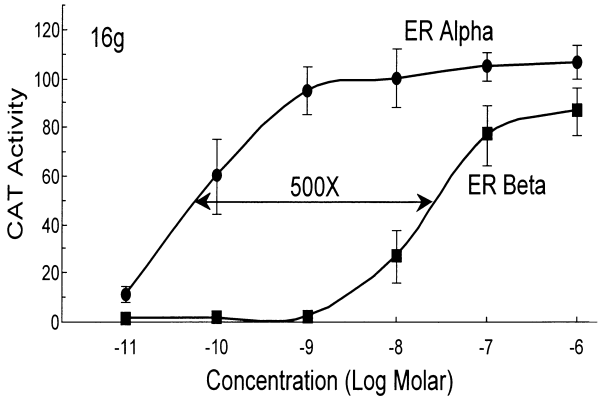


Figure 12. Transcription activation by ERα and ERβ in response to benzamide **16g**. Human endometrial cancer (HEC-1) cells were transfected with expression vectors for ERα or ERβ and an $(ERE)_3$-pS2-CAT reporter gene and were treated with the indicated concentrations of benzamide **16g** for 24 h. CAT activity was normalized for β-galactosidase activity from an internal control plasmid. Values are the mean ±SD for three or more separate experiments, and are expressed as a percent of the ERα or ERβ response with 1 nM E_2.

Because of the high activity of amide **16g** at 10^{-6} M on both ERα and ERβ, a full dose–response curve was determined to see whether any potency selectivity existed for either ERα or ERβ. As shown in Figure 12, benzamide **16g** behaves as an ERα potency selective agonist, displaying a 500-fold higher potency for activation of ERα over ERβ. It is of note that this high potency selectivity for ERα is greater than the 21-fold ERα affinity selectivity of this compound (cf. Table 5).

Conclusions

Through an analysis of potent non-steroidal estrogens, we have identified common substructural bibenzyl and homobibenzyl motifs in the structure of ER ligands. Based on this simple pharmacophore model, we have

Table 5. Benzamide ERα and ERβ binding affinities and transciptional activity

Compound	RBA (%) (uterine)	RBA (%)[a]			Agonism[b] % CAT Act.		Antagonism[b] % CAT Act. + E_2	
		ERα	ERβ	α/β ratio	ERα	ERβ	ERα	ERβ
11g	4.6	14	2.4	5.8	65	20	90	40
17a	7.5	23	15	1.5	60	20	65	45
16b	9.0	17	2.7	6.3	75	15	90	35
rac-**17b**	14	25	8.9	2.8	80	30	83	35
ent$_1$-**17b**	10	18	11	1.6	85	30	80	48
ent$_2$-**17b**	22	40	4.8	8.3	80	10	90	40
16g	15	27	1.3	21	99	99	100	97

[a]Relative binding affinities are the average of duplicate determinations (CV 0.3), determined with purifed RDα and ERβ preparations. For estradiol, RBA = 100. For details, see Experimental.

[b]HEC-1 cells were transfected with either REα or ERβ expression vectors and an $(ERE)_3$-pS2-CAT reporter gene. CAT activity was normalized for β-galactosidase activity from an internal control plasmid and is expressed as a percent of the ERα or ERβ response with 1 nM E_2. Benzamides were tested at 10^{-6} M concentration to test for agonism and at 10^{-6} M with 10^{-9} M E_2 to test for antagonism. These assays are generally reproductive with a CV of 30% relative.

made a substantial exploration of the amide functionality as a core replacement that might support compound libraries for developing novel SERMs. Using this approach, we prepared and tested representative examples of bis-phenolic amides which displayed both simple *N*-alkyl substituents and CF_3-containing *N*-alkyl substituents. Of the two classes examined, benzamides and acetamides, the benzamides displayed the highest affinity, in particular the CF_3-containing benzamides. The recent X-ray crystal structure of E_2 bound to ERα and structure–binding affinity relationships have allowed us to design a bis-phenolic benzamide **16g**, which has the highest affinity for any carboxamide ligand for the ER. This compound is also an ERα potency-selective agonist in cell-based assay of ER-mediated transcriptional activity. This work illustrates that ER ligands based on simple amide core structures can be readily prepared. High affinity ER binding, however, requires an appropriate distribution of bulk and functionality. The strong conformational preference of the basic anilide function in all of these ligands defines the scope of further structural and functional expansion of these series.

Experimental

General

Melting points were determined on a Thomas-Hoover UniMelt capillary apparatus and are uncorrected. All reagents and solvents were obtained from Aldrich, Fisher or Mallinckrodt. Tetrahydrofuran was distilled from sodium/benzophenone. Dimethylformamide was vacuum-distilled prior to use, and stored over 4 Å molecular sieves. *n*-Butyllithium was titrated with *N*-pivaloyl-*o*-toluidine. All reactions were performed under a dry N_2 atmosphere unless otherwise specified. Reaction progress was monitored by analytical thin-layer chromatography using GF silica plates purchased from Analtech. Visualization was achieved by short-wave UV light (254 nm) or potassium permanganate. Radial preparative-layer chromatography was performed on a Chromatotron instrument (Harrison Research, Inc., Palo Alto, CA) using EM Science silica gel Kieselgel 60 PF_{254} as adsorbent. Flash column chromatography was performed using Woelm 32–63 μm silica gel packing.

Logarithms of octanol–water partition coefficients (Log $P^{o/w}$) were determined using a standardized reverse phase HPLC Chromegabond MC 8 column.[23] HPLC separation of the enantiomers for **17b** was performed on an analytical ChiralPak AD (4.6×25 cm) column from Chiral Technologies using 10% *i*-propanol/hexane as solvent. ^1H and ^{13}C NMR spectra were recorded on either a General Electric QE-300 (300 MHz), Varian Unity 400 or 500 MHz spectrometers using $CDCl_3$, MeOD or $(CD_3)_2SO$ as solvent. Chemical shifts were reported as parts per million downfield from an internal tetramethylsilane standard ($\delta = 0.0$ for ^1H) or from solvent references. NMR coupling constants are reported in Hertz. ^{13}C NMR were determined using either the Attached Proton Test (APT) experiment or standard ^{13}C pulse sequence parameters. Low resolution and high resolution electron impact mass spectra were obtained on Finnigan MAT CH-5 or 70-VSE spectrometers. Elemental analyses were performed by the Microanalytical Service Laboratory of the University of Illinois.

Unless otherwise stated, a standard procedure for product isolation was used; this involved quenching by addition of water or an aqueous solution, exhaustive extraction with an organic solvent, washing the extracts, drying over Na_2SO_4, and solvent evaporation under reduced pressure. Quenching media, extraction solvents, and aqueous washes used are noted parenthetically after the phrase 'product isolation'.

Biological procedures

Relative binding affinity assay. Ligand binding affinities (RBAs) using lamb uterine cytosol as a receptor source were determined by a competitive radiometric binding assay using 10 nM [^3H]estradiol as tracer and dextran-coated charcoal as an adsorbant for free ligand.[32] Purified ERα and ERβ binding affinities were determined using a competitive radiometric binding assay using 10 nM [^3H]estradiol as tracer, commercially available ERα and ERβ preparations (PanVera Inc., Madison, WI), and hydroxylapatite (HAP) to adsorb bound receptor–ligand complex.[33] HAP was prepared following the recommendations of Williams and Gorski.[34] All incubations were done at 0 °C for 18–24 h. Binding affinities are expressed relative to estradiol on a percent scale (i.e. for estradiol, RBA = 100%). All essays were run in separate, duplicate experiments which were reproducible with a coefficient of variation of less than 30% relative.

Transcriptional activation assay. Human endometrial cancer (HEC-l) cells were maintained in culture and transfected as described previously.[31] Transfection of HEC-1 cells in 60 mm dishes used 0.4 mL of a calcium phosphate precipitate containing 2.5 μg of pCMVβGal as internal control, 2 μg of the reporter gene plasmid, 100 ng of the ER expression vector, and carrier DNA to a total of 5 μg DNA. CAT activity, normalized for the internal control β-galactosidase activity, was assayed as previously described.[31]

Molecular modeling

Small molecule modeling. Dihedral drive and Monte Carlo conformational searches for *N*-phenyl benzamides **16a** and **17a** and *N*-phenyl acetamide **27** were conducted using the MM2 force field as implemented in Macromodel v.5.5 with $CHCl_3$ as a solvent model. All generated conformers from Monte Carlo searches underwent full matrix assisted minimization using the PRCG function with a convergence criteria of 0.001 kcal/mol. Dihedral drives were conducted in 5° steps with a convergence criteria of 0.05 kcal/mol using 1000 minimization steps. Analysis of the energy versus torsion angle provided the estimated rotational barrier.

Receptor docking studies. The starting conformation used for docking studies for **16g** was obtained from a

random conformational search using the TRIPOS' force field (MAXIMIN) as implemented in the program SYBYL, version 6.5.2 (Tripos Inc., St. Louis, MO). The *cis* global minima obtained for benzamide **16g** was then overlaid with E_2 in the E_2-ERα LBD crystal structure[26] using a least squares multifitting of five atoms: atoms C(3), C(10), C(9), C(11), and C(12) of E_2 were fitted with the 1 and 4 carbons of the benzamide phenyl ring, the C=O carbon, the nitrogen and the C(2) carbon of the phenethyl group, respectively. The pre-positioned benzamide was then optimally docked in the ERα binding pocket using TRIPOS' Flexidock. Both hydrogen-bond donors and acceptors within the pocket surrounding the ligand (Glu_{353}, Arg_{394} and His_{524}) and the ligand itself, in addition to select torsional bonds were defined. The best docked receptor ligand complex from Flexidock then underwent a three-step minimization: first non-ring torsional bonds of the ligand were minimized in the context of the receptor using the torsmin command, followed by minimization of the side-chain residues within 8 Å of the ligand while holding the backbone and residues Glu_{353} and Arg_{394} fixed. A final third minimization of both the ligand and receptor was conducted using the anneal function (hot radius 8 Å, interesting radius 16 Å) while holding residues Glu_{353} and Arg_{394} fixed to afford the final model. Minimizations were done using the TRIPOS' Forcefield (MAXIMIN) with the Powell gradient method and default settings (final RMS < 0.05 kcal/mol·Å).

X-Ray crystallography

Cystallography details for 17a and 10b. Crystals of **17a** were obtained by slow evaporation from ether at 0 °C. Crystals were mounted on glass fibers with Paratone-N oil (Exxon) and immediately cooled to −75 °C in a cold nitrogen gas stream on the diffractometer. Standard peak search and indexing procedures gave rough cell dimensions, and least squares refinement using 5344 reflections yielded the cell dimensions as given in Table 6.

Data were collected with an area detector by using the measurement parameters listed in Table 6. No systematic absences are noted for the P-1 space group. The measured intensities were reduced to structure factor amplitudes and their esds by correction for background, scan speed, and Lorentz and polarization effects. While corrections for crystal decay were unnecessary (the data were corrected for crystal decay), a Ψ-scan absorption correction was applied, the maximum and minimum transmission factors being 0.991 and 0.876. Systematically absent reflections were deleted and symmetry equivalent reflections were averaged to yield the set of unique data. All 5344 data were used in the least squares refinement.

The structure was solved using direct methods (SHELXTL). The correct positions for the C, N, O, S, and F atoms were deduced from an E-map. Subsequent least-squares refinement and difference Fourier calculations revealed the positions of the remaining non-hydrogen atoms. The quantity minimized by the least-squares program was $\Sigma w(F_0^2-F_c^2)^2$, where $w = \{[\sigma(F_0^2)]^2 + (0.883P)^2\}^{-1}$ and $P = (F_0^2 + 2F_c^2)/3$. The analytical approximations to the scattering factors were used, and all structure factors were corrected for both real and imaginary components of anomalous dispersion. In the final cycle of least squares, independent anisotropic displacement factors were refined for the non-hydrogen atoms and the aromatic, methyl, and methine hydrogen atoms were fixed in 'idealized' positions with C–H=0.95 Å for the aromatic hydrogens, C–H=0.98 Å for the methyl hydrogens, and C–H=1.00 Å for the methine hydrogen. Successful convergence was indicated by the maximum shift/error of 0.001 for the last cycle. Final refinement parameters are given in Table 6. The largest peak in the final Fourier difference map (0.795 eÅ^{-3}) was located 1.64 Å from C(18). A final analysis of variance between observed and calculated structure factors showed no apparent errors.

Single crystals of **10b** were grown from MeOH by slow evaporation at 23 °C in a partially sealed scintillation

Table 6. Crystal data and structure refinement for thiocarboxamide **17a** and carboxamide **10b**

Complex	**17a**	**10b**
Empirical formula	$C_{18}H_{18}F_3NO_2S$	$C_{16}H_{17}NO_3$
fw	369.39	271.31
Temperature	198(2) K	198(2) K
Wavelength	0.71073 Å	1.54178 Å
Cryst syst	triclinic	monoclinic
Space group	P-1	$P2_1/n$
Unit cell dimensions	$a = 9.5099(7)$ Å	$a = 18.248(4)$ Å
	$b = 10.5351(8)$ Å	$b = 9.054(2)$ Å
	$c = 11.1127(8)$ Å	$c = 18.248(4)$ Å
Volume	868.07(11) Å^3	2916.4(10) Å^3
Z	2	8
Density, calcd	1.413 Mg/m^3	1.236 Mg/m^3
Abs coeff	0.228 mm^{-1}	0.695 mm^1
No. of indep refins	5344 [R(int) = 0.0293]	4796 (R(int) = 0.0556)
Refinement method	full matrix least-squares on F^2	full matrix least-squares on F^2
No. of data/restraints/params	3727/0/226	2727/0/362
Goodness-of-fit (GooF) on F^2	0.949	1.062
Final R indices ($I > 2\sigma(I)$)	R1 = 0.0502, wR2 = 0.1393	R 1 = 0.0624, wR2 = 0.1662
R indices (all data)	R1 = 0.0892, wR2 = 0.1533	R1 = 0.0767, wR2 = 0.1881

vial. Crystals were mounted on glass fibers with Paratone-N oil (Exxon) and immediately cooled to −75 °C in a cold nitrogen gas stream on the diffractometer. Standard peak search and indexing procedures gave rough cell dimensions. Initial inspection of the data suggested a C-centered orthorhombic cell, but no successful solution could be found in any orthorhombic space group. Eventually, a successful solution was found in a primitive monoclinic cell of half the volume in the space group $P2_1/n$. The refinement stalled at $wR_2 = 0.63$, despite having located all atoms and refining the non-hydrogen atoms anisotropically. The unusual equality in the lengths of the *a* and *c* axes, combined with the observation that $F_{obs} \gg F_{calc}$ for all the reflections in the 'most disagreeable reflections' list, suggested that the crystal was twinned. A twin law involving mirror reflection through the (101) plane was assumed, and a refinable parameter describing the relative volume fractions of the two twin individuals was added to the model. The intensities were calculated from the relation $F^2_{TOT} = f F^2_{hkl} + (1-f) F^2_{h'k'l'}$, where *f* is the volume fraction of twin individual one and F^2_{hkl} and $F^2_{h'k'l'}$ are the contributions from the two twins (the twin law specifies that h′k′l′ = lkh). The scale factor refined to 0.500(3), and the wR_2 factor dropped to an acceptible value of 0.185.

In the final cycle of least squares, independent anisotropic displacement factors were refined for the non-hydrogen atoms and the aromatic, methyl, and methine hydrogen atoms were fixed in 'idealized' positions with C–H=0.95 Å for the aromatic hydrogens, C–H=0.98 Å for the methyl hydrogens, and C–H = 1.00 Å for the methine hydrogen. Successful convergence was indicated by the maximum shift/error of 0.001 for the last cycle. Final refinement parameters are given in Table 6. The largest peak in the final Fourier difference map (0.795 eÅ^{-3}) was located 1.64 Å from C(18). A final analysis of variance between observed and calculated structure factors showed no apparent errors.

Chemical syntheses

4-Methoxyphenyl-4-methoxybenzene sulfonamide (3).[8] To a mixture of 4-methoxybenzenesulfonylchloride (1.0 equiv) and pyridine (1.1 equiv) in CH_2Cl_2 (0.5 M) at 0 °C was added dropwise to a solution of *p*-anisidine (1.5–5.0 equiv) in CH_2Cl_2 (1.5 M) over 30 min. The reaction mixture was warmed to rt and stirred until completion of reaction as indicated by TLC. Product isolation (H_2O, 2 N HCl) and recrystallized from EtOH afforded product as light red crystals (91%): mp 91–92.5 °C, mp[8] 93 °C.

General procedure for phase transfer *N*-alkylation of sulfonamides.[9] To a CH_2Cl_2 (0.06 M) solution of sulfonamide (1.0 equiv) was added an equal volume solution of NaOH (5 equiv) and $(n\text{-Bu})_4NSO_4H$ (0.1 equiv) in H_2O. Alkylhalide (2.0 equiv) was then added directly to the bi-phasic solution and stirred at rt. After 12 h the layers were separated. Product isolation (Na_2CO_3, brine) followed by flash chromatography afforded the pure *N*-alkyl benzene sulfonamide.

***N*-(4-Methoxyphenyl)-*N*-(ethyl)-4-methoxybenzene sulfonamide (4a).**[8] Purification by flash chromatography (20% EtOAc:hexane) afforded off-white powder (86%): mp 95–7 °C, mp[8] 100–104 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 311, *J* = 7.1 Hz), 3.52 (q, 2H, *J* = 7.0 Hz), 3.81 (s, 3H), 3.84 (s, 3H), 6.82 (d, 211, *J* = 8.8 Hz), 6.94 (d, 2H, *J* = 8.0 Hz), 6.96 (d, 2H, *J* = 8.0 Hz), 7.54 (d, 2H, *J* = 8.8 Hz).

***N*-(4-Methoxyphenyl)-*N*-(butyl)-4-methoxybenzene sulfonamide (4b).** Purification by flash chromatography (20%EtOAc:hexane) afforded transparent oil (81%): ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J* = 7.2 Hz), 1.34 (m, 4H), 3.46 (t, 2H, *J* = 6.8 Hz), 3.80 (s, 3H), 3.86 (s, 3H), 6.81 (d, 2H, *J* = 9.0 Hz), 6.92 (app t, 4H, *J* = 9.1 Hz), 7.51 (d, 2H, *J* = 9.0 Hz); MS (EI, 70 eV) *m*/*z* 349 (M^+); HRMS calcd for ($C_{18}H_{23}NO_4S$, 349.1347, found 349.1348).

***N*-(4-Methoxyphenyl)-*N*-(benzyl)-4-methoxybenzene sulfonamide (4c).** Recrystallization from 20% EtOAc/hexane afforded flocculent white crystals (93%): mp 141–142 °C; ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 3.87 (s, 3H), 4.67 (s, 2H), 6.89 (d, 2H, *J* = 11 Hz), 6.86 (d, 2H, *J* = 11.5 Hz), 6.94 (d, 2H, *J* = 11 Hz), 7.21 (m, 5H), 7.59 (d, 2H, *J* = 11 Hz); ^{13}C NMR ($CDCl_3$) δ 55.1, 55.4, 55.8, 114.2, 127.7, 128.5, 128.7, 129.9, 130.4, 130.4, 131.7, 136.3, 158.9, 163.0; HRMS calcd for $C_{21}H_{21}NSO_4$, 383.1191, found 383.118.

General demethylating procedure using BBr_3. To a solution of methyl ether compound in CH_2Cl_2 at −78 °C was added a 1.0 M BBr_3 in CH_2Cl_2 (3 equiv) dropwise over 15 mm. The reaction was allowed to reach rt and stir overnight or until disappearance of starting material as indicated by TLC. The mixture was then cooled to 0 °C. Product isolation (H_2O, Et_2O, brine) and purification via radial or flash chromatography or recrystallization from an appropriate solvent afforded the desired phenolic compounds.

General demethylating procedure using EtSH. To a stirred DMF solution of NaH (6.2 equiv of a 60% w/w dispersion) at 0 °C was added dropwise 6.0 equiv of EtSH. After 30 min the mixture was warmed to rt and a solution of the methyl ether protected compound in 5 mL DMF was added dropwise. The reaction mixture was heated to reflux for 4 h; then cooled in an ice-bath and acidified with 2 N HCl. Remaining product isolation (EtOAc, brine) and purification afforded the phenolic compounds.

***N*-(4-Hydroxyphenyl)-*N*-(ethyl)-4-hydroxybenzene sulfonamide (5a).** Deprotected according to BBr_3 procedure. SiO_2 plug (30% EtOAc/hexane) to afford off-white crystals (62%): ^{1}H NMR ($(CD_3)_2SO$) 6 0.98 (t, 3H, *J* = 7.2 Hz), 3.43 (q, 2H, *J* = 6.8 Hz), 6.67 (d, 2H, *J* = 8.7 Hz), 6.76 (d, 2H, *J* = 8.4 Hz), 6.86 (d, 2H, *J* = 8.5 Hz), 7.34 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($(CD_3)_2SO$) δ 14.1 (CH_3), 45.2 (CH_2), 115.7 (ArCH), 115.8 (ArCH), 122.6 (ArC), 128.1 (ArC), 129.9 (ArCH), 130.1 (ArCH), 157.1 (ArC), 161.6 (ArC); MS (EI, 70 eV) *m*/z 293 (M^+); HRMS calcd for $C_{14}H_{15}NSO_4$, 293.0721, found 293.0722.

***N*-(4-Hydroxyphenyl)-*N*-(butyl)-4-hydroxybenzene sulfonamide (5b).** Deprotected according to BBr_3 procedure to afford tan crystals, recrystallized from EtOAc/hexane (71%): mp 137–138 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 7.0 Hz), 1.35 (m, 4H), 3.48 (t, 2H, J = 7.0 Hz), 6.42 (d, 2H, J = 8.8 Hz), 6.87 (app t, 4H, J = 8.9 Hz), 7.47 (d, 2H, J = 9.0 Hz) ^{13}C NMR (CD_3)$_2$SO) δ 13.8 (CH_3), 19.2 (CH_2), 29.9 (CH_2), 49.7 (CH_2), 115.6 (ArCH), 115.7 (ArCH), 122.6 (ArCH), 128.0 (ArC), 129.9 (ArCH), 130.0 (ArC), 157.0 (ArC), 161.6 (ArC); MS (EI, 70 eV) m/z 321 (M^+); HRMS calcd for $C_{16}H_{19}NSO_4$, 321.1034, found 321.1035. Anal. ($C_{16}H_{19}N$·0.3 H_2O): C, 58.81; H, 6.05; N, 4.29. Found: C, 58.60; H, 6.03; N, 4.13.

***N*-(4-Hydroxyphenyl)-*N*-(benzyl)-4-hydroxybenzene sulfonamide (5c).** Deprotected according to BBr_3 procedure to afford title compound after purification by radial chromatography (10%): ^{1}H NMR ($CDCl_3$) δ 4.65 (s, 2H), 6.66 (d, 2H, J = 8.5 Hz), 6.80 (d, 2H, J = 8.5 Hz), 6.96 (d, 2H, 8.8), 7.21 (br s, 5H), 7.59 (d, 2H, J = 8.9 Hz); MS (EI, 70 eV) m/z 355 (M^+); HRMS calcd for $C_{19}H_{17}NSO_4$, 355.0878, found 355.0881.

***N*-(4-Methoxyphenyl)-4-methoxybenzamide (6).**[35] A CH_2Cl_2 solution of *p*-anisidine (1.3 equiv) was added dropwise to a stirring CH_2Cl_2 solution (2–5 mL) of pyridine (1.1 equiv) and *p*-anisoyl chloride (1.0 equiv) at 0 °C. Upon complete addition of amine (30 mm) mixture was allowed to reach rt, then re-cooled and vacuum filter to afford the crude carboxamide. Recrystallization from EtOH/benzene afforded the pure carboxamide as off-white crystals (72%): mp 199–200.5 °C, mp[32] 202–203 °C.

***N*-(1-Phenethyl)-4-methoxyaniline (7).**[7] To a 0 °C EtOH solution containing *p*-anisidine (1.0 equiv) and catalytic *p*-toluene sulfonic acid·H_2O (0.05 equiv) was added freshly distilled benzaldehyde dropwise. The mixture was allowed to reach rt and complete imine formation occurred within 0.5 h. The crude mixture was concentrated in vacuo, and product isolation followed (EtOAc, brine) to afford a dark brown powder. ^{1}H NMR confirmed imine which was directly used in the next step without further purification. *CH_3 addition*: Crude imine was dissolved in toluene and cooled to −78 °C. To this was added MeLi (1.0 M toluene solution, 3 equiv) dropwise over 15 mm. After 60 min at −78 °C, the crude mixture was warmed to rt and stirred for an additional 2 h. The reaction was then cooled in an ice-bath and quenched with cold MeOH followed by addition of satd NH_4Cl until neutral pH. Concentration in vacuo followed by remaining workup (EtOAc, H_2O, brine) afforded amine as a red oil. Kügelrohr distillation provided pure product, which crystallized on standing as a red–orange powder (75%): ^{1}H NMR ($CDCl_3$) δ 1.50 (d, 3H, J = 7.0 Hz), 3.69 (s, 3H), 4.41 (q, 1H, J = 7.0 Hz), 6.47 (AA′BB′, 2H, J = 9.0, 3.0 Hz), 6.69 (AA′BB′, 2H, J = 9.0, 3.5 Hz), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.4 (CH_3), 54.5 (CH), 55.9 (CH_3), 114.7 (ArCH), 114.9 (ArCH), 126.1 (ArCH), 127.0 (ArCH), 128.8 (ArCH), 141.7 (ArC), 145.7 (ArC), 152.1 (ArC); MS (El, 70 eV) m/z 227 (M^+); anal. ($C_{15}H_{17}NO$): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.31; H, 7.54; N, 6.27.

***N*-[2-(3-Methyl)butane]-4-methoxyaniline (8).** To a THF solution at 0 °C containing *p*-anisidine (1 equiv), 3-methyl-2-butanone (1.0 equiv), and acetic acid (1.0 equiv) was added solid $NaHB(OAc)_3$. The mixture was allowed to reach rt and stirred for 15 h. The mixture was re-cooled to 0 °C; careful workup (H_2O, EtOAc, $NaHCO_3$, brine, $MgSO_4$) and concentration in vacuo afforded crude amine. Kügelrohr distillation provided pure product as light yellow oil (71%): bp 100 °C (0.3 mm); ^{1}H NMR ($CDCl_3$) δ 0.93 (d, 3H, J = 6.5 Hz), 1.00 (d, 3H, J = 6.5 Hz), 1.10 (d, 3H, J = 6.0 Hz), 1.86 (m, 1H, J = 6.5 Hz), 3.23 (br s, 1H, ArNH), 3.28 (dq, 1H, J = 7.0, 6.0 Hz), 3.77 (s, 3H), 6.58 (d, 2H, J = 7.0 Hz), 6.80 (d, 211, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 16.5 (CH_3), 17.3 (CH_3), 19.3 (CH_3), 32.1 (CH), 54.5 (CH), 55.8 (CH_3), 114.6 (ArCH), 114.9 (ArCH), 142.1 (ArC), 151.7 (ArC); MS (EI, 70 eV) m/z 193 (M^+); anal. ($C_{12}H_{19}NO$): C, 74.57; H, 9.91; N, 7.25. Found: C, 74.46; H, 9.76; N, 7.32.

General procedure for phase transfer *N*-alkylation of carboxamides.[9,10] Alkylhalide (3 equiv) in benzene was added dropwise to a stirring mixture of carboxamide (1 equiv), finely powdered potassium hydroxide (2 equiv), and *n*-tetrabutylammonium bromide (0.05 equiv) in benzene (0.2 M) at rt. Reaction mixture was heated to 80 °C and maintained at this temperature until disappearance of starting material was observed by TLC (1–3 h). The reaction mixture was then cooled to rt and the salts removed by filtration. Product isolation (H_2O, brine), followed by flash chromatography (10–25% EtOAc/hexane) afforded product, usually as an oil.

General amidation procedures for anilines 7–8 and CF_3-containing anilines 14a–d. A 0.18 M benzene or toluene solution containing 1 equiv of aniline (**14a, 14b, 7–8**) in addition to 3 equiv of dry powdered K_2CO_3 and 1 equiv of pyridine was treated with 1.5 equiv of the corresponding acid chloride and heated between 80 and 110 °C. The reaction was monitored by TLC and the reaction cooled to rt upon completion. The crude mixture was filtered, concentrated in vacuo and taken up in Et_2O. Product isolation (H_2O, brine) and chromatographic purification afforded the protected carboxamide (**15a**–**e** and **9f** and **9g**).

Benzamides **15f** and **l5g** were prepared from anilines **14c** and **14d** and the corresponding acid chloride (1.5 equiv) using l,2-dichlorobenzene as solvent, 3 equiv of dry powdered K_2CO_3 and heated to 120–150 °C for 16 h or until disappearance of starting aniline. Reaction mixture was cooled to rt and eluted over silica with hexane to remove 1,2-dichlorobenzene. Gradient chromatography with 10, 20, and 30% EtOAc/hexane afforded the pure carboxamides **15f** and **15g** upon concentration.

***N*-(4-Methoxyphenyl)-*N*-(ethyl)-4-methoxybenzamide (9a).** Yellow oil (72%): ^{1}H NMR ($CDCl_3$) δ 1.12 (t, 3H, J = 7.2 Hz, CH_3), 3.62 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.84 (q, 2H, J = 7.0 Hz, CH_2), 6.57 (d, 2H,

$J = 8.9$ Hz, ArH *ortho* OCH_3, *meta* RNCO), 6.68 (d, 2H, $J = 8.9$ Hz, ArH *ortho* OCH_3, *meta* CONR), 6.87 (d, 2H, $J = 8.9$ Hz, ArH *ortho* RNCO), 7.20 (d, 2H, $J = 8.7$ Hz, ArH *ortho* CONR); ^{13}C NMR ($CDCl_3$) δ 12.7 (CH_3), 45.5 (CH_2), 55.0 (OCH_3), 55.2 (OCH_3), 112.8 (ArCH), 114.2 (ArCH), 128.4 (ArC), 128.9 (ArCH), 130.7 (ArCH), 136.3 (ArC), 157.8 (ArC), 160.2 (ArC), 169.6 (C=O); MS (EI, 70 eV) *m/z* 285 (M^+); HRMS calcd for $C_{17}H_{19}NO_3$, 285.1365, found 285.1364.

***N*-(4-Methoxyphenyl)-*N*-(2-propyl)-4-methoxybenzamide (9b).** Amber oil (43%): ^1H NMR ($CDCl_3$) δ 1.16 (d, 6H, $J = 6.5$ Hz), 3.72 (s, 3H), 3.75 (s, 3H), 5.09 (br s, 1H), 6.63 (d, 2H, $J = 8.5$ Hz), 6.74 (d, 2H, $J = 9.0$ Hz), 6.93 (d, 2H, $J = 8.5$ Hz), 7.21 (d, 2H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 55.3 (CH_3), 55.5 (CH_3), 113.0 (ArCH), 113.9 (ArCH), 129.1 (ArC), 130.4 (ArCH), 131.8 (ArCH), 132.5 (ArC), 158.6 (ArC), 160.1 (ArC), 170.5 (C=O); MS (EI, 70 eV) *m/z* 299 (M^+); HRMS calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1521.

***N*-(4-Methoxyphenyl)-*N*-(butyl)-4-methoxybenzamide (9c).** Yellow oil (81%): ^1H NMR ($CDCl_3$) δ 0.84 (t, 3H, $J = 7.3$ Hz, CH_3), 1.29 (sext, 2H, $J = 7.0$ Hz, $CH_3C\underline{H}_2$), 1.53 (quint, 2H, $J = 7.8$ Hz, $CH_2C\underline{H}_2CH_2$), 3.62 (s, 3H, OCH_3 *ortho* RNCO), 3.66 (s, 3H, OCH_3 *ortho* CONR), 3.78 (t, 2H, $J = 7.7$ Hz, $CH_2C\underline{H}_2N$), 6.58 (d, 2H, $J = 8.8$ Hz, ArH *ortho* OCH_3, *meta* RNCO), 6.68 (d, 2H, $J = 8.9$ Hz, ArH *ortho* OCH_3, and *meta* CONR), 6.88 (d, 2H, $J = 8.9$ Hz, ArH *ortho* RNCO), 7.19 (d, 2H, $J = 8.9$ Hz, ArH *ortho* CONR); ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 20.0 (CH_2), 29.5 (CH_2), 50.3 (CH_2), 54.9 (OCH_3), 55.1 (OCH_3), 112.7 (ArCH), 114.1 (ArCH), 128.4 (ArC), 128.6 (ArCH), 130.5 (ArCH), 136.5 (ArC), 157.6 (ArC), 160.0 (ArC), 169.6 (ArC); MS (EI, 70 eV) *m/z* 313 (M^+); HRMS calcd for $C_{19}H_{23}NO_3$, 313.7794, found 313.7879.

***N*-(4-Methoxyphenyl)-*N*-(benzyl)-4-methoxybenzamide (9e).** White flakes (82%): mp 104–106 °C; ^1H NMR ($CDCl_3$) δ 3.72 (s, 3H, OCH_3 *para* RNCO), 3.74 (s, 3H, OCH_3 *para* CONR), 5.09 (s, 2H, CH_2Ph), 6.68 (d, 2H, $J = 9.2$ Hz, ArH *ortho* OCH_3, and *meta* RNCO), 7.31 (m, 9H, Ph and ArH); ^{13}C NMR ($CDCl_3$) δ 54.3 ($PhCH_2$), 55.3 (OCH_3), 55.5 (OCH_3), 113.1 (ArCH), 114.3 (ArCH), 127.4 (ArCH), 128.6 (ArCH), 128.3 (ArC), 128.7 (ArCH), 128.9 (ArCH), 131.1 (ArCH), 137.0 (ArC), 138.0 (ArC), 158.0 (ArC), 160.6 (ArC), 170.2 (ArC); MS (EI, 70 eV) *m/z* 347 (M^+); HRMS calcd for $C_{22}H_{21}NO_3$, 347.1521, found 347.1522.

***N*-(4-Methoxyphenyl)-*N*-(1-phenethyl)-4-methoxybenzamide (9f).** Prepared according to general procedure above using aniline **7** and *p*-anisoyl chloride. Purification by flash chromatography (2% $(CH_3)_2CO/CH_2Cl_2$) afforded product as clear oil (70%): ^1H NMR ($CDCl_3$) δ 1.48 (d, 3H, $J = 6.8$ Hz), 3.67 (s, 3H), 3.69 (s, 3H), 6.38 (br q, 1H, $J = 6.8$ Hz), 6.56 (br d overlapping br s, 4H), 6.62 (d, 2H, $J = 8.8$ Hz), 7.23 (d, 2H, $J = 8.5$ Hz), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.9 (CH_3), 53.3 (CH), 55.2 (CH_3), 55.3 (CH_3), 112.9 (ArCH), 113.6 (ArCH), 127.5 (ArCH), 128.2 (ArCH), 128.3 (ArCH), 129.2 (ArC), 130.6 (ArCH), 131.5 (ArCH), 132.7 (ArC), 141.7 (ArC), 158.3 (ArC), 160.2 (ArC), 170.6 (C=O); MS (EI, 70 eV) *m/z* 361 (M^+).

***N*-(4-Methoxyphenyl)-*N*-(1-methyl-2-methyl-1-propyl)-4-methoxybenzamide (9g).** Prepared according to general procedure above using aniline **8** and *p*-anisoyl chloride. Purification by flash chromatography (25% EtOAc/hexane) afforded product as light yellow oil (90%): ^1H NMR ($CDCl_3$) δ 0.93 (d, 6H, $J = 6.7$ Hz), 1.90 (sept, 1H, $J = 7.0$ Hz), 3.69 (s, 3H), 3.71 (s, 3H), 3.73 (d, 2H, $J = 7.0$ Hz), 6.62 (d, 2H, $J = 8.5$ Hz), 6.71 (d, 2H, $J = 9.0$ Hz), 6.93 (d, 2H, $J = 8.6$ Hz), 7.20 (d, 2H, $J = 8.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.3 (CH_3), 27.0 (CH), 55.2 (CH_3), 55.4 (CH_3), 57.2 (CH_2), 113.0 (ArCH), 114.3 (ArCH), 128.7 (ArCH), 129.0 (ArC), 130.7 (ArCH), 137.1 (ArC), 157.8 (ArC), 160.3 (ArC), 170.3 (C=O); MS (EI, 70 eV) *m/z* 313 (M^+).

***N*-(4-Hydroxyphenyl)-*N*-(ethyl)-4-hydroxybenzamide (10a).** Deprotected according to BBr_3 procedure to afford off-white powder, recrystallized from MeOH (70%): mp 208–209 °C; ^1H NMR ($(CD_3)_2SO$) δ 1.03 (t, 3H, $J = 6.9$ Hz, CH_3), 3.72 (q, 2H, $J = 7.1$ Hz, CH_2), 6.52 (d, 2H, $J = 8.6$ Hz, ArH *meta* RNCO), 6.62 (d, 2H, $J = 8.5$ Hz, ArH *meta* CONR), 6.86 (d, 2H, $J = 8.6$ Hz, *ortho* RNCO), 7.06 (d, 2H, $J = 8.5$ Hz, *ortho* CONR), 9.48 (s, 1H, OH), 9.71 (s, 1H, OH); ^{13}C NMR ($(CD_3)_2SO$) δ 12.6 (CH_3), 39.1 (CH_2), 114.3 (ArCH), 115.7 (ArCH), 127.1 (ArC), 129.1 (ArC), 130.5 (ArCH), 134.7 (ArC), 155.7 (ArC), 158.3 (ArC), 168.9 (ArC); MS (EI, 70 eV) *m/z* 257 (M^+); HRMS calcd for $C_{15}H_{15}NO_3$, 257.1052, found 257.1051.

***N*-(4-Hydroxyphenyl)-*N*-(2-propyl)-4-hydroxybenzamide (l0b).** Deprotected according to BBr_3 procedure to afford powder, recrystallized from MeOH (77%): mp 210–212 °C; ^1H NMR (MeOD) δ 1.15 (d, 6H, $J = 6.8$ Hz), 4.94 (br s, 1H), 6.56 (br s, 2H), 6.67 (d, 2H, $J = 8.4$ Hz), 6.88; MS (EI, 70 eV) 271 (M^+); anal. ($C_{16}H_{17}NO_3 \cdot 0.1\ H_2O$): C, 70.36; H, 6.36; N, 5.13. Found: C, 70.35; H, 6.37; N, 4.90.

***N*-(4-Hydroxyphenyl)-*N*-(butyl)-4-hydroxybenzamide (10c).** Deprotected according to BBr_3 procedure and purified by flash chromatography (25% EtOAc/hexane) to afford off-white crystals (95%): mp 174–175 °C; ^1H NMR ($(CD_3)_2SO$) δ 0.84 (s, 3H), 1.25 (sext, 2H, $J = 7.6$ Hz), 1.43 (quint, 2H, $J = 7.6$ Hz), 3.69 (t, 2H, $J = 7.5$ Hz), 6.51 (d, 2H, $J = 8.6$ Hz), 6.61 (d, 2H, $J = 8.7$ Hz), 6.85 (d, 2H, $J = 8.7$ Hz), 7.03 (d, 2H, $J = 8.5$ Hz); ^{13}C NMR ($(CD_3)_2SO$) δ 14.1 (CH_3), 19.9 (CH_2), 40.2 (CH_2), 114.5 (ArCH), 115.9 (ArCH), 127.4 (ArC), 129.2 (ArCH), 130.6 (ArCH), 135.1 (ArC), 155.8 (ArC), 158.4 (ArC); MS (EI, 70 eV) *m/z* 285 (M^+); HRMS (EI) calcd for $C_{,7}H_{19}NO_3$, 285.1365, found 285.1368; anal. ($C_{17}H_{19}NO_3 \cdot 0.5\ H_2O$): C, 69.37; H, 6.85; N, 4.76. Found: C, 69.30; H, 6.65; N, 4.57.

***N*-(4-Hydroxyphenyl)-*N*-(2-methyl-1-propyl)-4-hydroxybenzamide (10d).** Deprotected according to BBr_3 procedure and purified by flash chromatography (25% EtOAc/hexane) to afford white foam (quant): mp 166 °C dec.; ^1H NMR ($(CD_3)_2SO$) δ 0.93 (d, 6H, $J = 6.5$ Hz),

1.82 (m, 1H, $J=6.5$ Hz), 3.66 (d, 2H, $J=7.5$ Hz), 6.59 (d, 2H, $J=8.5$ Hz), 6.68 (d, 2H, $J=9$ Hz), 6.94 (d, 2H, $J=8.5$ Hz), 7.10 (d, 2H, $J=8.5$ Hz); MS (EI, 70 eV) m/z 285 (M^+); anal. ($C_{17}H_{19}NO_3 \cdot l.0\ H_2O$): C, 67.31; H, 6.98; N, 4.62. Found: C, 67.45; H, 6.74; N, 4.41.

***N*-(4-Hydroxyphenyl)-*N*-(benzyl)-4-hydroxybenzamide (l0e).** Deprotected according to EtSH procedure and purified by flash chromatography (25% EtOAc/hexane), which upon solvent concentration and recrystallization from $CHCl_3$ afforded title compound as off-white flakes (60%): mp 103–105 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 4.95 (s, 2H, CH_2), 6.53 (d, 2H, $J=6.3$ Hz, ArH *meta* R*NCO*), 6.56 (d, 211, $J=6.2$ Hz, ArH *ortho* R*NCO*), 6.77 (d, 2H, $J=8.7$ Hz, ArH meta CONR), 7.13 (d, 2H, $J=8.7$ Hz, AsH *ortho* CONR), 7.25 (m, 5H, Ph), 9.67 (broad s, 2H, OH); ^{13}C NMR ($(CD_3)_2SO$) δ 53.1 (CH_2), 114.2 (ArCH), 115.5 (ArCH), 122.3 (ArC), 126.6 (ArC), 126.9 (ArCH), 127.9 (ArCH), 128.3 (ArCH), 128.7 (ArCH), 130.6 (ArCH), 134.9 (ArC), 137.9 (ArC), 155.5 (ArC), 158.5 (ArC), 169.4 (ArC); MS (EI, 70 eV) m/z 319 (M^+); HRMS (EI) calcd for $C_{20}H_{17}N0_3$, 319.1208, found 319.1206; anal. ($C_{20}H_{17}NO_3 \cdot 2.5\ H_2O$): C, 65.92; H, 6.09; N, 3.84. Found: C, 65.58; H, 5.81; N, 3.53.

***N*-4-Hydroxyphenyl-*N*-(1-phenethyl)-4-hydroxybenzamide (10f).** Deprotected according to BBr_3 procedure recrystallized from $MeOH/CH_2Cl_2$ to afford white powder (95%): mp 204–206 °C; ^{1}H NMR (MeOD) δ 1.50 (d, 3H, $J=6.8$ Hz), 4.95 (s, under MeOH), 6.24 (br s, 2H), 6.49 (br s, 2H), 6.54 (br s, 2H), 6.54 (d, 2H, $J=8$ Hz), 7.10 (d, 2H, $J=8$ Hz), 7.28 (m, 5H); ^{13}C NMR (MeOD) δ 17.4 (CH_3), 49.0 (CH), 115.3 (ArCH), 115.9 (ArCH), 124.9 (ArCH), 128.6 (ArCH), 128.9 (ArC), 129.1 (ArCH), 129.3 (ArCH), 131.4 (ArCH), 132.4 (ArC), 132.7 (ArCH), 142.5 (ArC), 157.9 (ArC), 159.8 (C=O); MS (EI, 70 eV) m/z 333 (M^+); HRMS (EI) calcd for $C_{21}H_{19}NO_3$, 333.1365, found 333.1360; anal. ($C_{21}H_{19}NO_3$): C, 75.66; H, 5.74; N, 4.20. Found: C, 75.51; H, 5.80; N, 4.21.

General thionation procedure[12]

The carboxamide (1.01 mmol) and Lawesson's reagent (0.51 mmol) in 3 mL of HMPA were heated to 80–100 °C until the carboxamide had been consumed. After disappearance of carboxamide, the reaction mixture was allowed to cool to rt and then poured onto 5 mL of water. Product was extracted repeatedly with Et_2O, dried over Na_2SO_4, rotary evaporated in vacuo and purified via flash chromatography. The protected thioamides were then directly used in the deprotection step with minimal purification.

***N*-(4-Hydroxyphenyl)-*N*-(ethyl)-4-hydroxythiobenzamide (11a).** Deprotected according to BBr_3 procedure and purified by flash chromatography (25% EtOAc/hexane) to afford yellow foam (63%): ^{1}H NMR ($(CD_3)_2SO$) δ 1.16 (t, 3H, $J=6.8$ Hz, CH_3), 4.34 (q, 2H, $J=6.8$ Hz, CH_2), 6.44 (d, 2h, $J=8.4$ Hz, ArH *meta* RNCS), 6.59 (d, 2H, $J=8.9$ Hz, ArH *meta* CSNR), 6.87 (d, 2H, $J=8.7$ Hz, ArH *ortho* RNCS), 6.99 (d, 2H, $J=8.6$ Hz, ArH *ortho* CSNR); ^{13}C NMR ($(CD_3)_2SO$) δ 11.1 (CH_3), 52.1 (CH_2), 114.1 (ArH), 115.6 (ArH), 115.7 (ArH), 122.6 (ArH), 128.5 (ArH), 129.8 (ArH), 135.3 (ArC), 136.4 (ArC), 156.3 (ArC), 157.6 (ArC), 201.0 (CS); MS (EI, 70 eV) m/z 273 (M^+); HRMS (EI) calcd for $C_{15}H_{15}NSO_2$, 273.0824, found 273.0824; anal. ($C_{15}H_5NSO_2 \cdot 0.3\ H_2O$): C, 64.63; H, 5.64; N, 5.02. Found: C, 64.51; H, 5.93; N, 4.64.

***N*-(4-Hydroxyphenyl)-*N*-(*i*-propyl)-4-hydroxythiobenzamide (11b).** Deprotected according to BBr_3 procedure and purified by flash chromatography (25% EtOAc/hexane) to afford yellow foam (98%): ^{1}H NMR (MeOD, *i*-propyl rotamers 1:4:1 ratio) δ 1.15 (d, 1H, $J=6.5$ Hz), 1.20 (d, 4H, $J=6.5$ Hz), 1.27 (d, 1H, $J=6.5$ Hz), 6.00 (sept, 1H, $J=6.5$ Hz), 6.46 (d, 2H, $J=8.5$ Hz), 6.61 (d, 2H, $J=9$ Hz), 6.81 (d, 2H, $J=8.5$ Hz), 6.96 (d, 2H, $J=8.5$ Hz) additional minor ArCH resonances not listed; ^{13}C NMR (MeOD) δ 20.6 (CH_3), 21.9 (CH_3 minor), 54.8 (CH), 114.8 (ArCH), 115.9 (ArCH), 130.1 (ArCH), 131.7 (ArCH), 133.4 (ArC), 137.8 (ArC), 157.9 (ArC), 158.0 (ArC), 204.4 (C=S); MS (EI, 70 eV) m/z 287 (M^+); HRMS, $C_{16}H_{17}NSO_2$, 287.0980; found, 287.0971.

***N*-(4-Hydroxyphenyl)-*N*-(*n*-butyl)-4-hydroxythiobenzamide (11c).** Deprotected according to BBr_3 procedure and purified by radial chromatography (5% MeOH/CH_2Cl_2) to afford yellow oil (10%): ^{1}H NMR ($(CD_3)_2$ SO) δ 0.84 (s, 3H, $J=7.5$ Hz, CH_3), 1.27 (sext, 2H, $J=6.8$ Hz, $CH_3\underline{CH_2}$), 1.61 (quint, 2H, $J=8.0$ Hz, CH_3 $CH_2\underline{CH_2}$), 4.30 (t, 2H, $J=7.7$ Hz, CH_2NCS), 6.43 (d, 2H, $J=8.5$ Hz, ArH *meta* RNCS), 6.58 (d, 2H, $J=$ 8.2 Hz, ArH *meta* CSNR), 6.87 (d, 2H, $J=8.2$ Hz, ArH *ortho* RNCS), 6.97 (d, 2H, $J=8.5$ Hz, ArH *ortho* CSNR); ^{13}C NMR ($(CD_3)_2SO$) δ 14.2 (CH_3), 19.7 (CH_2), 27.9 (CH_2), 56.8 (CH_2), 114.1 (ArCH), 115.9 (ArCH), 128.5 (ArCH), 129.9 (ArCH), 135.2 (ArC), 136.8 (ArC), 156.2 (ArC), 157.7 (ArC), 201.0 (C=S); MS (EI, 70 eV), m/z 301 (M^+); HRMS calcd for $C_{17}H_{19}NO_2S$, 301.1136; found 301.1133.

***N*-(4-Hydroxyphenyl)-*N*-(*i*-butyl)-4-hydroxythiobenzamide (11d).** Deprotected according to BBr_3 procedure and purified by flash chromatography (35% EtOAc/hexane) to afford yellow foam (86%): ^{1}H NMR ($CDCl_3$) δ 0.98 (d, 6H, $J=6.8$ Hz), 2.16 (m, 1H, $J=6.8$ Hz), 4.34 (d, 2H, $J=7.6$ Hz), 6.41 (d, 2H, $J=8.8$ Hz), 6.60 (d, 2H, $J=8.8$ Hz), 6.79 (d, 2H, $J=8.8$ Hz), 6.96 (d, 2H, $J=8.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.3, 26.9, 27.2, 50.8, 63.9, 114.5, 116.1, 127.9, 129.5, 136.4, 137.7, 155.4, 156.5, 203.0; MS (EI, 70 eV) m/z 301 (M^+); HRMS calcd for $C_{17}H_{19}NO_2S$, 301.1136; found, 301.1144.

***N*-(4-Hydroxyphenyl)-*N*-(benzyl)-4-hydroxythiobenzamide (11e).** Deprotected according to EtSH procedure and purified by flash chromatography (35% EtOAc/hexane) to afford yellow foam (16%): ^{1}H NMR ($(CDCl_3)$) δ 5.76 (s, 2H, CH_2), 6.59 (d, 2H, $J=8.4$ Hz, ArH *meta* RNCS), 6.61 (d, 211, $J=8.3$ Hz, ArH *meta* CSNR), 6.77 (d, 2H, $J=8.8$ Hz, ArH *ortho* RNCS), 7.27 (m, 5H, Ph), 7.38 (d, 2H, $J=6.4$ Hz, ArH *ortho* CSNR); MS (EI, 70 eV) m/z 335 (M^+); HRMS calcd for $C_{20}H_{17}NO_2S$, 335.0980; found, 335.0984.

***N*-(4-hydroxyphenyl)-*N*-(1-phenethyl)-4-hydroxythiobenzamide (11f).** Deprotected according to BBr_3 procedure

and recrystallized from $CHCl_3$ to afford light yellow powder (quant): mp 174–175 °C; ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3H, J = 7.2 Hz); 5.89 (br s, 1H); 6.27 (br s, 1H) 6.44 (d, 2H, J = 8.8 Hz), 6.5 (br s, 1H), 6.71 (br s, 1H), 6.96 (d, 2H, J = 8.8 Hz), 7.32 (m, 5H), 7.52 (q, 1H, J = 6.8 Hz); MS (EI, 70 eV) m/z 349 (M^+); anal. ($C_{21}H_{19}NO_2S$·0.4 H_2O): C, 70.72; H, 5.60; N, 3.93. Found: C, 70.88; H, 5.42; N, 3.98.

***N*-(4-Hydroxyphenyl)-*N*-[2-(3-methyl)-butyl]-4-hydroxythiobenzamide (11g).** Deprotected according to BBr_3 procedure and purified by flash chromatography (25% EtOAc/hexane) to afford foam (37%, two steps from carboxamide): ^{1}H NMR ($CDCl_3$) δ (major methyl rotamer) 0.95 (d, 3H, J = 6.6 Hz), 1.14 (d, 3H, J = 6.9 Hz), 1.21 (d, 3H, J = 6.3 Hz), 1.82 (br m, 1H), 5.82 (quin, 1H, J = 7.4 Hz), 6.30 (d, 2H, J = 8.5 Hz), 6.60 (br m, 4H), 6.83 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 17.1 (CH_3), 19.8 (CH_3), 20.9 (CH), 32.5 (CH), 114.7 (ArCH), 115.6 (ArCH), 128.8 (ArCH), 129.5 (ArCH), 133.2 (ArC), 137.2 (ArC), 155.2 (ArC), 155.3 (ArC), 204.4 (C=S); MS (EI, 70 eV) m/z 315 (M^+); anal. ($C_{18}H_{21}NO_2S$·0.8 H_2O): C, 65.54; H, 6.91; N, 4.35. Found: C, 65.15; H, 6.67; N, 3.91.

Triphenylphosphine-4-methoxyphenylimine (12a).[36] *p*-Anisidine was diazotized in 50% H_2SO_4 and then added to a NaN_3–sodium acetate buffered solution.[15] The azide was extracted with diethyl ether and the phenolic side-product removed by Na_2CO_3 wash. Concentration in vacuo afforded the crude azide which was directly used in the next step. *Ylide formation*: to an etheral solution of azide was added an equimolar solution of PPh_3 at rt. After the solution was heated under reflux for 2 h and N_2 evolution ceased, the solvent was concentrated and resulting Ph_3P=O oxide removed. The crude imine was passed over SiO_2 plug (ether) to remove additional oxide. Final concentration and tituration with hexanes afforded pure imine as orange crystals (53% from *p*-anisidine): mp 116–117.5 °C; mp[33] 119–120 °C.

Triphenylphosphine-phenylimine (12b).[14,37] A cold aqueous solution of $NaNO_2$ (1.2 equiv) was added dropwise to a solution of aniline in 10% HCl at 0–5 °C with vigorous stirring. The mixture was kept below 5 °C for 30 min, and then a solution of NaN_3 in water was added dropwise while the temperature was kept below 5 °C. After 1 h the reaction was warmed to rt and extracted with diethyl ether. The extracts were dried over Na_2SO_4 and concentrated to afford the crude azide[14] as an oil, which was directly used in the next step without additional purification. *Ylide formation:* same as described for **12a** to afford light yellow crystals upon solvent concentration (64% from aniline): mp 128–130 °C (mp[34] 131–132 °C).

***N*-(1,1,1-Trifluoro-2-propylidene)-4-methoxyaniline (13a).**[6] Ylide **12a** and trifluoroacetone were heated to reflux in C_6H_6 for 12 h. The reaction was cooled to rt and concentrated in vacuo. The residue was triturated with Et_2O to remove Ph_3PO and the resulting filtrate concentrated followed by Kügelrohr distillation under reduced pressure to afford product as light yellow oil (92%): bp 66 °C (0.1 mm); ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 3H), 3.81 (s, 3H), 6.79, 6.92 (AA′BB′, 4H, J = 8.8, 4.0 Hz); ^{13}C NMR δ 14.6 (CH_3), 55.6 (CH_3), 114.5 (ArCH), 120.5 (q, CF_3, J = 273 Hz), 121.1 (ArCH), 121.5 (ArCH), 140.5 (ArC), 157.1 (q, CCF_3, J = 33 Hz), 157.6 (ArC); MS (EI, 70 eV) m/z 217 (M^+); anal. ($C_{10}H_{10}NF_3O$): C, 55.30; H, 4.64; N, 6.45. Found: C, 55.59; H, 4.99; N, 6.64.

***N*-(1,1,1-Trifluoro-2-propyl)-4-methoxyaniline (14a).**[6] To a Et_2O solution of $LiAlH_4$ (0.5 equiv) at 0 °C was added a Et_2O solution of propylidene **13a** dropwise over 30 min. Upon complete addition the mixture was refluxed for 2 h. The mixture was then cooled to 0 °C and quenched using a 1:1:3 work up (H_2O:3M NaOH:H_2O). The resulting mixture was decanted into a separatory funnel, the aqueous layer separated and ether layer washed with brine, dried over $MgSO_4$ and concentrated. Purification by Kügelrohr distillation provided pure amine as light red oil (64%): bp 80 °C (0.2 mm); ^{1}H NMR ($CDCl_3$) δ 1.34 (d, 3H, J = 7.0 Hz), 3.32 (br s, 1H), 3.72 (s, 3H), 3.87 (m, 1H), 6.61 (AA′BB′, 2H, J = 8.8, 4.0 Hz), 6.77 (AA′BB′, 2H, J = 8.8, 3.5 Hz); ^{13}C NMR ($CDCl_3$) δ 15.2 (CH_3), 52.7 (q, $\underline{C}HCF_3$, J = 30 Hz), 55.8 (CH_3), 115.1 (ArCH), 115.4 (ArCH), 126.5 (q, CF_3, J = 280 Hz), 140.2 (ArC), 153.2 (ArC); MS (EI, 70 eV) m/z 219 (M^+).

***N*-(1,1,1-Trifluoro-2-phenethyl)-4-methoxyaniline (14b).** Prepared according to procedures outlined above from ylide **12a** and trifluoroacetophenone. The imine was isolated then used directly in reduction step to afford the title compound as a light yellow oil upon distillation (69%): bp 110 °C (0.1 mm); ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 4.10 (br s, 1H), 4.81 (q, 1H, J = 7.0 Hz), 6.61 (AA′BB′, 2H, J = 8.8, 4.0 Hz), 6.75 (AA′BB′, 2H, J = 8.8, 3.5 Hz), 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 55.8 (CH_3), 62.0 ($\underline{C}HCF_3$, q, J = 30 Hz), 115.0 (ArCH), 115.9 (ArCH), 125.5 (q, CF_3, J = 280 Hz), 128.2 (ArCH), 129.1 (ArCH), 129.3 (ArCH), 134.5 (ArC), 139.7 (ArC), 153.5 (ArC); MS (EI, 70 eV) m/z 281 (M^+); anal. ($C_{15}H_{14}NF_3O$): C, 64.05; H, 5.02; N, 4.98. Found: C, 63.90; H, 4.84; N, 5.05.

***N*-(1,1,1-Trifluoro-2-phenethyl)-aniline (14c).** Prepared according to procedures outlined above using ylide **12b** and trifluoroacetophenone. The imine was isolated then used directly in reduction to afford the title compound as a clear oil upon distillation (59%): bp 100 °C (0.5 mm); ^{1}H NMR ($CDCl_3$) δ 4.36 (d, 1H, J = 6.5 Hz, N$\underline{H}$), 4.96 (quint, 1H, J = 7.0 Hz), 6.68 (d, 2H, J = 8.0 Hz), 6.82 (t, 1H, J = 7.0 Hz), 7.20 (d, 2H, J = 7.0 Hz), 7.42 (m, 3H), 7.50 (d, 2H, J = 6.5 Hz), ^{13}C NMR ($CDCl_3$) δ 60.7 (q, $\underline{C}HCF_3$, J = 29 Hz), 114.1 (ArCH), 119.5 (ArCH), 122.5 (q, CF_3, J = 278 Hz), 128.1 (ArCH), 129.2 (ArCH), 129.4 (ArCH), 129.6 (ArCH), 134.3 (ArC), 145.8 (ArC); MS (EI, 70 eV) m/z 251 (M^+); anal. ($C_{14}H_{12}F_3N$): C, 66.93; H, 4.81; N, 5.57. Found: C, 66.79; H, 4.80; N, 5.54.

***N*-[1,1,1-Trifluoro-2-(3-methoxy)-phenethyl]-aniline (14d).** *2,2,2-Trifluoro-1-(3-methoxyphenyl)-ethanone precursor).*[13]

Mg turnings (1.25 g, 50 mmol), 3-methoxyphenyl bromide (9.35 g, 50 mmol), and anhydrous THF (50 mL) were gingerly heated until a vigorous reaction took place. When all the Mg turnings were dissolved the reaction mixture was cooled to 0 °C. A solution of *N*-trifluoroacetylpiperidine[35] (7.52 g, 45 mmol) in anhydrous THF (10 mL) was added to the Grignard reagent dropwise over 0.5 h with stirring at 0 °C. Upon complete addition, ice-bath was removed and the mixture stirred for 2 h. The reaction was quenched by the addition of satd aq NH_4Cl (5 mL), and the precipitates romoved by filtration. The filtrate was dried over $MgSO_4$, evaporated in vacuo, and the crude ketone distilled to give 6.6 g (72%) of a colorless liquid: bp 50 °C (0.5 mm) (bp[9] 84–85 °C (12 mm).

The above prepared 2,2,2-trifluoro-1-(3-methoxyphenyl)-ethanone was then reacted with ylide **12a** as described previously. Imine isolation and LAH reduction afforded the title compound as a light green oil upon distillation (80%): bp 125 °C (0.8 mm); ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 3H), 4.31 (br s, 1H), 4.87 (q, 1H, J = 7.2 Hz), 6.63 (d, 2H, J = 7.6 Hz), 6.76 (td, 1H, J = 7.6, 0.8 Hz), 6.89 (dd, 1H, J = 8.5, 2.4 Hz), 6.99 (br s, 1H), 7.03 (d, 1H, J = 7.6 Hz), 7.15 (m, 2H), 7.28 (t, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 55.1 (CH_3), 60.3 (q, $\underline{C}HCF_3$, J = 30 Hz), 113.8 (ArCH), 114.1 (ArCH), 119.1 (ArCH), 120.1 (ArCH), 124.9 (q, CF_3, J = 281 Hz), 128.7 (ArCH), 129.2 (ArCH), 129.8 (ArCH), 135.5 (ArC), 145.4 (ArC), 159.8 (ArC); MS (EI, 70 eV) m/z 281 (M^+); anal. ($C_{15}H_{14}F_3NO$): C, 64.05; H, 5.02; N, 4.98. Found: C, 64.15; H, 4.99; N, 4.84.

***N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-2-propyl)-4-methoxybenzamide (15a).**[6] Prepared according to general procedure for CF_3-containing anilines and purified by flash chromatography (25% EtOAc/hexane) to afford product as white powder (68%): mp 85–86 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (d, 3H, J = 7.0 Hz), 3.69 (s, 3H), 3.73 (s, 3H), 5.79 (sept, 1H, J = 6.5 Hz), 6.62 (d, 2H, J = 8.5 Hz), 6.75 (br s, 2H), 7.12 (br s, 2H), 7.22 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 12.5 (CH_3), 55.2 (CH_3), 55.4 (CH_3), 113.1 (ArCH), 114.1 (ArCH), 125.2 (q, CF_3, J = 282 Hz), 128.0 (ArC), 130.6 (ArCH), 131.7 (ArC), 159.0 (ArC), 160.6 (ArC), 171.6 (C=O); MS (EI, 70 eV) m/z 353 (M^+).

***N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-4-methoxybenzamide (l5b).** Prepared according to general procedure for CF_3-containing anilines and purified by flash chromatography (25% EtOAc/hexane) to afford product as transparent oil (77%): ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.69 (s, 3H), 6.05 (br s, 1H), 6.42 (br s, 1H), 6.61 (d overlapping br s, 3H, J = 8.5 Hz) 7.04 (br q, 1H, J_{HF} = 6.5 Hz), 7.25 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 55.1 (CH_3), 55.2 (CH_3), 58.8 (Ar$\underline{C}$HCF$_3$), 113.0 (ArCH), 113.6 (ArCH), 125.1 (q, $C\overline{F}_3$, J = 281 Hz), 127.5 (ArC), 128.5 (ArCH), 129.0 (ArCH), 130.0 (ArCH), 130.7 (ArCH), 131.9 (ArC), 132.0 (ArCH), 132.9 (ArCH), 158.8 (ArC), 160.5 (ArC), 171.4 (C=O); MS (EI, 70 eV) m/z 415 (M^+); HRMS calcd for $C_{23}H_{20}F_3NO_3$, 415.1395. Found, 415.1387.

***N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-benzamide (15c).** Prepared according to general procedure for CF_3-containing anilines and purified by flash chromatography (10% EtOAc/hexane) to afford product as light yellow oil (73%): bp 125 °C (0.3 mm); ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3H), 6.01 (br s, 1H), 6.52 (2 overlapping br s, 3H), 7.12 (m, 4H), 7.26 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 55.4 (CH_3), 58.1 ($CHCF_3$), 113.6 (ArCH), 125.1 (q, CF_3, J = 282 Hz), 127.9 (ArCH), 128.7 (ArCH), 129.2 (ArCH), 129.6 (ArCH), 130.2 (ArCH), 131.4 (ArC), 131.9 (ArC), 132.4 (ArCH), 135.7 (ArC), 159 (ArC), 172.1 (C=O); MS (EI, 70 eV) m/z 385 (M^+); anal. ($C_{22}H_{18}F_3NO_2$): C, 68.57; H, 4.71; N, 3.68. Found: C, 68.22; H, 5.03; N, 3.68.

***N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-3-methoxybenzamide (15d).** Prepared according to general procedure for CF_3-containing anilines and purified by flash chromatography (10% EtOAc/hexane) to afford product as transparent oil (79%): ^{1}H NMR ($CDCl_3$) δ 3.66 (2-s, 3H, ~1.2/1 ratio benzoyl rotamers), 3.88 (s, 3H), 6.78 (br d, 1H, J = 8.5 Hz), 6.8 (br s, 1H), 7.03 (q, 1H, J = 6.5 Hz, C$\underline{H}$CF$_3$), 7.25 (m, 5H), 7.65 (dd, 1H, J = 8.5, 2.3 Hz), 7.75 (app dt, 1H, J = 7.6, 0.8 Hz); MS (EI, 70 eV) m/z 415 (M^+).

***N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-2-methoxybenzamide (15e).** Prepared according to general procedure for CF_3-containing anilines and purified by flash chromatography (10% EtOAc/hexane) to afford product as transparent oil (36%, 84% corrected for recovered aniline); ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3H), 3.68 (s, 3H), 6.10 (br s, 1H), 6.43 (br s, 2H), 6.58 (d, 2H, J = 8.5 Hz), 6.72 (app t, 2H, J = 8.5 Hz), 7.21 (m, 7H); MS (EI, 70 eV) m/z 415 (M^+).

***N*-(Phenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-4-methoxybenzamide (15f).** Prepared according to the general procedure for CF_3-containing anilines using 1,2-dichlorobenzene as solvent and purified by flash chromatography (10% EtOAc/hexane) to afford product as a transparent oil (54%): ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 3H), 6.62 (d, 2H, J = 8.5 Hz), 7.11 (m, 3H), 7.25 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 55.1 (CH_3), 58.5 ($CHCF_3$), 113.0 (ArCH), 125.2 (q, CF_3, J = 282 Hz), 127.3 (ArC), 127.9 (ArCH), 128.6 (ArCH), 129.0 (ArCH), 129.9 (ArCH), 130.7 (ArCH), 130.9 (ArCH), 131.9 (ArC), 139.5 (ArC), 161.0 (ArC), 171.2 (C=O); MS (EI, 70 eV) m/z 385 (M^+); anal. ($C_{23}H_{20}NO_3F_3 \cdot 1.1\ CHCl_3$): C, 52.95; H, 3.89; N, 2.56. Found: C, 52.84; H, 3.90; N, 2.65.

***N*-(Phenyl)-*N*-[1,1,1-trifluoro-2-(3-methoxy)-phenethyl]-4-methoxybenzamide (15g).** Prepared according to general procedure for CF_3-containing anilines using 1,2-dichlorobenzene as solvent and purified by flash chromatography (10–25% EtOAc/hexane) to afford product as transparent oil (51%): ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.69 (s, 3H), 6.61 (d, 2H, J = 8.5 Hz), 6.77 (s, 1H), 6.88 (app td, 2H, J = 8.5, 3.5 Hz), 7.10 (m, 5H), 7.18 (app t, J = 8.0 Hz), 7.26 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 55.3 (CH_3), 55.4 (CH_3), 58.7 ($\underline{C}HCF_3$), 113.1

(ArCH), 115.0 (ArCH), 115.5 (ArCH), 122.5 (ArCH), 125.4 (q, CF_3, $J=281$ Hz), 127.5 (ArC), 128.1 (ArCH), 128.7 (ArCH), 129.7 (ArCH), 130.9 (ArCH), 131.1 (ArCH), 133.3 (ArC), 139.7 (ArC), 159.6 (ArC), 160.9 (ArC), 171.4 (C=O); MS (EI, 70 eV) m/z 415 (M^+).

***N*-(4-Hydroxyphenyl)-*N*-(1,1,1-trifluoro-2-propyl)-4-hydroxybenzamide (16a).**[6] Deprotected according to BBr_3 procedure and recrystallized from EtOAc/hexane to afford white powder (62%): mp 203–205 °C (mp[6] 207–207.5 °C); ^{1}H NMR (acetone-d_6) δ 1.24 (d, 3H, $J=6.5$ Hz), 5.78 (q, 1H, $J=6.5$ Hz), 6.62 (d, 2H, $J=8.8$ Hz), 6.78 (br s, 2H), 7.05 (br s, 2H), 7.18 (d, 2H, $J=8.8$ Hz), 8.61 (s, 1H), 8.70 (s, 1H); ^{13}C NMR (acetone-d_6) δ 12.6 (CH_3), 51.3 (q, CH, $^3J_{H\text{-}F}=30$ Hz), 114.9 (ArCH), 115.0 (ArCH), 116.2 (ArCH), 126.8 (q, CF_3, $^1J_{CF}=282$ Hz), 128.2 (ArC), 131.4 (ArCH), 131.6 (ArC), 157.7 (ArC), 159.3 (ArC), 171.8 (C=O); MS (EI, 70 eV) m/z 325 (M^+); anal. ($C_{16}H_{14}NO_3F_3$): C, 59.08; H 4.34; N, 4.31. Found: C, 59.14; H, 4.37; N, 3.96.

***N*-(4-Hydroxyphenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-4-hydroxybenzamide (16b).** Deprotected according to BBr_3 procedure and purified by radial chromatography (25% EtOAc/hexane) to afford product as thick oil (53%): ^{1}H NMR (MeOD) δ 5.91 (br s, 1H) 6.32 (br s, 1H), 6.54 (d, 2H, $J=8.8$ Hz), 6.62 (br s, 1H), 6.94 (q, 1H, $J_{H\text{-}F}=9.2$ Hz), 7.13 (d, 2H, $J=8.8$ Hz), 7.23 (m, 6H); ^{13}C NMR (MeOD) δ 60.2 (CH), 113.9 (ArCH), 114.5 (ArCH), 125.0 (q, CF_3, $J=282$ Hz), 125.8 (ArC), 128.0 (ArCH), 128.7 (ArCH), 129.6 (ArCH) 130.0 (ArCH), 130.2 (ArC), 131.3 (ArC), 131.8 (ArC), 156.9 (ArC), 158.8 (ArC), 172.7 (C=O); MS (EI, 70 eV) m/z 387 (M^+); anal. ($C_{21}H_{16}F_3NO_3\cdot0.1\ H_2O$): C, 64.81; H, 4.20; N, 3.60. Found: C, 64.68; H, 4.30; N, 3.45

***N*-(4-Hydroxyphenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-benzamide (16c).** Deprotected according to BBr_3 procedure and recrystallized from EtOAc/hexane to afford white powder (83%): mp 158–159 °C, ^{1}H NMR ($CDCl_3$) δ 5.91 (br s, 1H), 6.30 (br s, 1H), 6.61 (br s, 1H), 6.74 (s, 1H), 6.95 (q, 1H, $J=8.8$ Hz), 7.24 (m, 9H); MS (EI, 70 eV) m/z 371 (M^+); anal. ($C_{21}H_{16}F_3NO_2$): C, 67.92; H, 4.34; N, 3.77. Found: C, 68.05; H, 4.35; N, 3.63.

***N*-(4-Hydroxyphenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-3-hydroxybenzamide (16d).** Deprotected according to BBr_3 procedure and recrystallized from EtOAc/hexane to afford off-white powder (77%): mp 163–164 °C; ^{1}H NMR ($CDCl_3$) δ 5.92 (br s, 1H), 6.28 (br s, 1H), 6.64 (m, 2H), 6.96 (m, 3H), 7.31 (m, 7H); MS (EI, 70 eV) m/z 387 (M^+); anal. ($C_{21}H_{16}NO_3F_3\cdot H_2O$): C, 62.52; H, 4.48; N, 3.46. Found: C, 62.52; H, 4.17; N, 3.27.

***N*-(4-Hydroxyphenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-2-hydroxybenzamide (16e).** Deprotected according to BBr_3 procedure and recrystallized from EtOAc/hexane to afford off-white powder (59%): mp 191.5–193 °C; ^{1}H NMR (MeOD) δ 6.10 (br s, 2H), 6.59 (app q, 2H, $J=7.6$, 7.2 Hz), 6.96 (m, 3H), 7.32 (m, 6H); MS (EI, 70 eV) m/z 387 (M^+); anal. ($C_{21}H_{16}F_3NO_3\cdot0.7\ H_2O$): C, 63.06; H, 4.38; N, 3.50. Found: C, 63.04; H, 4.08; N, 3.50.

***N*-(Phenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-4-hydroxybenzamide (16f).** Deprotected according to BBr_3 procedure and recrystallized from EtOAc/hexane to afford off-white powder (quant): mp 114–116 °C; ^{1}H NMR ($CDCl_3$) δ 6.48 (d, 2H, $J=8.4$ Hz), 7.0 (m, 4H) 7.15 (d, 2H, $J=8.4$ Hz), 7.26 (d, 6H), 7.72 (s, 2H, exchange with D_2O); ^{13}C NMR (MeOD) δ 50.8 (CH), 114.9 (ArCH), 125.0 (q, CF_3, $J_{CF}=281$ Hz), 126.3 (ArC), 128.2 (ArCH), 128.6 (ArCH), 129.3 (ArCH), 130.0 (ArCH), 130.8 (ArCH), 131.0 (ArCH), 131.6 (ArC), 139.2 (ArC), 158.2 (ArC), 172.6 (C=O); MS (EI, 70 eV) m/z 371 (M^+); anal. ($C_{21}H_{16}F_3NO_2\cdot0.5\ H_2O$): C, 66.31; H, 4.50; N, 3.68. Found: C, 66.19; H, 4.27; N, 3.57.

***N*-(Phenyl)-*N*-(1,1,1-trifluoro-2-(3-hydroxyphenethyl))-4-hydroxybenzamide (16g).** Deprotected according to BBr_3 procedure and recrystallized from $CHCl_3$ to afford small off-white crystals (95%): mp 163–165 °C; ^{1}H NMR ($CDCl_3$) δ 6.43 (d, 2H, $J=8.5$ Hz), 6.67 (d, 1H, $J=8.0$ Hz), 6.82 (dd, 1H, $J=8.5$, 2 Hz), 6.91 (s, 1H), 7.08 (m, 8H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$) 114.9 (ArCH), 116.6 (ArCH), 117.0 (ArCH), 121.2 (ArCH), 124.6 (q, CF_3, $J=226$ Hz), 126.1 (ArC), 128.3 (ArCH), 128.6 (ArCH), 129.8 (ArCH), 130.6 (ArCH), 132.6 (ArC), 138.8 (ArC), 156.3 (ArC), 157.8 (ArC), 173.0 (C=O); MS (EI, 70 eV) m/z 387 (M^+); anal. ($C_{21}H_{16}F_3NO_3$): C, 65.12; H, 4.16; N, 3.62. Found: C, 64.78; H, 4.18; N, 3.38.

***N*-(4-Hydroxyphenyl)-*N*-(1,1,1-trifluoro-2-propyl)-4-hydroxythiobenzamide (17a).** Deprotected according to BBr_3 procedure and recrystallized from ether to afford yellow powder (93%): ^{1}H NMR (MeOD) δ 1.33 (d, 3H, $J=7.5$ Hz), 6.47 (d, 2H, $J=8$ Hz), 6.58 (d, 1H, $J=6.5$ Hz), 6.64 (d, 1H, $J=6$ Hz), 6.79 (d, 1H, $J=8.5$ Hz), 6.96 (d, 1H, $J=8.0$ Hz), 7.01 (d, 3H, $J=8.5$ Hz; ArCH *ortho* C=O and CHCF$_3$); MS (EI, 70 eV) m/z 341 (M^+); anal. ($C_{16}H_{14}F_3NO_2S\cdot0.1\ H_2O$): C, 56.00; H, 4.17; N, 4.08. Found: C, 55.76; H, 4.13; N, 3.74.

***N*-(4-Hydroxyphenyl)-*N*-(1,1,1-trifluoro-2-phenethyl)-4-hydroxythiobenzamide (17b).** Deprotected according to BBr_3 procedure and purified by chromatography (5% MeOH/CH_2Cl_2) to afford title compound as yellow foam (74%): ^{1}H NMR ($CDCl_3$) δ 5.47 (br s, 1H, OH), 5.58 (br s, 1H, OH), 5.86 (d, 1H, $J=5.5$ Hz, ArH *ortho* to OH on aniline ring), 6.25 (d, 1H, $J=5.5$ Hz, ArH *ortho* to OH on aniline ring), 6.36 (d, 2H, $J=8$ Hz, ArH *ortho* to OH on benzamide ring), 6.57 (d, 1H, $J=6$ Hz, ArH *ortho* to N–C=S), 6.93 (d, 2H, $J=9$ Hz, ArH *ortho* to C=S), 6.98 (d, 1H, $J=6$ Hz, ArH *ortho* to N–C=S), 8.39 (q, 1H, $J_{HF}=9$ Hz); ^{13}C NMR ($CDCl_3$) δ 63.8 (CHCF$_3$), 114.6 (ArCH), 115.0 (ArCH), 115.5 (ArCH), 125.1 (q, $J=163$ Hz, CF_3), 129.0 (ArCH), 129.3 (ArCH), 129.8 (ArCH), 129.9 (ArCH), 131.4 (ArC), 133.4 (ArC), 136.3 (ArC), 155.3 (ArC), 155.7 (ArC), 208.3 (C=S); MS (EI, 70 eV) m/z 403 (M^+); HRMS calcd for $C_{21}H_{16}F_3NO_2S$, 403.0853, found 403.0858; anal. ($C_{21}H_{16}F_3NO_2S\cdot0.3\ H_2O$): C, 61.70; H, 4.09; N, 3.43. Found: C, 61.68; H, 3.92; N, 3.25.

***N*-(4-Methoxyphenyl)-4-methoxyphenylacetamide (18).** To a 0 °C CH_2Cl_2 solution of *p*-anisidine (1.3 equiv) and pyridine (1.1 equiv) was added dropwise a CH_2Cl_2

solution (2–5 mL) of 4-methoxyphenylacetyl chloride (1.0 equiv). Upon complete addition (15 min) mixture was allowed to reach rt. Upon completion of the reaction, the mixture was diluted with CH_2Cl_2 folowed by product isolation (H_2O, $CuSO_4$, brine). Recrystallization from EtOAc/hexane afforded the title carboxamide as small white crystals (82%): mp 127–128 °C; ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 2H), 3.76 (s, 3H), 3.82 (s, 3H), 6.80 (d, 2H, J = 9.0 Hz), 6.92 (d, 2H, J = 8.5 Hz), 7.07 (s, 1H), 7.23 (d, 2H, J = 9.0 Hz), 7.30 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 43.7 (CH_2), 55.3 (CH_3), 55.5 (CH_3), 114.1 (ArCH), 114.6 (ArCH), 121.8 (ArCH), 126.5 (ArC), 130.7 (ArCH), 130.8 (ArC), 156.5 (ArC), 159.0 (ArC), 169.7 (C=O); MS (EI, 70 eV) m/z 271 (M^+); anal. ($C_{16}H_{17}NO_3$): C, 70.83; H, 6.32; N, 5.16. Found: C, 70.87; H, 6.29; N, 5.29.

***N*-(4-Methoxyphenyl)-*N*-(ethyl)-4-methoxyphenylacetamide (19).** Prepared according to phase transfer catalysis conditions described above for carboxamides. Purification by either Kügelrohr distillation or flash chromatography (25% EtOAc/hexane) afforded product as red–orange oil (quant): bp 150 °C (0.2 mm); ^{1}H NMR ($CDCl_3$) δ 1.08 (t, 3H, J = 7.0 Hz), 3.33 (s, 2H), 3.70 (q, 2H, J = 7.1 Hz), 3.78 (s, 3H), 3.84 (s, 3H), 6.77 (d, 2H, J = 8.5 Hz), 6.79 (d, 2H, J = 8.5 Hz), 6.97 (d overlapping, 2H, J = 8.5 Hz), 6.98 (d overlapping, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.2 (CH_3), 40.5 (CH_2), 44.4 (CH_2), 55.4 (CH_3O), 55.7 (CH_3O), 113.9 (ArCH), 114.8 (ArCH), 127.9 (ArC), 129.9 (ArCH), 130.2 (ArCH), 135.2 (ArC), 158.4 (ArC), 159.2 (ArC), 171.2 (C=O); MS (EI, 70 eV) m/z 299 (M^+); anal. ($C_{18}H_{21}NO_3$·0.1 $CHCl_3$): C, 69.83; H, 6.83; N, 4.50. Found: C, 69.82; H, 6.98; N, 3.98.

***N*-(4-Methoxyphenyl)-*N*-(ethyl)-α-ethyl-4-methoxyphenylacetamide (20a).** *n*-BuLi in hexane (1.56 M, 2.0 equiv) was added dropwise to a −78 °C THF (*i*-propyl)$_2$NH (2.2 equiv) solution, then warmed to 0 °C. After 0.5 h at 0 °C the mixture was re-cooled to −78 °C and a THF solution of acetamide **19** (1.0 equiv) added dropwise. After 20 min EtI (1.3 equiv) was added in one portion and the mixture allowed to reach rt. Product isolation (H_2O, Et_2O, Na_2SO_4) and purification by flash chromatography (25% EtOAc/hexane) as light yellow oil (95%): ^{1}H NMR ($CDCl_3$) δ 0.78 (t, 3H, J = 7.5 Hz, C$\underline{H}_3$ α-ethylacetamide), 1.05 (t, 3H, J = 7.0 Hz, C$\underline{H}_3$ *N*-ethyl), 1.60 (dquint, 1H, J = 14.0, 7.0 Hz, α-C$\underline{H}_2$), 2.04 (dquint, 1H, J = 14.0, 7.0 Hz, α-C$\underline{H}_2$), 3.27 (dd, 1H, J = 8.5, 7.0 Hz, C$\underline{H}$ α-benzylic), 3.67 (m, 2H, -NC$\underline{H}_2$CH$_3$), 3.77 (s, 3H), 3.85 (s, 3H), 6.75 (d, 2H, J = 8.8 Hz), 6.87 (br s, 4H), 6.98 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 12.5 (CH_3), 13.1 (CH_3), 28.5 (CH_2), 44.3 (CH_2), 55.2 (CH_3), 55.6 (CH_3), 113.7 (ArCH), 114.5 (ArCH), 129.2 (ArCH), 132.9 (ArC), 135.0 (ArC), 158.4 (ArC), 159.0 (ArC), 173.5 (C=O); MS (EI, 70 eV) m/z 327 (M^+); anal. ($C_{20}H_{25}NO_3$): C, 73.37; H, 7.70; N, 4.28. Found: C, 72.84; H, 7.56; N, 3.59.

***N*-(4-Methoxyphenyl)-*N*-(ethyl)-α-benzyl-4-methoxyphenylacetamide (20b).** Preparation as described in **20a** and purification by flash chromatography (15% EtOAc/hexane) afforded title compound as an oil (86%): ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.2 Hz, NCH$_2$C$\underline{H}_3$), 2.75 (dd, 1H, J = 12.8, 4.8 Hz, methine $\underline{H}$), 3.43 (m, 2H, NC$\underline{H}_2$CH$_3$), 3.58 (dd, 1H, J = 10.2, 5.1 Hz), 3.70 (dd, 1H, J = 13.3, 7.1 Hz) 3.76 (s, 3H), 3.79 (s, 3H), 6.15 (br s, 1H), 6.75 (d, 2H, J = 8.3 Hz), 6.78 (d, 2H, J = 6.7 Hz), 7.09 (m, 4H), 7.24 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 12.8 (CH_3), 41.5 (CH_2), 44.2 (CH_2), 50.3 (CH), 55.2 (OCH_3), 55.4 (OCH_3), 113.7 (ArCH), 114.3 (ArCH), 126.2 (ArCH), 128.2 (ArCH), 129.1 (ArCH), 129.4 (ArCH), 130.0 (ArCH), 132.4 (ArC), 134.6 (ArC), 140.1 (ArC), 158.5 (ArC), 158.9 (ArC), 172.5 (C=O); MS (EI, 70 eV) m/z 389 (M^+).

***N*-(4-Hydroxyphenyl)-*N*-(ethyl)-4-hydroxyphenylacetamide (21a).** Deprotected according to BBr_3 procedure and purified by chromatography (50% EtOAc/hexane) to afford tan foam (quant): mp 75 °C dec.; ^{1}H NMR ($(CD_3)_2SO$) δ 0.96 (t, 3H, J = 7.5 Hz), 3.16 (s, 2H), 3.36 (q, 2H, J = 7.5 Hz), 6.59 (d, 2H, J = 8.5 Hz), 6.78 (m, 4H), 6.97 (d, 2H, J = 8.5 Hz), 9.18 (br s, 1H), 9.62 (br s, 1H); MS (EI, 70 eV) m/z 271 (M^+); anal. ($C_{16}H_{17}NO_3$·0.9 H_2O): C, 66.84; H, 6.59; N, 4.87. Found: C, 66.95; H, 6.20; N, 4.77.

***N*-(4-Hydroxyphenyl)-*N*-(ethyl)-4-hydroxyphenylthioacetamide (21b).** Deprotected according to BBr_3 procedure and purified by chromatography (50% EtOAc/hexane) to afford tan powder (84%): mp 156–157 °C; ^{1}H NMR ($(CD_3)_2SO$) δ 1.08 (t, 3H, J = 7.0 Hz), 3.67 (s, 2H), 4.14 (q, 2H, J = 2 Hz), 6.54 (d, 2H, J = 8.5 Hz), 6.75 (app t, 4H, J = 8.0 Hz), 6.87 (d, 2H, J = 8.5 Hz), 9.17 (s, OH), 9.78 (s, OH); MS (EI, 70 eV) m/z 287 (M^+); HRMS calcd for $C_{16}H_{17}NO_2S$, 287.0980; found, 287.0977; anal. ($C_{16}H_{17}NO_2S$·0.2H_2O): C, 66.04; H, 6.03; N, 4.81. Found: C, 65.97; H, 6.03; N, 4.78.

***N*-(4-Hydroxyphenyl)-*N*-(ethyl)-α-ethyl-4-hydroxyphenylacetamide (22a).** Deprotected according to BBr_3 procedure and purified by chromatography (50% EtOAc/hexane) to afford white foam (70%): ^{1}H NMR ($CDCl_3$) δ 0.76 (t, 3H, J = 7.5 Hz), 1.04 (t, 3H, J = 7.0 Hz), 1.54 (m, 1H, C$\underline{H}_2$ β-amide), 1.94 (m, 1H, C$\underline{H}_2$ β-amide), 3.27 (t, 1H, J = 7.0 Hz, C$\underline{H}$ α-amide), 3.62 (m, 2H, -NC$\underline{H}_2$CH$_3$), 6.63 (d, 2H, J = 8.8 Hz), 6.79 (d, overlapping br s, 2H, J = 8.8 Hz), 7.05 (br s, 4H); ^{13}C NMR ($CDCl_3$) δ 12.5 (CH_3), 13.0 (CH_3), 28.2 (CH_2), 44.8 (CH_2), 50.7 (CH), 116.1 (ArCH), 128.6 (ArCH), 129.3 (ArCH), 131.7 (ArCH), 133.7 (ArC), 155.4 (ArC), 156.8 (ArC), 174.7 (C=O); MS (EI, 70 eV) m/z 299 (M^+); HRMS calcd for $C_{18}H_{21}NO_3$, 299.1521, found 299.1520.

***N*-(4-Hydroxyphenyl)-*N*-(ethyl)-α-ethyl-4-hydroxyphenylthioacetamide (22b).** Deprotected according to BBr_3 procedure and purified by chromatography (25% EtOAc/hexane) to afford yellow residue (95%): ^{1}H NMR (MeOD) δ 0.73 (t, 3H, J = 7.3 Hz), 1.14 (t, 3H, J = 7.2 Hz), 1.76 (m, 1H, C$\underline{H}_2$ β-amide), 2.17 (m, 1H, C$\underline{H}_2$ β-amide), 3.62 (dd, 1H, J = 7.8, 7.0 Hz, C$\underline{H}$ α-amide), 4.16 (m, 1H, C$\underline{H}_2$ α-NCO), 4.30 (m, 1H, C$\underline{H}_2$ α-NCO), 6.56 (dd, 1H, J = 8.4, 2.6 Hz), 6.56 (AA′BB′, 2H, J = 8.7, 2.3 Hz), 6.75 (dd, 1H, J = 8.4, 2.8 Hz), 6.91 (dd, 1H, J = 8.6, 2.7 Hz), 6.94 (AA′BB′, 2H, J = 8.5, 1.9 Hz),

7.0 (dd, 1H, $J=8.7$, 2.8 Hz); ^{13}C NMR ($CDCl_3$) δ 11.4 (CH_3), 12.6 (CH_3), 13.9 (CH_2), 52.3 (CH_2), 56.2 (CH), 115.0 (ArCH), 116.3 (ArCH), 128.5 (ArCH), 129.1 (ArCH), 129.9 (ArCH), 133.5 (ArC), 136.5 (ArC), 154.6 (ArC), 155.9 (ArC), 207.5 (C=S); MS (EI, 70 eV) m/z 315 (M^+); HRMS calcd for $C_{18}H_{21}NO_2S$, 315.1293; found, 315.1301.

***N*-(4-Hydroxyphenyl)-*N*-(ethyl)-α-benzyl-4-hydroxyphenylthioacetamide (22c).** Deprotected according to BBr_3 procedure and purified by chromatography (15% EtOAc/hexane) to afford yellow residue (47%): ^{1}H NMR (MeOD) δ 1.05 (t, 3H, $J=7.2$ Hz), 2.90 (dd, 1H, $J=12.9$, 4.9 Hz, PhC$\underline{H}_2$), 3.66 (dd, 1H, $J=12.9$, 9.5 Hz, PhC$\underline{H}_2$), 3.95 (m, 1H, $CH_3C\underline{H}_2$), 4.05 (dd, 1H, $J=9.3$, 5.2 Hz, $PhCH_2C\underline{H}$-), 4.30 (m, 1H, $CH_3C\underline{H}_2$), 6.02 (dd, 1H, $J=8.4$, 2.7 Hz), 6.56 (d, 2H, $J=8.3$ Hz), 6.66 (overlapping dds, 2H, $J=9.2$, 3.1 Hz), 6.75 (dd, 1H, $J=8.8$, 3.0 Hz), 7.00 (d, 2H, $J=8.7$ Hz), 7.10 (m, 5H); HRMS calcd for $C_{23}H_{23}NSO_2$, 377.1449; found, 377.1443.

***N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-2-propyl)-4-methoxyphenylacetamide (25).** Prepared according to general amidation procedure for CF_3-containing anilines; product isolation and purification via flash chromatography (25% EtOAc/hexane) afforded title compound as light yellow oil (40%): ^{1}H NMR ($CDCl_3$) δ 1.16 (d, 3H, $J=7$ Hz), 3.32 (s, 2H), 3.76 (s, 3H), 3.84 (s, 3H), 5.61 (sept, 1H, $J=7.6$ Hz), 6.77 (d, 2H, $J=8.9$ Hz), 6.90 (m, 3H), 6.92 (d, 2H, $J=8.9$ Hz), 7.06 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 12.5 (CH_3), 40.7 (CH_2), 50.1 (q, $\underline{C}HCF_3$, $J=31$ Hz), 55.3 (CH_3O), 55.6 (CH_3O), 113.9 (ArCH), 114.3 (ArCH), 114.6 (ArCH), 125.1 (q, CF_3. $J=283$ Hz), 127.0 (ArC), 129.9 (ArC), 130.2 (ArCH), 132.0 (ArCH), 158.6 (ArC), 159.9 (ArC), 172.8 (C=O); HRMS calcd for $C_{19}H_{20}NF_3O_3$, 367.1395, found, 367.1394; anal. ($C_{19}H_{20}NF_3O_3$): C, 62.12; H, 5.49; N, 3.81. Found: C, 61.76; H, 5.58; N, 3.66.

***N*-(4-Methoxyphenyl)-*N*-(1,1,1-trifluoro-2-propyl)-α-methyl-4-methoxyphenylacetamide (26).** *n*-BuLi in hexane (1.56 M, 2.0 equiv) was added dropwise to a −78 °C THF (*i*-propyl)$_2$NH (2.2 equiv) solution, then warmed to 0 °C. After 0.5 h at 0 °C the mixture was re-cooled to −78 °C and a THF solution of *N*-(1,1,1-trifluoro-2-propyl) substituted acetamide **25** (1.0 equiv) was added dropwise. After 20 min MeI (1.3 equiv) was added in one portion and the mixture allowed to reach rt. Crude product isolation (H_2O, Et_2O, Na_2SO_4) afforded an amber oil (83%) which was determined by both ^{1}H NMR and HPLC to be an approx. 1:1 ratio of diastereomers for the expected product: ^{1}H NMR ($CDCl_3$) δ 1.05 (2-ds, 3H, $J=7.5$ Hz), 1.28 (2-ds, 3H, $J=7.5$ Hz), 3.42 (overlapping qs, 1H, $J=7.5$ Hz), 5.58 (m, 1H, $C\underline{H}CF_3$), 6.44 (2-dds, 1H, $J=8.8$, 2.8 Hz), 6.68 (dd, 0.5 H, $J=8.8$, 2.8 Hz), 6.70 (m, 2.5H), 6.81 (m, 2H), 7.01 (2-dds, 1H, $J=8.4$, 2.3 Hz), 7.20 (2-dds, 1H, $J=8.4$, 2.3 Hz); HPLC (254 nm) 25% EtOAc/hexane, Micropac SiO_2 column: 5.82 min. (46.2%), 7.19 min. (53.7%), sd±5%.

***N*-(4-Hydroxyphenyl)-*N*-(1,1,1-trifluoro-2-propyl)-α-methyl-4-hydroxyphenylacetamide (27).** Deprotection using BBr_3 procedure and chromatography (35% EtOAc/hexane) afforded title compound as a white powder (95%) with a 1:1 ratio of diastereomers as found by ^{1}H NMR: mp 165–170 °C; ^{1}H NMR (MeOD) δ 1.10 (overlapping ds, 3H, $J=7.5$ Hz), 1.25 (overlapping ds, 3H, $J=7.5$ Hz), 3.49 (overlapping qs, 1H, $J=7.5$ Hz), 5.52 (m, 1H, $C\underline{H}CF_3$), 6.43 (2-dds, 1H, $J=8.8$, 2.8 Hz), 6.57 (dd, 0.5H, $J=8.8$, 2.8 Hz), 6.64 (m, 2.5H), 6.72 (m, 2.5H), 6.86 (app td, 1H, $J=8.4$, 2.3 Hz), 7.07 (2-dds, 1H, $J=8.4$, 2.3 Hz); MS (EI, 70 eV) m/z 353 (M^+); HRMS calcd for $C_{18}H_{18}NF_3O_3$, 353.1238; found, 353.1235.

***N*-(4-Hydroxyphenyl)-*N*-(1,1,1-trifluoro-2-propyl)-4-hydroxyphenylthioacetamide (28).** Carboxamide **25** (0.3 mmol, 100 mg) was treated with Lawesson's reagent as outlined in general procedure. Product isolation (H_2O, Et_2O, Na_2SO_4) and radial chromatography (20% EtOAc/hexane) afforded 5 mg of protected thiocarboxamide in low yield (5%). Subsequent deprotection using BBr_3 procedure afforded the title compound as a light yellow residue upon SiO_2 purification (30% EtOAc/hexane, quant): ^{1}H NMR (MeOD) δ 1.24 (d and m, 3H, $J=7.8$ Hz), 3.85 (ABq, 2H, $J=13$ Hz), 5.56 (sept, 1H, $J=7.8$ Hz), 6.72 (m, 4H), 6.85 (m, 4H); HPLC: Whatman C18 column, 90%MeOH:10%H_2O $R_t=3.123>98\%$ pure at 254 nm.

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