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X-Ray and theoretical structural study of novel 5,6,7,8-tetrahydrobenzo-4*H*-pyrans

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Abstract—The X-ray crystal structure of three substituted tetrahydrobenzo-4*H*-pyrans (**6a–c**) is presented and the experimental findings compared with the theoretical values calculated at the semiempirical (AM1, PM3) and ab initio (HF/6-31G*) levels. A good agreement between both experimental and theoretical data is found showing a flattened boat conformation for the 4*H*-pyran ring and a pseudo-axial orientation of the aryl ring on the C4 position. The geometrical features of these systems (**6a–c**) reveal that they present the structural requirements to act as calcium antagonists. © 2002 Published by Elsevier Science Ltd.

1. Introduction

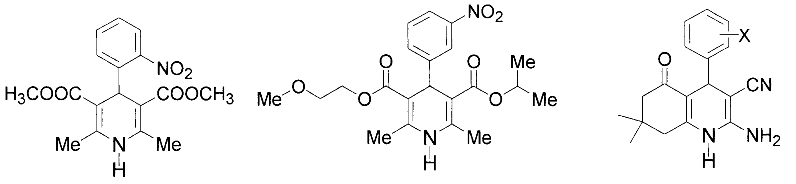
The synthesis of 1,4-dihydropyridines (1,4-DHPs) has attracted much attention along the last three decades due the calcium modulator effect they display.[1] It is well-established that the pharmacological activity of this family of compounds is determined by their structural features,[2–4] and major efforts have been devoted to the preparation of novel derivatives and to the definition of the structure–activity relationship based on crystallographic studies. Nifedipine (**1**) is considered as the prototype of 1,4-DHP, which has been widely investigated as well as other related structures such as nimodipine (**2**)[5] which exhibits strong calcium antagonist effect.

Recently, we have reported the synthesis and structural study of novel 1,4,5,6,7,8-hexahydroquinolines (**3**), in which the 1,4-DHP ring bearing an amino and a cyano groups on C2 and C3, respectively, is fused to one carbocyclic ring.[6]

The 4*H*-pyran ring can be considered as the oxa-analogue of the biologically active 1,4-dihydropyridine system. Therefore, we have reported the synthesis of a wide variety of 4*H*-pyran derivatives[7–9] as well as their study by mass spectrometry[10,11] and NMR spectroscopy.[12,13]

In addition, the X-ray crystal structure of some monocyclic 4*H*-pyran derivatives showed that their geometrical features were similar to those found for the biologically active 1,4-DHPs.[14–16]

In order to determine the influence of the presence of a fused carbocyclic ring on the structure of 4*H*-pyran ring, we



1 **2** **3**

Chart 1.

Keywords: tetrahydrobenzo-4*H*-pyrans; theoretical calculations; X-ray data.

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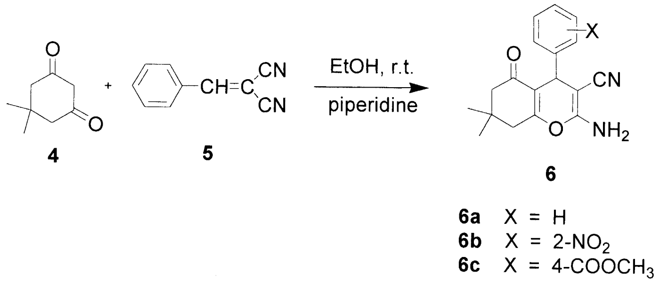


Scheme 1.

present in this paper the X-ray crystal structure of three substituted tetrahydrobenzo-4*H*-pyrans (**6a–c**).

The structural properties of these tetrahydrobenzo-4*H*-pyrans (**6a–c**) were also studied by theoretical calculations at the semiempirical (AM1, PM3) and ab initio (HF/6-31G*) levels. The calculated data were compared with those obtained experimentally from X-ray structural analysis.

This comparative study will enable to determine the validity of theoretical methods to predict the geometrical features of carbocyclic-fused 4*H*-pyran systems and therefore, their applications as potential candidates as calcium antagonists (Chart 1).

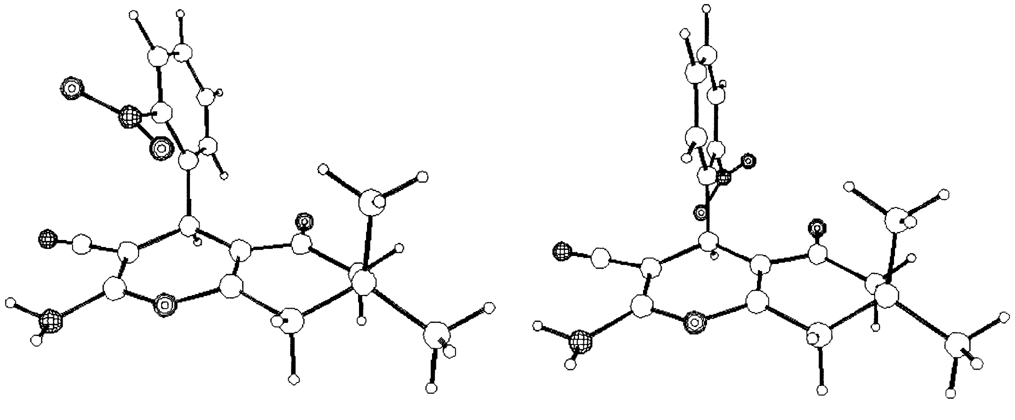
2. Results and discussion

2-Amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrobenzo-4*H*-pyrans (**6a–c**) were synthesized by following the general procedure from 6-*exo-dig* cyclisation of δ-oxonitriles first reported by our group[17,18] (Scheme 1).

The compounds were obtained as crystalline solids after recrystallisation from ethanol and their structures were confirmed by spectroscopic methods (Section 3).

Compounds **6** show in the IR spectra the bands corresponding to the C≡N and C=O groups at ~2200 and 1680 cm^{-1}, respectively. The ^{1}H NMR spectra of compounds **6** show the proton on C4 as a singlet at δ 4.6–4.0. The two protons on C6 appear as an AB system with a coupling constant of J~16 Hz, indicating that these two protons are not equivalents. The protons on C8 appear as a broad singlet.

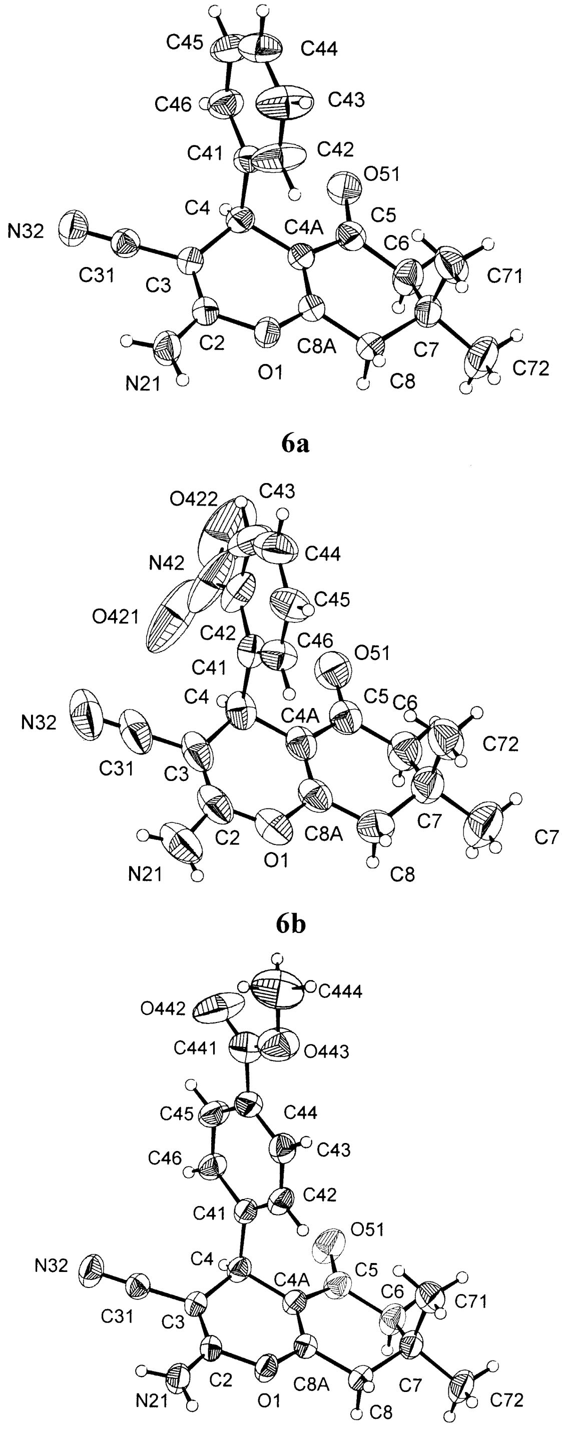
The two olefinic double bonds between C2 (δ 156–159) and C3 (δ 57–68), and C8a (δ 159–164) and C4a (δ 110–118) in compounds **6a–c** clearly show the presence of a push–pull effect which is responsible for the δ values found for these olefinic carbon atoms. This finding has been previously observed in other related molecules.[19–22] All signals were unambiguously assigned by DEPT 90 and 135° and HMQC experiments. A further support to the spectroscopic assignment was based on the HMBC, NOE and COSY experiments (Section 3).



Conformer *ap* **Conformer *sp***

	AM1	PM3	HF/6-31G*
sp	0.6	0.2	0.7
ap	0.0	0.0	0.0

Figure 1. Relative energy for conformers *sp* and *ap* of **6b** [^{a}(kcal mol^{-1}), ^{b}(Hartree)].



6a

6b

6c

Figure 2. X-ray structure of compounds **6a–6c** showing the numbering scheme.

In previous works, we have widely used X-ray crystallography and theoretical calculations for determining the conformational features of 1,4-DHPs and 3,4-dihydropyridone derivatives[23–25] and we have proved that ab initio and semiempirical calculations (at AM1 level) reproduce adequately the geometry of this type of compounds. Considering the analogies of the structure of compounds **6a–c** with such derivatives, we have used herein theoretical methods at semiempirical and ab initio levels to compare the results with the data obtained by X-ray crystallography.

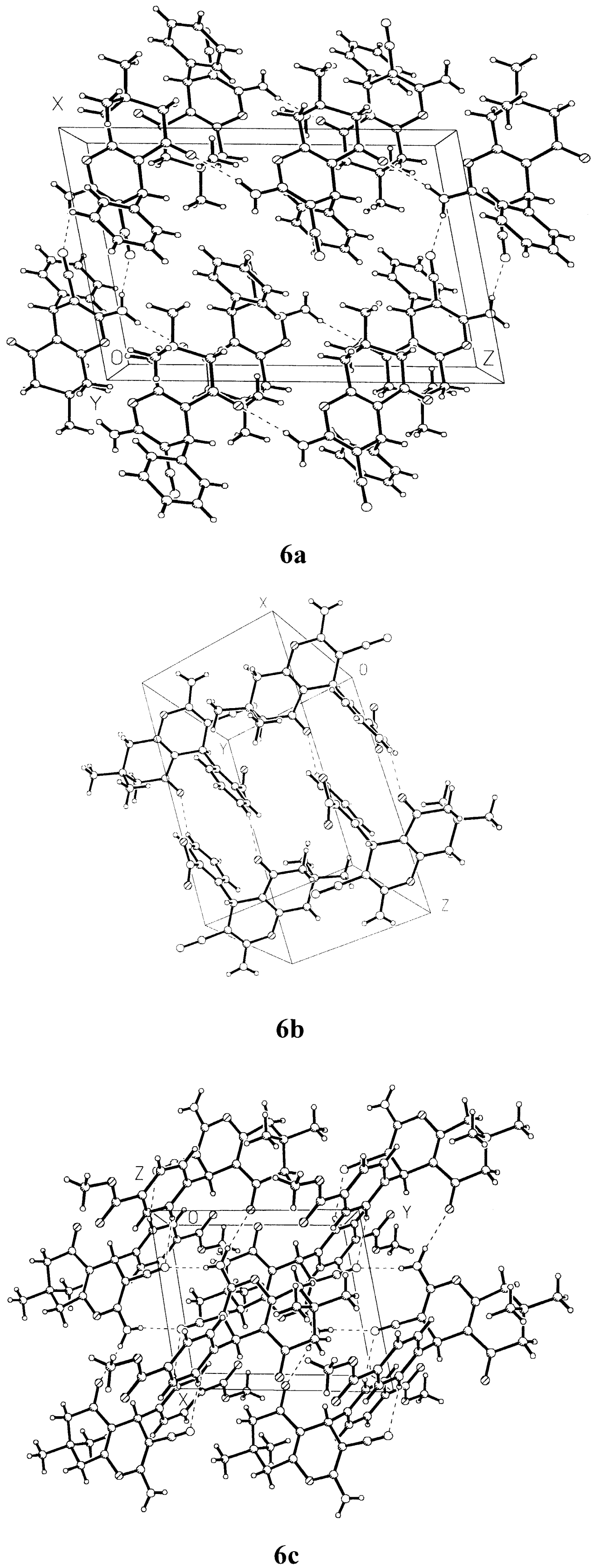
Semiempirical and ab initio methods showed that the 4*H*-pyran ring adopts a flattened boat conformation with both C4 and O1 atoms lying above of the plane formed by C2, C3, C4a, C8a atoms. For example, in compound **6a**, the torsion angle C8a–C2–C3–C4 is −11.1° and C3–C4a–C8a–O1 is −9.8°. The aryl substituent on C4 is located in a pseudo-axial position and lies nearly perpendicular to the mean plane of 4*H*-pyran ring. The torsion angle that describes this parameter C46–C41–C4–C4a for compound **6a** is 90.3° (131.53° X-ray). The value of C42–C41–C4–C4a for **6b** is 107.8° (AM1) and −57.6° (X-ray) and for **6c** C46–C41–C4–C4a is 89.8° (AM1) and 144.92° (X-ray).

The calculated (AM1, PM3 and HF/6-31G* ab initio) heats of formation for compound **6b** reveal that the conformer *ap* (antiperiplanar) in which the nitro substituent of the phenyl ring lies above the 4*H*-pyran ring is slightly more stable (less than 1 kcal mol^{-1}) than conformer *sp* (synperiplanar), with the substituent on the phenyl ring on the same side as the hydrogen of the 4*H*-pyran ring (Fig. 1).

X-Ray data show that the conformer *sp* is the only present in the crystal (Fig. 2). This finding can be accounted for by the interactions occurring in the crystal, leading to conformer *sp* which has a similar energy to that of conformer *ap* (Fig. 1). Although the ap geometry of the nitro substituent on the phenyl ring is not usual, it has been previously found in some other related molecules.[26,27] The X-ray structure of compounds **6a–c** are shown in Fig. 2, together with their atomic labelling schemes.

In all compounds, the 4*H*-pyran ring has a boat conformation with two local pseudo-mirror planes, one running along C4···O1 and the other through the midpoints of the C4a–C8a and C2–C3 bonds, with puckering parameters[28] Q=0.227(2) Å, θ=101.9(5)° and φ=352.9(5)° for compound **6a**, Q=0.096(2) Å, θ=119.5(12)° and φ=7.9(18)° for compound **6b** and Q=0.166(2) Å, θ=72.6(7)° and φ=175.9(7)° for compound **6c**. The cyclohexanone ring has an intermediate half-chair/sofa conformation with a local pseudo-twofold axis through the midpoints of C6–C7 and C4a–C8a bonds, and a local pseudo-mirror plane along C7···C4a (puckering parameters: **6a**: Q=0.452(2) Å, θ=126.8(3)° and φ=347.1(3)°; **6b**: Q=0.463(3) Å, θ=122.5(4)° and φ=346.6(4)° and **6c**: Q=0.448(2) Å, θ=56.2(3)° and φ=169.9(4)°).

AM1 semiempirical calculations also predicted the same conformation for the cyclohexanone ring, being the C6, C5, C4a, C8a and C8 atoms essentially in the same plane. For example, the dihedral angles C6–C5–C4a–C8a and C5–C4a–C8a–C8 calculated by AM1 for **6a** are −0.7 and 5.0°, respectively (5.1 and 2.2° determined by X-ray). For **6b**, these dihedral angles are 5.9° by AM1 (0.9°, X-ray) and 1.9° by AM1 (7.7°, X-ray). Similarly, for **6c**, the values are −0.6° AM1 (1.0°, X-ray) and 4.9° AM1 (5.2°, X-ray). The dihedral angle C7–C6–C5–C4a for **6a** is −28.8° (AM1) and −34.6° (X-ray), for **6b** is −34.7° (AM1) and −33.0° (X-ray), and for **6c** is −28.8 (AM1) and −30.9 (X-ray), showing that C7 is out of the plane. The cyano group at



6a

6b

6c

Figure 3. Packing of the molecules of compounds **6a**–**6c** in the unit cell showing their hydrogen bond network.

Table 1. Most relevant bond distances, valence angles and dihedral angles for the most stable conformation of compound **6a** calculated by semi-empirical AM1 and ab initio HF/6-31G*. Bond distances are given in Å and angles in degrees (standard deviations in parenthesis)

	X-Ray	AM1	HF/6-31G*
Bond distance			
O1–C2	1.377(2)	1.401	1.345
O1–C8a	1.374(2)	1.390	1.361
C2–C3	1.350(3)	1.371	1.340
C3–C4	1.522(2)	1.497	1.518
C4–C4a	1.511(2)	1.499	1.514
C4a–C8a	1.337(2)	1.351	1.325
C4–C41	1.522(3)	1.504	1.531
C3–C31	1.413(3)	1.412	1.430
C31–N32	1.148(3)	1.165	1.139
C2–N21	1.339(3)	1.379	1.359
C5–O51	1.224(2)	1.237	1.196
Valence angles			
C2–O1–C8a	118.18(14)	115.4	119.4
O1–C2–C3	121.58(16)	121.9	122.3
C2–C3–C4	122.59(16)	121.5	122.5
C3–C4–C4a	107.67(14)	109.6	108.1
C4–C4a–C8a	122.53(15)	121.3	122.5
C4a–C8a–O1	122.79(16)	123.2	122.5
C8–C8a–O1	110.98(15)	111.1	111.1
C5–C4a–C4	119.11(15)	118.8	118.8
C4–C3–C31	118.09(15)	117.6	119.6
N21–C2–O1	109.62(15)	110.7	110.4
N32–C31–C3	178.4(2)	179.5	178.4
O51–C5–C4a	120.71(17)	122.5	121.1
Dihedral angles			
O1–C2–C3–C4	−7.7(3)	−0.1	1.2
C2–C3–C4–C4a	21.1(2)	20.6	13.5
C3–C4–C4a–C8a	−18.3(2)	−21.9	−15.0
C4–C4a–C8a–O1	2.1(3)	2.6	4.4
C4a–C8a–O1–C2	14.4(2)	19.7	10.1
C8a–O1–C2–C3	−11.3(2)	−20.8	−11.7
$\sum\|\rho\|$	*74.9*	*85.7*	*55.9*
C8a–C2–C3–C4a	−1.31(8)	0.6	0.7
C8a–C2–C3–C4	−13.5(2)	−11.1	−7.1
C3–C4a–C8a–O1	−8.6(2)	−9.8	−4.3
C6–C5–C4a–C8a	5.1(3)	−0.7	0.8
C5–C4a–C8a–C8	2.2(3)	5.0	5.0
C7–C8–C8a–C4a	20.0(3)	20.0	19.4
N32–C31–C3–C2	−145(7)	−164.4	−1.4
O51–C5–C4a–C8a	−177.06(18)	176.3	176.7
C7–C6–C5–C4a	−34.6(3)	−28.8	−31.0
C2–C3–C4–C41	−103.8(2)	−102.9	−110.8
C42–C41–C4–C4a	−49.2(2)	−90.1	−67.0
C46–C41–C4–C4a	131.53(18)	90.3	113.0

C3 is coplanar with the endocyclic double bond as a consequence of the π conjugation.

For the three studied compounds, Fig. 3 shows that the crystal structures are stabilised by means of strong intermolecular hydrogen bonds and weak interactions. In compound **6a**, the N21 atom is involved in two intermolecular hydrogen bonds: N21···N32 $(-x+1,\ -y+1,\ -z+2)=$ 3.019(3) Å, and N21···O51 $(x,\ 1/2-y,\ 1/2+z)=$ 3.008(2) Å. An intermolecular weak interaction of the type, C···O is present: C8···O51=3.482(2) Å. In **6b**, the two molecules related by the symmetry centre form a dimer by means of a hydrogen bond N21···N32: N21···N32 $(-x+1,\ -y-1,\ -z)=$3.105(4) Å. Two intermolecular weak interactions of the type, C···O are present: C44···O51= 3.329(3) Å and C46···O422=3.239(4) Å. The crystal

Table 2. Most relevant bond distances, valence angles and dihedral angles for the most stable conformation of compound **6b** calculated by semiempirical AM1 and ab initio HF/6-31G*. Bond distances are given in Å and angles in degrees (standard deviations in parenthesis)

	X-Ray	AM1 (ap)	AM1 (sp)	HF/6-31G*(ap)	HF/6-31G*(sp)
Bond distance					
O1–C2	1.365(3)	1.398	1.401	1.339	1.345
O1–C8a	1.377(3)	1.386	1.390	1.356	1.360
C2–C3	1.351(4)	1.373	1.372	1.343	1.341
C3–C4	1.513(3)	1.494	1.498	1.516	1.517
C4–C4a	1.505(3)	1.495	1.500	1.515	1.514
C4a–C8a	1.334(3)	1.352	1.351	1.326	1.325
C4–C41	1.531(3)	1.508	1.508	1.542	1.538
C3–C31	1.242(4)	1.412	1.412	1.429	1.431
C31–N32	1.143(4)	1.165	1.164	1.139	1.139
C2–N21	1.346(4)	1.376	1.376	1.354	1.357
C5–O51	1.225(3)	1.238	1.236	1.198	1.196
Valence angle					
C2–O1–C8a	118.95(19)	116.6	115.8	120.0	119.5
O1–C2–C3	122.4(2)	122.4	122.1	122.4	122.6
C2–C3–C4	122.8(2)	122.1	121.9	122.3	122.6
C3–C4–C4a	109.10(19)	110.9	110.3	108.9	108.5
C4–C4a–C8a	123.05(19)	121.9	121.8	122.2	123.0
C4a–C8a–O1	122.7(2)	123.9	123.4	122.9	122.7
C8–C8a–O1	111.4(2)	110.7	110.7	110.9	111.2
C5–C4a–C4	118.3(2)	118.3	118.4	119.0	118.1
C4–C3–C31	118.8(2)	117.2	117.6	119.5	120.0
N21–C2–O1	109.9(2)	110.6	110.6	110.6	110.3
N32–C31–C3	179.0(3)	179.5	179.9	179.0	177.1
O51–C5–C4a	119.9(2)	122.2	122.4	175.2	120.7
Dihedral angle					
O1–C2–C3–C4	−4.3(4)	−0.2	1.7	−1.6	0.7
C2–C3–C4–C4a	10.0(3)	11.4	15.1	10.1	7.3
C3–C4–C4a–C8a	−11.2(3)	−1.8	−15.8	−10.7	−8.6
C4–C4a–C8a–O1	6.7(3)	1.0	−0.5	3.0	2.0
C4a–C8a–O1–C2	0.7(3)	11.3	18.6	7.2	7.3
C8a–O1–C2–C3	−1.9(3)	−11.6	−19.1	−7.9	−8.6
$\sum\|\rho\|$	***34.8***	***37.3***	***70.8***	***40.5***	***34.5***
C8a–C2–C3–C4a	0.5(1)	0.2	0.3	0.3	0.6
C8a–C2–C3–C4	−5.2(3)	−6.2	−8.3	−5.5	−3.6
C3–C4a–C8a–O1	0.2(2)	−5.7	−9.5	−3.2	−3.0
C6–C5–C4a–C8a	0.9(3)	−3.4	5.9	−0.6	3.7
C5–C4a–C8a–C8	7.7(3)	4.5	1.9	6.2	3.3
C7–C8–C8a–C4a	16.1(3)	22.6	18.8	18.9	19.2
N32–C31–C3–C2	140(18)	−163.3	−163.9	−4.0	16.7
O51–C5–C4a–C8a	178.2(2)	173.7	−176.0	175.2	−179.7
C7–C6–C5–C4a	−33.0(3)	−25.2	−34.7	−30.0	−33.1
C2–C3–C4–C41	−110.5(2)	−115.1	−107.1	−119.5	−115.4
C42–C41–C4–C4a	120.3(2)	−76.9	107.8	−82.4	114.0
C46–C41–C4–C4a	−57.6(2)	104.4	−71.1	103.5	−63.5

structure of **6c** shows that the N21 atom is involved in a bifurcated intermolecular hydrogen bond: N21···N32 $(-x+1, -y+2, -z+1)$=3.114(3) Å, and N21···O51 $(x+1, y, z)$=2.973(2) Å. An intermolecular weak interaction of the type, C···N is present: C46···N32=3.306(3) Å.

The geometrical features predicted for the minimum energy conformation calculated by AM1 and ab initio calculations (HF/6-31G*) and determined by X-ray analysis for **6a–c** are listed in Tables 1–3. In general, the predicted values compare quite well with the experimental data.

It can be observed in Tables 1–3 that X-ray analysis shows a more flattened boat conformation for the pyran ring than that predicted from AM1 theoretical calculations (the sum of the absolute values of the internal torsion angles of the pyran ring is a measure of its planarity ($\sum|\rho|$[29]). Compound **6a** exhibits a $\sum|\rho|$ of 74.9°, **6b**, 34.8° and **6c**, 57.4°. Hence **6b** is the most flattened compound. However, ab initio calculations predicted a more flattened boat conformation than that found by X-ray analysis.

It is important to note that the geometrical parameters calculated for the most stable conformation are in good agreement with those found by X-ray analysis. These findings suggest that ab initio calculations (HF/6-31G*) and also semiempirical methods (AM1) are useful for predicting conformational features on this class of compounds in a similar way to that previously found for the related 1,4-dihydropyridine derivatives.

In summary, we have carried out the synthesis and characterisation of novel tetrahydrobenzo-4*H*-pyran derivatives and determined their structure by X-ray analysis and theoretical calculations at the semiempirical and ab initio levels. Both methods show a flattened boat conformation for the 4*H*-pyran ring with a pseudo-axial orientation of the aryl ring in position C-4.

Table 3. Most relevant bond distances, valence angles and dihedral angles for the most stable conformation of compound **6c** calculated by semiempirical AM1 and ab initio HF/6-31G*. Bond distances are given in Å and angles in degrees (standard deviations in parenthesis)

	X-Ray	AM1	HF/6-31G*
Bond distance			
O1–C2	1.370(2)	1.400	1.344
O1–C8a	1.376(2)	1.390	1.361
C2–C3	1.360(2)	1.372	1.341
C3–C4	1.514(2)	1.497	1.517
C4–C4a	1.505(2)	1.499	1.514
C4a–C8a	1.333(2)	1.351	1.326
C4–C41	1.519(3)	1.505	1.531
C3–C31	1.413(3)	1.411	1.430
C31–N32	1.147(3)	1.165	1.139
C2–N21	1.329(2)	1.376	1.358
C5–O51	1.223(3)	1.237	1.196
Valence angle			
C2–O1–C8a	118.96(14)	115.6	119.4
O1–C2–C3	121.20(16)	121.9	122.3
C2–C3–C4	122.94(16)	121.5	122.5
C3–C4–C4a	108.68(14)	109.9	108.2
C4–C4a–C8a	122.46(16)	121.4	122.5
C4a–C8a–O1	123.18(16)	123.3	122.6
C8–C8a–O1	110.83(16)	111.1	111.2
C5–C4a–C4	118.79(16)	118.8	118.7
C4–C3–C31	118.04(15)	117.6	119.6
N21–C2–O1	11041(15)	110.7	110.4
N32–C31–C3	178.54(19)	179.4	178.4
O51–C5–C4a	120.87(17)	122.4	121.0
Dihedral angle			
O1–C2–C3–C4	6.6(3)	0.3	−1.0
C2–C3–C4–C4a	16.5(2)	19.4	13.0
C3–C4–C4a–C8a	−15.3(3)	−20.9	−14.5
C4–C4a–C8a–O1	4.3(3)	2.5	4.1
C4a–C8a–O1–C2	8.0(3)	18.9	10.1
C8a–O1–C2–C3	−6.7(3)	−20.2	−11.6
$\sum\|\rho\|$	***57.4***	***82.2***	***54.3***
C8a–C2–C3–C4a	0.52(9)	0.7	0.7
C8a–C2–C3–C4	10.0(2)	−10.3	−6.9
C3–C4a–C8a–O1	4.6(2)	−9.3	−4.3
C6–C5–C4a–C8a	1.0(3)	−0.6	1.2
C5–C4a–C8a–C8	5.2(3)	4.9	4.8
C7–C8–C8a–C4a	18.8(3)	20.1	19.3
N32–C31–C3–C2	172(8)	−178.1	1.0
O51–C5–C4a–C8a	178.6(2)	176.4	177.2
C7–C6–C5–C4a	−30.9(3)	−28.8	−31.3
C2–C3–C4–C41	−107.5(2)	−104.1	−111.2
C42–C41–C4–C4a	−39.4(2)	−90.1	−66.9
C46–C41–C4–C4a	144.92(18)	89.8	113.3

The geometrical features of the studied tetrahydrobenzo-4*H*-pyrans (**6a–c**) are quite similar to the structurally related 1,4-DHPs and therefore exhibit the structural properties to act as potential calcium modulators.

3. Experimental

3.1. General

Melting points were determined in a capillary tube in an Electrothermal C14500 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker DPX300 spectrometer (300 MHz—^{1}H and 75.47 MHz—^{13}C). Chemical shifts are given as δ values against tetramethylsilane as the internal standard and J values are given in Hz. The IR spectra were measured with a Shimadzu FTIR 8300 instrument as potassium bromide pellets. Mass spectra were obtained with a Hewlett Packard 5989 A spectrometer. Microanalyses were performed in a Perkin–Elmer 2400 CHN by the Servicio de Microanálisis of Universidad Complutense de Madrid. The reactions were monitored by TLC performed on silica-gel plates (Merck 60F$_{250}$) and using hexane–ethylacetate (8:2) as eluent. Commercially available starting materials and reagents were purchased from commercial sources (BDH and Fluka) and were used without further purification. Aromatic aldehydes were distilled before used.

Semiempirical calculations (AM1[30] and PM3[31]) were carried out using the MOPAC 6.0[32] molecular orbitals set. Previously, the molecular geometry was optimised by means of the Allinger's Molecular Mechanics[33] with PCMODEL program.[34] Ab initio calculations were carried out with Gaussian 98 program.[35] Calculations were performed on an IBM-RS6000.

3.2. X-Ray structure analysis

Crystals of **6a–c** were grown by slow evaporation from methanol solutions. The crystallographic and experimental data for these compounds are summarised in Table 4. Measurements were carried out using a Siemens P4 four-circle diffractometer with graphite monochromated Cu Kα radiation. The intensity data were collected using ω–2θ scans, with ω scan width equal to the low range plus the high range plus the separation between the Kα_1 and Kα_2 positions. Empirical absorption correction, via ψ scans was applied.[36] Three standard reflections were monitored every 100 reflections (intensity decay: none).

The structure was solved by direct methods and Fourier synthesis. Non-H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed to 1.3 times U$_{eq}$ of their parent atoms. Data collection: XSCANS.[37] Cell refinement: XSCANS.[37] Data reduction: XSCANS.[37] Program(s) used to solve structure: SHELXS97.[38] Program(s) used to refine structure: SHELXL97.[39] Molecular graphics: DIAMOND.[40] Software used to prepare material for publication: PLATON.[41] Crystallographic Data Centre as supplementary publication numbers (**6a**, CCDC 165337; **6b**, CCDC 165338; **6c**, CCDC 165337). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccd.cam.acuk].

3.3. Synthesis of arylidenemalononitriles (5a–c)

These compounds were obtained by following the method previously reported in the literature.[42]

3.4. Synthesis of 2-amino-4-aryl-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyrane (6a–c): general procedure

A mixture of dimedone (5,5-dimethyl-1,3-cyclohexanedione) (40 mmol), the appropriate arylidenemalononitrile (40 mmol) and catalytic amount of piperidine in ethanol

Table 4. Crystal data and structural refinement details for **6a–c**

Parameter	**6a** (X=H)	**6b** X=(2-NO$_2$)	**6c** (X=4-COOCH$_3$)
Solvent	Methanol	Methanol	Methanol
Empirical formula	$C_{18}H_{18}N_2O_2$	$C_{18}H_{17}N_3O_4$	$C_{20}H_{20}N_2O_4$
Formula weight	294.35	339.35	352.38
Crystal size (mm)	0.30×0.30×0.10	0.44×0.40×0.08	0.40×0.22×0.12
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$	$P\bar{1}$
a (Å)	11.3150(5)	7.6566(4)	8.0402(4)
b (Å)	9.4740(4)	8.4992(4)	9.2500(2)
c (Å)	14.9175(6)	13.3019(4)	13.1556(7)
α (°)	90.0	94.188(4)	80.433(2)
β (°)	99.363(3)	99.648(4)	74.872(4)
γ (°)	90.0	94.282(4)	77.721(2)
V (Å^3) Z	1577.8(1), 4	847.77(6), 2	916.52(7), 2
d_{calc} (g m^{-3})	1.2391(1)	1.3294(1)	1.2769(1)
Wavelength (Å)	1.54178	1.54178	1.54178
Temperature (K)	293(2)	293(2)	293(2)
Theta range (°)	$3.71 < \theta < 69.11$	$3.71 < \theta < 69.11$	$3.71 < \theta < 69.19$
Limiting indices, h	−1, 13	−1, 8	−9, 1
k	−1, 11	−10, 10	−11, 11
l	−18, 18	−16, 16	−13, 13
Reflections collected	3865	3811	3782
Independent reflections	2207	2448	2569
Data/restraints/parameters	2731/0/202	3048/0/229	3129/0/239
Goodness-of-fit on F^2	1.036	1.042	1.042
Final R indices [I>2$\sigma(I)$]	R=0.047, wR=0.131	R=0.057, wR=0.175	R=0.050, wR=0.141
Largest difference peak (e Å^{-3})	0.17	0.25	0.30
Largest difference hole (e Å^{-3})	−0.21	−0.28	−0.18

(40 mL) was stirred at room temperature. After 1 h, a precipitated was formed. The solid was collected by filtration. Further purification was accomplished by recrystallisation from ethanol.

3.4.1. 2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4*H*-benzopyran (6a). Compound **6a** was obtained as a white solid (ethanol) in 70% yield, mp 237–238°C; $\nu_{\max}$/cm^{-1} 3396 and 3325 (NH), 2200 (CN), 1679 (C=O), 1660 (C=C), 1604 (C=C); ^{1}H NMR (DMSO-d$_6$) δ 7.29–7.09 (m, 5H, phenyl protons), 6.99 (s, 2H, NH$_2$), 4.14 (s, 1H, 4-H), 2.38 (br s, 2H, 8-H), 2.24 (d, 1H, 6-H, J=16 Hz), 2.14 (d, 1H, 6′-H, J=16 Hz), 1.01 (s, 3H, CH$_3$), 0.92 (s, 3H, CH$_3$); ^{13}C NMR (DMSO-d$_6$) δ 195.7 (CO), 162.5 (C8a), 158.6 (C2), 144.8 (C1′), 128.4 (C2′, C6′), 127.2 (C3′, C5′), 126.6 (C4′), 119.8 (CN), 112.8 (C4a), 58.2 (C3), 50.1 (C6), 39.6 (C8), 35.6 (C4), 31.8 (C7), 28.5 (CH$_3$), 26.8 (CH$_3$); MS: *m*/*z* (%): 294 (M$^+$, 14%), 293 (M$^+$−H, 25), 217 (M$^+$−C$_6$H$_5$, 100), 161 (5). Anal. Calcd for $C_{18}H_{18}N_2O_2$ (294.35): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.53; H, 6.31; N 9.47.

3.4.2. 2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(2′-nitrophenyl)-5-oxo-4*H*-benzopyran (6b). Compound **6b** was obtained as a pale yellow solid (ethanol) in 70% yield, mp 195–197°C; $\nu_{\max}$/cm^{-1} 3450 and 3373 (NH), 2198 (CN), 1685 (C=O), 1670 (C=C), 1637 (C=C), 1525 and 1350 (NO$_2$); ^{1}H NMR (DMSO-d$_6$) δ 8.09 (d, 1H, H3′, J=7.3 Hz), 7.54 (m, 3H, H4′, H5′, H6′), 7.18 (s, 2H, NH$_2$), 4.31 (s, 1H, H4), 2.50 (br s, 2H, 8-H), 2.21 (d, 1H, H6′, J=16.0 Hz), 2.12 (d, 1H, H-6′, J=16.0 Hz), 1.02 (s, 3H, CH$_3$), 0.95 (s, 3H, CH$_3$); ^{13}C NMR (DMSO-d$_6$) δ 195.9 (CO), 163.1 (C8a), 157.6 (C2), 150.1 (C2′), 133.1 (C1′), 136.8 (C5′), 130.1 (C6′), 125.5 (C4′), 121.1 (C3′), 119.5 (CN), 118.2 (C4a), 58.4 (C3), 49.4 (C6), 39.5 (C8), 35.2 (C4), 31.2 (C7), 28.2 (CH$_3$), 26.8 (CH$_3$); MS: *m*/*z* (%) 339 (M$^+$, 12), 308 (100, M$^+$−NO), 292 (15), 217 (M$^+$−C$_6$H$_4$NO$_2$, 87), 161 (12). Anal. Calcd for $C_{18}H_{17}N_3O_3$ (323.35): C, 66.86; H, 5.30; N, 13.00. Found: C, 66.70; H, 5.46; N 13.10.

3.4.3. 2-Amino-4-(4′-carboxymethyl)-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyran (6c). Compound **6c** was obtained as a white solid (ethanol) in 82% yield, mp 280–282°C; $\nu_{\max}$/cm^{-1} 3381and 3317 (NH), 2192 (CN), 1720 (C=O), 1685 (C=O), 1654 (C=C), 1606 (C=C); ^{1}H NMR (DMSO-d$_6$) δ 7.86 (d, 2H, H3′, H5′, J=8.2 Hz), 7.27 (d, 2H, H2′, H6′, J=8.2 Hz), 7.08 (s, 2H, NH$_2$), 4.24 (s, 1H, H4), 3.80 (s, 3H OCH$_3$), 2.48 (br s, 2H, 8-H), 2.23 (d, 1H, H6′, J=16.0 Hz), 2.06 (d, 1H, H-6′, J=16.0 Hz), 1.01 (s, 3H, CH$_3$), 0.92 (s, 3H, CH$_3$); ^{13}C NMR (DMSO-d$_6$) δ 195.5 (CO), 165.9 (CO), 162.7 (C8a), 158.5 (C2), 149.9 (C4′), 129.3 (C3′, C5′), 127.9 (C1′), 127.5 (C2′,C6′), 119.4 (CN), 112.7 (C4a), 57.4 (C3), 51.9 (OCH$_3$), 49.8 (C6), 39.6 (C8), 35.6 (C4), 31.7 (C7), 28.2 (CH$_3$), 26.7 (CH$_3$); MS: *m*/*z* (%): 352 (M$^+$, 21), 293 (17, M$^+$−COOCH$_3$), 286 (13), 271 (100), 227 (63), 217 (M$^+$−C$_6$H$_4$COOCH$_3$, 34), 161 (7). Anal. Calcd for $C_{20}H_{20}N_2O_4$ (352.39): C, 68.17; H, 5.72; N, 7.95. Found: C, 68.31; H, 5.66; N 7.67.

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