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Design, synthesis, and structure of alkyl 1*H*-pyrazolecarboxylates from a raspberry ketone methyl ether

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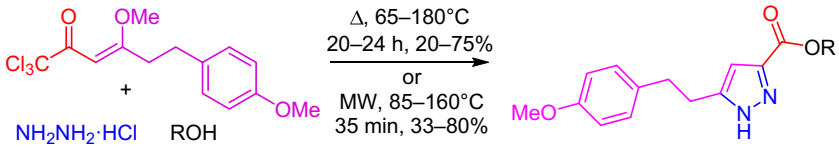
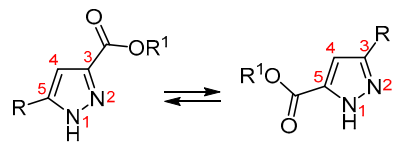


R = Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, *i*-Am, hexadecyl

This paper reports a one-pot synthesis of 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylates *via* cyclocondensation of 1,1,1-trichloro-4-methoxy-6-(4-methoxyphenyl)hex-3-en-2-one with hydrazine hydrochloride in ROH (R = Me, Et, *n*-Pr, *i*-Pr, *i*-Bu, *i*-Am, hexadecyl) under conventional and microwave heating. Yields are comparable in both methods, but under MW heating the reaction proceeds faster. The antioxidant activity of the compounds was measured using DPPH radical scavenging assay. It was observed, that the increase of the alcohol chain length decreases the antioxidant potential of the raspberry ketone derived molecular system.

Keywords: 4-alkoxy-1,1,1-trichloroalk-3-en-2-ones, 1*H*-pyrazolecarboxylates, raspberry ketone, antioxidants, microwave irradiation.

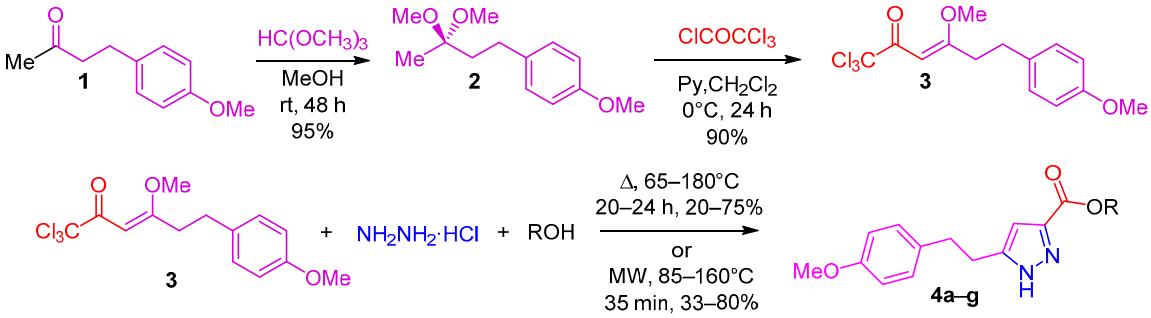
1*H*-Pyrazole is a very important structural motif, attracting much attention in organic synthesis, medicinal chemistry, and agrochemistry.[1] Among 1*H*-pyrazoles, 3- or 5-carboxylates have important applications as anti-inflammatory and antioxidant agents.[2] A versatile and interesting synthetic methodology using 1,1,1-trichloro-4-methoxyalk-3-en-2-ones to produce 1*H*-pyrazolecarboxylates has been developed as one-pot process, when both [C–C–C + N–N] cyclization and hydrolysis of the trichloromethyl group to the carboxyl one occur. Using the acetal acylation reaction, it is possible to design the dielectrophilic 1,1,1-trichloro-4-methoxy-3-alken-2-one by selecting the respective alkyl methyl ketone precursor.[3,4] Followed by the cyclocondensation reaction with hydrazine the choice of the alcohol as a solvent and reactant will define the molecular structure of the alkyl 1*H*-pyrazolecarboxylate obtained. This methodology gives an opportunity to regiospecifically and in very good yields produce a series of 1*H*-pyrazolecarboxylates, which exist in a solution as a mixture of 1,3- and 1,5-tautomers (Fig. 1).[5,6]



R = H, Me, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17}, *n*-C_9H_{19}, *n*-$C_{11}H_{23}$, *n*-$C_{13}H_{27}$
Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-PhC_6H_4
R^1 = Me, Et, CH_2CF_3

Figure 1. Structures of 1,3- and 1,5-tautomers of 1*H*-pyrazole-5(3)-carboxylates obtained from 1,1,1-trichloro-4-methoxyalk-3-en-2-ones.

Scheme 1. Synthesis of 1,1,1-trichloro-4-methoxy-6-(4-methoxyphenyl)hex-3-en-2-one (**3**) and 1*H*-pyrazole-5(3)-carboxylates **4a**–**g** under conventional and microwave heating



4 a R = Me, **b** R = Et, **c** R = *n*-Pr, **d** R = *i*-Pr, **e** R = *i*-Bu, **f** R = *i*-Am, **g** R = hexadecyl

Antioxidants are molecules that prevent cellular damage by scavenging or regulating the generation and elimination of reactive oxygen and nitrogen species (ROS and RNS, respectively).[7] Natural antioxidants include molecules found in leaf, fruit, and root extracts, such as zingerone,[8] raspberry ketone (4-(4-hydroxyphenyl)butan-2-one),[9] and their ethers.[10] The search for new antioxidants as drug candidates is an active field of medicinal chemistry.[11,12]

The goal of the present work was to obtain different alkyl 1*H*-pyrazolecarboxylates containing 2-(4-methoxyphenyl)ethyl moiety as new molecular prototypes of the compounds with already recognized antioxidant activity, using conventional and microwave heating methods. The use of focused microwave irradiation to decrease reaction times and improve yields has already been demonstrated for 1*H*-pyrazoles.[11,13] In addition, antioxidant activity of the newly synthesized molecules by DPPH radical scavenging test *in vitro* has been assessed.[14] The transformation of the trichloromethyl group bound to 1*H*-pyrazole has become a priority for our research group due to the diversification of trichloromethyl-substituted substrates together with the possibility of the diversification of substituted hydrazines.[4] Employing [3+2] cyclocondensation reaction and using alternative synthetic methodologies such as microwave irradiation,[15] use of ionic liquids,[16] solvent-free,[17] it is possible to obtain 1*H*-pyrazoles with interesting structural characteristics and numerous application possibilities, such as the development of new biological mediators.[4,13,14]

Synthesis of alkyl 1*H*-pyrazole-3-carboxylate precursors was carried out in three steps. The first step involved the large-scale production of 1-(3,3-dimethoxybutyl)-4-methoxybenzene (**2**) from 4-(4-methoxyphenyl)butan-2-one (raspberry ketone methyl ether) (**1**) and trimethyl orthoformate; compound **2** was obtained in quantitative 95% yield (Scheme 1). Then the acylation with trichloroacetyl chloride was applied to produce the dielectrophilic precursor of the target 1*H*-pyrazolecarboxylates in almost quantitative 90% yield. Trichloroacetyl derivative **3** was obtained with sufficient purity and used in the following transformations without additional purification. Both steps were performed based on the literature methods.[3] Finally, the last step was [3+2] cyclocondensation between NH_2NH_2·HCl and 1,1,1-trichloro-4-methoxy-6-(4-methoxyphenyl)hex-3-en-2-one (**3**), carried out in a series of alcohols: MeOH, EtOH, *n*-PrOH, *i*-PrOH, *i*-BuOH, isoamyl alcohol, and hexadecyl alcohol. These cyclocondensations were carried out using conventional heating and under microwave irradiation (Scheme 1). Initially, the [3+2] cyclocondensation between compound **3** and NH_2NH_2·HCl in MeOH (2 ml) was conducted at reflux (65°C) for 20 h. The completion of the reaction was controlled by TLC until the total consumption of the precursor and the appearance of only one product. Then MeOH was distilled off, and the solid (grease) residue was worked up to give methyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (**4a**) in 75% yield.

This synthetic protocol between compound **3** and NH_2NH_2·HCl was extended to cyclocondensations of the series of other alcohols. For the reactions in EtOH, *n*-PrOH, and *i*-PrOH, the mixture was heated at the boiling point of the respective alcohol for 20–24 h, leading to corresponding alkyl 1*H*-pyrazole-3-carboxylates **4b**–**d** in relatively poor yields (35–68%). Upon the cyclocondensations in *i*-BuOH, isoamyl alcohol, and hexadecyl alcohol, the reaction mixture was kept at 110°C for 24 h, leading to the respective alkyl 1*H*-pyrazole-3(5)-carboxylates **4e**–**g** in even worse yields (20–58%) (Scheme 1). Knowing that microwave-assisted syntheses lead to better yields in shorter reaction times, this methodology was applied in order to decrease reaction time and improve the yields of the alkyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylates. The optimum conditions for carrying out microwave-assisted [3+2] cyclocondensation reactions were ascertained by carrying out the reaction of 1,1,1-trichloro-4-methoxy-6-(4-methoxyphenyl)hex-3-en-2-one (**3**) with NH_2NH_2·HCl in *i*-BuOH (ε 15);[18] a time of 35 min was determined for the consumption of all the precursor **3**, and isobutyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (**4e**) obtained in slightly better yield (66%), in comparance to conventional heating. This procedure was extended to the reactions with other alcohols excluding hexadecyl alcohol resulting in no rapid heating and consequently no homogenization of the reaction medium. This remained a solid hydrazine salt even after 1 h in the microwave oven. This was overcome by the addition of MeCN as a solvent, resulting in the desired transformation – hexadecyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (**4g**) was obtained in a slightly better yield

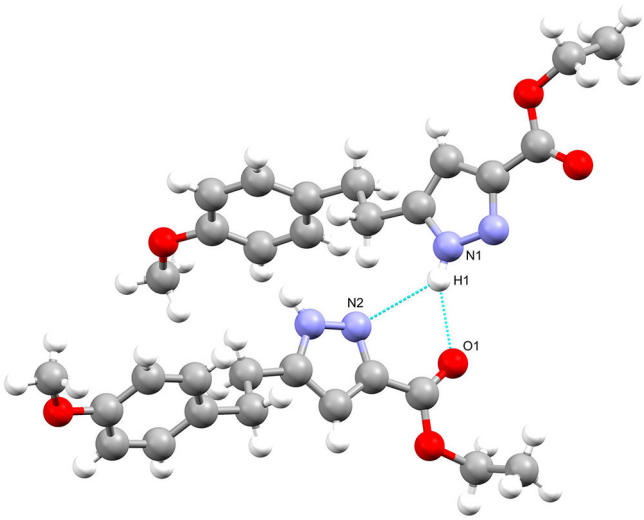


Figure 3. Representation of the bidentate 5-membered pseudoring in the molecular packing of compound **4b**.

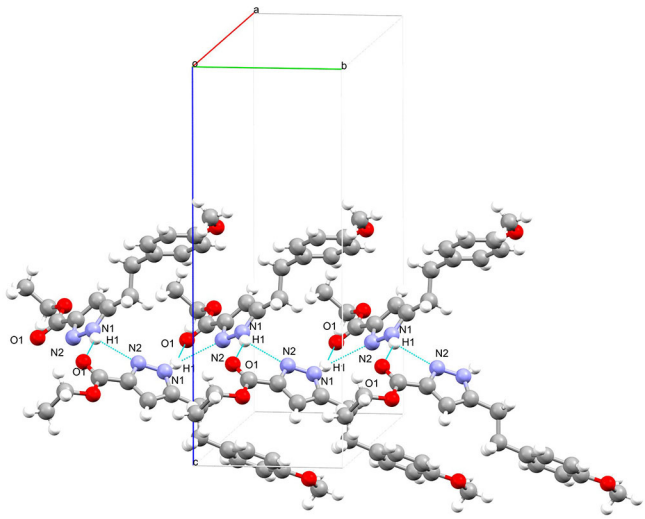


Figure 4. Representation of molecules forming infinite chains along the plane *b*, *c* in the crystal of compound **4b**.

determined by different refinements of the structure indicating lower indices of disagreement when compared to this H(1) atom in the other nitrogen atom of the molecule. This data is in accordance with the bond lengths found for the heterocycle C–N bonds. The bond lengths found for N(1)–C(5) and N(2)–C(3) were 1.349 and 1.331 Å, respectively, indicating the best representation of the structure, corroborating the assignment of the H(1) ring position.[19] Another finding in the molecule is that the dihedral angle found for N(2)–C(3)–C(13)–O(1) was 8.47° revealing that the heterocycle and carbonyl are almost in the same plane indicating a possible electronic resonance between the two fragments of the molecule.[20]

The crystalline structure of compound **4b** is stabilized by hydrogen bonds forming infinite chains along a plane *b*, *c*, heterocycle and carbonyl group are almost in the same plane indicating a possible electronic resonance between them. In this molecule, two strong hydrogen bonds were found, with the N(1)H group being the proton donor in the interactions with the N(2) pyrazole atom together with the carboxyl O(1) atom acting as H-acceptors.[20] The interatomic distances found were 2.128 and 2.564 Å for H(1)···O(1) and H(1)···N(2), respectively, and 2.928 and 3.199 Å, smaller than the sum of Van der Waals radii of the atoms involved[21] for N(1)···O(1) and N(1)···N(2), respectively in the interactions N(1)–H(1)···O(1) (Fig. 4).

Considering the information about the antioxidant activity of the raspberry ketone,[22] its alkyl ether derivatives,[23] and also 1*H*-pyrazoles,[2] we decided to study the antioxidant activity of the new hybrid molecules containing both ester function and 1*H*-pyrazole. This preliminary study aims to evaluate the antioxidant activity of alkyl 1*H*-pyrazole-3-carboxylates **4a**–**g** by comparing the obtained data with ascorbic acid data (Table 2), a standard antioxidant compound widely used in different therapeutic applications. To study the antioxidant activity of the synthesized compounds, the DPPH radical scavenging assay was employed.[24] This test is widely used to investigate the antioxidant activity of synthetic compounds by transferring hydrogen atoms or electrons followed by protons, mainly for its simplicity and efficiency.[25]

The results described in Table 3 showed that alkyl 5-(4-methoxyphenethyl)-1*H*-pyrazole-3-carboxylates **4a**–**g** display antioxidant activity. Methyl and ethyl derivatives **4a**,**b** displayed highest activity at the 10 μM concentration, however, antioxidant activity increases much less than the activity of the standard ascorbic acid, with increased concentration. All compounds in the series **4a**–**g** follow the same trend, while each unit of ascorbic acid concentration corresponds to 2.0 to 2.59% inhibition of the absorption of DPPH colored radicals (Table 2), increasing the concentration of the samples tested by forty times, 10 to 400 μM, caused the activity per unit of concentration to decrease. Overall, the antioxidant activity in the series of compounds **4a**–**g** demonstrates the potential of 1*H*-pyrazole nitrogen or benzyl carbon radical intermediates in reducing DPPH radicals.

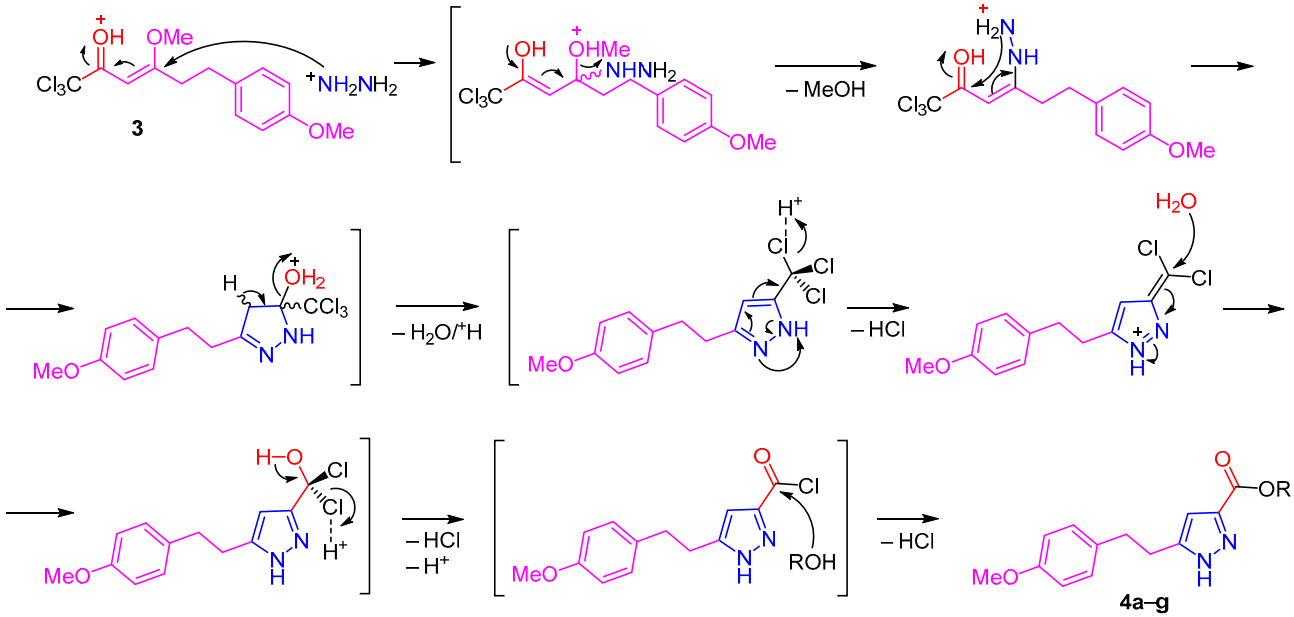
To conclude, a methodology for the synthesis of alkyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylates was developed. The synthetic methodology we have found is simple and efficient for obtaining diverse alkyl 1*H*-pyrazolecarboxylates using conventional heating and microwave irradiation, including obtaining the fatty derivative – hexadecyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-

Table 2. DPPH antioxidant activity of ascorbic acid used as standard*

Concentration, μM	Inhibition rate, %
1	2.0 ± 0.8
5	11.5 ± 0.5**
10	22.6 ± 0.7**
15	34.3 ± 1.9**
20	51.9 ± 1.4**

* Values are expressed as mean ± SE of percentage of inhibition by the compound compared to the control in EtOH.
** $p < 0.001$ indicates significant difference when compared with control sample.

Scheme 2. The proposed mechanism of [3+2] cyclocondensation leading to 1*H*-pyrazole-3-carboxylates **4a**–**g**



(41%), after 35 min (Scheme 1). The proposed mechanism of the transformation is described in Scheme 2.[6]

Regardless of the method used, alkyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylates **4a**,**b**,**e** have shown the best yields and did not require purification for spectroscopic analysis. Compounds **4c**,**d**,**f**,**g** required recrystallization from hexane. However, considering the need for the high purity of the products necessary for the antioxidant activity analysis the entire series was recrystallized from hexane. Yields are presented in Table 1. All isolated alkyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylates **4a**–**g** were identified using ^{1}H and ^{13}C NMR spectroscopy and HRMS. X-ray diffraction was used for the identification of the single crystal of ethyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (**4b**).

The HRMS analyses confirm the formation of compounds **4a**–**g** since all showed an acceptable experimental molecular ion value $[M+H]^+$. The ^{1}H NMR spectra for all compounds **4a**–**g** exhibit two multiplet signals assigned to two methylene groups of the phenylethyl moiety, with typical chemical shift values of 2.91–2.99 and 2.98–3.16 ppm, and signals from 4-methoxyphenyl group, a singlet at 3.78 ppm and two doublets in the characteristic aromatic region, 6.81–6.82 and 7.08–7.11 ppm with J_{HH} = 8.0 Hz. The singlet at 6.56–6.63 ppm is typical for H-4 proton of the 4-unsubstituted 1*H*-pyrazole-3(5)-carboxylates.[5] Signals were also observed that prove the presence of the ester groups corresponding to each alcohol tested in this work. The structures of compounds **4a**–**g** were confirmed by the presence of the aromatic 1*H*-pyrazole ring signals around 147.5–148.5 ppm for C-3 atom, 106.7–109.7 ppm for C-4 atom, 138.8–140.9 ppm for C-5 atom, and 158.7–161.8 ppm for CO_2R atom in ^{13}C NMR spectra. Sets of signals proving the presence of the 2-(4-methoxyphenyl)-ethyl moiety and the respective alcohol fragment in each product **4a**–**g** were observed.

The single crystal of compound **4b** was obtained by the slow evaporation from hexane solution at room temperature. 1*H*-Pyrazole **4b** crystallized in the monoclinic crystalline system and $P2_1/n$ space group with only one independent molecule in the asymmetric unit (Fig. 2). The assignment of H(1) atom to N(1) atom (Fig. 3) was

Table 1. Yields of 1*H*-pyrazole-5(3)-carboxylates **4a**–**g** under conventional and MW heating

Compound	R	Yield*, %	
		Conventional heating	MW heating
4a	Me	75	80
4b	Et	68	74
4c	*n*-Pr	48	55
4d	*i*-Pr	35	43
4e	*i*-Bu	58	66
4f	*i*-Am	20	33
4g	Hexadecyl	31	40

* Yield of compounds after crystallization from hexane.

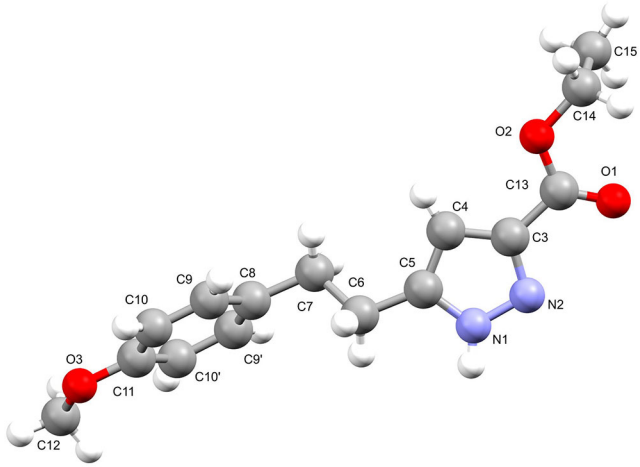


Figure 2. Projection of the molecular structure of compound **4b** showing the atomic numbering scheme.

Table 3. Evaluation of DPPH radical scavenging activity of 1*H*-pyrazole-3-carboxylates **4a**–**g** (inhibition rate, %)*

Compound	Concentration, μM					
	10	25	50	100	200	400
4a	9.2 ±1.8**	12.8 ± 2.5***	11.1 ± 0.2***	12.2 ± 0.4***	13.6 ± 0.2***	16.6 ± 1.3***
4b	14.4 ± 1.2***	17.3 ± 0.6***	17.1 ± 0.5***	18 ± 0.9***	20.1 ± 0.6***	21.5 ± 0.1***
4c	0.8 ± 0.3	0.7 ± 0.3	2.2 ± 0.3	1.8 ± 0.3	3.3 ± 0.3	3.8 ± 0.1
4d	4.4 ± 0.4	4.3 ± 0.2	7.6 ± 0.2	10.6 ± 1.3	23.4 ± 1.2	28.2 ± 2.4
4e	nd*[4]	nd	nd	5.6 ± 1.6	3.7 ± 2.6	5.9 ± 0.1
4f	2.7 ± 0.2*[5]	2.1 ± 0.5**	3.2 ± 0.1**	2.5 ± 0.5**	2.7 ± 0.1*[5]	2.7 ± 0.9*[5]
4g	3.2 ± 0.4	3.8 + 0.1	1.6 ± 0.1	0.9 ± 0.1	3.6 ± 2.7	1.7 ± 0.1

* Values are expressed as mean ± SE of percentage of inhibition by the compound compared to the control 60 μM DPPH solution in EtOH.
** $p < 0.01$, indicates significant difference when compared with control sample.
*** $p < 0.001$, indicates significant difference when compared with control sample.
*[4] nd – not detectable.
*[5] $p < 0.05$, indicates significant difference when compared with control sample.

3-carboxylate. When we compare conventional heating with microwave irradiation, it was observed that the latter significantly reduces the reaction time from 20 h to 35 min, although yields were only slightly higher after purification by crystallization from hexane. In addition, the antioxidant activity results in DPPH assay indicated that several of the obtained compounds exhibit good antioxidant activity, when compared to the activity of ascorbic acid.

Experimental

IR spectrum of compound **4b** was obtained on a Shimadzu IRPrestige-21 spectrophotometer. The analysis was performed in the solid state, using the diffuse reflectance technique, with readings in the region 4000–500 cm^{-1}. Spectrum was treated using the ACD software package, located at the School of Chemistry and Food at the Federal University of Rio Grande (FURG). The ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively), as well as COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC spectra, were acquired on a Bruker Ascend 400 spectrometer in $CDCl_3$ with TMS as internal standard. Atom numbering in the ^{1}H and ^{13}C NMR spectra assignments does not correspond to the IUPAC nomenclature and is given in the Supplementary information file for each compound. High-resolution mass spectra were obtained on an Agilent 6460 Triple Quadrupole connected to a 1200 series LC and equipped with a solvent degasser, binary pump, column oven, auto-sampler. The Agilent QQQ 6460 tandem mass spectrometer was operated in positive jet stream electrospray ionization (ESI) mode. Nitrogen was used as the 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. The jet stream sheath gas temperature was 250°C with a flow rate of 11 l/min. All samples were infused into the ESI source at a 5 ml/min flow rate. Data was acquired in positive MS total ion scan mode (mass scan range *m*/*z* 50–650) and in positive MS/MS product ion scan mode source at the University of Caxias do Sul (UCS). The melting points were determined using a Fisatom 430D melting point determiner with three capillary tubes, and thermometer up to 360°C. Microwave reactions were performed using a CEM Discover SP W/ActiVent microwave reactor model no 909155, in a 5-ml vials with stirring option, using Teflon caps, under completely sealed environment with reactor specifications: voltage 180/240 V AC; max current 6.3 A; frequency 50/60 Hz; max microwave power 300 W. The reaction temperature 85–160°C was reached in a ramp time of 2–5 min and hold time was set for 35 min.

Synthesis of 1*H*-pyrazole-3-carboxylates 4a–g (General procedure). Conventional heating method. In a round-bottom 25-ml flask, 1,1,1-trichloro-4-methoxy-6-(4-methoxyphenyl)hex-3-en-2-one (**3**) (2 mmol), hydrazine dihydrochloride (2.2 mmol), and alcohol (2 ml) were added. The mixture was stirred at reflux temperature for 20–24 h. Then solvent was evaporated under reduced pressure and the solid residue was diluted with CH_2Cl_2 and washed with distilled H_2O. The organic phase was neutralized with 10% $CaCO_3$ solution, washed with distilled H_2O, dried over anhydrous Na_2SO_4, and solvent was evaporated. Compounds **4c**,**d**,**f**,**g**,**h** were recrystallized from hexane.

Microwave irradiation method. A compatible vessel in a Discover SP reactor for microwave synthesis was filled with 1,1,1-tricloro-4-methoxy-6-(4-methoxyphenyl)hex-3-en-2-one (**3**) (2 mmol), hydrazine dihydrochloride (2.2 mmol), and alcohol (2 ml). Alcohol itself was used as a solvent, except for compound **4g**, when MeCN (2 ml) was used since the alcohol is solid compound. After the container was sealed, the sample was irradiated with stirring in a closed system for 35 min, the irradiation power was in the range of 1–50 W, pressure between 0–100 psi, and the reaction temperature 85–160°C. After completion, the reaction mixture was subsequently cooled to 50°C with compressed air. The reaction mixture was treated as described for the conventional heating method. Compounds **4c**,**d**,**f**,**g** were recrystallized from hexane.

Methyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (4a). Yield 195 mg (75%, thermal), 209 mg (80%, MW), amber grease. ^{1}H NMR spectrum, δ, ppm

(*J*, Hz): 9.41 (1H, s, NH); 7.10 (2H, d, *J* = 8.5, H-2,6 Ar); 6.81 (2H, d, *J* = 8.6, H-3,5 Ar); 6.63 (1H, s, H pyrazole); 3.94 (3H, s, CO_2CH_3); 3.78 (3H, s, OCH_3); 3.16 (2H, t, *J* = 7.6, 6-CH_2); 2.99 (2H, t, *J* = 7.6, 7-CH_2). ^{13}C NMR spectrum, δ, ppm: 159.6 (C-13); 158.3 (C-11); 148.5 (C-3); 138.8 (C-5); 131.7 (C-8); 129.5 (C-9); 114.1 (C-10); 107.9 (C-4); 55.4 (C-12); 52.9 (C-14); 34.0 (C-6); 27.8 (C-7). Found, *m*/*z*: 261.1246 $[M+H]^+$. $C_{14}H_{17}N_2O_3$. Calculated, *m*/*z*: 261.1239.

Ethyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (4b). Yield 187 mg (68%, thermal), 203 mg (74%, MW), amber solid, mp 78–80°C. IR spectrum, ν, cm^{-1}: 1750 (C=O), 1500 (Ar), 1050 (C–O), 860 (Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.08 (2H, d, *J* = 8.5, H-2,6 Ar); 6.82 (d, *J* = 8.6, 2H, H-3,5 Ar); 6.60 (1H, s, H pyrazole); 4.36 (2H, q, *J* = 7.1, C<u>H</u>$_2$CH$_3$); 3.78 (3H, s, OCH_3); 3.00 (2H, t, *J* = 7.1, 6-CH_2); 2.94 (2H, t, *J* = 7.1, 7-CH_2); 1.36 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 161.6 (C-13); 158.2 (C-11); 148.1 (C-3); 140.7 (C-5); 132.8 (C-8); 129.4 (C-9); 114.1 (C-10); 106.9 (C-4); 61.2 (C-14); 55.4 (C-12); 34.6 (C-6); 28.6 (C-7); 14.4 (C-15). Found, *m*/*z*: 275.1387 $[M+H]^+$. $C_{15}H_{19}N_2O_3$. Calculated, *m*/*z*: 275.1396.

Propyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (4c). Yield 139 mg (48%, thermal), 160 mg (55%, MW), brown solid, mp 80–82°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.08 (2H, d, *J* = 8.5, H-2,6 Ar); 6.81 (2H, d, *J* = 8.5, H-3,5 Ar); 6.58 (1H, s, H pyrazole); 4.26 (2H, t, *J* = 6.8, OCH_2); 3.78 (3H, s, OCH_3); 2.95 (2H, q, *J* = 7.3, 6-CH_2); 2.93 (2H, t, *J* = 7.6, 7-CH_2); 1.79–1.73 (2H, m, $CH_2C\underline{H}_2CH_3$); 0.99 (3H, t, *J* = 7.4, $CH_2CH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 160.3 (C-13); 156.8 (C-11); 146.7 (C-3); 139.7 (C-5); 131.5 (C-8); 128.1 (C-9); 112.7 (C-10); 105.5 (C-4); 65.3 (C-14); 54.0 (C-12); 33.3 (C-6); 27.2 (C-7); 20.8 (C-15); 13.9 (C-16). Found, *m*/*z*: 289.1559 $[M+H]^+$. $C_{16}H_{21}N_2O_3$. Calculated, *m*/*z*: 289.1552.

Isopropyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (4d). Yield 101 mg (35%, thermal), 124 mg (43%, MW), amber solid, mp 93–95°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.81 (1H, s, NH); 7.11 (2H, d, *J* = 8.6, H-2,6 Ar); 6.82 (2H, d, *J* = 8.6, H-3,5 Ar); 6.63 (1H, s, H pyrazole); 5.27–5.21 (1H, m, C<u>H</u>$(CH_3)_2$); 3.78 (3H, s, OCH_3); 3.15 (2H, t, *J* = 7.7, 6-CH_2); 2.98 (2H, t, *J* = 7.7, 7-CH_2); 1.38 (6H, d, *J* = 6.5, $CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum, δ, ppm: 164.6 (C-13); 158.2 (C-11); 148.4 (C-3); 139.1 (C-5); 131.5 (C-8); 129.1 (C-9); 113.8 (C-10); 107.6 (C-4); 70.3 (C-14); 55.0 (C-12); 33.8 (C-6); 27.5 (C-7); 21.5 (C-15,16). Found, *m*/*z*: 289.1565 $[M+H]^+$. $C_{16}H_{21}N_2O_3$. Calculated, *m*/*z*: 289.1552.

Isobutyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (4e). Yield 166 mg (58%, thermal), 200 mg (66%, MW), beige solid, mp 108–110°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.09 (2H, d, *J* = 8.6, H-2,6 Ar); 6.82 (2H, d, *J* = 8.6, H-3,5 Ar); 6.58 (1H, s, H pyrazole); 4.07 (2H, d, *J* = 6.8, OC<u>H</u>$_2$); 3.78 (3H, s, OCH_3); 3.01–2.97 (2H, m, 6-CH_2); 2.93–2.90 (2H, m, 7-CH_2); 2.08–2.01 (1H, m, C<u>H</u>$(CH_3)_2$); 0.98 (6H, d, *J* = 8.0, $CH_2CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum, δ, ppm: 161.8 (C-13); 158.2 (C-11); 148.0 (C-3); 140.7 (C-5); 132.9 (C-8); 129.4 (C-9); 114.0 (C-10); 106.8 (C-4); 71.0 (C-14); 55.3 (C-12); 34.7 (C-6); 28.6 (C-15); 27.9 (C-7); 19.2 (C-16,17). Found, *m*/*z*: 303.1701 $[M+H]^+$. $C_{17}H_{23}N_2O_3$. Calculated, *m*/*z*: 303.1709.

Isopentyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (4f). Yield 63 mg (20%, thermal), 105 mg (33%, MW), amber grease. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.09 (2H, d, *J* = 8.6, H-2,6 Ar); 6.81 (2H, d, *J* = 8.6, H-3,5 Ar); 6.56 (1H, s, H pyrazole); 4.32 (2H, t, *J* = 6.9, OCH_2); 3.78 (3H, s, OCH_3); 3.02–2.98 (2H, m, 6-CH_2); 2.94–2.90 (2H, m, 7-CH_2); 1.76–1.73 (1H, m, C<u>H</u>$(CH_3)_2$); 1.67–1.60 (2H, quint, *J* = 6.8, $CH_2C\underline{H}_2CH(CH_3)_2$); 0.95 (6H, d, *J* = 4.0, $CH_2CH_2CH(C\underline{H}_3)_2$). ^{13}C NMR spectrum, δ, ppm: 161.8 (C-13); 158.1 (C-11); 147.5 (C-3); 140.9 (C-5); 132.8 (C-8); 129.4 (C-9); 113.9 (C-10); 106.7 (C-4); 63.8 (C-14); 55.3 (C-12); 37.7 (C-15); 34.5 (C-6); 28.4 (C-7); 25.7 (C-16); 22.6 (C-17,18). Found, *m*/*z*: 317.1875 $[M+H]^+$. $C_{18}H_{25}N_2O_3$. Calculated, *m*/*z*: 317.1865.

Hexadecyl 5-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrazole-3-carboxylate (4g). Yield 146 mg (31%, thermal), 188 mg (40%, MW), white solid, mp 78–80°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.08 (2H, d, *J* = 8.6, H-2,6 Ar); 6.81 (2H, d, *J* = 8.6, H-3,5 Ar); 6.59 (1H, s, H pyrazole); 4.28 (2H, t, *J* = 6.8, OCH_2); 3.78 (3H, s, OCH_3); 3.01–2.96 (2H, m, 6-CH_2); 2.92–2.88 (2H, m, *J* = 7.5, 7-CH_2); 1.79–1.67 (2H, m, 15-CH_2); 1.39–1.35 (2H, m, 16-CH_2); 1.25 (28H, s, 17–30-CH_2); 0.88 (3H, t, *J* = 6.8, CH_3). ^{13}C NMR spectrum, δ, ppm: 171.3 (C-13); 129.3 (C-9); 114.0 (C-10); 109.7 (C-4); 64.8 (C-14); 55.3 (C-12); 45.3 (C-15); 32.0 (C-6); 29.5 (C-7); 22.8 (C-17,18); 14.2 (C-29). Found, *m*/*z*: 471.3572 $[M+H]^+$. $C_{29}H_{47}N_2O_3$. Calculated, *m*/*z*: 471.3587.

Antioxidant activity of compounds 4a–g in DPPH scavenging test. The antioxidant activity of compounds **4a**–**g** was measured using the DPPH radical scavenging test according to a modified method by Brand-Williams et al.[25] 60 μM DPPH solution in EtOH (2 ml) was added to the solution of the test compound (at 10, 25, 50, 100, 200, and 400 μM concentration) in EtOH (2 ml), and the mixture was incubated in assay tubes and kept in the dark for 30 min. The decrease in absorbance was determined at 515 nm on a UV/Vis spectrophotometer Biospectro, commercial synthetic ascorbic acid (1–20 μM) was used for comparison.[22] The results were expressed as a percentage of reduction of the DPPH control in EtOH solution (Table 3).

Single crystal X-ray diffraction data of compound 4b was obtained on a Bruker D8 QUEST diffractometer using CuKα radiation (λ 1.54080 Å) with a KAPPA four-circle goniometer equipped with a PHOTON II CPAD area detector at the Federal University of Santa Maria. The structure was solved by direct methods using SHELXT and refined with SHELXL.[26] All non-hydrogen atoms were refined using anisotropic displacement parameters in SHELXL. The hydrogen atom positions were calculated starting from the idealised positions. Absorption corrections were performed using multiscan methods. The molecular structure was visualized using the Mercury[27] program. Full crystallographic data of compound **4b** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1965453).

Supplementary information file containing ^{1}H and ^{13}C NMR spectra, HRMS data of all synthesized compounds, IR spectrum and X-ray data of compound **4b** is available at the journal website at http://link.springer.com/journal/10593.

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