APB *Advanced Pharmaceutical Bulletin,***2011**, 1(1), 1-9
doi: 10.5681/apb.2011.001
http://apb.tbzmed.ac.ir/

Synthesis of Novel 1,4- Dihydropyridine Derivatives Bearing Biphenyl-2'-Tetrazole Substitution as Potential Dual Angiotensin II Receptors and Calcium Channel Blockers

Javid Shahbazi Mojarrad[1,3], Zahra Zamani[1], Hossein Nazemiyeh[2,3], Saeed Ghasemi[1], Davoud Asgari[1,2]*

[1]*Department of Medicinal Chemistry, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran*

[2]*Research Center for Pharmaceutical Nanotechnology, Tabriz University of Medical Sciences, Tabriz, Iran*

[3]*Department of Pharmacognosy, of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran*

ARTICLE INFO

Article Type:
Research Article

Article History:
Received: 13May 2011
Accepted: 5 July 2011
ePublished: 20 July 2011

Keywords:
1,4-Dihydropyridine
Biphenyl-2'-tetrazole
Angiotensin II Blocker
Calcium Channel blocker

ABSTRACT

Introduction: We report the synthesis of novel 1,4-dihydropyridine derivatives containing biphenyl-2'-tetrazole moieties. We hypothesized that merging the key structural elements present in an AT_1 receptor antagonist with key structural elements in 1,4-dihydropyridine calcium channel blockers would yield novel analogs with potential 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´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-4(or 5)-yl]- 3, 5-pyridinedicarboxylate analogs. ***Methods***: These compounds were obtained by two methods starting from biphenyltetrazolyl-4-(or 5)-imidazolecarboxaldehyde intermediates employing in classical Hantzsch condensation reaction. In the first method, triphenylmethyl protecting group of 4- or 5-carboxaldehyde intermediate was first removed in acidic media and then classical Hantzsch reaction was employed in order to obtain the final products. In the second method, without further deprotection process, protected 4- or 5-carboxaldehyde intermediate directly was used in Hantzsch reaction. ***Results***: The second method was more efficient than the first method since the deprotection and ring closure reaction occurs simultaneously in one pot. ***Conclusion:*** Eight novel dihydropridines analogs were synthesized using classic Hantzsch condensation reaction. Chemical structures of the compounds were characterized by ^{1}H NMR, infrared and mass spectroscopy.

Introduction

Angiotensin receptor blockers (ARBs) such as Losartan and Telmisartan (Figure 1) are potent chemicals, which antagonize angiotensin II (Ang II) by preventing Ang II from binding to Ang II receptor (AT_1) on vascular smooth muscle. As a result, blood vessels dilate and blood pressure is reduced. The vasodilatation actions of ARBs are due to reduced concentration of intracellular Ca^{+2} ions.[1]

On the other hand, 1,4-dihydropyridines (DHP) containing substituted heterocycles on the C_4 position, such as Nifedipine,[2-8] have shown to reduce the influx of extracellular Ca^{+2} ions through the L-type potential-dependent calcium channel therefore reducing the hypertension.[1]Arun et al. have demonstrated that Nifedipine was able to vasodilate the contraction of thoracic aorta isolated from diabetic rats[9] induced by the Angiotensin II. The vazodilation of thoractic aorta was concluded to be due to enhanced functional coupling between AT_1 receptors and DHP-sensitive L-type calcium channels.

***Corresponding author:** Davoud Asgari (PhD), Department of Medicinal Chemistry, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran, P.O.Box: 51664-147766, Tel: 98-411-3372250; Fax: 98-411-3344798 , E-mail: dasgari@tbzmed.ac.ir or d.asgari@yahoo.com

We have hypothesized that merging the key structural elements present in an AT_1 receptor antagonists such as [2′-(acidic moiety)biphenyl-4-yl] imidazole pharmacophores with key structural elements in 1,4-dihydropyridine calcium channel blockers would yield compounds with potential dual activity for both receptors. Advantages of combination therapy of ARBs and CCBs which include low dose, low side effect, cardioprotection, renoprotection and anti-atherosclerosis are reported in literatures.[10-12]

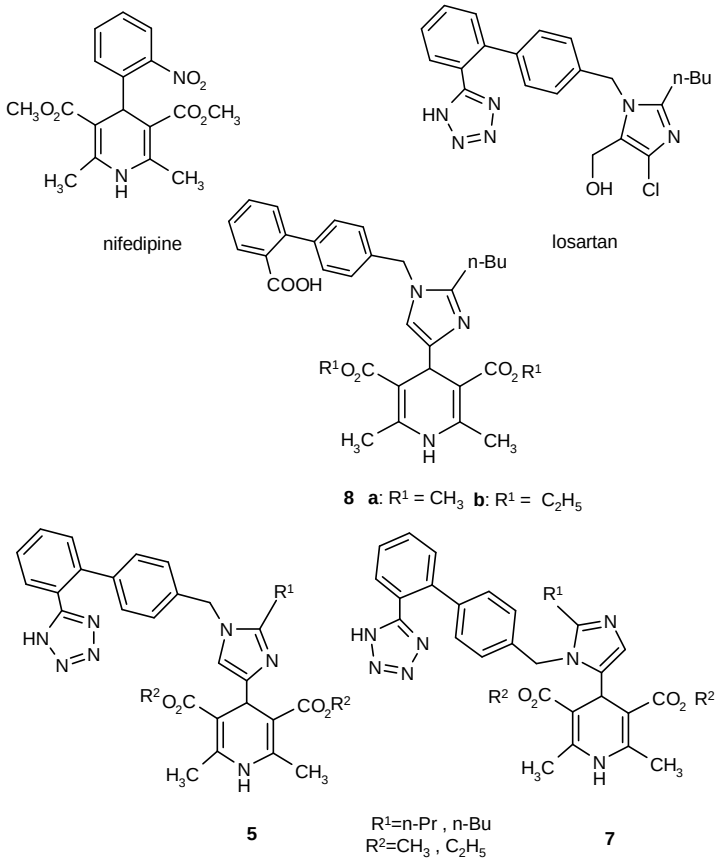


Figure 1. Chemical structure of nifedipine, losartan and designed dual CCB-ARB (compounds **5**, **7** and **8**)

In the previous work, this strategy led to the design and synthesis of novel 4-[2′-(carboxylic acid)biphenyl-4-yl] imidazolyl-1,4-dihydropyridine-3,5-dicarboxylates as potential dual acting angiotensin II inhibitors and calcium channel blockers.[13] Recently, Hadizadeh et al. have also reported the synthesis and activity studies of novel dihydropyridines containing methyl biphenyl -2'-caboxylic acid moieties. Among the synthesized analogs, compounds **8a** and **8b** (Figure 1) showed to have both calcium channel and AT_1 receptor blocking activities. Their effects on AT_1 receptors are 1000 and 100,000 times more than losartan respectively.[14] Herein, we report the design and synthesis of novel 4-[[2′-(tetrazole-5-yl)biphenyl-4-yl] imidazol-4 or 5-yl]-1,4-dihydropyridine-3,5-dicarboxylates (**5** and **7**) (Figure 1). These analogs were synthesized, first by N^1-alkylation of 2-alkylimidazole-4(5)-carboxaldehydes (**1**) with tritylated 4′-(bromomethyl) biphenyl-2-yl] tetrazole to afford compounds **2** and **3**. Then, using two methods, compounds **2** and **3** were subjected to Hantzsch condensation reactions[13-15] to obtain final dihydropyridine products in moderately yields.

Materials and methods

N-(triphenylmethyl-5-[4′-(bromomethyl) biphenyl-2-yl] tetrazole was purchased from Sinosource Pharma Ltd. (Hengsha Guangzhou, China). 2-Alkyl-imidazole-4(5)-carboxaldehyde**1** was prepared according to the literature.[13,16,17] 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 Bruken-Spectrospin 200 MHz spectrometer. (Varian, Switzerland).
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 (Potassium bromide 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 are within ± 0.4% of the theoretical values.

2-n-Propyl-1-[[2´-[(triphenylmethyl) tetrazole-5-yl] biphenyl -4-yl] methyl] imidazole-4(5)-carboxaldehyde (2a, 3a)

To a solution of 2-propyl-imidazole-4(5)-carboxaldehyde**1a** (5 g, 33 mmoles, 1 eq.) in dry dimethylformamide (90 mL), was added K_2CO_3 (9.1 g, 66 mmoles, 2 eq.) and the reaction mixture was stirred at room temperature for 30 minutes. Then *N*-(triphenylmethyl-5-[4´-(bromomethyl) biphenyl-2-yl] tetrazole (20 g, 73 mmoles, 1.1 eq.) was added and stirring continued for 24 hours. The reaction mixture was filtered and solvents removed under reduced pressure. To the residue was added water (30 mL) and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and solvents removed to give a viscous material. Column chromatography using toluene/ethyl acetate(80:20) as eluent afforded 2.84 g (13.5 %) of 2-propyl-1-[[2´-(triphenylmethyl) tetrazole-5-yl]biphenyl -4-yl]methyl]imidazole-5-carboxaldehyde (**3a**) (regioisomer of lower R*f* value) and 5.2 g (23 %) of 2-propyl-1-[[2´-[(triphenylmethyl) tetrazole-5-yl]biphenyl -4-yl]methyl]imidazole-4-carboxaldehyde (**2a**) (regioisomer of higher R*f* value).

2a: mp: 128 – 130 °C, ir (potassium bromide) ν 3050 (C-H, aromatic), 2964 (C-H, aliphatic), 1685 cm^{-1} (C = O). ^{1}H NMR (deuteriochloform) δ 9.81 (S, 1H, CHO), 8.03 (dd, 1H, $J_{3',4'}$ =6 , $J_{3',5'}$ =2.1 Hz, H-3' phenyl), 7.52-7.25 (m, 12H, H aromatic), 7.24 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 6.98 (dd, 6H, $J_{2",3"}$ =6.1, $J_{2",4"}$ =1.7 Hz, H orthotrityl), 6.93 (d, 2H, J=8.4 Hz, H-3,5 phenyl), 5.00 (s, 2H, NCH_2), 2.68 (t, 2H, J=7.4Hz, $CH_3CH_2\underline{CH_2}$), 1.90–1.72 (m, 2H, CH_2), 1.03 ppm (t, 3H, J=7.3Hz, CH_3).

3a: mp: 144 – 146°C, ir (potassium bromide) ν 3050 (C-H, aromatic), 2964 (C-H, aliphatic), 1666 cm^{-1} (C=O). ^{1}H NMR (deuteriochloform) δ 9.69 (S, 1H, CHO), 8.15 (dd, 1H, $J_{3',4'}$ =6 , $J_{3',5'}$ =2 Hz, H-3' phenyl), 7.81 (s, 1H, H imidazole), 7.53-7.25 (m, 12H, H aromatic), 7.14 (d, 2H, J=8.3 Hz, H-2,6 phenyl), 6.99 (dd, 6H, $J_{2",3"}$ =6.1, $J_{2",4"}$ =1.3 Hz, H orthotrityl), 6.88 (d, 2H, J=8.4 Hz, H-3,5 phenyl), 5.44 (s, 2H, NCH_2), 2.60 (t, 2H, J=7.3 Hz, $CH_3CH_2\underline{CH_2}$), 1.85–1.63 (m, 2H, CH_2), 0.97 ppm (t, 3H, =7.3 Hz, CH_3).

2-n-Butyl-1-[[2´-[(triphenylmethyl) tetrazole-5-yl] biphenyl -4-yl] methyl] imidazole-4(5)-carboxaldehyde (2b, 3b).

These compounds were prepared by the method described for (**2a, 3a**).

2b: mp: 134-136 °C, ir (potassium bromide) ν 3050 (C-H, aromatic), 2958 (C-H, aliphatic), 1605 cm^{-1} (C=O). ^{1}H NMR (deuteriochloform) δ 9.81(s, 1H, CHO), 8.04 (dd, 1H, $J_{3',4'}$=6.6, $J_{3',5'}$=3 Hz, H-3' phenyl), 7.56-7.23 (m, 12H, H aromatic), 7.21(d, 2H, J=8.2 Hz, H-2,6 phenyl), 6.97 (dd, 6H,$J_{2",3"}$=6, $J_{2",4"}$=1 Hz, H orthotrityl), 6.85 (d, 2H, J=8.4 Hz, H-3,5 phenyl), 5.00 (s, 2H, NCH_2), 2.71 (t, 2H, J=7.5 Hz, $CH_3CH_2CH_2\underline{CH_2}$), 1.84-1.24 (m, 4H, CH_2), 0.98 ppm (t, 3H, J=7.2 Hz, CH_3).

3b: mp: 148-150 °C, ir (potassium bromide) ν 3050 (C-H, aromatic), 2950 (C-H, aliphatic), 1672 cm^{-1} (C=O). ^{1}H NMR (deuteriochloform) δ 9.69 (S, 1H, CHO), 7.97 (dd, 1H, $J_{3',4'}$ =6.6, $J_{3',5'}$ =3 Hz, H-3 phenyl), 7.82 (s, 1H, H imidazole), 7.57-7.25 (m, 12H, H aromatic), 7.14 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 6.97 (dd. 6H, $J_{2",3"}$= 8, $J_{2",4"}$= 1.1 Hz, H orthotrityl), 6.77 (d, 2H, J=8.4 Hz, H-3,5 phenyl), 5.51 (s, 2H, NCH_2), 2.62 (t, 2H, J=7.3 Hz, $CH_3CH_2CH_2\underline{CH_2}$), 1.77 – 1.27 (m, 4H, CH_2), 0.93 ppm (t, 3H, J=7.2 Hz, CH_3).

First method: removal of protective trityl group and then dihydropyridine ring closure.

2-n-Propyl-1-[[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-4-carboxaldehyde (4a)

A solution of 2a (2.32 g, 3.8 mmoles) in a mixture of tetrahydrofuran (55 mL) and 10% HCl (27.5 mL) was stirred at 25°C for 4 hours. To the reaction mixture, 30 mL of 10% sodium hydroxide was added and the solvents removed under vacuum. Then water was added to the residue and filtered. Finally pH of the filtrate was adjusted to 3-4 and filtered again to separate **4a** (1.01 g, 71%).
Compounds **4b**, **6a** and **6b** were prepared according to the method described for 4a with the 69%, 82% and 65% yields respectively. The crude product was used in the Hantzsch reaction to provide dihydropyridine compounds (**5a-d** and **7a-d**).

Dimethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-propyl-1-[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-4-yl]-3,5-pyridinedicarboxylate (5a)

A solution of 4a (0.52 g, 1.2 mmoles, 1eq.), methyl acetoacetate (0.3 g, 2.6 mmoles, 2.2 eq.) and ammonium hydroxide 25% (0.4 mL) in methanol (4.8 mL) was

protected from light and stirred at 25 °C for 30 minutes and then refluxed overnight. The solvent was removed under vacuum and then purified with column chromatography (elution: chloroform-methanol 95:5) to provide **5a** in (0.35 g) 44% yield with mp 148 – 150 °C; IR (potassium bromide) ν 3417 (N-H), 3050 (C-H, aromatic), 2950 (C-H, aliphatic), 1695 (C=O), 1498 cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO-d_6) δ 9.09 (br s, 1H, NH), 7.61–7.39 (m, 4H, H aromatic), 7.09 (d, 2H, J=8 Hz, H-2,6 phenyl), 6.98 (d, 2H, J=8.2 Hz, H-3,5 phenyl), 6.80 (s, 1H, H imidazole), 5.12 (s, 2H, NCH_2), 4.88 (s, 1H, HC_4 DHP), 3.55 (s, 6H, OCH_3), 2.61 (t, 2H, J=7 Hz, $CH_3CH_2\underline{CH_2}$), 2.22 (s, 6H, CH_3 DHP), 1.51–1.40 (m, 2H, CH_2), 0.85 ppm (t, 3H, J=7.1 Hz, CH_3). ms: m/z (%) 524 (2), 286 (31), 373 (2), 358 (14), 288 (33), 252 (27), 229 (34), 192 (100), 165 (61), 134 (67), 96 (89), 45 (57). *Anal.*calcd. for $C_{31}H_{33}N_7O_4$: C, 65.59; H, 5.86; N, 17.27. Found: C, 65.72; H, 5.99; N, 17.02.

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-propyl-1-[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-4-yl] -3,5-pyridinedicarboxylate (5b)

A solution of 4a (0.48 g, 1.3 mmoles), ethyl acetoacetate (0.37 g, 2.9 mmoles) and ammonium hydroxide 25% (0.42 mL) in ethanol (5.2 mL) was reacted according to the method described for 4a. Purification was done with column chromatography (elution: chloroform-methanol 95:5) to afford **5b** in (0.32 g) 42% yield with mp 149 – 151 °C;
IR (potassium bromide) ν 3450 (N-H), 3050 (C-H, aromatic), 2974 (C-H, aliphatic), 1685 (C=O), 1498 cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO-d_6) δ 8.99 (br s, 1H, NH), 7.62–7.39 (m, 4H, H aromatic), 7.09 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 7.01 (d, 2H, J=8.4 Hz, H-3,5 phenyl), 6.84 (s, 1H, H imidazole), 5.15 (s, 2H, NCH_2), 4.88 (s, 1H, HC_4 DHP), 4.11–3.93 (m, 4H, OCH_2), 2.64 (t, 2H, J=7.4 Hz, $CH_3CH_2\underline{CH_2}$), 2.22 (s, 6H, CH_3 DHP), 1.51–1.40 (m, 2H, CH_2), 1.14 (t, 6H, J=7.1 Hz, $OCH_2\underline{CH_3}$), 0.84 ppm (t, 3H, J=7.3 Hz, CH_3). ms: m/z (%) 373 (6), 302 (14), 272 (18), 251 (33), 206 (66), 225 (47), 192 (100), 178 (86), 165 (54). *Anal.*calcd. for $C_{33}H_{37}N_7O_4$: C, 66.54; H, 6.26; N, 16.46. Found: C, 66.45; H, 6.53; N, 16.59.

Dimethyl 1, 4-dihydro-2, 6-dimethyl -4-[2-n-butyl-1-[[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-4-yl] -3,5-pyridinedicarboxylate (5c)

A solution of 4b (0.50 g, 1.3 mmoles), methyl acetoacetate (0.35 g, 3 mmoles) and ammonium hydroxide 25% (0.50 mL) in methanol (5 mL) was reacted according to the method described for 5a. Purification was done with column chromatography (elution: chloroform-methanol 95:5) to afford **5c** in (0.14 g) 19% yield with mp 153 – 155 °C; IR (potassium bromide) ν 3411 (N-H), 3064 (C-H, aromatic), 2954 (C-H, aliphatic), 1693 (C=O), 1500cm^{-1}(C=C, aromatic). ^{1}H NMR (DMSO-d_6) δ 9.14 (br s, 1H, NH), 7.63 – 7.47 (m, 4H, H aromatic), 7.10 (d, 2H, J=8.3 Hz, H-2,6 phenyl), 6.99 (d, 2H, J=8.3 Hz, H-3,5 phenyl), 6.87 (s, 1H, H imidazole), 5.11 (s, 2H, NCH_2), 4.88 (s, 1H, HC_4 DHP), 3.56 (s, 6H, OCH_3), 2.61 (t, 2H, J=8 Hz, $CH_3CH_2\underline{CH_2}$), 2.22 (s, 6H, CH_3 DHP), 1.46–1.14 (m, 4H, CH_2), 0.83 ppm (t, 3H, J=7.3 Hz, CH_3). ms: m/z (%) 372 (10), 330 (24), 273 (11), 252 (6), 223 (34), 192 (100), 165 (79), 134 (81). *Anal.*calcd. for $C_{32}H_{35}N_7O_4$: C, 66.07; H, 6.06; N, 16.86. Found: C, 65.93; H, 6.32; N, 16.70.

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-butyl-1-[[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-4-yl] -3, 5-pyridinedicarboxylate (5d)

A solution of 4b (0.51 g, 1.3 mmoles), ethyl acetoacetate (0.38 g, 2.9 mmoles) and ammonium hydroxide 25% (0.5 mL) in ethanol (5 mL) was reacted according to the method described for 5a. Purification was done with column chromatography (elution: chloroform-methanol 95:5) to afford **5d** in (0.31 g) 38% yield with mp 154 – 156 °C; IR (potassium bromide) ν 3386 (N-H), 3050 (C-H, aromatic), 2.964 (C-H, aliphatic), 1685 (C=O), 1496 cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO-d_6) δ 8.88 (br s, 1H, NH), 7.62–7.39 (m, 4H, H aromatic), 7.09 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 7.00 (d, 2H, J=8.2 Hz, H-3,5 phenyl), 6.82 (s, 1H, H imidazole), 5.14 (s, 2H, NCH_2), 4.88 (s, 1H, HC_4 DHP), 4.11–3.88 (m, 4H, OCH_2), 2.61 (t, 2H, J=8.2 Hz, $CH_2CH_2\underline{CH_2}$), 2.21 (s, 6H, CH_3 DHP), 1.41–1.20 (m, 4H, CH_2), 1.15 (t, 6H, J=7.1 Hz, $OCH_2\underline{CH_3}$), 0.82 ppm (t, 3H, J=7.3 Hz, CH_3). ms: m/z (%) 387 (9), 359 (5), 316 (13), 278 (13), 251 (20), 206 (72), 179 (100), 165 (28). *Anal.*calcd. for $C_{34}H_{39}N_7O_4$: C, 66.97; H, 6.45; N, 16.08. Found: C, 66.12; H, 6.61; N, 16.28.

Dimethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-propyl-1-[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-5-yl]-3,5-pyridinedicarboxylate (7a)

A solution of 6a (0.15 g, 0.4 mmoles), methyl acetoacetate (0.10 g, 0.90 mmoles) and ammonium hydroxide 25% (0.10 mL) in methanol (2 mL) was reacted according to the method described for 5a. Purification was done with column chromatography (elution: chloroform-methanol 95:5) to afford **7a** in (0.11 g) 48% yield with mp 174 – 176°C;
IR (potassium bromide) ν 3400 (N-H), 3046 (C-H, aromatic), 2950 (C-H, aliphatic), 1680 (C=O), 1490 cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO-d_6) δ 9.16 (br s, 1H, NH), 7.59–7.38 (m, 4H, H aromatic), 7.07 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 6.73 (d, 2H, J=8 Hz, H-3,5 phenyl), 6.49 (s, 1H, H imidazole), 5.26 (s, 2H, NCH_2), 4.91 (s, 1H, HC_4 DHP), 3.36 (s, 6H, OCH_3), 2.33 (t, 2H,

J=7.4 Hz, CH_3 $CH_2\underline{CH_2}$), 2.17 (s, 6H, CH_3 DHP), 1.53–1.41 (m, 2H, CH_2), 0.81 ppm (t, 3H, J=7.3 Hz, CH_3). ms: m/z (%), 358 (6), 300 (6), 252 (12), 232 (13), 223 (20), 192 (81), 178 (87), 165 (100). *Anal*.calcd. for $C_{31}H_{33}N_7O_4$: C, 65.59; H, 5.86; N, 17.27. Found: C, 65.77; H, 6.04; N, 17.38.

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-propyl-1-[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-5-yl]-3, 5-pyridinedicarboxylate (7b)

A solution of 6a (0.22 g, 0.59 mmoles), ethyl acetoacetate (0.17 g, 1.3 mmoles) and ammonium hydroxide 25% (0. 20 mL) in ethanol (2.5 mL) was reacted according to the method described for 5a. Purification was done with column chromatography (elution: chloroform-methanol 95:5) to afford **7b** in (0.15 g) 43% yield with mp 170 – 172 °C; IR (potassium bromide) ν 3450 (N-H), 3050 (C-H, aromatic), 2974 (C-H, aliphatic), 1676 (C=O), 1496cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO-d_6) δ 9.08 (br s, 1H, NH), 7.70–7.40 (m, 4H, H aromatic), 7.05 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 6.75 (d, 2H, J=8.3 Hz, H-3,5 phenyl), 6.52 (s, 1H, H imidazole), 5.26 (s, 2H, NCH_2), 5.01 (s, 1H, HC_4 DHP), 3.98–3.75 (m, 4H, OCH_2), 2.32 (t, 2H, J=7.4 Hz, $CH_3CH_2\underline{CH_2}$), 2.13 (s, 6H, CH_3 DHP), 1.49–1.29 (m, 2H, CH_2), 1.08 (t, 6H, J=7 Hz, $OCH_2\underline{CH_3}$), 0.79 ppm (t, 3H, J=7.4 Hz, CH_3). ms: m/z (%) 595 [M^++1] (2), 300 (5), 252 (10), 225 (20), 207 (38), 78 (25), 46 (100). *Anal*.calcd. for $C_{33}H_{37}N_7O_4$: C, 66.54; H, 6.26; N, 16.46. Found: C, 66.76; H, 6.21; N, 16.53.

Dimethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-butyl-1-[[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-5-yl]-3, 5-pyridinedicarboxylate (7c).

A solution of 6b (0.36 g, 0.93 mmoles), methyl acetoacetate (0.23 g, 2.05 mmoles) and ammonium hydroxide 25% (0.30 mL) in methanol (4 mL) was reacted according to the method described for 5a. Purification was done with column chromatography (elution: chloroform-methanol 95:5) to afford **7c** in (0.28 g) 52% yield with mp 156 – 158 °C; IR (potassium bromide) ν 3442 (N-H), 3050 (C-H, aromatic), 2958 (C-H, aliphatic), 1704 (C=O), 1496cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO-d_6) δ 9.19 (br s, 1H, NH), 7.62–7.43 (m, 4H, H aromatic), 7.07 (d, 2H, J= 7.5 Hz, H-2,6 phenyl), 6.78 (d, 2H, J=8 Hz, H-3,5 phenyl), 6.58 (s, 1H, H imidazole), 5.32 (s, 2H, NCH_2), 4.95 (s, 1H, HC_4 DHP), 3.38 (s, 6H, OCH_3), 2.38 (t, 2H, J=7.2 Hz, $CH_3CH_2\underline{CH_2}$), 2.18 (s, 6H, CH_3 DHP), 1.44–1.11 (m, 4H, CH_2), 0.77 ppm (t, 3H, J=7.2 Hz, CH_3). ms: m/z (%) 582 (4), 535 (12), 347 (11), 314 (12), 249 (14), 221 (28), 192 (100), 178 (95), 165 (54). *Anal*.calcd. for $C_{32}H_{35}N_7O_4$: C, 66.07; H, 6.06; N, 16.86. Found: C, 66.31; H, 5.98; N, 16.95.

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-butyl-1-[[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-5-yl]-3, 5-pyridinedicarboxylate (7d)

A solution of 6b (0.36 g, 0.93 mmoles), ethyl acetoacetate (0.26 g, 2.05 mmoles) and ammonium hydroxide 25% (0.3 mL) in ethanol (4 mL) was reacted according to the method described for 5a. Purification was done with column chromatography (elution: chloroform-methanol 95:5) to afford **7d** in (0.27 g) 47% yield with mp 150 – 152 °C; IR (potassium bromide) ν3423 (N-H), 3072 (C-H, aromatic), 2964 (C-H, aliphatic), 1677 (C=O), 1492 cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO -d_6) δ 9.16 (br s, 1H, NH), 7.65–7.41 (m, 4H, H aromatic), 7.05 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 6.78 (d, 2H, J=8.2 Hz, H-3,5 phenyl), 6.60 (s, 1H, H imidazole), 5.31 (s, 2H, NCH_2), 5.04 (s, 1H, HC_4 DHP), 3.99–3.76 (m, 4H, OCH_2), 2.38 (t, 2H, J=7.2 Hz, $CH_3CH_2\underline{CH_2}$), 2.14 (s, 6H, CH_3 DHP), 1.40–1.09 (m, 4H, CH_2), 1.08 (t, 6H, J=7.1 Hz, $OCH_2\underline{CH_3}$), 0.75 ppm (t, 3H, J=7.3 Hz, CH_3). ms: m/z (%) 287 (6), 252 (10), 246 (18), 206 (27), 174 (42), 106 (11), 77 (19), 45 (100). *Anal*.calcd. for $C_{34}H_{39}N_7O_4$: C, 66.97; H, 6.45; N, 16.08. Found: C, 67.22; H, 6.71; N, 15.81.

Second method:Dihydropyridine ring closure

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-propyl-1-[[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-4-yl]-3, 5-pyridinedicarboxylate (5b).

A solution of 2a (1.2 g, 1.95 mmoles), ethyl acetoacetate (0.56 g, 4.3 mmoles) and ammonium hydroxide (0.75 mL) in ethanol (7.5 mL) was protected from light and stirred at 25°C for 30 minutes and then refluxed over night. The solvents were removed under vacuum and purification was achieved with column chromatography (elution: chloroform-methanol 95:5) to provide **5b** in(0.51g) 0.44% yield with mp 151 – 152 °C; IR (potassium bromide) ν 3450 (N-H), 3050 (C-H, aromatic), 2974 (C-H, aliphatic), 1685 (C=O), 1498cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO-d_6) δ 8.99 (br s, 1H, NH), 7.62–7.39 (m, 4H, H aromatic), 7.09 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 7.01 (d, 2H, J=8.4 Hz, H-3,5 phenyl), 6.84 (s, 1H, H imidazole), 5.15 (s, 2H, NCH_2), 4.88 (s, 1H, HC_4 DHP), 4.11–3.93 (m, 4H, OCH_2), 2.64 (t, 2H, J=7.4 Hz, $CH_3CH_2\underline{CH_2}$), 2.22 (s, 6H, CH_3 DHP), 1.51–1.40 (m, 2H, CH_2), 1.14 (t, 6H, J=7.1 Hz, $OCH_2\underline{CH_3}$), 0.84 ppm (t, 3H, J=7.3 Hz, CH_3). *Anal*.calcd. for $C_{33}H_{37}N_7O_4$: C, 66.54; H, 6.26; N, 16.46. Found: C, 66.36; H, 6.06; N, 16.61.

Dimethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-butyl-1-[[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-4-yl]-3, 5-pyridinedicarboxylate (5c)

A solution of 2b (0.81 g, 1.3 mmoles), methyl acetoacetate (0.37 g, 2.9 mmoles) and ammonium hydroxide 25% (0.5 mL) in methanol (5 mL) was reacted according to the method described in second method for compound 5b. Purification was done with column chromatography (elution: chloroform-methanol 95:5) to afford **5c** in(0.36 g) 34% yield with mp 154 – 156 °C; IR (potassium bromide) ν 3411 (N-H), 3064 (C-H, aromatic), 2954 (C-H, aliphatic), 1693 (C=O), 1500 cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO-d_6) δ 9.14 (br s, 1H, NH), 7.63 – 7.47 (m, 4H, H aromatic), 7.10 (d, 2H, J=8.3 Hz, H-2,6 phenyl), 6.99 (d, 2H, J=8.3 Hz, H-3,5 phenyl), 6.87 (s, 1H, H imidazole), 5.11 (s, 2H, NCH_2), 4.88 (s, 1H, HC_4 DHP), 3.56 (s, 6H, OCH_3), 2.61 (t, 2H, J=8 Hz, $CH_3CH_2\underline{CH_2}$), 2.22 (s, 6H, CH_3 DHP), 1.46–1.14 (m, 4H, CH_2), 0.83 ppm (t, 3H, J=7.3 Hz, CH_3). *Anal.*calcd. for $C_{32}H_{35}N_7O_4$: C, 66.07; H, 6.06; N, 16.86. Found: C, 66.24; H, 6.18; N, 16.81.

Dimethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-propyl-1-[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-5-yl]-3, 5-pyridinedicarboxylate (7a)

A solution of 3a (1.0 g, 1.6 mmoles), methyl acetoacetate (0.41 g, 3.6 mmoles) and ammonium hydroxide 25% (0.6 mL) in methanol (6 mL) was reacted according to the method described in second method for compound 5b. Purification was done with column chromatography (elution: chloroform-methanol 95:5) to afford **7a** in (0.38 g) 42% yield with mp 174 – 176°C; IR (potassium bromide) ν 3400 (N-H), 3046 (C-H, aromatic), 2950 (C-H, aliphatic), 1680 (C=O), 1490 cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO- d_6) δ 9.16 (br s, 1H, NH), 7.59–7.38 (m, 4H, H aromatic), 7.07 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 6.73 (d, 2H, J=8 Hz, H-3,5 phenyl), 6.49 (s, 1H, H imidazole), 5.26 (s, 2H, NCH_2), 4.91 (s, 1H, HC_4 DHP), 3.36 (s, 6H, OCH_3), 2.33 (t, 2H, J=7.4 Hz, CH_3 $CH_2\underline{CH_2}$), 2.17 (s, 6H, CH_3 DHP), 1.53–1.41 (m, 2H, CH_2), 0.81 ppm (t, 3H, J=7.3 Hz, CH_3). *Anal.*calcd. for $C_{31}H_{33}N_7O_4$: C, 65.59; H, 5.86; N, 17.27. Found: C, 65.46; H, 5.94; N, 17.48.

Diethyl 1, 4-dihydro-2, 6-dimethyl-4-[2-n-propyl-1-[2´-(1H-tetrazole-5-yl) biphenyl -4-yl] methyl] imidazole-5-yl]-3, 5-pyridinedicarboxylate (7b)

A solution of 3a (1.0 g, 1.6 mmoles), ethyl acetoacetate (0.47 g, 3.6 mmoles) and ammonium hydroxide 25% (0.6 mL) in ethanol (6 mL) was reacted according to the method described in second method for compound 5b. Purification was done with column chromatography (elution: chloroform-methanol 95:5) to afford **7b** in (0.45 g) 47% yield with mp 169 – 171 °C; IR (potassium bromide) ν 3450 (N-H), 3050 (C-H, aromatic), 2974 (C-H, aliphatic), 1676 (C=O), 1496cm^{-1} (C=C, aromatic). ^{1}H NMR (DMSO- d_6) δ 9.08 (br s, 1H, NH), 7.70–7.40 (m, 4H, H aromatic), 7.05 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 6.75 (d, 2H, J=8.3 Hz, H-3,5 phenyl), 6.52 (s, 1H, H imidazole), 5.26 (s, 2H, NCH_2), 5.01 (s, 1H, HC_4 DHP), 3.98–3.75 (m, 4H, OCH_2), 2.32 (t, 2H, J=7.4 Hz, $CH_3CH_2\underline{CH_2}$), 2.13 (s, 6H, CH_3 DHP), 1.49–1.29 (m, 2H, CH_2), 1.08 (t, 6H, J=7 Hz, $OCH_2\underline{CH_3}$), 0.79 ppm (t, 3H, J=7.4 Hz, CH_3). *Anal.*calcd. for $C_{33}H_{37}N_7O_4$: C, 66.54; H, 6.26; N, 16.46. Found: C, 66.61; H, 6.14; N, 16.32.

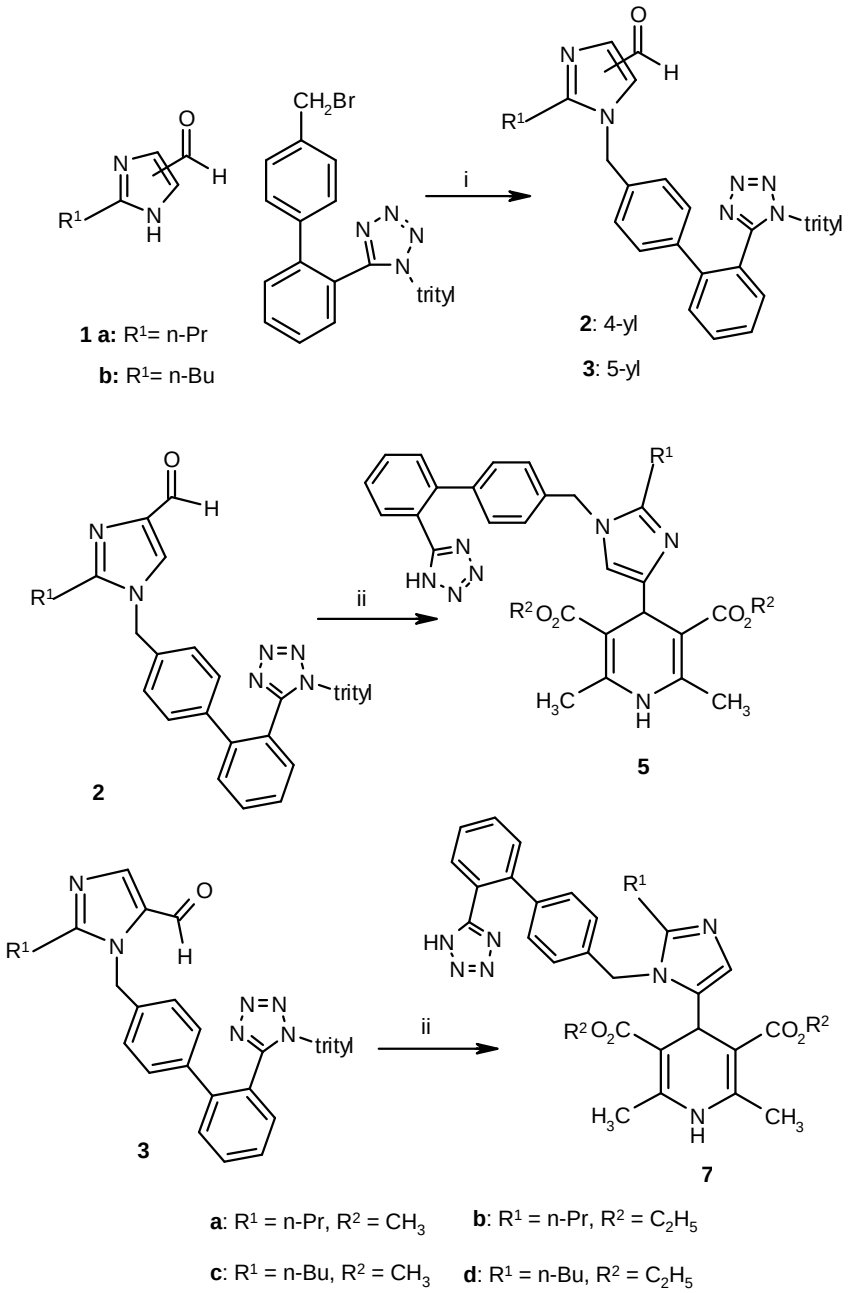
Results and discussion

2-alkylimidazole-4(5)-carboxaldehyde derivatives were prepared according to procedure described previously.[13,16,17] The N^1-alkylation of 2-alkylimidazole-4(5)-carboxaldehydederivativeswith*N*-1-(triphenylmethyl)-5-[4´-(bromomethyl)biphenyl-2-yl] tetrazole afforded biphenyl imidazole regioisomers**2** and **3** in 1:2 ratio respectively (Scheme 1). The regioisomers were then separated using column chromatography.
The structures of regioisomers were confirmed by ^{1}H NMR. ^{1}H NMR spectra of regioisomer **3** showed the benzylichydrogens (*N*-CH_2Ph) were more deshielded (5.51 ppm) than benzylichydrogens of regioisomer 1 (5.00 ppm).

Using two methods described below, the final products were obtained in moderate yields.
In the first method, trityl protecting group was deprotected in acidic media (10% HCl solution), then classic Hantzsch reaction was performed using alkyl acetoacetate and 25% ammonium hydroxide solution to obtain the final dihydropyridine products **(5a-d** and **7a-d)** in moderate yields. Chemical structures of the compounds were analyzed by ^{1}H NMR, infrared, mass spectroscopy and elemental analysis. Based on ^{1}H NMR of compounds **5** and **7**anddepending on the type of regioisomers, protons of H-N, H-C_4, $O\underline{CH_2}CH_3$ and OCH_3 on 1,4-dihydropyridines were appeared within 8.6-10.6 ppm as a broad singlet, 4.8-5.1 ppm as a singlet, 3.7-4.1 as multiplet and 3.4-3.6 ppm as a singlet respectively. The six hydrogens of 2,6-dimethyl-DHP are appeared as a singlet in 2.2 ppm. The ^{1}H NMR spectrums corresponding to the methylene group on the carboethoxy substituent showed a rather more complex splitting pattern than a simple quartet. This behavior is due to existence of two diasterotopichydrogens of the methylene group. Similar splitting pattern for diethyl 4-(nitroaryl)-1,4-dihydropyridine-3,5-dicarboxylate derivatives has been reported previously.[13,18]
In addition, mass spectroscopy analysis of **5** and **7** showed expectable fragmentation and hence established the structure of dihydropyridine derivatives. The Mass spectrum fragmentation pattern of compound **5a** is shown in Figure2 and is in agreement with the suggested structure. Comparable fragmentations were previously reported for some dihydropyridine derivatives.[13,19-21]

In the second method, trityl protected regioisomer2 or **3** were subjected to classic Hantzsch reaction to afford the final analogs in moderate yields. ^{1}H NMR indicated that trityl protective group was removed during the dihydropyridine ring closure reaction, thereby avoiding addition step to remove the trityl protecting group. All aromatic hydrogens for trityl group were disappeared (6H at 6.98 ppm as di-doublet for H-ortho and 9H at 7.52-7.25 ppm as multiple for H-meta and para).

Thus, the second method was concluded to be more efficient than the first method since the deprotection and ring closure reaction occurs simultaneously in one pot.



Scheme 1. Condition of synthesis: i) K_2CO_3, DMF, room temperature and then isomer resolution; ii) **first method:** 1) HCl 10% to afford deprotected compound 4 and 6; 2) $CH_3COCO_2R^2$, NH_3 25%, reflux; **second method:** $CH_3COCO_2R^2$, NH_3 25%, reflux (deprotection and ring closure in one pot)

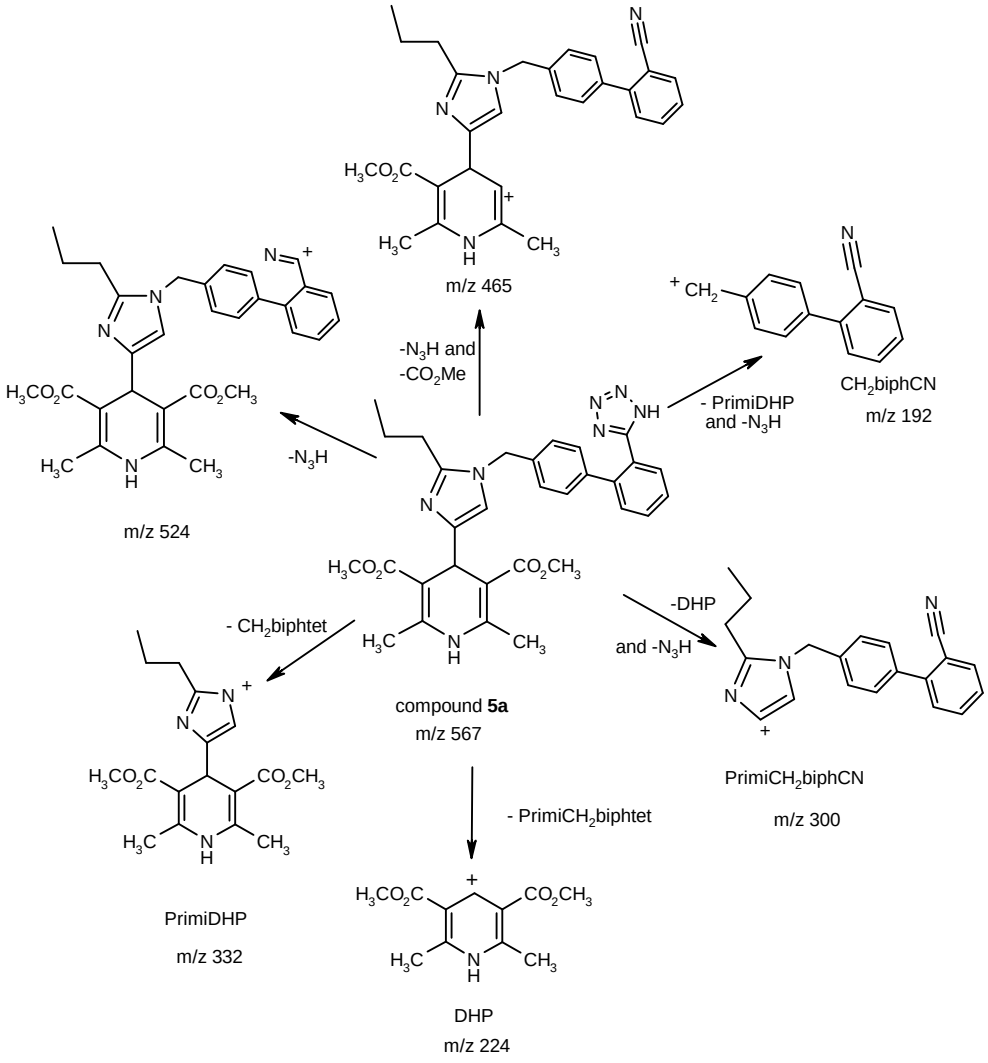


Figure 2. Proposed fragmentation pathways of compound 5a in mass spectroscopy

Conclusion

Eight novel dihydropridines analogs were synthesized using classic Hantzsch condensation reaction. The key structural elements present in an AT_1 receptor antagonist (biphenyltetrazolyl imidazole) were merged with key structural elements in calcium channel blockers (1,4-dihydropyridine) to afford the products with potential dual activity for both receptors. The chemical structures of novel compounds were confirmed with ^{1}H NMR and mass spectroscopy analysis. The dihydropridines analogs were obtained by two methods. The second method was more efficient than the fisrt method since the deprotection and ring closure reaction occurs simultaneously in one pot.

Ethical issues

Not Applicable.

Conflict of interests

The author claims that there is no conflict of interest.

Acknowledgment

We are grateful to the research vice of Tabriz University of Medical Sciences for financial support. We also thank the Drug Applied Research Center of Tabriz University of Medical Sciences for providing facilities for ^{1}H NMR spectroscopy. The authors wish to acknowledge Dr. Mohsen Amini, a member of faculty of pharmacy Tehran University of Medical Sciences for providing mass spectroscopy.

References

1. Williams DA, Lemke TL. Foye`s Principles of Medical Chemistry. 15th ed. Philadelphia: Lippincott Williams & Wilkins; 2002. 533-561.
2. Shafiee A, Hadizadeh F, Foroumadi A. Syntheses of substituted pyrrolo [3,2- d] imidazoles. *Ind J Chem* 1997; 36: 813.
3. Foroumadi A, Analuie N, Rezvanipour M, Sepehri G, Najafipour H, Sepehri H. Synthesis and calcium channel antagonist activity of nifedipine analogues with methylthio imidazole substituent. *IL Farmaco* 2002; 57:195.
4. Hosseini M, Miri R, Amini M, Mirkhani H, Hemmateenejad B, Ghodsi S, Alipour E, Shafiee A. Synthesis, QSAR and calcium channel antagonist activity of new 1,4 dihydropyridine derivatives containing1-methyl-4,5-dichloroimidazolyl substituents. *Arch Pharm (Weinheim)* 2007; 340: 549-56.
5. Shafiee A, Rastkary N, Jorjani M. Synthesis and calcium channel antagonist activity of new 1,4-dihydropyridine derivatives containing 4-nitroimidazolyl substituents. *Arzneimittelforschung* 2002; 52: 537-42.
6. Shafiee A, Rastkary N, Jorjani M, Shafaghi B. Synthesis and antihypertensive activities of new 1,4-dihydropyridine containing nitroimidazolyl substituent with a nitrooxy group at the 3-ester position. *Arch Pharm (Weinheim)* 2002; 335: 69-76.
7. Shahbazi-Mojarrad J, Miri R, Knaus EE. Design and synthesis of methyl 2-methyl-7,7-dihalo-5-phenyl-2-azabicyclo[410] hept-3-ene-4-carboxylates with calcium channel antagonist activity. *Bioorg Med Chem* 2004; 12: 3215-20.
8. Shahbazi-Mojarrad J, Vo D, Velazquez C, Knaus EE. Design and synthesis of alkyl 7,7-dihalo-3-methyl-5-(nitrophenyl)-2-azabicyclo[410]hept-3-ene-4-carboxylates with calcium channel antagonist activity. *Bioorg Med Chem* 2005; 13: 4085.
9. Arun KHS, Kaul CL, Ramarao P. AT1 receptors and L-type calcium channels: functional coupling in supersensitivity to angiotensin II in diabetic rats. *Cardiovascular Research* 2005; 65: 374-386
10. Hasebea N, Kikuchi K. Controlled release nifedipine and candesartan low-dose combination therapy in patients with essential hypertension: NICE Combi (Nifedipine and Candesartan Combination) Study. *Journal of Hypertension* 2005; 23: 445.
11. Okuda NT, Hayashi Mori T, Inamoto S, et al. Nifedipine enhances the cardioprotective effect of an angiotensin-II receptor blocker in an experimental animal model of heart failure. *Hypertens Res* 2005; 28: 431-8.
12. Swales P, Williams B. Calcium channel blockade in combination with angiotensin-converting enzyme inhibition or angiotensin II (AT1-receptor) antagonism in hypertensive diabetics and patients with renal disease and hypertension. *J Renin Angiotensin Aldosterone Syst* 2002; 3:79-89.
13. Shahbazi-Mojarrad J, Nazemiyeh H, Kaviani F. 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. *J Iran Chem Soc* 2010; 7: 171.
14. Hadizadeh F, Imenshahidi M, Esmaili P, Taghiabadi M. Synthesis and Effects of Novel Dihydropyridines as Dual Calcium Channel Blocker and Angiotensin Antagonist on Isolated Rat Aorta. *Iranian Journal of Basic Medical Sciences* 2010; 13: 195.
15. Sausins AE, Duburs G. Synthesis of 1,4-dihydropyridine in Chemistry of Heterocyclic Compounds, Springer New York,. 1992; 28(4): 363.
16. Weidenhagen R, Herrmann R. Eine neue synthese von imidazol- derivaten. *Ber* 1935; 68: 1953- 1961.
17. Carini DJ, Duncia JV, Aldrich PE, Chiu AT, Johnson AL, Pierce WA, et al. Nonpeptide angiotensin II receptor antagonists: the discovery of a series of N-(biphenylylmethyl) imidazoles as potent, orally active antihypertensives. *J Med Chem* 1991; 34: 2525-47.
18. Shafiee A, ShahbaziMojarrad J, Jalili MA, Adhami HR, Hadizadeh F. Syntheses of substituted pyrrolo [2,3-d]imidazole-5-carboxylates and substituted pyrrolo[3,2-d]imidazole-5-carboxylates. J *Heterocycl Chem* 2002; 39: 367.
19. DaSilva JA, Barríab CS, Jullianb C, Navarreteb P, NúñezVergaraa L, Squellaa JA. Unexpected diastereotopic behaviour in the 1H NMR spectrum of 1,4-dihydropyridine derivatives triggered by chiral and prochiralcentres. *J Braz Chem Soc* 2005; 16: 112.
20. Núnnez-Vergara LJ, Navarrete-Encina PA, Salas S, Conde B, Carbajo j, Squella JA, Camargo C. Analyses by GC-MS and GC-MS-MS of the hantzsch synthesis products using hydroxy- and methoxy-aromatic aldehydes. *J Pharm Biomed Anal* 2007; 44: 236-42.
21. Lopez-Alarcon C, Squella JA, Núnnez-Vergara LJ, Baez H, Camargo C. Gas chromatography/mass spectrometric study of non-commercial C-4-substituted 1,4-dihydropyridines and their oxidized derivatives. *Rapid Commun Mass Spectrom* 2002; 16: 2229-38.