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Short Report

Straightforward and Clean Ultrasound-Promoted Synthesis of 2-(4,5-Dihydro-1*H*-pyrazol-1-yl)pyrimidines

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A series of twelve novel 2-(pyrazol-1-yl)pyrimidine derivatives was easily obtained under ultrasonic conditions by the cyclocondensation reaction of 1-carboxamidino-pyrazoles with 4-methoxyvinyl-trifluoromethyl ketones using ethanol as an environment-friendly solvent in the presence of potassium hydroxide. Comparison of the ultrasound-promoted reaction with classical methodology shows that the former is faster and gives better yield. The products were isolated in excellent purity grades without purification by chromatography or recrystalization.

Keywords: 2-(4,5-dihydro-1*H*-pyrazol-1-yl)pyrimidines, pyrazolylpyrimidines, sonochemistry, pyrimidines, pyrazoles

Introduction

In the past years, significant efforts have been made in preparing 2-(pyrazol-1-yl)pyrimidines derivatives and several studies have pointed such compounds as promising bioactive molecules. In this direction, epirizole has been therapeutically applied as a nonsteroidal anti-inflammatory and analgesic agent in Japan.[1] Additionally, 2-(pyrazol-1-yl)pyrimidine derivatives have shown ulcerogenicity and protective activity against lesions induced by acidic anti-inflammatory agents in the rat stomach,[2] as well as fungicidal,[3] herbicidal,[4] and cardiotonic activities.[5] Recently, several 2-(pyrazol-1-yl)pyrimidines were prepared and they showed efficacy as A_{2A} adenosine receptor antagonists for the treatment of Parkinson's disease.[6,7] Moreover, structurally related 4-(pyrazol-4-yl)pyrimidines were recently identified as potent c-Jun N-terminal kinase (JNK)[8] and cyclin-dependent kinase (CDK)[9] protein inhibitors with potential application in the treatment of type 2 diabetes and human neoplasia, respectively. In the field of material chemistry, pyrazolylpyrimidines have attracted attention due to potential application as ligands for the synthesis of transition metal complexes[10] which manifest luminescence[11] and catalytic activity.[12]

2-(Pyrazol-1-yl)pyrimidines are generally synthesized by the cyclocondensation of 1,3-dieletrophiles and 1-carboxamidino-pyrazoles[13,14] or 2-hidrazinopyrimidines[15] in [3+3] or [3+2] processes, respectively. One-pot cyclocondensation of aminoguanidine bicarbonate with two equivalents of 4-alkoxyvinyl-trifluoromethyl ketones afforded trifluoromethyl-substituted 2-(pyrazol-1-yl) pyrimidines in moderate to good yields in long reaction times (4-8 h) in ethanol under reflux.[16] Similarly, tetraaryl-substituted 2-(pyrazol-1-yl)pyrimidines were obtained in moderate yields when chalcones were used as the 1,3-dielectrophile in the cyclocondensation reaction

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with aminoguanidine bicarbonate under essentially the same conditions.[17] The disadvantage of using such one-pot reaction is that both pyrazole and pyrimidine rings substituents are the same.

In the last years, our synthetic efforts have focused on the preparation of a variety of heterocyclic compounds[18-21] and in sonochemically promoted reactions in environmentally benign solvents,[22-25] as well as in the biological activity evaluation of the novel molecules.[26-29] The use of ultrasound to accelerate reactions has proven to be a particularly important tool for reaching the green chemistry goals of minimization of waste and reduction of energy requirements.[30] In concern, several studies clearly showed the importance of taking advantage of the unique features of ultrasound-assisted reactions in the synthesis of heterocyclic compounds.[31,32]

In this context, we report here a clean and straightforward procedure to prepare a series of novel 2-(4,5-dihydro-1*H*-pyrazol-1-yl)pyrimidines under ultrasonic irradiation using ethanol as a green solvent in short reaction times and dispensing the use of complicated work-up.

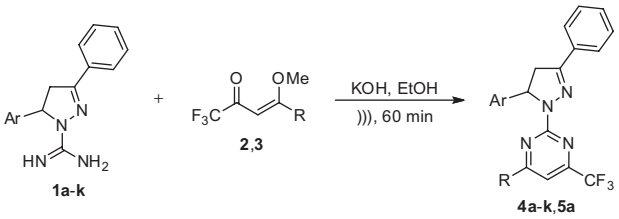
Results and Discussion

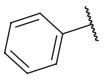
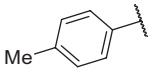
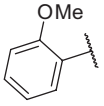
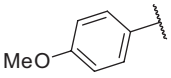
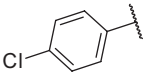
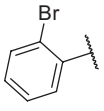
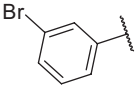
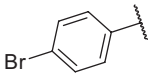
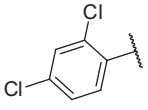
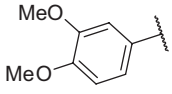
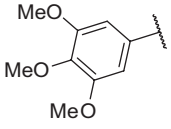
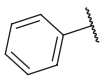
The building blocks 1-carboxamidino-4,5-dihydro-1*H*-pyrazoles **1a**-**k** and 4-alkoxyvinyl-trifluoromethyl ketones **2** and **3** were prepared according to previously reported procedures.[22,33] The novel products **4a**-**k** and **5a** were obtained in good yields by the ultrasound-promoted cyclocondensation reaction between compounds **1a**-**k** and α,β-unsaturated ketones **2** or **3** in a molar ratio of 1:1 in the presence of 0.5 eq of KOH (Table 1). The reaction time was determined by monitoring the consumption of the starting materials by thin layer chromatography (TLC). The isolation of the pure products was achieved after keeping the crude reaction mixtures in a refrigerator followed by filtration of the white solid precipitates formed. The scope of the methodology is illustrated by the preparation of a series of twelve compounds.

A mixture of two products was detected by gas chromatography (GC) when 1-carboxamidino-4,5-dihydro-1*H*-pyrazole **1a** and 4-alkoxyvinyl-trifluoromethyl ketone **3** were allowed to react using ethanol as solvent. The mass spectra of these products showed that they correspond to the desired methyl ester derivative and the ethyl ester derivative formed as coproduct due to a partial parallel transesterification reaction. In order to circumvent this mixture formation, methanol was used as solvent for the preparation of the pyrazolylpyrimidine **5a**, exclusively.

All the synthesized compounds were fully characterized by ^{1}H and ^{13}C nuclear magnetic resonance (NMR), infrared

Table 1. Reaction conditions, melting points and yields of synthesized compounds **4a**-**k** and **5a**



Product	Ar	R	m.p. / °C	Yield[a] / %
4a		Me	173-174	67
4b		Me	169-171	70
4c		Me	189-193	66
4d		Me	161-163	68
4e		Me	226-228	73
4f		Me	215-218	82
4g		Me	200-201	78
4h		Me	235-238	61
4i		Me	214-215	83
4j		Me	140-142	64
4k		Me	214-217	78
5a		$-(CH_2)_2CO_2Me$	157-160	85[b]

[a]Yield of the isolated product; [b]this reaction was carried out using methanol as solvent.

(IR) spectroscopy and high-resolution mass spectrometry (HRMS) or elemental analysis. The IR, ^{1}H and ^{13}C NMR spectra of products showed sets of signals corresponding to the proposed structures and in agreement with data reported in the literature for analogous molecules.[14] The structures were confirmed by elemental analysis or HRMS.

In order to show the beneficial effect of the ultrasonic irradiation in our sonochemical synthesis, we performed two control experiments in the absence of ultrasonic irradiation: first, the starting materials **1a** and **2** were allowed to react for 60 min in 2:2:1 molar ratio with KOH under room temperature in ethanol; then, the reaction was carried out under reflux for 24 h. Under the former silent condition the formation of product **4a** was not observed. The reaction conducted under reflux furnished a mixture of **1a** and **4a** in approximately 1:1 molar ratio, as determined by ^{1}H NMR.

Although the mechanism of the ultrasound-promoted cyclocondensation reaction was not yet experimentally established, a possible explanation is proposed in Scheme 1. Initially, the reaction involves the attack from 1-carboxamidino-4,5-dihydro-1*H*-pyrazoles **1** to the β-position of 4-alkoxyvinyl-trifluoromethyl ketones **2**, **3**, leading to intermediates **I** which are in equilibrium with **II**. In the next step, intermediates **II** eliminate MeOH to give intermediates **III**. Then an intramolecular nucleophilic attack of imino nitrogen to the carbonyl leads to intermediates **IV**, which are in equilibrium with **V**. Finally, the elimination of water from **V** occurs to give the compounds **4**, **5**.

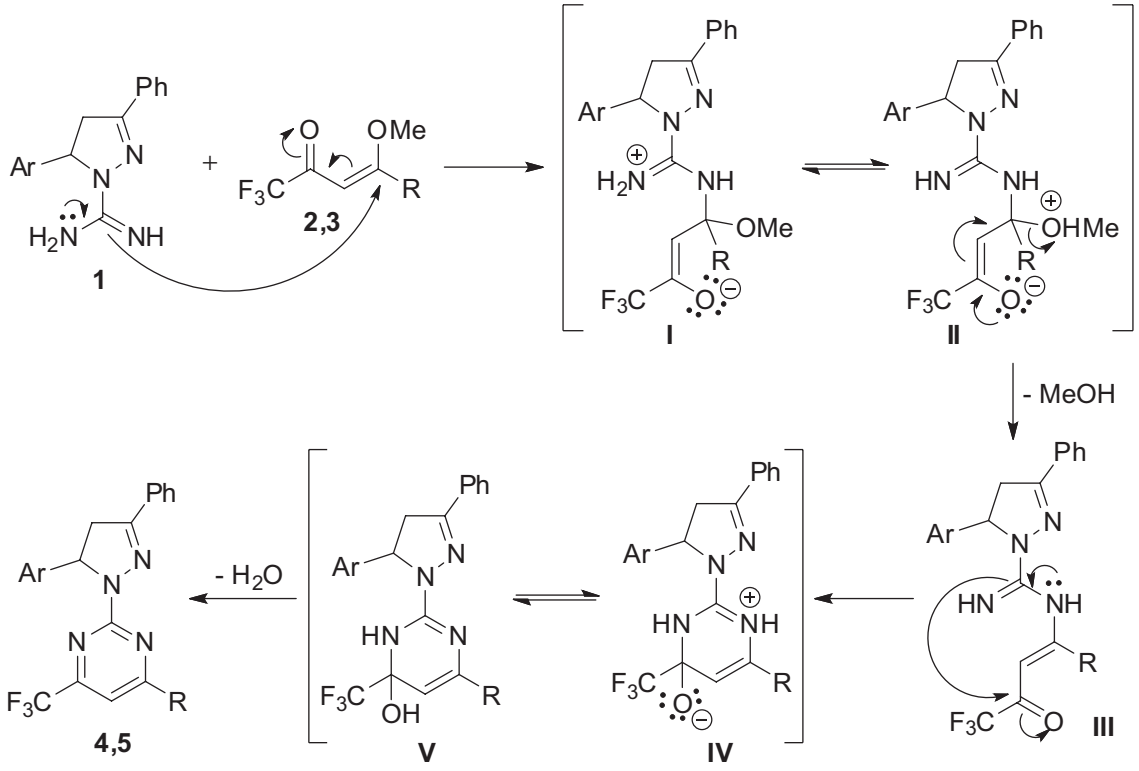
Conclusions

In summary, we developed an efficient, clean and facile method for the preparation of a series of 2-(4,5-dihydro-1*H*-pyrazol-1-yl)pyrimidines. Our sonochemical method offers several advantages over existing methods, including improved yields, cleaner reactions, simple work-up and very short reaction times, which makes it an useful and environmentally attractive strategy for the synthesis of pyrazolylpyrimidines derivatives, compounds with promising bioactivity.

Experimental

General methods

The sonicated reactions were carried out with a microtip probe connected to a 500 W Sonics Vibracell ultrasonic processor operating at 20 kHz at 20% of the maximum power output. The progress of reactions was monitored by TLC. Melting points were recorded in open capillary on an Instrutherm DF-3600 II apparatus and are uncorrected. Infrared spectra were acquired on a JASCO-4100 spectrometer as KBr pellets. Low-resolution



Scheme 1. Proposed mechanism for the ultrasound-promoted cyclocondensation reaction.

mass spectra were obtained on a Varian 210 MS connected to a Varian 431 GC. The GC was equipped with a split-splitless injector, cross-linked to a Varian Factor Four™ capillary column (30 m × 0.25 mm), and helium was used as the carrier gas. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX400 spectrometer (400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C) in 5 mm sample tubes at 298 K in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. The elemental analyses (CHN) were obtained from a PerkimElmer CHN 2400 analyzer. For the high resolution mass analyses, compounds were dissolved in a solution of 50% (v/v) chromatographic grade acetonitrile, 50% (v/v) deionized water and 0.1% formic acid. The solutions were infused directly individually into the electrospray ionization (ESI) source by means of a syringe pump (Harvard Apparatus) at a flow rate of 10 μL min^{-1}. ESI(+)-MS were acquired using a hybrid high-resolution and high accuracy (5 μL L^{-1}) microTof quadrupole time-of-flight (Q-TOF) mass spectrometer (Bruker Scientific) under the following conditions: capillary and cone voltages were set to +3500 and +40 V, respectively, with a de-solvation temperature of 100 °C. The data were collected in the *m*/*z* range of 70-700 at the speed of two scans *per* second, providing the resolution of 50,000 (full width at half maximum (FWHM)) at *m*/*z* 200. All reagents and solvents were used as obtained commercially. 1-Carboxamidino-pyrazoles and 4-alkoxyvinyl-trifluoromethyl ketones were prepared by us following reported procedures.[22,33]

General procedure for the ultrasound-promoted synthesis of 2-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)-6-(trifluoromethyl) pyrimidines **4a**-**k**

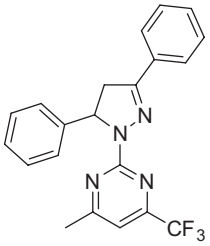
To a 50 mL vial were added the 1-carboxamidino-4,5-dihydro-1*H*-pyrazoles **1a**-**k** (0.5 mmol), the 4-alkoxyvinyl-trifluoromethyl ketone **2** (0.5 mmol), ethanol (10 mL) and KOH (0.25 mmol). The reaction mixture was sonicated for 60 min at room temperature (25 °C). The crude products were allowed to cool in a refrigerator. The precipitates obtained were filtered through a Büchner funnel under vacuum, washed with distilled water and dried in a desiccator to give the pure 2-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)-6-(trifluoromethyl)pyrimidine derivatives **4a**-**k** without further purification.

Procedure for the ultrasound-promoted synthesis of methyl 3-(2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-6-(trifluoromethyl)pyrimidin-4-yl)propanoate (**5a**)

To a 50 mL vial were added the 1-carboxamidino-4,5-dihydro-1*H*-pyrazole **1a** (0.5 mmol), the 4-alkoxyvinyl-trifluoromethyl ketone **3** (0.5 mmol), methanol (10 mL) and KOH (0.25 mmol). The reaction mixture was sonicated for 60 min at room temperature (25 °C). The crude products were allowed to cool in a refrigerator. The precipitates obtained were filtered through a Büchner funnel under vacuum, washed with distilled water and dried in a desiccator to give the pure methyl 3-(2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-6-(trifluoromethyl)pyrimidin-4-yl)propanoate (**5a**) without further purification.

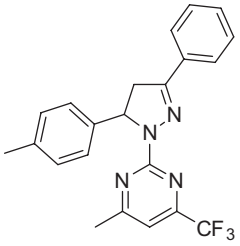
Characterization data for compounds **4a**-**k** and **5a**

2-(3,5-Diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-6-(trifluoromethyl)pyrimidine (**4a**)



Whitish solid; m.p. 173-174 °C; IR (KBr) ν_{max} / cm^{-1} 3039, 2918, 1587-1482, 1394, 835-691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H, CH_3), 3.32 (dd, 1H, *J* 5.0, 17.5 Hz, H_A), 3.85 (dd, 1H, *J* 12.0, 17.5 Hz, H_B), 5.74 (dd, 1H, *J* 5.0, 12.0 Hz, H_C), 6.74 (s, 1H, H5), 7.18-7.43 (m, 8H, Ar), 7.84-7.87 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 42.2, 62.2, 106.9 (q, *J* 2.6 Hz, C5), 120.6 (q, *J* 275.2 Hz, CF_3), 126.9, 127.5, 128.5, 130.0, 131.5, 142.2, 153.7, 155.8 (q, *J* 35.5 Hz, C6), 158.2, 171.2; anal. calcd. for $C_{21}H_{17}F_3N_4$: C, 65.96; H, 4.48; N, 14.65; found: C, 66.06; H, 4.47; N, 14.60.

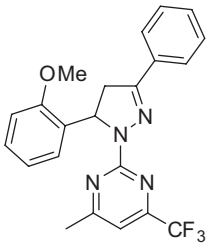
4-Methyl-2-(3-phenyl-5-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-6-(trifluoromethyl)pyrimidine (**4b**)



Whitish solid; m.p. 170-171 °C; IR (KBr) ν_{max} / cm^{-1} 3059, 3022, 2948, 2921, 1587-1491, 1391, 817-692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.22 (dd, 1H, *J* 4.8, 17.5 Hz, H_A), 3.75 (dd, 1H, *J* 11.9, 17.5 Hz, H_B), 5.64 (dd, 1H, *J* 4.8, 11.9 Hz, H_C), 6.67 (s, 1H, H5), 6.99 (d, 2H, *J* 7.8 Hz, Ar), 7.14 (d, 2H, *J* 7.9 Hz, Ar), 7.32-7.34 (m, 3H, Ar), 7.77-7.80 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 24.7, 42.3, 62.0, 106.8 (q, 1H, *J* 2.6 Hz, C5), 120.7 (q, *J* 275.3 Hz, CF_3), 126.5, 127.0, 128.5, 129.2, 129.9, 131.8, 137.2, 139.3, 153.8, 156.0 (q, *J* 34.8 Hz, C6), 158.3, 171.1; HRMS $[MH]^+$ calcd. for $C_{22}H_{20}F_3N_4$: 379.0232; found 379.0247.

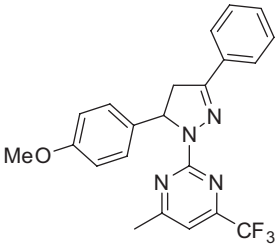
2-(5-(2-Methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-6-(trifluoromethyl)pyrimidine (**4c**)

Yellowish solid; m.p. 189-192 °C; IR (KBr) ν_{max} / cm^{-1} 3064, 3024, 2967, 2841, 1583-1487, 1387, 1242, 1031,



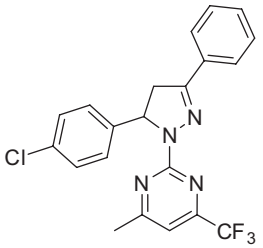
754-687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H, CH_3), 3.14 (dd, 1H, *J* 5.1, 17.4 Hz, H_A), 3.71 (dd, 1H, *J* 12.1, 17.4 Hz, H_B), 3.77 (s, 3H, OCH_3), 5.95 (dd, 1H, *J* 5.1, 12.1 Hz, H_C), 6.65 (s, 1H, H5), 6.70-6.74 (m, 1H, Ar), 6.79-6.80 (m, 1H, Ar), 7.04-7.12 (m, 2H, Ar), 7.28-7.33 (m, 3H, Ar), 7.75-7.78 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 41.2, 55.6, 57.7, 106.6 (q, *J* 2.7 Hz, C5), 110.9, 120.6, 120.7 (q, *J* 275.4 Hz, CF_3), 126.9, 127.1, 128.4, 128.4, 129.7, 130.0, 132.0, 154.4, 156.0 (q, *J* 35.4 Hz, C6), 156.7, 158.5, 171.0; HRMS $[MH]^+$ calcd. for $C_{22}H_{21}F_3N_4O$: 413.1589; found: 413.1609.

2-(5-(4-Methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-6-(trifluoromethyl)pyrimidine (**4d**)



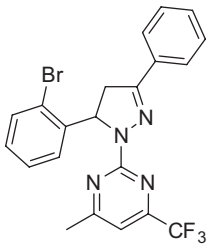
Yellowish solid; m.p. 161-163 °C; IR (KBr) ν_{max} / cm^{-1} 3065, 3033, 2994, 2832, 1586-1489, 1387, 1244, 1039, 827-691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H, CH_3), 3.24 (dd, 1H, *J* 4.7, 17.6 Hz, H_A), 3.66 (s, 3H, OCH_3), 3.75 (dd, 1H, *J* 12.0, 17.6 Hz, H_B), 5.62 (dd, 1H, *J* 4.7, 11.9 Hz, H_C), 6.67 (s, 1H, H5), 6.71 (d, 2H, *J* 8.7 Hz, Ar), 7.18 (d, 2H, *J* 8.8 Hz, Ar), 7.32-7.33 (m, 3H, Ar), 7.77-7.80 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 42.1, 55.1, 61.6, 106.8 (q, 1H, *J* 2.7 Hz, C5), 120.6 (q, *J* 275.3 Hz, CF_3), 113.8, 124.7, 126.9, 127.9, 128.5, 129.9, 131.6, 134.3, 153.7, 155.8 (q, *J* 35.7 Hz, C6), 158.2, 158.9, 171.1; HRMS $[MH]^+$ calcd. for $C_{22}H_{20}F_3N_4O$: 413.1589; found: 413.1592.

2-(5-(4-Chlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-6-(trifluoromethyl)pyrimidine (**4e**)



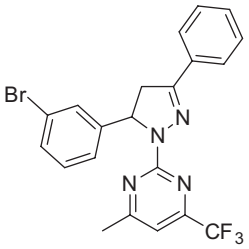
Yellowish solid; m.p. 226-228 °C; IR (KBr) ν_{max} / cm^{-1} 3065, 2921, 1587-1491, 1390, 832-691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H, CH_3), 3.21 (dd, 1H, *J* 4.9, 17.6 Hz, H_A), 3.78 (dd, 1H, *J* 12.1, 17.6 Hz, H_B), 5.63 (dd, 1H, *J* 4.9, 12.0 Hz, H_C), 6.70 (s, 1H, H5), 7.15-7.20 (m, 4H,Ar), 7.33-7.35 (m, 3H, Ar), 7.78-7.80 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 42.2, 61.7, 107.1 (q, *J* 2.6 Hz, C5), 120.6 (q, *J* 275.3 Hz, CF_3), 127.0, 128.0, 128.6, 128.7, 130.1, 131.5, 133.4, 140.8, 153.7, 156.1 (q, *J* 35.7 Hz, C6), 158.1, 171.3; anal. calcd. for $C_{21}H_{16}ClF_3N_4$: C, 60.51; H, 3.87; N, 13.44; found: C, 60.61; H, 3.89; N, 13.40.

2-(5-(2-Bromophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-6-(trifluoromethyl)pyrimidine (**4f**)



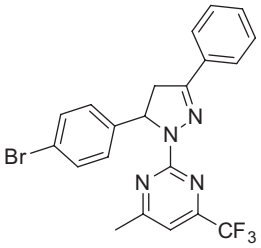
Whitish solid; m.p. 215-218 °C; IR (KBr) ν_{max} / cm^{-1} 3062, 2922, 1585-1490, 1388, 821-691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H, CH_3), 3.10 (dd, 1H, *J* 4.9, 17.8 Hz, H_A), 3.85 (dd, 1H, *J* 12.2, 17.3 Hz, H_B), 6.03 (dd, 1H, *J* 4.9, 12.1 Hz, H_C), 6.71 (s, 1H, H5), 6.98-7.08 (m, 3H, Ar), 7.31-7.32 (m, 3H, Ar), 7.47-7.51 (m, 1H, Ar), 7.76-7.77 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 41.5, 62.0, 107.1 (q, *J* 2.7 Hz, C5), 120.6 (q, *J* 275.2 Hz, CF_3), 122.1, 126.9, 127.8, 128.5, 128.7, 130.0, 131.6, 132.9, 141.1, 153.7, 156.2 (q, *J* 35.7 Hz, C6), 158.3, 171.3; HRMS $[MH]^+$ calcd. for $C_{21}H_{17}BrF_3N_4$: 461.0589; found: 461.0600.

2-(5-(3-Bromophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-6-(trifluoromethyl)pyrimidine (**4g**)



Whitish solid; m.p. 200-201 °C; IR (KBr) ν_{max} / cm^{-1} 3065-3008, 2926, 1585-1489, 1390, 831-689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H, CH_3), 3.26 (dd, 1H, *J* 5.1, 17.7 Hz, H_A), 3.81 (dd, 1H, *J* 12.1, 17.7 Hz, H_B), 5.62 (dd, 1H, *J* 5.1, 12.0 Hz, H_C), 6.73 (s, 1H, H5), 7.07 (t, 1H, *J* 7.8 Hz, Ar), 7.19 (d, 1H, *J* 7.8 Hz, Ar), 7.28 (d, 1H, *J* 7.8 Hz, Ar), 7.34-7.37 (m, 3H, Ar), 7.43 (s, 1H, Ar), 7.80-7.82 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 42.1, 61.7, 107.2 (q, *J* 2.7 Hz, C5), 120.5 (q, *J* 275.2 Hz, CF_3), 122.6, 125.2, 127.0, 128.6, 129.7, 130.1, 130.2, 130.7, 131.2, 144.3, 153.9, 156.1 (q, *J* 35.3 Hz, C6), 157.8, 171.3; anal. calcd. for $C_{21}H_{16}BrF_3N_4$: C, 54.68; H, 3.50; N, 12.15; found: C, 54.86; H, 3.48; N, 12.15.

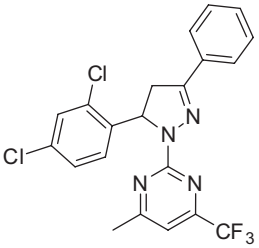
2-(5-(4-Bromophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-6-(trifluoromethyl)pyrimidine (**4h**)



Yellowish solid; m.p. 235-238 °C; IR (KBr) ν_{max} / cm^{-1} 3063, 3021, 2948, 2918, 1587-1490, 1390, 831-692; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H, CH_3), 3.19 (dd, 1H, *J* 5.0, 17.6 Hz, H_A), 3.77 (dd, 1H, *J* 12.0, 17.6 Hz, H_B), 5.61 (dd, 1H, *J* 5.0, 12.0 Hz, H_C), 6.69 (s, 1H, H5), 7.11-

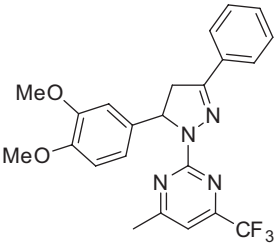
7.13 (m, 2H, Ar), 7.30-7.34 (m, 5H, Ar), 7.75-7.78 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 42.1, 61.8, 107.1 (q, *J* 2.5 Hz, C5), 120.6 (q, *J* 275.3 Hz, CF_3); 121.4, 126.9, 128.3, 128.6, 130.1, 131.4, 131.7, 141.3, 153.6, 156.0 (q, *J* 35.5 Hz, C6), 158.2, 171.3; anal. calcd. for $C_{21}H_{16}BrF_3N_4$: C, 54.68; H, 3.50; N, 12.15; found: C, 54.85; H, 3.51; N, 12.11.

2-(5-(2,4-Dichlorophenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-6-(trifluoromethyl)pyrimidine (**4i**)



Yellowish solid; m.p. 214-215 °C; IR (KBr) ν_{max} / cm^{-1} 3013, 2922, 1587-1490, 1387, 832-689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H, CH_3), 3.11 (dd, 1H, *J* 5.5, 17.6 Hz, H_A), 3.84 (dd, 1H, *J* 12.1, 17.6 Hz, H_B), 6.00 (dd, 1H, *J* 5.5, 12.1 Hz, H_C), 6.74 (s, 1H, H5), 7.02-7.03 (m, 2H, Ar), 7.33-7.35 (m, 4H, Ar), 7.77-7.80 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 41.3, 59.5, 107.3 (q, *J* 2.7 Hz, C5), 120.5 (q, *J* 275.6 Hz, CF_3), 127.0, 127.6, 127.7, 128.6, 129.5, 130.2, 131.5, 133.0, 133.7, 138.3, 153.8, 156.3, 158.3, 171.4; HRMS $[MH]^+$ calcd. for $C_{21}H_{16}Cl_2F_3N_4$: 451.0704; found: 451.0693.

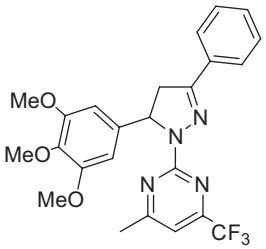
2-(5-(3,4-Dimethoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-methyl-6-(trifluoromethyl)pyrimidine (**4j**)



Yellowish solid; m.p. 140-142 °C; IR (KBr) ν_{max} / cm^{-1} 3082, 2952-2832, 1585-1489, 1389, 1238, 1026, 831-691; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.27 (dd, 1H, *J* 4.9, 17.6 Hz, H_A), 3.76 (dd, 1H, *J* 12.1, 17.8 Hz, H_B), 5.61 (dd, 1H, *J* 4.9, 12.0 Hz, H_C), 6.68-6.69 (m, 1H, Ar), 6.69 (s, 1H, H5), 6.80-6.82 (m, 2H, Ar), 7.33-7.34 (m, 3H, Ar), 7.79-7.81 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7, 42.3, 55.9, 62.0, 106.8 (q, *J* 2.6 Hz, C5), 110.4, 111.5, 118.8, 120.7 (q, *J* 275.2 Hz, CF_3), 126.9, 128.5, 129.9, 131.7, 135.1, 148.6, 149.1, 153.7, 155.9 (q, *J* 35.4 Hz, C6), 158.4, 171.1; HRMS $[MH]^+$ calcd. for $C_{23}H_{22}F_3N_4O_2$: 443.1695; found: 443.1710.

4-Methyl-2-(3-phenyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-6-(trifluoromethyl)pyrimidine (**4k**)

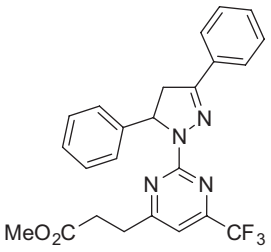
Yellowish solid; m.p. 214-217 °C; IR (KBr) ν_{max} / cm^{-1} 3076, 2959-2825, 1584-1487, 1385, 1245, 1010, 833-693; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H, CH_3), 3.28 (dd, 1H, *J* 5.4, 17.7 Hz, H_A), 3.70 (s, 6H, OCH_3), 3.71 (s, 3H, OCH_3), 3.77 (dd, 1H, *J* 12.1, 17.7 Hz, H_B), 5.57 (dd, 1H, *J* 5.3, 12.0 Hz, H_C), 6.49 (s, 2H, Ar), 6.71 (s, 1H, H5),



7.32-7.35 (m, 3H, Ar), 7.78-7.80 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 42.3, 56.1, 60.7, 103.9, 107.0 (q, *J* 2.6 Hz, C5), 120.6 (q, *J* 275.4 Hz, CF_3), 126.9, 128.5, 130.0, 131.5, 137.7, 138.0, 153.4, 153.9, 156.0 (q, *J* 35.0 Hz, C6), 158.3, 171.1; anal. calcd. for $C_{24}H_{23}F_3N_4O_3$: C, 61.01; H, 4.91; N, 11.86; found: C, 61.17; H, 4.91; N, 11.84.

Methyl 3-(2-(3,5-diphenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-6-(trifluoromethyl)pyrimidin-4-yl)propanoate (**5a**)

Yellowish solid; m.p. 157-160 °C; IR (KBr) ν_{max} / cm^{-1} 3085, 3023, 2950-2917, 1735, 1584-1486, 864-700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.21 (dd, 1H, *J* 5.1, 17.5 Hz, H_A), 3.56 (s, 3H, CO_2CH_3), 3.76



(dd, 1H, *J* 12.0, 17.5 Hz, H_B), 5.61 (dd, 1H, *J* 5.1, 12.0 Hz, H_C), 6.70 (s, 1H, H5), 7.10-7.24 (m, 5H, Ar), 7.31-7.33 (m, 3H, Ar), 7.75-7.77 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.1, 32.4, 42.4, 51.6, 62.5, 106.4 (q, *J* 2.7 Hz, C5), 120.6 (q, *J* 75.4 Hz, CF_3), 126.2, 126.9, 127.4, 128.5, 128.6, 129.9, 137.7, 142.4, 153.7, 156.4 (q, *J* 35.5 Hz, C6), 158.3, 172.1, 172.8; anal. calcd. for $C_{24}H_{21}F_3N_4O_2$: C, 63.43; H, 4.66; N, 12.33; found: C, 63.61; H, 4.69; N, 12.28.

Supplementary Information

Supplementary information (^{1}H and ^{13}C NMR spectra) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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