Synthesis and Structural Study of Novel 1,4,5,6,7,8-hexahydroquinolines

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This work is dedicated to the memory of Professor Raymond N. Castle

A new series of 1,4,5,6,7,8-hexahydroquinolines (**9a-j**) has been synthesized and their structural features studied by X-ray analysis and theoretical calculations at semiempirical and *ab initio* levels. A good correlation is found between the most stable conformation predicted for compounds **9** and that obtained by experimental X-ray diffraction for **9h**. The obtained geometrical features for **9** are similar to those found for other related active calcium modulators.

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Introduction.

The design and synthesis of 1,4-dihydropyridines (1,4-DHPs) has attracted much attention along the last thirty years due to the calcium antagonist effect they display [1]. The establishment of the pharmacological action as drugs for the treatment of cardiovascular diseases such as angina, hypertension or arrhythmia was mainly based on the structural studies carried out by X-ray diffraction on differently substituted 1,4-DHPs [2].

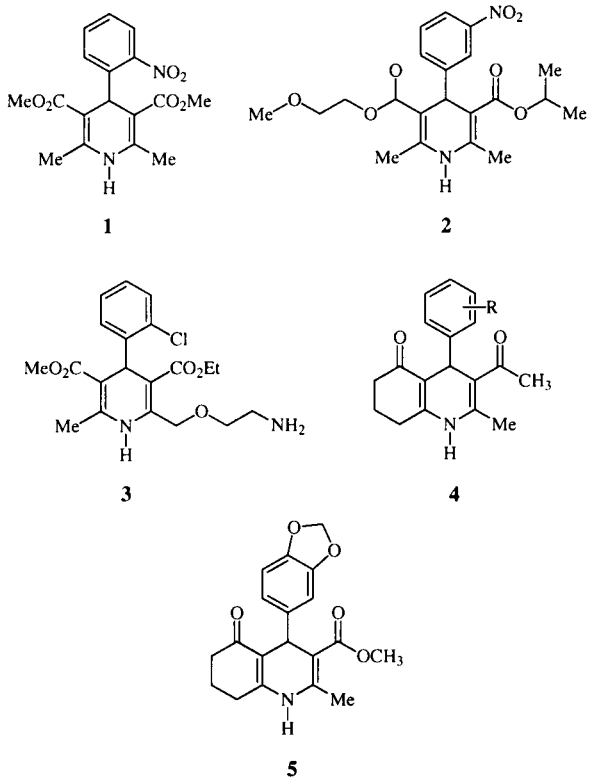
Nifedipine (**1**) is considered as the prototype of 1,4-DHP which has been widely investigated as well as other related structures such as nimodipine (**2**) [3] or amlodipine (**3**) [4] which exhibit strong calcium antagonist effect.

These 1,4-DHPs (**1–3**) are endowed with ester groups on C3 and C5 positions. Other 1,4-DHP derivatives bearing other substituents such as acyl, sulphonyl or nitrile have also showed calcium antagonist activity [5-10]. On the other hand, 1,4-DHPs fused to a carbocyclic ring have shown calcium antagonist or agonist activity [11].

We have recently reported on the synthesis of 1,4-DHPs fused to one or two carbo and heterocyclic rings and studied their structure in comparison with the simpler related monocyclic 1,4-DHPs [12]. Recently, other differently substituted hexahydroquinoline derivatives of type **4** bearing an acyl group on C3 have been exhaustively studied as interesting calcium antagonist modulators [13]. Furthermore, bicyclic systems **5** in which the 1,4-DHP is fused to a cyclohexanone ring have been reported to exhibit calcium modulatory properties [14].

In this paper we describe the synthesis of novel 1,4,5,6,7,8-hexahydroquinolines (**9**) bearing amino and cyano groups on C2 and C3, respectively. The structural study of the new compounds has been carried out by theoretical calculations at the semiempirical (AM1), and *ab initio* (HF/3-21G) levels, and X-ray crystallography for **9h**.

Chart 1



Results and Discussion.

The preparation of compounds **9a-j** has been carried out by refluxing equimolar amounts of the corresponding arylidenemalononitrile (**6**), dimedone (**7**) and excess of ammonium acetate in acetic acid as solvent (See Scheme 1), in a similar way to that reported for other related structures [15]. Compounds **9** are obtained as crystalline solids in 55 – 75 % yields.

Alternatively, by refluxing equimolar amounts of dimedone (**7**), the appropriate 5-arylidenemalononitrile derivatives (**6**) and excess of ammonium acetate in absolute ethanol, in the presence of catalytic amounts of pyperidine, compounds **9** were obtained in 5 hours in similar yields (60 – 78%). The obtained compounds were purified by further recrystallization from ethanol.

Compounds **9** show in the ir spectra, the presence of three bands for the NH groups at 3475 –3300 cm^{-1} and the

Scheme 1

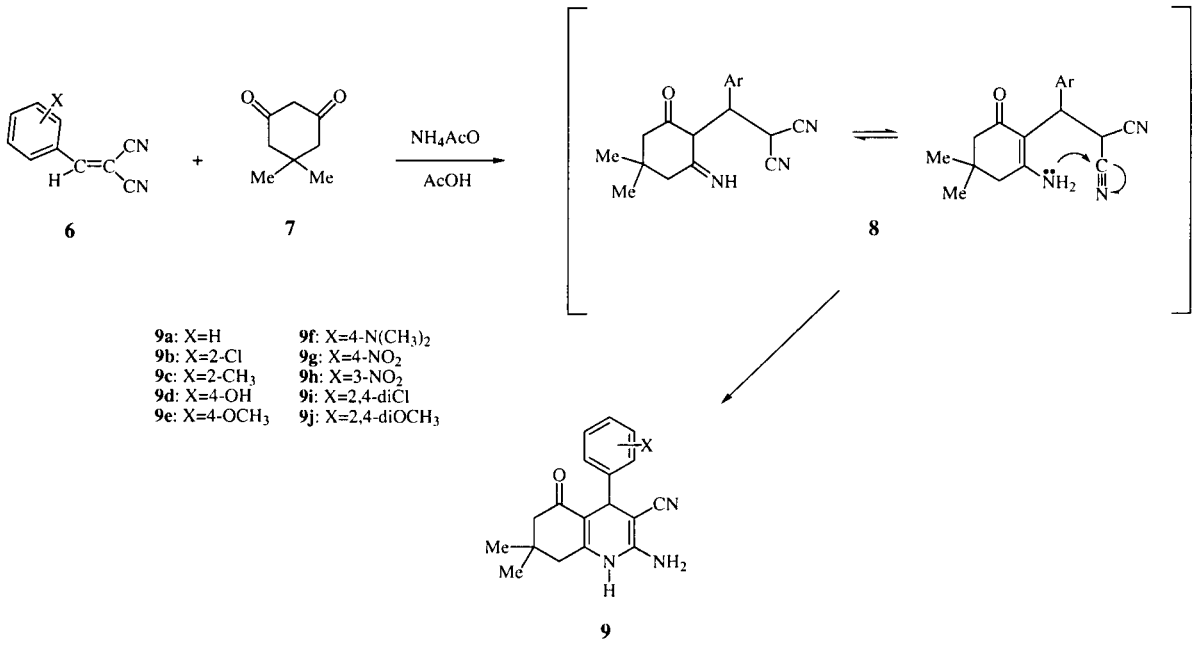


Table 1

Compound	C2	q2	C3	q3	C8a	q8a	C4a	q4a
9a	158.6	0.170	58.2	-0.182	162.5	0.073	112.8	-0.225
9b	159.5	0.168	57.6	-0.181	164.0	0.073	112.6	-0.225
9c	158.2	0.168	58.2	-0.179	162.4	0.072	113.4	-0.225
9d	155.8	0.160	58.6	-0.178	161.8	0.071	113.2	-0.221
9e	157.9	0.166	58.7	-0.183	162.2	0.077	113.7	-0.225
9f	158.4	0.163	59.0	-0.179	161.9	0.075	113.3	-0.224
9g	158.6	0.171	57.0	-0.195	163.2	0.069	111.7	-0.221
9h	157.6	0.190	58.9	-0.205	163.2	0.096	112.1	-0.243
9i	158.7	0.172	56.1	-0.183	163.4	0.074	111.4	-0.228
9j	156.9	0.156	58.1	-0.170	159.2	0.064	110.1	-0.220

Charge Density Values and Chemical Shifts for Atoms Involved in the push pull Effect for Compounds **9a-j**.

Formation of the hexahydroquinolines **9** takes place as depicted in Scheme 1 through a Hantzsch-like mechanism by conjugated addition of the enamine intermediate, obtained from dimedone (**7**) and ammonium acetate, to the arylidenemalononitrile derivatives (**6**) followed by imino-enamino tautomerism (**8**) and subsequent 6-*exo-trig* cyclization [16].

bands corresponding to the C≡N and C=O groups at ~2220 and 1680 cm^{-1}, respectively.

The ^1H NMR spectra of compounds **9** show the NH proton of the pyridine ring at ~9.3 ppm and the NH_2 at δ ~ 7.0 both appearing as a singlet. The proton on C4 appears 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 except in **9b, 9d** and **9f** that appear as an AB system (J ~ 18 Hz).

The two olefinic double bonds between C2 (δ 156 - 159) and C3 (δ 57 - 68), and between C8a (δ 159 - 164) and C4a (δ 110 - 118) in compounds **9a-j** 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 [17]. In Table 1 appears the assignment for the carbon atoms involved in the push-pull effect and the charge density values calculated by AM1 method. The calculated charge values for the olefinic carbons are in good agreement with the experimental ^{13}C-NMR spectra observed for the push-pull system. 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 (see experimental section).

X-ray crystallography has been widely used for the structural and conformational analysis of DHPs [18] and determination of the favored conformation has allowed for accounting of pharmacological effects of the DHP ring [19].

We report herein the first computational study on the structure of hexahydroquinolines. The results of semiempirical molecular orbital calculations (AM1) are compared with the data obtained by *ab initio* (HF/3-21G) and X-ray crystallography study for **9h**.

Initially, we have carried out the determination of the favored geometry for all novel compounds **9a-j** with the semiempirical AM1 method. This method reveals in all cases, that the 1,4-dihydropyridine ring adopts a flattened boat conformation, in which the carbon atoms of the olefinic double bonds are in the same boat main plane and the aryl substituent on C4 in a pseudoaxial disposition (see Figure 1).

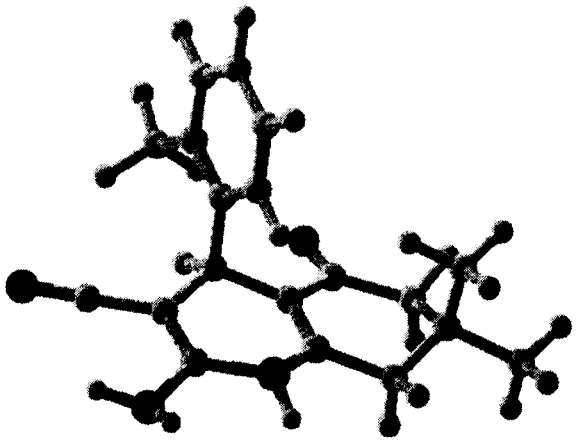
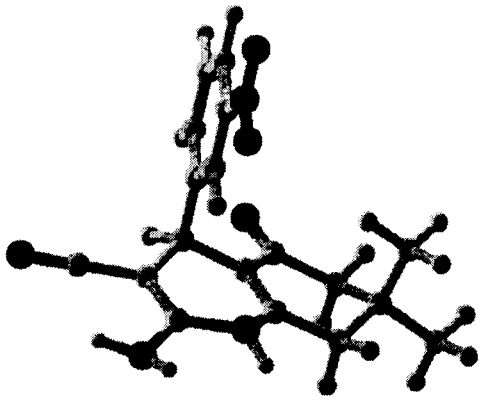
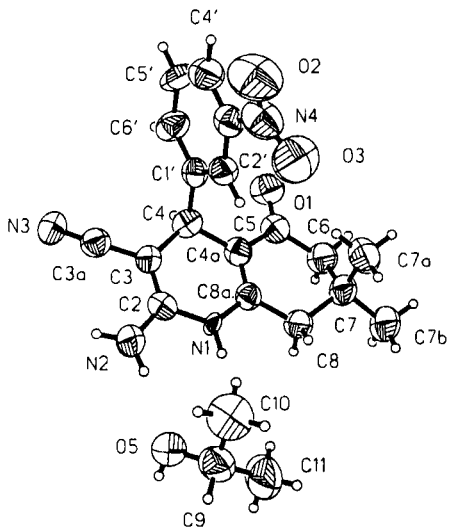


Figure 1



A



B

Figure 2

The calculated (AM1) heats of formation for compounds **9a-j** reveal that conformer *sp* (synperiplanar), with the substituent on the phenyl ring on the same side as the hydrogen of the dihydropyridine (CH), is slightly more stable than conformer *ap* (antiperiplanar) in which the substituent on the phenyl ring lies above the dihydropyridine ring (~ 0.3 – 3.3 kcal/mol). The only exception was compound **9h** (X = 3-NO_2) for which both AM1 and *ab initio* HF/3-21G calculations predicted that the conformer is 1.7 and 1.8 kcal/mol, respectively, more stable than conformer *sp*. This finding is in agreement with the conformation found by X-ray analysis.

The crystal structure of compound **9h** (Figure 2 B) shows that the 1,4-dihydropyridine ring has a boat conformation with puckering parameters [20] Q = 0.107(5)Å, θ = 107.3(3)° and φ = 3(3)°, with two local pseudo-mirror planes, one running along N1···C4 and the

Table 2

Compound	9a	9b	9c	9d	9e	9f	9g	9i	9j
Bond Distances									
N1-C2	1.418	1.418	1.418	1.424	1.418	1.418	1.428	1.418	1.419
C2-C3	1.382	1.382	1.382	1.381	1.383	1.382	1.386	1.383	1.381
C3-C4	1.500	1.500	1.500	1.499	1.498	1.498	1.519	1.499	1.500
C4-C4a	1.499	1.500	1.500	1.502	1.501	1.500	1.500	1.500	1.500
C4a-C8a	1.364	1.364	1.364	1.367	1.364	1.364	1.380	1.364	1.364
C8a-N1	1.403	1.403	1.402	1.407	1.404	1.404	1.407	1.403	1.404
C4-C1'	1.506	1.507	1.508	1.505	1.505	1.504	1.503	1.507	1.504
C5-O	1.238	1.238	1.239	1.239	1.239	1.239	1.239	1.238	1.238
Valence Angles									
C2-N1-C8a	118.0	117.9	118.0	116.9	117.8	117.8	116.2	117.9	117.7
C3-C4-C4a	111.0	111.0	111.0	110.5	110.8	110.9	109.9	111.0	100.8
C3-C-N	179.2	179.6	179.3	179.1	179.2	179.1	179.3	179.4	179.3
C4a-C5-O	122.2	122.3	122.2	122.6	122.3	122.3	121.3	122.3	122.5
Dihedral Angles									
N1-C2-C3-C4	-0.9	-0.8	-1.4	-1.5	-1.0	-0.9	-0.9	-0.7	-0.9
C2-C3-C4-C4a	18.4	18.5	17.2	22.4	20.0	19.0	25.3	18.7	19.0
C3-C4-C4a-C8a	-19.9	-19.4	-19.1	-22.8	-21.7	-20.2	-23.9	-19.6	-20.1
C4-C4a-C8a-N1	2.1	1.0	2.2	-0.8	2.4	1.5	-3.4	0.9	1.3
C4a-C8a-N1-C2	19.3	20.3	18.4	27.1	20.8	20.5	32.3	20.6	20.7
C8a-N1-C2-C3	-20.6	-21.0	-20.0	-27.2	-22.4	-21.5	-30.5	-21.2	-21.6
$\Sigma\|\rho\|$ [b]	81.2	81.0	78.3	101.8	88.3	83.6	116.3	81.7	83.6
C4a-C5-C6-C7	-19.8	-23.0	-17.4	-27.3	-24.6	-22.4	-27.4	-23.9	-22.3
C8a-C4a-C5-O	168.9	171.8	166.7	176.3	173.0	171.1	178.7	172.6	171.2
C2-C3-C4-C1'	-105.4	105.3	-106.2	-101.8	-103.9	-104.8	-99.4	-105.1	-104.8
C3-C4-C1'-C2'	69.7	-102.4	-117.0	35.4	37.2	43.6	56.5	78.2	-104.1

[a] The numbering scheme is shown in Figure 2 (B). [b] $\Sigma|\rho|$ Sum of the modular values of internal dihedral angles of dihydropyridine ring [23]. Most Relevant Bond Distances, Valence Angles and Dihedral Angles for the Most Stable Conformation of Compounds B[a] Calculated by Semiemprical AM1. Bond distances are given in Å and angles in degrees. (Standard Deviations in parenthesis).

other through the midpoints of C2-C3 and C4a-C8a bonds. This is in agreement with the previously reported conformation of the 1,4-DHP moiety in an analogous structure [21]. Although the unexpected antiperiplanar geometry of the nitro substituent on the phenyl ring is not usual, it has been found in some other related molecules [22]. The dihedral angle between the least-squares planes of the phenyl ring and the 1,4-DHP moiety is 85.9(3)° and the mean Csp2---Csp2 bond length within this ring is 1.374(7)Å. The cyclohexanone ring has an intermediate half-chair/envelop conformation [Q = 0.446(6)Å, θ = 124.2(8)° and φ = 346.(9)°] with a local pseudo-twofold axis through the midpoints of the C6-C7 and C4a-C8a bonds, and a local pseudo-mirror plane along C7···C4a. The cyano group at C3 is coplanar with the endocyclic double bond as a consequence of the π conjugation.

This compound crystallizes with an isopropanol molecule in the asymmetric unit that helps to stabilize the crystal structure. There is one hydrogen bond between the isoproanol molecule and the N2 amine group of the host molecule [N2...O5 2.836(6)Å] and two intermolecular hydrogen bonds [N2...N3 (9-x, -y+1, -z) 3.069(7) Å, O5...O1 (x, -1+y, z) 2.949(6) Å]. The host molecules are linked via these hydrogen bonds forming dimers. The hydrogen bond pattern does not impose large conformational differences between this compound and previously studied analogous [21]. The preference for forming intermolecular strong hydrogen bonds may be decisive for the conformation adopted in the crystal lattice.

The geometrical features predicted for the minimum energy conformations of **9a-j** calculated by AM1 (Table 2) and by AM1 and *ab initio* calculations and determined by X-ray analysis for **9h**, are listed in Table 3, showing the most relevant bond distances, valence angles and dihedral angles. In general, the predicted values (AM1) compared quite well with the experimental data despite AM1 calculations overestimate the double bond distance value and underestimate the single bond distance values.

As we can see in Table 2, the C4a-C4-C1'-C6' torsion angle shows that the plane of the phenyl ring is approximately bisecting the pyridine ring. This inter-ring orientation is preferred in the *ortho* phenyl substituted derivatives (**9b**, **9c**, **9i**, and **9j**) because it minimizes the steric strain imposed by the *ortho* phenyl substituent. The value of the dihedral angle C1'-C4-C3-C2, lower than 120°, shows that the phenyl group is in axial position.

It can be observed in Table 3, that X-ray analysis shows a more flattened boat conformation for the

Table 3

Compound 9h Bond Distances	AM1	AM1 [b]	HF/321G	X-ray
N1-C2	1.415	1.411	1.381	1.343(7)
C2-C3	1.385	1.388	1.347	1.357(7)
C3-C4	1.497	1.496	1.518	1.514(7)
C4-C4a	1.500	1.500	1.518	1.516(7)
C4a-C8a	1.365	1.367	1.330	1.327(7)
C8a-N1	1.400	1.395	1.384	1.360(6)
C4-C1'	1.507	1.508	1.535	1.517(7)
C5-O1	1.239	1.239	1.220	1.226(8)
O...N2	-	2.178	-	2.836(6)
Valence Angles				
C2-N1-C8a	118.4	118.9	121.6	119.6(4)
C3-C4-C4a	111.0	111.0	109.8	108.0(4)
C3-C3a-N3	179.1	179.2	179.24	178.5(6)
C4a-C5-O1	122.2	122.4	121.46	120.7(5)
Dihedral Angles				
N1-C2-C3-C4	-0.3	-1.2	-6.9	-3.0(8)
C2-C3-C4-C4a	20.5	20.8	22.0	10.0(7)
C3-C4-C4a-C8a	-21.4	-22.0	-22.6	-10.4(7)
C4-C4a-C8a-N1	2.2	3.4	8.1	4.0(8)
C4a-C8a-N1-C2	20.3	18.9	10.3	4.7(7)
C8a-N1-C2-C3	-21.1	-19.8	-10.8	-5.1(7)
$\Sigma\|\rho\|$ [c]	85.8	86.1	80.7	37.2(7)
C4a-C5-C6-C7	-27.9	-28.8	-34.4	-33.5(8)
C8a-C4a-C5-O	176.3	176.6	179.6	-179.7(6)
C2-C3-C4-C1'	-103.2	-102.7	-99.37	-112.3(6)
C3-C4-C1'-C2'	36.6	50.2	34.0	71.5(6)

[a]The numbering scheme is shown in Figure2 (B). [b]Calculated considering the presence of an isopropanol solvent molecule. [c]Sum of the modular values of internal dihedral angles of dihydropyridine ring [23]. Most Relevant Bond Distances, Valence Angles and Dihedral Angles for the Most Stable Conformation of Compound **9h**[a]. Bond Distances are Given in Å and Angles in Degrees. (Standard Deviations in parenthesis).

pyridine ring than that predicted from theoretical calculations {see in Tables 2 and 3 the internal dihedral angles of the dihydropyridine ring ($\Sigma|\rho|$ 23])}. This fact could be accounted for by the presence of a solvate molecule in the crystal structure that form hydrogen bonds with its host, tending to planarize the molecules to form a more compact crystal packing.

Theoretical calculations were also performed considering the presence of an isopropanol solvent molecule at the semiempirical AM1 level. The calculated data were not significantly modified in comparison with the values obtained for the isolated molecule, as it is shown in Table 3.

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* (HF/3-21G) and also semiempirical methods (AM1) are useful for predicting conformational features on this class of compounds.

In summary, the 2-amino-3-cyanohexahydroquinolines prepared exhibit geometrical and conformational features of interest for further biological studies in the search of calcium modulatory properties.

EXPERIMENTAL

Melting points were determined in a capillary tube in a 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 machine. 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: ethyl acetate (8:2) as the 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 [24] were carried out with the semiempirical AM1 method by using the MOPAC 7.0 [25] molecular orbitals set. Previously, the molecular geometry was optimized by using Allinger's Molecular Mechanics [26] with PCMODEL program [27]. The *ab nitio* calculations were carried out with Gaussian 94 program [28]. Calculations were performed on an IBM-RS6000.

3-Arylidenemalononitriles (**6a-j**).

These compounds were obtained by following the method previously reported in the literature [29].

2-Amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolines (**9a-j**).

General Procedure.

A mixture of dimedone (5,5-dimethyl-1,3-cyclohexanedione) (40 mmol), the appropriate arylidenemalononitrile (40 mmol) and ammonium acetate (42 mmol) in acetic acid (40 ml) was heated at reflux for 5 hours and then poured into ice-water. The solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from ethanol.

2-Amino-3-cyano-7,7-dimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline (**9a**).

Compound **9a** was obtained as a white solid (ethanol) in 70% yield, mp 237-238°; IR (KBr): 3396, 3325 and 3300 (NH), 2200 (CN), 1679 (C=O), 1660 (C=C), 1604 (C=C) cm^{-1}; ^1H NMR (dimethylsulfoxide-d_6) δ 9.27 (s, 1H, NH), 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 (dimethylsulfoxide-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 293 (M^+, 14%), ($[M+H]^+$, 66), 217 ($[M+H]^+$–C_6H_5, 100), 161 (24).

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.70; H, 6.53; N, 14.32. Found: C, 73.53; H, 6.41; N 14.47

2-Amino-4-(2-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**9b**).

Compound **9b** was obtained as a white solid (ethanol) in 72% yield, mp 211-213°; ir(potassium bromide): 3392, 3327 and 3255 (NH), 2198 (CN), 1681 (C=O), 1664 (C=C), 1604 (C=C) cm^{-1}; ^1H NMR (dimethylsulfoxide-d_6) δ 9.31 (s, 1H, NH), 7.35 (d, 1H, 3'-H, J = 7.6), 7.24 – 7.14 (m, 3H, 4'-H, 5'-H, 6'-H), 7.03 (s, 2H, NH_2), 4.68 (s, 1H, 4-H), 2.41 (d, 1H, 8-H, J = 18 Hz), 2.33 (d, 1H, 8'-H, J = 18 Hz), 2.17 (d, 1H, 6-H, J = 15.0 Hz), 2.10 (d, 1H, 6'-H, J = 15.0 Hz), 1.03 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR (dimethylsulfoxide-d_6) δ 196.5 (CO), 164.0 (C8a), 159.5 (C2), 142.2 (C1'), 132.9 (C2'), 130.8 (C6'), 130.3 (C3') 129.0 (C4'), 128.3 (C5'), 120.1 (CN), 112.6 (C4a), 57.6 (C3), 50.7 (C6), 40.5 (C8), 33.6 (C4), 32.6 (C7), 29.2 (CH_3), 27.7 (CH_3); ms: m/z 397/399 (M^+, <1%), 328/330 ($[M+H]^+$, 11/4), 217 ($[M+H]^+$–C_6H_4Cl, 62), 161 (17), 293 (100), 227 (23).

Anal. Calcd. for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82. Found: C, 65.67; H, 5.61; N 12.79.

2-Amino-3-cyano-7,7-dimethyl-(2'-methylphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**9c**).

Compound **9a** was obtained as a white solid (ethanol) in 65% yield, mp 212-213°; IR (KBr): 3475, 3375, 3300 and 3255 (NH), 2196 (CN), 1681 (C=O), 1660 (C=C) cm^{-1}; ^1H NMR (dimethylsulfoxide-d_6) δ 8.89 (s, 1H, NH), 6.93 (s, 2H, NH_2), 6.97 (d, 1H, H3'), 7.16 – 7.05 (m, 3H, 4'-H, 5'-H, 6'-H), 4.50 (s, 1H, 4-H), 2.56 (s, 3H, CH_3), 2.44 (br s, 2H, 8-H), 2.21 (d, 1H, 6-H, J = 16.3 Hz), 2.14 (d, 1H, 6'-H, J = 16.3 Hz), 1.05 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (dimethylsulfoxide-d_6) δ 195.7 (CO), 162.4 (C8a), 158.2 (C2), 143.5 (C1'), 134.7 (C2'), 129.8 (C3'), 127.8 (C6'), 127.2 (C4'), 126.7 (C5'), 119.7 (CN), 113.4 (C4a), 58.2 (C3), 56.0 (CH_3), 49.9 (C6), 39.4 (C8), 32.7 (C4), 31.8 (C7), 28.3 (CH_3), 26.7 (CH_3); ms: m/z 307 (M^+, 14%), 308 ($[M+H]^+$, 53), 293 (19), 217 ($[M+H]^+$–$C_6H_4CH_3$, 100), 161 (22), 133 (11).

Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.24; H, 6.89; N, 13.67. Found: C, 74.50; H, 6.40; N 13.49.

2-Amino-3-cyano-4-(4'-hydroxyphenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**9d**).

Compound **9d** was obtained as a white solid (ethanol) in 63% yield, mp 208-210°; IR (KBr): 3400, 3330 and 3300 (NH), 2196 (CN), 1683 (C=O), 1647 (C=C) 1610 (C=C), 1371 (CO) cm^{-1}; ^1H NMR (dimethylsulfoxide-d_6) δ 9.10 (s, 1H, NH), 6.93 (s, 2H, NH_2), 6.91 (d, 2H, 2'-H, 6'-H, J = 8.3 Hz), 6.70 (s, 1H, OH), 6.65 (d, 2H, 3'-H, 5'-H, J = 8.3 Hz), 4.06 (s, 1H, 4-H), 2.52 (d, 1H, 8-H, J = 17 Hz), 2.43 (d, 1H, 8'-H, J = 17 Hz), 2.24 (d, 1H, 6-H, J = 15.8 Hz), 2.08 (d, 1H, d, 6'-H, J = 15.8 Hz), 1.02 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (dimethylsulfoxide-d_6) δ 195.5 (CO), 161.8 (C8a), 158.2 (C4'), 155.8 (C2), 135.0 (C1'), 128.0 (C2', C6'), 119.5 (CN), 114.8 (C3', C5'), 113.2 (C4a), 58.6 (C3), 49.9 (C6), 39.7 (C8), 34.6 (C4), 31.6 (C7), 28.3 (CH_3), 26.6 (CH_3); ms: m/z 309 (M^+, 27%), 310 (M^++H^+, 100), 217 ($[M+H]^+$–C_6H_4OH, 98), 161 (26), 293 (23), 227 (15).

Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.62; H, 6.21; N 13.72.

2-Amino-3-cyano-7,7-dimethyl-4-(4'-methoxyphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**9e**).

Compound **9e** was obtained as a white solid (ethanol) in 65% yield, mp 204-206°; IR (KBr): 3373, 3305 and 3255 (NH), 2198 (CN), 1683 (C=O), 1654 (C=C), 1606 (C=C), 1369 (CO), 1247 (CO) cm^{-1}; ^1H NMR (dimethylsulfoxide-d_6) δ 9.12 (s, 1H, NH), 7.03 (d, 2H, 2'-H, 6'-H, J = 8.6 Hz), 6.92 (s, 2H, NH_2), 6.82 (d, 2H, 3'-H, 5'-H, J = 8.6 Hz), 4.10 (s, 1H, 4-H), 3.68 (s, 3H, OCH_3), 2.44 (br s, 2H, 8-H), 2.23 (d, 1H, 6-H, J = 16.3 Hz), 2.06 (d, 1H, 6-H, J = 16.3 Hz), 1.01 (s, 3H, CH_3), 0.93 (s, 3H, CH_3); ^{13}C NMR (dimethylsulfoxide-d_6) δ 195.7 (CO), 162.2 (C8a), 158.4 (C4'), 157.9 (C2), 136.8 (C1'), 128.2 (C2', C6'), 119.8 (CN), 113.7 (C4a), 113.0 (C3', C5'), 58.7 (C3), 55.0 (CH_3), 50.0 (C6), 40.7 (C8) 34.7 (C4), 32.8 (C7), 28.4 (CH_3), 26.8 (CH_3); ms: m/z 323 (M^+, 27%), 324 (M^++H^+, 100), 309 (15), 217 ($[M+H]^+$–$C_6H_4OCH_3$, 74), 161 (22), 293 (47), 227 (<1).

Anal. Calcd. for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.62; H, 6.67; N 12.68.

2-Amino-3-cyano-7,7-dimethyl-4-(4'-*N*,*N*-dimethyl-aminophenyl)-5-oxo-1,4,5,6,7,8-hexa hydroquinoline (**9f**).

Compound **9f** was obtained as a pale yellow solid (ethanol) in 65% yield, mp 224-226°; IR (KBr): 3381, 3319, 3253 and 3209 (NH), 2191 (CN), 1681 (C=O), 1654 (C=C), 1608 (C=C), 1338 (CN) cm^{-1}; ^1H NMR (dimethylsulfoxide-d_6) δ 9.03 (s, (1H, NH), 6.93 (d, 2H, 2'-H, 6'-H, J = 8.5 Hz), 6.87 (s, 2H, NH_2), 6.62 (d, 2H, 3'-H, 5'-H, J = 8.3 Hz), 4.04 (s, 1H, 4 H), 2.83 (s, 6H, 2 CH_3), 2.52 (d, 1H, 8-H, J = 18.0 Hz), 2.42 (d, 1H, 8'-H, J = 18.0 Hz), 2.23 (d, 1H, 6-H, J = 16.1 Hz), 2.06 (d, 1H, 6'-H, J = 16.1 Hz), 1.02 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (dimethylsulfoxide-d_6) δ 195.7 (CO), 161.9 (C8a), 158.4 (C2), 149.3 (C4'), 132.6 (C1'), 127.8 (C2', C6'), 120.0 (CN), 113.3 (C4a), 112.4 (C3', C5'), 59.0 (C3), 50.1 (C6), 43.1 (CH_3), 42.9 (CH_3), 40.0 (C8), 34.3 (C4), 31.8 (C7),

28.6 (CH_3), 26.8 (CH_3); ms: m/z 336 (M^+, 30%), 337 ([M+H]$^+$, 100), 293 (23), 271 (20), 217 ([M+H]$^+$–$C_6H_4N(CH_3)_2$, 11), 161 (7).

Anal. Calcd. for $C_{20}H_{24}N_4O$: C, 71.40; H, 7.19; N, 16.65. Found: C, 71.22; H, 6.97; N 16.88.

2-Amino-3-cyano-7,7-dimethyl-4-(4'-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**9g**).

Compound **9g** was obtained as a pale yellow solid (ethanol) in 75% yield, mp 209-210°; IR (KBr): 3450, 3373 and 3332 (NH), 2198 (CN), 1685 (C=O), 1670 (C=C), 1637 (C=C), 1525 and 1350 (NO_2) cm^{-1}; ^{1}H NMR (dimethylsulfoxide-d_6) δ 9.31 (s, 1H, NH), 8.16 (d, 2H, 2'-H, 6'-H, J = 8.0 Hz), 7.43 (d, 2H, 3'H, 5'-H, J = 8.0 Hz), 7.19 (s, 2H, NH_2), 4.35 (s, 1H, 4-H), 2.52 (br s, 2H, 8-H), 2.25 (d, 1H, 6-H, J = 16.0 Hz), 2.08 (d, 1H, 6'-H, J = 16.0 Hz), 1.02 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (dimethylsulfoxide-d_6) δ 195.7 (CO), 163.2 (C8a), 158.6 (C2), 152.3 (C4'), 146.3 (C1'), 128.7 (C2',C6'), 123.7 (C3', C5'), 119.4 (CN), 111.7 (C4a), 57.0 (C3), 49.7 (C6), 39.5 (C8), 35.5 (C4), 31.8 (C7), 28.3 (CH_3), 27.9 (CH_3); MS: m/z 338 (M^+, <1%), 339 ($M+H]^+$, 62), 332 (25), 292 (15), 217 ([M+H]$^+$–$C_6H_4NO_2$, 100), 161 (26).

Anal. Calcd. for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.62; H, 5.41; N 16.62.

2-Amino-3-cyano-4-(3'-nitrophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**9h**).

Compound **9h** was obtained as a pale yellow solid (ethanol) in 70% yield, mp 197-198°C; IR (KBr): 3450, 3373 and 3332 (NH), 2198 (CN), 1685 (C=O), 1670 (C=C), 1637 (C=C), 1525 and 1350 (NO_2) cm^{-1}; ^{1}H NMR (dimethylsulfoxide-d_6) δ 9.29 (s, 1H, NH), 8.09 (d, 1H), 8.00 (s, 1H), 7.59 (m, 2H), 7.15 (s, 2H, NH_2), 4.32 (s, 1H, H4), 2.48 (br s, 2H, 8-H), 2.22 (d, 1H, 6-H, J = 16.0 Hz), 2.14 (d, 1H, 6'-H, J = 16.0 Hz), 1.02 (s, 3H, CH_3), 0.95 (s, 3H, CH_3); ^{13}C NMR (dimethylsulfoxide-d_6) δ 196.8 (CO), 163.2 (C8a), 157.6 (C2), 150.5 (C3'), 143.3 (C1'), 136.8 (C6'), 130.1 (C5'), 125.8 (C2'), 121.1 (C4'), 119.4 (CN), 118.1 (C4a), 58.9 (C3), 49.7 (C6), 39.5 (C8), 35.5 (C4), 31.8 (C7), 28.1 (CH_3), 26.8 (CH_3); ms: m/z 338 (M^+, 3%), 339 ([M+H]$^+$, 12), 332 (8), 308 (100, M^+-NO), 292 (15), 217 ([M+H]$^+$–$C_6H_4NO_2$, 87), 161 (12).

Anal. Calcd. for $C_{18}H_{18}N_4O_3$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.71; H, 5.47; N 16.73.

X-ray Structure Analysis.

Crystals of **9h** were grown by slow evaporation from a mixture of isopropanol and ethanol (1:1). Crystals lost solvent after crystallization, so it was necessary to protect the crystal used for the X-ray experiment from the atmosphere. The crystal was bathed with silicon grease and mounted in the diffractometer for measurements.

Crystal Data.

A prismatic colorless crystal (0.52 x 0.18 x 0.04 mm) was used for the analysis. $C_{18}H_{18}N_4O_3 \cdot C_3H_8O$, M = 398.46, Triclinic, a = 8.7510(10), b = 10.330(2), c = 12.102(2) Å, α = 80.300(2), β = 88.840(10), γ = 82.070(10)°, V = 1068.0(3) Å^3 (by least-squares refinement on diffractometer angles for 22 automatically centred reflections with $7.49 < \theta < 27.46$ °, λ = 1.54178 Å, T = 293(2) K), space group P $\bar{1}$, Z = 2, D_c = 1.239 g cm^{-3}, μ = 0.71 mm^{-1}. Detailed crystallographic data for compound **9h** have been deposited at the Cambridge Crystallographic Data Centre and are available on request.

Data Collection and Processing.

A Siemens P4 four-circle diffractometer with graphite monochromated and Cu-Kα radiation was used for data collection. 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 $K\alpha_1$ and $K\alpha_2$ positions; 4675 reflections measured ($3.71 < \theta < 69.16°$, $-9 < h < 1$, $-12 < k$ 12, $-14 < l <$ 14), 3832 unique (merging R = 0.07), $F^2 \geq 2\sigma(F)^2$, which were retained in all calculations. Empirical absorption correction, *via* ψ scan was applied [30]. Three standard reflections were monitored every 100 reflections (intensity decay: none).

Structure Solution and Refinement.

The structure was solved by direct methods and Fourier synthesis. Non-H atoms were refined anisotropically by full-matrix least-squares techniques (final values: R = 6.6%, wR = 16.7%). 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 Ueq of their parent atoms. Data collection: XSCANS [31]. Cell refinement: XSCANS [31]. Data reduction: XSCANS [31]. Program(s) used to solve structure: SHELXS97 [32]. Program(s) used to refine structure: SHELXL97 [33]. Molecular graphics: DIAMOND [34] Software used to prepare material for publication: PLATON [35].

2-Amino-3-cyano-4-(2',4'-dichlorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinolines (**9i**).

Compound **9i** was obtained as a pale yellow solid (ethanol) in 74% yield, mp 190-192°; IR (KBr): 3361, 3321 and 3332 (NH), 2191 (CN), 1685 (C=O), 1658 (C=C), 1606 (C=C) cm^{-1}; ^{1}H NMR (dimethylsulfoxide-d_6) δ 9.27 (s, 1H, NH), 7.63 (d, 1H, 3'-H, J = 2.1 Hz), 7.36 (dd, 1H, 5'-H, J = 2.1 Hz and J = 8.4 Hz), 6.99 (d, 1H, 6'-H, J = 8.4 Hz), 6.93 (s, 2H, NH_2), 4.06 (s, 1H, 4-H), 2.42 (br s, 2H, 8-H), 2.26 (d, 1H, 6-H, J = 16.0 Hz), 2.19 (d, 1H, 6'-H, J = 15.0 Hz), 1.05 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}C NMR (dimethylsulfoxide-d_6) δ 195.6 (CO), 163.4 (C8a), 158.7 (C2), 140.8 (C1'), 133.1 (C2'), 131.8 (C4'), 131.5 (C6'), 128.8 (C3'), 127.7 (C5'), 119.1 (CN), 111.4 (C4a), 56.1 (C3), 49.9 (C6), 39.4 (C8) 32.7 (C4), 31.8 (C7), 28.4 (CH_3), 27.0 (CH_3); ms: m/z 361/363/365 (M^+, <1%), 362/364/366 (M^++H^+, 100/33/9), 327/328 (100/30), 271 (20), 217 ([M^++H^+]-$C_6H_3Cl_2$, 62), 161 (17).

Anal. Calcd. for $C_{18}H_{17}Cl_2N_3O$: C, 59.68; H, 4.73; N, 11.60. Found: C, 59.54; H, 4.61; N 11.72.

2-Amino-3-cyano-7,7-dimethyl-4-(2',4'-dimethoxyphenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline (**9j**).

Compound **9j** was obtained as a pale yellow solid (ethanol) in 55% yield, mp 178-180°; IR (KBr): 3400, 3373 and 3200 (NH), 2202 (CN), 1664 (C=O), 1608 (C=C), 1587 (C=C), 1490 (CO) cm^{-1}; ^{1}H NMR (dimethylsulfoxide-d_6) δ 9.12 (s, 1H, NH), 6.70 (d, 1H, 6'-H, J = 8.4 Hz), 6.53 (d, 1H, 3'-H, J = 2.2 Hz), 6.39 (dd, 1H, 5'-H, J = 8.4 and J = 2.2 Hz), 6.93 (s, 2H, NH_2), 4.07 (s, 1H, 4-H), .3.85 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.14 (br s, 2H, 8-H), 2.03 (d, 1H, 6-H, J = 16.0 Hz), 1.80 (d, 1H, 6'-H, J = 16.0 Hz), 1.02 (s, 3H, CH_3), 0.94 (s, 3H, CH_3); ^{13}C NMR (dimethylsulfoxide-d_6) δ 193.9 (CO), 159.2 (C8a), 157.4

(C2'), 157.0 (C4'), 156.9 (C2), 129.1 (C6'), 119.6 (CN), 118.8 (C1'), 110.1 (C4a), 104.6 (C5'), 98.4 (C3'), 58.1 (C3), 55.5 (OCH_3), 54.9 (OCH_3), 50.1 (C6), 39.8 (C8), 32.9 (C4), 31.9 (C7), 29.3 (CH_3), 26.3 (CH_3); ms: m/z 353 (M^+, 100%), 138 (79).

Anal. Calcd. for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.82; H, 6.41; N 11.72.

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