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ORIGINAL PAPER

An efficient and regioselective synthesis of 1,1′-oxalylbis [3-(alkyl/aryl/heteroaryl)-5-(trihalomethyl)-1*H*-pyrazoles] from 4-alkoxy-1,1,1-trihaloalk-3-en-2-ones

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Abstract This work describes the regioselective synthesis of two new series of 1,1′-oxalylbis[3-(alkyl/aryl/heteroaryl)-4,5-dihydro-5-hydroxy-5-(trihalomethyl)-1*H*-pyrazoles], where the 3-substituents are H, Me, C_6H_5, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 4,4′-BiPh, and 2-furyl, in a one-pot methodology with ethanol as solvent, from the reaction of 4-alkoxy-4-(alkyl/aryl/heteroaryl)-1,1,1-trihaloalk-3-en-2-ones with oxalyldihydrazide (51–89%). Complementarily, the dehydration reactions of five examples of the described oxalylbispyrazolines are also reported, which furnished the respective 1,1′-oxalylbis [3-(alkyl/aryl/heteroaryl)-5-(trihalomethyl)-1*H*-pyrazoles] in 53–78% yields without the two C(O)–N bond cleavages.

Keywords Oxalyldihydrazide · Ketones · Pyrazolines · Pyrazoles · Bispyrazoles

Introduction

Since 1967, it has been estimated that the incidence of people with diabetogenic genes is one in four and that the rate of increase of diabetes is approximately three times that of the population in general [1]. Moreover, Grunwald [2] stated that there is still hope and need for oral hypoglycemic agents with mechanisms of action other than those of the compounds presently available. The first works on animals revealed that 5-methylpyrazole-3-carboxylic acid derivatives very nearly approached this goal [3–5], showing that a carbonyl function attached to a pyrazole nucleus was a promising structure.

In 1972, Lotti and Vezzosi synthesized 13 1-(alkanoyl)aroyl-substituted 3,5-dimethylpyrazoles from the reaction of 3,5-dimethyl-1*H*-pyrazoles with an appropriate acid chloride in diethylether as solvent and in the presence of triethylamine. As a result, most of these compounds showed hypoglycemic activity greater than that of 1-butyl-3-(4-tolylsulfonyl)urea (tolbutamide). In the same paper 1,1′-oxalylbis(3,5-dimethylpyrazole) was also synthesized and evaluated, showing interesting hypoglycemic activity [6].

In 1975, some 1,1′-adipyl- and 1,1′-oxalylbis(3,5-dimethylpyrazoles) and the respective 2-pyrazolin-5-ones were prepared by the reaction of adipyl/oxalylhydrazine with 1,3-dicarbonyl compounds and evaluated as potential antidiabetics [7].

In 1988, a study on tautomerism in a series of condensation products of 1,3-dicarbonyl compounds and dihydrazides of dicarboxylic acids was reported [8]. This study demonstrated the crystalline state of 1,1′-malonyl- and 1,1′-oxalylbispyrazolines. The authors also observed 1,1′-oxalylbis[5-(*t*-butyl)-4,5-dihydro-5-hydroxy-1*H*-pyrazole] as a diastereomeric mixture in solution. Later the synthesis, electron spin resonance (ESR) spectra, and magnetic susceptibility of binuclear copper(II) complexes based on some 1,1′-dicarbonyl-linked bispyrazolines were reported in 1989 [9].

In 1998, a series of α-keto esters was prepared in good yields by the formation of *N*-acylpyrazoles, followed by the appropriate Grignard reactions [10]. In the first step, 1,1′-oxalylbis(3,5-dimethylpyrazole) was obtained in 64% yield when the reaction of 3,5-dimethyl-1*H*-pyrazole with oxalyl chloride was carried out in toluene as solvent and also in the presence of triethylamine. In a recent work, El-Sayed et al. [11] reported the N-acylation of 5(3)-hydroxy-3(5)-

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substituted-1*H*-pyrazoles, on average in 75% yields, employing different acyl halides.

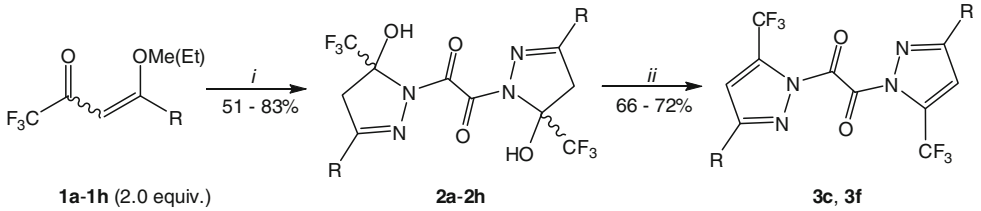
In 2009, we reported a one-step and regioselective procedure for the synthesis of a novel series of 1,1′-carbonylbis[3-(alkyl/aryl/heteroaryl)-4,5-dihydro-5-hydroxy-5-(trifluoromethyl)-1*H*-pyrazoles] [12–14] from the cyclocondensation reactions of 4-alkoxy-4-(aryl/heteroaryl)-1,1,1-trifluoroalk-3-en-2-ones with carbohydrazide. As a synthetic alternative, in 2010, two new series of 1,1′-carbonylbis[3-(aryl/heteroaryl)-5-(trihalomethyl)-1*H*-pyrazoles] [15] were synthesized by us in a one-pot methodology from the reaction of 4-methoxy-4-(aryl/heteroaryl)-1,1,1-trihalobut-3-en-2-ones with 1,3-diaminoguanidine monohydrochloride. The heterocycles were obtained regioselectively in good yields (62–86%) and short reaction time.

In the course of our ongoing interest in new heterocyclic scaffolds which present promising pharmacological activity, we have explored the application of 4-alkoxy-4-(alkyl/aryl/heteroaryl)-1,1,1-trihaloalk-3-en-2-ones **1**, **4** in the synthesis of novel 1,1′-oxalylbis[4,5-dihydro-5-hydroxy-5-(trihalomethyl)-1*H*-pyrazoles] **2**, **5** and the respective dehydrated bispyrazole systems **3**, **6**.

Thus, considering the biological importance of 2-pyrazolines and the fact that trifluoro(chloro)methylated analogs, such as 1,1′-oxalylbispyrazoles **2**, **3**, **5**, **6** have not yet been produced, it would be of interest to demonstrate a simple and environmentally benign method to obtain these heterocycles. Herein, we report results of the reaction of these *β*-alkoxyvinyl trihalomethyl ketones with oxalyldihydrazide in ethanol as solvent, which was expected to deliver the new bis[4,5-dihydro-5-hydroxy-5-(trihalomethyl)-1*H*-pyrazoles] bearing an oxalyl moiety on the newly formed ring system, thus offering opportunities for structural variations due to the presence of the uncommon trihalomethyl group at position 5 and alkyl, aryl or heteroaryl substituents at position 3 of the bispyrazolines and the respective bispyrazoles (Schemes 1, 2).

Results and discussion

4-Alkoxy-4-(alkyl/aryl/heteroaryl)-1,1,1-trihaloalk-3-en-2-ones **1a**, **1b**, **4a**, **4b** [16], **1c**–**1f**, **4c**–**4f** [17], **1g** [18], and **1h** [19] are readily available CCC synthetic blocks and were prepared from trifluoroacetylation [20] or trichloroacetylation

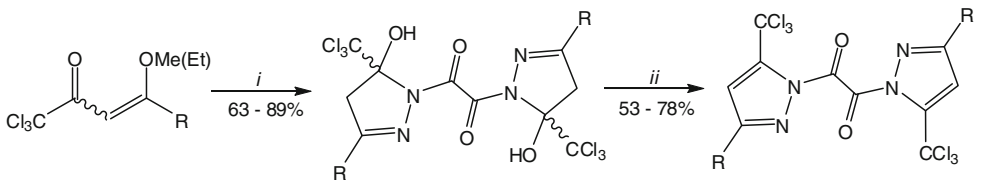


1a-**1h** (2.0 equiv.) **2a**-**2h** **3c**, **3f**

1-3	a	b	c	d	e	f	g	h
R	H	Me	Ph	4-FC_6H_4	4-ClC_6H_4	4-$NO_2C_6H_4$	BiPh-4-yl	2-Furyl

i:$(NH_2NHCO)_2$ (1.0 equiv.), EtOH/H_2O, 2-5h, 80°C; *ii*:$SOCl_2$, Pyridine, Benzene, 0-80°C, 1h

Scheme 1



4a-**4f** (2.0 equiv.) **5a**-**5f** **6c**, **6e**, **6f**

4-6	a	b	c	d	e	f
R	H	Me	Ph	4-FC_6H_4	4-ClC_6H_4	4-BrC_6H_4

i :$(NH_2NHCO)_2$ (1.0 equiv.), EtOH/H_2O, 2-5h, 80°C; *ii*:$SOCl_2$, Pyridine, Benzene, 0-80° C, 1h

Scheme 2

reactions [21] of enol ethers commercially available or generated in situ from the respective aryl- or heteroaryl methyl ketone acetals with trifluoroacetic anhydride or with trichloroacetyl chloride, respectively, in the presence of pyridine, as described in [16–19].

Subsequently, we reacted pure ketones **1** and **4** with oxalyldihydrazide, regioselectively obtaining in a one-step reaction novel 1,1′-oxalylbis[4,5-dihydro-5-hydroxy-5-(trihalomethyl)-1*H*-pyrazoles] **2** and **5** and subsequently the respective dehydrated bispyrazole systems **3** and **6**. The reactions of 4-alkoxy-4-(alkyl/aryl/heteroaryl)-1,1,1-trihaloalk-3-en-2-ones **1**, **4** with oxalyldihydrazide in 2:1 molar ratio using a mixture of ethanol/water (20:1 v/v) as an ecofriendly solvent were carried out under mild conditions under reflux (80 °C) for 2–5 h.

After stirring under these conditions, thin-layer chromatography (TLC) showed that the reactions proceeded smoothly and gave the products in 51–83% yields for the trifluoromethyl-substituted system **2** (Scheme 1) and in 63–89% yields for the trichloromethylated bispyrazolines **5** (Scheme 2). Compounds **2** and **5** were isolated as stable white solids by crystallization from the original reaction solvent, but only after reducing the volume to half, following mild refrigeration at approximately 5 °C for 1–2 days.

Presumably, the reactions start with the Michael addition of the amino groups of oxalyldihydrazide at the β-carbon atom of the enones **1** and **4** furnishing addition products. The aminoether functions are unstable in alcohol/water (reaction solvent), and the alkoxy groups are eliminated as methanol (R ≠ H) or ethanol (R = H). Subsequently, two intramolecular cyclization reactions occur involving the carbonyl functions of the nonisolated bis-β-enaminones and the second nitrogens of the dinucleophile reagent. In addition, the elimination of two water molecules is not likely to occur in the bispyrazoline structures **2** and **5** due to the electron-withdrawing effect of the hydroxy and trihalomethyl groups, the weak acid reaction condition employed (ethanol/water), and also due to the electronic effect of the carbonyl substituent of the oxalyl moiety at the N-1 position of both rings. This structural feature allowed the isolation of the new 1,1′-oxalylbis[4,5-dihydro-5-hydroxy-5-(trihalomethyl)-1*H*-pyrazoles] in accordance with results and mechanisms (Fig. 1) obtained previously for reactions of similar enones with carbohydrazide [12] and cyanoacetohydrazide [13, 14], but not with diaminoguanidine [15].

In recent years, the treatment of 2-pyrazolines in an acidic medium using either pure sulfuric acid, P_2O_5, mixtures of sulfuric acid in boiling acetic acid, acetic acid in boiling ethanol, hydrochloric acid/ethanol, acetic anhydride, or acetic acid have been the most employed methods for dehydration [22]. However, in many cases, acid-sensitive groups are lost during the dehydration reaction due to the acidic conditions and temperature.

In 2001, Zhu et al. [23] performed the dehydration of 4,5-dihydro-5-hydroxy-4-(2-hydroxyethyl)-5-(trifluoromethyl)-1-(pentafluorophenyl)- and -1-(tetrafluorophenyl)-1*H*-pyrazoles by treatment with P_2O_5 to obtain the respective pyrazoles. However, in the same study, under the same reaction condition, 4,5-dihydro-1-(heptafluorobutanoyl)-5-hydroxy-4-(2-hydroxyethyl)-5-(trifluoromethyl)-1*H*-pyrazole did not furnish the aromatic compound, and it was necessary to employ thionyl chloride and pyridine in chloroform as dehydration medium to obtain the respective pyrazole, which was purified only by column chromatography. In contrast to the use of P_2O_5, no experimental details were reported for the employment of thionyl chloride in the cited work.

After a review of the literature and in an attempt to obtain aromatic pyrazoles for further biological assays, we chose thionyl chloride/pyridine [24–26] as the dehydration agent and report here the conditions required to accomplish the dehydration of **2** and **5**, which present a hydroxy and trihalomethyl, aryl, and oxalyl group attached directly to the C-5, C-3, and N-1 atom of the bispyrazoline rings, respectively (Schemes 1, 2). In spite of the relative difficulty of this elimination, because of the presence of these substituents, **2c**, **2f**, **5c**, **5e**, and **5f** were dehydrated to give the respective bispyrazole derivatives **3c**, **3f**, **6c**, **6e**, and **6f** in 66–72% yields for the trifluoromethyl-substituted system **3** (Scheme 1) and in 53–78% yields for the trichloromethylated bispyrazolines **6** (Scheme 2), only by stirring a mixture of **2** and **5**, thionyl chloride, and pyridine at 80 °C for about 1 h in benzene as solvent, according to similar procedures described in the literature [24–26]. Compounds **3** and **6** were easily isolated as stable white or yellow solids and were recrystallized from ethanol.

The structures of 1,1′-oxalylbis[4,5-dihydro-5-hydroxy-5-(trifluoromethyl)-1*H*-pyrazoles] **2a–2h** were deduced from nuclear magnetic resonance (NMR) experiments and by comparison with NMR data of other 2-pyrazolines formerly synthesized in our laboratory [12–23].

Due to the symmetry, compounds **2** showed only one set of peaks and presented ^{1}H NMR chemical shifts in dimethyl sulfoxide (DMSO)-d_6 for the hydroxy protons in the range of $\delta = 8.59$ ppm, and the four methylene protons (H4) are shown as typical AB systems as two doublets; one of them is on average at $\delta = 3.89$ and the other at 3.50 ppm, with a geminal coupling constant of 19 Hz.

The ^{13}C{^{1}H} NMR spectra also exhibited only one set of peaks, despite the fact that two stereogenic carbons are present in each molecule. The oxalyl derivatives **2** also presented the typical ^{13}C NMR chemical shifts of both pyrazoline rings at $\delta = 149.8$ ppm (C3) and 44.7 ppm (C4). Due to the presence of the CF_3 group, both C5

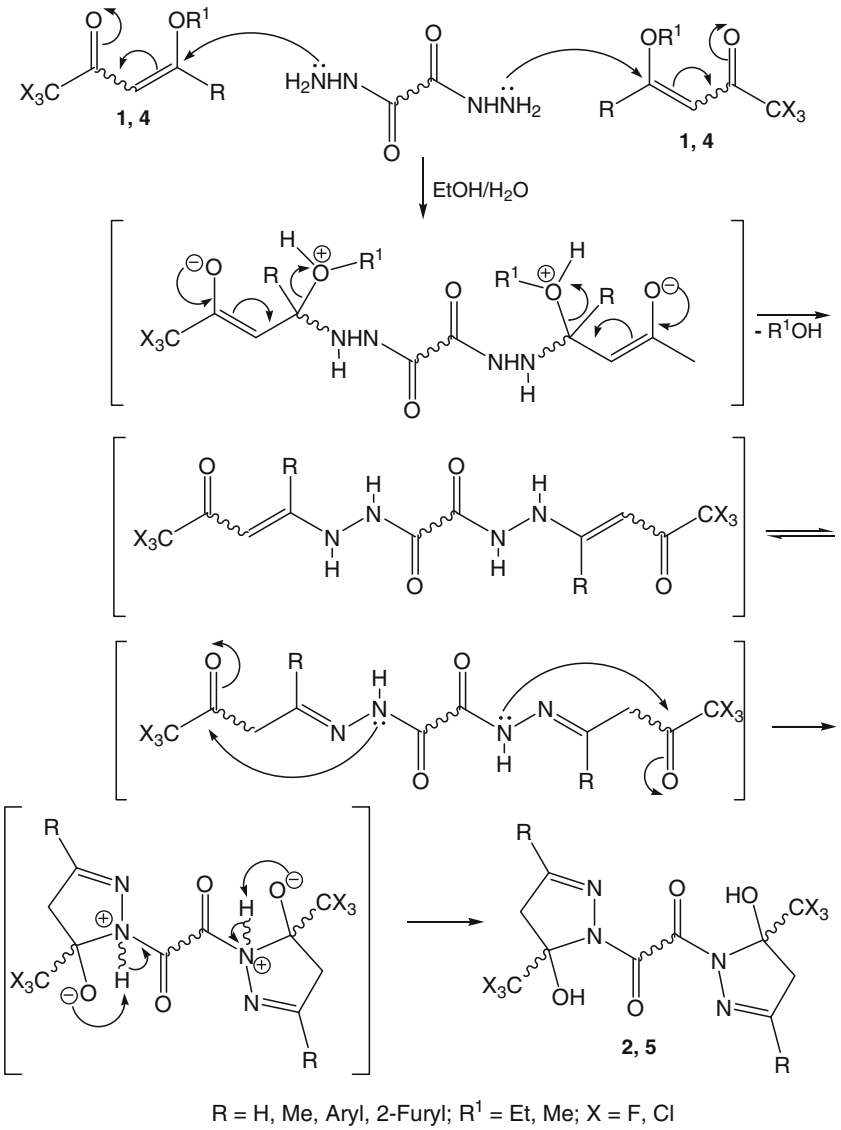


Fig. 1 Proposed mechanism for the synthesis of **2a**–**2h** and **5a**–**5f**

carbons presented a characteristic quartet at 90.8 ppm with $^{2}J_{CF} = 35$ Hz. Also, both CF_3 groups showed a typical quartet at 121.9 ppm with $^{1}J_{CF} = 286$ Hz, and the two carbonyl carbons (oxalyl moiety) showed one NMR signal on average at 159.4 ppm. All signals are consistent with ^{1}H and ^{13}C NMR chemical shifts of the 2-pyrazolines and the oxalyl moiety for this symmetrical system.

The dehydrated trifluoromethylated compounds **3**, being a symmetrical system, presented one set of signals in both ^{1}H and ^{13}C NMR spectra and, in comparison with **2**, showed typical chemical shifts of the pyrazole ring for both H-4 on average at 8.17 ppm as singlet peaks. The $^{13}C\{^{1}H\}$ NMR spectra exhibited chemical shifts for both pyrazole ring carbons on average at 151.2 (C3), 101.7 (C4), 137.6 (C5, $^{2}J_{CF} = 38$), and 122.1 ppm (CF_3, $^{1}J_{CF} = 289$). Both carbonyl carbons showed only one singlet in the range of 158.7 ppm.

In contrast to the trifluoromethyl-substituted bispyrazolines **2a**–**2h**, 1,1′-oxalylbis[4,5-dihydro-5-hydroxy-5-(trichloromethyl)-1*H*-pyrazoles] **5a**–**5f** showed two sets of NMR signals. Thus, as expected, the $^{13}C\{^{1}H\}$ NMR spectra also exhibited two peaks for each carbon of the pyrazoline rings as well as for the oxalyl moiety.

The chemical shifts of the four diastereotopic methylene protons (H4) appeared as two multiplets in the narrow ranges of 4.37–3.42 and 4.05–3.27 ppm. The hydroxy protons, as two singlets, are shown in the ^{1}H NMR spectra in the range of 8.72–8.01 ppm. Compounds **5** also presented the typical $^{13}C\{^{1}H\}$ NMR spectra where the chemical shifts for non-symmetrical structures showed separate signals for each

pyrazoline ring carbon in the narrow ranges of 156.7–152.1 (C3), 50.3–46.6 (C4), 102.8–101.0 (C5), and 103.0–102.5 ppm (CCl_3). Both carbonyl carbons of the oxalyl moiety appeared as two singlets in the range of 162.3–156.7 ppm, which is consistent with NMR chemical shift assignments when compared with compounds **2** and literature data for trichloromethyl-substituted 2-pyrazolines [21, 27].

The trichloromethylated bispyrazoles **6**, also a symmetrical system, presented one set of signals in both ^{1}H and ^{13}C NMR spectra and in comparison with **5** showed typical chemical shifts of the pyrazole rings for both H-4 on average at 8.07 ppm as one singlet peak. The ^{13}C{^{1}H} NMR spectra exhibited chemical shifts for both pyrazole ring carbons on average at 154.4 (C3), 84.6 (C4), 147.0 (C5), and 112.5 ppm (CCl_3). Both carbonyl carbons showed only one singlet on average at 158.3 ppm.

To explain the spectroscopic behavior differences of the trihalomethyl-substituted bispyrazoline series **2** and **5** by NMR spectral data, the following considerations should be mentioned. Initially, it appears that each molecule of the series **2** and **5** has two chiral centers at carbons-5, which are separated by an oxalyl moiety. This fact suggests the possible presence of two pairs of diastereomers: 5*S**, 5′*S**/5*R**, 5′*R** (*racemate*) and 5*S**, 5′*R**/5*R**, 5′*S** (*meso*) for both series. However, the analysis of ^{1}H and ^{13}C NMR spectra showed that only one pair of diastereomers was isolated for the trifluoromethyl-substituted series **2** and that two pairs were obtained for the trichloromethylated series **5**, since only one set of signals was obtained for **2** and two sets were observed for **5**. However, there is no apparent reason to explain the diastereoselectivity found for series **2** and **5**. Thus, we were surprised to observe that the NMR chemical shifts for the two pairs of diastereomers in **2** are isochronous and for compounds **5** anisochronous. Second, it was also interesting to observe the magnetic behavior of the dehydrated systems **3** and **6**, where there are no chiral centers. In this case, for both series no anisochrony was observed, demonstrating that the magnetic anisochrony for the series **2**–**3** and **5**–**6** depends on the presence of the stereogenic carbons and the trihalomethyl groups. Third, a similar effect was observed previously by Yusupov et al. [8] for 1,1′-oxalylbis[5-(*t*-butyl)-4,5-dihydro-5-hydroxy-1*H*-pyrazole], where the *t*-butyl group induced the formation of diastereomers.

Thus, we suggest that CCl_3, a bulky group in comparison with CF_3, induces the appearance of different sets of signals for compounds **5a**–**5f** due to their magnetic anisotropy, which is stronger than that of the CF_3 group. On the other hand, a CF_3 group presents a weaker magnetic anisotropy than a CCl_3 group and its magnetic influence is less observable in the bispyrazoline system **2** also due, in part, to the distance between the two chiral centers. It is noteworthy that, according to the literature [33], the degree of anisochrony is not only a function of the distance from a chiral center but also can vary with the solvent used in the analysis. Unfortunately, compounds **2**–**3** and **5**–**6** are weakly soluble in nonpolar solvents to give more conclusions.

Complementarily, we also performed X-ray diffraction measurements (Fig. 2) for a monocrystal of compound **5c** (5*S**, 5′*R**/5*R**, 5′*S**—*meso*). The crystallographic data of **5c** showed relevant information for the structural determination of this compound. Briefly, molecule **5c** shows that the five-membered 2-pyrazolines are planar, and the phenyl ring is attached to the C-3 of each pyrazoline. The torsion angles of N(2)–N(1)–C(1)–O(1), N(2a)–N(1a)–C(2)–O(2), and O(1)–C(1)–C(2)–O(2) are 171.5(4)°, −164.7(4)°, and 75.6(6)°, respectively, demonstrating that each carbonyl group is almost coplanar in relation to the 2-pyrazoline rings, but not to each other. It was also observed that both phenyl rings are almost coplanar to the respective attached pyrazolines and present torsion angles of −178.9(4)° for N(2)–C(3)–C(31)–C(32) and −10.1(6)° for N(2a)–C(3a)–C(31a)–C(32a).

In conclusion, we consider the regioselective reaction reported here to be a useful, simple, and convenient method, which employs commercially available reagents, an environmentally benign method (ethanol as solvent), and mild conventional conditions to obtain the novel and interesting trihalomethylated series of 1,1′-oxalylbis(3-substituted-2-pyrazolines). On the other hand, the dehydrated 1,1′-oxalylbis(1*H*-pyrazoles) could be obtained only in presence of an aromatic solvent (benzene or toluene).

Experimental

Unless otherwise indicated all common reagents and solvents were used from commercial suppliers without further purification. Oxalyldihydrazide was obtained commercially from Aldrich (ACS grade). All melting points were determined using open capillaries on an Electrothermal MelTemp 3.0 apparatus. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 200 spectrometer (^{1}H at 200 MHz and ^{13}C at 50 MHz), 5 mm sample tubes, 298 K, digital resolution ±0.01 ppm, in DMSO-d_6 for **2**, **3**, **5**, **6** using tetramethylsilane (TMS) as internal reference or fluorobenzene as external reference (^{19}F NMR). The diffraction measurements were carried out by graphite-monochromatized Mo K_α radiation with $\lambda = 0.71073$ Å on a Bruker SMART CCD diffractometer [28]. The structure of **5c** was solved with direct methods using SHELXS-97 program [29], and refined on F^2 by full-matrix least-squares using the SHELXL-97 package [30]. The absorption correction was performed by Gaussian methods [31]. Anisotropic displacement parameters for nonhydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH_3), 0.97 Å

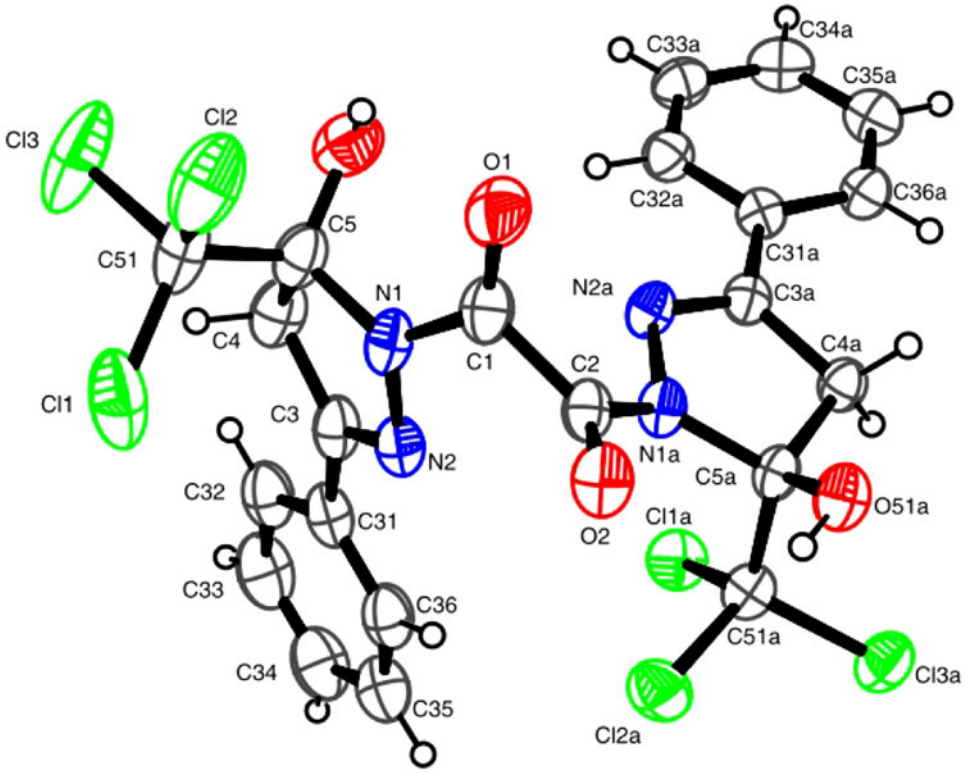


Fig. 2 A view of the compound **5c** [(5*S**, 5′*R**/5*R**, 5′*S**)—(*meso*)] with atomic labeling. Displacement *ellipsoids* are drawn at the 50% probability level. H atoms are represented by *circles* of arbitrary radii

(methylene CH_2), 0.98 Å (methine CH), 0.93 Å (aromatic CH), and 0.82 Å (OH) using a riding model. The hydrogen isotropic thermal parameters were kept equal to *U*iso(H) = χ*U*eq (carrier C atom), with $\chi = 1.5$ for methyl groups and $\chi = 1.2$ otherwise. The valence angles C–C–H and H–C–H of methyl groups were set to 109.5°, and the H atoms were allowed to rotate around the C–C bond. The molecular graph was prepared using ORTEP3 for Windows [32]. Crystallographic data for the structure of **5c** (*meso*) have been deposited with the Cambridge Crystallographic Data Centre and allocated deposition number CCDC 711243. Copies of the data can be obtained free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax +44-1223-336033 or via http://www.ccdc.cam.ac.uk/conts/retrieving.html).

General procedure for the synthesis of 1,1′-oxalylbis[4,5-dihydro-5-hydroxy-5-(trihalomethyl)-1H-pyrazoles] ***2a–2h*** *and* ***5a–5f***

A solution of 4-substituted 4-methoxy-1,1,1-trihaloalk-3-en-2-ones **1a–1h** (10 mmol) and oxalyldihydrazide (5 mmol) in 20 cm^3 ethanol and 1 cm^3 distilled water was stirred at 80 °C for 2–5 h. After the reaction time the solvent was evaporated to half its volume on a rotatory evaporator under reduced pressure. After cooling (≤5 °C) for 1–2 days the compounds **2a–2h** and **5a–5f** were obtained pure directly by filtration, washed with cold ethanol/water (20:1 v/v), and dried under vacuum.

1,1′-Oxalylbis[4,5-dihydro-5-(trifluoromethyl)-1H-pyrazol-5-ol] (**2a**, $C_{10}H_8F_6N_4O_4$)
White solid, yield 72%; m.p.: 172–174 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.36$ (s, 2H, 2OH), 7.28 (s, 2H, 2H-3), 3.44 (d, $J = 19$ Hz, 2H, H-4, H-4′), 3.15 (d, $J = 19$ Hz, 2H, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 159.7$ (2C=O), 147.1 (2C-3), 122.7 (q, $^1J = 285$ Hz, $2CF_3$), 89.0 (q, $^2J = 34$ Hz, 2C-5), 45.6 (2C-4) ppm; ^{19}F NMR (376 MHz, DMSO-d_6): $\delta = -76.5$ (s, $2CF_3$) ppm.

1,1′-Oxalylbis[4,5-dihydro-3-methyl-5-(trifluoromethyl)-1H-pyrazol-5-ol] (**2b**, $C_{12}H_{12}F_6N_4O_4$)
White solid, yield 77%; m.p.: 212–213 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.24$ (s, 2H, 2OH), 3.45 (d, 2H, $J = 20$ Hz, H-4, H-4′), 3.09 (d, 2H, $J = 20$ Hz, H-4, H-4′), 1.93 (s, 6H, 2Me) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 160.5$ (2C=O), 155.4 (2C-3), 122.5 (q, $^1J = 285$ Hz, $2CF_3$), 90.3 (q, $J = 34$ Hz, 2C-5), 47.5 (2C-4), 15.2 (2Me) ppm; ^{19}F NMR (376 MHz, DMSO-d_6): $\delta = -76.5$ (s, $2CF_3$) ppm.

1,1′-Oxalylbis[4,5-dihydro-3-phenyl-5-(trifluoromethyl)-1H-pyrazol-5-ol] (**2c**, $C_{22}H_{16}F_6N_4O_4$)
White solid, yield 54%; m.p.: 224–225 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.67$ (s, 2H, 2OH), 7.72–7.77 (m, 4H, 2 Ar), 7.45–7.56 (m, 6H, 2Ar), 4.03 (d, 2H, $J = 19$ Hz, H-4, H-4′), 3.65 (d, 2H, $J = 19$ Hz, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 161.4$ (2C=O), 154.1 (2C-3), 131.5, 130.0, 129.1, 127.0 (12C, 2Ar), 120.6 (q, $^1J = 286$ Hz, $2CF_3$), 91.7 (q, $^2J = 35$ Hz, 2C-5), 44.7 (2C-4) ppm; ^{19}F NMR (376 MHz, DMSO-d_6): $\delta = -76.6$ (s, $2CF_3$) ppm.

1,1′-Oxalylbis[3-(4-fluorophenyl)-4,5-dihydro-5-(trifluoromethyl)-1H-pyrazol-5-ol] (**2d**, $C_{22}H_{14}F_8N_4O_4$)
White solid, yield 51%; m.p.: 204–205 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.63$ (s, 2H, 2OH), 7.69–7.76 (m, 4H, 2Ar), 7.28–7.37 (m, 4H, 2Ar), 4.03 (d, 2H, $J = 19$ Hz, H-4, H-4′), 3.62 (d, 2H, $J = 19$ Hz, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 163.2$ (d, $^1J = 253$ Hz, 2C, 2 Ar), 161.0 (2C=O), 152.9 (2C-3), 129.0 (d, $^4J = 3$ Hz, 2C, 2 Ar), 127.9 (d, $^3J = 9$ Hz, 4C, 2Ar), 116.0 (d, $^2J = 22$ Hz, 4C, 2Ar), 122.7 (q, $^1J = 286$ Hz, $2CF_3$), 90.9 (q, $^2J = 35$ Hz, 2C-5), 44.2 (2C-4) ppm; ^{19}F NMR (376 MHz, DMSO-d_6): $\delta = -76.5$ (s, $2CF_3$), −107.9 (s, 2F-Ph) ppm.

1,1′-Oxalylbis[3-(4-chlorophenyl)-4,5-dihydro-5-(trifluoromethyl)-1H-pyrazol-5-ol] (**2e**, $C_{22}H_{14}Cl_2F_6N_4O_4$)
White solid, yield 64%; m.p.: 223–225 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.66$ (s, 2H, 2OH), 7.66–7.76 (m, 4H, 2 Ar), 7.53–7.55 (m, 4H, 2 Ar), 4.03 (d, 2H, $J = 19$ Hz, H-4, H-4′), 3.62 (d, 2H, $J = 19$ Hz, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 167.3$ (2C=O), 152.6 (2C-3), 135.5, 128.7, 128.6, 128.4 (12C, 2Ar), 122.5 (q, $^1J = 283$ Hz, $2CF_3$), 91.0 (q, $^2J = 35$ Hz, 2C-5), 44.0 (2C-4) ppm; ^{19}F NMR (376 MHz, DMSO-d_6): $\delta = -76.6$ (s, $2CF_3$) ppm.

1,1′-Oxalylbis[4,5-dihydro-3-(4-nitrophenyl)-5-(trifluoromethyl)-1H-pyrazol-5-ol] (**2f**, $C_{22}H_{14}F_6N_6O_8$)
White solid, yield 83%; m.p.: 307–308 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.79$ (s, 2H, 2OH), 8.29–8.35 (m, 4H, 2Ar), 7.89–7.97 (m, 4H, 2Ar), 4.15 (d, 2H, $J = 19$ Hz, H-4, H-4′), 3.71 (d, 2H, $J = 19$ Hz, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 152.2$ (2C=O), 148.4 (2C-3), 135.3, 127.7, 123.7, 123.6 (12C, 2 Ar), 122.1 (q, $^1J = 286$ Hz, $2CF_3$), 91.6 (q, $^2J = 35$ Hz, 2C-5), 43.8 (2C-4) ppm; ^{19}F NMR (376 MHz, DMSO-d_6): $\delta = -76.5$ (s, $2CF_3$) ppm.

1,1′-Oxalylbis[3-(1,1′-biphenyl-4-yl)-4,5-dihydro-5-(trifluoromethyl)-1H-pyrazol-5-ol] (**2g**, $C_{34}H_{24}F_6N_4O_4$)
White solid, yield 63%; m.p.: 200–202 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.67$ (s, 2H, 2OH), 7.70–7.78 (m, 12H, 2biPh), 7.38–7.50 (m, 6H, 2 biPh), 4.08 (d, 2H, $J = 18$ Hz, H-4, H-4′), 3.68 (d, 2H, $J = 18$ Hz, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 152.9$ (2C=O), 142.2 (2C-3), 138.7, 129.9, 129.7, 128.6, 128.5, 128.4, 126.6, 126.3 (24C, 2biPh), 120.1 (q, $^1J = 287$ Hz, $2CF_3$), 91.1 (q, $^2J = 35$ Hz, 2C-5), 44.0 (2C-4) ppm; ^{19}F NMR (376 MHz, DMSO-d_6): $\delta = -76.5$ (s, $2CF_3$) ppm.

1,1′-Oxalylbis[3-(2-furyl)-4,5-dihydro-5-(trifluoromethyl)-1H-pyrazol-5-ol] (**2h**, $C_{18}H_{12}F_6N_4O$)
White solid, yield 58%; m.p.: 118–120 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.63$ (s, 2H, 2OH), 7.90 (s, 2H, 2Fur), 6.98–7.01 (m, 2H, 2Fur), 6.67–6.68 (m, 2H, 2 Fur), 3.89 (d, 2H, $J = 18$ Hz, H-4, H-4′), 3.50 (d, 2H, $J = 18$ Hz, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 160.5$ (2C=O), 146.1 (2C-3), 145.0, 144.9, 114.7, 112.3 (8C, 2Fur), 122.2 (q, $^1J = 287$ Hz, $2CF_3$), 90.6 (q, $^2J = 35$ Hz, 2C-5), 43.9 (2C-4) ppm; ^{19}F NMR (376 MHz, DMSO-d_6): $\delta = -75.6$ (s, $2CF_3$) ppm.

1,1′-Oxalylbis[4,5-dihydro-5-(trichloromethyl)-1H-pyrazol-5-ol] (**5a**, $C_{10}H_8Cl_6N_4O_4$)
Yellow solid, yield 89%; m.p.: 197–198 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.21$ (s, 2H, 2OH), 8.01 (d, 2H, $J = 2$ Hz, 2H-3), 3.48–3.55 (m, 2H, H-4, H-4′), 3.27–3.38 (m, 2H, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 161.8$ (C=O), 160.9 (C=O′), 156.7 (C-3), 155.8 (C-3′), 103.0 (CCl_3), 102.8 (CCl_3′), 101.2 (C-5), 101.1 (C-5′), 50.3 (C-4), 50.2 (C-4′) ppm.

1,1’-Oxalylbis[4,5-dihydro-3-methyl-5-(trichloromethyl)-1H-pyrazol-5-ol] (**5b**, $C_{12}H_{12}Cl_6N_4O_4$)
Yellow solid, yield 63%; m.p.: 190–191 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.03$ (s, 2H, 2OH), 3.58–3.42 (m, 2H, H-4, H-4′), 3.38–3.25 (m, 2H, H-4, H-4′), 1.96–1.92 (m, 6H, 2Me) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 157.2$ (C=O), 156.7 (C=O′), 152.1 (2C-3), 102.8 (CCl_3), 102.6 (CCl_3′), 101.0 (2C-5), 50.2 (2C-4), 18.3 (2Me) ppm.

1,1′-Oxalylbis[4,5-dihydro-3-phenyl-5-(trichloromethyl)-1H-pyrazol-5-ol] (**5c**, $C_{22}H_{16}Cl_6N_4O_4$)
Yellow solid, yield 69%; m.p.: 210–211 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.69$ (s, 1H, OH), 8.64 (s, 1H, OH′), 7.77–7.85 (m, 4H, 2Ar), 7.33–7.66 (m, 6H, 2Ar), 3.93–4.13 (m, 2H, H-4, H-4′), 3.63–3.88 (m, 2H, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 162.1$ (C=O), 161.3 (C=O′), 154.2 (C-3), 154.1 (C-3′), 130.9, 129.7, 129.3, 128.6, 128.5, 126.8, 126.6, 126.4 (12C, 2 Ar), 102.8 (CCl_3), 102.6 (CCl_3′), 102.1 (C-5), 101.9 (C-5′), 47.0 (C-4), 46.7 (C-4′) ppm.

1,1′-Oxalylbis[3-(4-fluorophenyl)-4,5-dihydro-5-(trichloromethyl)-1H-pyrazol-5-ol] (**5d**, $C_{22}H_{14}Cl_6F_2N_4O_4$)
Yellow solid, yield 72%; m.p.: 178–180 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.72$ (s, 1H, OH), 8.56 (s, 1H, OH′), 7.83–7.90 (m, 4H, 2Ar), 7.25–7.32 (m, 4H, 2Ar),

4.13–4.37 (m, 2H, H-4, H-4′), 3.69–4.05 (m, 2H, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 162.3$ (d, $^1J = 253$ Hz, 2C, 2 Ar), 161.2 (C=O), 160.6 (C=O′), 153.5 (C-3), 153.4 (C-3′), 129.3 (d, $^4J = 3$ Hz, 2C, 2 Ar), 127.5 (d, $^3J = 9$ Hz, 4C, 2Ar), 115.7 (d, $^1J = 22$ Hz, 4C, 2 Ar), 102.9 (CCl_3), 102.7 (CCl_3'), 102.2 (C-5), 102.1 (C-5′), 47.0 (C-4), 46.8 (C-4′) ppm.

1,1′-Oxalylbis[3-(4-chlorophenyl)-4,5-dihydro-5-(trichloromethyl)-1H-pyrazol-5-ol] (**5e**, $C_{22}H_{14}Cl_8N_4O_4$)
Yellow solid, yield 77%; m.p.: 255–256 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.70$ (s, 2H, 2OH), 7.81–7.87 (m, 4H, 2Ar), 7.50–7.55 (m, 4H, 2Ar), 4.00–4.14 (m, 2H, H-4, H-4′), 3.71–3.95 (m, 2H, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 162.1$ (C=O), 161.2 (C=O′), 153.7 (C-3), 153.3 (C-3′), 135.6, 135.5, 128.7, 128.6, 128.5. 128.4, 128.3, 128.2 (12C, 2Ar), 102.8 (CCl_3), 102.5 (CCl_3'), 102.3 (C-5), 102.2 (C-5′), 46.8 (C-4), 46.6 (C-4′) ppm.

1,1′-Oxalylbis[3-(4-bromophenyl)-4,5-dihydro-5-(trichloromethyl)-1H-pyrazol-5-ol]
(**5f**, $C_{22}H_{14}Br_2Cl_6N_4O_4$)
Yellow solid, yield 80%; m.p.: 262–263 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.71$ (s, 1H, OH), 8.59 (s, 1H, OH′), 7.73–7.80 (m, 4H, 2Ar), 7.66–7.69 (m, 4H, 2Ar), 3.93–4.15 (m, 2H, H-4, H-4′), 3.61–3.81 (m, 2H, H-4, H-4′) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 162.2$ (C=O), 161.4 (C=O′), 153.9 (C-3), 153.7 (C-3′), 131.8, 129.1, 128.9, 128.8, 128.4, 128.2, 124.7, 124.6 (12C, 2Ar), 102.9 (CCl_3), 102.8 (CCl_3'), 102.4 (C-5), 102.3 (C-5′), 46.9 (C-4), 46.7 (C-4′) ppm.

General procedure for the synthesis of 1,1′-oxalylbis [5-(trihalomethyl)-1H-pyrazoles] ***3c, 3f, 6c, 6e, 6f***

A solution of the respective bispyrazolines **2** or **5** (2.8 mmol) and 3 cm^3 pyridine (37.1 mmol) in 50 cm^3 benzene was cooled to 0 °C, and 1.22 cm^3 thionyl chloride (16.8 mmol) diluted in 25 cm^3 benzene was added dropwise over 10 min. The solution was stirred for additional 30 min, during which time the temperature was allowed to rise to 20 °C. The mixture was then heated under reflux (bath temperature 80 °C) for 1 h and then filtered to remove the pyridine hydrochloride at room temperature. The solution was extracted twice with benzene (2 × 50 cm^3) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure on a rotatory evaporator left **3c**, **3f**, **6c**, **6e**, **6f** as white or yellow solid products, which were purified by recrystallization from ethanol.

1,1′-Oxalylbis[3-phenyl-5-(trifluoromethyl)-1H-pyrazole] (**3c**, $C_{22}H_{12}F_6N_4O_2$)
White solid, yield 72%; m.p.: 163–164 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.27$ (s, 2H, H-4, H-4′), 7.81–7.83 (m, 4H, 2Ar), 7.48–7.49 (m, 6H, 2Ar) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 156.7$ (2C=O), 155.4 (2C-3), 133.2 (q, $^2J = 38$ Hz, 2C-5), 128.9, 128.7, 128.5, 126.0 (12C, 2Ar), 122.8 (q, $^1J = 294$ Hz, $2CF_3$), 100.5 (2C-4) ppm; ^{19}F NMR (376 MHz, DMSO-d_6): $\delta = -60.4$ (s, $2CF_3$) ppm.

1,1′-Oxalylbis[3-(4-nitrophenyl)-5-(trifluoromethyl)-1H-pyrazole] (**3f**, $C_{22}H_{10}F_6N_6O_6$)
Yellow solid, yield 66%; m.p.: 203–204 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.07$ (s, 2H, H-4, H-4′), 7.89–7.92 (m, 4H, 2Ar), 7.28–7.37 (m, 4H, 2 Ar) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 160.8$ (2C=O), 147.0 (2C-3), 142.1 (q, $^2J = 38$ Hz, 2C-5), 133.9, 128.1, 126.4, 124.3 (12C, 2Ar), 121.5 (q, $^1J = 285$ Hz, $2CF_3$), 103.0 (2C-4) ppm; ^{19}F NMR (376 MHz, DMSO-d_6): $\delta = -60.5$ (s, $2CF_3$) ppm.

1,1′-Oxalylbis[3-phenyl-5-(trichloromethyl)-1H-pyrazole] (**6c**, $C_{22}H_{12}Cl_6N_4O_2$)
White solid, yield 54%; m.p.: 195–196 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.05$ (s, 2H, H-4, H-4′), 7.84–7.86 (m, 4H, 2Ar), 7.37–7.45 (m, 4H, 2Ar) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 157.0$ (2C=O), 153.5 (2C-3), 146.9 (2C-5), 130.1, 128.6, 127.8, 125.9 (12C, 2Ar), 112.3 ($2CCl_3$), 84.6 (2C-4) ppm.

1,1′-Oxalylbis[3-(4-chlorophenyl)-5-(trichloromethyl)-1H-pyrazole] (**6e**, $C_{22}H_{10}Cl_8N_4O_2$)
White solid, yield 78%; m.p.: 227–229 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.07$ (s, 2H, H-4, H-4′), 7.76 (d, 4H, $J = 8$ Hz, 2Ar), 7.64 (d, 4H, $J = 8$ Hz, 2Ar) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 156.9$ (2C=O), 152.8 (2C-3), 147.0 (2C-5), 131.8, 128.0, 127.6, 124.0 (12C, 2Ar), 112.5 ($2CCl_3$), 84.5 (2C-4) ppm.

1,1′-Oxalylbis[3-(4-bromophenyl)-5-(trichloromethyl)-1H-pyrazole] (**6f**, $C_{22}H_{10}Br_2Cl_6N_4O_2$)
White solid, yield 53%; m.p.: 197–198 °C; ^{1}H NMR (200 MHz, DMSO-d_6): $\delta = 8.09$ (s, 2H, H-4, H-4′), 7.85 (d, 4H, $J = 8$ Hz, 2Ar), 7.52 (d, 4H, $J = 8$ Hz, 2Ar) ppm; ^{13}C NMR (50 MHz, DMSO-d_6): $\delta = 161.0$ (2C=O), 157.0 (2C-3), 147.1 (2C-5), 135.3, 128.9, 128.5, 126.8 (12C, 2Ar), 112.6 ($2CCl_3$), 84.6 (2C-4) ppm.

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