One-Step Hydroxy Substitution of 4,4′-Dimethoxybenzhydrol with Amides, Lactams, Carbamates, Ureas and Anilines

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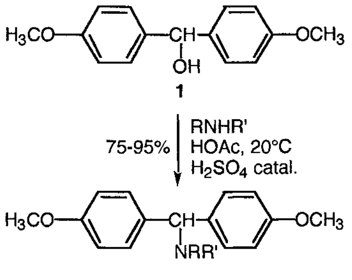
A series of amides, lactams, carbamates, ureas and anilines, equipped with various functionalities, were readily *N*-alkylated with the 4,4′-dimethoxybenzhydryl residue by reaction with 4,4′-dimethoxybenzhydrol [bis(4-methoxyphenyl)methanol] in acetic acid, at room temperature, under H_2SO_4 catalysis.

An important current aim in the field of biomaterial technology is the improvement of the biocompatibility of synthetic polymers by tailor-made derivatization of their surface.[1] Our interest in this field led us to examine selective surface modifications of poly(aryl ether ether ketone) (PEEK) films used as new supports for in vitro mammalian cell cultivation.[2] The reduced surface[3] (PEEK-OH) was considered as a versatile key intermediate for the covalent coupling of simple chemicals covering a wide range of functionalities and polarities, on the one hand, and for the anchorage of specific signal mediators to biological systems, on the other hand. To define the proper conditions of the surface chemistry, a model study was carried out,[4] using the commercially available 4,4′-dimethoxybenzhydrol [bis(4-methoxyphenyl)methanol, **1**] as a representative substrate of the polymer PEEK-OH repeated unit. The selected wetting solvent, essential for performing chemistry at the polymer/liquid interface, was acetic acid. Therefore, we considered the possibility of substituting, in a one-step process, the hydroxy group of **1** by various nucleophilic reagents in acetic acid solution. The previous literature mentions this type of reaction for the protection of the carboxamide function of *N*-benzyloxycarbonyl-L-glutamine and asparagine.[5–7] Examining the scope and limitation of this *N*-alkylation procedure, we found that the 4,4′-dimethoxybenzhydryl group was readily transferred from its alcohol precursor **1** to a large variety of nitrogen derivatives, provided that they are able to act as a soft nucleophile in acidic medium (Scheme).



R	R'	Products	Table
CO-H	H	**2**	1
CO-Alkyl	H	**3-8**	1
CO-Aryl	H	**9-11**	1
CO-Alkyl	Alkyl	**12-13**	1
CO-OAlkyl	H	**14**	2
CO-OAryl	H	**15**	2
CO-NH_2	H	**16**	2
CO-NHAryl	H	**17**	2
Aryl	$CONH_2$	**18**	2
Aryl	H	**19-27**	3

Scheme

The reactions of 4,4′-dimethoxybenzhydrol (**1**) with a series of amides (1–2 equivalents) were conducted at room temperature in acetic acid solution (0.5 g/10–15 mL) for 18–48 hours, in the presence of a catalytic amount of sulfuric acid. The substitution reaction most probably occurs via the protonated alcohol giving the carbenium ion of 4,4′-dimethoxybenzhydryl[8] which is trapped by the amide NH_2 group to give the corresponding *N*-4,4′-dimethoxybenzyhydrylamides **2–11** (Table 1), usually in excellent yields. We determined that the presence of a strong acidic catalyst is absolutely necessary to readily perform this alkylation reaction.

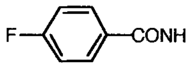
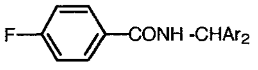
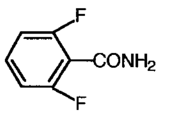
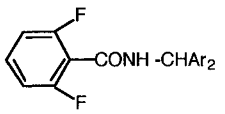
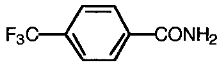
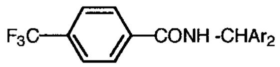
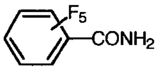
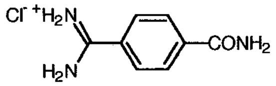
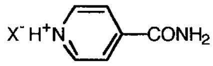
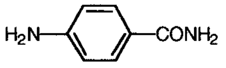
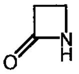
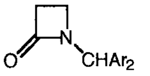
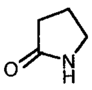
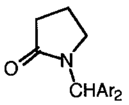
In the case of fluoroacetamide (Table 1, entry 4) the isolated yield of *N*-alkylamide **5** was moderate. This result emphasizes the crucial role of electron-withdrawing substituents in the carboxamide reactivity. Indeed, amides bearing strong electron-withdrawing groups completely lose their nucleophilic power and fail to give the substitution reaction (Table 1, entries 5, 6, 8, 11, 15, 16, and 17). In the absence of an efficient quencher, the cationic intermediate slowly reacts with its alcohol precursor **1** to furnish the symmetrical ether **28**[4,9–11] (Table 1, footnote c).

Small ring lactams could be similarly *N*-alkylated with 4,4′-dimethoxybenzhydrol in acetic acid to give quantitatively the compounds **12** and **13** (Table 1, entries 19 and 20). This interesting result broadens the field of application of the 4,4′-dimethoxybenzhydryl moiety as a protective group;[12,13] indeed, relatively few methods exist for the direct protection of lactams.[14] Most often the protective groups are incorporated as handles to introduce nitrogen into the final molecules; therefore, these groups are already present in the synthons used for the target construction, a strategy particularly well-illustrated in azetidinone chemistry.[15–18]

Treated with the alcohol **1** under standard conditions, carbamates and ureas gave the corresponding *N*-substituted products **14–18** (Table 2). With phenylurea (Table 2, entry 4), we obtained an equimolar mixture of the two possible regiomers **17** and **18** which could be separated by column chromatography. No reaction was observed with hydroxyurea (Table 2, entry 5), or with semicarbazide (entry 6).

Amides, lactams and related compounds are ambident nucleophiles susceptible to alkylation at the oxygen or nitrogen atom. *O*-Alkylation is usually observed, under

Table 1. Reactions of **1** with Amides and Lactams

Entry	Reagent	Reagent Equiv	Product (Ar = 4-MeOC$_6$H$_4$)		Yield (%) (Reaction Time)	mp (°C)	R_f
1	$HCONH_2$	2	$HCONHCHAr_2$	**2**	75 (15 h)	149.7–150.2	0.26 (EtOAc/PE, 50 : 50)^a
2	CH_3CONH_2	2	$CH_3CONHCHAr_2$	**3**	79 (18 h)	162.6–164.1	0.20 (CH$_2$Cl$_2$/EtOAc, 95 : 5)^a
3	$ClCH_2CONH_2$	1.2	$ClCH_2CONHCHAr_2$	**4**	88 (24 h)	120.4–120.9	0.71 (EtOAc/PE, 50 : 50)^a
4	FCH_2CONH_2	2	$FCH_2CONHCHAr_2$	**5**	38^c (18 h)	120.6–122.3	0.80 (CHCl$_3$/MeOH, 99 : 1)^a
5	Cl_3CCONH_2	1.2	–	–	0^c	–	–
6	F_3CCONH_2	2	–	–	0^c	–	–
7	EtO_2CCONH_2	1.2	$EtO_2CCONHCHAr_2$	**6**	83 (24 h)	(oil)	0.62 (CH$_2$Cl$_2$/EtOAc, 95 : 5)^a
8	HO_2CCONH_2	1.9	–	–	0^c	–	–
9	$BnO_2C(CH_2)_2CONH_2$	2	$BnO_2C(CH_2)_2CONHCHAr_2$	**7**	73 (18 h)	102–104	0.35 (CH$_2$Cl$_2$/EtOAc, 95 : 5)^b
10	$HO_2C(CH_2)_2CONH_2$	1.2	$HO_2C(CH_2)_2CONHCHAr_2$	**8**	85 (24 h)	148–150	0.10 (EtOAc)^a
11	$Cl^{-}\,{}^{+}H_3NCH_2CONH_2$	1.2	–	–	0^c	–	–
12		2		**9**	97 (18 h)	166.2–170.2	0.54 (CH$_2$Cl$_2$/EtOAc, 95 : 5)^a
13		2		**10**	86 (18 h)	191.1–194	0.72 (CH$_2$Cl$_2$/EtOAc, 95 : 5)^a
14		2		**11**	81 (18 h)	178–180	0.67 (CHCl$_3$/MeOH, 99 : 1)^a
15		1.2	–	–	0^c	–	–
16		1.2	–	–	0^c	–	–
17		1.2	–	–	0^c	–	–
18		1.2	see Table 3	**25**	85 (18 h)	81–82	0.30 (EtOAc)^a
19		1.1		**12**	98 (18 h)	(oil)	0.57 (EtOAc)^a
20		1.1		**13**	96 (18 h)	94–95	0.34 (EtOAc)^a

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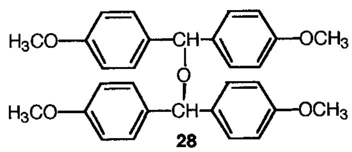
[a] Silica gel.

[b] Alumina.

[c] 

28

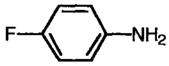
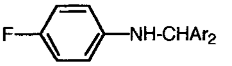
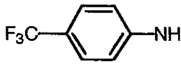
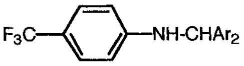
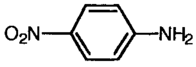
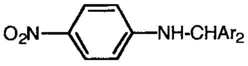
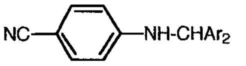
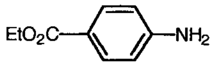
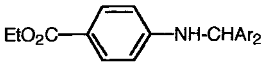
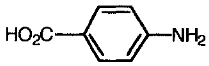
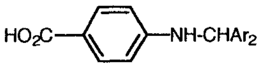
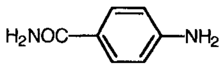
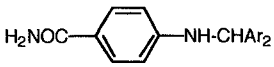
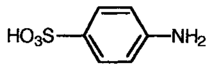
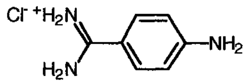
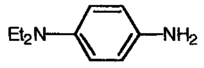
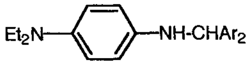
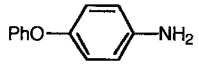
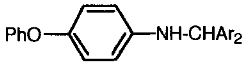
The symmetrical ether **28** was formed in 20–40%.

Table 2. Reactions of **1** with Carbamates, Ureas, Hydroxyurea and Semicarbazide

Entry	Reagent	Reagent Equiv	Product (Ar = 4-$MeOC_6H_4$)		Yield (%) (Reaction Time)	mp (°C)	R_f (silica gel)
1	MeO_2CNH_2	2	$MeO_2CNHCHAr_2$	**14**	85 (18 h)	141.2–141.9	0.74 (EtOAc/PE, 50 : 50)
2	PhO_2CNH_2	1.9	$PhO_2CNHCHAr_2$	**15**	80 (18 h)	161–163	0.3 (CH_2Cl_2/C_6H_{12}, 75 : 25)
3	H_2NCONH_2	1.2	$H_2NCONHCHAr_2$	**16**	84 (18 h)	(dec)	0.15 (EtOAc)
4	$PhNHCONH_2$	2	$PhNHCONHCHAr_2$ + $H_2NCON(Ph)CHAr_2$	**17** **18**	48 (18 h) 45 (18 h)	(dec) 82–84	0.93 (CH_2Cl_2/EtOAc, 50 : 50) 0.29 (CH_2Cl_2/EtOAc, 50 : 50)
5	$HONHCONH_2$	2	–	–	0[a]	–	–
6	$H_2NNH_2CONH_2$	2	–	–	0[a]	–	–

[a] See footnote c Table 1.

Table 3. Reactions of **1** with Anilines

Entry	Reagent	Reagent Equiv	Product (Ar = 4-$MeOC_6H_4$)		Yield (%) (Reaction) Time)	mp (°C)	R_f
1		1.2		**19**	86 (24 h)	(oil)	0.67 (CH_2Cl_2/C_6H_{12}, 80 : 20)[a]
2		1.2		**20**	93 (24 h)	(oil)	0.75 (CH_2Cl_2/C_6H_{12}, 90 : 10)[a]
3		1.2		**21**	82 (24 h)	114–116	0.37 (CH_2Cl_2/C_6H_{12}, 80 : 20)[a]
4		1.2		**22**	90 (24 h)	(oil)	0.31 (CH_2Cl_2)[a]
5		2		**23**	91 (18 h)	138–140	0.21 (CH_2Cl_2)[a]
6		1.2		**24**	92 (24 h)	173–175	0.59 (EtOAc)[a]
7		1.2		**25**	85 (18 h)	80–82	0.30 (EtOAc)[a]
8		1.2	–	–	0[c]	–	–
9		1.2	–	–	0[c]	–	–
10		2		**26**	71 (18 h)	(oil)	0.34 (CH_2Cl_2/C_6H_{12}, 90 : 10)[b]
11		2		**27**	81 (18 h)	(oil)	0.33 (CH_2Cl_2/C_6H_{12}, 50 : 50)[a]

[a] Silica gel.
[b] Alumina.
[c] See footnote c, Table 1.

neutral conditions, with strong electrophilic reagents, i.e., tertiary oxonium or sulfonium salts, esters of fluorosulfonic or trifluoromethanesulfonic acids and dimethyl sulfate.[19] On the other hand, *N*-alkylation is favored with alkyl halides forming relatively stable carbenium ions.[20] Similarly, alkylation by alcohols under acidic conditions usually gives products arising from *N*-substitution.[20] Hydrogen bonding between the protonated alcohol and the carbonyl oxygen of the substrate could possibly govern the regioselectivity of the nucleophilic attack. However, the initial formation of *O*-substituted derivatives which rearrange into the thermodynamically more stable *N*-alkylation products cannot be excluded.[21] Such rearrangement is normally observed in acidic medium.[21] Accordingly, our results appear fully consistent with the previous literature; we did not isolate products arising from *O*-alkylation.

Interestingly, we found that aniline derivatives were also readily *N*-alkylated with **1** under standard conditions (Table 3). In the particular case of 4-aminobenzamide (Table 3, entry 7), the reaction was totally chemoselective in favor of aniline NH_2 substitution over amide NH_2 substitution. As already mentioned in the case of amides, the efficiency of the coupling was dramatically reduced for substrates bearing strong electron-withdrawing substituents (Table 3, entries 8–9). Otherwise, the reaction appeared quite practical for a large variety of substituted anilines, giving the derivatives **19–27** in excellent yield. We have further examined the possibility to smoothly remove the 4,4′-dimethoxybenzhydryl group from the protected anilines. Selective cleavage of the *N*-(4,4′-dimethoxybenzhydryl) moiety in lactams results from an oxidative treatment with ceric ammonium nitrate.[17–18] However, the most general procedure to remove electron-rich benzyl[22–25] and benzhydryl groups[6,26] makes use of strong acids for example, trifluoroacetic acid. We found that the best procedure for deprotecting the anilines **19–27** was treatment with dry HBr in acetic acid at 20 °C. The corresponding free anilines could be precipitated from diethyl ether as hydrobromide salts, and thus readily separated from 4,4′-dimethoxybenzhydryl bromide.

All the products collected in Tables 1–3 were fully characterized by their IR, NMR and mass spectroscopic data (see Experimental Section). Typically, the benzhydryl proton (Ar_2CHNHR) appeared in the ^1H NMR spectra around $\delta = 6.1–6.3$ and $\delta = 5.3–5.5$ for the aminocarbonyl derivatives (R = COR″, Tables 1 and 2) and the aminoaryl derivatives (R = Aryl, Table 3) respectively. The coupling constant of this proton with the vicinal NH proton was 7.5–8.5 Hz and 0–4 Hz for the aminocarbonyl derivatives and the aminoaryl derivatives respectively; the corresponding NH chemical shifts were around $\delta = 6.3–7.5$ and 4.1–4.9. In the ^{13}C NMR spectra, the benzhydryl carbon atom (Ar_2CHNHR) gave a signal around $\delta = 56–59$ and $\delta = 63–64$ for the amide, carbamate and urea families, and the aniline family respectively.

In conclusion, our model study has shown that the direct coupling of functionalized carboxamides and anilines could represent an efficient and versatile strategy for PEEK-OH film derivatization; the method allows the fixation of various structural motifs able to modulate the hydrophilic/hydrophobic character of the polymer surface that strongly impacts on the bioadhesive properties of the derived culture substrates.[27–28] At the present time, some designed surface modifications of PEEK-OH films have been successfully performed according to this original methodology.

Melting points were determined with an Electrothermal microscope and are uncorrected. IR spectra were taken with a Perkin-Elmer 1710 instrument and calibrated with polystyrene, only the most significant and diagnostic adsorption bands being reported. The ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer (at 200 MHz and 50 MHz, respectively), in $CDCl_3$ (unless otherwise mentioned) with TMS as internal standard. MS were obtained on a Varian MAT44 instrument. Microanalyses were performed at the University College of London (Dr. Alan Stones, Christopher Ingold Laboratories). Compounds **2**, **4**, **6–8**, **11–27** gave satisfactory microanalyses C ± 0.65, H ± 0.45, N ± 0.43, except **16** C + 1.13.

Column chromatography was carried out with silica gel 60, 70–230 mesh ASTM supplied by Merck, and with neutral alumina (medium activity, 150 mesh) supplied by Aldrich. TLC were performed on silica gel or neutral alumina (type E) plates (Merck 60 F_{254}); product visualization was effected with UV light, iodine vapor, and a spray of permanganate solution [$KMnO_4$ (3 g), K_2CO_3 (20 g), HOAc (5 mL), water (300 mL)]. HPLC analyses were performed on Waters equipment including two pumps 600–6000, a Lambda-Max Model 481C spectrometer or 486 Tunable Absorbance detector (detection at 254 nm), and a Merck Hitachi D-2500 chromato-integrator. We used C_{18} reversed-phase columns from Vydac (model 218 TP 54 for analytical purposes and model 218 TP 152022 for semi-preparative purposes).

Glacial acetic acid p.a. was purchased from Janssen Chimica and used as received. Benzyl succinamate (Table 1, entry 9) was prepared from succinamic acid (1 equiv), BnBr (1 equiv) and Et_3N (1 equiv) in DMF for 5 h at 130 °C, and purified by column chromatography on neutral alumina (CH_2Cl_2/acetone, 75 : 25). All the other reagents of Tables 1–3 are commercially available from Aldrich and used as received. The solvents for chromatography were dried as usual and distilled.

Substitution of 4,4′-Dimethoxybenzhydrol with Amides, Lactams, Carbamates, Ureas and Anilines; General Procedure:

4,4′-Dimethoxybenzhydrol (**1**, 0.5 g, 2.04 mmol) dissolved in HOAc (10–15 mL) was treated with RNHR′ (1.1 to 2 equiv) and concd H_2SO_4 (25 μL), for 18–48 h at 20 °C with stirring (the product may precipitate). The mixture was poured into ice-cool water (120 mL); the product was filtered off and/or extracted with EtOAc (3 x 40 mL). The organic phase was washed with brine (2 x 40 mL), dried ($MgSO_4$) and concentrated under vacuum. If necessary, the residue was dissolved in CH_2Cl_2 (50 mL), washed with 5% $NaHCO_3$ (2 x 30 mL) and worked up as usual. Purification was effected by crystallization, column chromatography or HPLC. In the ^1H NMR spectra, the signals due to the 4-methoxyphenyl groups appeared at $\delta = 3.77–3.81$ (s, 6 H), 6.82–6.90 (d, 4 H, $J = 8.7$ Hz) and 7.12–7.24 (d, 4 H, $J = 8.7$ Hz); in the IR spectra, the aryl-O*Me* structure gave a typical band at 2830–2840 cm^{-1}.

N-(4,4′-Dimethoxybenzhydryl)formamide (**2**); purification by crystallization from i-PrOH.

IR (KBr): $\nu = 3282, 1658, 1611, 1536, 1510\ cm^{-1}$.

^1H NMR: $\delta = 6.10$ (br d, 1 H, N*H*CO), 6.23 (d, 1 H, $J = 8$ Hz, C*H*), 8.31 (s, 1 H, *H*CO).

^{13}C NMR: $\delta = 54.46, 55.22, 113.94, 128.40, 133.29, 158.83, 160.13$.

MS (EI): *m*/*z* (%) = 271 (100, M), 270 (44), 227 (35), 134 (34), 44 (36).

N-(4,4′-Dimethoxybenzhydryl)acetamide (**3**); purification by crystallization from CH_2Cl_2/Et_2O (1 : 5).

IR (KBr): ν = 3304, 1645, 1611, 1544 cm^{-1}.

^{1}H NMR: δ = 2.03 (s, 3 H), 6.15 (d, 1 H, J = 7.6 Hz, C*H*), 6.22 (d, 1 H, J = 7.6 Hz, N*H*CO).

^{13}C NMR: δ = 23.30, 55.22, 55.26, 113.88, 128.43, 133.91, 158.73, 168.95.

MS (EI): m/z (%) = 286 (M + 1, 25), 242 (3), 227 (61), 226 (100), 135 (10), 43 (4).

N-(4,4'-Dimethoxybenzhydryl)chloroacetamide (**4**); HPLC purification (MeOH/H$_2$O, 70:30; 19.8 mL/min; t_R 7.06 min).

IR (CH$_2$Cl$_2$): ν = 3405, 1670, 1610, 1580, 1500, 1175, 1030, 825 cm^{-1}.

^{1}H NMR: δ = 4.11 (s, 2 H), 6.16 (d, 1 H, J = 8.2 Hz, C*H*), 7.10 (br d, 1 H, N*H*CO).

^{13}C NMR: δ = 45.36, 57.96, 58.81, 116.82, 131.10, 135.83, 161.74, 167.51.

MS (EI): m/z (%) = 321 (M for ^{37}Cl, 9), 319 (M for ^{35}Cl, 27), 284 (100), 242 (15), 227 (27).

N-(4,4'-Dimethoxybenzhydryl)fluoroacetamide (**5**); purification by crystallization from CH$_2$Cl$_2$/Et$_2$O (1:5).

IR (KBr): ν = 3315, 1655, 1612, 1538 cm^{-1}.

^{1}H NMR: δ = 4.86 (d, 2 H, $J_{H\text{-}F}$ = 47.3 Hz), 6.23 (d, 1 H, J = 7.6 Hz, C*H*), 6.82 (d, 1 H, J = 7.6 Hz, CON*H*).

^{13}C NMR: δ = 55.02, 55.14, 80.15 (d, $J_{C\text{-}F}$ = 185.9 Hz), 113.91, 128.32, 133.01, 158.84, 166.41 (d, $J_{C\text{-}F}$ = 17.6 Hz).

MS (FAB): m/z = 304 ($C_{17}H_{18}FNO_3$ + 1).

Ethyl N-(4,4'-Dimethoxybenzhydryl)oxamate (**6**); HPLC purification (MeOH/H$_2$O, 70:30; 9.9 mL/min; t_R 18 min).

IR (neat): ν = 3325, 1730, 1690, 1605, 1580, 1505, 1455, 1240 cm^{-1}.

^{1}H NMR: δ = 1.38 (t, 3 H, J = 7.1 Hz), 4.34 (q, 2 H, J = 7.1 Hz), 6.17 (d, 1 H, J = 8.6 Hz, C*H*), 7.64 (d, 1 H, J = 8.6 Hz, CON*H*).

^{13}C NMR: δ = 15.98, 57.28, 58.27, 65.34, 116.11, 130.74, 134.76, 157.54, 161.13, 162.83.

MS (EI): m/z (%) = 343 (M, 15), 314 (7), 242 (100), 227 (45).

Benzyl N-(4,4'-Dimethoxybenzhydryl)succinamate (**7**); purification by column chromatography on neutral alumina (CH$_2$Cl$_2$/cyclohexane, 90:10).

IR (KBr): ν = 3319, 1732, 1642, 1612, 1537 cm^{-1}.

^{1}H NMR: δ = 2.53 (t, 2 H, J = 6.4 Hz), 2.73 (t, 2 H, J = 6.4 Hz), 5.10 (s, 2 H), 6.11 (d, 1 H, J = 7.7 Hz, C*H*), 6.28 (d, 1 H, J = 7.7 Hz, CON*H*), 7.32 (s, 5 H).

^{13}C NMR: δ = 29.73, 31.27, 55.29, 56.06, 66.54, 114.09, 128.10, 128.20, 128.50, 128.55, 134.08, 135.89, 158.96, 170.18, 172.73.

MS (EI): m/z (%) = 433 (M, 1), 279 (37), 271 (22), 242 (32), 227 (78), 167 (49), 149 (100), 135 (47).

N-(4,4'-Dimethoxybenzhydryl)succinamic Acid (**8**); purification by crystallization from CH$_2$Cl$_2$/hexane (1:3).

IR (CH$_2$Cl$_2$): ν = 3420, 1740, 1675, 1600, 1507, 1173, 1030 cm^{-1}.

^{1}H NMR: δ = 2.55 (m, 2 H), 2.70 (m, 2 H), 6.10 (d, 1 H, J = 7.9 Hz, C*H*), 6.29 (d, 1 H, J = 7.9 Hz, CON*H*).

^{13}C NMR: δ = 32.28, 33.44, 57.89, 58.89, 116.72, 131.16, 136.22, 161.56, 173.78, 179.09.

MS (EI): m/z (%) = 343 (M, 22), 325 (3), 299 (3), 284 (95), 242 (48), 227 (100).

N-(4,4'-Dimethoxybenzhydryl)-4-fluorobenzamide (**9**); purification by crystallization from CH$_2$Cl$_2$/Et$_2$O (1:3).

IR (KBr): ν = 3284, 1637, 1604, 1531 cm^{-1}.

^{1}H NMR: δ = 6.34 (d, 1 H, J = 7.6 Hz, C*H*), 6.64 (d, 1 H, J = 7.6 Hz, N*H*CO), 7.11 (dd, 2 H, J = 8.8 and 8.6 Hz), 7.83 (dd, 2 H, J = 8.8 and 5.3 Hz).

^{13}C NMR: δ = 55.27, 56.41, 114.02, 115.35 and 115.78 (two lines of d, $J_{C\text{-}F}$ = 21.9 Hz), 128.57, 129.30 and 129.48 (two lines of d, $J_{C\text{-}F}$ = 9.0 Hz), 130.38 and 130.45 (two lines of d, $J_{C\text{-}F}$ = 3.2 Hz), 133.70, 158.88, 162.23 and 167.24 (two lines of d, $J_{C\text{-}F}$ = 252 Hz), 165.36.

MS (EI): m/z (%) = 366 (M + 1, 12), 365 (M, 100), 242 (25), 227 (37), 226 (26), 139 (7), 134 (30), 123 (45).

N-(4,4'-Dimethoxybenzhydryl)-2,6-difluorobenzamide (**10**); Purification by crystallization from CH$_2$Cl$_2$/Et$_2$O (1:4).

IR (KBr): ν = 3251, 1641, 1550 cm^{-1}.

^{1}H NMR: δ = 6.37 (d, 1 H, J = 7.6 Hz, C*H*), 6.57 (d, 1 H, J = 7.6 Hz, N*H*CO), 6.94 (m, 2 H), 7.36 (m, 1 H).

^{13}C NMR: δ = 55.26, 56.50, 111.72 and 111.89 (two lines of d, J_{C-F} = 22.9 Hz), 111.77 and 112.23 (two lines of d, J_{C-F} = 22.9 Hz), 114.02, 128.59, 131.47, 131.88 and 131.67 (three lines of dd, J_{C-F} = 10.2 Hz and 10.3 Hz), 133.28, 157.44, 157.56, 162.47 and 162.59 (four lines of dd, J_{C-F} = 252.3 and 6.2 Hz), 158.09, 159.32.

MS (EI): m/z (%) = 384 (M + 1, 18), 383 (M, 100), 242 (25), 227 (38), 226 (35), 156 (3), 141 (58), 134 (30).

N-(4,4'-Dimethoxybenzhydryl)-4-trifluoromethylbenzamide (**11**); purification by column chromatography on silica gel (CH$_2$Cl$_2$/EtOAc, 90:10).

IR (KBr): ν = 3317, 1640, 1581, 1614, 1537 cm^{-1}.

^{1}H NMR: δ = 6.32 (d, 1 H, J = 7 Hz, C*H*), 6.74 (d, 1 H, J = 7 Hz, N*H*CO), 7.66 (d, 2 H, J = 7 Hz), 7.88 (d, 2 H, J = 7 Hz).

^{13}C NMR: δ = 55.29, 56.59, 114.09, 125.6 (q, $J_{C\text{-}F}$ = 3.9 Hz), 127.55, 128.56, 133.4, 137.51, 158.9, 165.25, CF_3-C (not visible).

MS (EI): m/z (%) = 415 (M, 47), 242 (19), 227 (100), 189 (2), 173 (25), 145 (15), 134 (24).

N-(4,4'-Dimethoxybenzhydryl)azetidin-2-one (**12**); purification by column chromatography on silica gel (CH$_2$Cl$_2$).

IR (film): ν = 1746, 1610, 1585, 1510, 1303, 1250, 1176, 1033 cm^{-1}.

^{1}H NMR: δ = 2.95 (t, 2 H, J = 4.1 Hz), 3.18 (t, 2 H, J = 4.1 Hz), 6.07 (s, 1 H, C*H*).

^{13}C NMR: δ = 35.57, 37.43, 54.95, 58.03, 119.73, 128.89, 131.01, 158.76, 166.96.

MS (EI): m/z (%) = 297 (M, 1.7), 281 (12), 220 (38), 205 (100), 151 (16), 115 (15), 86 (45), 84 (70).

N-(4,4'-Dimethoxybenzhydryl)pyrrolidin-2-one (**13**); purification by crystallization from *i*-Pr$_2$O.

IR (KBr): ν = 1663, 1611, 1510, 1421, 1324, 1300, 1278, 1250, 1173, 1031 cm^{-1}.

^{1}H NMR: δ = 2.01 (m, 2 H), 2.48 (t, 2 H, J = 7.9 Hz), 3.19 (t, 2 H, J = 7.0 Hz), 6.51 (s, 1 H, C*H*).

^{13}C NMR: δ = 18.12, 31.18, 44.06, 55.18, 57.42, 113.83, 129.48, 131.07, 158.9, 174.62.

MS (EI): m/z (%) = 311 (M, 100), 282 (24), 227 (40), 125 (15).

Methyl N-(4,4'-Dimethoxybenzhydryl)carbamate (**14**); purification by crystallization from *i*-PrOH.

IR (KBr): ν = 3338, 1694, 1614, 1532, 1511 cm^{-1}.

^{1}H NMR: δ = 3.67 (s, 3 H), 5.29 (br d, 1 H, OCON*H*), 5.87 (d, 1 H, J = 7.2 Hz, C*H*).

^{13}C NMR: δ = 52.2, 55.3, 57.85, 114.05, 129.33, 134.29, 156.2, 158.96.

MS (EI): m/z (%) = 301 (3, M), 272 (22), 227 (100), 180 (40), 107 (37), 91 (82).

Phenyl N-(4,4'-Dimethoxybenzhydryl)carbamate (**15**); purification by flash chromatography on silica gel (CH$_2$Cl$_2$/cyclohexane, 75:25) and crystallization from *i*-PrOH.

IR (CH$_2$Cl$_2$): ν = 2956, 1740, 1611, 1511, 1479, 1242 cm^{-1}.

^{1}H NMR: δ = 5.65 (br d, 1 H, OCON*H*), 5.95 (d, 1 H, J = 8.1 Hz, C*H*), 7.1–7.33 (m, 5 H).

^{13}C NMR: δ = 55.2, 58.1, 114.1, 121.5, 125.2, 128.4, 129.17, 134.86, 151.1, 153.7, 159.0.

MS (EI): m/z (%) = 363 (3, M), 269 (31), 227 (100), 94 (10), 45 (21).

1-(4,4'-Dimethoxybenzhydryl)urea (**16**); purification by precipitation from Et$_2$O/EtOAc (50:50).

IR (KBr): ν = 3355, 3324, 1627, 1563, 1509, 1461, 1303, 1253, 1176 cm^{-1}.

^{1}H NMR (CDCl$_3$ + 10% DMSO-d_6): δ = 4.90 (br s, 2 H), 5.95 (d, 1 H, J = 7 Hz, C*H*), 6.23 (d, 1 H, J = 7 Hz, N*H*CO).

^{13}C NMR (CDCl$_3$ + 10% DMSO-d_6): δ = 54.63, 55.26, 113.68, 130.18, 136.19, 156.57, 158.01.

1-(4,4'-Dimethoxybenzhydryl)-2-phenylurea (**17**); purification by column chromatography on silica gel (CH$_2$Cl$_2$/EtOAc, 50 : 50).

IR (KBr): ν = 3300, 1633, 1610, 1597, 1557, 1509, 1304, 1247, 1175 cm^{-1}.

^{1}H NMR: δ = 5.66 (m, 2 H), 5.95 (d, 1 H, J = 7 Hz, C*H*), 7.10–7.28 (m, 5 H).

MS (FAB): m/z = 363 (M + 1).

1-(4,4'-Dimethoxybenzhydryl)-1-phenylurea (**18**); purification by column chromatography on silica gel (CH$_2$Cl$_2$/EtOAc, 50 : 50).

IR (KBr): ν = 3500–3200, 1667, 1608, 1592, 1539, 1508, 1246, 1175, 1033 cm^{-1}.

^{1}H NMR: δ = 4.72 (br s, 2 H, N*H*$_2$), 5.38 (s, 1 H, C*H*), 7.00–7.23 (m, 5 H).

^{13}C NMR: δ = 56.59, 57.28, 115.70, 123.75, 132.16, 132.20, 138.25, 143.04, 158.76, 160.02.

MS (FAB): m/z = 363 (M + 1).

N-(4,4'-Dimethoxybenzhydryl)-4-fluoroaniline (**19**); HPLC purification (MeOH/H$_2$O, 70 : 30; 15 mL/min, t_R 15.85 min.).

IR (CH$_2$Cl$_2$): ν = 3405, 1603, 1580, 1500, 1420 cm^{-1}.

^{1}H NMR: δ = 4.06 (m, 1 H, N*H*), 5.34 (s, 1 H, C*H*), 6.40–6.52 (m, 2 H), 6.75–6.90 (m, 2 H).

^{13}C NMR: δ = 57.23, 64.27, 116.10, 116.31, 117.26 and 117.70 (two lines of d, $J_{C\text{-}F}$ = 22.2 Hz), 130.43, 137.26, 145.83, 155.46, and 160.14 (two lines of d, $J_{C\text{-}F}$ = 234.0 Hz), 160.83.

MS (EI): m/z (%) = 337 (M, 6), 335 (10), 242 (2), 227 (100).

N-(4,4'-Dimethoxybenzhydryl)-4-trifluoromethylaniline (**20**); purification by column chromatography on silica gel (CH$_2$Cl$_2$/cyclohexane, 90 : 10).

IR (neat): ν = 3400, 1610, 1585, 1520, 1505, 1320, 1240 cm^{-1}.

^{1}H NMR: δ = 4.45 (br s, 1 H, N*H*), 5.45 (br s, 1 H, C*H*), 6.53 (d, 2 H, J = 8.4 Hz), 7.35 (d, 2 H, J = 8.4 Hz).

^{13}C NMR: δ = 57.25, 63.36, 114.70, 116.23, 128.36, 128.44, 128.51 and 128.59 (four lines of q, $J_{C\text{-}F}$ = 3.9 Hz), 130.49, 136.44, 151.72, 161.02, CF_3-C (not visible).

MS (EI): m/z (%) = 387 (M, 5), 242 (3), 227 (100), 161 (10).

N-(4,4'-Dimethoxybenzhydryl)-4-nitroaniline (**21**); HPLC purification (MeOH/H$_2$O, 70 : 30; 9.9 mL/min; t_R 19.65 min).

IR (CH$_2$Cl$_2$): ν = 3415, 1600, 1580, 1500, 1465, 1320, 1170, 1110, 1030, 830 cm^{-1}.

^{1}H NMR: δ = 4.92 (d, 1 H, J = 4 Hz, N*H*), 5.54 (d, 1 H, J = 4 Hz, C*H*), 6.49 (d, 2 H, J = 9.1 Hz), 8.02 (d, 2 H, J = 9.1 Hz).

^{13}C NMR: δ = 57.27, 63.22, 114.10, 116.35, 118.01, 128.17, 130.46, 135.41, 154.13, 161.21.

MS (EI): m/z (%) = 364 (M, 3), 227 (100), 212 (6).

4-Cyano-N-(4,4'-dimethoxybenzhydryl)aniline (**22**); HPLC purification (MeOH/H$_2$O, 70 : 30; 9.9 mL/min; t_R 18.05 min).

IR (CH$_2$Cl$_2$): ν = 3410, 2200, 1600, 1580, 1510, 1430, 1325, 1260, 1167, 1030, 890 cm^{-1}.

^{1}H NMR: δ = 4.67 (d, 1 H, J = 4.4 Hz, N*H*), 5.47 (d, 1 H, J = 4.4 Hz, C*H*), 6.50 (d, 2 H, J = 8.7 Hz), 7.36 (d, 2 H, J = 8.7 Hz).

^{13}C NMR: δ = 57.96, 63.78, 101.95, 115.82, 116.26, 123.0, 131.11, 136.22, 136.48, 152.91, 161.78.

MS (EI): m/z (%) = 344 (M, 4), 343 (8), 342 (3), 242 (11), 227 (100).

Ethyl 4-(4,4'-Dimethoxybenzhydrylamino)benzoate (**23**); purification by column chromatography on silica gel (CH$_2$Cl$_2$/cyclohexane, 90 : 10).

IR (KBr): ν = 3980, 1682, 1602, 1511, 1460, 1440, 1393, 1367, 1332, 1285, 1245 cm^{-1}.

^{1}H NMR: δ = 1.33 (t, 3 H, J = 7.1 Hz), 4.28 (q, 2 H, J = 7.1 Hz), 4.58 (d, 1 H, J = 4.5 Hz, N*H*), 5.50 (d, 1 H, J = 4.5 Hz, N*H*), 6.50 (d, 2 H, J = 8.8 Hz), 7.80 (d, 2 H, J = 8.8 Hz).

^{13}C NMR: δ = 14.35, 55.18, 60.07, 61.04, 112.33, 114.12, 118.99, 128.45, 131.27, 134.34, 150.83, 158.93, 166.74.

MS (EI): m/z (%) = 391 (M, 1), 228 (12), 227 (100), 120 (5).

4-(4,4'-Dimethoxybenzhydrylamino)benzoic Acid (**24**); HPLC purification (MeOH/H$_2$O, 55 : 45; 19.8 mL/min; t_R 12.70 min).

IR (CH$_2$Cl$_2$): ν = 3480, 3410, 3200–2400, 1708, 1670, 1600, 1500, 1170, 1030, 835 cm^{-1}.

^{1}H NMR: δ = 4.65 (m, 1 H, N*H*), 5.52 (s, 1 H, C*H*), 6.50 (d, 2 H, J = 8.8 Hz), 7.85 (d, 2 H, J = 8.8 Hz).

^{13}C NMR: δ = 57.4, 63.73, 115.06, 116.88, 120.50, 131.18, 134.83, 136.89, 154.15, 161.66, 174.70.

MS (EI): m/z (%) = 344 (M – 18, 1), 258 (31), 242 (3), 227 (100).

4-(4,4'-Dimethoxybenzhydrylamino)benzamide (**25**); HPLC purification (MeOH/H$_2$O, 55 : 45; 19.8 mL/min; t_R 21.08 min).

IR (CH$_2$Cl$_2$): ν = 3670, 3505, 3400, 1660, 1600, 1590, 1500, 1360, 1325, 1170, 1030, 830 cm^{-1}.

^{1}H NMR: δ = 4.58 (br s, 1 H, N*H*), 5.49 (br s, 1 H, C*H*), 5.70 (m, 2 H, CON*H*$_2$), 6.52 (d, 2 H, J = 8.3 Hz), 7.59 (d, 2 H, J = 8.3 Hz).

^{13}C NMR: δ = 57.26, 63.20, 114.61, 116.18, 123.68, 130.49, 131.09, 136.42, 152.26, 160.95, 171.34.

MS (EI): m/z (%) = 362 (M, 0.25), 242 (100), 227 (22), 135 (22), 120 (6).

N-(4,4'-Dimethoxybenzhydryl)-4-diethylaminoaniline (**26**); purification by column chromatography on neutral alumina (CH$_2$Cl$_2$/cyclohexane, 90 : 10).

IR (neat): ν = 3396, 1610, 1585, 1510, 1464, 1442, 1340, 1302, 1285, 1175 cm^{-1}.

^{1}H NMR: δ = 1.05 (t, 6 H, J = 6.9 Hz), 3.17 (q, 4 H, J = 6.9 Hz), 4.20 (br s, 1 H, N*H*), 5.31 (br s, 1 H, C*H*), 6.49 (d, 2 H, J = 7.3 Hz), 6.64 (d, 2 H, J = 7.3 Hz).

^{13}C NMR: δ = 12.49, 45.87, 55.21, 62.69, 113.99, 114.91, 128.42, 136.09, 140.39, 158.69.

MS (FAB): m/z (%) = 400 (M + 1, 27), 390 (M, 62), 227 (100).

N-(4,4'-Dimethoxybenzhydryl)-4-phenoxyaniline (**27**); purification by flash chromatography on silica gel (CH$_2$Cl$_2$/cyclohexane, 50 : 50).

IR (film): ν = 3405, 1610, 1587, 1505, 1489, 1303, 1245, 1174, 1034 cm^{-1}.

^{1}H NMR: δ = 4.10 (br s, 1 H, N*H*), 5.37 (s, 1 H, C*H*), 6.50 (d, 2 H, J = 8.9 Hz), 6.80–7.00 (m, 5 H), 7.20–7.35 (m, 2 H).

^{13}C NMR: δ = 55.21, 62.29, 114.13, 114.46, 117.35, 120.82, 121.98, 128.44, 129.44, 135.47, 144.11, 147.97, 158.87.

MS (EI): m/z (%) = 411 (M, < 0.1), 272 (33), 227 (100), 185 (33), 169 (10), 149 (17), 135 (22).

Deprotection of *N*-(4,4'-Dimethoxybenzhydryl)anilines 19–27; General Procedure:

The *N*-(4,4'-dimethoxybenzhydryl)aniline (0.5 g) was dissolved in 33% HBr in HOAc (0.5 to 3 mL) and left for 30 min at r.t. with stirring. The excess HBr and HOAc was removed by azeotropic distillation under vacuum using toluene. Addition of dry Et$_2$O to the residue quantitatively precipitated the deprotected aniline as its hydrobromide salt, a material identical with the authentic sample prepared by addition of HBr to the corresponding aniline. Concentration of the ethereal layer gave 4,4'-dimethoxybenzhydryl bromide; yield: 95–100%.

^{1}H NMR: δ = 3.79 (s, 6 H, OC*H*$_3$), 6.31 (s, 1 H, C*H*Br), 6.85 (d, 4 H, J = 8.7 Hz, Ar), 7.38 (d, 4 H, J = 8.7 Hz, Ar).

MS (EI): m/z (%) = 308 and 306 ($C_{15}H_{15}BrO_2$).

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