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Synthesis, structure and biological activity of 3(5)-trifluoromethyl-1*H*-pyrazoles derived from hemicurcuminoids

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ABSTRACT

Six new 3(5)-trifluoromethyl-5(3)-substituted-styryl-1*H*-pyrazoles have been synthesized and their tautomerism studied in solution and in the solid state. The determination of their structures has been based on multinuclear NMR spectroscopy together with GIAO/B3LYP/6–311++G(d,p) theoretical calculations of eight structures for each pyrazole (two tautomers and four conformations). Five out of the six compounds present inhibition percentages of the iNOS isoform higher than 50%. With regard to the nNOS inhibitory activity, only two of the studied compounds show an inhibition of about 50%. Finally, concerning the eNOS, there is a compound presenting a low percentage of inhibition (40.2%) attaining in the other cases 50%.

1. Introduction

The interest in curcumin [(1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione] [1–9] has prompted many structural studies on this β-diketone tautomerism [10–14] as well as on the synthesis and structural studies of hemicurcuminoids, compounds resulting from the replacement of one styryl branch of curcumin (2-methoxy-4-vinylphenol) by a simpler group, for instance, a phenyl group [11,15].

The discovery that the six-membered pseudoaromatic ring of the enol of curcumin [16] [(1*E*,4*Z*,6*E*)-5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,4,6-triene-3-one] can be replaced by the five-membered ring of the heteroaromatic 1*H*-pyrazole [17] maintaining but also modifying the biological properties of curcumin, has resulted in many works [18–22] including two by our group [23,24] (Fig. 1).

Combining both approaches (hemicurcuminoids and pyrazoles) results in hemicurcuminoid pyrazoles (Fig. 1). We will now describe the case R = CF_3 (Fig. 2), that can exist in two distinct forms **a** and **b**. The atom numbering of the pyrazole ring is different in both tautomers **a** and **b**. According to the IUPAC rules [25], the numbering of the system has to be carried out in such a way that it must start at the N*H* and the two heteroatoms are given the lowest set of locants. Thus, the carbon atoms 3 and 5 exchange their numbering on going from tautomer **a** to **b**. There is ample information in the literature that a trifluoromethyl group is an interesting pharmacophore [26–28] even in pyrazole derivatives [29–31] including the well-known anti-inflammatory Celecoxib [32].

2. Experimental

2.1. General remarks

All chemicals cited in the synthetic procedures are commercial compounds. Melting points were determined by DSC with a SEIKO DSC 220C connected to a model SSC5200H disk station. Thermograms (sample size 0.003–0.005 g) were recorded with a scan rate

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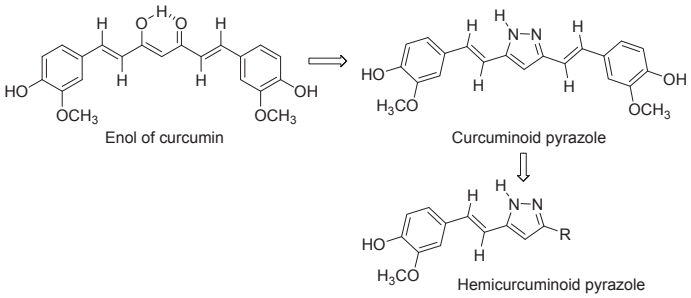

Fig. 1. The transition between curcumin and hemicurcuminoid pyrazoles [the pyrazole derived from the reaction of curcumin with hydrazine is called (mainly in pharmaceutical papers) "hydrazinocurcumine"].

of 5.0 °C/min. Column chromatography was performed on silicagel (Merck 60, 70–230 mesh) and elemental analyses using a Perkin–Elmer 240 apparatus.

2.2. Chemistry

2.2.1. General procedure for the preparation of pyrazole derivatives

Compounds **1**–**6** were prepared by reacting the corresponding β-diketones (1 mmol) with hydrazine hydrate 98% (1.5 mmol) in acetic acid (5 mL) [24]. After heating at reflux for 2 h the reaction mixture was poured into water. The precipitate was filtered off, washed with water and dried. In all cases pyrazoles were obtained as white solids after recrystallization from EtOH/H_2O.

2.2.2. (E)-3(5)-[β-(2-fluoro-4-hydroxyphenyl)-ethenyl]-5(3)-trifluoromethyl-1H-pyrazole (*1*)

Compound **1** was prepared from (*E*)-1,1,1-trifluoro-6-(2-fluoro-4-hydroxyphenyl)hex-5-ene-2,4-dione [11,15] (yield: 75%). Mp = 223.1 °C. Anal. Calc. for $C_{12}H_8F_4N_2O$: C, 52.95; H, 2.96; N, 10.29%. Found: C, 52.83; H, 2.96; N, 10.26%.

2.2.3. (E)-3(5)-[β-(3-fluoro-4-hydroxyphenyl)-ethenyl]-5(3)-trifluoromethyl-1H-pyrazole (*2*)

Compound **2** was prepared from (*E*)-1,1,1-trifluoro-6-(3-fluoro-4-hydroxyphenyl)hex-5-ene-2,4-dione [11,15] (yield: 88%). Mp = 204.5 °C. Anal. Calc. for $C_{12}H_8F_4N_2O$: C, 52.95; H, 2.96; N, 10.29%. Found: C, 52.98; H, 3.12; N, 10.41%.

2.2.4. (E)-3(5)-[β-(2,4-difluoro-3-hydroxyphenyl)-ethenyl]-5(3)-trifluoromethyl-1H- pyrazole (*3*)

Compound **3** was prepared from (*E*)-6-(2,4-difluoro-3-hydroxyphenyl)-1,1,1-trifluorohex-5-ene-2,4-dione [11,15] (yield: 64%). Mp = 212.6 °C. Anal. Calc. for $C_{12}H_7F_5N_2O$: C, 49.67; H, 2.43; N, 9.65%. Found: C, 49.87; H, 2.63; N, 9.72%.

2.2.5. (E)-3(5)-[β-(2,5-difluoro-4-hydroxyphenyl)-ethenyl]-5(3)-trifluoromethyl-1H-pyrazole (*4*)

Compound **4** was prepared from (*E*)-6-(2,5-difluoro-4-hydroxyphenyl)-1,1,1-trifluorohex-5-ene-2,4-dione [11,15] (yield: 77%). Mp = 227.1 °C. Anal. Calc. for $C_{12}H_7F_5N_2O$: C, 49.67; H, 2.43; N, 9.65%. Found: C, 49.32; H, 2.50; N, 9.81%.

2.2.6. (E)-3(5)-[β-(4-fluoro-3-methoxyphenyl)-ethenyl]-5(3)-trifluoromethyl-1H-pyrazole (*5*)

Compound **5** was prepared from (*E*)-1,1,1-trifluoro-6-(4-fluoro-3-methoxyphenyl)hex-5-ene-2,4-dione [11,15] (yield: 91%). Mp = 168.0 °C. Anal. Calc. for $C_{13}H_{10}F_4N_2O$: C, 54.55; H, 3.52; N, 9.79%. Found: C, 54.32; H, 3.59; N, 9.85%.

2.2.7. (E)-3(5)-[β-(4-hydroxy-3-methoxyphenyl)-ethenyl]-5(3)-trifluoromethyl-1H-pyrazole (*6*)

Compound **6** was prepared from (*E*)-1,1,1-trifluoro-6-(4-hydroxy-3-methoxyphenyl)hex-5-ene-2,4-dione [11,15] (yield: 98%). Mp = 165.0 °C. Anal. Calc. for $C_{13}H_{11}F_3N_2O_2$: C, 54.93; H, 3.90; N, 9.86%. Found: C, 54.63; H, 3.76; N, 9.60%.

2.3. NMR measurements

Solution NMR spectra were recorded on a Bruker DRX 400 (9.4 T, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C, 40.54 MHz for ^{15}N and 376.50 MHz for ^{19}F) spectrometer with a 5-mm inverse-detection H-X probe equipped with a z-gradient coil (^{1}H, ^{13}C, ^{15}N) and with a QNP 5 mm probe (^{19}F), at 295 K. Chemical shifts (δ in ppm) are given from internal solvent, DMSO-d_6 2.49 for ^{1}H and 39.5 for ^{13}C, HMPA-d_{18} 2.51 to the upfield multiplet for ^{1}H and 35.8 for ^{13}C. External references were used for ^{15}N and ^{19}F, nitromethane and $CFCl_3$ respectively. Coupling constants (J in Hz) are accurate to ± 0.2 Hz for ^{1}H, ± 0.6 Hz for ^{13}C and ±0.8 Hz for ^{19}F. Typical parameters for ^{1}H NMR spectra were spectral width 6500 Hz and pulse width 7.5 μs at an attenuation level of 0 dB. Typical parameters for ^{13}C NMR spectra were spectral width 21 kHz, pulse width 10.6 μs at an attenuation level of −6 dB and relaxation delay 2 s; WALTZ-16 was used for broadband proton decoupling; the FIDs were multiplied by an exponential weighting (lb = 2 Hz) before Fourier transformation. 2D (^{1}H–^{13}C) gs-HMQC, (^{1}H–^{13}C) gs-HMBC and 2D (^{1}H–^{15}N) gs-HMQC, (^{1}H–^{15}N) gs-HMBC were acquired and processed using standard Bruker NMR software and in non-phase-sensitive mode [33]. Gradient selection was achieved through a 5%

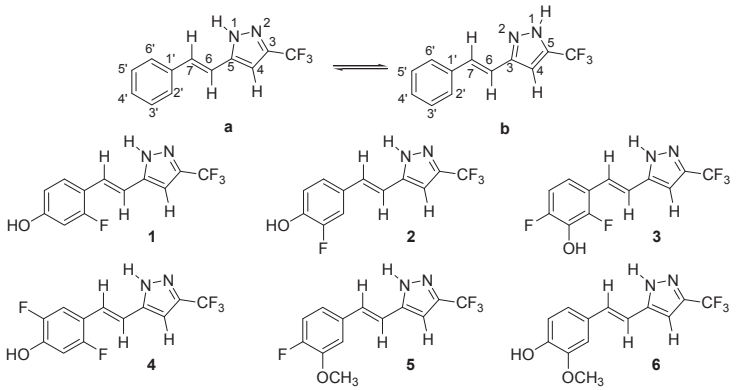

Fig. 2. The six pyrazoles studied in this work that can exist in two tautomeric forms, **a** (3-CF_3) and **b** (5-CF_3).