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A comparative study of 2,4-quinazolinediones by X-ray crystallography. The role of the OMe group on the hydrogen bonding motifs formation

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Abstract. Two quinazolinediones were crystallized and the molecular structures solved by monocrystal X-ray diffraction analysis. The title compounds include the only variation of the -OMe substituent at *orto* or *meta* positions of the aromatic ring. The results were contrasted with the analogous *para* substituted derivative allowing a complete structural comparison in order to see the substituent effect. The formation of different hydrogen bonding motifs was observed which are relevant to the design of supramolecular assemblies.

Keywords: X-ray crystallography, quinazolinediones, hydrogen bonding

1. Introduction

Quinazolinediones are heterocyclic compounds with important pharmacological and biological properties [1–6]. There are different synthetic pathways described for their preparation, most of them involving anthranilic acid derivatives [7–12]. Recently a one - pot procedure using ionic liquids as catalyst and microwave irradiation was reported with high yields [13]. Despite the significant number of quinazolinedione derivatives described in the literature, the structural analysis by X-ray crystallography is still less known. A crystal data base analysis till 2011 reveals that there are only about eleven molecular structures solved by X-ray crystallographic analysis [14].

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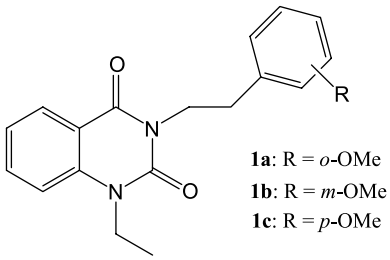
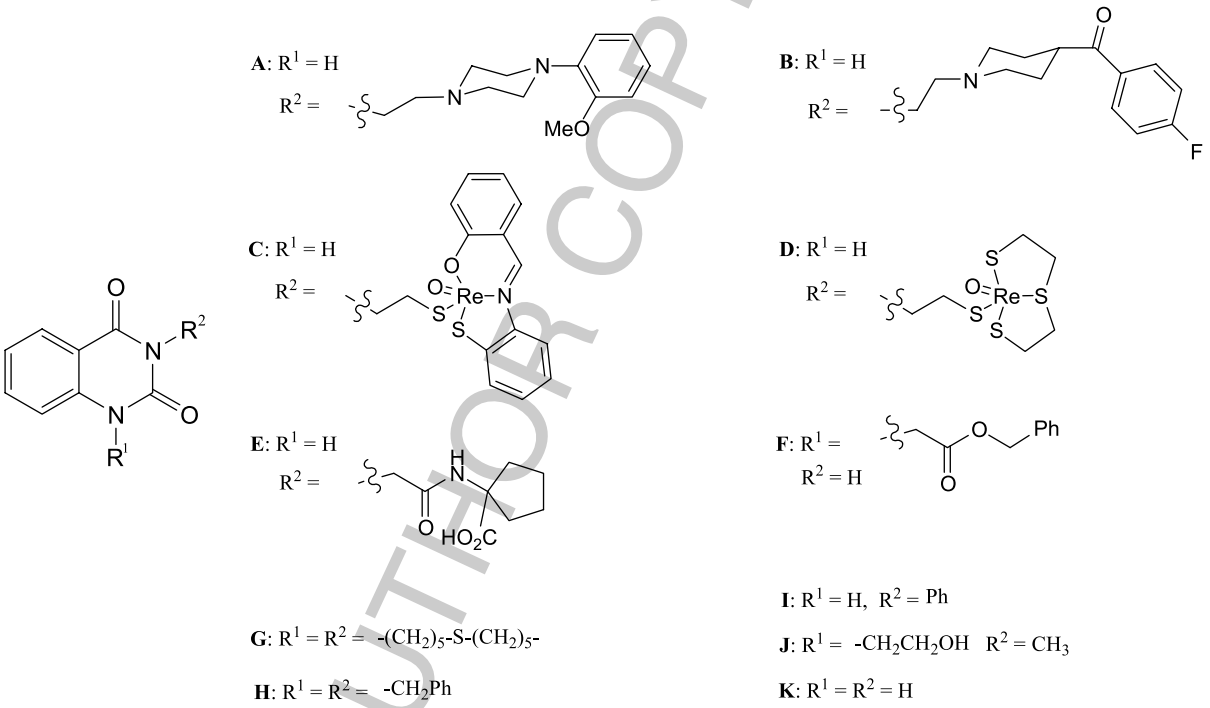
ISSN 1024-1221/12/$27.50



Scheme 1. Chemical diagram for compounds analyzed herein **1a**-**1c**.



Scheme 2. Analogous structures (**A-K**) analyzed by X-ray diffraction. Data from CCDC [14].

2. Experimental

The compounds described herein were synthesized as reported before [13]. Suitable crystals for X-ray diffraction analysis for **1a**-**1b** were grown by slow evaporation of a concentrated chloroform solution. X-ray diffraction studies were performed on a Bruker-APEX diffractometer with a CCD area detector, Mo Kα-radiation, $\lambda = 0.71073$ Å, graphite monochromator. Frames were collected at $T = 293$ K by ω-rotation ($\Delta/\omega = 0.3^{\circ}$) at 10 s per frame. The measured intensities were reduced to F^2. Structure solution, refinement and data output were carried out with the SHELXTL program package [15]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically calculated positions using a riding model. Crystallographic data have been deposited with CCDC, deposition numbers 893912 and 893913 for **1a** and **1b** respectively, and is freely available upon request from the following web site: www.ccdc.cam.ac.uk/data_request/cif

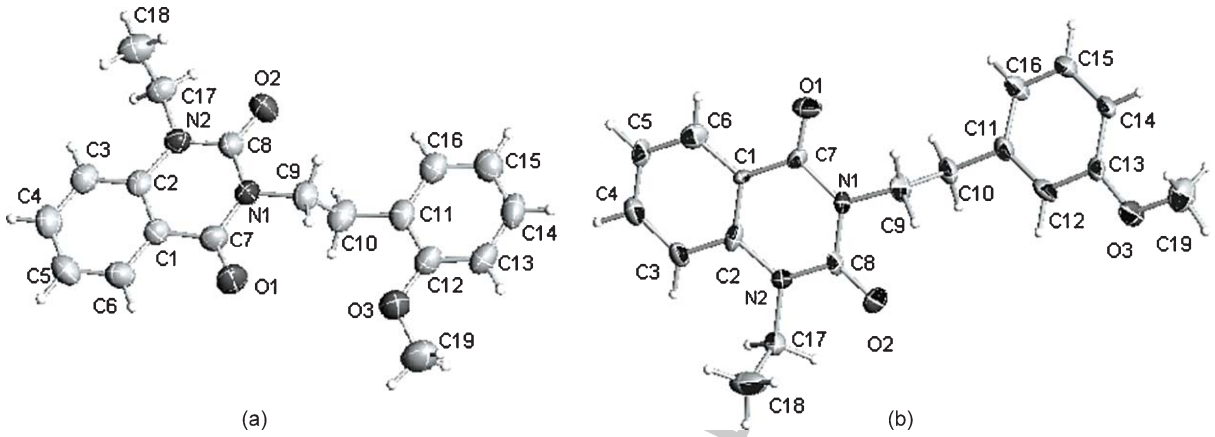


Fig. 1. Molecular structure for compounds **1a** (a) and **1b** (b). Thermal ellipsoids are at the 50% probability level.

Table 1
Crystallographic data for compounds **1a**, **1b** and **1c**[13]

Identification code	**1a**	**1b**	**1c**
Empirical formula	$C_{19}H_{20}N_2O_3$	$C_{19}H_{20}N_2O_3$	$C_{19}H_{20}N_2O_3$
Formula weight	324.37	324.37	324.37
Crystal size [mm^3]	0.38 × 0.30 × 0.22	0.44 × 0.32 × 0.18	0.80 × 0.60 × 0.10
Crystal system	Orthorhombic	Orthorhombic	Monoclinic
Space group	*P2(1)2(1)2(1)*	*P2(1)2(1)2(1)*	*P2(1)/c*
Unit cell dimensions			
a [Å]	7.4870(15)	7.735(2)	7.2301(16)
b [Å]	14.823(3)	18.103(5)	8.982(2)
c [Å]	14.877(3)	23.296(6)	25.717(5)
α[Å]	90.00	90.00	90.00
β[°]	90.00	90.00	91.83(3)
γ[Å]	90.00	90.00	90.00
Volume [Å^3]	1651.0(6)	3262.1(15)	1669.2(6)
Z	4	8	4
ρ_{calcd} [g/cm^3]	1.305	1.321	1.291
μ [mm^{-1}]	0.089	0.090	0.088
Collected refl.	14153	26164	4123
Independent refl. (R_{int})	2449(0.0614)	4820(0.1220)	2111 (0.0230)
Parameters	219	437	218
R [$I > 2\sigma$ (I)] R_1/wR_2	0.0612/0.1231	0.0686/0.1518	0.1077/0.3465
R (all data) R_1/wR_2	0.0749/0.1282	0.0899/0.1668	0.1686/0.3707
S	1.143	0.966	2.037

3. Results and discussion

The crystal structures correspond to the quinazolinedione derivatives shown in Scheme 1, which included the only variation of the OMe group attached to different position of an aromatic ring (*orto* **1a**, *meta* **1b** and *para* **1c**). The aromatic substituted fragment is situated on the nitrogen atom located at

Table 2
Selected bond distances (Å), bond angles (°) and torsion angles (°) for compounds **1a**, **1b** and **1c** and related compounds **A-K**[14]

	1a	**1b**	**1c**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**
N2-C8	1.372	1.351	1.377	1.346	1.352	1.349	1.354	1.340	1.370	1.379	1.374	1.372	1.365	1.347
N1-C8	1.390	1.399	1.387	1.412	1.416	1.388	1.389	1.399	1.369	1.398	1.388	1.412	1.396	1.374
N1-C7	1.376	1.391	1.385	1.387	1.409	1.395	1.357	1.403	1.383	1.372	1.388	1.383	1.390	1.388
N2-C17[a]	1.468	1.477	1.467	0.748	1.069	0.860	0.850	0.943	1.452	1.480	1.474	0.911	1.482	0.859
C8-O2	1.212	1.220	1.219	1.214	1.217	1.231	1.181	1.237	1.232	1.209	1.222	1.201	1.227	1.238
N1-C9[a]	1.475	1.450	1.472	1.478	1.468	1.474	1.487	1.441	1.490	1.485	1.479	1.455	1.468	–
C7-O1	1.215	1.211	1.213	1.242	1.224	1.202	1.211	1.222	1.219	1.221	1.222	1.213	1.227	1.221
C8-N1-C9	116.3	116.8	115.9	116.4	117.4	115.8	116.7	118.9	–	117.6	116.8	116.4	117.3	–
C7-N1-C9	118.2	120.0	118.9	119.5	118.6	119.7	120.8	117.1	–	117.3	117.8	118.1	117.7	–
N1-C9-C10-C11	175.0	173.2	158.7	176.1	175.9	165.2	169.5	179.3	–	71.9	–	–	–	–
C8-N1-C9-C10	84.8	84.1	85.3	89.9	93.6	76.7	93.3	101.1	–	101.5	97.3	115.1	–	–
O2-C8-N1-C9	0.5	4.3	4.5	3.6	3.5	3.5	1.1	0.5	–	0.9	2.5	1.4	0.6	–

[a]For analogous compounds **A**-**K**, C17 and C9 represents the first atom of the corresponding chain.

Table 3
Hydrogen-bonding geometries in the crystal structures of compounds **1a**-**1c** (Å, °)

H· · · bond	D-H	H· · · A	D· · · A	D-H· · · A	Symmetry codes
Compound **1a**					
C5-H5· · · O1	0.93	2.51	3.26	137	−1/2 + x, 5/2-y, 1 − z
C6-H6· · · O1	0.92	3.04	3.52	113	−1/2 + x, 5/2-y, 1 − z
C16-H16· · · O2	0.93	2.66	3.31	126	1/2 + x, 3/2-y, 1 − z
C15-H15· · · O2	0.93	2.79	3.36	120	1/2 + x, 3/2-y, 1 − z
Compound **1b**					
C23-H23· · · O2	0.93	2.59	3.18	122	3/2-x, -y, −1/2 + z
C24-H24· · · O2	0.93	2.51	3.13	124	3/2-x, -y, −1/2 + z
C19-H19A· · · O1	0.96	2.61	3.57	177	1-x,1/2 + y, 1/2 − z
C4-H4· · · O5	0.93	2.63	3.21	120	3/2-x, 1-y, −1/2 + z
C5-H5· · · O5	0.93	2.51	3.15	125	3/2-x, 1-y, −1/2 + z
Compound **1c**					
C17-H17A· · · O2	0.93	2.46	3.32	153	x, −1 + x, z
C4-H4A· · · O1	0.93	2.62	3.34	135	x, −1 + x, z

the middle of the two carbonyl groups. Even though the molecular structure of **1c** has been reported [13], structural data are included for comparative purposes. Compounds **1a** and **1b** crystallize as well–shaped transparent white prisms and their molecular structures are shown in Fig. 1. Crystallographic data are listed in Table 1. Table 2 contains selected bond distances, bond angles and torsion angles of the three quinazolinediones (**1a**-**1c**). Also, the data for a series of eleven additional analogous structures (**A**-**K**) taken from the CCDC till 2011 have been included (Scheme 2) [14].

From the data, only small differences in the bond distances around the six-membered heterocycles were observed, giving evidence of the delocalization present in this fragment, as noticed previously

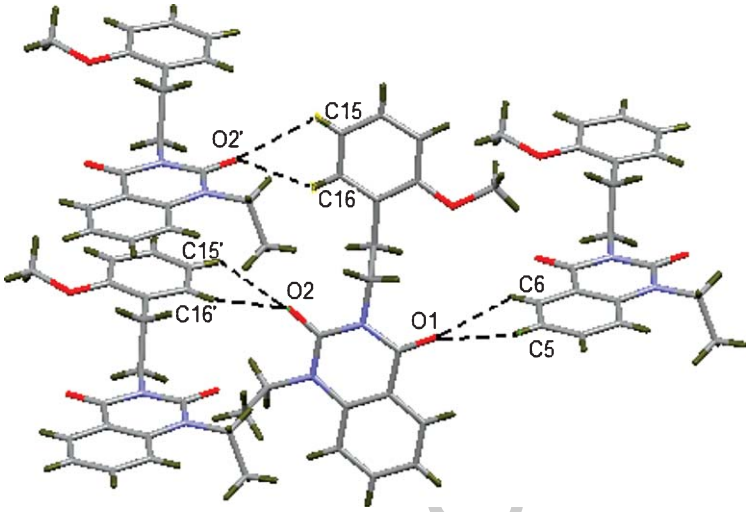


Fig. 2. Hydrogen bonding interactions observed in compound **1a**.

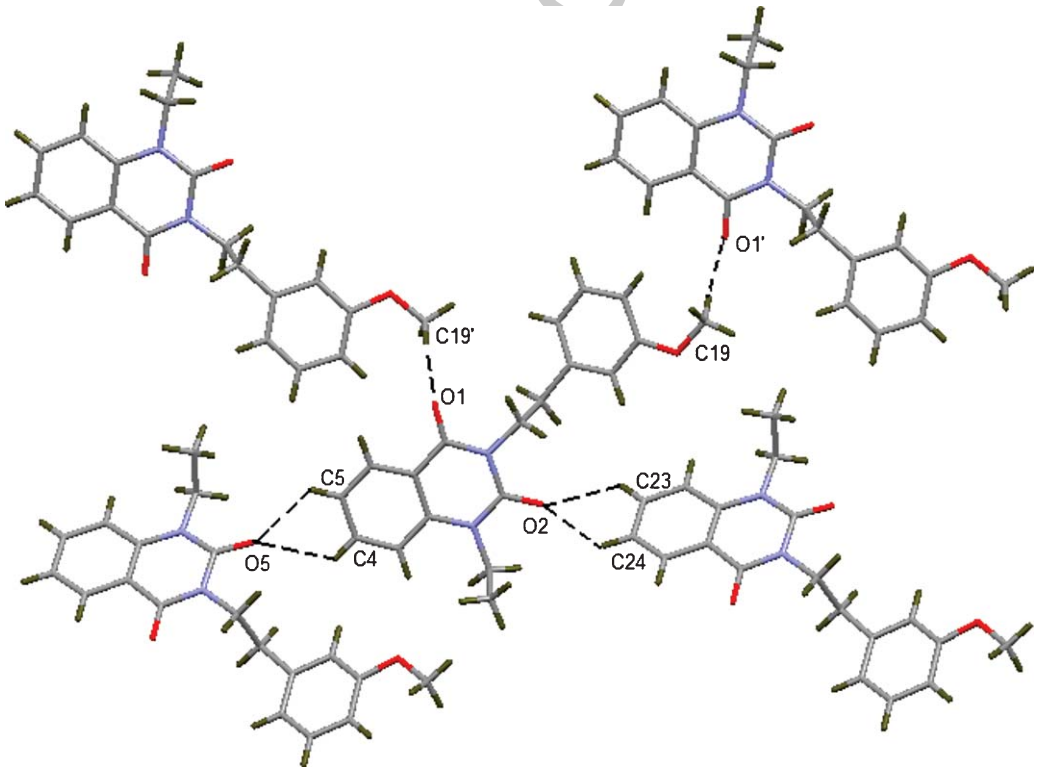


Fig. 3. Hydrogen bonding interactions observed in compound **1b**.

for analogous compounds [14]. Significant effects on the bond distances by the presence of the OMe groups located on the aromatic ring where not observed. For instance, the both C-O bond distances are in the range of 1.211 to 1.220 Å. The most different bond distance is found at the C8-N2 and C9-N1

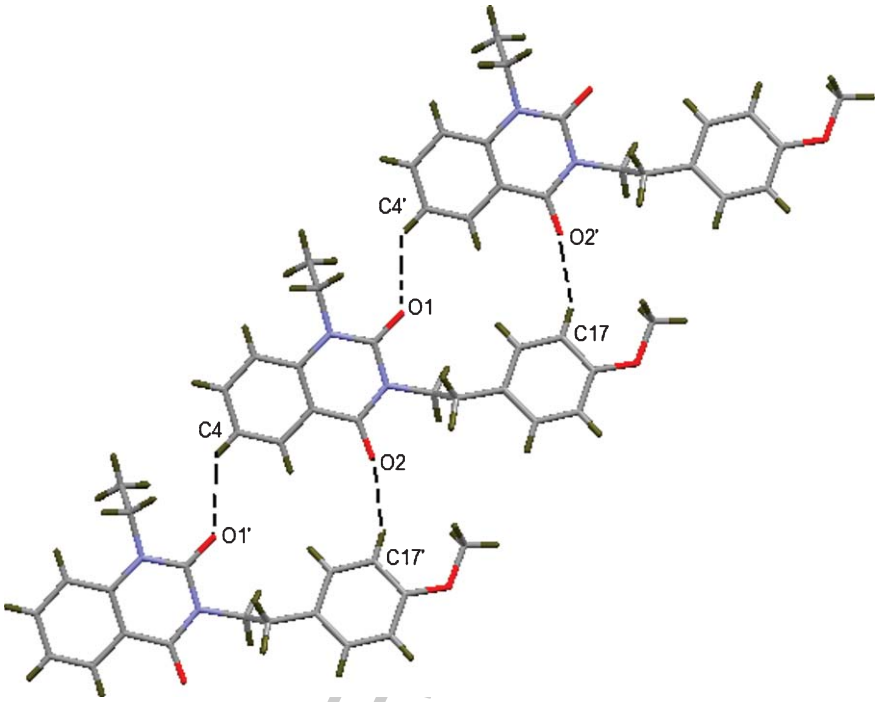


Fig. 4. Hydrogen bonding interactions observed in compound **1c**.

bonds, having values of 1.372, 1.351 and 1.377 Å for the former and 1.475, 1.450 and 1.472 Å for the later for compounds **1a**, **1b** and **1c** respectively, being in both cases the shortest for compound **1b**. Nonetheless, these values are similar with the observed for analogous compounds (**A**-**K**, Table 2) which are in the range of 1.340 to 1.379 Å and 1.441 to 1.487 Å for C8-N2 and C9-N1 bonds respectively. The lowest values are for compounds including a large chain attached to N1 (**A**-**E**). The bond angle C8-N1-C9 is shorter (*ca* ∼116.3) compared with the angle C7-N1-C9 (*ca* ∼119.0) mainly owing to the asymmetry of the heterocycle, these values are consistent with the sp^2 hybrid character of the N1 atom. The same pattern was observed for **A**-**D** analogous compounds which include a large chain at the N1 position (R^2).

The molecular structure reveals that the two planar regions are in a *trans* orientation in relation to the ethylene moiety having dihedral angles N1-C9-C10-C11 of 175.0, 173.2, 158.7°, for compounds **1a**-**1c**, respectively. In fact, the two planar regions are not coplanar itself; they have a deviation of 4.29, 19.94 and 14.86° for **1a**-**1c**, respectively, being the bigger for compound having the OMe group in *meta* position. Furthermore, ethyl and metoxy groups have a *syn* disposition in **1b** and **1c** derivatives but *anti* in **1a** perhaps to a plausible hindrance effect.

The differences mentioned above make some difference at the unit cell, wherein contacts by hydrogen bonding interactions lead to different arrays. All three crystal structures (**1a**-**1c**) are stabilized by intermolecular C-H· · ·O contacts (Table 3, Figs. 2–4), in which carbonyl oxygen atoms act as hydrogen bond acceptors. In fact, the carbonyl oxygen atom in compounds **1a** and **1b** acts as double donor forming a birfurcate bond. By contrast, any oxygen atom from the OMe group is involved in hydrogen bonding bonds formation. Nonetheless, it was noticed that the OCH_3 group can participates as C-H donor group in the formation of hydrogen bonds as observed for compound **1b** (Fig. 3).

All three cases showed $\pi - \pi$ stacking interactions having different arrangement. For instance, for compound **1a** it occurs between the heterocycle ring and the aromatic OMe substituted, nevertheless for compounds **1b** and **1c** the $\pi - \pi$ contacts occur between the two aromatic rings of the quinazolinedione fragment being in **1b** alternate and in **1c** overlapped.

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