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Synthesis and Regioselective Hydrolysis of Novel Dialkyl 4-Imidazolyl-1,4-Dihydropyridine-3,5-dicaroxlates as Potential Dual Acting Angiotensin II Inhibitors and Calcium Channel Blockers

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Most of the known effects of angiotensin II are mediated *via* AT_1 receptor by increasing intracellular Ca^{2+} by influx of extracellular Ca^{2+}. Combination therapies of angiotensin receptor blocker (ARB) with calcium channel blocker (CCB) which act through L-type calcium channel have beneficial therapeutic and protective effects on cardiovascular system. Thus, it was hypothesized that merging the key structural elements present in an AT_1 receptor antagonist (telmisartan) with key structural elements in 1,4-dihydropyridine calcium channel blockers (nifedipine) would yield a compound with dual activity for both receptors. This strategy led to the design and synthesis of dialkyl 1,4-dihydro-2,6-dimethyl-4-[2-n-alkyl-1-[(2′-carboxybiphenyl-4-yl)methyl]imidazole-4(or 5)-yl]-3,5-pyridinedicarboxylates (**4** and **6**). The synthesis of compounds **4** and **6** was accomplished through the reaction of 2-n-alkyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-4(or 5)-carboxaldehydes with alkyl acetoacetate followed by regioselctive hydrolysis of carboethoxybiopheny to carboxybiphenyl that are essential for ARB activity. It is suggested that existence of hindrance by substituted groups prevent hydrolysis of esteric groups on dihydropyridine ring. The structures of the compounds were characterized by ^{1}H-nuclear magnetic resonance, infrared and mass spectroscopy.

Keywords: Dual mechanism, Angiotensin II antagonist, Calcium channel blocker, 1,4-Dihydropyridine

INTRODUCTION

The rennin-angiotensin system (RAS) is a master regulator of blood pressure and fluid homeostasis. Angiotensin II (Ang II) acts on a wide spectrum of target tissues including the adrenals, vascular smooth muscle, endothelium, kidney and so on. It is not only a steroidogenic and vasoactive peptide but also a growth factor-like agent able to induce hypertrophy and hyperplasia *via* AT_1 [1-3]. Most of the known effects of Ang II in adult tissues are attributable to AT_1 which increases intracellular Ca^{2+} by influx of extracellular Ca^{2+} to induce vasoconstriction and immediately elevates blood pressure [4].

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Angiotensin receptor blockers (ARBs), such as Losartan, Telmisartan (Fig. 1), antagonize Ang II effects on vascular smooth muscle and are used for controlling hypertension. Their vasodilatation actions are due to reduction of intracellular Ca^{2+} [5].

Structure activity relationships (SAR) of 1,4-dihydropyridines (1,4-DHP) indicate that substituted heterocycles on the C_4 position of 1,4-DHP ring can be CCB [6-12]. It has been reported that the compounds, dialkyl 1,4-dihydro-2-[2-(dimethylamino)ethyl]-6-methyl-4-(1-benzyl-2-alkylthio-5-imidazolyl)-3,5-pyrdinedicarboxylates [13] and dialkyl 1,4-dihydro-2,6-dimethyl-4-[2-methylthio-1-(phenyl-amino)-1H-imidazole-5-yl]-3,5-pyridinedicarboxylates **A**, are CCB (see Fig. 1) [14].

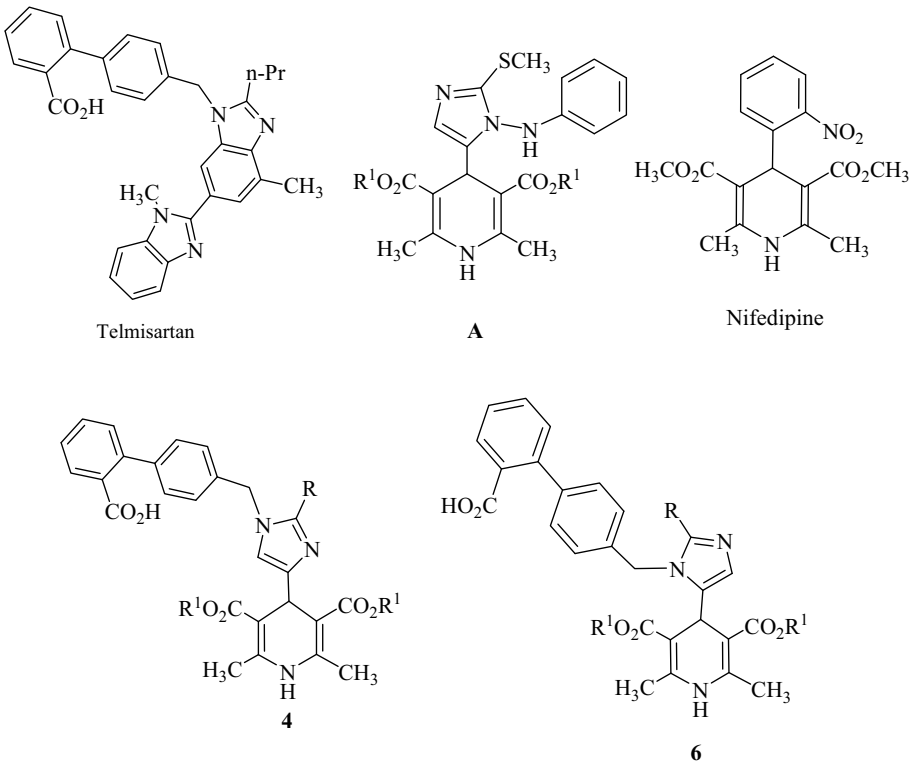


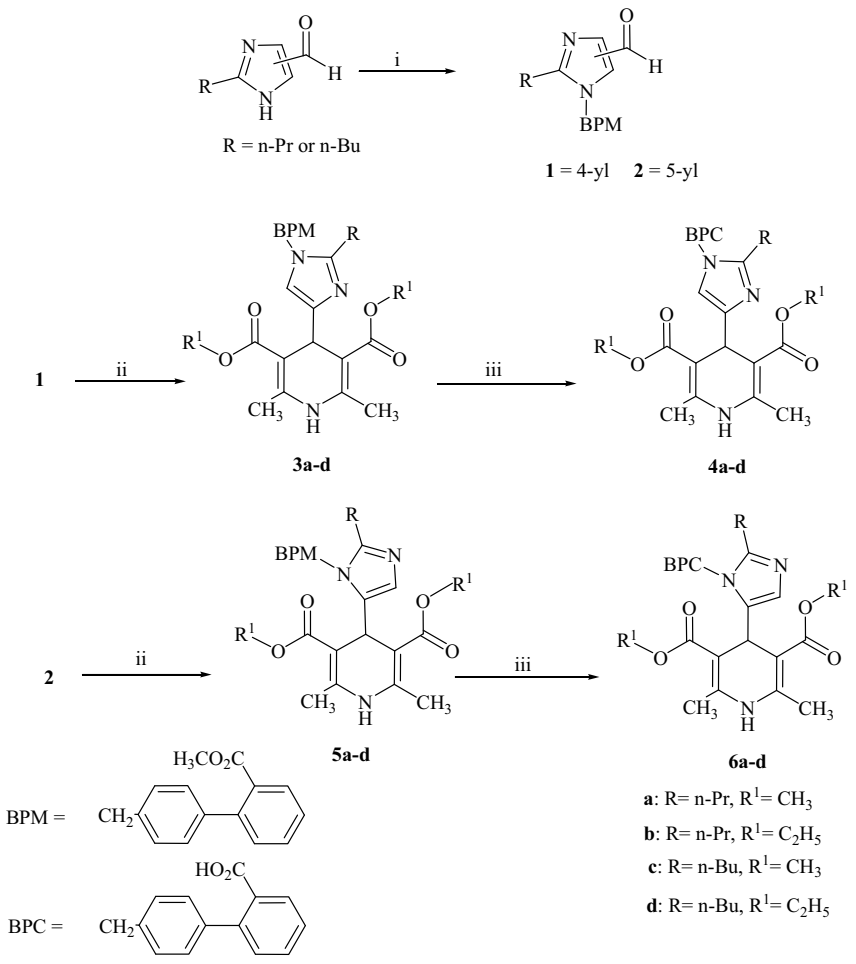
Fig. 1. Chemical structure of some CCB (compound **A** and nifedipine), ARB (telmisartan) and designed dual CCB-ARB (compound **4** and **6**).

On the basis of SAR of ARBs, the C_4 and C_5 position of imidazole ring can be substituted with other lipophilic and hydrogen acceptor groups [6]. Telmisartan as a potent ARB, has a bulky group (benzoimidazole) in the C_6 position of benzoimidazole ring.

For the following reasons: 1) the existence of correlation between L-type calcium channel and AT_1 receptor [15], 2) low dose and low side effect of combination therapy of a CCB and ARB [16], 3) beneficial effect of monotherapy alone or combination therapy of a CCB and ARB in controlling blood pressure [17,18], 4) cardioprotection, renoprotection and anti-atherosclerosis activity of CCB and ARB [19-21], 5) dual antagonists such as monatepil [22] and alatriopril [23,24] and 2'-substituted N-3-isoxazolyl biphenylsulfonamide derivatives [25] having potent antihypertensive effect, 6) bulky groups in C_4 and C_5 position of imidazole ring and substituted heterocycles on the C_4 position of 1,4-DHP ring retained biological activity, we hypothesized that merging the key structural elements present in AT_1 receptor antagonists (2′-carboxybiphenyl-4-yl)methylimidazole with key structural elements in 1,4-dihydropyridine calcium channel blockers (dialkyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) would yield a compound with dual activity for both receptors. This strategy led to the design and synthesis of dialkyl 1,4-dihydro-2,6-dimethyl-4-[2-n-alkyl-1-[(2′-carboxybiphenyl-4-yl)methyl]imidazole-4(or 5)-yl]-3,5-pyridinedicarboxylates (**4** and **6**) (see Fig. 1).

CHEMISTRY

Scheme 1 shows synthesis of 1,4-dihydropyridines with 2'-carboxybiphenyl moiety (**4a-d** and **6a-d)**. 2-Alkyl-imidazole-4(5)-carboxaldehyde [26,27] was reacted with methyl 4′-(bromomethyl)biphenyl-2-carboxylate in the presence of



Scheme 1. Synthesis of 1,4-dihydropyrides with 2'-carboybiphenyl moiety, reagents and conditions: i) K_2CO_3, DMF, methyl 4´-(bromomethyl)biphenyl-2-carboxylate, 24 h, room temperature , ii) NH_3 25%, methyl or ethyl acetoacetate, alcohol, reflux, iii) KOH, H_2O/alcohol (1:1), reflux

K_2CO_3 to give **1a-b** and **2a-b**. The two isomers were separated by chromatography [28,29]. Dihydropyridine compounds (**3a-d** and **5a-d**) were prepared by the classic Hantzsch reaction of methyl or ethyl acetoacetate and ammonium hydroxide with **1a-b** and **2a-b** respectively [30]. Finally mild hydrolysis of **3a-d** and **5a-d** in alkaline solution provided compounds **4a-d** and **6a-d**, respectively [28].

EXPERIMENTAL

Methyl 4´-(bromomethyl) biphenyl-2-carboxylate was obtained from Sinosource Pharma Ltd. (Hengsha Guangzhou, China). 2-Alkyl-imidazole-4(5)-carboxaldehyde was prepared according to the literature [28,29]. Other chemicals were purchased from Merck Chemical Company (Darmstadt, Germany). Melting points were determined by a Gallenkamp capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Bruker-Spectrospin 200 MHz spectrometer (Bruker, Germany). Tetramethylsilane was used as an internal standard. Mass spectra were obtained using a Finnigan Mat TSQ-70 spectrometer at 70 eV (Finnigan Mat, Bremen, Germany). The FT-IR spectrum was recorded on a Shimadzu FTIR 4300 spectrometer (KBr disks) (Shimadzu, Kyoto, Japan). The purity of compounds was confirmed by TLC using

different mobile phases. Elemental analyses were carried out on a Heraeus CHN-O rapid elemental analyzer (Heraeus GmbH, Germany) for C, H and N and the results were within ± 0.4% of the theoretical values.

Preparation of 2-n-Alkyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-4-carboxaldehyde (1a,b) and its Regioisomer 2-n-Alkyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-5-carboxaldehyde (2a,b)

A solution of 2-n-propyl-imidazole-4(5)-carboxaldehyde (30 mmol) in anhydrous dimethylformamide (90 ml) and anhydrous K_2CO_3 (8.3 g, 60 mmol) were stirred at room temperature for 30 min. Then methyl 4′-(bromomethyl)biphenyl-2-carboxylate (10.4 g, 33 mmol) was added to the reaction mixture and stirring was continued for 24 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with 30 ml of water and extracted with ethyl acetate (3 × 30 ml). The combined organic phases were dried over anhydrous sodium sulfate and the solvent was removed to give a viscous liquid. Column chromatography using toluene-ethyl acetate (70:30) as eluent afforded 14% of **2a,b** (regioisomer of higher R_f value) and 3.21 g (29%) of **1a,b**.

General Procedure for the Preparation of Dialkyl 1,4-Dihydro-2,6-dimethyl-4-[2-alkyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl] Imidazole-4(5)-yl]-3,5-pyridinedicarboxylate

A solution of aldehyde (**1a-b** or **2a-b**) ((1.5 mmol), methyl or ethyl acetoacetate (3 mmol) and ammonium hydroxide (0.5 ml) in 5 ml of methanol was protected from light and stirred at 25 °C for 30 min and then refluxed over night. The solvents removed under vacuum and purification with column chromatography provided **3a-d** or **5a-d**.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-propyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-4-yl]-3,5-pyridinedicarboxylate (3a). Yield: 45%; m.p.: 208-210 °C; FT-IR (KBr): υ 3400 (N-H), 1695 cm^{-1} (C=O, ester); MS: m/z (%) 513 (15), 300 (30), 251 (15), 225 (100), 177 (32), 150 (14); Anal. Calcd. for $C_{32}H_{35}N_3O_6$: C, 68.92; H, 6.33; N, 7.53. Found: C, 69.01; H, 6.52; N, 7.41.

Diethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-propyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-4-yl]-3,5-pyridinedicarboxylate (3b). Yield: 58%; m.p.: 180-182 °C; FT-IR (KBr): υ 3500 (N-H), 1714 (C=O, ester), 1693 cm^{-1} (C=O, ester DHP); MS: m/z (%) 585 [M^+] (6), 570 (10), 512 (16), 315 (14), 252 (13), 226 (100), 192 (53),225 (76), 165 (10); Anal. Calcd. for $C_{34}H_{39}N_3O_6$: C, 69.72; H, 6.71; N, 7.17. Found: C, 69.85; H, 6.86; N, 7.02.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-4-yl]-3,5-pyridinedicarboxylate (3c). Yield: 37%; mp: 199-201 °C; FT-IR (KBr): υ 3425 (N-H), 1737 (C=O, ester), 1693 cm^{-1} (C=O, ester DHP); MS: m/z (%) 572 [M^++1] (43), 557 (17), 513 (23), 347 (17), 346 (11), 225 (92), 224 (100), 165 (24); Anal. Calcd. for $C_{33}H_{37}N_3O_6$: C, 69.33; H, 6.52; N, 7.35. Found: C, 69.40; H, 6.64; N, 7.29.

Diethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-4-yl]-3,5-pyridinedicarboxylate (3d). Yield: 60%; m.p.: 184-186 °C; FT-IR (KBr): υ 3500 (N-H), 1722 (C=O, ester), 1691 cm^{-1} (C=O, ester DHP); MS: m/z (%) 599 [M^+] (4), 526 (21), 373 (19), 314 (33), 252 (10), 225 (81), 223 (45), 132 (100); Anal. Calcd. for $C_{35}H_{41}N_3O_6$: C, 70.09; H, 6.89; N, 7.01. Found: C, 70.21; H, 7.05; N, 6.86.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-propyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-5-yl]-3,5-pyridinedicarboxylate (5a). Yield: 39%; m.p.: 189-190 °C; FT-IR (KBr): υ 3357 (N-H), 1730 (C=O, ester), 1699 cm^{-1} (C=O, ester DHP); MS: m/z (%) 558 [M^++1] (8), 499 (12), 333 (11), 278 (22), 225 (100), 206 (91), 195 (43), 179 (28); Anal. Calcd. for $C_{32}H_{35}N_3O_6$: C, 68.92; H, 6.33; N, 7.53. Found: C, 69.11; H, 6.47; N, 7.43.

Diethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-propyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-5-yl]-3,5-pyridinedicarboxylate (5b). Yield: 61%; m.p.: 176-178 °C; FT-IR (KBr): υ 3400 (N-H), 1728 (C=O, ester), 1693 cm^{-1} (C=O, ester DHP); MS: m/z (%) 586 [M^++1] (14), 571 (5), 513 (19), 360 (8), 251 (8), 225 (100), 166 (10); Anal. Calcd. for $C_{34}H_{39}N_3O_6$: C, 69.72; H, 6.71; N, 7.17. Found: C, 69.90; H, 6.87; N, 7.32.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-butyl-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-5-yl]-3,5-pyridinedicarboxylate (5c). Yield: 43%; m.p.: 170-172 °C; FT-IR (KBr): υ 3448 (N-H), 1730 cm^{-1} (C=O, ester); MS: m/z

(%) 571 [M^+] (46), 556 (21), 512 (54), 346 (18), 225 (100), 223 (59), 165 (23); Anal. Calcd. for $C_{33}H_{37}N_3O_6$: C, 69.33; H, 6.52; N, 7.35. Found: C, 69.48; H, 6.61; N, 7.46.

Diethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-butyl-1-[(2´-carbomethoxybiphenyl-4-yl)methyl]imidazole-5-yl]-3,5-pyridinedicarboxylate (5d). Yield: 43%; m.p.: 128-130 °C; FT-IR (KBr): υ 3400 (N-H), 1730 (C=O, ester), 1697 cm^{-1} (C=O, ester DHP); MS: m/z (%) 600 [M^++1] (3), 527 (7), 251 (8), 225 (26), 207 (100), 178 (13); Anal. Calcd. for $C_{35}H_{41}N_3O_6$: C, 70.09; H, 6.89; N, 7.01. Found: C, 70.28; H, 7.05; N, 6.88.

General Method for the Hydrolysis of Esteric Group on Biphenyl Moiety of Compounds 3a-d and 5a-d

Compound (**3a-d** or **5a-d**) (0.9 m mol) was dissolved in 4.5 ml of methanol and then 0.25 ml of water and 2.7 ml of methanol solution of potassium hydroxide (0.5 N) were added. The reaction mixture was refluxed for 30 h. The progress of the reaction was monitored with TLC. After completion of the reaction, the solvent was removed under vacuum and to the residue was added water. The solution was adjusted to pH 4 with dilute hydrochloric acid. The precipitated solid was collected by filtration. Column chromatography (elution: 10-20% methanol/chloroform) afforded compounds **4a-d** or **6a-d**.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-propyl-1-[(2´-carboxybiphenyl-4-yl)methyl]imidazole-4-yl]-3,5-pyridinedicarboxylate (4a). Yield: 65%; m.p.: 140-142 °C; FT-IR (KBr): υ 3431 [(N-H), (OH, acid)], 1691 cm^{-1} (C=O, acid and ester DHP); MS: m/z (%) 499 (7), 346 (6), 286 (31), 225 (47), 211 (50), 192 (53), 165 (100); Anal. Calcd. for $C_{31}H_{33}N_3O_6$: C, 68.49; H, 6.12; N, 7.73. Found: C, 68.54; H, 6.22; N, 7.85.

Diethyl 1,4-dihydro-2,6-dimethyl--4-[2-n-propyl-1-[(2´-carboxybiphenyl-4-yl)methyl]imidazole-4-yl]-3,5-pyridinedicarboxylate (4b). Yield: 71%; m.p.: 135-136 °C; FT-IR (KBr): υ 3450 [(N-H), (O-H, acid)], 1689 cm^{-1} (C=O, acid and ester DHP); MS: m/z (%) 572 [M^++1] (5), 498 (14), 360 (10), 319 (33), 300 (50), 251 (19), 211 (100), 165 (63); Anal. calcd. for $C_{33}H_{37}N_3O_6$: C, 69.33; H, 6.52; N, 7.35. Found: C, 69.49; H, 6.71; N, 7.51.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-butyl-1-[(2´-carboxybiphenyl-4-yl)methyl]imidazole-4-yl]-3,5-pyridinedicarboxylate (4c). Yield: 65%; m.p.: 150-152 °C; FT-IR (KBr): υ 3480 [(N-H), (O-H, acid)], 1693 cm^{-1} (C=O, acid and ester DHP); MS: m/z (%) 558 [M^++1] (9), 499 (11), 333 (5), 225 (100), 165 (14); Anal. Calcd. for $C_{32}H_{35}N_3O_6$: C, 68.92; H, 6.33; N, 7.53. Found: C, 68.99; H, 6.41; N, 7.44.

Diethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-butyl-1-[(2´-carboxybiphenyl-4-yl)methyl]imidazole-4-yl]-3,5-pyridinedicarboxylate (4d). Yield: 62.5%; m.p.: 123-125 °C; FT-IR (KBr): υ 3500 [(N-H), (O-H, acid)], 1687 cm^{-1} (C=O, acid and ester DHP); MS: m/z (%) 586 [M^++1] (8), 513 (14), 360 (6), 314 (8), 251 (19), 225 (100), 205 (73), 166 (38); Anal. Calcd. for $C_{34}H_{39}N_3O_6$: C, 69.72; H, 6.71; N, 7.17. Found: C, 69.87; H, 6.84; N, 7.35.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-propyl-1-[(2´-carboxybiphenyl-4-yl)methyl]imidazole-5-yl]-3,5-pyridinedicarboxylate (6a). Yield: 74%; m.p.: 148-150 °C; FT-IR (KBr): υ 3490 [(N-H), (O-H, acid)], 1690 cm^{-1} (C=O, acid and ester DHP); MS: m/z (%) 543 [M^+] (13), 484 (19), 332 (18), 300 (24), 225 (69), 211 (100), 166 (30), 165 (60); Anal. Calcd. for $C_{31}H_{33}N_3O_6$: C, 68.49; H, 6.12; N, 7.73. Found: C, 68.60; H, 6.23; N, 7.65.

Diethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-propyl-1-[(2´-carboxybiphenyl-4-yl)methyl]imidazole-5-yl]-3,5-pyridinedicarboxylate (6b). Yield: 56%; m.p.: 153-155 °C; FT-IR (KBr): υ 3500 [(N-H), (O-H, acid)], 1690 cm^{-1} (C=O, acid and ester DHP); MS: m/z (%) 572 [M^++1] (8.5), 512 (16), 247 (13), 226 (100), 225 (51), 165 (19); Anal. Calcd. for $C_{33}H_{37}N_3O_6$: C, 69.33; H, 6.52; N, 7.35. Found: C, 69.53; H, 6.69; N, 7.30.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-butyl-1-[(2´-carboxybiphenyl-4-yl)methyl]imidazole-5-yl]-3,5-pyridinedicarboxylate (6c). Yield: 62%; m.p.: 149-150 °C; FT-IR (KBr): υ 3465 [(N-H), (O-H, acid)], 1701 cm^{-1} (C=O, acid and ester DHP); MS: m/z (%) 557 [M^+] (4), 513 (10), 345 (14), 225 (100), 164 (64), 152 (15); Anal. Calcd. for $C_{32}H_{35}N_3O_6$: C, 68.92; H, 6.33; N, 7.53. Found: C, 69.01; H, 6.48; N, 7.59.

Diethyl 1,4-dihydro-2,6-dimethyl-4-[2-n-butyl-1-[(2´-carboxybiphenyl-4-yl)methyl]imidazole-5-yl]-3,5-pyridinedicarboxylate (6d). Yield: 68%; m.p.: 161-163 °C; FT-IR (KBr): υ 3444 [(N-H), (OH, acid)], 1690 cm^{-1} (C=O, acid and ester DHP); MS: m/z (%) 586 [M^++1] (10), 513 (11), 360 (5), 225 (100), 165 (9); Anal. Calcd. for $C_{34}H_{39}N_3O_6$: C, 69.72; H, 6.71; N, 7.17. Found: C, 69.83; H, 6.90; N, 7.01.

RESULTS AND DISCUSSION

The direct alkylation of 2-alkylimidazole-4(5)-carboxaldehyde was performed with methyl 4′-(bromomethyl)biphenyl-2-carboxylate (Scheme 1). A 2:1 mixture of regioisomers was obtained using column chromatography [31], resulting from nonselective alkylation at the 1 or 3 positions. ^{1}H NMR spectra of compounds **1** and **2** show that the benzylic hydrogen (*N*-CH_2) of compound **2** was more deshielded than that of compound **1** which appeared at 5.63 and 5.17 ppm respectively [29,31]. Dihydropyridines have been classically synthesized using the "Hantzsch dihydropyridine synthesis" described in 1882. Variations of the conditions of the reaction using acidic medium or catalytic reagents are described [32].

In the present work, we prepared 1,4-dihydropyridines by reaction of regioisomers **2** or **1** with ethyl or methyl acetoacetate in the presence of ammonia at reflux temperature. On the basis of ^{1}H NMR spectrums of compounds **3** and **5** H-N, H-C_4, OCH_2CH_3 and OCH_3 of 1,4-dihydropyridines appeared at 8.6-10.6 ppm as broad singlet, 4.8-5.1 ppm as singlet, 3.9-4.1 as multiple and 3.4-3.6 ppm as singlet respectively. The six hydrogens of 2,6-dimethyl-DHP appeared as singlet at 2.2 ppm. Depending on type of substituted imidazole (4-yl or 5-yl) and type of solvent ($CDCl_3$ or DMSO-d_6), the methoxy of biphenyl ring overlapped with methoxy of DHP or appeared separately (see Table 1). The ^{1}H NMR spectrums corresponding to the methylene group on the carboethoxy substituent shows a rather more complex splitting pattern than a simple quartet. This behavior is due to a non-equivalence of the two hydrogen of the methylene group. The methylene hydrogen of the carboethoxy group in these compounds is diasterotopic. This effect only has been observed for ethyl ester but not for methyl ester. In $CDCl_3$ the carboethoxy group appeared as a simple quartet but in DMSO-d_6 complex splitting pattern was observed. DaSilva *et al*. reported similar splitting pattern for diethyl 4-(nitroaryl)-1,4-dihydropyridine-3,5-dicarboxylate derivatives [33].

Compounds **3** and **5** having 4-[2-n-alky-1-[(2′-carbomethoxybiphenyl-4-yl)methyl]imidazole-4(or 5)-yl] as bulky substituent and 2,6-dimethyl on DHP ring can induce space hindrance on ester groups at 3 and 5 position of DHP. Therefore, ester on biphenyl could be regioselectively hydrolyzed to carboxylic acid without hydrolysis of esters on DHP ring.

To confirm the hydrolysis of carbomethoxy group on biphenyl, we investigated the ^{1}H NMR spectra of compounds **4** and **6**. The peak of OCH_3 on biophenyl of compounds **3b**, **3d**, **5b** and **5d** appeared at 3.5-3.7 ppm while in compounds **4b**, **4d**, **6b** and **6d** disappeared. In addition, peaks related to OCH_2CH_3 group on 3 and 5 position of DHP ring did not change. The OCH_2 was observed at 3.9-4.1 ppm for 4H as multiplet. The chemical shift of OCH_3 on biphenyl and dihydropyridine were at 3.7 and 3.5 ppm ($CDCl_3$) for compounds **3a** and **5a** or 3.5 and 3.4 ppm (DMSO-d_6) for compounds **3c**, **5c**, respectively. In addition after hydrolysis, the ^{1}H NMR spectra data showed the chemical shift for OCH_3 on dihydropyridine at 3.38 (**6a**), 3.42 (**6c**), 3.57 (**4a**) and 3.56 ppm (**4c**) (see Table 1). In addition MS of the compounds showed molecular weight, expectable fragmentation and established the existence of carboxylic acid group on biphenyl ring and dialkyl ester on dihydropyridine. The Mass spectrum fragmentation pattern of compounds **3d** and **4a** is shown in Fig. 2 and is in agreement with the suggested structure. Comparable fragmentations were previously reported for some dihydropyridine derivatives [34,35].

CONCLUTIONS

Bulky substituent on C_4 position of dihydropyridines (compounds **3a-d** and **5a-d**) could be synthesized through Hantzsch dihydropyridine synthesis. Their chemical structures were confirmed with ^{1}H NMR and mass spectroscopy studies. The side ester on carbomethoxyphenyl is regioselectively hydrolyzed to carboxylic acid in alkaline solution. Compounds **4** and **6** have key elemental structure for angiotensin II receptor and calcium channel blockers activity. Therefore compounds **4** and **6** could be candidates as dual angiotensin receptor and calcium channel blockers.

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Table 1. ^{1}H NMR Spectroscopy Data for Synthesized Compounds in DMSO-d_6

Compd.	1,4-Dihydropyridine moiety					Imidazolyl biphenyl moiety		
	N-H	C_4H	2,6-DiCH_3	3,5-Di-OCH_3 or di-$O\underline{CH_2}CH_3$	3,5-Di$OCH_2\underline{CH_3}$	HC_5 imi or HC_4 imi	CH_2-N	OCH_3
1a,b[i]	-	-	-	-	-	7.55	5.15	3.65
2a,b[ii]	-	-	-	-	-	7.80	5.65	3.65
3a	8.65 (brs)	4.87 (s)	2.18 (s)	3.55(s)	-	6.49 (s)	5.04 (s)	3.55(s)
3b	8.84 (brs)	4.91 (s)	2.20 (s)	3.92-4.13 (m)	1.16 (t, 6H, J = 8 Hz)	6.51 (s)	5.06 (s)	3.58 (s)
3c $CDCl_3$	10.60 (brs)	5.08 (s)	2.27 (s)	3.65 (s)	-	6.69 (s)	5.08 (s)	3.70 (s)
3d $CDCl_3$	10.60 (brs)	5.07 (s)	2.28 (s)	4.12 (q, 4H, J = 8 Hz, J = 14 Hz)	1.20 (t, 6H, J = 8 Hz)	6.68 (s)	5.09 (s)	3.69 (s)
4a	8.80 (brs)	4.87 (s)	2.21 (s)	3.57 (s)	-	6.56 (s)	5.07 (s)	-
4b	9.27 (brs)	4.94 (s)	2.27 (s)	3.95-4.13 (m)	1.11 (t, 6H, J = 7 Hz)	7.31 (s)	5.36 (s)	-
4c	8.84 (brs)	4.88 (s)	2.20 (s)	3.56 (s)	-	6.57 (s)	5.06 (s)	-
4d	8.94 (brs)	4.89 (s)	2.22 (s)	3.92-4.12 (m)	1.12 (t, 6H, J = 8 Hz)	7.31 (s)	5.19 (s)	-
5a	9.13 (brs)	4.94 (s)	2.20 (s)	3.42 (s)	-	6.47 (s)	5.32 (s)	3.59 (s)
5b	9.10 (s)	5.04 (s)	2.20 (s)	3.79-4.05 (m)	1.08 (t, 6H, J = 8 Hz)	6.47 (s)	5.30 (s)	3.58 (s)
5c $CDCl_3$	6.88 (brs)	5.10 (s)	2.31 (s)	3.51 (s)	-	6.78 (s)	5.43 (s)	3.69 (s)
5d	9.06 (s)	5.04 (s)	2.17 (s)	3.82-4.02 (m)	1.08 (t, 6H, J = 8 Hz)	6.46 (s)	5.29 (s)	3.58 (s)
6a	9.17 (brs)	4.92 (s)	2.18 (s)	3.38 (s)	-	6.44 (s)	5.30 (s)	-
6b	9.09 (s)	5.00 (s)	2.17 (s)	3.80-4.00 (m)	1.04 (t, 6H, J = 7 Hz)	6.42 (s)	5.26 (s)	-
6c	9.31 (brs)	5.03 (s)	2.21 (s)	3.42 (s)	-	6.87 (s)	5.47 (s)	-
6d	9.14 (s)	5.04 (s)	2.18 (s)	4.03-3.78 (m)	1.11-1.04 (m)	6.51 (s)	5.32 (s)	-

[i]**a**: R = n-Pr, 4-yl substitution isomer; **b**: R = n-Bu, 4-yl substitution isomer; [ii]**a**: R = n-Pr, 5-yl substitution isomer; **b**: R = n-Bu, 5-yl substitution isomer; hydrogen of carboxaldehyde in ^{1}H NMR ($CDCl_3$) appeared at 9.65 ppm as singlet for compounds **1** and **2**. n-Pr: 2.30 (t, 2H, J = 8 Hz, CH_2-imidazole), 1.56- 1.41 (m, 2H, CH_2), 0.79 ppm (t, 3H, J = 8 Hz, CH_3). n-Bu: 2.51 (t, 2H, J = 8 Hz, CH_2-imidazole), 1.45-1.24 (m, 4H, CH_2), 0.80 ppm (t, 3H, J = 8 Hz, CH_3). Biphenyl: 6.92 (d, 2H, J = 8 Hz, H-3, 5 phenyl), 7.31 (d, 2H, J = 8 Hz, H-2,6 phenyl), 7.59-7.34 (m, 3H, aromatic), 7.75 (dd, 1H, $J_{3',5''}$ = 2 Hz, $J_{3',4'}$ = 8 Hz, H-3' phenyl), brs: broad singlet, d: doublet, m: multiple, q: quartet, s: singlet, t: triplet.

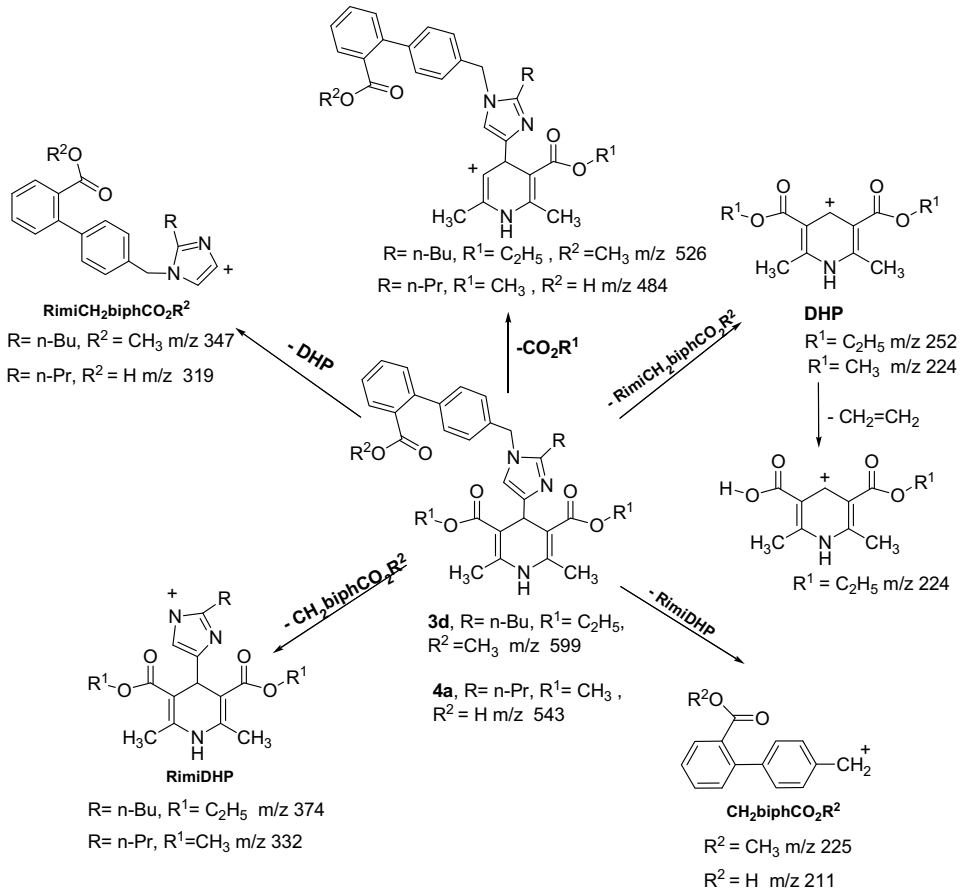

Fig. 2. Proposed fragmentation pathways of compounds **3d** and **4a** in mass spectroscopy.

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REFERENCES

[1] S. Greco, M.G. Elia, A. Muscella, C. Storelli, S. Marsigliante, Cell Calcium 32 (2002) 1.

[2] M. Munakata, A. Nagasaki, T. Nunokawa, T. Sakuma, H. Kato, K. Yoshinaga, T. Toyota, AJH 17 (2004) 1050.

[3] K. Kimura, A. Tojo, Y. Hirata, H. Hayakawa, A. Goto, M. Omata, Blood Pressure, Supplement 3 (1994) 71.

[4] M. De Gasparo, Drugs 62 (2002) 1.

[5] H.M. Siragy, M. Bedigian, Curr. Hypertens. Rep. 1 (1999) 289.

[6] M. Harrold, in: D.A. Williams, T.L. Lemke (Eds.), Foye`s Principles of Medical Chemistry, 5th ed., Lippincott Williams & Wilkins, Philadelphia, 2002.

[7] A. Shafiee, F. Hadizadeh, A. Foroumadi, Ind. J. Chem. (Sec. B) 36 (1997) 813.

[8] A. Shafiee, R. Miri, A.R. Dehpour, F. Soleymani, Pharmaceut. Sci. 2 (1996) 541.

[9] M. Hosseini, R. Miri, M. Amini, H. Mirkhani, B. Hemmateenejad, S. Ghodsi, E. Alipour, A. Shafiee, Arch. Pharm. 340 (2007) 549.

[10] A. Shafiee, N. Rastkary, M. Jorjani, Arzneimittelforschung 52 (2002) 537; M. Amini, A.A. Golabchifar, A.R. Dehpour, H.M. Pirali, A. Shafiee, Arzneimittelforschung 52 (2002) 21.

[11] A. Shafiee, N. Rastkary, M. Jorjani, B. Shafaghi, Arch. Pharm. 335 (2002) 69.

[12] M. Amini, A.A. Golabchifar, A. R. Dehpour, H.M. Pirali, A. Shafiee, Arzneimittelforschung 52 (2002) 21.

[13] F. Hadizadeh, B.F. Anaraki-Firooz, S.I.H. Taqvi, Iran. J. Pharmaceut. Sci. 1 (2004) 27.

[14] R. Miri, H. Niknahad, G. Vesal, A. Shafiee, IL Farmaco 57 (2002) 123; A. Foroumadi, N. Analuie, M. Rezvanipour, G. Sepehri, H. Najafipour, H. Sepehri, IL Farmaco 57 (2002) 195; A. Zarghi, H. Sadeghi, A. Fassihi, M. Faizi, A. Shafiee, Il Farmaco 58 (2003) 1077.

[15] K.H.S. Arun1, C.L. Kaul, P. Ramarao, Cardiovascular Res. 65 (2005) 374.

[16] M. Munakata, A. Nagasaki, T. Nunokawa, T. Sakuma, H. Kato, K. Yoshinaga, T. Toyota, Am. J. Hypertens. 17 (2004)1050.

[17] D. Poldermans, R. Glazer, S. Karagiannis, M. Wernsing, J. Kaczor, Y.T. Chiang, J. Yen, R. Gamboa, I. Fomina, Clin. Ther. 29 (2007) 279.

[18] M. Iwai, R. Chen, A. Ide, J. Iwanami, H. Tomochika, Y. Tomono, M. Mogi, M. Horiuchi, J. Hypertens. 24 (2006) 2023.

[19] N. Okuda, T. Hayashi, T. Mori, S. Inamoto, M. kabe, S. Mieno, H. Horimoto, Y. Kitaura, Hypertens. Res. 28 (2005) 431.

[20] S. Kuriyama, H. Tomonari, G. Tokudome, M. Origuchi, H. Hayashi, H. Kobayashi, M. Ishikawa, T. Hosoya, Hypertens. Res. 25 (2002) 849.

[21] M. Takayama, E. Arakawa, K. Yao, Y. Ina, H. Sato, K. Hasegawa, H. Kohno, T. Ohno, Pharmacol. 77 (2006) 179.

[22] A. Ikeno, T. Sumiya, H. Minato, B. Fujitani, Y. Masuda, K. Hosoki, M. Kurono, M. Yasuba, Jpn. J. Pharmacol. 78 (1998) 303.

[23] J. Bralet, C. Marie, C. Mossiat, J.M. Lecomte, C. Gros, J.C. Schwartz, J. Pharmacol. Exp. Therap. 270 (1994) 8.

[24] N.K. Singh, R.K. Goyal, Clin. Exp. Hypertens. 21 (1999) 137.

[25] N. Murugesan, Z. Gu, L. Fadnis, J.E. Tellew, R.A.F. Baska, Y. Yang, S.M. Beyer, H. Monshizadegan, K.E. Dickinson, M.T. Valentine, W. Griffith Humphreys, S.J. Lan, W.R. Ewing, K.E. Carlson, M.C. Kowala, R. Zahler, J.E. Macor, J. Med. Chem. 48 (2005) 171.

[26] R. Weiden hagen, R. Herrmann, Ber. 68 (1935) 1953.

[27] S.P.A. Watson, Synt. Commun. 22 (1992) 2971.

[28] D.J. Carini, J.V. Duncia, P.E. Aldrich, A.T. Chiu, A.L. Johnson, M.E. Pierce, W.A. Price, J.B. Santella, G.J. Wells, R.R. Wexler, P.C. Wong, S.E. Yoo, P.B.M.W.M. Timmermans, J. Med. Chem. 34 (1991) 2525.

[29] S.C. Shilcrat, M.K. Mokhallalati, J.M.D. Fortunak, L.N. Pridgen, J. Org. Chem. 62 (1997) 8449.

[30] F. Hadizadeh, A. Shafiee, R. Kazemi, J. Sci., I. R. Iran 13 (2002) 29.

[31] A. Shafiee, J. S. Mojarrad, M.A. Jalili, H.R. Adhami, F. Hadizadeh, J. Heterocyclic Chem. 39 (2002) 367.

[32] A.E. Sausins, G. Duburs, Chemistry of Heterocyclic Compounds 28 (1992) 363; M.A. Zolfigol, M. Mokhlesi, J. Iran. Chem. Soc. Supplement 5 (2008) S91.

[33] J.A. DaSilva, C.S. Barríab, C. Jullianb, P. Navarreteb, L. Núñez Vergaraa, J.A. Squellaa, J. Braz. Chem. Soc. 16 (2005) 112.

[34] L.J. Núñnez-Vergara, P.A. Navarrete-Encina, S. Salas, B. Conded, J. Carbajo, J.A. Squella, C. Camargo, J. Pharmaceut. Biomed. Anal. 44 (2007) 236.

[35] C. L´opez-Alarc´on, J.A. Squella, L.J. Núñnez-Vergara, H. Baez, C. Camargo, Rapid Commun. Mass Spectrom. 16 (2002) 2229.