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# A One-Pot Synthesis of Fluoro α-Acylamino Amide-Xanthates Via An IMCR-Post Transformation Strategy †

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**Abstract:** A series of six novel amide-xanthate products containing several fluorine atoms were prepared in moderate to good yields (40–92%) via a isocyanide based multicomponent reaction (IMCR) of 5-CR by Ugi-4CR followed by $S_N2$ sequence in one pot manner. The design of molecules with fluorine atoms is of interest in medicinal chemistry and a research line of our interest. The role of fluorine atoms in biological properties is well documented, improving bioavailability, lipophilicity, and metabolic resistance in bioactive molecules.

**Keywords:** Multicomponent reaction; amide-xanthates; heterocycle peptidomimetics; fluorine atoms

## 1. Introduction

Multicomponent reactions (MCRs) are defined as reactions in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product and there have many advantages over traditional multi step sequential [1]. Among the MCRs, the isocyanide based multicomponent reactions (IMCRs) are most relevant for the synthesis of peptidomimetics. The Ugi four-component reaction (Ugi-4CR) are probably one of the most utilized IMCRs during the last decade, this reaction allows the rapid preparation of α-acylamino amides derivatives. Ugi-4CR products can exemplify a wide variety of substitution patterns and are precursors to the synthesis of peptidomimetics that have potential pharmaceutical applications [2].

The role of fluorine atoms in organic compounds to improve bioavailability, lipophilicity and metabolic resistance in bioactive molecules is well-documented [3]. Therefore, the synthesis of fluoro α-acylamino amides as a synthetic platform can be an important alternative for the synthesis of heterocycles of interest in medical chemistry.

On the other hand, xanthate is an interesting functional group and has synthetic potential from radical chemistry [4]. Therefore, the one-pot incorporation of this functional group after an IMCR is an interesting strategy for the synthesis of privileged heterocyclic peptidomimetics (PHPs) via post-MCR transformation. Examples of these are azaspirodienones (1), oxindoles (2), tetrazol-azepinoindolones (3) [5–7].

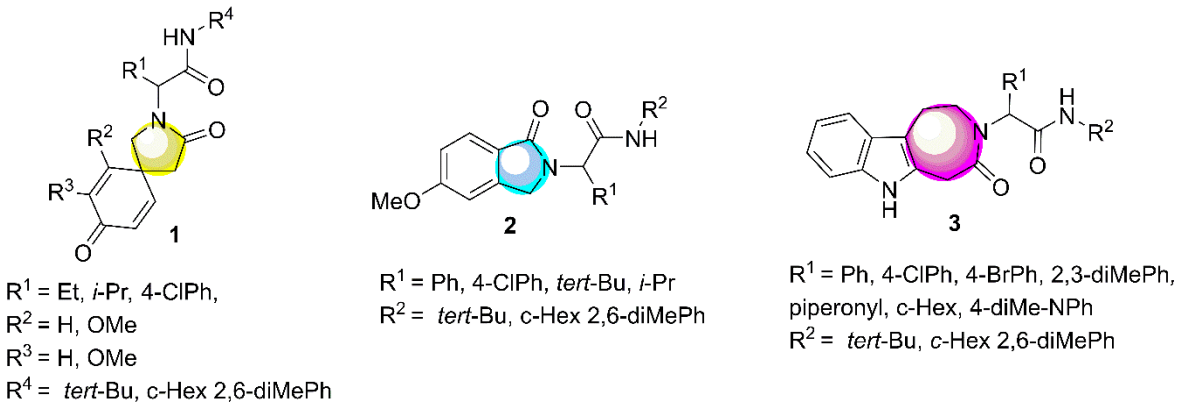
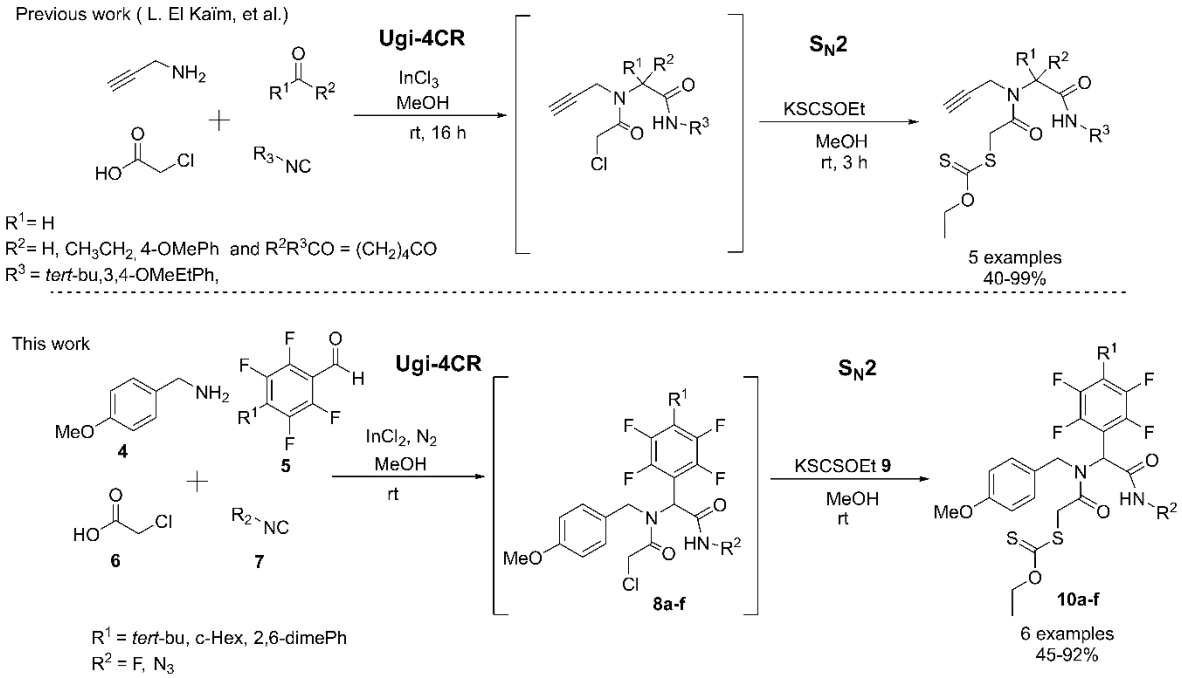



**Figure 1.** Some PHPs synthesized via post-MCR transformation from xanthates.

The conventional synthesis of xanthates involves the use of alcohols, $CS_2$ and alkyl halides with a strong base as hydroxide, which is particularly problematic it is also a substantial nucleophile, capable of hydrolyzing numerous functionalities, and it is generally restricted to alkyl substituents (see Scheme 1) [8]. The most effective methodologies for the synthesis of complex xanthates is using an IMCR followed by $S_N2$ with potassium ethyl xanthogenate salt (see Scheme 1) [5–7,9].

The methodology described here allow us the one-pot synthesis via Ugi-4CR coupled $S_N2$ strategy of fluoro $\alpha$-acylamino amide-xanthates (10a–f). These complex xanthate products are important precursors for the synthesis of PHP products (Scheme 1).



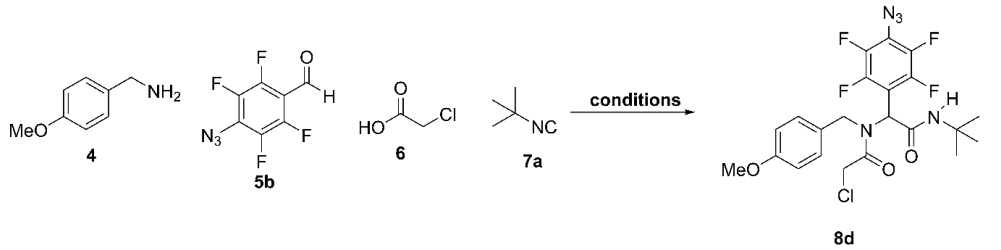

**Scheme 1.** Previous works and this work.

## 2. Results and Discussion

In order to develop conditions for the synthesis of $\alpha$-acylamino amide-xanthates, we started the optimization for the synthesis of $\alpha$-acylamino amide analogue 8d by reacting 4-methoxybenzylamine (4), 4-azido-2,3,5,6-tetrafluorobenzaldehyde (5), chloroacetic acid (6) and *tert*-butyl isocyanide (7) in methanol anhydrous. Initially we performed the Ugi-4CR at room temperature, in the absence of catalyst, the 8d product was generated in 72% after 7 days (Entry 1, Table 1). The success of the Ugi-4CR lies in the formation of the imine, which was favored by Lewis acids. When 10 mol% $InCl_3$ was employed as catalyst the 8d was obtained in 35% of yield after 3h of reaction time (Entry 2). The yield

was increased, when the reaction was performed during 24 h, the yield was of 66%. (Entry 3). The use of MW does not lead to the desired product, the reaction did not show significant progress after one hour at 50 °C (Entry 4). The best reaction conditions were obtained when 20% mol of InCl3 and 1.4 equiv. carboxylic acid, after 24 h of reaction at room temperature (Entry 5).

**Table 1.** Reaction optimizing conditions 8d.

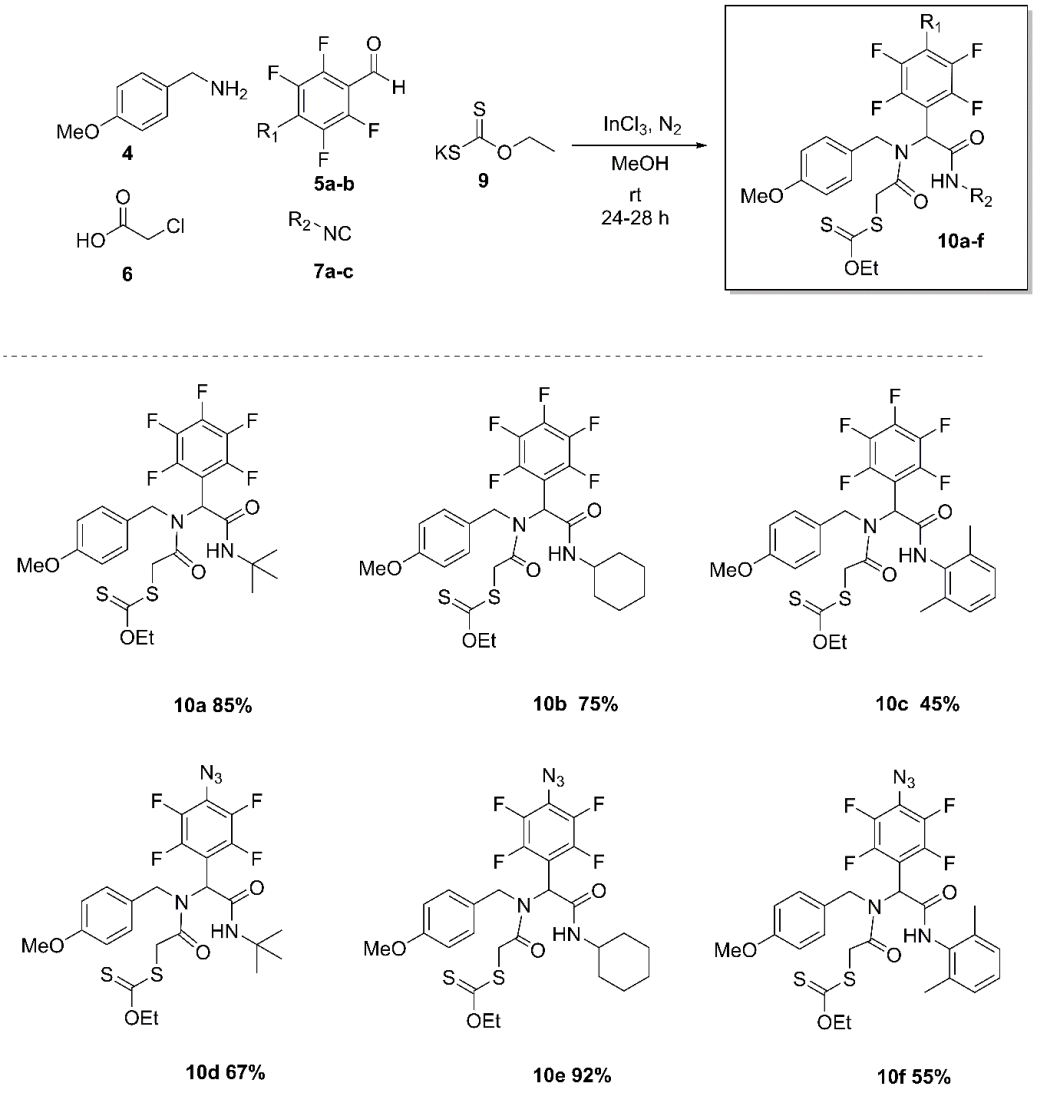



| Entry | Solvent [c] | Additive | T (°C) | Time | Yield (%) [f] |
|---|---|---|---|---|---|
| 1 [a] | MeOH | --- | rt | 7 days | 72 |
| 2 [a] | MeOH | $InCl_3$ [d] | rt | 3 h | 35 |
| 3 [a] | MeOH | $InCl_3$ [d] | rt | 24 h | 66 |
| 4 [a] | MeOH | $InCl_3$ [d] | 50 °C MW | 1 h | nd |
| 5 [b] | MeOH | $InCl_3$ [e] | rt | 24 h | 75 |

[a] Reactions performed with 1.0 equiv. 4-methoxybenzylamine (4), 1.0 equiv. of 4-azido-2,3,5,6-tetrafluorobenzaldehyde (5b), 1.0 equiv. of chloroacetic acid (6) and 1.0 equiv. of *tert*-butyl isocyanide (7a). [b] Reactions performed with 1.4 equiv. of 4-methoxybenzylamine (4), 1.0 equiv. of 4-azido-2,3,5,6-tetrafluorobenzaldehyde (5b), 1.4 equiv. of chloroacetic acid (6) and 1.0 equiv. of *tert*-butyl isocyanide (7a). [c] [1.0 M] anhydrous [d] 10% mol. [e] 20% mol [f] Isolated yield. rt = room temperature. nd = not determined.

Once time that the synthesis of the Ugi-4CR products was optimized, the one-pot synthesis of the $\alpha$-acylamino amide-xanthates was carried out, through a $S_N2$-type reaction when adding the potassium salt of xanthic acid to form the Ugi-product xanthate 10d. The versatility of the developed methodology was examined using different aldehydes as 4-azido-2,3,5,6-tetrafluorobenzaldehyde (5a) and 2,3,4,5,6-pentafluorobenzaldehyde (5b**)**, isocyanides as *tert*-butyl, cyclohexyl and 2,6-dimethylphenyl (7a–c). The respective amide-xanthate products 10a–f were obtained in moderate to good yields (40–92%).

Figure 2 show the $^1H$ and $^{13}C$ NMR spectra of the fluoro $\alpha$-acylamino amide-xanthate 10a.




**Scheme 2.** Substrate scope.

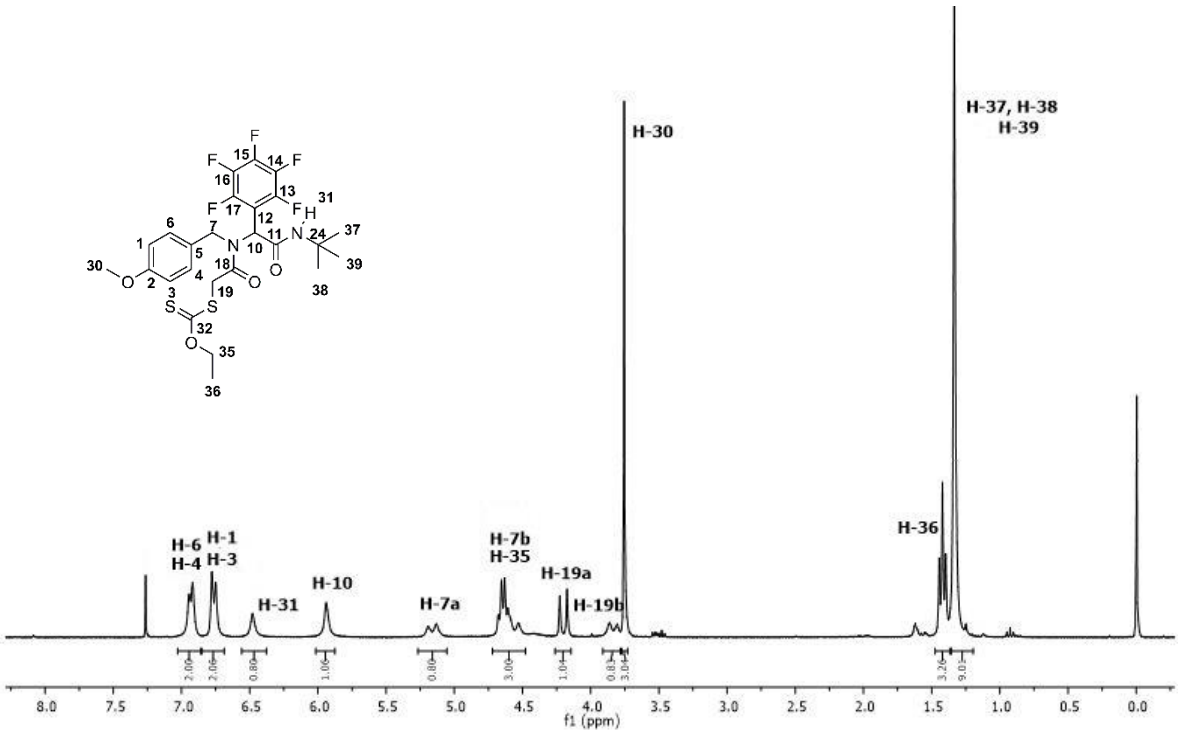



**Figure 2.** [1]H NMR spectrum of fluoro $\alpha$-acylamino amide-xanthate 10a.

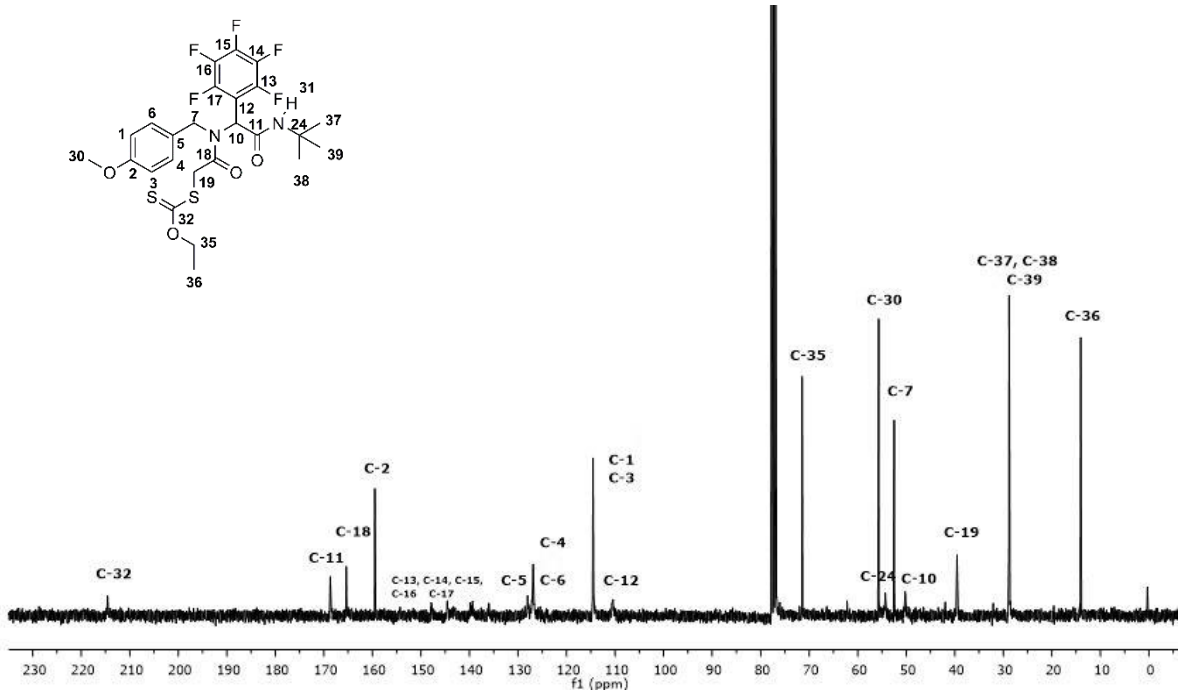



**Figure 3.** [13]C NMR spectrum of fluoro $\alpha$-acylamino amide-xanthate 10a.

## 3. Experimental Section

### *3.1. General Information, Instrumentation, and Chemicals*

[1]H and [13]C NMR spectra were acquired on Varian Gemini spectrometers (200 MHz) and Varian Unity (300 MHz). The solvent used was deuterated chloroform ($CDCl_3$). Chemical shifts are reported in parts per million (δ/ppm). The internal reference for [1]H NMR spectra is trimethylsilane at 0.0 ppm. The internal reference for [13]C NMR spectra is $CDCl_3$ at 77.0 ppm. Coupling constants are reported in Hertz (*J*/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s),

doublet (d), triplet (t), quartet (q), and multiplet (m). NMR spectra were analyzed using the MestreNova software version 10.0.1–14719. IR spectra were acquired on a Perkin Elmer 100 spectrometer using an Attenuated Total Reflectance (ATR) method with neat compounds. The absorbance peaks are reported in reciprocal centimeters ($\upsilon_{max}/cm^{-1}$). Reaction progress was monitored by Thin-Layer Chromatography (TLC) on precoated silica-gel 60 $F_{254}$ plates and the spots were visualized under UV light at 254 or 365 nm. Mixtures of hexane with ethyl acetate (EtOAc) were used to run TLC and for measuring retention factors ($R_f$). Flash column chromatography was performed using silica gel (230–400 mesh) and mixtures of hexane with EtOAc in different proportions (*v*/*v*) as the mobile phase. All reagents were purchased from Sigma-Aldrich and were used without further purification. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package. The purity for all the synthesized products (up to 99%) was assessed by NMR.

### *3.2. Synthesis and Characterization of the Fluoro α-Acylamino Amide-Xanthates 10a–f*

General procedure 1 (GP1): In a round–bottomed flask equipped with a magnetic stirring bar, to a 0.3 M solution of p-methoxyaniline (1.0 equiv.) in anhydrous MeOH under nitrogen atmosphere at room temperature, 4-Methoxybenzylamine (1.4 equiv.) and InCl3 (10% mol) were added. After 60 min, chloroacetic acid (1.4 equiv.) and $InCl_3$ (10% mol) were added. Later, *tert*-butyl isocyanide (1.0 equiv.) were added. The reaction mixture was stirred for 21–25 h at room temperature and then, the potassium ethyl xanthogenate salt (1.5 equiv.) was added. The reaction mixture was stirred for 3 h at room temperature. The solvent was removed until dryness. The crude was diluted in excess of AcOEt and washed with brine. The combined organic layer was dried over anhydrous $Na_2SO_4$. The solvent was removed until dryness. The crude was purified by silica-gel column chromatography to afford the products 10a–f.

#### 3.2.1. S-(2-((2-(tert-Butylamino)-2-oxo-1-(perfluorophenyl)ethyl)(4-methoxybenzyl)amino)-2-oxoethyl) O-ethyl carbonodithioate (10a)

The product was obtained in 85% as a white solid after purification by silica-gel column chromatography using a mixture of ethyl acetate with hexanes (15–20% *v*/*v*) as eluent $R_f$ = 0.43 (hexanes–AcOEt, 8/2, *v*/*v*); mp = 130–134 °C, FT-IR (ATR) $\upsilon_{max}/cm^{-1}$ 1696, 1646 (C=O amide), 3276 (NH amide); $^1$H NMR (300 MHz, $CDCl_3$, TMS): δ 6.93 (d, *J* = 9.0 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 6.48 (s, 1H), 5.94 (s, 1H), 5.16 (d, *J* = 18.0, 1H), 4.68 − 4.53 (m, 3H), 4.20 (d, *J* = 18.0 Hz, 1H), 3.83 (d, *J* = 18.0 Hz, 1H), 3.75 (s, 3H), 1.42 (t, J = 6.0 Hz, 3H), 1.33 (s, H, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS): δ 214.6, 168.7 , 165.4, 159.5, 147.9, 144.5, 139.9, 139.4, 136.0, 128.0, 126.9, 114.5, 110.4, 71.5, 55.7, 54.3, 52.5, 50.2, 39.5, 28.8, 14.0.

#### 3.2.2. S-(2-((2-(Cyclohexylamino)-2-oxo-1-(perfluorophenyl)ethyl)(4-methoxybenzyl)amino)-2-oxoethyl) O-ethyl carbonodithioate (10b)

The product was obtained in 75% as a white solid after purification by silica-gel column chromatography using a mixture of ethyl acetate with hexanes (15–20% *v*/*v*) as eluent $R_f$ = 0.38 (hexanes–AcOEt, 8/2, *v*/*v*); mp = 148–152 °C, FT-IR (ATR) $\upsilon_{max}/cm^{-1}$ 1654, 1614 (C=O amide) 3345 (NH amide); $^1$H NMR (200 MHz, $CDCl_3$, TMS): δ 6.93 (d, *J* = 10.0 Hz, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 6.55 (s, 1H), 6.26 (d, *J* =8.0, 1H), 5.20 (d, *J* = 18.0, 1H), 4.70 − 4.50 (m, 3H), 4.21 (d, *J* = 16.0 Hz, 1H), 3.84 − 3.75 (m, 5H), 2.00 − 1.00 (m, 13H); $^{13}$C NMR (50 MHz, $CDCl_3$, TMS): δ 215.3, 168.7, 165.4, 159.4, 148.6, 143.7, 140.2, 139.0, 135.1, 127.8, 126.8, 114.5, 110.3, 71.6, 55.6, 53.8, 50.2, 49.4, 39.3, 33.0, 25,7, 25.2, 14.0.

#### 3.2.3. S-(2-((2-((2,6-Dimethylphenyl)amino)-2-oxo-1-(perfluorophenyl)ethyl)(4-methoxybenzyl)amino)-2-oxoethyl) O-ethyl carbonodithioate (10c)

The product was obtained in 40% as a white solid after purification by silica-gel column chromatography using a mixture of ethyl acetate with hexanes (15–20% *v*/*v*) as eluent $R_f$ = 0.28 (hexanes–AcOEt, 8/2, *v*/*v*); mp = 166–170 °C, FT-IR (ATR) $\upsilon_{max}/cm^{-1}$ 1663, 1613 (C=O amide), 3251 (NH amide); $^1$H NMR (300 MHz, $CDCl_3$, TMS): δ 7.71 (s, 1H), 7.15 − 7.05 (m, 3H), 6.94 (d, *J* = 9.0 Hz, 2H)),

6.88 (s, 1H), 6.78 (d, *J* = 9.0 Hz, 2H), 5.37 (d, *J* = 18.0, 1H), 4.70 − 4.53 (m, 3H), 4.29 (d, *J* = 18.0 Hz, 1H), 3.87 − 3.62 (m, 4H), 2.22 (s, 6H), 1.38 (t, J = 6.0 Hz, 3H), 1.33 (s, H, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS): δ 216.0, 169.2, 165.4, 165.1, 159.6, 136.0, 133.2, 128.6, 128.0, 127.7, 126.7, 114.7, 109.8, 71.8, 55.8, 53.7, 50.1, 39.2, 18.7, 14.0.

3.2.4. S-(2-((1-(4-Azido-2,3,5,6-tetrafluorophenyl)-2-(tert-butylamino)-2-oxoethyl)(4-methoxybenzyl)amino)-2-oxoethyl) O-ethyl carbonodithioate (10d)

The product was obtained in 67% as a white solid after purification by silica-gel column chromatography using a mixture of ethyl acetate with hexanes (15–20% *v*/*v*) as eluent $R_f$ = 0.38 (hexanes–AcOEt, 8/2, *v*/*v*); mp = 80–84 °C, FT-IR (ATR) $\upsilon_{max}$/cm$^{-1}$ 1697, 1651 (C=O amide), 2122 ($N_3$), 3343 (NH amide); $^1$H NMR (300 MHz, $CDCl_3$, TMS): δ 6.94 (d, *J* = 9.0 Hz, 2H)), 6.78 (d, *J* = 9.0 Hz, 2H), 6.47 (s, 1H), 6.92 (s, 1H), 5.15 (d, *J* = 18.0, 1H), 4.68 − 4.53 (m, 3H), 4.20 (d, *J* = 18.0 Hz, 1H), 3.85 − 3.77 (m, 4H), 1.42 (t, J = 6.0 Hz, 3H), 1.33 (s, H, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS): δ 214.4, 168.6, 165.5, 159.4, 147.7, 144.4, 142.2, 139.0, 128.2, 126.9, 120.6, 114.4, 110.7, 71.3, 55.6, 54.2, 52.2, 50.1, 39.5, 28.7, 14.0.

3.2.5. S-(2-((1-(4-Azido-2,3,5,6-tetrafluorophenyl)-2-(cyclohexylamino)-2-oxoethyl)(4-methoxybenzyl)amino)-2-oxoethyl) O-ethyl carbonodithioate (10e)

The product was obtained in 92% as a white solid after purification by silica-gel column chromatography using a mixture of ethyl acetate with hexanes (15–20% *v*/*v*) as eluent $R_f$ = 0.33 (hexanes–AcOEt, 8/2, *v*/*v*); mp = 132–136 °C, FT-IR (ATR) $\upsilon_{max}$/cm$^{-1}$ 1660 (C=O amide), 2123 ($N_3$), 3378 (NH amide); $^1$H NMR (300 MHz, $CDCl_3$, TMS): δ 6.94 (d, *J* = 9.0 Hz, 2H)), 6.78 (d, *J* = 9.0 Hz, 2H), 6.47 (s, 1H), 6.92 (s, 1H), 5.15 (d, *J* = 18.0, 1H), 4.68 − 4.53 (m, 3H), 4.20 (d, *J* = 18.0 Hz, 1H), 3.85 − 3.77 (m, 4H), 1.42 (t, J = 6.0 Hz, 3H), 1.33 (s, H, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS): δ 215.1, 168.7, 165.5, 159.3, 148.3, 143.0, 138.2, 137.9, 128.0, 126.9, 120.7, 114.4, 110.6, 71.5, 55.6, 53.8, 50.1, 49.4, 39.3, 33.0, 25.7, 25.2, 14.0.

3.2.6. S-(2-((1-(4-Azido-2,3,5,6-tetrafluorophenyl)-2-((2,6-dimethylphenyl)amino)-2-oxoethyl)(4-methoxybenzyl)amino)-2-oxoethyl) O-ethyl carbonodithioate e (10f)

The product was obtained in 55% as a white solid after purification by silica-gel column chromatography using a mixture of ethyl acetate with hexanes (15–20% *v*/*v*) as eluent $R_f$ = 0.24 (hexanes–AcOEt, 8/2, *v*/*v*); mp = 136–140 °C, FT-IR (ATR) $\upsilon_{max}$/cm$^{-1}$ 1672, 1656 (C=O amide), 2122 ($N_3$), 3358 (NH amide); $^1$H NMR (300 MHz, $CDCl_3$, TMS): δ 6.94 (d, *J* = 9.0 Hz, 2H)), 6.78 (d, *J* = 9.0 Hz, 2H), 6.47 (s, 1H), 6.92 (s, 1H), 5.15 (d, *J* = 18.0, 1H), 4.68 − 4.53 (m, 3H), 4.20 (d, *J* = 18.0 Hz, 1H), 3.85 − 3.77 (m, 4H), 1.42 (t, J = 6.0 Hz, 3H), 1.33 (s, H, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$, TMS): δ 216.0, 169.0, 165.3, 159.5, 147.8, 143.3, 138.0, 136.0, 133.2, 128.6, 128.0, 126.8, 121.1, 114.6, 109.9, 71.8, 55.7, 53.6, 50.0, 39.2, 18.7, 14.0.

## 4. Conclusions

In conclusion, we have developed a one-pot strategy via the Ugi-4CR / $S_N2$ process toward the synthesis of fluoro α-acylamino amide-xanthates. The main contributions of this work are the design and development of a MCR based protocol towards a synthetic platform of peptidomimetic heterocycles than containing several fluorine atoms, with the aim of improving their biological properties.

**Author Contributions:** R.G.-M. have made a substantial, direct, and intellectual contribution to the work and M.A.R.-G. and T.R.I.-R. contributes significantly to the designing and analyzing the results. All authors discussed the whole project, wrote the publication, and approved it for publication.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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