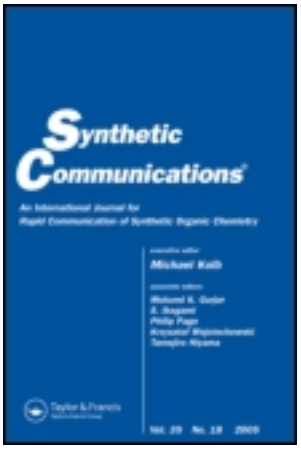


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Tetrahydro-2(1H)quinazolinones, Cyclopenta[d]-2(1H)pyrimidinones and Their Thioxo Analogs from 2-Trifluoroacetyl-1-methoxycycloa

Helio G. Bonacorso [a], Michelle B. Costa [a], Itamar S. Lopes [a], Marlí R. Oliveira [a], Roberta L. Drekener [a], Marcos A. P. Martins [a], Nilo Zanatta [a] & Alex F. C. Flores [a]

[a] Núcleo de Química de Heterociclos—NUQUIMHE, Departamento de Química, Universidade Federal de Santa Maria, Santa Maria, Brazil

Published online: 21 Aug 2006.

Synthetic Communications®, 35: 3055–3064, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500278818

Synthesis of Tetrahydro-2(1*H*)quinazolinones, Cyclopenta[*d*]-2(1*H*)pyrimidinones, and Their Thioxo Analogs from 2-Trifluoroacetyl-1-methoxycycloalkenes

Helio G. Bonacorso, Michelle B. Costa, Itamar S. Lopes, Marlí R. Oliveira, Roberta L. Drekener, Marcos A. P. Martins, Nilo Zanatta, and Alex F. C. Flores
Núcleo de Química de Heterociclos—NUQUIMHE, Departamento de Química, Universidade Federal de Santa Maria, Santa Maria, Brazil

Abstract: A series of six (8)-alkyl-4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)quinazolinones, 4-trifluoromethyl-cyclopenta[*d*]-2(1*H*)pyrimidinones, and their thioxo analogs from the reaction of five β-alkoxyvinyl trifluoromethyl ketones, derived from alkylated cyclohexanones and cyclopentanone with urea and thiourea, is reported. The reactions were carried out in a single step in propan-2-ol as solvent and boron trifluoride diethyl etherate as catalyst in 18–65% yield.

Keywords: Quinazolines, quinazolinones, pyrimidines, pyrimidinones, cycloalkenes

Quinazolines are of great interest for combinatorial library synthesis because of their wide spectrum of biological activities including CNS depressant,[1] analgesic,[2] antibacterial,[3] and anti-HIV[4] activity. Recently, Corbett et al.[4] reported that 4-alkenyl and 4-alkynyl-3,4-dihydro-4-trifluoromethyl-2(1*H*)quinazolinones were potent nonnucleoside reverse transcriptase inhibitors

Received in the USA June 30, 2005
Address correspondence to Helio G. Bonacorso, Núcleo de Química de Heterociclos—NUQUIMHE, Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS, Brazil. E-mail: heliogb@base.ufsm.br

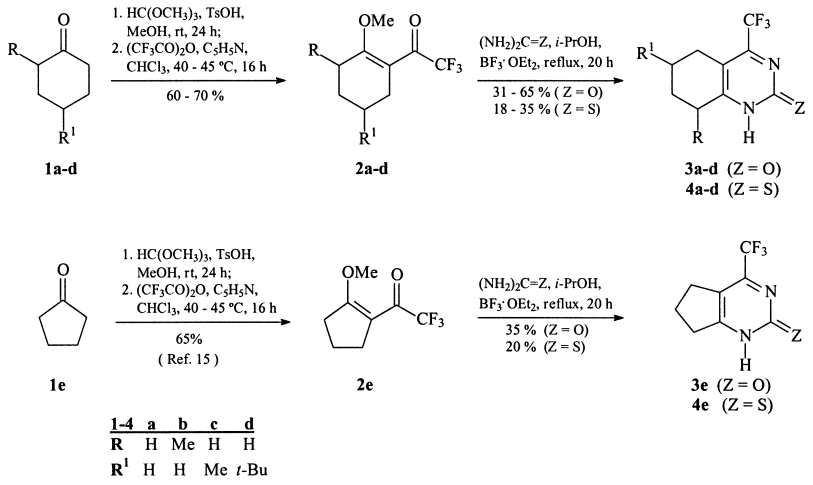
(NNRTIs) of human immunodeficiency virus type 1 (HIV-1). Some of these derivatives exhibited low nanomolar potency toward wild-type RF virus and various single and many multiple amino-acid-substituted HIV-1 mutant viruses. In the same year, 4-polyfluoroalkyl-5,6-oligomethylenepyrimidines have been obtained from the reaction of 2-polyfluoroacyl cycloalkanones derived from cyclopentanone and cyclohexanone with guanidine, urea, thiourea, methylisothiourea, benzamidine, guanylthiourea, dicyanodiamine, and trifluoroacetylurea by Lewis acid catalysis. A decrease in the yield with an increasing in length of the polyfluoroalkyl substituent in the cycloalkanone was observed for reagents with lower nucleophilicity (urea, thiourea, and dicyanodiamide).[5] In 2002, Yarim et al. described how 4-(3-chlorophenyl)- and 4-(3-bromophenyl)-1,7,7-trimethyl-1,2,3,4,5,6,7,8,-octahydroquinazoline-2,5-dione were synthesized by condensing N-methylurea with 5,5-dimethyl-l,3-cyclohexanedione and appropriate aromatic aldehydes according to the Biginelli reaction. These compounds exhibited a calcium antagonist activity on isolated rat ileum and were the most active derivatives compared with nicardipine, used as a reference drug.[6]

Since 1991, studies about the regiochemistry of the cyclocondensation reactions of β-alkoxyvinyl trihalomethyl ketones with urea,[7–9] N-methylurea,[10] 2-methyl-2-thiopseudourea sulfate,[11] guanidine hydrochloride,[12] acetamidine and benzamidine hydrochloride,[13] and N-methyl thiourea[14] have been developed in our research group. However, the employment of β-alkoxyvinyl trihalomethyl ketones with a Lewis acid as catalyst to generate a substituted six- or five-membered carbocycle fused at positions 5 and 6 of the pyrimidine ring resulting in tetramethylene-2(1*H*)pyrimidinones (tetrahydroquinazolinones), cyclopenta[*d*]-2(1*H*)pyrimidin-ones, or their thioxo analogs has not yet been reported.

Despite extensive studies devoted to the synthesis of acyclic β-alkoxyvinyl trihalomethyl ketones and their cyclocondensation reactions involving a variety of nitrogen dinucleophiles, the synthesis and reactions of cyclic β-alkoxyvinyl trihalomethyl ketones has been much less developed. Thus, considering the importance of 2(1*H*)quinazolinones, we now report the synthesis of novel 4(6)-alkyl-2-trifluoroacetyl-l-methoxycyclohexen (and cyclopenten) and the application of these new functionalized cycloalken to synthesize 5,6,7,8-tetrahydro-2(1*H*)quinazolinones, cyclopenta[*d*]-2(1*H*)-pyrimidinones, and their thioxo analogs.

The β-methoxyvinyl trifluoromethyl ketones **2a** and **2e** derived from cyclohexanone (**1a**) and cyclopentanone (**1e**) were prepared previously.[15] I herein, we reported the synthesis of new β-methoxyvinyl trifluoromethyl ketones **2b–d** derived from alkyl-substituted cyclohexanones (**1b–d**). Reaction of the respective 1,1-dimethylcyclohexanone acetals with trifluoroacetic anhydride by a procedure similar to the one described in the literature[15] furnished new heterocycle precursors in high purity and in good yield (Scheme 1).

The cyclization reactions of **2a–e** with urea were carried out in propan-2-ol in the presence of a catalytic amount of boron trifluoride diethyl etherate.



Scheme 1.

The mixtures were stirred for 20 h at reflux to afford 4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)quinazolinones (**3a**–**d**) and 4-trifluoromethyl-cyclopenta[*d*]-2(1*H*)pyrimidinone (**3e**), respectively. Similarly, cyclization of vinylketones **2a**–**e** with thiourea gave 4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)thioquinazolinones (**4a**–**d**) and 4-trifluoromethyl-cyclopenta[*d*]-2(1*H*)thiopyrimidinone (**4e**), in moderate to good yield. All cyclization reactions were monitored by TLC.

Previously, our research group[7–14] synthesized trihalomethyl-2(1*H*)-pyrimidinones using a mixture of methanol and concentrated hydrochloric acid. We found that the use of boron trifluoride diethyl etherate as catalyst, instead of using the conventional procedure, gave more satisfactory results.[7] Herein, we demonstrated that the reaction of β-methoxyvinyl trifluoromethyl ketone **2d** with urea gave a higher yield (50% of **3d**) when catalyzed by boron trifluoride diethyl etherate than the reaction carried out in methanol–hydrochloric acid (<20% of **3d**). Compounds **3a**, **4a**, and **4e** have been previously synthesized by Sevenard et al., who reacted 2-trifluoroacetylcyclohexanone with urea and thiourea or 2-trifluoroacetylcyclopentanone with thiourea in 64%, 34%, and 16% yields, respectively.[5] These improved yields were obtained only when the reactions were carried out in propan-2-ol in the presence of boron trifluoride diethyl etherate. These reactions, when conducted in our laboratory without boron trifluoride diethyl etherate, rendered <30% yield with urea for **3a** and <10% yield with thiourea for **4a** and **4e**.

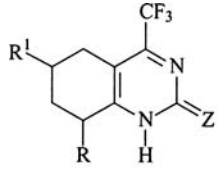
In the present work we have synthesized the same three products (**3a**, **4a**, and **4e**) reported by Sevenard[5] but now using cyclic β-methoxyvinyl trifluoromethyl ketones **2a** and **2e** instead of 1,3-diketones. In this case, we obtained

very similar yields of 65%, 35%, and 20%, respectively. However, we observed a decrease in yield (Table 1) when the enones **2** bear an alkyl substituent on positions 4 (R^1 = Me and *t*-Bu) and 6 (R = Me). Because of the reaction conditions and the reagents adopted in this work, it seems that the thermodynamic stability of products **3** and **4** governs its formation, but one can observe that when a methyl group is attached to the carbon 6 (e.g., **2b**), a reasonable steric interference should be considered in the quinazolinone synthesis pathway.

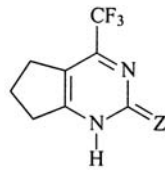
As expected, a minor steric interference is observable for substituents attached to carbon-4 at the cyclohexenes **2c**–**d**. In comparation to the synthesis of quinazolinones **3a**–**d**, a decrease of the yields for the synthesis of thioquinazolinones **4a**–**d** was observed. However, in this case, the substituent effect of the alkyl groups attached to carbon 6 (**2b**) and carbon 4 (**2c**–**d**) does not decrease the yield. After 1 h at reflux we observed that all cyclizations involving thiourea showed a dark yellow color and had an unpleasant sulfide-like smell. Thus, the lower yield obtained for these cyclizations may probably be due to the decomposition of the thiourea.

In conclusion, the present methodology allows us to obtain a series of trifluoromethylated 5,6,7,8-tetrahydro-2(1*H*)quinazolinones, cyclopenta[*d*]-2(1*H*)pyrimidinones, and their thioxo analogs from β-alkoxyvinyl trifluoromethyl ketones, derived from substituted cyclohexanones and cyclopentanone,

Table 1. Yields for the synthesis of 4-trifluoromethyl-5,6,7,8-tetrahydro 2(1*H*)quinazolinones and 4-trifluoromethyl-cyclopenta[*d*]-2(1*H*)pyrimidinone, and their thioxo analogs (**3a**–**e**, **4a**–**e**)



3a-d, 4a-d



3e, 4e

No.	R	R^1	Z	Yield (%)
3a	H	H	O	65
3b	Me	H	O	31
3c	H	Me	O	40
3d	H	*t*-Bu	O	50
3e	—	—	O	35
4a	H	H	S	35
4b	Me	H	S	20
4c	H	Me	S	18
4d	H	*t*-Bu	S	25
4e	—	—	S	20

in a single step and in moderate to good yield. In addition we observed that the cyclization yield depends on two factors. The reaction yield is very sensitive to first the nucleophile employed [i.e., urea (31–65%) and thiourea (18–35%)], and second the inclusion of alkyl substituents at positions 4 and 6 of the vinyl ketones.

EXPERIMENTAL

Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz and ^{13}C at 100.62 MHz) with 5-mm sample tubes, at 298 K, at digital resolution ± 0.01 ppm, in $CDCl_3$ (**2a–e**) or in DMSO-d_6 (**3, 4a–e**), and using TMS as internal reference. Mass spectra were registered in a Hewlett-Packard Company 6890 GC connected to a HP 5973 Mass Selective Detector and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector, autosampler, and cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier gas. The CHN elemental analyses were performed on a Perkin Elmer 2400 CHN elemental analyzer (USP University, São Paulo, Brazil).

Synthesis of 2-Trifluoroacetyl-1-methoxycycloalkenes

Trifluoroacetic anhydride (60 mmol) was added dropwise to a stirred solution of dimethoxy acetals derived from cycloalkanones (30 mmol) and pyridine (60 mmol, 4.8 g) in chloroform (30 mL) kept at 0°C (ice bath). The mixture was stirred for 16 h at 45°C. The mixture was quenched and extracted with 0.1 M hydrochloric acid solution (3×15 mL) and then with water (1×15 mL). The organic layer was dried with magnesium sulfate and filtered. The filtrate was evaporated and the products were obtained in high purity by distillation under reduced pressure.

Data

2-Trifluoroacetyl-1-methoxycyclohexene (2a). Yellow oil; yield 68%; bp 43–45°C/2.8 mbar. Lit.[15]: yield 65%; bp 106–109/10 mbar. ^{1}H NMR ($CDCl_3$) $\delta = 3.7$ (s, 3H, OCH_3); 2.45–2.42 (m, 2H, CH_2); 2.33–2.30 (m, 2H, CH_2); 1.80–1.74 (m, 2H, CH_2); 1.65–1.59 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) $\delta = 181.4$ (C=O, $^{2}J_{CF} = 35.3$); 170.1 (C-1); 116.8 (CF_3, $^{1}J_{CF} = 288.9$); 110.4 (C-2); 54.8 (OCH_3); 25.9 (CH_2); 24.1 (CH_2); 22 (CH_2); 21.6 (CH_2).

MS [m/z (%)] for $C_9H_{11}F_3O_2$ (208.18): 208 (M^+, 42), 139 (100), 79 (66), 69 (31).

6-Methyl-2-trifluoroacetyl-1-methoxycyclohexene (2b). Yellow oil; yield 60%; bp 79–81°C/3.5 mbar. ^{1}H NMR ($CDCl_3$) $\delta = 3.7$ (s, 3H, OCH_3); 2.77 (m, 1H, CH_2); 2.52–2.44 (m, 1H, CH_2); 2.20–2.05 (m, 1H, CH_2); 1.72–1.59 (m, 4H, CH_2); 1.2 (d, 3H, $J_{HH} = 7.1$, CH_3). ^{13}C NMR ($CDCl_3$) $\delta = 182.9$ (C═O, $^2J_{CF} = 36.7$); 172.7 (C-1); 116.6 (CF_3, $^1J_{CF} = 288.9$); 112.1 (C-2); 55.4 (OCH_3); 29.7 (CH_2); 28.9 (CH_2); 24.4 (CH_2); 18.2 (CH_2); 17.6 (CH_3). MS [m/z (%)] for $C_{10}H_{13}F_3O_2$ (222.20): 222 (M^+, 24), 153 (100), 93 (33), 69 (15).

4-Methyl-2-trifluoroacetyl-1-methoxycyclohexene (2c). Yellow oil; yield 60%; bp 89–92°C/3.4 mbar. ^{1}H NMR ($CDCl_3$) $\delta = 3.7$ (s, 3H, OCH_3); 2.53–2.40 (m, 3H, CH_2); 1.89–1.77 (m, 2H, CH_2); 1.67–1.61 (m, 1H, CH_2); 1.45–1.30 (m, 1H, CH_2); 1.0 (d, 3H, $J_{HH} = 6.6$, CH_3). ^{13}C NMR ($CDCl_3$) $\delta = 181.3$ (C═O, $^2J_{CF} = 35.3$); 169.9 (C-1); 116.8 (CF_3, $^1J_{CF} = 289.6$); 109.8 (C-2); 54.9 (OCH_3); 32.2 (CH_2); 29.9 (CH_2); 27.9 (CH_2); 25.8 (CH_2); 20.7 (CH_3). MS [m/z (%)] for $C_{10}H_{13}F_3O_2$ (222.20): 222 (M^+, 8), 153 (100), 69 (9).

4-(1,1-Dimethyethyl)-2-trifluoroacetyl-1-methoxycyclohexene (2d). Yellow oil; yield 60%; bp 84–86°C/1.5 mbar. ^{1}H NMR ($CDCl_3$) $\delta = 3.7$ (s, 3H, OCH_3); 2.68–2.47 (m, 2H, CH_2); 2.41–2.35 (m, 1H, CH_2); 1.98–1.86 (m, 2H, CH_2); 1.33–1.21 (m, 2H, CH_2); 0.9 (s, 9H, $3CH_3$). ^{13}C NMR ($CDCl_3$) $\delta = 181.6$ (C═O, $^2J_{CF} = 35.3$); 170.1 (C-1); 116.8 (CF_3, $^1J_{CF} = 289.6$); 110.3 (C-2); 54.9 (OCH_3); 43.5 (CH_2); 32.1 (CH_2); 27.3, 27.1 (t-Bu); 25.5 (CH_2); 23.3 (CH_2). MS [m/z (%)] for $C_{13}H_{19}F_3O_2$ (264.28): 264 (M^+, 21), 249 (66), 111 (50), 57 (100).

2-Trifluoroacetyl-1-methoxycyclopentene (2e). Yellow oil; yield 65%; bp 49–50°C/3.2 mbar. Lit.[15]: yield 70%; bp 97–99°C/10 mbar. ^{1}H NMR ($CDCl_3$) $\delta = 3.9$ (s, 3H, OCH_3); 2.80–2.76 (m, 2H, CH_2); 2.70–2.66 (m, 2H, CH_2); 1.99–1.91 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) $\delta = 177.4$ (C-1); 175.4 (C═O, $^2J_{CF} = 36.03$); 116.5 (CF_3, $^1J_{CF} = 290.3$); 107.9 (C-2); 58.4 (OCH_3); 31.6 (CH_2); 28.2 (CH_2); 19.1 (CH_2). MS [m/z (%)] for $C_8H_9F_3O_2$ (194.15): 194 (M^+, 17), 125 (100), 95 (7), 67 (22).

Synthesis of 4-Trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)quinazolinones, 4-Trifluoromethyl-cyclopenta[*d*]-2(1*H*)pyrimidinone, and their thioxo analogs (3a–e, 4a–e)

Ketone **2** (5 mmol) and boron trifluoride diethyl etherate (sol. 45% in MeOH) (10 drops) were added to a stirred solution of urea or thiourea (7 mmol) in

propan-2-ol (10 mL) kept at room temperature (20–25°C). The mixture was stirred for 20 h at 85°C for compounds **3a–d** and **4a–d** and at 65°C for **3e** and **4e**. After cooling (<10°C), the crystalline solids were filtered off, washed with water to remove the residual urea or thiourea, and recrystallized from ethanol.

Data

4-Trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)quinazolinone (3a). Yellow solid; yield 65%; mp 208–210°C. Lit.[5]: yield 64%; mp 206–207°C. ^{1}H NMR (DMSO-d_6) $\delta = 12.6$ (s, 1H, NH); 2.7 (m, 2H, CH_2); 2.5 (m, 2H, CH_2); 1.7 (m, 4H, CH_2). ^{13}C NMR (DMSO-d_6) $\delta = 162.9$ (C=0); 158.6 (C-4, $^2J = 31.8$); 155.9 (C-8a); 120.6 (CF_3, $^1J = 279$); 109.4 (C-4a); 27.6 (CH_2); 21.4 (CH_2); 21.2 (CH_2); 20 (CH_2). MS [m/z (%)] for $C_9H_9F_3N_2O$ (218.18) = 218 (*M*+, 100), 149 (27), 69 (30).

8-Methyl-4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)quinazolinone (3b). Yellow solid; yield 31%; mp 187–189°C. ^{1}H NMR (DMSO-d_6) $\delta = 12.5$ (s, 1H, H-1), 2.92–2.84 (m, 1H, CH), 2.62–2.60 (m, 2H, CH_2), 1.87–1.85 (m, 2H, CH_2), 1.73–1.66 (m, 2H, CH2), 1.3 (d, 3H, H-9). ^{13}C NMR (DMSO-d_6) $\delta = 168.1$ (C=0); 157.6 (C-4, $^2J_{CF} = 52.3$); 150.9 (C-8a); 120.6 (CF_3, $^1J_{CF} = 278.3$); 110.7 (C-4a); 37.2 (C-8); 27.9 (CH_2); 22.1 (CH_2); 20.2 (CH_3); 18.2 (CH_2). MS [m/z (%)] for $C_{10}H_{11}F_3N_2O$ (232.21) = 232 (*M*+, 49), 217 (100), 163 (3), 69 (8). Anal. calcd. for $C_{10}H_{11}F_3N_2O$ (232.21) = C, 51.73; H, 7.77; N, 12.06%. Found: C, 51.82; H, 4.47; N, 11.92%.

6-Methyl-4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)quinazolinone (3c). Yellow solid; yield 40%; mp 212–214°C. ^{1}H NMR (DMSO-d_6) $\delta = 12.5$ (s, 1H, H-1), 2.74–2.70 (m, 3H, CH_2), 2.18–2.05 (m, 1H, CH_2), 1.80 (m, 2H, CH_2), 1.42–1.32 (m, 1H, CH), 1.0 (d, 3H, CH_3). ^{13}C NMR (DMSO-d_6) $\delta = 162.5$ (C=O), 158.2 (C-4, $^2J_{CF} = 31.8$), 155.7 (C-8a), 120.4 (CF_3, $^1J_{CF} = 279.04$), 108.9 (C-4a), 29.5 (CH_2), 27.8 (CH_2), 27.4 (C-6), 20.9 (CH_3). MS [m/z (%)] for $C_{10}H_{11}F_3N_2O$ (232.21) = 232 (*M*+, 100), 217 (87), 163 (16), 69 (22). Anal. calcd. for $C_{10}H_{11}F_3N_2O$ (232.21) = C, 51.73; H, 7.77; N, 12.06%. Found: C, 51.96; H, 4.67; N, 12.15%.5

6-(1,1-Dimethylethyl)-4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*) quinazolinone (3d). Yellow solid; yield 50%; mp 229–231°C. ^{1}H NMR (DMSO-d_6) $\delta = 12.5$ (s, 1H, H-1), 2.79–2.75 (m, 1H, CH), 2.67–2.63 (m, 2H, CH_2), 2.24–2.17 (m, 1H, CH_2), 1.95–1.93 (m, 1H, CH_2), 1.38–1.29 (m, 2H, CH_2), 0.9 (s, 9H, $3CH_3$). ^{13}C NMR (DMSO-d_6) $\delta = 168.5$ (C=O), 164.3 (C-4,

$^{2}J_{CF} = 33.2$), 161.7 (C-8a), 126.4 (CF_3, $^{1}J_{CF} = 278.3$), 115.4 (C-4a), 48.6 (C-6), 37.9 (CH_2), 34.6 (C_{quat}), 32.7 ($3CH_3$), 28.8 (CH_2), 27.3 (CH_2). MS [m/z (%)] for $C_{13}H_{17}F_3N_2O$ (274.29) = 274 (*M*+, 5), 218 (76), 69 (3), 56 (100). Anal. calcd. for $C_{13}H_{17}F_3N_2O$ (274.29) = C, 56.93; H, 6.25; N, 10.21%. Found: C, 56.64; H, 6.00; N, 10.31%.

4-Trifluoromethyl-cyclopenta[*d*]-2(1*H*)pyrimidinone (3e). Brown solid; yield 35%; mp 183–185°C. ^{1}H NMR (DMSO-d_6) $\delta = 12.6$ (s, 1H, NH), 2.93–2.86 (m, 4H, CH_2), 2.13–2.05 (m, 2H, CH_2). ^{13}C NMR (DMSO-d_6) $\delta = 176.8$ (C=O), 160.4 (C-8a), 152.7 (C-4, $^{2}J_{CF} = 31.1$), 120.6 (CF_3, $^{1}J_{CF} = 276.2$), 118.2 (C-4a), 32.2 (CH_2), 27.04 (CH_2), 21.9 (CH_2). MS [m/z (%)] for $C_8H_7F_3N_2O$ (204.15) = 204 (*M*+, 83), 107 (100), 135 (55). Anal. calcd. for $C_8H_7F_3N_2O$ (204.15) = C, 47.07; H, 3.46; N, 13.72%. Found: C, 47.66; H, 4.07; N, 14.58%. (highly hygroscopic compound).

4-Trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)thioquinazolinone (4a). Yellow solid; yield 35%; mp 130–132°C. Lit.[5]: yield 34%; mp 123°C. ^{1}H NMR (DMSO-d_6) $\delta = 14.2$ (s, 1H, H-1), 2.8 (m, 2H, CH_2), 2.6 (m, 2H, CH_2), 1.73–1.72 (m, 4H, CH_2). ^{13}C NMR (DMSO-d_6) $\delta = 171.9$ (C-2), 164.3 (C-8a), 151.8 (C-4, $^{2}J_{CF} = 40.97$), 125.7 (C-4a), 120.9 (CF_3, $^{1}J_{CF} = 275.5$), 32.3 (CH_2), 22.9 (CH_2), 20.7 (CH_2), 18.5 (CH_2). MS [m/z (%)] for $C_9H_9F_3N_2S$ (234.24) = 234 (*M*+, 100), 165 (22), 69 (1).

8-Methyl-4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)thioquinazolinone (4b). Yellow solid; yield 20%; mp 176–178°C. ^{1}H NMR (DMSO-d_6) $\delta = 2.93$–2.89 (m, 2H, CH_2), 2.88–2.84 (m, 2H, CH_2), 2.01–1.97 (m, 2H, CH_2), 1.87–1.85 (m, 2H, CH_2), 1.75–1.73 (m, 2H, CH_2), 1.54–1.48 (m, 2H, CH_2), 1.40–1.34 (m, 1H, CH), 1.27–1.25 (m, 1H, CH), 1.12 (d, 3H, CH_3), 1.02 (d, 3H, CH_3). ^{13}C NMR (DMSO-d_6) $\delta = 174.9$ (C=O), 164.2 (C-8a), 151.8 (C-4, $^{2}J_{CF} = 33.2$), 124.9 (C-4a), 120.8 (CF_3, $^{1}J_{CF} = 276.9$), 35.7 (C-8), 28.8 (CH_2), 23.2 (CH_2), 19.2 (CH_3), 18.9 (CH_2). MS [m/z (%)] for $C_{10}H_{11}F_{13}N_2S$ (248.27) = 248 (*M*+, 79), 233 (100), 179 (17), 69 (9). Anal. calcd. for $C_{10}H_{11}F_{13}N_2S$ (248.27) = C, 48.38; H, 4.47; N, 11.28%. Found: C, 48.63; H, 4.25; N, 11.29%.

6-Methyl-4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)thioquinazolinone (4c). Yellow solid; yield 18%; mp 167–169°C. ^{1}H NMR (DMSO-d_6) $\delta = 14.3$ (s, 1H, H-1), 2.79–2.64 (m, 3H, CH_2), 2.19–2.05 (m, 1H, CH_2), 1.78 (m, 2H, CH_2), 1.45–1.31 (m, 1H, CH), 1.0 (d, 3H, CH_3, $J_{HH} = 6.0$). ^{13}C NMR (DMSO-d_6) $\delta = 171.5$ (C=O), 164.3 (C-8a), 153.8 (C-4, $^{2}J_{CF} = 33.2$), 120.3, ($CF_3 J_{CF} = 278.3$), 114.9 (C-4a), 29.6 (CH_2), 27.4 (CH_2), 26.9 (CH_2), 26.7 (C-6), 20.8 (CH_3). MS [m/z (%)] for $C_{10}H_{11}F_{13}N2S$ (248.27) = 248 (*M*+, 100), 233 (44), 179 (12), 149 (31). Anal. calcd. for $C_{10}H_{11}F_{13}N_2S$ (248.27) = C, 48.38; H, 4.47; N, 11.28%. Found: C, 48.66; H, 4.28; N, 11.20%.

6-(1,1-Dimethylethyl)-4-trifluoromethyl-5,6,7,8-tetrahydro-2(1*H*)thioquinazolinone (4d). Yellow solid; yield 25%; mp 126–128°C. ^{1}H NMR (DMSO-d_6) $\delta = 14.2$ (s, 1H, H-1), 2.99–2.90 (m, 2H, CH_2), 2.54 (m, 1H, CH), 2.06–2.05 (m, 1H, CH_2), 1.54–1.38 (m, 2H, CH_2), 0.9 (s, 9H, $3CH_3$). ^{13}C NMR (DMSO-d_6) $\delta = 171.6$ (C═O), 163.6 (C-8a), 152.2 (C-4, $^2J_{CF} = 33.2$), 126.4 (C-4a), 121.0 (CF_3, $^1J_{CF} = 277.6$), 42.5 (C-6), 32.9 (CH_2), 31.9 (C_{quat}), 26.6 ($3CH_3$), 24.4 (CH_2), 22.1 (CH_2). MS [m/z(%)] for $C_{13}H_{17}F_3N_2S$ (290.35) = 290 ($M+$, 49), 234 (61), 69 (3), 56 (100). Anal. calcd. for $C_{13}H_{17}F_3N_2S$ (290.35) = C, 53.78; H, 5.90; N, 9.65%. Found: C, 54.14; H, 5.99; N, 10.02%.

4-Trifluoromethyl-cyclopenta[*d*]-2(1*H*)thiopyrimidinone (4e). Brown solid; yield 20%; mp 138–140°C. Lit.[5]: yield 16%; mp 130–131°C ^{1}H NMR (DMSO-d_6) $\delta = 3.07$–2.98 (m, 4H, CH_2), 2.15–2.11 (m, 2H, CH_2). ^{13}C NMR (DMSO-d_6) $\delta = 181.5$ (C-2), 166.3 (C-7a), 148.5 (C-4, $^2J = 36$), 129.9 (C-4a), 120.6 (CF_3, $^1J = 275.5$), 33.4 (CH_2), 27.4 (CH_2), 21.6 (CH_2). MS [m/z (%)] for $C_8H_7F_3N_2S$ (220.21) = 220 ($M+$, 100), 201 (8), 151 (46), 69 (17).

ACKNOWLEDGMENTS

The authors are thankful to Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial support. Fellowships from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (to M. R. Oliveira and M. B. Costa) and Fundação de Apoio à Ciência e Tecnologia (FATEC) (to R. L. Drekener) are also acknowledged.

REFERENCES

1. Weaver, L. C.; Jones, W. R.; Kerley, T. L. *Arch. Int. Pharmacodyn.* **1963**, *143*, 119.
2. Leszkovskzky, E. I.; Tardos, L. *Acta Physiol.* **1964**, 81.
3. Elslager, E. F.; Colbry, N. L.; Davoll, J.; Hutt, M. P.; Johnson, J. L.; Werbel, L. M. *J. Med. Chem.* **1984**, *27*, 1740.
4. Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhardt, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *J. Med. Chem.* **2000**, *43*, 2019.
5. Sevenard, D. V.; Khomutov, O. G.; Koryakova, O. V.; Sattarova, V. V.; Kodess, M. I.; Stelten, J.; Loop, I.; Lork, E.; Pashkevich, K. I.; Röschenthaler, G.-V. *Synthesis* **2000**, 1738.
6. Yarim, M.; Saraç, S.; Kiliç, F. S.; Erol, K. *Il Farmaco* **2002**, *58*, 17.
7. Zanatta, N.; Pachoski, I. L.; Martins, M. A. P.; Blanco, I. *J. Braz. Chem. Soc.* **1991**, *2*, 118.

8. Zanatta, N.; Madruga, C. C.; Marisco, P. C.; Flores, A. F. C.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **2000**, *37*, 1213.
9. Bonacorso, H. G.; Lopes, I. S.; Wastowski, A. D.; Zanatta, N.; Martins, M. A. P. *J. Fluorine. Chem.* **2003**, *120*, 29.
10. Blanco, I.; Pacholski, I. L.; Zanatta, N.; Martins, M. A. P. *Quim. Nova* **1993**, *16*, 15.
11. Zanatta, N.; Madruga, C. C.; Clerici, E.; Martins, M. A. P. *J. Heterocycl. Chem.* **1995**, *32*, 735.
12. Zanatta, N.; Corteline, M. F.M.; Carpes, M. J. S.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1997**, *34*, 509.
13. Zanatta, N.; Fagundes, M. B.; Ellenshon, R.; Marques, M.; Bonacorso, H. G.; Martins, M. A.P. *J. Heterocycl. Chem.* **1998**, *35*, 451.
14. Bonacorso, H. G.; Martins, M. A. P.; Bittencourt, S. R. T.; Lourega, R. V.; Zanatta, N.; Flores, A. F.C. *J. Fluorine Chem.* **1999**, *99*, 177.
15. Flores, A. F. C.; Siqueira, G. M.; Freitag, R. A.; Zanatta, N.; Martins, M. A. P. *Quím. Nova* **1994**, *17*, 298; *Chem. Abstr.* **1994**, *121*, 230377.