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A new synthetic approach to *N*-substituted 1,4-dihydropyridines

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Abstract—Some novel *N*-substituted 1,4-dihydropyridines (DHPs) (**15a–d**) have been synthesized by reaction of 2-amino-5-formyl-4*H*-pyran (**10**) with primary amines. Formation of 1,4-DHPs involves ring cleavage of the 4*H*-pyran ring by nucleophilic attack of the respective amine and subsequent 6-*exo-dig* cyclization. Treatment of the pyran system **10** with hydrazines under the same reaction conditions leads, however, to the corresponding hydrazone derivatives **12a**,**b**. Two different reaction routes are observed depending whether the amine or hydrazine derivative is used as nucleophilic reagent. A competition between 1,4 versus 1,2 addition reaction pathway is proposed.

1. Introduction

Since Nifedipine (**1**) was successfully introduced in the market at the beginning of 1975 for the treatment of coronary diseases,[1] there has been a great deal of attention in the study of 4-aryl-1,4-dihydropyridines (DHPs) as a consequence of their pharmacological activity as the most important class of the calcium channel modulators.[2–4] To this day, many chemical modifications have been carried out on the DHP ring looking for drugs with longer bioavailability or greater tissue selectivity. The presence of different substituents[5] or heteroatoms[6] (**2**) has allowed an expansion of the structure–activity relationship thus getting a better insight into the molecular interactions at the receptor level. The knowledge of stereochemical/conformational requirements for activity[7] requires the study of other related analogues of the DHP ring. In this regard, it has been reported[8] the synthesis of modified structures bearing nitro and fused lactone groups on the DHP ring (**3**,**4**). These exhibit calcium agonist effects opposite to those of the calcium antagonists **1** and **2**.

Starting from a pyran ring suitably functionalyzed with a reactive conjugated carbonyl system (**10**) and different primary amines, we report in this paper a novel simple one-step synthesis of previously unknown DHPs (**15a–d**) with a substituted nitrogen atom. A complex mechanistic pathway is proposed to explain this transformation. The synthesis of hydrazone derivatives (**12a**,**b**) starting from the same pyran system **10** and hydrazines is also discussed (Chart 1).

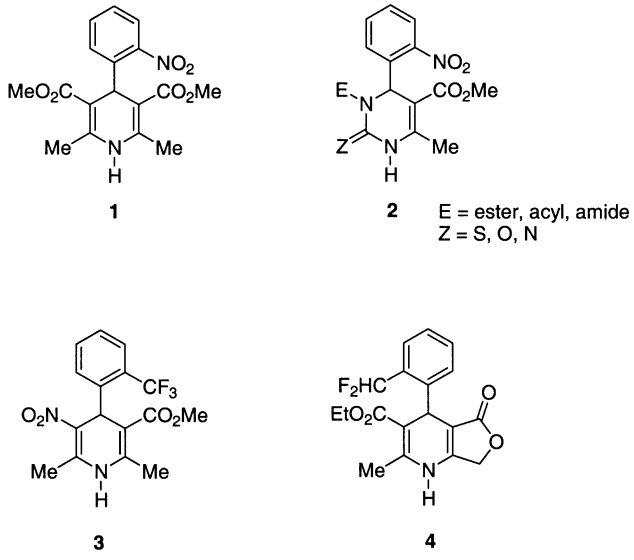

Chart 1.

2. Results and discussion

The preparation of the new 5-formyl-4*H*-pyran **10** is depicted in Scheme 1. The synthetic sequence starts from commercially available propargylic alcohol (**5**) by oxidation with cromium trioxide/sulfuric acid in butanone at 0°C to afford propynal (**6**) which was obtained in a considerably lower yield than described in the literature (91%),[9] despite different attempts carried out in order to optimize this reaction step (solvents with higher boiling point such as pentanone, different Vigreux columns in the purification process, mechanical stirring instead of magnetic stirring, PCC as the oxidizing reagent).

Keywords: 1,4-dihydropyridines; cyclization; hydrazines; 4*H*-pyrans.
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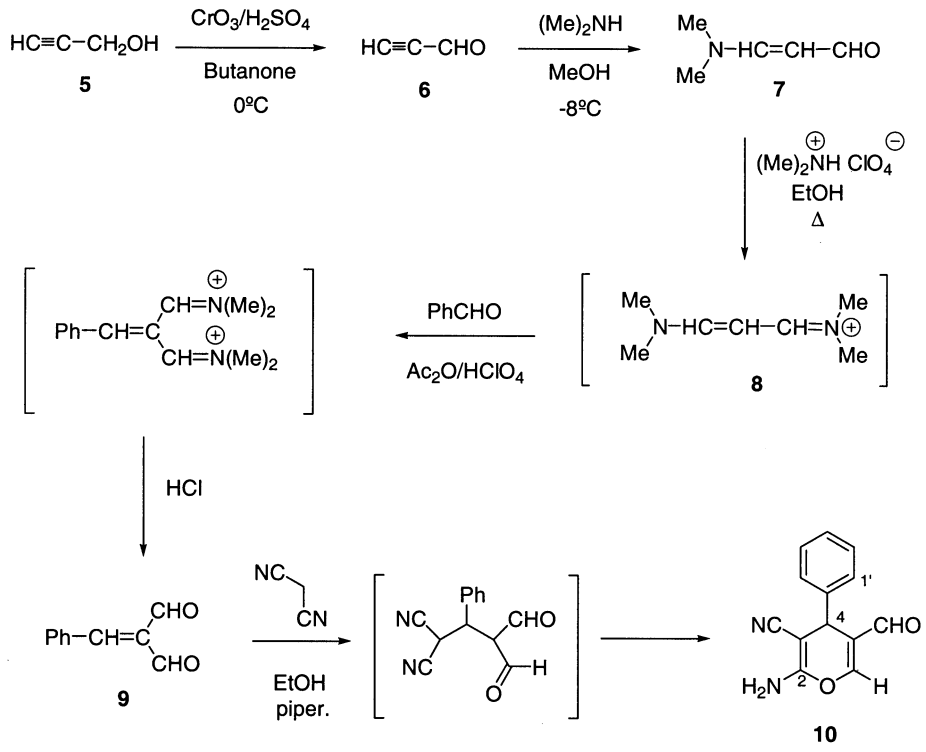


Scheme 1.

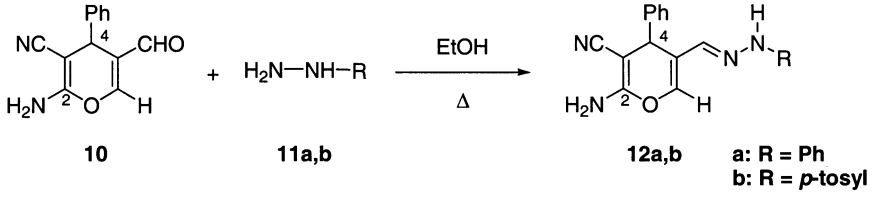
Addition of dry dimethylamine to a solution of propynal (**6**) in dry methanol yielded 3-dimethylaminopropenal (**7**),[10] which on reaction with dimethylamine perchlorate gave 3-dimethylaminopropenylidenedimethylammonium perchlorate (**8**).[10] Treatment of **8** with benzaldehyde in acetic anhydride at 0°C using perchloric acid as the catalyst, followed by acidic hydrolysis afforded benzylidenemalonaldehyde (**9**).[11] Finally, Michael addition of malononitrile to the dialdehyde **9** led to 5-formyl-4*H*-pyran (**10**) in a moderate yield (46%).

It should be pointed out that formation of the corresponding 1,2-addition product to the carbonyl group was not observed to any extent, which is in agreement with other previously reported results.[12]

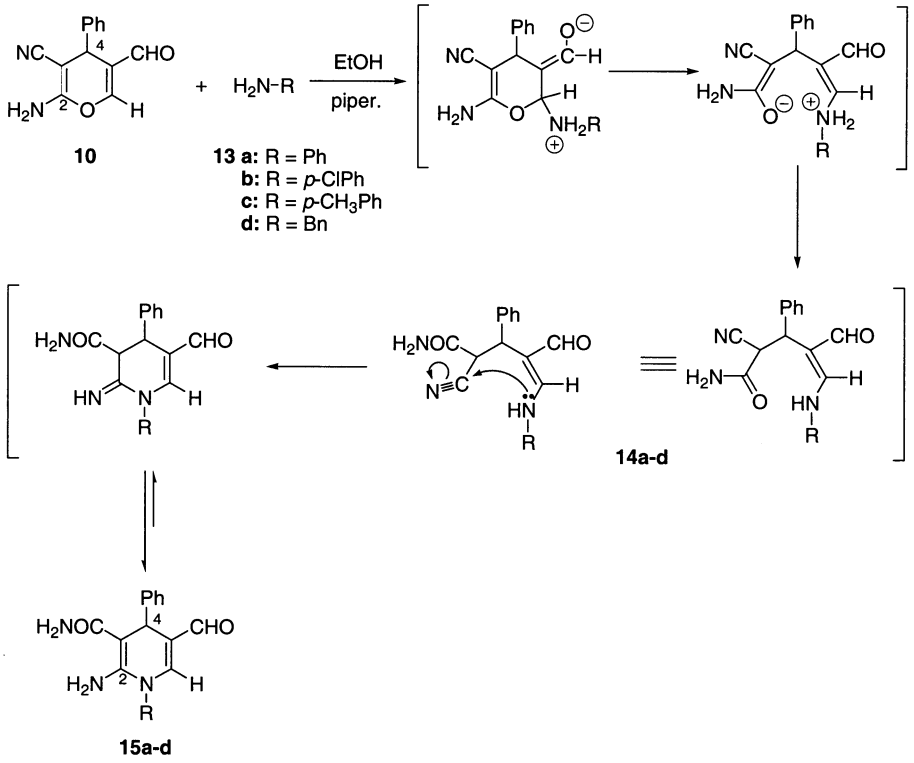
Pyran **10** shows in the IR spectrum the presence of the π-conjugated formyl and cyano groups at 1665 and 2210 cm^{-1}, respectively. In the ^1H NMR spectrum the aldehyde group appears as a singlet at 9.36 ppm. The amino group gives rise to a signal at 4.58 ppm as a broad singlet. The hydrogen atom at position C-6 in the 4*H*-pyran ring appears in the aromatic region at 7.31–7.22 ppm. The signal at 4.42 ppm reveals the presence of the proton (H-4) attached to the sp^3 carbon atom of the 4*H*-pyran ring.

Due to the scarcity of available information on the ^{13}C NMR spectra of these compounds,[13] we have carried out the assignments of the signals of the pyran system **10** based on a ^{13}C NMR study of 4*H*-pyran derivatives[14] and by recording off-resonance and DEPT experiments. It is worth mentioning the signal at 57.6 ppm due to the olefinic carbon C-3 of the pyran ring. The chemical shift of this carbon is rather unusual for a sp^2 carbon, as a result of the combined effects of the O, NH_2 and CN groups, and is probably among the lowest ever observed for an ethylenic carbon. This finding has been previously observed in other related molecules.[15]

The novel 2-amino-4*H*-pyran bearing an easily functionalizable carboxaldehyde group at C-5 position (**10**) can be considered as a key compound for further derivatizations. In this regard, we decided to study the behavior of such 4*H*-pyran ring in the presence of different hydrazine and amine derivatives. Thus, treatment of formyl containing pyran **10** with hydrazines (**11a**,**b**) in refluxing ethanol led to the corresponding hydrazone derivatives **12a**,**b** by means of a 1,2 addition process to the conjugated carbonyl system (Scheme 2). Compounds **12a**–**b** were obtained as stable solids in moderate yields (41–65%).



Scheme 2.



Scheme 3.

The IR spectra of derivatives **12a**,**b** show several bands at 3480–3180 cm^{-1} corresponding to both hydrazone and amino groups. The stretching vibration of the conjugated cyano group appears at 2200 cm^{-1}. The protons HC═N and HC═C can be observed as multiplets in the aromatic region of the ^1H NMR spectra. Compound **12b** shows the NH_2 protons at 6.89 ppm as a broad singlet. The proton on C-4 appears at 4.40–4.13 ppm. Off-resonance and DEPT experiments have allowed the assignments of the signals of the ^{13}C NMR spectra. Neither of the above techniques allows us to establish unambiguously the signals corresponding to both C-6 and HC═N, which appear in the off-resonance spectrum, as doublets with a coupling constant 160–196 Hz. The final assignment has been achieved taking into account the theoretical values which predict a higher deshielding for the HC═N proton.

In view of the fact that reaction with hydrazines brings about the formation of hydrazone derivatives **12**, treatment of pyran **10** with different amines (**13a**–**d**) should lead to the corresponding Schiff bases. However, in this case, the novel 1,4-dihydropyridines **15a**–**d** were isolated as the only reaction products in 30–51% yields (Scheme 3).

The reaction can be rationalized by the cleavage of the pyran ring by nucleophilic attack of the amine at the electron deficient C-6 position, followed by the favored 6-*exo-dig* cyclization.[16] This cyclization involves nucleophilic attack by the amino group at the cyano group in the non-isolated open-chain intermediate **14**. The final imino–enamino tautomerism gives the dihydropyridine systems **15a**–**d**.

The different behavior of the pyran system **10** towards hydrazines **11** and amines **13** can be explained considering the nature of the nucleophilic reagent employed in the reaction. Thus, when hydrazine compounds are used, a 1,2 addition process to the carbonyl system takes place due to the high stability of the corresponding hydrazones which quickly precipitate from the reaction mixture. On the other hand, the Schiff bases resulting from the 1,2 addition of amines to the formyl containing pyran **10** should not be as stable as the hydrazones and a 1,4 competitive conjugated addition is preferred, yielding the final 1,4-dihydropyridines **15a**–**d**.

The IR spectra of compounds **15a**–**d** show two bands at 1680–1625 cm^{-1} corresponding to both formyl and carbamoyl groups. ^1H NMR and ^{13}C NMR data of the novel compounds **15a**–**d** are given in Tables 1 and 2, respectively.

Table 1. ^1H NMR spectroscopic data of *N*-substituted 1,4-dihydropyridines (**15a**–**d**)

Compound	NH_2	$CONH_2$	CHO	H-4	Arom/H-6
15a	4.98 (s)	6.84 (s)	9.15 (s)	4.82 (s)	7.53–7.24 (m)
15b	5.00 (s)	6.82 (s)	9.18 (s)	4.83 (s)	7.57–7.26 (m)
15c	5.00 (s)	6.83 (s)	9.15 (s)	4.80 (s)	7.51–7.26 (m)
15d	4.95 (s)	6.83 (s)	9.17 (s)	4.80 (s)	7.43–7.21 (m)/6.78 (s)

Table 2. ^{13}C NMR spectroscopic data of *N*-substituted 1,4-dihydropyridines (**15a–d**)

Compounds	C-2	C-3	C-4	C-5	C-6	$CONH_2$	CHO	C_{ipso}[a]
15a	149.9	80.7	34.8	120.4	147.9	171.4	188.7	146.6
15b	150.5	80.7	36.6	121.3	145.6	172.1	188.3	144.8
15c	151.0	80.1	36.6	120.7	146.4	172.3	188.4	145.1
15d	150.2	80.9	34.4	120.0	148.8	164.4	171.3	146.3

[a] Carbon atom of the R group directly linked to the nitrogen atom of the 1,4-dihydropyridine.

The signals of the ^{13}C NMR spectra have been unambiguously assigned by off-resonance and DEPT experiments and, in some cases, by HMBC techniques.

In summary, we report the synthesis of *N*-substituted 1,4-dihydropyridines **15a–d** as novel modified DHP rings by ring transformation of the formyl-containing 2-amino 4*H*-pyran **10** by reaction with amines. This pyran system, synthesized for the first time by means of a multi-step reaction procedure, has also been allowed to react with hydrazines to form the respective hydrazone derivatives (**12a**,**b**) in which the pyran skeleton is preserved.

The novel *N*-substituted 1,4-DHPs are suitably functionalized for further chemical transformations.

3. Experimental

3.1. General

Melting points were determined in a capillary tube in a Thermolab apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were measured with a Varian Unity XL-300 and a Bruker AC-200. The IR spectra were recorded with a Perkin–Elmer 781 Spectrophotometer. Microanalyses were performed by the Servicio de Microanálisis of Universidad Complutense de Madrid.

3.1.1. 2-Amino-3-cyano-4-phenyl-4*H*-pyran-5-carboxaldehyde (10). A solution of benzylidenemalonaldehyde[11] (0.01 mol) in ethanol (30 mL) containing a few drops of piperidine was treated with malononitrile (0.66 g, 0.01 mol). The reaction mixture was stirred for a few minutes. The solid product so formed, was collected by filtration and crystallized from ethanol. 46% yield, mp 192°C (dec.). IR (KBr disk) ν (cm^{-1}): 3360, 3310, 3195 (N–H), 2880, 2210 (C≡N), 1665 (C=O), 1605, 1495, 1455, 1405, 1380, 1300, 1225, 1195. ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.36 (s, 1H, CHO), 7.31–7.22 (m, 6H, 5 ArH and HC=C), 4.58 (s broad, 2H, NH_2), 4.42 (s, 1H, H-4). ^{13}C NMR (DMSO, 75 MHz) δ: 189.7 (CHO), 158.7 (C-2), 157.3 (C-6), 143.6 (C-1′), 128.4 (C-2′), 127.4 (C-3′), 126.9 (C-4′), 121.6 (C-5), 119.6 (CN), 57.6 (C-3), 34.9 (C-4). $C_{13}H_{10}O_2N_2$: calcd. C 69.02; H 4.46; N 12.38; found C 68.54; H 4.61; N 12.30.

3.2. Synthesis of hydrazone and *p*-tosylhydrazone derivatives (12a,b). General procedure

A suspension of 2-amino-3-cyano-4-phenyl-4*H*-pyran-5-carboxaldehyde (**10**) (100 mg, 0.44 mmol) in ethanol (15 mL) was heated until total solution of the starting material. The corresponding hydrazine derivative (**11a**,**b**) (0.44 mmol) was added and the reaction mixture was refluxed for a variable time (2–5 h), then allowed to cool to room temperature. The solid product formed was collected by filtration in good purity.

3.2.1. Phenylhydrazone of 2-amino-3-cyano-4-phenyl-4*H*-pyran-5-carboxaldehyde (12a). 65% yield, mp 215–217°C. IR (KBr disk) ν (cm^{-1}): 3480, 3380, 3290 (N–H and NH_2), 2200 (C≡N), 1670 (C=C), 1625, 1590 (C=N and H_2N–C=C≡N), 1575, 1495, 1400, 1260, 1240, 1180, 1125, 910. ^1H NMR (DMSO, 300 MHz) δ: 9.99 (s, 1H, NH), 7.35–6.65 (m, 14H, 10 ArH, NH_2, HC=N and HC=C), 4.40 (s, 1H, H-4). ^{13}C NMR (DMSO, 75 MHz) δ: 159.1 (C-2), 144.8, 144.7 (arom), 140.0 (HC=N), 132.5 (C-6), 128.5, 127.7, 126.9, 125.9 (arom), 119.9 (CN), 117.9 (arom), 117.6 (C-5), 111.2 (arom), 57.0 (C-3), 36.7 (C-4). $C_{19}H_{16}ON_4$: calcd C 72.15; H 5.06; N 17.72; found C 72.04; H 5.10; N 17.79.

3.2.2. *p*-Tosylhydrazone of 2-amino-3-cyano-4-phenyl-4*H*-pyran-5-carboxaldehyde (12b). 41% yield, mp 198–199°C. IR (KBr disk) ν (cm^{-1}): 3440, 3340, 3180 (N–H and NH_2), 2200 (C≡N), 1670 (C=C), 1640, 1600 (C=N and H_2N–C=C≡N), 1500, 1410, 1320, 1235, 1170, 1060, 960. ^1H NMR (DMSO, 300 MHz) δ: 11.10 (s, 1H, NH), 7.45–7.01 (m, 11H, 9 ArH, HC=N and HC=C), 6.89 (s broad, 2H, NH_2), 4.13 (s, 1H, H-4), 2.35 (s, 3H, CH_3). ^{13}C NMR (DMSO, 75 MHz) δ: 159.0 (C-2), 144.1, 143.5, 143.4 (arom), 142.5 (HC=N), 135.5 (C-6), 129.0, 127.8, 126.7, 126.5, 126.1 (arom), 119.6 (CN), 116.3 (C-5), 56.7 (C-3), 35.9 (C-4), 20.1 (CH_3). $C_{20}H_{18}O_3N_4S$: calcd C 60.91; H 4.57; N 14.21; found C 60.88; H 4.79; N 14.08.

3.3. Synthesis of *N*-substituted 1,4-dihydropyridine derivatives (15a–d). General procedure

A suspension of 2-amino-3-cyano-4-phenyl-4*H*-pyran-5-carboxaldehyde (**10**) (100 mg, 0.44 mmol) in ethanol (15 mL) was heated until total solution. The corresponding amine (**13a–d**) (0.44 mmol) was added and the reaction mixture was refluxed for 2–6 h, then allowed to cool to room temperature. The solid that precipitated was isolated by filtration with high purity.

3.3.1. 2-Amino-3-carbamoyl-5-formyl-1,4-diphenyl-1,4-dihydropyridine (15a). 38% yield, mp 209–211°C. IR (KBr disk) ν (cm^{-1}): 3480, 3400, 3310, 2870, 2840, 1675, 1650, 1585, 1470, 1385, 1255, 1190, 1180, 1080. ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.15 (s, 1H, CHO), 7.53–7.24 (m, 11H, 10 ArH and H-6), 6.84 (s, 2H, $CONH_2$), 4.98 (s, 2H, NH_2), 4.82 (s, 1H, H-4). ^{13}C NMR (DMSO, 50 MHz) δ: 188.7 (CHO), 171.4 ($CONH_2$), 149.9 (C-2), 147.9 (C-6), 146.6 (C_{arom}–N), 139.0, 129.8, 128.4, 127.7, 127.4, 127.3, 125.7 (arom), 120.4 (C-5), 80.7 (C-3), 34.8 (C-4). $C_{25}H_{22}ON_4$: calcd C 76.11; H 5.62; N 14.21; found C 75.97; H 5.29; N 13.97.

3.3.2. 2-Amino-3-carbamoyl-1-(*p*-chlorophenyl)-5-formyl-4-phenyl-1,4-dihydropyridine (15b). 40% yield, mp 188–189°C. IR (KBr disk) ν (cm^{-1}): 3480, 3460, 3140, 2830, 1680, 1655, 1580, 1480, 1400, 1250, 1190, 1095, 1020. ^1H

NMR ($CDCl_3$, 300 MHz) δ: 9.18 (s, 1H, CHO), 7.57–7.26 (m, 10H, 9 ArH and H-6), 6.82 (s, 2H, $CONH_2$), 5.00 (s, 2H, NH_2), 4.83 (s, 1H, H-4). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 188.3 (CHO), 172.1 ($CONH_2$), 150.5 (C-2), 145.6 (C-6), 144.8 (C_{arom}–N), 137.0, 135.7, 130.7, 129.1, 128.8, 127.6, 127.1 (arom), 121.3 (C-5), 80.7 (C-3), 36.6 (C-4). $C_{19}H_{16}O_2N_3Cl$: calcd C 64.59; H 4.53; N 11.90; found C 64.28; H 4.38; N 11.89.

3.3.3. 2-Amino-3-carbamoyl-5-formyl-4-phenyl-1-(*p*-tolyl)-1,4-dihydropyiridine (15c). 30% yield, mp 199–200°C. IR (KBr disk) ν (cm^{-1}): 3440, 3360, 1650, 1570, 1510, 1475, 1410, 1375, 1330, 1255, 1190, 1110, 1030. ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.15 (s, 1H, CHO), 7.51–7.26 (m, 10H, 9 ArH and H-6), 6.83 (s, 2H, $CONH_2$), 5.00 (s, 2H, NH_2), 4.80 (s, 1H, H-4), 2.45 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 188.4 (CHO), 172.3 ($CONH_2$), 151.0 (C-2), 146.4 (C-6), 145.1 (C_{arom}–N), 140.0, 135.8, 131.0, 128.7, 127.6, 127.5, 127.0 (arom), 120.7 (C-5), 80.1 (C-3), 36.6 (C-4), 21.3 (CH_3). $C_{20}H_{19}O_2N_3$: calcd C 72.07; H 5.71; N 12.61; found C 71.76; H 6.06; N 12.44.

3.3.4. 2-Amino-1-benzyl-3-carbamoyl-5-formyl-4-phenyl-1,4-dihydropyridine (15d). 51% yield, mp 200–202°C. IR (KBr disk) ν (cm^{-1}): 3450, 3340, 3160, 1670, 1625, 1490, 1460, 1390, 1260, 1205, 1190, 1150, 1100. ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.17 (s, 1H, CHO), 7.43–7.21 (m, 10H, ArH), 6.83 (s, 2H, $CONH_2$), 6.78 (s, 1H, H-6), 4.95 (s, 2H, NH_2), 4.87 (d, 1H, J=26.4 Hz, CH_2), 4.82 (d, 1H, J=26.4 Hz, CH_2), 4.80 (s, 1H, H-4). ^{13}C NMR (DMSO, 75 MHz) δ: 171.3 (CHO), 164.4 ($CONH_2$), 150.2 (C-2), 148.8 (C-6), 146.3 (C_{arom}–CH_2N), 136.6, 128.1, 127.2, 127.1, 126.9, 126.8, 125.3 (arom), 120.0 (C-5), 80.9 (C-3), 51.3 (CH_2N), 34.4 (C-4). $C_{20}H_{19}O_2N_3$: calcd C 72.07; H 5.71; N 12.61; found C 71.82; H 5.88; N 12.28.

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