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Activation of hydrocinnamic acids with pentafluorophenol *versus* pentafluorothiophenol: Reactivity towards hexylamine

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ABSTRACT

In this work we describe and compare the synthesis of four new hexylamides of hydrocinnamic acids, namely hexylamide of hydrocinnamic, 3,4-dimethoxyhydrocinnamic, 4-hydroxy-3-methoxyhydrocinnamic and 3,4-dihydroxyhydrocinnamic acids via pentafluorophenyl esters (PFPEs) *versus* pentafluorophenyl thioesters (PFPTs) intermediates. It was found that the PFPE are the best intermediates for this kind of synthesis giving reactions with less by products, easier work-up, higher overall yields and with the best reactivity towards hexylamine. The X-ray structures of two PFPE are also reported.

1. Introduction

Oxidative stress has been implicated in the pathophysiology of neurodegenerative diseases [1]. Since our endogenous antioxidant defenses are not always completely effective it seems reasonable to propose that exogenous antioxidants could be very effective in diminishing the cumulative effects of oxidative damage. However, the therapeutic use of most of the antioxidants investigated as therapeutic agents is limited since they do not cross the blood–brain barrier (BBB). Therefore, novel antioxidant molecules designed for potential neuroprotective treatment should have a high degree of lipophilicity in order to penetrate the BBB [1]. In this context we have designed and synthesised new lipophylic antioxidants, based on compounds with well-known antioxidant properties, by introducing an alkyl chain in hydrocinnamic acids via an amide bond. For this, several hexylamides have been prepared by different ways.

One way to perform amidation reactions is via carboxylic group activated intermediates, particularly active esters [2]. A commonly used active ester is the pentafluorophenyl ester (PFPE) [3–8], which is usually prepared from the reaction of a carboxylic acid with pentafluorophenol using a diimide, such as dicyclohexylcarbodiimide (DCC), as a coupling agent [3,4,7]. A valuable application of PFPE is in the peptide synthesis [3–5,9–12]. These active esters are relatively non-polar, stable to chromatographic purification and extended storage [4,9]. More recently, pentafluorophenyl thioesters (PFPT) were also shown to be good intermediates for the conversion of hindered acids in amides proving to be very good N-acylating agents in particular situations [13]. Nevertheless, very few papers describing the use of PFPT as intermediates for the synthesis of amides have been found in the literature [14,15].

In this work the above-mentioned methods have been explored throughout the study of carboxylic acid activation of several hydrocinnamic acids with pentafluorophenol (PFP) *versus* pentafluorothiophenol (PFTP). Accordingly, the reactivity of the activators towards a series of hydrocinnamic acids has been pointed out as well as the reactivity of the active esters towards hexylamine in order to produce the respective hexylamides.

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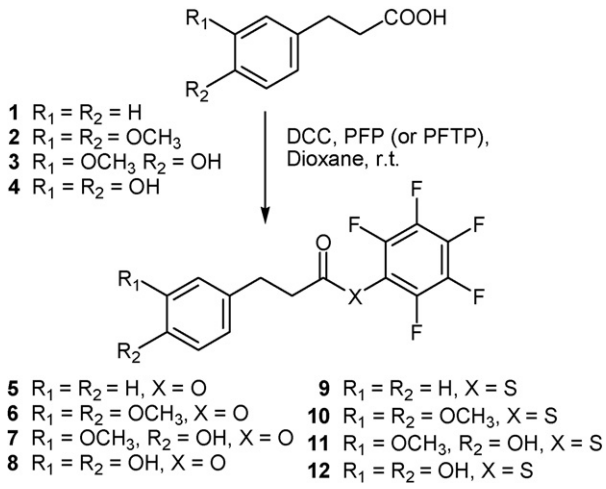
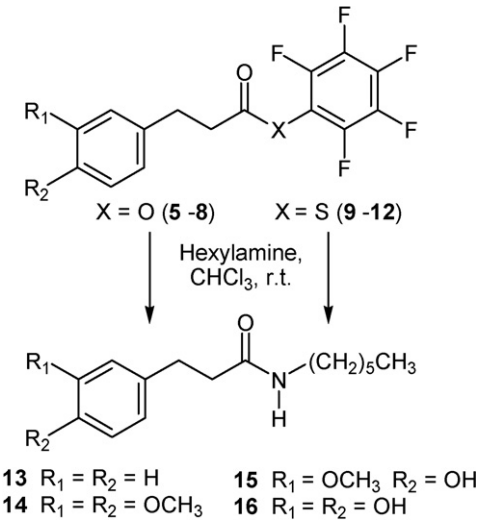


Scheme 1. Synthesis of PFPE **5**–**8** and PFPT **9**–**12**.



Scheme 2. Synthesis of hexylamides **13**–**16**.

2. Results and discussion

The synthesis of hexylamides (**13**–**16**) begins with the known hydrocinnamic acids (**1**–**4**) which are converted into the corresponding PFPE (**5**–**8**) and PFPT (**9**–**12**) by reaction with PFP or PFTP, respectively, and DCC, in dioxane, at room temperature (Scheme 1) [16]. Subsequent reaction of the active esters (**5**–**8**) and thioesters (**9**–**12**) with hexylamine, in chloroform, at room temperature provided the required hexylamides (**13**–**16**) (Scheme 2) [17].

Looking at Table 1, one can see that activation of hydrocinnamic acids with PFP occurs almost with the same reaction time as activation with PFTP. However, with PFP, the described reaction time corresponds to complete reactions whereas with PFTP corresponds to incomplete reactions. In fact, when using PFTP, it was possible to observe by TLC that after 1.5 h of activation for compound **1** and after 4 h of activation for compounds **2**, **3** and **4**, no more PFTP remained in reaction, in spite of had been used in excess. On the contrary, a lot of hydrocinnamic acid remained in reaction. This can be explained by the observation that after 1.5 or 4 h, respectively, the most part of the PFTP had been transformed in another product, which is visible on a TLC plate, and therefore the activation reaction cannot proceed anylonger. This product could result from PFTP decomposition (Supporting information).

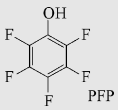
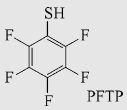
Concerning the yields of the activation reactions using PFP *versus* PFTP (Table 1) it is clear that PFP produces better yields than PFTP, when compared on the basis of pure reaction products. This was the expected result considering the existence of an incomplete reaction when using PFTP as pointed out in the previous discussion. Besides, the usual purification by column chromatography was insufficient to obtain the pure PFPT (**9**–**12**). Therefore, further purification by crystallisation was performed which lead to a dramatic decrease of the yield due to product degradation during this process. Compound **12** could not be further purified by crystallisation because it is oil and attempts to make a second chromatography result in complete degradation of the product. That is why the amount of product obtained after column chromatography is reported (Table 1).

It was also noted that the yields of PFPE and PFPT are higher as the number of hydroxyl groups in the aromatic ring is lower reaching the best yields for compounds **6** and **10**, the dimethoxy substituted PFPE and PFPT, respectively (Table 1). The absence of substituents as in the case of compounds **5** and **9** diminished the yield relatively to compounds **6** and **10**, respectively, showing some benefit with the presence of activating electron donor groups in the aromatic ring, for this kind of reactions. The hydroxyl groups being activating groups are very reactive substituents giving rise to reactions with more side products, whish appears reflected in the lower yields obtained for compounds **7**, **11** and **8**, **12**.

Compounds **5** [18], **8** [17], and **9** [19], had been previously synthesised, being **5** and **9** obtained by a different way.

Compounds **5**–**12** were fully characterised by physical and spectroscopic data. Particularly ^{19}F NMR pointed out the presence

Table 1
Reaction (Rx)–time and yield of reactions of hydrocinnamic acids (**1**–**4**) with PFP *versus* PFTP.

	 PFP			 PFTP		
Acids	Rx–time (h)	Yield (%)[a]	Product	Rx–time (h)[b]	Yield (%)[c,d]	Product
1	0.5	78	**5**	1.5	79/17	**9**
2	4	87	**6**	4	95/29	**10**
3	4	61	**7**	4	74/15	**11**
4	4	42	**8**	4	37/[e]	**12**

[a] Yield after column chromatography (one TLC spot).
[b] Incomplete reactions.
[c] Amount of product after column chromatography (not pure/TLC).
[d] Yield after column chromatography and crystallisation (one TLC spot).
[e] Not possible to purify due to product instability.

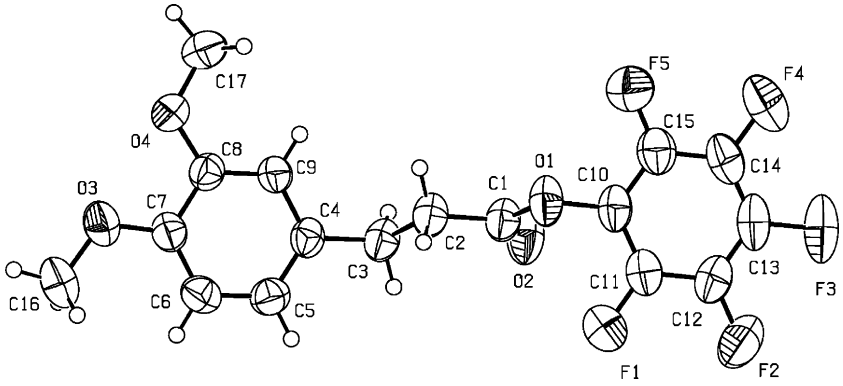


Fig. 1. ORTEP structure for PFPE **6**.

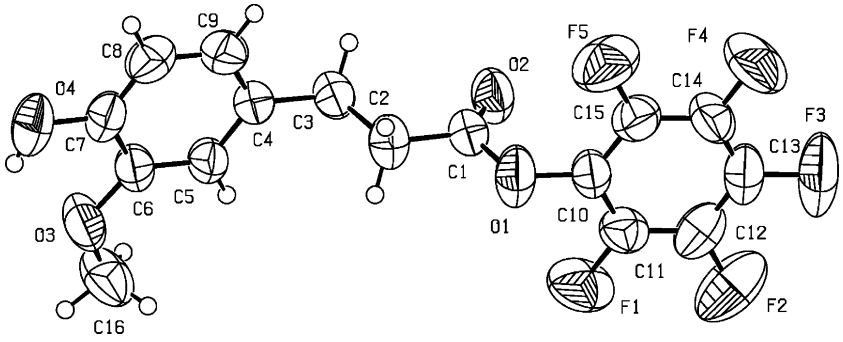


Fig. 2. ORTEP structure for PFPE **7**.

of five aromatic fluorine atoms in these compounds. In fact, the ^{13}C NMR signals of the carbon atoms in the pentafluorophenyl ring bearing the fluorine atoms are not easy to acquire, even by increasing the number of scans, using higher sample amounts or using a powerful 500 MHz NMR spectrometer. However, we include in Supporting information a representative ^{13}C NMR spectrum of compound **9** acquired along several hours in an almost saturated solution of $CDCl_3$ and using a 500 MHz NMR spectrometer. The complex splitting patterns due to the strong coupling between carbon and fluorine atoms significantly lowers the intensity of the ^{13}C NMR signals of the fluorinated carbons. In order to avoid this drawback, we investigate a ^{13}C double resonance fluorine decoupling technique applied to the representative compound **9** (Supporting information). This appears to be also a suitable technique to easily and rapidly acquire the ^{13}C signals of these carbon atoms that can be seen now as intense singlet peaks. Nevertheless, ^{19}F NMR still seems to be the right option to elucidate the structure of the pentafluorophenyl ring.

Compounds **6** and **7** were further studied by X-ray crystallography [20] (Figs. 1 and 2). Selected metric parameters are listed in Tables 2 and 3. Apart from the aromatic ring substituents, both molecules are very similar. The 3-methoxy group, common to compounds **6** and **7**, is located in different stereo positions, being towards the right of the molecule on **6** and towards the left on **7**. This is a consequence of the stereo position of the hydroxyl group of **7** leading to an intramolecular O4–H44–O3 hydrogen bond with an O4–O3 distance of 2.601(3) Å and an angle of 115.79°. In both

Table 2
Selected bond lengths and bond angles for **6**.

Bond	Bond length (Å)	Angle	Bond angle (°)
C1–C2	1.482 (4)	C4–C3–C2	113.4 (3)
C2–C3	1.515 (4)	C5–C4–C3	121.4 (3)
C3–C4	1.508 (4)	C10–C11–C12	120.5 (4)
C4–C9	1.399 (4)	C11–C10–C15	119.1 (3)
C6–C7	1.380 (5)	C7–O3–C16	117.8 (3)
C8–C9	1.378 (4)	C8–O4–C17	117.4 (3)
C10–C11	1.375 (5)	C10–O1–C1	115.6 (3)
C10–C15	1.383 (6)	O1–C1–C2	110.8 (3)
C14–C15	1.365 (5)	O1–C10–C11	121.0 (3)
C13–F3	1.347 (4)	O1–C10–C15	119.8 (3)
C1–O1	1.385 (4)	O2–C1–C2	128.1 (3)
C1–O2	1.186 (4)	O2–C1–O1	121.1 (3)
C8–O4	1.370 (4)	O3–C7–C6	124.8 (3)
C10–O1	1.375 (4)	O4–C8–C9	124.8 (3)
C17–O4	1.418 (5)	F1–C11–C10	119.8 (3)

Table 3
Selected bond lengths and bond angles for **7**.

Bond	Bond length (Å)	Angle	Bond angle (°)
C1–C2	1.486 (3)	C4–C3–C2	112.3 (2)
C2–C3	1.507 (3)	C5–C4–C3	119.9 (2)
C3–C4	1.511 (3)	C10–C11–C12	120.8 (2)
C4–C9	1.386 (3)	C11–C10–C15	118.7 (2)
C6–C7	1.384 (3)	C7–C8–O4	120.9 (2)
C8–C9	1.385 (4)	C6–O3–C16	118.5 (2)
C10–C11	1.370 (3)	C10–O1–C1	117.1 (2)
C10–C15	1.366 (3)	O1–C1–C2	109.8 (2)
C14–C15	1.366 (4)	O1–C10–C11	120.1 (2)
C13–F3	1.337 (3)	O1–C10–C15	121.1 (2)
C1–O1	1.378 (3)	O2–C1–C2	129.0 (2)
C1–O2	1.177 (3)	O2–C1–O1	121.3 (2)
C6–O3	1.368 (3)	O3–C6–C5	126.3 (2)
C10–O1	1.375 (3)	O3–C6–C7	113.4 (2)
C16–O3	1.409 (3)	F1–C11–C10	119.0 (2)

Table 4
Reaction (Rx)–time and yield of reactions of PFPE and PFPT with hexylamine and overall yield of amides (**13**–**16**) from hydrocinnamic acids (**1**–**4**).

Amides	PFPE (**5**–**8**)			PFPT (**9**–**12**)		
	Rx–time (min)	Yield (%)	Overall yield (calcd %)	Rx–time (min)	Yield (%)	Overall yield (calcd %)
13	15	69	54	10	59	10
14	30	75	65	15	56	16
15	15	99	60	10	68	10
16	15	90	38	10	74[a]	–[b]

[a] Decreased yield due to the impure starting material **12**.
[b] Not calculated due to absence of the partial yield of the previous reaction.

structures, the bond distances C1–O1 and C10–O1 (Figs. 1 and 2; Tables 2 and 3) are significantly different from the expected values [21], the first one being higher and the last one smaller, a fact also noticed in a similar pentafluorophenyl ester structure, previously reported by our group [22].

Considering now the preparation of the hexylamides **13**–**16** from PFPE *versus* PFPT (Table 4) it was possible to observe very short reaction times being even shorter from PFPT. Nevertheless, the yields are again 10–30% more favourable to PFPE. In this case, the yields increased from **13**, the amide with no substituents in the aromatic ring, to **16**, the amide with two hydroxyls in the aromatic ring, reaching 99% with the 4-hydroxy-3-methoxy substituted compound **15**. Once more, the presence of activating electron donor groups in the aromatic ring of active esters and thioesters is favourable to the amidation reaction. The short reaction time of these amidation reactions could prevent now the existence of undesirable side reactions involving the hydroxyl groups.

Concerning overall yields of amides from hydrocinnamic acids (Table 4) one can see the existence of the same pattern of yields observed in the preparation of PFPE and PFPT, that is an higher yield for the dimethoxy substituted compound **14** and a smaller yield for compounds with hydroxyl substituents, as **15** and **16**. This is due to the contribution of the partial yields of the activation reactions to the overall yields.

Compounds **13**–**16** were also fully characterised by physical and spectroscopic data. HRMS data have been obtained to support the molecular structure assignment.

Detailed results concerning antioxidant profiles of the prepared lipophilic amides will be reported elsewhere.

3. Conclusion

In summary, four new amides have been synthesised using active esters (PFPE and PFPT) as well as eight intermediate esters and thioesteres (**5**–**12**). It was possible unequivocally conclude that PFPE are the best intermediates for the kind of synthesis and the kind of compounds studied because they gave rise to reactions with less by products, easier work-up, and higher overall yields. In addition, they disclose the best reactivity towards the nucleophilic hexylamine. They are also more stable than PFPT, particularly when phenol groups are present. The existence of activating electron donor groups in the aromatic ring of PFPE and PFPT seems to be favourable to the amidation reaction. In addition, two new PFPE have been studied by X-ray crystallography.

4. Experimental

Mps were determined on a Reichert Thermopan hot block apparatus and were not corrected. IR spectra were recorded on a Jasco 420FT-IR spectrometer. The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at 300, 75.6 and 282.4 MHz, respectively, on a Bruker-AMX 300 spectrometer. Chemical shifts were recorded in δ values (ppm) downfield from TMS as internal standard for ^{1}H and ^{13}C and upfield from $CFCl_3$ as internal standard for ^{19}F NMR. The HRMS analyses were made on a QTof instrument from Applied Biosystems using the electrospray technique. X-ray diffraction analysis of **6** and **7** was measured using a MACH-3 Nonius diffractometer.

Chemicals were purchased from Sigma, Aldrich and Fluka and used as supplied by the manufacturers. Solvents were dried, when referred, according described procedures.

Activation reaction of hydrocinnamic acids were also performed in other experimental conditions particularly in which concern temperature (beginning the reaction at 0 °C) and the use of an inert atmosphere (N_2), but with similar results.

4.1. General procedure to obtain the PFPE (5–8) and PFPT (9–12)

A mixture of the hydrocinnamic acid (3.5 mmol), DCC (849 mg, 4 mmol), and pentafluorophenol or pentafluorothiophenol (743 mg, 4 mmol or 0.6 ml, 4.4 mmol, respectively), in anhydrous dioxane (15 ml) was stirred at room temperature during 4 h (unless specified). After this time, the mixture was cooled to 0 °C, and dicyclohexylurea was separated and removed by filtration. The filtrate was taken to dryness and the residue was subjected to flash column chromatography (silica gel 60 – particle size: 0.040–0.063 mm) to provide the PFPE as solids and the PFPT as solids or, in case of **12**, as oil.

4.2. Pentafluorophenyl 3-phenylpropanoate (5)

Reaction time: 0.5 h; chromatography solvent: petroleum ether (PE)/Et_2O 9:1. Yield 855 mg, 78%: mp 31–32 °C; IR (ATR): ν 1778 (C=O), 1514, 1454, 984 cm^{-1}; ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 7.32–7.30 (m, 5H, Ar-H), 3.15 (t, J = 7.0 Hz, 2H, CH_2), 3.01 (t, J = 7.0 Hz, 2H, CH_2); ^{13}C NMR (75.4 MHz, Me_2SO-d_6): δ 168.9, 139.5, 128.4 (2C), 128.2 (2C), 126.3, 33.9, 29.8; ^{19}F NMR (282.4 MHz, Me_2SO-d_6): δ-176.8 (d, J = 25 Hz, 2F), −181.5 (t, J = 23 Hz, 1F), −186.0 to −186.2 (m, 2F).

4.3. Pentafluorophenyl 3-(3,4-dimethoxyphenyl)propanoate (6)

Chromatography solvent: PE/$CHCl_3$ 7:3. Yield 1.14 g, 87%: mp 72–73 °C; IR (ATR): ν 1791 (C=O), 1512, 1463, 986 cm^{-1}; ^{1}H NMR (300 MHz, Me_2SO-d_6): δ 6.92–6.80 (m, 3H, Ar-H), 3.74 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.09 (t, J = 7.0 Hz, 2H, CH_2), 2.92 (t, J = 7.0 Hz, 2H, CH_2); ^{13}C NMR (75.4 MHz, Me_2SO-d_6): δ 168.9, 148.6, 147.3, 131.9, 120.0, 112.1, 111.7, 55.4, 55.3, 34.2, 29.5; ^{19}F NMR (282.4 MHz, Me_2SO-d_6): δ −176.9 (dd, J = 23 Hz, J = 3 Hz, 2F), −181.5 (t, J = 24 Hz, 1F), −186.0 to −186.2 (m, 2F); HRMS: m/z $[M+Na]^+$ calcd for $C_{17}H_{13}F_5O_4$: 399.0626; found: 399.0632.

4.4. Pentafluorophenyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (7)

Chromatography solvent: PE/Et_2O 7:3. Yield 763 mg, 61%: mp 96–97 °C; IR (ATR): ν 3522 (O–H), 1793 (C=O), 1517, 1455, 986 cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6): δ 8.78 (br s, 1H, OH), 6.88–6.68 (m, 3H, Ar-H), 3.75 (s, 3H, OCH_3), 3.09 (t, J = 7.4 Hz, 2H, CH_2), 2.89 (t, J = 7.4 Hz, 2H, CH_2); ^{13}C NMR (75.4 MHz, Me_2SO-d_6): δ 169.0, 147.4, 144.9, 130.2, 120.3, 115.3, 112.4, 55.4, 34.4, 29.6; ^{19}F NMR (282.4 MHz, Me_2SO-d_6): δ −176.9 (dd, J = 23 Hz, J = 3 Hz, 2F), −181.6 (t, J = 24 Hz, 1F), −186.1 to −186.2 (m, 2F); HRMS: m/z $[M+Na]^+$ calcd for $C_{16}H_{11}F_5O_4$: 385.0469; found: 385.0471.

4.5. Pentafluorophenyl 3-(3,4-dihydroxyphenyl)propanoate (8)

Chromatography solvent: PE/Et_2O 6:4. Yield 502 mg, 42%: mp 74–75 °C; IR (ATR): ν 3466 (O–H), 1759 (C=O), 1517, 1450, 985 cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6): δ 8.77 (s, 1H, OH), 8.75 (s, 1H, OH), 6.66–6.50 (m, 3H, Ar-H), 3.02 (t, J = 7.3 Hz, 2H, CH_2), 2.82 (t, J = 7.3 Hz, 2H, CH_2); ^{13}C NMR (75.4 MHz, Me_2SO-d_6): δ 168.9, 145.1, 143.7, 130.3, 118.8, 115.7, 115.4, 34.5, 29.4; ^{19}F NMR (282.4 MHz, Me_2SO-d_6): δ −176.7 (dd, J = 25 Hz, J = 3 Hz, 2F), −181.6 (t, J = 23 Hz, 1F), −186.1 to −186.3 (m, 2F).

4.6. S-Pentafluorophenyl 3-phenylpropanethioate (9)

Reaction time: 1.5 h; chromatography solvent: PE. Amount of product obtained: 913 mg, 79%; further purification by crystallisation (*n*-hexane) gave 197 mg, 17% of yield: mp 67–68 °C; IR (ATR): ν 1728 (C=O), 1642, 1510, 1484, 963 cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6): δ 7.30–7.18 (m, 5H, Ar-H), 3.23 (t, J = 7.4 Hz, 2H, CH_2), 2.94 (t, J = 7.4 Hz, 2H, CH_2); ^{13}C NMR (75.4 MHz, Me_2SO-d_6): δ 173.7, 140.8, 128.3 (2C), 128.2 (2C), 125.9, 35.2, 30.0; ^{19}F NMR (282.4 MHz, Me_2SO-d_6): δ −156.1 to −156.2 (m, 2F), −171.6 (t, J = 23 Hz, 1F), −183.5 to −183.7 (m, 2F).

4.7. S-Pentafluorophenyl 3-(3,4-dimethoxyphenyl)propanethioate (10)

Chromatography solvent: PE/$CHCl_3$ 6:4. Amount of product obtained: 1.26 g, 92%; further purification by crystallisation (Et_2O) gave 397 mg, 29% of yield: mp 68–69 °C; IR (ATR): ν 1728 (C=O), 1641, 1510, 1484, 963 cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6): δ 6.89–6.74 (m, 3H, Ar-H), 3.74 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.21 (t, J = 7.4 Hz, 2H, CH_2), 2.88 (t, J = 7.4 Hz, 2H, CH_2); ^{13}C NMR (75.4 MHz, Me_2SO-d_6): δ 173.9, 148.5, 147.0, 133.3, 119.9, 112.1, 111.7, 55.4, 55.3, 35.5, 30.0; ^{19}F NMR (282.4 MHz, Me_2SO-d_6): δ −156.1 to −156.2 (m, 2F), −171.6 (t, J = 23 Hz, 1F), −183.5 to −183.8 (m, 2F); HRMS: m/z $[M+Na]^+$ calcd for $C_{17}H_{13}F_5O_3S$: 415.0397; found: 415.0408.

4.8. S-Pentafluorophenyl 3-(4-hydroxy-3-methoxyphenyl) propanethioate (11)

Chromatography solvent: PE/Et_2O 7:3. Amount of product obtained: 974 mg, 74%; further purification by crystallisation (Et_2O) gave 197 mg, 15% of yield: mp 82–83 °C; IR (ATR): ν 3485 (O–H), 1723 (C=O), 1643, 1517, 1455, 959 cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6): δ 8.78 (s, 1H, OH), 6.84–6.61 (m, 3H, Ar-H), 3.75 (s, 3H, OCH_3), 3.18 (t, J = 7.4 Hz, 2H, CH_2), 2.85 (t, J = 7.4 Hz, 2H, CH_2); ^{13}C NMR (75.4 MHz, Me_2SO-d_6): δ 173.9, 147.3, 144.6, 131.6, 120.2, 115.2, 112.4, 55.5, 35.7, 30.0; ^{19}F NMR (282.4 MHz, Me_2SO-d_6): δ −156.1 to −156.2 (m, 2F), −171.6 (t, J = 23 Hz, 1F), −183.5 to −183.7 (m, 2F).

4.9. S-Pentafluorophenyl 3-(3,4-dihydroxyphenyl)propanethioate (12)

Chromatography solvent: PE/Et_2O 5:5. Amount of product obtained: 466 mg, 37%, as oil. IR (NaCl plates): ν 3427 (O–H), 1719 (C=O), 1639, 1514, 1455, 963 cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6): δ 8.74 (s, 1H, OH), 8.71 (s, 1H, OH), 6.61–6.42 (m, 3H, Ar-H), 2.98 (t, J = 7.3 Hz, 2H, CH_2), 2.65 (t, J = 7.3 Hz, 2H, CH_2); ^{19}F NMR (282.4 MHz, Me_2SO-d_6): δ −156.1 to −156.2 (m, 2F), −171.5 (t, J = 23 Hz, 1F), −183.6 to −183.7 (m, 2F).

Note: Due to the instability of compound **12** it was not possible to obtain satisfactory ^{13}C NMR spectra.

4.10. General procedure to obtain the hexylamides (13–16) from PFPE or PFPT

A solution of PFPE or PFPT (0.35 mmol), hexylamine (0.1 ml; 0.75 mmol) in $CHCl_3$ (2 ml) was stirred at room temperature for 15 min (unless specified). After this time, the mixture was cooled and the ammonium salt formed was separated by filtration. The filtrate was taken to dryness and the residue was subjected to flash column chromatography (silica gel 60 – particle size: 0.040–0.063 mm) to provide the hexylamides as white solids or, in one case, as oil.

4.11. N-Hexyl-3-phenylpropanamide (13)

From PFPE: chromatography solvent: $CHCl_3$/EtOAc 9:1; yield: 56 mg, 69%.

From PFPT: chromatography solvent: $CHCl_3$/EtOAc 9:1; yield: 48 mg, 59%.

Mp 29–30 °C; IR (ATR): ν 3316 (N–H stretch), 1635 (C=O), 1539 (N–H bend) cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6): δ 7.78 (t, J = 5.1 Hz, 1H, NH) 7.29–7.14 (m, 5H, Ar-H) 3.04–2.97 (m, 2H, $NHCH_2$) 2.80 (t, J = 7.7 Hz, 2H, CH_2) 2.34 (t, J = 7.7 Hz, 2H, CH_2) 1.35–1.20 (m, 8H, $4CH_2$) 0.86 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75.47 MHz, Me_2SO-d_6): δ 171.0, 141.3, 128.2 (4C), 125.8, 38.4, 37.0, 31.1, 31.0, 29.1, 26.0, 22.0, 13.9; HRMS: m/z $[M+H]^+$ calcd for $C_{15}H_{23}NO$: 234.1857; found: 234.1859.

4.12. N-Hexyl-3-(3,4-dimethoxyphenyl)propanamide (14)

From PFPE: chromatography solvent: $CHCl_3$/EtOAc 7:3; yield: 77 mg, 75%.

From PFPT: chromatography solvent: $CHCl_3$/EtOAc 7:3; yield: 57 mg, 56%.

Mp 58–59 °C; IR (ATR): ν 3298 (N–H stretch), 1636 (C=O), 1547 (N–H bend) cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6): δ 7.76 (t, J = 5.2 Hz, 1H, NH), 6.83–6.79 (m, 2H, Ar-H), 6.68 (dd, J = 8.1 Hz, J = 1.6 Hz, 1H, Ar-H), 3.72 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.03–2.97 (m, 2H, $NHCH_2$), 2.73 (t, J = 7.6 Hz, 2H, CH_2), 2.32 (t, J = 7.6 Hz, 2H, CH_2), 1.35–1.21 (m, 8H, $4CH_2$), 0.85 (t, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75.47 MHz, Me_2SO-d_6): δ 171.1, 148.5, 146.9, 133.8, 119.9, 112.1, 111.7, 55.4, 55.3, 38.4, 37.3, 31.0, 30.7, 29.1, 26.0, 22.0, 13.9; HRMS: m/z $[M+H]^+$ calcd for $C_{17}H_{27}NO_3$: 294.2069; found: 294.2068.

4.13. N-Hexyl-3-(4-hydroxy-3-methoxyphenyl)propanamide (15)

From PFPE: chromatography solvent: $CHCl_3$/EtOAc 6:4; yield: 97 mg, 99%.

From PFPT: chromatography solvent: $CHCl_3$/EtOAc 6:4; yield: 66 mg, 68%.

Mp 81–82 °C; IR (ATR): ν 3514 (O–H), 3295 (N–H stretch), 1635 (C=O), 1545 (N–H bend) cm^{-1}; ^1H NMR (300 MHz, Me_2SO-d_6): δ

8.68 (s, 1H, OH), 7.75 (t, J = 5.4 Hz, 1H, NH), 6.74 (d, J = 1.7 Hz, 1H, Ar-H), 6.64 (d, J = 7.9 Hz, 1H, Ar-H), 6.56 (dd, J = 8.0 Hz, J = 1.8 Hz, 1H, Ar-H), 3.73 (s, 3H, OCH_3), 3.04–.97 (m, 2H, $NHCH_2$), 2.69 (t, J = 7.7 Hz, 2H, CH_2), 2.30 (t, J = 7.7 Hz, 2H, CH_2), 1.36–1.20 (m, 8H, $4CH_2$), 0.86 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75.47 MHz, Me_2SO-d_6): δ 171.2, 147.3, 144.5, 132.1, 120.2, 115.1, 112.3, 55.4, 38.4, 37.5, 31.0, 30.8, 29.1, 26.0, 22.0, 13.9; HRMS: m/z $[M+H]^+$ calcd for $C_{16}H_{25}NO_3$: 280.1912; found: 280.1913.

4.14. N-Hexyl-3-(3,4-dihydroxyphenyl)propanamide (16)

From PFPE: chromatography solvent: $CHCl_3$/EtOAc 4:6; yield: 83 mg, 90%, as oil.

From PFPT: chromatography solvent: $CHCl_3$/EtOAc 4:6; yield: 69 mg, 74%, as oil.

IR (NaCl plates): ν 3319 (O–H and N–H stretch), 1628 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, Me_2SO-d_6) δ 8.6 (s, 2H, OH) 7.74 (t, J = 5.5 Hz, 1H, NH), 6.61–6.55 (m, 2H, Ar-H), 6.41 (dd, J = 8 Hz, J = 2.0 Hz, 1H, Ar-H) 3.03–2.97 (m, 2H, $NHCH_2$), 2.61 (t, J = 7.7 Hz, 2H, CH_2), 2.25 (t, J = 7.7 Hz, 2H, CH_2), 1.37–1.20 (m, 8H, $4CH_2$), 0.86 (t, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR (75.47 MHz, Me_2SO-d_6): δ 171.2, 144.9, 143.2, 132.1, 118.6, 115.6, 115.3, 38.4, 37.5, 31.0, 30.6, 29.1, 26.1, 22.0, 13.9; HRMS: m/z $[M+H]^+$ calcd for $C_{15}H_{23}NO_3$: 266.1750; found: 266.1748.

4.15. X-ray crystallographic data for 6

Suitable crystals were obtained as thin needles from the slow evaporation of a Et_2O solution. $C_{17}H_{13}F_5O_4$; colourless, cubic; FW = 376.27; monoclinic, space group P21 (No. 4); a = 9.0835(11), b = 8.3577(8), c = 11.0398(5) Å; α = 90, β = 98.780(7), γ = 90°; V = 828.29(13) Å^3; Z = 2; D_{calc} = 1.509 g cm^{-3}, F(000) = 384; μ (Cu Kα) = 1.266 mm^{-1}; T = 293 K; direct methods (Shelxs) for structure solution.

4.16. X-ray crystallographic data for 7

Suitable crystals were obtained as thin needles from the slow evaporation of a Et_2O solution. $C_{16}H_{11}F_5O_4$; colourless, prism; FW = 362.25; monoclinic, space group P21/n (No. 14); a = 10.0240(9), b = 15.0869(13), c = 10.2681(5) Å; α = 90, β = 93.007(8), γ = 90°; V = 1550.7(2) Å^3; Z = 4; D_{calc} = 1.552 g cm^{-3}, F(000) = 736; μ (Cu Kα) = 1.329 mm^{-1}; T = 293 K; direct methods (Shelxs) for structure solution.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2008.09.013.

References

[1] B. Halliwell, Drugs Aging 18 (2001) 685–716.
[2] P.D. Bailey, I.D. Collier, K.M. Morgan, Amides, in: C.J. Moody (Ed.), Comprehensive Organic Functional Group Transformations, vol. 5, Pergamon, Cambridge, 1995, pp. 257–391.
[3] T.E. Stevens, W.H. Graham, J. Am. Chem. Soc. 89 (1967) 183–184.
[4] M. Green, J. Berman, Tetrahedron Lett. 31 (1990) 5851–5852.
[5] S.P. East, M.M. Joullie, Tetrahedron Lett. 39 (1998) 7211–7214.
[6] K.H. Lee, S.S. Yoon, Bull. Korean Chem. Soc. 28 (2007) 136–138.
[7] E. Boyd, S. Chavda, J. Eames, Y. Yohannes, Tetrahedron: Asym. 18 (2007) 476–482.
[8] N. Vogel, P. Théato, Macromol. Symp. (2007) 383–391.
[9] P. Watts, C. Wiles, S.J. Haswell, E. Pombo-Villar, P. Styring, Chem. Commun. (2001) 990–991.
[10] U. Schmidt, J. Langner, J. Chem. Soc., Chem. Commun. (1994) 2381–2382.
[11] J. Deng, Y. Hamada, T. Shioiri, Tetrahedron Lett. 37 (1996) 2261–2264.
[12] R. Ramesh, S. Rajasekaran, R. Gupta, S. Chandrasekaran, Org. Lett. 8 (2006) 1933–1936.
[13] A.P. Davis, J.J. Walsh, Tetrahedron Lett. 35 (1994) 4865–4868.
[14] A.P. Davis, J.J. Walsh, Chem. Commun. (1996) 449–451.
[15] A.P. Davis, S. Menzer, J.J. Walsh, D.J. Williams, Chem. Commun. (1996) 453–455.
[16] H. Zhao, N. Neamati, A. Mazumder, S. Sunder, Y. Pommier, T.R. Burke Jr., J. Med. Chem. 40 (1997) 1186–1194.
[17] T.R. Burke Jr., M.R. Fesen, A. Mazumder, J. Wang, A.M. Carothers, D. Grunberger, J. Driscoll, K. Kohn, Y. Pommier, J. Med. Chem. 38 (1995) 4171–4178.
[18] L.A. Cohen, S. Takahashi, J. Am. Chem. Soc. 95 (1973) 443–448.
[19] H. Nambu, K. Hata, M. Matsugi, Y. Kita, Chem. Eur. J. 11 (2005) 719–727.
[20] CCDC 675578 and 675579, contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdcc.uk/conts/retrieving.html.
[21] F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen, R. Taylor, J. Chem. Soc., Perkin Trans. 2 (1987) S1–S2.
[22] L.C.R. Andrade, J.A. Paixão, M.J.M. Almeida, E.J. Tavares da Silva, F.M.F. Roleira, Acta Cryst. E62 (2006) o193–o194.