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Article

Efficient Synthesis of New Biheterocyclic 5-[(5-Trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidines

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Neste trabalho relatamos a ciclocondensação entre a 2-metil-7-trifluorometilpirazolo[1,5-*a*] pirimidino-5-propanoil hidrazida derivada da 2-metil-5-(metilpropanoato-3-il)-7-trifluorometilpirazolo[1,5-*a*]pyrimidina e doze versáteis 1,1,1-trifluoro-4-alcóxi-3-alquen-2-onas [$F_3CC(O)C(R^2)=C(R^1)OMe$ onde R^1 = H, Me, $(CH_2)_2CHCMe_2$, $(CH_2)_2Ph$, $(CH_2)_2CO_2Me$, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, EtO e R^2 = H; R^1, R^2 = -$(CH_2)_4$-, -$(CH_2)_5$-; R^1 = Ph e R^2 = Me]. A estrutura molecular dos produtos 5-[(5-trifluorometil-5-hidroxi-4,5-diidro-1*H*-pirazol-1-il)-1-propan-1-ona-3-il]-2-metil-7-trifluorometilpirazolo[1,5-*a*]pirimidinas, novos bihetererociclos contendo o espaçador propionil, foram atribuídas com base nos dados de ressonância magnética nuclear (NMR) de ^1H, ^{13}C e ^{19}F, e espectrometria de massas (MS).

Twelve new 5-[(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidines were prepared by cyclocondensation between 2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine-5-propanoyl hydrazide derived from 2-methyl-5-(methylpropanoate-3-yl)-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine and a series of versatile 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones [$F_3CC(O)C(R^2)=C(R^1)OMe$ where R^1 = H, Me, $(CH_2)_2CHCMe_2$, $(CH_2)_2Ph$, $(CH_2)_2CO_2Me$, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, EtO and R^2 = H; R^1, R^2 = -$(CH_2)_4$-, -$(CH_2)_5$-; R^1 = Ph and R^2 = Me]. The structures of new propionyl-spaced biheterocycles were derived from ^1H, ^{13}C, and ^{19}F nuclear magnetic resonance (NMR) spectroscopy and mass spectrometric (MS) data.

Keywords: heterocycles, pyrazolo[1,5-*a*]pyrimidines, pyrazoles, levulinic acid

Introduction

There has been increasing interest in the chemistry of organic trifluoromethyl compounds, largely due to the fact that they show enhanced biological activity and can be used as medicinal or agricultural chemicals, in addition to their role in the development of new potential technological materials. The presence of trifluoromethyl groups in organic substances modifies the physicochemical profile, increasing lipophilicity and metabolic stability.[1-3] The synthesis of trifluoromethyl heterocycles using a readily available building block with a trifluoromethyl group has often been found to be superior to selective introduction of a trifluoromethyl group into heterocyclic compounds as well as conversion of a carboxylic group into a trifluoromethyl group.[4-8]

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Heterocycles are present in a wide variety of drugs, biomolecules and biologically active compounds, and they are often key structural units in pharmaceuticals and agrochemicals.[9] Among them, pyrazolo[1,5-*a*]pyrimidine rings have been shown to possess anti-inflammatory activity,[10,11] inhibitory activity against monoamine oxidase, which is crucial in compounds used for the treatment of Parkinson's and Alzheimer's diseases,[12] anticonvulsant activity[13,14] and cytotoxicity against cancer cell lines.[15,16] In addition, some pyrazole derivatives are used as insecticides,[17,18] analytical reagents for the complexation of transition metal ions[19,20] and ultraviolet stabilizers in the dyeing industry. Owing to their versatile chemotherapeutic uses, a large amount of research has been focused on these nuclei.[21]

Recently, we reported the synthesis of methyl 1,1,1-trihalo-4-methoxy-6-oxo-4-heptenoates, derived

from renewable levulinic acid, as building blocks for the production of promising trifluoromethyl containing heterocyclic systems.[22,23] In a continuation of our interest in the versatility of precursors 7,7,7-trihalo-4-methoxy-6-oxo-4-heptenoates, we herein report an efficient procedure for synthesizing new heterocyclic systems using a propionyl spacer between heterocyclic pyrazolo[1,5-*a*]pyrimidine and pyrazole nuclei, namely 5-[(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidines. The behavior of 2-methyl-7-trifluoromethylpyrazolo[1,5-*a*] pyrimidine-5-propanoyl hydrazide (**2**) towards some 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones as potential precursors for interesting biologically active biheterocyclic systems was investigated.

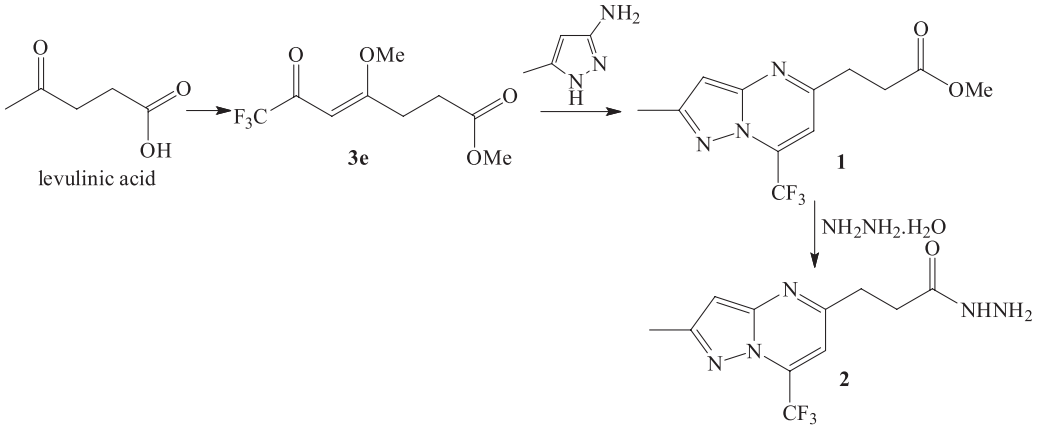
Results and Discussion

The 2-methyl-7-trifluoromethylpyrazolo[1,5-*a*] pyrimidine-5-propanoyl hydrazide (**2**) was obtained from 2-methyl-5-(methylpropanoate-3-yl)-7-trifluoromethyl pyrazolo[1,5-*a*]pyrimidine **1** as described previously (Scheme 1).[22]

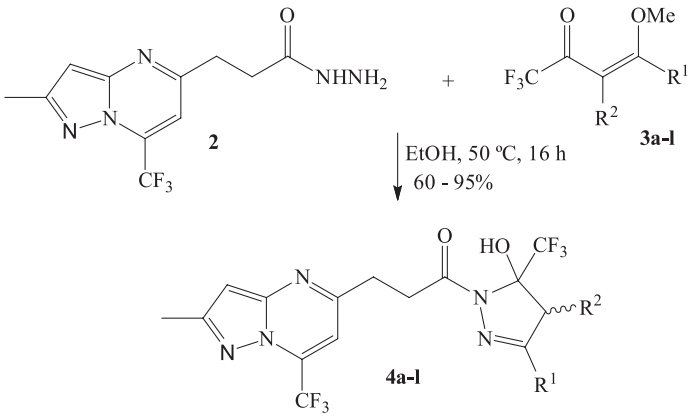
Various 1,1,1-trifluoro-4-methoxy-3-alken-2-ones (**a**-**l**) were obtained by reacting enol ether or acetal with trifluoroacetic anhydride.[23,24] The reaction between **3e** and 3-amino-5-methyl-1*H*-pyrazole was performed under conditions described previously[22] and there was exclusive formation of 2-methyl-5-(methylpropanoate-3-yl)-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine **1** (Scheme 1).[22] The condensation of 3-heteroarylpropanoyl hydrazide **2** with 1,1,1-trifluoro-4-methoxy-3-penten-2-one (**3b**) was carried out in MeOH at 25 °C for 24 h, and the reactants were not consumed (see Supplementary Information). When performing the reaction at 50 °C, the reactants were completely consumed after 16 h, leading to biheterocyclic derivative **4b** at a yield of 89%. At the refluxing temperature of MeOH, 65 ºC, the reaction led to the same product within the same reaction time with only a slight decrease in yield (85%). The reaction conducted in EtOH at 50 ºC also led to product **4b** at 85% yield, although this is again slightly lower than the 89% yield achieved with MeOH; we chose to use EtOH for further cyclocondensations due its lower toxicity and greater eco-affinity. These conditions were extended for the entire series of 1,1,1-trifluoro-4-alkoxy-3-alken-2-ones for cyclocondensations with hydrazide **2** (Scheme 2), the 4,5-dihydro-1*H*-pyrazole derivatives **4a**-**l** were the only products obtained in the [3 + 2] cyclocondensation reactions. We attempted to perform the aromatization of 1*H*-pyrazoles (**4b**, **4d**, **4f**, **4l**) using 98% H_2SO_4, however, probably due to the hydrolysis of the carboxamide bond, we isolated 3-[(2-methyl-7-trifluoromethyl)pyrazolo[1,5-*a*] pyrimidin-5-yl]propanoic acid (**5**), but no amount of the corresponding aromatic 1-substituted 1*H*-pyrazoles.

After the cyclocondensation reactions, each product was isolated, purified by recrystallization or column chromatography, and identified by nuclear magnetic resonance (NMR) spectroscopy, liquid chromatography-electrospray ionization mass spectrometry (LC-ESI-MS) and elemental analysis.

The ^{1}H NMR spectra for biheterocyclic derivatives **4a**-**l** showed a general feature, namely displaying signals related to two methylenes from the propionyl chain and the diastereotopic H-4 from the 1*H*-pyrazole ring overlapping at about δ 2.9 to 3.5 ppm.[25] The signal related to methylenes from the propionyl chain consisted of two triplets (multiplets) or an enlarged singlet. The signal for H-6 from the pyrimidine ring was at δ 7.1 to 7.4 ppm. The ^{13}C NMR spectra showed the characteristic signals for each derivative series. Two quartet signals related to the CF_3 group were found at about δ 120 ppm with $^3J_{CF}$ 275 Hz, the one related to C6 from the pyrimidine ring was at about δ 155 ppm with J_{CF} 36 Hz, and the one related to C5 from the pyrazole ring was at about δ 90 to 92 ppm with $^3J_{CF}$ 35 Hz. The signals



Scheme 1. Synthesis of 2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine-5-propanoyl hydrazine.



	a	b	c	d	e	f	g	h	i	j	k	l
R^1	H	Me	$-(CH_2)_2CHC(Me)_2$	$-(CH_2)_2Ph$	$-(CH_2)_2CO_2Me$	Ph	$4\text{-}MeC_6H_4$	$4\text{-}MeOC_6H_4$	OEt	$-(CH_2)_4-$	$-(CH_2)_5-$	Ph
R^2	H	H	H	H	H	H	H	H	H			Me

Scheme 2. Synthesis of 5-[(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*] pyrimidines.

related to propionyl methylenes appeared at 31 to 32 ppm, and the carbonyl carbon signal appeared at about 174 ppm (see Supplementary Information).

Conclusions

In conclusion, we present a novel method for synthesizing biheterocyclic products, demonstrating the versatility of precursors methyl 7,7,7-trifluoro-4-methoxy-oxohept-6-enoate in cyclocondensations [3 + 3] and [3 + 2]. The dielectrophilic moiety in precursors **3a-l** regioselectively reacts with both the 3-amino-5-methyl-1*H*-pyrazole as well as hydrazide dinucleophiles. This is an efficient protocol for the preparation of diverse 5-[(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*] pyrimidine derivatives at good yields. These compounds are interesting structural analogues to central nervous system chemical mediators, making them good subjects for studies of biological activity. To the best of our knowledge, no biheterocyclic 5-[(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidines have been previously described.

Experimental

^1H and ^{13}C NMR spectra were collected at 300 K using a Bruker 5 mm dual probe on a Bruker DPX 400 spectrometer (^1H at 400.13 MHz, ^{19}F at 376.4 MHz and ^{13}C at 100.62 MHz). Chemical shifts (δ) are quoted in ppm from tetramethylsilane (TMS) and coupling constants (*J*) are given in Hz. The chemical shifts in the ^{19}F NMR spectrum are quoted in ppm from fluorobenzene at –113.15 ppm which was referenced from $CFCl_3$ at 0 ppm. Melting points were determined using open capillaries on an Electrothermal Mel-Temp 3.0 apparatus. The electrospray ionization (ESI) mass spectra were performed on an Agilent 6460 Triple Quadrupole connected to a 1200 series LC and equipped with a solvent degasser, binary pump, column oven, auto-sampler, and an ESI source. The Agilent QQQ 6460 tandem mass spectrometer was operated in the positive jet stream ESI mode. Nitrogen was used as a nebulizer, turbo (heater) gas, curtain gas, and collision activated dissociation gas. The capillary voltage was set at +3500 V and the nozzle voltage was at +500 V. The ion source gas temperature was 300 °C with a flow rate of 5 L min^{-1}. The jet stream sheath gas temperature was 250 °C with a flow rate of 11 L min^{-1}. All samples were infused into the ESI source at a flow rate of 5 µL min^{-1}. Data were acquired in positive MS total ion scan mode (mass scan range *m/z* 50-650) and in positive MS/MS product ion scan mode. The mass spectra recorded were evaluated by the Qualitative Analysis software from Agilent Technologies. CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (University of São Paulo (USP), Brazil).

Synthesis of 2-methyl-7-trifluoromethylpyrazolo[1,5-*a*] pyrimidine-5-propanehydrazine **2**: general procedure

A solution of 5 mmol 2-methyl-5-(methylpropanoate-3-yl)-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**1**) and 12.5 mmol hydrazine monohydrate in 15 mL anhydrous methanol was heated under reflux for 5 h. MeOH was

evaporated under reduced pressure. Then, the solid was washed with distilled water. Product **2** was obtained (80%) as a white solid; m.p. (H_2O) 180-181 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (s, 3H, CH_3), 2.73 (t, 2H, J_{HH} 6.93 Hz, CH_2), 3.01 (s, 2H, NH_2), 3.24 (t, 2H, J_{HH} 6.93 Hz, CH_2), 6.50 (s, 1H, H3), 6.98 (s, 1H, H6), 7.14 (s, 1H, NH); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 14.6 (CH_3), 31.4 (CH_2), 32.7 (CH_2), 96.8 (C-3), 105.7 (q, J_{CF} 4.15 Hz, C-6), 119.5 (q, J_{CF} 274.4 Hz, CF_3), 133.4 (q, J_{CF} 37.3 Hz, C-7), 150.0 (C-2), 156.5 (C-3a), 159.3 (C-5), 172.9 (CO); ^{19}F{^{1}H} ($CDCl_3$, 376.4 MHz) δ –61.86 (s, CF_3); ESI-MS $(M + H + Na)^+$ *m/z:* 311.2.

General procedure for the synthesis of 5-[(5-trifluoromethyl-5-hydroxy-(3-substituted)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethyl) pyrazolo[1,5-*a*]pyrimidines (**4**)

A solution of 2-methyl-7-trifluoromethylpyrazolo[1,5-*a*] pyrimidine-5-propanoyl hydrazide (**2**) (3 mmol) and 1,1,1-trifluoro-4-alkoxy-3-alken-2-one (**3a**-**l**, 3 mmol) in 10 mL ethanol were stirred at 50 °C until complete dissolution, and the resulting solution was stirred for 16 h. EtOH was removed and residue was dissolved in CH_2Cl_2 (30 mL); the organic layer was washed with water (3 × 30 mL) and dried with Na_2SO_4. The solvent was evaporated, resulting in products **4a**-**l**. The crystalline compounds were purified by column chromatography on a silica gel (SilicaFlashR G60, 70-230 mesh) with hexane/ CH_2Cl_2 (3:1) as an eluent.

5-[(5-Trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4a**): 87% yield as a yellowish white solid; m.p. 81-83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (s, 3H, CH_3), 3.18-3.37 (m, 4H, CH_2CH_2), 6.48 (s, 1H, H3), 6.99 (s, 1H, H6), pyrazole: 3.18-3.37 (m, 2H, H4'a/ H4'b), 6.96 (m, 1H, H3'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7 (CH_3), 31.9 (CH_2), 32.1 (CH_2), 96.9 (C-3), 105.6 (q, J_{C-F} 4.23 Hz, C-6), 119.7 (q, J_{CF} 274.4 Hz, CF_3), 133.2 (q, J_{CF} 37.0 Hz, C-7), 150.1 (C-2), 156.4 (C-3a), 159.1 (C-5), 174.2 (CO), pyrazole: 44.7 (C-4'), 90.1(q, J_{CF} 34.5 Hz, C-5'), 123.1 (q, J_{CF} 287.8 Hz, CF_3), 144.8 (C-3'); ESI-MS $(M + H)^+$ *m/z:* 410.2; anal. calcd. for $C_{15}H_{13}F_6N_5O_2$ 409.1 g mol^{-1}: C, 44.02; H, 3.20; N, 17.11; found: C, 44.3; H, 3.25; N, 17.4.

5-[(5-Trifluoromethyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4b**): 80% yield as yellow orange solid, m.p. 79-81 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.04 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 3.14-3.30 (m, 6H, -CH_2-, H-4 pyr), 6.49 (s, 1H, H-3), 7.0 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7 (CH_3), 15.6 (CH_3), 32.1 (-CH_2-), 32.3 (-CH_2-), 46.7 (C-4, pyr), 91.5 (q, $^2J_{CF}$ 34.7 Hz, C-5 pyr), 96.9 (C-3 pym), 105.7 (q, $^3J_{CF}$ 4.1 Hz, C-6 pym), 121.3 (q, J_{CF} 274.5 Hz, CF_3), 123.9 (q, J_{CF} 287.8 Hz, CF_3), 133.2 (q, $^2J_{CF}$ 37.3 Hz, C-7 pym), 150.1 (C-2 pym), 154.7 (C-3 pyr), 156.4 (C-3*a* pym), 159.1 (C-5 pym), 172.9 (C=O); ^{19}F NMR ($CDCl_3$, 376.4 MHz) δ –68.9 (pym), –81.8 (pyr); ESI-MS $(M + H)^+$ *m/z:* 424.2; anal. calcd. for $C_{15}H_{13}F_6N_5O_2$ 423.11 g mol^{-1}: C, 45.4; H, 3.57; N, 16.54; found: C, 45.1; H, 3.6; N, 16.8.

5-[(5-Trifluoromethyl-5-hydroxy-3-(2-methylpent-3-enyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-pro pan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4c**): 68% yield as white solid, m.p. 86-87 °C; ^{1}H NMR 400 MHz, $CDCl_3$ δ ppm: 1.62 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 2.28 (m, 2H, -CH_2-), 2.37 (m, 2H, -CH_2-), 2.54 (s, 3H, CH_3), 2.68 (t, 2H, -CH_2-), 2.91 (t, 2H, -CH_2-), 3.06 (d, 1H, $^2J_{HH}$ 10 Hz, H-4 pyr), 3.19-3.3 (m, 5H, -CH_2-, H-4 pyr), 5.08 (t, 1H, $^3J_{HH}$ 6.6 Hz, =CH), 6.49 (s, 1H, H-3), 7.0 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7 (CH_3), 17.7 (CH_3), 24.8 (-CH_2-), 25.6 (CH_3), 29.9 (-CH_2-), 32.1 (-CH_2-), 32.4 (-CH_2-), 32.4 (-CH_2-), 45.6 (C-4, pyr), 91.3 (q, $^2J_{CF}$ 34.2 Hz, C-5 pyr), 96.8 (C-3 pym), 105.7 (q, $^3J_{CF}$ 4.1 Hz, C-6 pym), 119.8 (q, J_{CF} 274.5 Hz, CF_3), 121.9 (=CH), 123.7 (q, J_{CF} 287.4 Hz, CF_3), 133.6 (C=), 133.1 (q, $^2J_{CF}$ 37.0 Hz, C-7 pym), 150.1 (C-2 pym), 156.4 (C-3*a* pym), 158.2 (C-3 pyr), 159.4 (C-5 pym), 173.7 (C=O); ^{19}F NMR ($CDCl_3$, 376.4 MHz) δ –68.9 (pym), –81.8 (pyr); ESI-MS $(M + H)^+$ *m/z:* 492.3; anal. calcd. for $C_{21}H_{23}F_6N_5O_2$ 491.18 g mol^{-1}: C, 51.32; H, 4.72; N, 14.25; found: C, 51.5; H, 4.8; N, 14.2.

5-[(5-Trifluoromethyl-5-hydroxy-3-(2-phenylethyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4d**): 60% yield as pale brown solid, m.p. 135-136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (s, 3H, CH_3), 2.68 (t, 2H, -CH_2-), 2.91 (t, 2H, -CH_2-), 3.03 (d, 1H, $^2J_{HH}$ 10 Hz, H-4 pyr), 3.14-3.25 (m, 5H, -CH_2-, H-4 pyr), 6.49 (s, 1H, H-3), 6.9 (s, 1H, H-6), 7.18-7.31 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8 (CH_3), 31.5 (-CH_2-), 32.1 (-CH_2-), 32.2 (-CH_2-), 32.4 (-CH_2-), 45.8 (C-4, pyr), 91.3 (q, $^2J_{CF}$ 34.3 Hz, C-5 pyr), 96.9 (C-3 pym), 105.7 (q, $^3J_{CF}$ 4.2 Hz, C-6 pym), 119.8 (q, J_{CF} 275.5 Hz, CF_3), 122.1 (q, J_{CF} 287.5 Hz, CF_3), 126.5, 128.2, 128.6 (Ph), 133.2 (q, $^2J_{CF}$ 37.1 Hz, C-7 pym), 139.9 (Ph), 150.1 (C-2 pym), 156.5 (C-3*a* pym), 157.5 (C-3 pyr), 159.4 (C-5 pym), 173.8 (C=O); ^{19}F NMR ($CDCl_3$, 376.4 MHz) δ –68.9 (pym), –81.7 (pyr); ESI-MS $(M + H)^+$ *m/z:* 514.3; anal. calcd. for $C_{23}H_{21}F_6N_5O_2$ 513.16 g mol^{-1}: C, 53.8; H, 4.12; N, 13.64; found: C, 54.0; H, 4.15; N, 13.5.

Methyl 3-(5-hydroxy-1-(3-(2-methyl-7-trifluoromethyl-pyrazolo[1,5-*a*]pyrimidin-5-yl)propa noyl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-3-yl)propanoate (**4e**): 89% yield as white solid, m.p. 92-94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.48 (s, 3H, CH_3), 2.61 (m, 4H, -CH_2-), 3.01- 3.18 (m, 6H, -CH_2-, H-4 pyr), 3.63 (s, 3H, OCH_3), 6.42 (s, 1H, H-3), 6.9 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7 (CH_3), 25.1 (-CH_2-), 29.9 (-CH_2-), 32.0 (-CH_2-), 32.2 (-CH_2-), 46.0 (C-4, pyr), 51.9 (OMe), 91.4 (q, $^2J_{CF}$ 33.0 Hz, C-5 pyr), 96.8 (C-3 pym), 105.6 (q, $^3J_{CF}$ 4.1 Hz, C-6 pym), 119.9 (q, J_{CF} 277.7 Hz, CF_3), 123.1 (q, J_{CF} 283.4 Hz, CF_3), 133.2 (q, $^2J_{CF}$ 42.0 Hz, C-7 pym), 150.1 (C-2 pym), 156.4 (C-3*a* pym), 156.6 (C-3 pyr), 159.3 (C-5 pym), 172.3 (C=O), 173.7 (C=O); ESI-MS $(M + H)^+$ *m/z:* 496.3; anal. calcd. for $C_{19}H_{19}F_6N_5O_4$ 495.13 g mol^{-1}: C, 46.07; H, 3.87; N, 14.14; found: C, 46.2; H, 3.9; N, 14.35.

5-[(5-Trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoro-methylpyrazolo[1,5-*a*]pyrimidine (**4f**): 68% yield as orange solid, m.p. 94.8-96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.52 (s, 3H, CH_3), 3.1-3.42 (m, 4H, -CH_2-), 3.51 (d, 1H, $^2J_{HH}$ 18.6 Hz, H-4 pyr), 3.67 (d, 1H, $^2J_{HH}$ 18.6 Hz, H-4 pyr), 6.47 (s, 1H, H-3), 7.0 (s, 1H, H-6), 7.44 (m, 3H, Ph), 7.67 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6 (CH_3), 32.2 (-CH_2-), 32.5 (-CH_2-), 43.4 (C-4, pyr), 92.0 (q, $^2J_{CF}$ 33.0 Hz, C-5 pyr), 96.9 (C-3 pym), 105.6 (q, $^3J_{CF}$ 5.0 Hz, C-6 pym), 119.6 (q, J_{CF} 274.5 Hz, CF_3), 122.8 (q, J_{CF} 287.5 Hz, CF_3), 126.2, 126.6, 129.5, 131.2 (Ph), 133.3 (q, $^2J_{CF}$ 36.0 Hz, C-7 pym), 150.1 (C-2 pym), 153.3 (C-3 pyr), 156.4 (C-3*a* pym), 159.3 (C-5 pym), 174.0 (C=O); ^{19}F NMR ($CDCl_3$, 376.4 MHz) δ –68.9 (pym), –81.3 (pyr); ESI-MS $(M + H)^+$ *m/z:* 486.2; anal. calcd. for $C_{21}H_{17}F_6N_5O_2$ 485.13 g mol^{-1}: C, 51.96; H, 3.53; N, 14.43; found: C, 52.1; H, 3.5; N, 14.5.

5-[(5-Trifluoromethyl-5-hydroxy-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4g**): 66% yield as yellow solid, m.p. 118.0-120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.39 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.2-3.42 (m, 4H, -CH_2-), 3.49 (d, 1H, $^2J_{HH}$ 18.6 Hz, H-4 pyr), 3.64 (d, 1H, $^2J_{HH}$ 18.6 Hz, H-4 pyr), 6.47 (s, 1H, H-3), 7.0 (s, 1H, H-6), 7.22 (d, 2H, $^3J_{HH}$ 8.0 Hz, Ph), 7.56 (d, 2H, $^3J_{HH}$ 8.0 Hz, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6 (CH_3), 21.4 (CH_3), 32.2 (-CH_2-), 32.5 (-CH_2-), 43.4 (C-4, pyr), 91.9 (q, $^2J_{CF}$ 35.0 Hz, C-5 pyr), 96.9 (C-3 pym), 105.6 (q, $^3J_{CF}$ 5.0 Hz, C-6 pym), 119.6 (q, J_{CF} 270.0 Hz, CF_3), 121.9 (q, J_{CF} 277.5 Hz, CF_3), 126.6, 127.2, 129.6 (Ph), 133.3 (q, $^2J_{CF}$ 34.0 Hz, C-7 pym), 141.7 (Ph), 150.2 (C-2 pym), 153.4 (C-3 pyr), 156.4 (C-3*a* pym), 159.3 (C-5 pym), 174.0 (C=O); ^{19}F NMR ($CDCl_3$, 376.4 MHz) δ –68.9 (pym), –81.4 (pyr); ESI-MS $(M + H)^+$ *m/z:* 500.2; anal. calcd. for $C_{22}H_{19}F_6N_5O_2$ 499.14 g mol^{-1}: C, 52.91; H, 3.83; N, 14.02; found: C, 53.1; H, 3.9; N, 14.2.

5-[(5-Trifluoromethyl-5-hydroxy-3-(methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4h**): 95% yield as red solid, m.p. 77-79 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.53 (s, 3H, CH_3), 3.2-3.40 (m, 4H, -CH_2-), 3.48 (d, 1H, $^2J_{HH}$ 18.5 Hz, H-4 pyr), 3.63 (d, 1H, $^2J_{HH}$ 18.5 Hz, H-4 pyr), 3.86 (s, 3H, CH_3), 6.48 (s, 1H, H-3), 6.93 (d, 2H, $^3J_{HH}$ 8.0 Hz, Ph), 7.0 (s, 1H, H-6), 7.62 (d, 2H, $^3J_{HH}$ 8.0 Hz, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8 (CH_3), 32.2 (-CH_2-), 32.5 (-CH_2-), 43.4 (C-4, pyr), 55.5 (OMe), 91.8 (q, $^2J_{CF}$ 34.0 Hz, C-5 pyr), 96.9 (C-3 pym), 105.7 (q, $^3J_{CF}$ 4.0 Hz, C-6 pym), 114.3 (Ph), 119.6 (q, J_{CF} 270.0 Hz, CF_3), 121.9 (q, J_{CF} 277.5 Hz, CF_3), 126.6, 127.2, 129.6 (Ph), 133.3 (q, $^2J_{CF}$ 34.0 Hz, C-7 pym), 141.7 (Ph), 150.2 (C-2 pym), 153.4 (C-3 pyr), 156.4 (C-3*a* pym), 159.3 (C-5 pym), 174.0 (C=O); ^{19}F NMR ($CDCl_3$, 376.4 MHz) δ –68.9 (pym), –81.3 (pyr); ESI-MS $(M + H)^+$ *m/z:* 516.2; anal. calcd. for $C_{22}H_{19}F_6N_5O_3$ 515.14 g mol^{-1}: C, 51.27; H, 3.72; N, 13.59; found: C, 51.4; H, 3.7; N, 13.8.

5-[(3-Ethoxy-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoro-methylpyrazolo[1,5-*a*]pyrimidine (**4i**): 75% yield as white solid, m.p. 97.3-99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (t, 3H, $^3J_{HH}$ 6.5 Hz, CH_3), 2.54 (s, 3H, CH_3), 3.0-3.30 (m, 6H, -CH_2-, H-4 pyr), 4.23 (q, 2H, $^3J_{HH}$ 6.5 Hz, -CH_2-), 6.49 (s, 1H, H-3), 7.0 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0 (CH_3), 14.7 (CH_3), 32.1 (-CH_2-), 32.2 (-CH_2-), 40.7 (C-4, pyr), 66.2 (OMe), 91.8 (q, $^2J_{CF}$ 34.4 Hz, C-5 pyr), 96.8 (C-3 pym), 105.7 (q, $^3J_{CF}$ 4.1 Hz, C-6 pym), 119.5 (q, J_{CF} 274.4 Hz, CF_3), 124.1 (q, J_{CF} 287.8 Hz, CF_3), 133.2 (q, $^2J_{CF}$ 37.0 Hz, C-7 pym), 150.1 (C-2 pym), 156.4 (C-3*a* pym), 159.6 (C-5 pym), 161.8 (C-3 pyr), 173.2 (C=O); ^{19}F NMR ($CDCl_3$, 376.4 MHz) δ –68.9 (pym), –82.6 (pyr); ESI-MS $(M + H)^+$ *m/z:* 454.3; anal. calcd. for $C_{17}H_{17}F_6N_5O_3$ 453.12 g mol^{-1}: C, 45.04; H, 3.78; N, 15.45; found: C, 44.8; H, 3.65; N, 15.8.

5-[1-(3-Hydroxy-3-trifluoromethyl-3,3a,4,5,6,7-hexahydroindazol-2-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4j**): 63% yield as yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26-1.63 (m, 8H, -$(CH_2)_4$-), 2.55 (s, 3H, CH_3), 3.04 (m, 1H, CH), 3.18-3.3 (m, 4H, -CH_2-), 6.49 (s, 1H, H-3), 7.0 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7 (CH_3), 23.7, 25.9, 26.4, 27.7 (cyclo-CH_2-), 31.2 (-CH_2-), 32.5 (-CH_2-), 51.8 (C-4, pyr), 90.7 (q, $^2J_{CF}$ 34.0 Hz, C-5 pyr), 96.9 (C-3 pym), 105.6 (q,

$^3J_{CF}$ 4.0 Hz, C-6 pym), 118.8 (q, J_{CF} 274.8 Hz, CF_3), 120.1 (q, J_{CF} 287.9 Hz, CF_3), 133.1 (q, $^2J_{CF}$ 34.0 Hz, C-7 pym), 150.0 (C-2 pym), 156.4 (C-3*a* pym), 159.1 (C-5 pym), 161.0 (C-3 pyr), 174.1 (C=O); ESI-MS $(M + H)^+$ *m/z:* 464.3; anal. calcd. for $C_{19}H_{19}F_6N_5O_2$ 463.14 g mol^{-1}: C, 49.25; H, 4.13; N, 15.11; found: C, 49.4; H, 4.3; N, 15.2.

1-(3-Hydroxy-3-trifluoromethyl-3,3a,4,5,6,7,8,9-octahydrocycloocta[c]pyrazol-2-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4k**): 79% yield as yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (m, 3H, -CH_2-), 1.82 (m, 5H, -CH_2-), 2.53 (s, 3H, CH_3), 2.65 (m, 2H, -CH_2-), 2.73 (m, 2H, -CH_2-), 3.04 (m, 1H, CH), 3.22 (m, 4H, -CH_2-), 6.48 (s, 1H, H-3), 7.0 (s, 1H, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6 (CH_3), 23.7, 25.4, 26.7, 28.0, 29.5, 30.7 (cyclo-CH_2-), 31.6 (-CH_2-), 32.2 (-CH_2-), 54.6 (C-4, pyr), 91.5 (q, $^2J_{CF}$ 34.0 Hz, C-5 pyr), 96.8 (C-3 pym), 105.6 (q, $^3J_{CF}$ 4.0 Hz, C-6 pym), 122.5 (q, J_{CF} 275.0 Hz, CF_3), 123.7 (q, J_{CF} 287.5 Hz, CF_3), 133.1 (q, $^2J_{CF}$ 35.0 Hz, C-7 pym), 150.1 (C-2 pym), 156.4 (C-3*a* pym), 159.4 (C-5 pym), 163.5 (C-3 pyr), 174.0 (C=O); ESI-MS $(M + H)^+$ *m/z:* 492.3; anal. calcd. for $C_{21}H_{23}F_6N_5O_2$ 491.18 g mol^{-1}: C, 51.32; H, 4.72; N, 14.25; found: C, 51.5; H, 4.72; N, 14.5.

1-(5-Trifluoromethyl-5-hydroxy-4-methyl-3-phenyl-4,5-dihydropyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4l**): 68% yield as pale brown solid; m.p. 99-101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3H, $^3J_{HH}$ 8 Hz, Me), 2.42 (s, 3H, CH_3), 3.1-3.32 (m, 4H, -CH_2-), 3.71 (d, 1H, $^3J_{HH}$ 8 Hz, H-4 pyr), 6.37 (s, 1H, H-3), 6.9 (s, 1H, H-6), 7.36 (m, 3H, Ph), 7.63 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.6 (Me),14.6 (Me), 32.0 (-CH_2-), 32.2 (-CH_2-), 46.0 (C-4, pyr), 92.3 (q, $^2J_{CF}$ 35.0 Hz, C-5 pyr), 96.9 (C-3 pym), 105.6 (q, $^3J_{CF}$ 5.0 Hz, C-6 pym), 120.1 (q, J_{CF} 274.5 Hz, CF_3), 123.8 (q, J_{CF} 287.5 Hz, CF_3), 127.2, 129.3, 129.5, 131.2 (Ph), 133.3 (q, $^2J_{CF}$ 36.0 Hz, C-7 pym), 150.1 (C-2 pym), 153.3 (C-3 pyr), 156.4 (C-3*a* pym), 159.3 (C-5 pym), 174.2 (C=O); ESI-MS $(M + H)^+$ *m/z:* 500.2; anal. calcd. for $C_{22}H_{19}F_6N_5O_2$ 499.14 g mol^{-1}: C, 52.91; H, 3.83; N, 14.02; found: C, 53.0; H, 3.85; N, 14.1.

Supplementary Information

Supplementary information is available free of charge at http://jbcs.sbq.org.br as PDF file.

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