Synthesis of Some C-3,4,5-Substituted 2,6-Dimethyl-1,4-dihydropyridines (4-DHPs)

Patricio A. Navarrete-Encina
Faculty of Chemical and Pharmaceutical Sciences, Advanced Organic Synthesis Laboratory, University of Chile, Santiago, Chile

Juan A. Squella
Faculty of Chemical and Pharmaceutical Sciences, Bioelectrochemistry Laboratory, University of Chile, Santiago, Chile

J. Carbajo and B. Conde
Faculty of Experimental Sciences, Huelva, Spain

Luis J. Núñez-Vergara
Faculty of Chemical and Pharmaceutical Sciences, Bioelectrochemistry Laboratory, University of Chile, Santiago, Chile

Abstract: A series of C-3,4,5-substituted 2,6-dimethyl-1,4-dihydropyridines (1,4-DHPs) with pharmacological properties were prepared by a variation from the classical Hantzsch synthesis. The procedure involves treatment of the respective aldehyde with either ethyl-3-aminocrotonate or 3-aminocrotonitrile in anhydrous acetic acid at temperatures not exceeding 60°C, thus minimizing by-product formation. The structures of title compounds were elucidated by ^{1}H NMR, ^{13}C NMR, FTIR, and elemental analysis.

Keywords: cyclization, 1,4-dihydropyridines, nitrogen heterocycles

Address correspondence to Patricio A. Navarrete-Encina, Faculty of Chemical and Pharmaceutical Sciences, Advanced Organic Synthesis Laboratory, University of Chile, Casilla 233, Santiago R.M., Chile. E-mail: pnavarre@uchile.cl

INTRODUCTION

Dihydropyridine (DHP) calcium antagonists decrease vascular contractility and arterial tone by modulating the activity of the L class of voltage-gated calcium channels in a variety of tissues.[1] Other additional effects such antioxidant activity in various experimental models have been reported.[2a,b] In line with this, our laboratory has recently reported the direct reactivity between some commercial and newly synthesized 1,4-DHP derivatives with free radicals.[3a–c]

1,4-Dihydropyridines were first synthesized by Hantzsch[4a,b] and over the years a great variety of 1,4-DHPs have been synthesized that have different substitutions on C_2, C_3, C_4, C_5, and C_6 positions of the DHP ring.[5a,b,c]. Because the pharmacological prototype of 1,4-dihydropyridine, nifedipine, does not have optimum pharmacokinetic and pharmacodynamic characteristics, several attempts have been made to synthesize other drugs of this class with additional properties, such as antioxidants[6] and releasers of nitric oxide.[7a,b] The structure–activity relationship of the dihydropyridines indicated that most of the desired properties rely on the structural characteristics of the substituent at 4-position of the dihydropyridine nucleus, especially if that substituent is an aromatic phenyl ring. Introduction of electron-donating substituents and electron-withdrawing substituents produced relevant changes in pharmacological effects.[8a]

Particularly for optimal activity of 1,4-dihydropyridines as antagonists, some moieties are essential and can be summarized as (a) the presence of the intact 1,4-dihydropyridine ring, (b) the secondary nitrogen in the heterocycle, and (c) a space-filling substituent in *para*-position of the dihydropyridine ring; also (d) the presence of ester groups at 3- and 5-positions and methyl groups in 2- and 6-positions on the dihydropyridine ring are relevant to conserve the antagonistic effects of the derivatives.[9]

In this article, the synthesis of some 5-nitrofuryl DHPs derivatives was also included. The idea behind this structural variation was based on a previous knowledge that some commercial calcium channel blockers and other 1,4-dihydropyridines having a 5-nitrofuryl substituent displayed significant inhibitory effects on epimastigotes cultures of *Trypanosoma cruzi*.[10a–d] Considering that there is a need for new 1,4-DHPs, we have synthesized some C-3,4,5-substituted 2,6-dimethyl-1,4-DHPs that have the presence of at least one hydroxyl group in the aromatic ring at 4-position as a common structural characteristic, maintaining ethoxycarbonyl groups at positions 3 and 5, and others having a 5-nitrofuryl substituent at 4-position but different substituents at positions 3 and 5 of the DHP.

We failed in our attempts to synthesize the compounds using the conventional classical Hantszch's dihydropyridine synthesis (with the exception of compound **IX**) or obtained poor yields.

RESULTS AND DISCUSSION

Synthesis of the Derivatives

The 1,4-dihydropyridine compounds described in this work were synthesized by a procedure involving mixing ethylaminocrotonate or aminocrotonitrile and the respective aldehyde in anhydrous acetic acid. Although the Hantzsch synthesis was first published well more then a century ago, the dihydropyridines we synthesized cannot be directly obtained by the Hantzsch method, and all of them are new compounds (with the exception of compound **IX**, which was previously obtained using the classical Hantzsch synthesis).[11] The synthesized compounds are listed in Table 1 in accordance with Fig. 1. These dihydropyridines derivatives were identified and characterized by ^{1}H NMR and ^{13}C NMR spectroscopy using a 300-MHz spectrometer (Bruker, WM 300), infrared spectroscopy (FT-IR Paragon spectrometer, 100PC), and elemental analysis (Perkin Elmer, 240 B).

It was not possible to synthesize the 2-hydroxyphenyl derivative because of poor yields and by-product formation using either the classical Hantszch method or the variation just described. We are attempting an indirect synthetic route leading to the compound. Yields of 2,4-dihydroxyphenyl and 2,5-dihydroxyphenyl derivatives were also relatively poor (25% and 24% respectively). These results may be attributed to adduct formation in the case of the reaction of 2-hydroxyaldehydes and 3-aminocrotonitrile, as was previously reported for the reaction of 3-aminocrotononitrile with salicylaldehyde.[12] In that work, Hafiz describes the formation of a 2:2 adduct as the main reaction product, instead of the DHP derivative, as a result of a further reaction of the aldehyde with the DHP formed. Attempts to isolate the adduct failed.

Table 1. Synthesized compounds

Compound	R	R^1	R^2
I	3-Hydroxyphenyl	$-CO_2Et$	$-CO_2Et$
II	4-Hydroxyphenyl	$-CO_2Et$	$-CO_2Et$
III	2,4-Dihydroxyphenyl	$-CO_2Et$	$-CO_2Et$
IV	3,4-Dihydroxyphenyl	$-CO_2Et$	$-CO_2Et$
V	2,5-Dihydroxyphenyl	$-CO_2Et$	$-CO_2Et$
VI	3,5-Dihydroxyphenyl	$-CO_2Et$	$-CO_2Et$
VII	4-Hydroxy-3-Methoxyphenyl	$-CO_2Et$	$-CO_2Et$
VIII	3-Hydroxy-4-Methoxyphenyl	$-CO_2Et$	$-CO_2Et$
IX	2-Nitrofuro-5-yl	$-CO_2Et$	$-CO_2Et$
X	2-Nitrofuro-5-yl	-CN	-CN
XI	2-Nitrofuro-5-yl	-CN	$-CO_2Et$

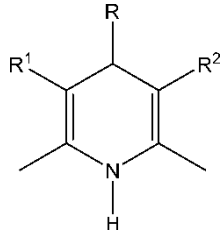
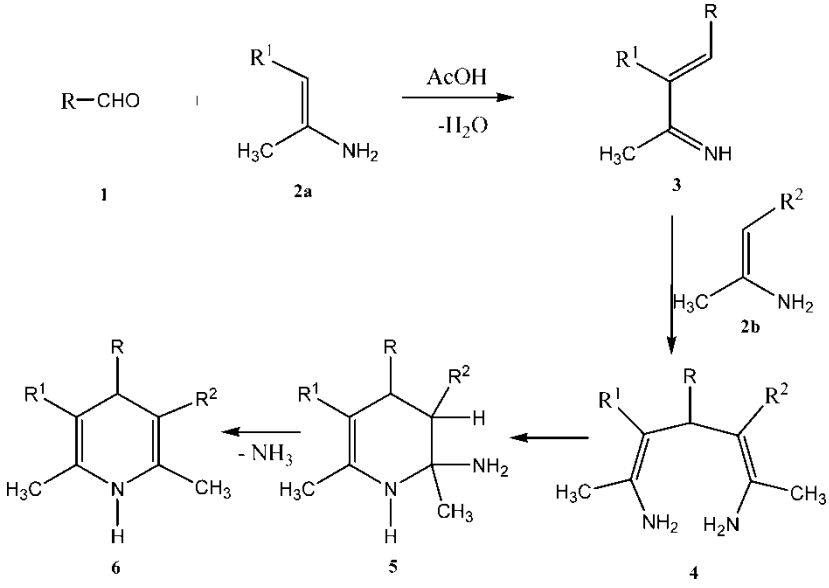


Figure 1. General chemical structure of the synthesized compounds.

A proposal for a general mechanism in the case of the 5-nitrofuryl-DHPs is described in Scheme 1; however, we did not isolate any of the intermediates. In this mechanism, the formation of compound **6** is assumed to be formed via initial condensation of the aldehyde **1** with one molecule of enamine **2a** to yield the unstable ylidene derivative **3**.[13] Reaction of the ylidene with another molecule of enamine **2b** yields the diamine **4**, which cyclizes into **5**. Loss of $NH_3$from **5** yields the final product **6**.

We have also concluded that the acid-catalyzed condensation reaction of one molecule of aldehyde and two molecules of enamines is a facile and efficient synthetic route to prepare these kinds, of 2,6-dimethyl-1,4-dihydropyridine derivatives.



Scheme 1. Proposed reaction pathway for the synthesis of the C-3,4,5-1,4-DHP derivatives. R, R^1, and R^2 are in accordance with Table 1.

EXPERIMENTAL

General Synthetic Procedure for Compounds I–X

A mixture of the respective aldehyde (0.016 mol) and ethylaminocrotonate (4.2 mL, 0.033 mol) is heated in an Erlenmeyer flask in a water bath until complete dissolution of the aldehyde. After addition of anhydrous acetic acid (15 mL), the mixture is further heated for 1 h. It is important not to exceed 60°C, thus minimizing by-product formation. The orange, viscous solution is filtered off and left until room temperature is attained. Water is carefully added (one drop at a time) until cloudiness is obtained; this is necessary to further precipitate the DHP. The solution is warmed again to obtain a clear solution and left overnight, thus permitting the slow crystallization of the derivative.

3-Cyano-5-ethoxycarbonyl-4-(2′-furyl-5′-nitro)-2,6-dimethyl-1,4-dihydropyridine (XI)

Ethyl 3-aminocrotonate (**A**) (0.65 g, 5 mmol), 3-aminocrotononitrile (**B**) (0.41 g, 5 mmol), and 5-nitro-2-furaldehyde (**C**) (0.63 g, 5 mmol) were separately dissolved in glacial acetic (10 mL). Solutions A and B were slowly added to solution C at 45°C, with vigorous stirring. The resulting mixture was gently heated for 15 min. The product was precipitated from the reaction mixture by careful addition of water. The precipitate was filtered off and washed with ethyl ether. The crude product was purified twice by column chromatography (adsorbent: silica gel; eluting solvents: EtOAc–petroleum ether 1:3; dichloromethane).

Physical Characterization

2,6-Dimethyl-3,5-dietoxycarbonyl-4-(3-dihydroxyphenyl)-1,4-dihydropyridine (**I**)

Yield: 85%. Mp: 188–191°C. IR (KBr): ν_{max} 3351.1, 1649.8, 1594.5, 1473.3, 1367.6, 1216.8, 1127.6, 1018.4. ^{1}H NMR (300 MHz, acetone-d6): 1.2 (t, $J = 7.0$, 6H, -CH_3); 2.3 (s, 6H, -CH_3); 2.9 (s, 1H, C-H); 4.1 (q, $J = 7.0$, 4H, -CH_2); 5.0 (s, 1H, -OH); 6.9 (m, 4H, aromatic); 7.8 (s, 1H, N-H). ^{13}C NMR (75 MHz, acetone-d6): ppm 13.8(2); 17.9(2); 29.0; 38.6; 58.9(2); 103.3(2); 114.4(2); 115.0; 119.1; 130.5; 144.3; 165.3; 205.5(2). Anal. calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.87; H, 6.69; N, 4.06.

2,6-Dimethyl-3,5-dietoxycarbonyl-4-(4-hydroxyphenyl)-1,4-dihydropyridine (**II**)

Yield: 70%. Mp: 232–235°C. IR (KBr): ν_{max} 3354.1, 1655.8, 1591.7, 1478.5, 1367.1, 1220.3, 1122.4, 1019.7. ^{1}H NMR (300 MHz, acetone-d6): 1.2

(t, $J = 7.0$, 6H, -CH_3); 2.3 (s, 6H, -CH_3); 2.9 (s, 1H, C-H); 4.1 (q, $J = 7.0$, 4H, -CH_2); 5.0 (s, 1H, -OH); 6.6 (d, $J = 8.0$, 2H, aromatic); 6.8 (d, $J = 8.0$, 2H, aromatic); 7.8 (s, 1H, N-H). ^{13}C NMR (75 MHz, acetone-d6): ppm 13.6(2); 18.3(2); 30.0; 37.9; 59.3(2); 107.5(2); 113.2(2); 118.0; 119.3; 132.7; 141.2; 161.4(2); 207.3. Anal. calcd. for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.16; H, 6.68; N, 4.08.

2,6-Dimethyl-3,5-dietoxycarbonyl-4-(2,4-dihydroxyphenyl)-1,4-dihydropyridine (**III**)

Yield: 25%. Mp: 190.0–193.0°C. IR (KBr): ν_{max} 3334.3, 1724.6, 1699.4, 1627.1, 1627.1, 1560.1, 1442.4, 1384.6, 1241.0, 1096.6, 1030.7, 839.1, 800.3. ^{1}H NMR (300 MHz, acetone-d6): δ 1.4 (t, $J = 7.0$, 6H, -CH_3); 2.6 (s, 6H, -CH_3); 2.7 (s, 1H, C-H); 4.9 (q, $J = 7.0$, 4H, -CH_2); 6.7 (s, 1H, 3-aromatic); 6.8 (d, $J = 6.4$, 1H, 5-aromatic); 8.4 (d, $J = 6.4$, 1H, 6-aromatic); 9.4 (s, 1H, N-H). ^{13}C NMR (75 MHz, acetone-d6): ppm 13.9(2); 18.8(2), 23.3; 29.4; 61.5(2); 96.0(2); 102.2; 112.2; 113.3; 126.6(2); 161.7; 197.5; 204.8(2). Anal. calcd. for $C_{19}O_6NH_{23}$: C, 63.15; H, 6.41; N, 3.87. Found: C, 63.39; H, 6.38; N, 3.89.

2,6-Dimethyl-3,5-dietoxycarbonyl-4-(3,4-dihydroxyphenyl)-1,4-dihydropyridine (**IV**)

Yield: 62%. Mp: 195.0–197.0°C. IR (KBr): ν_{max} 3411.3, 1666.4, 1470.9, 1370.8, 1274.6, 1218.8, 1123.0, 1020.7, 781.0. ^{1}H NMR (300 MHz, acetone-d6): δ 1.2 (t, $J = 7.0$, 6H, -CH_3); 2.3 (s, 6H, -CH_3); 3.0 (s, 1H, C-H); 4.0 (q, $J = 7.0$, 4H, -CH_2); 4.9 (s, 2H, -OH); 6.6 (s, 1H, 2-aromatic); 6.8 (d, $J = 7.0$, 1H, 6-aromatic); 7.6 (d, $J = 7.0$, 1H, 5-aromatic); 7.8 (s, 1H, N-H). ^{13}C NMR (75 MHz, acetone d6): ppm 13.8(2); 17.9(2); 29.0; 38.6; 58.9(2); 103.3(2); 114.4; 115.1; 119.1; 140.5; 144.3(2); 165.3; 205.5(2). Anal. calcd. for $C_{19}O_6NH_{23}$: C, 63.15, H, 6.41; N, 3.87. Found: C, 62.95; H, 6.40; N, 3.89.

2,6-Dimethyl-3,5-dietoxycarbonyl-4-(2,5-dihydroxyphenyl)-1,4-dihydropyridine (**V**)

Yield: 24%. Mp: 245°C. IR (KBr): ν_{max} 3256.7, 1726.7, 1687.1, 1555.1, 1464.1, 1399.7, 1231.3, 1102.2, 1028, 819.5. ^{1}H NMR (300 MHz, acetone-d6): δ 1.3 (t, $J = 7.0$, 6H, -CH_3); 2.5 (s, 6H, -CH_3); 2.6 (s, 1H, C-H); 4.3 (q, $J = 7.0$, 4H, -CH_2); 7.0 (d, $J = 5.8$, 1H, 4-aromatic); 7.1 (s, 2H, -OH); 7.1 (s, 1H, 6-aromatic); 7.8 (d, $J = 5.8$, 1H, 3-aromatic); 8.7 (s, 1H, N-H). ^{13}C NMR (75 MHz, acetone-d6): ppm 13.6(2); 18.7(2); 23.1; 29.1; 61.7(2); 95.7(2); 109.7; 117.4; 120.5; 149.2(2); 154.1; 159.9; 205.2(2). Anal. calcd. for $C_{19}O_6NH_{23}$: C, 63.15; H, 6.41; N, 3.87. Found: C, 63.39; H, 6.40; N, 3.86.

2,6-Dimethyl-3,5-dietoxycarbonyl-4-(3,5-dihydroxyphenyl)-1,4-dihydropyridine (**VI**)

Yield: 60%. Mp: 245–247°C. IR (KBr): ν_{max} 3403.7, 2979.6, 1672.2, 1599.0, 1473.1, 1373.3, 1221.2, 1156.5, 1004.2, 844.6, 800.3, 619.5. ^{1}H NMR (300 MHz, acetone-d6): δ 1.1 (t, $J = 7.0$, 6H, -CH_3); 2.2 (s, 6H, -CH_3); 2.9 (s, 1H, C-H); 3.9 (m, 4H, -CH_2); 4.8 (s, 2H, -OH); 6.2 (s, 1H, 4-aromatic); 7.7 (s, 2H, 2,6-aromatic); 7.8 (s, 1H, N-H). ^{13}C NMR (75 MHz, acetone-d6): ppm 13.8(2); 17.9(2); 29.0; 39.1; 59.0(2); 100.2(2); 102.8; 106.2; 144.6; 150.4(2); 158.0, 167.2; 205.4(2). Anal. calcd. for $C_{19}O_6NH_{23}$: C, 63.15; H, 6.41; N, 3.87. Found: C, 62.90; H, 6.43; N, 3.89.

2,6-Dimethyl-3,5-dietoxycarbonyl-4-(4-hydroxy-3-methoxyphenyl)-1,4-dihydropyridine (**VII**)

Yield: 80%. Mp: 161–163°C. IR (KBr): ν_{max} 3350.5, 2982.8, 1680.9, 1653.2, 1514.4, 1490.1, 1217.8, 1122.5. ^{1}H NMR (300 MHz, acetone-d6): δ 1.2 (t, $J = 7.0$, 6H, -CH_3); 2.3 (s, 6H, -CH_3); 3.7 (s, 3H, -OCH_3); 4.1 (q, $J = 7.0$, 4H, -CH_2); 5.0 (s, 1H, -CH); 7.0 (m, 4H, aromatic); 6.9 (s, 1H, N-H); 7.8 (s, 1H, -OH); ^{13}C NMR (75 MHz, acetone-d6): ppm 14.2(2); 19.6(2); 41.5; 55.9; 60.1(2); 96.8(2); 111.8; 117.6; 121.5; 133.2; 144.9; 148.86(2); 149.1; 166.1(2). Anal. calcd. for $C_{20}H_{25}NO_5$: C; 66.83; H; 7.01; N; 3.89. Found: C, 66.78; H, 6.98; N, 3.88.

2,6-Dimethyl-3,5-dietoxycarbonyl-4-(3-hydroxy-4-methoxyphenyl)-1,4-dihydropyridine (**VIII**)

Yield: 62%. Mp: 166–168°C. IR (KBr): ν_{max} 3316.2, 1669.1, 1483.3, 1372.0, 1270.6, 1114.9, 1016.4, 765.4. ^{1}H NMR (300 MHz, acetone-d6): δ 1.2 (t, $J = 7.0$, 6H, -CH_3); 2.7 (s, 6H, -CH_3); 3.7 (s, 3H, -OCH_3); 4.1 (q, $J = 7.0$, 4H, -CH_2); 4.9 (s, 1H, -CH); 6.3 (s, 1H, N-H); 7.1 (m, 3H, aromatic); 8.1 (s, 1H, -OH). ^{13}C NMR (75 MHz, acetone-d6): ppm 14.23(2); 19.60(2); 41.05; 58.05; 60.13(2); 98.82(2); 114.03; 115.32; 119.25; 133.52; 146.17; 149.10(2); 150.36; 166.13(2). Anal. calcd. for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.89. Found: C, 66.95; H, 7.03; N, 3.90.

2,6-Dimethyl-3,5- diethoxycarbonyl-4-(5′-nitro-2′-furyl)-1,4-dihydropyridine (**IX**)

Yield: 60%. Mp: 184.2°C. IR (KBr): ν_{max} 3346.7, 1704.3, 1656.0, 1517, 1487.9, 1400.0, 1355.0, 1211.9, 1114.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, $J = 7.1$, 6H, -CH_3); 2.36 (s, 6H, -CH_3); 4.15 (q, $J = 7.1$, 2H, -CH_2); 5.27 (s, 1H, -CH); 6.19 (s, 1H, N-H); 6.26 [d, $J = 3.4$, 1H, -CH (3-furyl)], 7.21 [d, $J = 3.4$, 1H, -CH (4-furyl)]. ^{13}C NMR (75 MHz, $CDCl_3$): ppm 166.8 (2); 162.7 (2); 146.4 (2); 113.2; 108.9, 99.0 (2); 60.2 (2); 34.6; 19.6

(2); 14.3 (2). Anal. calcd. for $C_{17}H_{20}N_2O_7$: C, 56.04; H, 5.53; N, 7.69. Found: C, 55.85; H, 5.54; N, 7.72.

3,5-Dicyano-2,6-dimethyl-4-(5′-nitro2′-furyl)-1,4-dihydropyridine (**X**)

Yield: 63%. Mp: 225°C. IR (KBr): ν_{max} 3369.2, 2205.9, 1665.8, 1536.3, 1505.1, 1393.1, 1358.8. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.07 (s, 6 H, -CH_3); 4.92 (s, 1H, -CH); 6.82 [d, $J = 3.8$, 1H, -CH (3-furyl)], 7.70 [d, $J = 3.8$, 1H, -CH (4-furyl)]; 9.81 (s, 1H, N-H). ^{13}C NMR (75 MHz, DMSO-d_6): ppm 159.7 (2); 158.0 (2); 121.8 (2); 114.9; 111.9; 73.8 (2); 33.9; 20.8 (2). Anal. calcd. for $C_{13}H_{10}N_4O_3$: C; 57.78; H; 3.73; N; 20.73. Found: C; 57.75; H; 3.73; N; 20.65.

3-Cyano-5-ethoxycarbonyl-2,6-dimethyl-4-(5′-nitro-2′-furyl)-1,4-dihydropyridine (**XI**)

Yield: 80%. Mp: 161.9°C. IR (KBr): ν_{max} 3317.9, 2199.4, 1664.3, 1638.5, 1527.1, 1493.1, 1383.0, 1355.5, 1257.0, 1115.7. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, $J = 7.1$, 3H, -CH_3); 2.18 [s, 3H, -CH_3 (2)]; 2.38 [s, 3H, -CH_3 (6)]; 4.12 (q, $J = 7.1$, 2H, -CH_2); 4.90 (s, 1H, -CH); 6.04 (s, 1H, N-H); 6.38 [d, $J = 3.7$, 1H, -CH (3-furyl)], 7.24 [d, $J = 3.7$, 1H, -CH (4-furyl)]. ^{13}C NMR (75 MHz, $CDCl_3$): ppm 166.2; 160.0 (2); 147.6; 146.3; 118.6; 113.0; 109.5; 97.6; 81.8; 60.5; 35.9; 19.7; 18.5; 14.2. Anal. calcd. for $C_{15}H_{15}N_3O_5$: C, 56.78; H, 4.76; N, 13.24. Found: C, 56.56; H, 4.77; N; 13.19.

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REFERENCES

1. Godfrain, T. Cardioselectivity of calcium antagonists. *Cardiovas. Drugs Therap.* **1994**, *8*, 353–364.
2. (a) Mak, I. T.; Kramer, J. H.; Weglicki, W. B. Antioxidant properties of active and inactive isomers of nicardipine in cardiac membranes, endothelial-cells, and perfused rat hearts. *Cor. Artery Disc.* **1992**, *3* (11), 1095–1103; (b) Mason, R. P.; Mak, I. T.; Trumbore, M. W.; Mason, P. E. Antioxidant properties of calcium antagonists related to membrane biophysical interactions. *Am. J. Cardiol.* **1999**, *84*, 16L–22L.
3. (a) Ortiz, M. E.; Nuñez-Vergara, L. J.; Camargo, C.; Squella, J. A. Oxidation of Hantzsch 1,4-dihydropyridines of pharmacological significance by electrogenerated superoxide. *Pharm. Res.* **2004**, *21* (3), 428–435; (b) Yañez, C.; López-Alarcón, C.; Camargo, C.; Valenzuela, V.; Squella, J. A.; Nuñez-Vergara, L. J. Structural effects on the reactivity 1,4-dihydropyridines with alkylperoxyl

radicals and ABTS radical cation. *Bioorg. Med. Chem.* **2004**, *12* (9), 2459–2468; (c) Nunez-Vergara, L. J.; López-Alarcón, C.; Navarrete-Encina, P. A.; Atria, A. M.; Camargo, C.; Squella, J. A. Electrochemical and EPR characterization of 1,4-dihydropyridines: Reactivity towards alkyl radicals. *Free Rad. Res.* **2003**, *37* (1), 109–120.

4. (a) Stout, D. M.; Meyers, A. I. Recent advances in the chemistry of dihydropyridines. *Chem. Rev.* **1982**, *82*, 223–243; (b) Eisner, U.; Kuthan, J. The chemistry of dihydropyridines. *Chem. Rev.* **1972**, *72* (1), 1–42.
5. (a) Ilavsky, D.; Milata, V. Syntheses and spectral properties of unsymmetrically 3,5-disubstituted 2,6-dimethyl-1,4-dihydropyridines. *Collect. Czech. Chem. Comm.* **1996**, *61*, 1233–1243; (b) Zenouz, A. M.; Oskuie, M. R.; Mollazadeh, S. Synthesis of novel asymmetrical 1,4-dihydropyridine derivatives. *Synth. Commun.* **2005**, *35* (22), 2895–2903; (c) Zenouz, A. M.; Allahverdi, S. S.; Raissossadat, M.; Sadeghi, Q. Synthesis of the C-2 functionalized 1,4-dihydropyridines. *Asian J. Chem.* **2005**, *17* (4), 2639–2643.
6. López-Alarcón, C.; Navarrete, P.; Camargo, C.; Squella, J. A. Nuñez-Vergara, L. J. Reactivity of 1,4-dihydropyridines toward alkyl, alkylperoxyl radicals, and ABTS radical cation. *Chem. Res. Toxicol.* **2003**, *16* (2), 208–215.
7. (a) Velasquez, C.; Vo, D.; Knaus, E. E. Syntheses, calcium channel modulation effects, and nitric oxide release studies of O-2-alkyl-1-(pyrrolidin-1-yl)-diazen-1-ium-1,2-diolate-4-aryl(heteroaryl)-1,4-dihydro-2,6-dimethyl-3-nitropyridine-5-carboxylates. *Drug. Dev. Res.* **2003**, *60* (3), 204–216; (b) Di Stilo, A.; Visentin, S.; Cena, C.; Gasco, A. M.; Ermondi, G.; Gasco, A. New 1,4-dihydropyridines conjugated to furoxanyl moieties, endowed with both nitric oxide-like and calcium channel antagonist vasodilator activities. *J. Med. Chem.* **1998**, *41* (27), 5393–5401.
8. (a) Satoh, Y.; Ichihashi, M.; Okumura, K. Studies on nivaldipine.1: Synthesis and structure-activity relationships of 1,4-dihydropyridines containing novel substituents at the 2-position. *Chem. Pharm. Bull.* **1991**, *39*, 3189; (b) Kanno, H.; Yamaguchi, H.; Okamiya, Y.; Sunakawa, K.; Takeshita, T.; Naruchi, T. Synthesis and antihypertensive activity of 1,4-dihydropyridine derivatives with a 4-(disubstituted phenyl) ring and an aminoalkyl ester group: Highly potent and long-lasting calcium antagonists. *Chem. Pharm. Bull.* **1992**, *40* (8), 2049.
9. Mannhold, R. Calcium antagonists: Basic chemical and pharmacological properties. *Drugs of Today* **1984**, *20* (2), 69–90.
10. (a) Núñez-Vergara, L. J.; Squella, J. A.; Bollo-Dragnic, S.; Morello, A.; Repetto, Y.; Aldunate, J.; Letelier, M. Nitro aryl 1,4-dihydropyridine derivatives: Effects on Trypanosoma cruzi. *Comp. Biochem. Physiol.* **1997**, *118* (1), 105–111; (b) Núñez-Vergara, L. J.; Squella, J. A.; Bollo-Dragnic, S.; Marín-Catalán, R.; Pino, L.; Díaz, G.; Letelier, M. E. *Gen. Pharmacol.* **1998**, *30* (1), 85; (c) Maya, J. D.; Morello, A.; Repetto, Y.; Tellez, R.; Rodriguez, A.; Zelada, O.; Puebla, P.; Caballero, E.; Medarte, M.; Núñez-Vergara, L. J.; Squella, J. A.; Bontá, M.; Bollo, S.; San Feliciano, A. Effects of 3-chloro-phenyl-1,4-dihydropyridine derivatives on *Trypanosome cruzi* epimastigotes. *Comp. Biochem. Physiol.* **2000**, *125C*, 103–109; (d) Maya, J. D.; Morello, A.; Repetto, Y.; Rodríguez, A.; Puebla, P.; Caballero, E.; Medarde, M.; Núñez-Vergara, L. J.; Squella, J. A.; Ortiz, M. E.; Fuentealba, J.; San Feliciano, A. *Trypanosoma cruzi:* Inhibition of parasite growth and respiration by oxazolo(thiazolo)pyridine derivatives and its relationship to redox potential and lipophilicity. *Exp. Parasitol.* **2001**, *99*, 1–6.

11. Zhang, Y. H.; Zhang, Z. Q.; Wu, Q. Synthesis of alkyl 2,6-dimethyl-(substituted or unsubstituted furyl)-1,4-dihydropyridine-3,5-dicarboxylates. *Acta Pharmaceutica Sinica.* **1991**, *26* (5), 375–378.
12. Hafiz, I. S. A.; Darwish, E. S.; Mahmoud, F. F. Utility of 3-aminocrotononitrile in the synthesis of new methyl 1,4-dihydropyridine, methylquinoline and thiophene derivatives: Reactivity of the methyl function in alkyl 1,4-dihydropyridine and methyl quinoline derivatives towards some electrophilic reagents. *J. Chem. Res. Synop.* **1999**, *9*, 536.
13. Katritzky, A. R.; Ostercamp, D. L.; Yousaf, T. The mechanism of Hantzsch pyridine synthesis: A study by ^{15}N and ^{13}C NMR spectroscopy. *Tetrahedron.* **1986**, *42* (20), 5729–5738.