β-Alkoxyvinyl trifluoromethyl ketones as efficient precursors for the one-pot synthesis of bis-(4,5-dihydro-1*H*-pyrazol-1-yl)methanones and 1*H*-pyrazolyl-1-carbohydrazides

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Abstract

The one-pot and regioselective synthesis of a novel series of 3-aryl(heteroaryl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazolyl-1-carbohydrazides and bis-(3-aryl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)methanones from the cyclocondensation reactions of 4-alkoxy-4-aryl(heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones, where aryl substituents are H, Me, Ph, 4-OMePh, 4-ClPh, 4-BrPh, 4,4'-biphenyl and heteroaryl are 2-thienyl and 2-furyl, with carbohydrazide is reported.

Keywords: Carbohydrazides, enones, 2-pyrazolines, bis-(4,5-dihydropyrazoles)-methanones, pyrazoles

Introduction

The pyrazole ring is present in a wide variety of biologically active compounds.¹ Many pyrazole derivatives are known to exhibit a wide range of medicinal properties such as anti-inflammatory, hypoglycemic, analgesic, anti-pyretic, anti-bacterial, sedative-hypnotic and anticoagulant activity.²⁻⁵ Recently, some arylpyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activity⁶ and carboxylate/carbohydrazide derivatives suppress A549 lung cancer cell growth.⁷⁻⁹ Figure 1 shows some pyrazole derivatives with hypoglycemic activity (I, II) and agents against A549 lung cell cancer (III, IV).

Usually, bis-pyrazoles and hydrazino-pyrazoles can be prepared from the reactions of hydrazines and 1,3-dicarbonyl fragments under severe synthetic conditions or a multi-step sequence is required. Also the formation of isomeric compounds is observed in some cases.¹ On the other hand, several pyrazoles analogues were synthesized by derivatising the pyrazoles. For sample, the majority of the bis-1*H*-pyrazoles were prepared either by alkylation or acylation of

unsubstituted 1*H*-pyrazoles in reactions with phosgene, esters or dihalides. These modifications in the pyrazoles ring of a basic substituent moiety should provide potential bioactivities.^{5,7,9}

For the regioselective synthesis of bis-pyrazoles and hydrazino-pyrazoles, appropriately and symmetric substituted enones were needed. On the other hand, the most convenient method to construct trifluoromethylated compounds is the use of fluorine-containing building blocks as starting reagents. Thus β -alkoxyvinyl trifluoromethyl ketones are versatile blocks for the heterocyclic synthesis and direct construction of fluorinated compounds.¹⁰⁻¹⁷ It is well-known that the introduction of a trifluoromethyl group into heterocyclic compounds may have a significant influence on their biological and physical properties.¹⁸



Figure 1. Pyrazole derivatives.

Thus, in the continuation of our works, we report here a practical and regioselective methodology for the preparation of a series of 3-aryl(heteroaryl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazolyl-1-carbohydrazides (2) and bis-(3-aryl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)methanones (3) from the reaction of 4-alkoxy-4-aryl(heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones (1) and carbohydrazide, in one-pot method (Scheme 1).

Results and Discussion

Since the 1970s, according to previous publications,^{13,19-20} research groups have reported the systematic synthesis of 4-alkoxy-4-aryl(heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones (1) from the trifluoroacetylation reaction of the respective enolethers (1a-b) or acetals (1c-i) with trifluoracetic anhydride. In particular, the synthetic potential of β -alkoxyvinyl trifluoromethyl ketones to obtain a series of novel trifluoromethylated pyrazoles has recently been explored and their biological evaluation reported by us.^{10,13,21-23}

The reactions of 4-alkoxy-4-aryl(heteroaryl)-1,1,1-trifluoro-3-alken-2-ones (**1b-e**,**1h-i**) with carbohydrazide were carried out in 1:1 molar ratio in ethanol, and all reactions were monitored by TLC. The most satisfactory results were obtained when the reactions were performed under

mild conditions. Thus, to an ice-cold stirred mixture of carbohydrazide/ethanol, is added dropwise a mixture of the enone (1) and ethanol. After of the end of the slow addition, the mixture is stirred for more four hours at 50 °C. The pure compounds (**2b-e**, **2h-i**) are obtained by recrystallization from ethanol. It was observed that when the trifluoromethylated enone (1) is added to the carbohydrazide at 25-50 °C, a mixture of hydrazino-1*H*-pyrazole (**2**) and bis-1*H*-pyrazole (**3**) can be isolated.

The structures of 3-aryl(heteroaryl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazolyl-1-carbohydrazide (**2b-e**, **2h-i**) were deduced from NMR experiments and by comparison with NMR data of other 2-pyrazolines formerly synthesized in our laboratory. Compounds **2** showed the ¹H chemical shifts of the methylene protons (H4) as a characteristic AB system with a doublet in average at δ 3.68 and the other doublet at δ 3.36 ppm, respectively with a geminal coupling constant in average at 18-19 Hz. The hydroxy protons are shown in the ¹H NMR spectra at δ 7.90 ppm. Moreover, NH and NH₂ show signs in the range of δ 8.54 ppm and δ 4.19 ppm, respectively. Compounds **2** present the typical ¹³C chemical shifts of the pyrazoline ring at δ 149.6 ppm (C3) and δ 44.7 ppm. The C5 presents a characteristic quartet at δ 90.8 ppm with ²*J*_{CF} = 33 Hz, due to the attached CF₃ group. The CF₃ group shows a typical quartet at δ 122.8 ppm with ¹*J*_{CF} = 285 Hz. The carbonyl carbon showed signal in the range of δ 155.1 ppm.



i = Ethanol, 4 hours, 0-50 °C; ii = Ethanol, 5-16 hours, 50 °C

1-3	a	b	c	d	e	f	g	h	i
R	Н	Me	Ph	4-OMePh	4-ClPh	4-BrPh	4.4'-Biphenvl	2-Thienvl	2-Furvl

Scheme 1

Subsequently, the reactions of 4-alkoxy-4-aryl(heteroaryl)-1,1,1-trifluoro-3-alken-2-ones (1a, 1c, 1f-g) and carbohydrazide were carried out at a molar ratio of 2:1 respectively, in ethanol

as solvent, was stirred at 50 °C for 5-16 hours giving the corresponding bis-pyrazolyl system (**3a**, **3c**, **3f-g**), in 73-89% yield. All reactions were stirred until consumption of ketones (1) and were confirmed by TLC. After reaction time the pure compounds (**3a**, **3c**, **3f-g**) are obtained by recrystallization from ethanol (Scheme 1).

The unambiguous ¹H and ¹³C NMR chemical shift assignments of carbonyl-1,1'-Bis-3-aryl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole (**3a**, **3c**, **3f-g**), in DMSO-*d*₆ as solvent, were done by comparison with NMR data of other 2-pyrazolines formerly synthesized in our laboratory. Compounds **3** showed the chemical shifts of the diasterotopic methylene protons (H4) as a characteristic AB system and as a doublet on average at δ 3.76 and another one at δ 3.43 with a geminal coupling constant on average at 18-19 Hz. The hydroxy protons appear in the ¹H NMR spectra in the vicinity of δ 7.83. Compounds **3** present the typical ¹³C NMR chemical shifts of pyrazoline ring carbons on average 147.7 (C3), 44.1 (C4), 91.4 (C5, ²*J*_{CF} = 34) and 122.5 (CF₃, ¹*J*_{CF} = 285). The carbonyl carbon showed signs in the range of δ 152.2.



iii = SOCl₂, Pyridine, Benzene, 0-80 °C, 1h.; iv = Acetic acid, 120 °C, 4h.; v = Sulfuric acid, 90 °C, 2h.

Scheme 2

Finally, the compound bis-(5-trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)methanone (**3c**) was subjected to dehydration reactions, using acetic acid /ethanol,¹³ at reflux for 4 hours or with sulfuric acid/ethanol²⁴ at reflux for 4 hours (Scheme 2). In both cases, it was obtained the aromatized pyrazole (**5c**), but is observed, simultaneous removal of the carbonyl function. Due to the relative difficulty of this elimination, because of the presence of trifluoromethyl and the carbonyl groups at positions 5 and 1 of pyrazole (**3**), respectively, other synthetic procedure was performed. After a review of the literature and in an attempt to obtain aromatic pyrazoles, we choose thionyl chloride/pyridine^{10,25} as the dehydration agent for the compound (**3c**). Again, was observed the isolation of aromatic pyrazole (**5c**) with the cleavage of the C(O)-N bonds.

Conclusions

In conclusion, one can consider the cyclocondensation reaction reported here as a useful, simple, and convenient procedure to obtain new regioselective 4,5-dihydro-1*H*-pyrazolyl-1-carbohydrazides (**2**) and bis-(4,5-dihydro-1*H*-pyrazolyl)methanones (**3**) from trifluoromethylated enones and carbohydrazide in a one-step method. The subsequent dehydration reaction of bis-(pyrazolyl)methanones under various conditions was not possible until now.

Experimental Section

General Procedures. Unless otherwise indicated all common reagents and solvents were used from commercial suppliers without further purification. All melting points were determined using open capillaries on an Electrothermal Mel-Temp 3.0 apparatus and are uncorrected. ¹H and ¹³C NMR spectra were acquired on a Bruker DPX 200 spectrometer (¹H at 200.13 MHz and ¹³C at 50.32 MHz), 5 mm sample tubes, 298 K, digital resolution \pm 0.01 ppm, in DMSO-*d*₆ for (**2**, **3**) using TMS as internal reference. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University, USP/Brazil).

General procedure for synthesis of 3-aryl(heteroaryl)-5-trifluoromethyl-5-hydroxy-4,5dihydro-1*H*-pyrazolyl-1-carbohydrazides (2)

To an ice-cold stirred mixture of carbohydrazide (10 mmol) and ethanol (10 mL) was added dropwise a mixture of 4-alkoxy-4-aryl(heteroaryl)-1,1,1-trifluoro-3-alken-2-ones **1b-e**, **1h-i** (10 mmol) diluted in ethanol (10 mL). After the end of the slow addition, the mixture was stirred for more 4 hours at 50 °C. The pure compounds **2b-e**, **2h-i** were obtained by recrystallization from ethanol.

5-Trifluoromethyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-**pyrazolyl-1-carbohydrazide** (2b). Yield 49%, m.p. 161-162 °C. ¹H NMR (DMSO- d_6): δ (*J*, Hz), 7.90 (s, 1H, NH); 7.41 (s, 1H, OH); 4.11 (s. 2H, NH₂); 3.29-3.39 (d, 1H, H-4, 19); 2.93-3.03 (d, 1H, H-4,), 1.96 (s, 3H, Me). ¹³C NMR (DMSO- d_6): δ (*J*, Hz), 155.1 (C=O); 151.7 (C-3); 123.2 (q, ¹*J*=285, CF₃); 90.5 (q, ²*J*=33, C-5); 47.6 (C-4); 15.0 (Me). Anal. Calcd. for C₆H₉F₃N₄O₂ (226.07): C, 31.86; H, 4.01; N, 24.77%. Found: C, 32.16; H, 3.98; N, 24.51%.

5-Trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-**pyrazolyl-1-carbohydrazide** (2c). Yield 86%, m.p. 234-235 °C. ¹H NMR (DMSO- d_6): δ (*J*, Hz), 8.41 (s, 1H, NH); 7.71 (s, 1H, OH); 7.84-7.89 (m, 2H, Ar), 7.43-7.46 (m, 3H, Ar); 4.18 (s, 2H, NH₂); 3.74-3.83 (d, 1H, H-4,18); 3.41-3.51 (d, 1H, H-4,18). ¹³C NMR (DMSO- d_6): δ (*J*, Hz), 154.6 (C=O); 149.2 (C-3); 130.4; 130.0; 128.5; 126.6 (Ar); 125.5 (q, ¹*J*=285, CF₃); 91.1 (q, ²*J*=33, C-5); 44.1 (C-4). Anal. Calcd. for C₁₁H₁₁F₃N₄O₂, (288.08): C, 45.84; H, 3.85; N, 19.44%. Found: C, 45.66; H, 3.96; N, 19,22%.

5-Trifluoromethyl-5-hydroxy-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazolyl-1-carbo-

hydrazide (2d). Yield 52%, m.p. 147-148 °C. ¹H NMR (DMSO- d_6): δ (*J*, Hz), 9.38 (s, 1H, NH); 8.33 (s, 1H, OH); 7.79-7.81 (d, 2H, Ar), 6.98-7.01 (m, 2H, Ar); 4.16 (s, 2H, NH₂); 3.81 (s, 3H, OMe); 3.71-3.81 (d, 1H, H-4, 19); 3.41-3.46 (d, 1H, H-4, 19). ¹³C NMR (DMSO- d_6): δ (*J*, Hz), 160.8 (C=O); 154.8 (C-3); 149.1; 128.3; 127.4; 122.9 (Ar); 123.1 (q, ¹*J*=284, CF₃); 90.9 (q, ²*J*=33, C-5); 55.2 (OMe); 44.3 (C-4). Anal. Calcd. for C₁₂H₁₃F₃N₄O₃ (318.09): C, 45.29; H, 4.12; N, 17.60%. Found: C, 45.85; H, 4.17; N, 17.29%.

3-(4-Chlorophenyl)-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H***-pyrazolyl-1-carbohydrazide (2e).** Yield 76%, m.p. 205-206 °C. ¹H NMR (DMSO-*d*₆): δ (*J*, Hz), 9.55 (s, 1H, NH); 8.46 (s, 1H, OH); 7.89-7.91 (d, 2H, Ar), 7.50-7.53 (d, 2H, Ar); 4.18 (s, 2H, NH₂); 3.76-3.80 (d, 1H, H-4, 18); 3.43-3.48 (d, 1H, H-4, 18). ¹³C NMR (DMSO-*d*₆): δ (*J*, Hz), 154.5 (C=O); 148.2 (C-3); 134.6; 129.3; 128.5; 128.3 (Ar); 123.4 (q, ¹*J*=284, CF₃); 91.3 (q, ²*J*=33, C-5); 44.0 (C-4). Anal. Calcd. for C₁₁H₁₀ClF₃N₄O₂ (322.04): C, 40.95; H, 3.12; N, 17.36%. Found: C, 41.01; H, 3.57; N, 17.81%.

5-Trifluoromethyl-5-hydroxy-3-(2-thienyl)-4,5-dihydro-1*H*-pyrazolyl-1-carbohydrazide

(2h). Yield 80%, m.p. 230-231 °C. ¹H NMR (DMSO- d_6): δ (*J*, Hz), 8.02 (s, 1H, NH); 7.72 (s, 1H, OH); 7.72-7.73 (m, 1H, Ar); 7.49-7.50 (m, 1H, Ar); 7.13-7.16 (m, 1H, Ar); 4.18 (s, 2H, NH₂); 3.77-3.82 (d, 1H, H-4, 18); 3.46-3.51 (d, 1H, H-4, 18). ¹³C NMR (DMSO- d_6): δ (*J*, Hz), 154.3 (C=O); 145.4 (C-3); 133.1; 129.7; 129.2; 127.5 (Ar); 123.5 (q, ¹*J*=285, CF₃); 90.9 (q, ²*J*=33, C-5); 44.6 (C-4). Anal. Calcd. for C₉H₉F₃N₄O₂S (294.04): C, 36.74; H, 3.08; N, 19.04%. Found: C, 36.70; H, 3.38; N, 18.89%.

5-Trifluoromethyl-3-(2-furyl)-5-hydroxy-4,5-dihydro-1*H*-**pyrazolyl-1-carbohydrazide** (2i). Yield 44%, m.p. 216-217 °C. ¹H NMR (DMSO-*d*₆): δ (*J*, Hz), 8.03 (s, 1H, NH); 7.78 (s, 1H, OH); 7.88-7.89 (d, 1H, Ar); 7.02-7.03 (d, 1H, Ar); 6.66-6.67 (m, 1H, Ar); 4.38 (s, 2H, NH₂); 3.68-3.73 (d, 1H, H-4, 19); 3.36-3.41 (d, 1H, H-4, 19). ¹³C NMR (DMSO-*d*₆): δ (*J*, Hz), 151.5 (C=O); 148.8 (C-3); 145.4; 145.3; 113.4; 112.1 (Ar); 118.1 (q, ¹*J*=285, CF₃); 90.6 (q, ²*J*=33, C-5); 44.0 (C-4). Anal. Calcd. for C₉H₉F₃N₄O₃ (278.06): C, 38.86; H, 3.26; N, 20.14%. Found: C, 38.84; H, 3.60; N, 20.11%.

General procedure for synthesis of bis-(3-aryl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)methanones (3).

A solution of 4-alkoxy-4-aryl(heteroaryl)-1,1,1-trifluoro-3-alken-2-ones **1a**, **1c**, **1f-g** (20 mmol), carbohydrazide (10 mmol) and ethanol (10 mL) was stirred at 50 °C for 5-16 hours. After the reaction time the pure compounds **3a**, **3c**, **3f-g** were obtained by recrystallization from ethanol.

Bis-(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H***-pyrazol-1-yl)methanone (3a).** Yield 89%, m.p. 98-99 °C. ¹H NMR (DMSO- d_6): δ (*J*, Hz), 7.48 (s, 2H, OH); 7.10 (s, 2H, H-3); 3.32-3.37 (d, 2H, H-4, 19); 3.01-3.06 (d, 2H, H-4, 19). ¹³C NMR (DMSO- d_6): δ (*J*, Hz), 154.5 (C=O); 142.8 (C-3); 120.2 (q, ¹*J*=285, CF₃); 89.1 (q, ²*J*=33, C-5); 45.4 (C-4). Anal. Calcd. for C₉H₈F₆N₄O₃ (334.05): C, 32.35; H, 2.41; N, 16.77%. Found: C, 32.10; H, 2.85; N, 15.52%.

Bis-(5-trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H***-pyrazol-1-yl)methanone** (3c). Yield 78%, m.p. 217-218 °C. ¹H NMR (DMSO- d_6): δ (*J*, Hz), 7.90 (s, 2H, OH); 7.71-7.75 (m, 4H, Ar); 7.43-7.45 (d, 6H, Ar); 3.84-3.90 (d, 2H, H-4, 18); 3.52-3.58 (d, 2H, H-4, 18). ¹³C NMR (DMSO- d_6): δ (*J*, Hz), 151.6 (C=O); 149.9 (C-3); 130.6; 130.2; 128.7; 126.3 (Ar); 123.5 (q, ¹*J*=282, CF₃); 92.2 (q, ²*J*=33, C-5); 43.8 (C-4). Anal. Calcd. for C₂₁H₁₆F₆N₄O₃ (486.11): C, 51.86; H, 3.32; N, 11.52%. Found: C, 51.82; H, 3.61; N, 11.72%.

Bis-(3-bromophenyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H***-pyrazol-1-yl) methanone (3f**). Yield 86%, m.p. 171-172 °C. ¹H NMR (DMSO-*d*₆): δ (*J*, Hz), 7.98 (s, 2H, OH); 7.62-7.66 (m, 8H, Ar); 3.86-3.91 (d, 2H, H-4, 18); 3.50-3.55 (d, 2H, H-4, 18). ¹³C NMR (DMSO-*d*₆): δ (*J*, Hz), 151.2 (C=O); 148.6 (C-3); 131.8; 131.2; 129.8; 129.7 (Ar); 123.2 (q, ¹*J*=286, CF₃); 92.3 (q, ²*J*=35, C-5); 43.6 (C-4). Anal. Calcd. for C₂₁H₁₄Br₂F₆N₄O₃ (641.93): C, 39.16; H, 2.19; N, 8.70%. Found: C, 39.36; H, 2.51; N, 9.08%.

Bis-(5-trifluoromethyl-5-hydroxy-3-(4,4'-biphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)

methanone (3g). Yield 73%, m.p. 222-223 °C. ¹H NMR (DMSO-*d*₆): δ (*J*, Hz), 7.98 (s, 2H, OH); 7.71-7.84 (m, 12H, Ar); 7.38-7.49 (m, 6H, Ar); 3.92-3.96 (d, 2H, H-4, 18); 3.57-3.62 (d, 2H, H-4, 18). ¹³C NMR (DMSO-*d*₆): δ (*J*, Hz), 151.6 (C=O); 149.5 (C-3); 141.6; 141.5; 138.9; 129.5; 129.4; 128.7; 126.8; 126.7 (Ar); 123.1 (q, ¹*J*=285, CF₃); 92.2 (q, ²*J*=35, C-5); 43.7 (C-4). Anal. Calcd. for C₃₃H₂₄F₆N₄O₃ (638.18): C, 62.07; H, 3.79; N, 8.77%. Found: C, 62.00; H, 4.03; N, 8.84%.

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References

- (a) Elguero, J. *Pyrazoles* in Katritzky, A. R.; Rees, C. W.; Scriven. E. F.V. *Comprehensive Heterocyclic Chemistry*, Vol. 3, pp 1-75; Pergamon Press, Oxford, New York, 1st ed. 1995.
 (b) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronk, M. V. *J. Org. Chem.* 2001, *66*, 6787.
- 2. Lee, K. Y.; Kim, J. M.; Kim, J. N. Tetrahedron Lett. 2003, 44, 6737.
- Jia, Z. J.; Wu, Y.; Huang, W.; Zhang, P.; Song, Y.; Woolfrey, J.; Sinha, U.; Arfsten, A. E.; Edwards, S. T.; Hutchaleelaha, A.; Hollenbach, S. J.; Lambing, J. L.; Scarborough, R. M.; Zhu, B. *Bioorg. Med. Chem. Lett.* 2004, 14, 1229.
- 4. Wright, J. B.; Dulin, W. E.; Markillie, J. H. J. Med. Chem. 1964, 7, 102.
- 5. Soliman, R.; Darwish. S. A. S. J. Med. Chem. 1963, 26, 1659.
- 6. Genin, M. J.; Biles, C.; Keiser, B. J.; Poppe, S. M.; Swaney, S. M.; Tarpley, W. G.; Yagi, Y.; Romero, D. L. *J. Med. Chem.* **2000**, *43*, 1034.

- 7. Wei, F.; Zhao, B.; Huang, B.; Zhang, L.; Sun, C.; Dong, W.; Shin, D.; Miao, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6342.
- Xia, Y.; Dong, Z.; Zhao, B.; Ge, X.; Meng, N.; Shin, D.; Miao, J. *Bioorg. Med. Chem. Lett.* 2007, 15, 6893.
- 9. Fan, C.; Zhao, B.; Wei, F.; Zhang, G; Dong, W.; Miao, J. *Bioorg. Med. Chem. Lett.* 2008, 18, 3860.
- Bonacorso, H. G.; Wentz, A. P.; Lourega, R. V.; Cechinel, C. A.; Moraes, T. S.; Coelho, H. S.; Zanatta, N.; Martins, M. A. P.; Hoerner, M.; Alves, S. H. J. Fluorine Chem. 2006, 127, 1066.
- 11. Bonacorso, H. G.; Costa, M. B.; Lopes, I. S.; Oliveira, M. R.; Drekener, R. L.; Martins, M. A. P.; Zanatta, N.; Flores, A. F. C. *Synthetic Comm.* **2005**, *35*, 3055.
- Bonacorso, H. G.; Oliveira, M. R.; Costa, M. B.; Silva, L. B.; Wastowski, A. D.; Martins, M. A. P.; Zanatta, N.; Flores, A. F. C. J. Heterocycl. Chem. 2005, 42, 631.
- 13. Bonacorso, H. G.; Cechinel, C. A.; Oliveira, M. R.; Costa, M. B.; Martins, M. A. P.; Zanatta, N.; Flores, A. F. C. J. Heterocycl. Chem. 2005, 6, 1055.
- 14. Bonacorso, H. G.; Lourega, R. V.; Deon, E. D.; Zanatta, N.; Martins, M. A. P. *Tetrahedron Lett.* **2007**, *48*, 4835.
- Machado, P.; Rosa, F. A.; Rossatto, M.; Sant'Anna, G. S.; Sauzem, P. D.; Silva, R. M. S.; Rubin, M. A.; Ferreira, J.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. ARKIVOC 2007, (xvi), 281.
- Zanatta, N.; Borchhardt, D. M.; Flores, D. C.; Coelho, H. S.; Marchi, T. M.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. J. Heterocycl. Chem. 2008, 45, 335.
- 17. Bonacorso, H. G.; Ferla, A.; Cechinel, C. A.; Zanatta, N.; Martins, M. A. P. J. Heterocycl. *Chem.* **2008**, 45, 483.
- 18. Park, B. K.; Kitterringham, N. R.; O'Neill, P. M. Annu. Rev. Pharmacol. Toxicol. 2001, 41, 443.
- (a) Siqueira, G. M.; Flores, A. F. C.; Clar. G.; Zanatta, N.; Martins, M. A. P. *Quim. Nova*, 1994, *17*, 24. (b) *Chem Abstr.* 1995, *122*, 187063. (c) Hojo, M.; Masuda, R.; Kamitori, Y. *Tetrahedron Lett.* 1976, 1009. (d) Hojo, M.; Masuda, R.; Okada, E. *Synthesis*, 1986, 1013.
 (e) Hojo, M.; Masuda, R.; Kokuryo,Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* 1976, 499. (f) Hojo ,M.; Masuda, R.; Okada, E. *Tetrahedron Lett.* 1986, *27*, 353. (g) Hojo, M.; Masuda, R.; Okada, E. *Synthesis*, 1990, 347. (h) Hojo, M.; Masuda, R.; Okada, E.; Mochizuki, Y. *Synthesis*, 1992, 455. (i) Effenberger, F.; Maier, R.; Schonwalder, K. H.; Ziegler, T.; *Chem. Ber.* 1982, *115*, 2766. (j) Effenberger, F.; Schonwalder, K. H.; *Chem. Ber.* 1984, *117*, 3270.
- 20. Flores, A.F.C.; Brondani, S.; Zanatta, N.; Martins, M.A.P. Tetrahedron Lett. 2002, 43, 8701.
- Cunico, W.; Cechinel, C. A.; Bonacorso, H. G.; Martins, M. A. P.; Zanatta, N.; Souza, M. V. N.; Freitas, I. O.; Soares, R. P.P.; Krettli, A. U. J. Bioorg. Med. Chem. Lett. 2006, 16, 649.
- Silva, P. E. A.; Ramos, D. F.; Bonacorso, H. G.; Iglesia, A. I.; Oliveira, M. R.; Coelho, T.; Navarini, J.; Morbidni, H. R.; Zanatta, N.; Martins, M. A. P. *Int. J. Antimicro. Ag.* 2008, *32*, 139.

- Sauzem, P. D.; Machado, P.; Rubin, M. A.; Sant'Anna, G. S.; Faber, H. B.; Souza, A. H.; Mello, C. F.; Beck, P.; Burrow, R. A.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *Eur. J. Med. Chem.* 2008, 43, 1237.
- 24. Bonacorso, H. G.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P.; Naue, J. A. J. Fluorine Chem. **1998**, *92*, 23.
- 25. Padwa, A. J. Org. Chem. 1965, 30, 1274.