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New potential calcium channel modulators: design and synthesis of compounds containing two pyridine, pyrimidine, pyridone, quinoline and acridine units under microwave irradiation

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Abstract—The synthesis of bifunctional pyridine, pyrimidine, pyridone, quinoline and acridine derivatives was investigated using dialdehyde as a precursor. A rapid and efficient method was developed for the synthesis of a range of bifunctional monocyclic, bicyclic and tricycilc products related to 1,4-DHPs with the aim of finding new classes of biologically active compounds.

1,4-Dihydropyridines (1,4-DHPs) are well-known compounds as a consequence of their pharmacological profile as the most important calcium channel modulators.[1] Extensive efforts have been exerted on developing methodology for the modification of the 1,4-DHPs ring.[2]

4-Aryl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1,4-DHP) derivatives are widely used for the treatment of cardiovascular diseases (hypertension, angina pectoris, infarction).[3] 1,4-DHPs having different ester groups on the 3- and 5-positions possess a stereogenic carbon on the 4-position in the 1,4-DHP nucleus, and their two enantiomers often show different biological activities.[4] Many heterocyclic compounds having a 1,4-dihydropyridine nucleus are also known to have a wide range of biological activities. Quinoline derivatives have good amoebici-dal, bactericidal, fungicidal and antimalarial activities.[5] Dihyropyridone are potential calcium channel modulators.[6] Dihydropyrimidinone derivatives have exhibited attractive pharmacological profiles, serving as the integral backbones of several calcium channel blocks, antihypertensive agents, alpha-la-antagonists and neuropeptide Y (NPY) antagonists.[7] The discovery of acridines as anticancer drugs, antimalarial and antitumor agents has attracted the attention of organic chemists and thus led to intensive interest in the synthesis of several drugs based on acridine.[8] It is well established that slight structural modification on the DHP ring may bring remarkable changes of pharmacological effect.[9]

However, so far attention has mainly been paid to the synthesis of monofunctional 1,4-DHPs derivatives and the bifunctional ones are seldom investigated. Furthermore, introduction of substituents to pyridine ring often require prolonged reaction time to achieve acceptable yields under conventional or photolysis conditions.[10]

The efficiency of microwave irradiation (MWI) in promoting organic synthesis[11,12] and the success of their application in these heterocyclic syntheses prompted us to extend those procedures to the synthesis of two bifunctional compounds containing two 1,4-DHPs nuclei.

Herein, we wish to report that microwave irradiation provides a convenient and efficient approach to a range of bifunctional monocyclic, bicyclic and tricycilc precursors to 1,4-DHPs with dialdehyde **1** as starting material.

When a mixture of *p*-phenylenedialdehyde or *m*-phenylenedialdehyde **1** and active methylene compounds **2** (in

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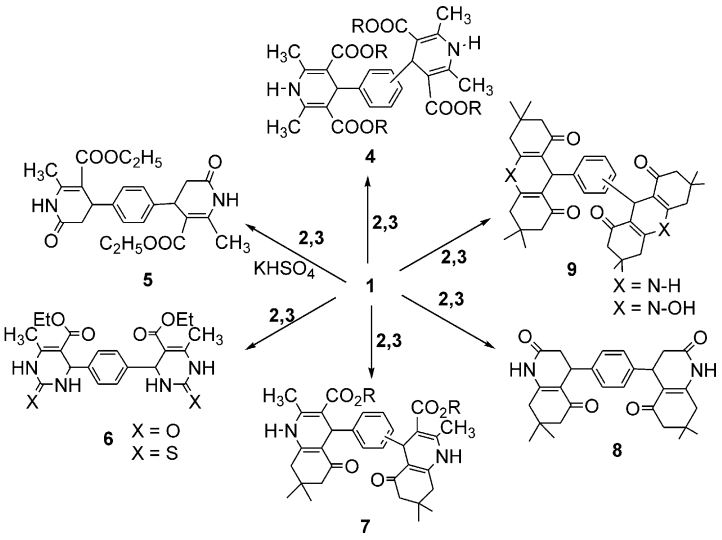
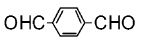
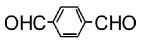
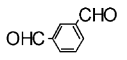
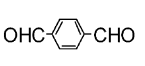
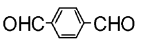
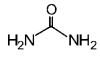
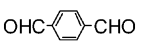
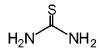
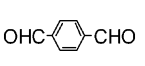
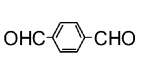
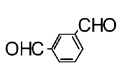
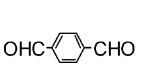
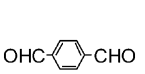
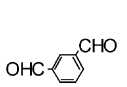
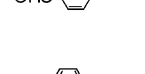
proper ratio) was radiated with microwave (300W) irradiation using small amount of glycol as energy transfer reagent (Scheme 1), the reactions were completed in 5–9 min. The reaction mixture was then cooled and poured into cold water and filtered. The solid was washed with a small amount of ethanol. The crude products were purified by recrystallization from 95% ethanol or acetone to afford products with good yields



Scheme 1. Synthetic route of bifunctional 1,4-DHPs derivatives.

Table 1. Synthesis of bifunctional 1,4-DHPs derivatives

Entry	Product	Starting material				Ratio	Time (min)	Yield (%)
		1	2	3				
1	**4a**			—	NH_4OAc	1:4:3	7	75
2	**4b**			—	NH_4OAc	1:4:3	8	78
3	**4c**			—	NH_4OAc	1:4:3	7	70
4	**5**				NH_4OAc	1:2:2:3	8	83
5	**6a**					1:2:2.4	7	91
6	**6b**					1:2:2.4	8	88
7	**7a**				NH_4OAc	1:2:2:3	9	92
8	**7b**				NH_4OAc	1:2:2:3	8	90
9	**7c**				NH_4OAc	1:2:2:3	8	89
10	**8**				NH_4OAc	1:2:2:3	8	85
11	**9a**			—	NH_4OAc	1:4:3	5	93
12	**9b**			—	NH_4OAc	1:4:3	8	90
13	**9c**			—	NH_2OH·HCl NaOAc	1:4:2	8	92

(70–93%). All the reactions were followed by TLC and the experiments were replicated in order to ensure the reproducibility. The main results for the synthesis of these compounds are listed in Table 1. Therefore, these reactions have the advantage of short reaction time, good yields, convenient work up procedures and being environmentally friendly.[13] The mechanisms are similar to that reported in earlier work.[14]

These new classes of compounds are interesting new lead compounds for biological activity evaluation. This work is in progress in our laboratories.

The structures of these compounds are established by spectroscopic and analytical data. The IR spectra of compound **5** show the NH stretching at 3200 and 3100 cm^{-1} region. The ^1H NMR spectra of compound **5** show the NH proton absorption at 9.84 ppm. The two protons at C-3 appear at 2.39–2.93 ppm and form a part of an ABX system which was confirmed by the appearance of a doublet of doublets at 4.01–4.08 ppm corresponding to the proton at C-4 split by coupling with the protons on C-3 ($J_{3,4}=1.9$ and $J_{3',4}=7.9$ Hz).

The ^1H NMR spectra of compound **8** show the NH proton at 10.05 ppm. The two protons on C-3 appear at 2.18–2.89 ppm and form a part of an ABX system which was confirmed by a doublet of doublets at 4.06–4.08 ppm corresponding to the proton on C-4 split by coupling with the protons on C-3 ($J_{3,4}=1.1$ and $J_{3',4}=8.4$ Hz). The two protons on C-6 appear as an AB system, with a couping constant $\sim$15.6 Hz, indicating that these two protons are not equivalent.

The IR of **9** shows the OH group at around 3225 cm^{-1} and the two carbonyl groups at 1667 and 1660 cm^{-1}. Meanwhile, the ^1H NMR spectrum of **9c** shows the OH proton at 10.73 ppm.

The IR and ^1H NMR of compounds **3**, **4**, **6** and **7** are consistent with the respective structures, and these compounds showed good elemental analysis results.

In summary, keeping in view the utility of MWI and the pharmacological importance of the above-mentioned heterocycles, we have synthesized a series of new bifunctional 1,4-DHPs derivatives using MWI in order to provide a facile, rapid, efficient, and environmentally friendly method. These compounds may show interesting and unique properties.

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13. The general procedure is represented as bellow: **A** dry flask (25 mL) was charged with *m*-phenylenedialdehyde (2 mmol) or *p*-phenylenedialdehyde (2 mmol), corresponding **2** and **3** (except **6**) in proper ratio, glycol (2 mL), proper catalyst (for **6**, potassium hydrogen sulfate (2

mmol)) in a microwave oven. The flask was then connected with refluxing equipment. After irradiation for 5–9 min. (irradiation sequences were interrupted with a cooling period in between), the reaction mixture was cooled and poured into cold water, then filtered and washed with ethanol (3 mL). The crude products were purified by recrystallization from 95% ethanol or acetone to afford products. Spectra of six compounds are summarized as follows: **4a**. mp > 300 °C; IR (KBr, ν, cm^{-1}): 3354, 2954, 2864, 1652, 1483, 1220, 1122, 1017; ^1H NMR (DMSO-d_6) (δ, ppm): 2.24 (6H, s, 2×CH_3), 2.50 (6H, s, 2×CH_3), 3.55 (12H, s, 4×CH_3), 4.46 (2H, s, 2×CH), 6.97 (4H, s, ArH), 8.60 (2H, s, 2×NH); CHN analysis: %C (calcd 64.11, found 63.92), %H (calcd 6.15, found 5.88), %N (calcd 5.34, found 5.10); **5**. mp > 300 °C; IR (KBr, ν, cm^{-1}): 3200, 3100, 2950, 1702, 1645, 1490, 1431, 1420, 1285, 1225, 1175, 1103, 962, 845, 800, 676, 565; ^1H NMR (DMSO-d_6) (δ, ppm): 1.09 (6H, t, J = 7.0 Hz, 2×CH_3), 2.29 (6H, s, 2×CH_3), 2.41 (2H, dd, J = 16.3 Hz, J = 1.9 Hz, B part of ABX, 2×3-H), 2.89 (2H, dd, J = 16.3 Hz, J = 7.9 Hz, A part of ABX, 2×3′-H), 3.96 (4H, q, J = 6.9 Hz, 2×OCH_2), 4.06 (2H, dd, J = 7.6 Hz, J = 1.9 Hz, X part of ABX, 2×4-H), 7.05 (4H, s, ArH), 9.84 (2H, s, 2×NH); CHN analysis: %C (calcd 65.14, found 64.88), %H (calcd 6.83, found 6.62), %N (calcd 6.33, found 6.14); **6a**. mp > 300 °C; IR (KBr, ν, cm^{-1}): 3231, 3112, 2973, 1700, 1458, 1374, 1321, 1227, 1171, 1094, 808, 663 cm^{-1}; ^1H NMR (DMSO-d_6) (δ, ppm): 1.09 (6H, t, J = 7.2 Hz, 2×CH_3), 2.22 (6H, s, 2×CH_3), 3.97 (4H, q, J = 7.2 Hz, 2×OCH_2), 5.10 (2H, s, 2×CH), 7.17 (4H, s, ArH), 7.70 (2H, s, 2×NH), 9.18 (2H, s, 2×NH); CHN analysis: %C (calcd 60.74, found 60.56), %H (calcd 7.22, found 6.97), %N (calcd 11.81, found 11.59); **7a**. mp > 300 °C; IR (KBr, ν, cm^{-1}): 3291, 3082, 2955, 1698, 1604, 1488, 1381, 1310, 1281, 1213, 1187, 1168, 1142, 1110, 1078, 1016, 800, 739, 609, 592, 533; ^1H NMR (DMSO-d_6) (δ, ppm): 0.79 (6H, s, 2×CH_3), 0.97 (6H, s, 2×CH_3), 1.94–2.49 (8H, m, 4×CH_2), 2.25 (6H, s, 2×CH_3), 3.50 (6H, s, 2×CH_3), 4.77 (2H, s, 2×CH), 6.90 (4H, s, ArH), 9.00 (2H, s, 2×NH); CHN analysis: %C (calcd 71.31, found 71.05), %H (calcd 7.04, found 6.79), %N (calcd 4.89, found 4.62); **8**. mp > 300 °C; IR (KBr, ν, cm^{-1}): 3379, 3149, 2956, 1713, 1605, 1494, 1378, 1282, 1216, 1149; ^1H NMR (DMSO-d_6) (δ, ppm): 0.98 (6H, s, 2×CH_3), 1.04 (6H, s, 2×CH_3), 2.31 (2H, dd, J = 15.6 Hz, 2×6-H), 2.24 (2H, dd, J = 15.6 Hz, 2×6′-H), 2.31 (2H, dd, J = 15.2 Hz, J = 1.1 Hz, B part of ABX, 2×3-H), 2.88 (2H, dd, J = 8.4 Hz, J = 15.2 Hz, A part of ABX, 2×3′-H), 4.07 (2H, dd, J = 8.4 Hz, J = 1.1 Hz, X part of ABX, 2×4-H), 7.00 (4H, s, ArH), 10.05 (2H, s, 2×NH); CHN analysis: %C (calcd 73.02, found 72.93), %H (calcd 7.00, found 6.77), %N (calcd 6.08, found 5.87); **9c**. mp > 300 °C; IR (KBr, ν, cm^{-1}): 3225, 2954, 2871, 1667, 1660, 1504, 1462, 1504, 1462, 1369, 1229, 1154, 1010, 808, 661, 582; ^1H NMR (DMSO-d_6) (δ, ppm): 0.82 (12H, s, 4×CH_3), 1.02 (12H, s, 4×CH_3), 2.00–2.65 (16H, m, 8×CH_2), 4.47 (2H, s, 2×CH), 6.95 (4H, s, ArH), 10.73 (2H, s, 2×OH). CHN analysis: %C (calcd 77.59, found 77.34), %H (calcd 7.41, found 7.28), %N (calcd 4.29, found 4.10).

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