

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

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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 AT₁ 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 dihydropyridines analogs were synthesized using classic Hantzsch condensation reaction. Chemical structures of the compounds were characterized by ¹H 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 (AT₁) 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 C₄ 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 rats⁹ induced by the Angiotensin II. The vazodilation of thoracic aorta was concluded to be due to enhanced functional coupling between AT₁ receptors and DHP-sensitive L-type calcium channels.

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We have hypothesized that merging the key structural elements present in an AT₁ 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

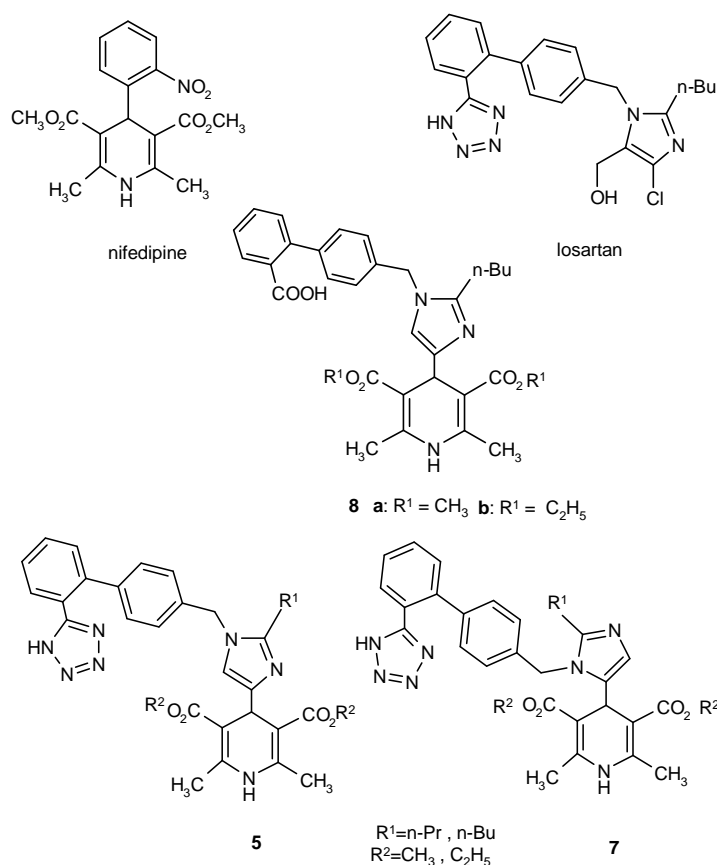


Figure 1. Chemical structure of nifedipine, losartan and designed dual CCB-ARB (compounds **5**, **7** and **8**)

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'-carboxylic acid moieties. Among the synthesized analogs, compounds **8a** and **8b** (Figure 1) showed to have both calcium channel and AT₁ receptor blocking activities. Their effects on AT₁ 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 N¹-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 reactions¹³⁻¹⁵ 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. ^1H NMR spectra were obtained with a Bruker-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 $\pm 0.4\%$ 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 mmol, 1 eq.) in dry dimethylformamide (90 mL), was added K_2CO_3 (9.1 g, 66 mmol, 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 mmol, 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). ^1H NMR (deuteriochloroform) 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, $J=7.4$ Hz, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.90-1.72 (m, 2H, CH_2), 1.03 ppm (t, 3H, $J=7.3$ Hz, CH_3).

3a: mp: 144 – 146 °C, ir (potassium bromide) ν 3050 (C-H, aromatic), 2964 (C-H, aliphatic), 1666 cm^{-1} (C=O). ^1H NMR (deuteriochloroform) 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.85-1.63 (m, 2H, CH_2), 0.97 ppm (t, 3H, $J=7.3$ 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). ^1H NMR (deuteriochloroform) 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, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$), 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). ^1H NMR (deuteriochloroform) 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, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$), 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 mmol) 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 mmol, 1 eq.), methyl acetoacetate (0.3 g, 2.6 mmol, 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). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 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 $\text{C}_{31}\text{H}_{33}\text{N}_7\text{O}_4$: 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 mmol), ethyl acetoacetate (0.37 g, 2.9 mmol) 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). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 2.22 (s, 6H, CH_3 DHP), 1.51–1.40 (m, 2H, CH_2), 1.14 (t, 6H, J=7.1 Hz, OCH_2CH_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 $\text{C}_{33}\text{H}_{37}\text{N}_7\text{O}_4$: 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 mmol), methyl acetoacetate (0.35 g, 3 mmol) 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), 1500 cm^{-1} (C=C, aromatic). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 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 $\text{C}_{32}\text{H}_{35}\text{N}_7\text{O}_4$: 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 mmol), ethyl acetoacetate (0.38 g, 2.9 mmol) 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), 2964 (C-H, aliphatic), 1685 (C=O), 1496 cm^{-1} (C=C, aromatic). ^1H 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, $\text{CH}_2\text{CH}_2\text{CH}_2$), 2.21 (s, 6H, CH_3 DHP), 1.41–1.20 (m, 4H, CH_2), 1.15 (t, 6H, J=7.1 Hz, OCH_2CH_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 $\text{C}_{34}\text{H}_{39}\text{N}_7\text{O}_4$: 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 mmol), methyl acetoacetate (0.10 g, 0.90 mmol) 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). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 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 $\text{C}_{31}\text{H}_{33}\text{N}_7\text{O}_4$: 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 mmol), ethyl acetoacetate (0.17 g, 1.3 mmol) 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), 1496 cm^{-1} (C=C, aromatic). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 2.13 (s, 6H, CH_3 DHP), 1.49–1.29 (m, 2H, CH_2), 1.08 (t, 6H, $J=7$ Hz, OCH_2CH_3), 0.79 ppm (t, 3H, $J=7.4$ Hz, CH_3). ms: m/z (%) 595 [$\text{M}^+ + 1$] (2), 300 (5), 252 (10), 225 (20), 207 (38), 78 (25), 46 (100). *Anal.* calcd. for $\text{C}_{33}\text{H}_{37}\text{N}_7\text{O}_4$: 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 mmol), methyl acetoacetate (0.23 g, 2.05 mmol) 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), 1496 cm^{-1} (C=C, aromatic). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 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

$\text{C}_{32}\text{H}_{35}\text{N}_7\text{O}_4$: 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 mmol), ethyl acetoacetate (0.26 g, 2.05 mmol) 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) ν 3423 (N-H), 3072 (C-H, aromatic), 2964 (C-H, aliphatic), 1677 (C=O), 1492 cm^{-1} (C=C, aromatic). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 2.14 (s, 6H, CH_3 DHP), 1.40–1.09 (m, 4H, CH_2), 1.08 (t, 6H, $J=7.1$ Hz, OCH_2CH_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 $\text{C}_{34}\text{H}_{39}\text{N}_7\text{O}_4$: 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 mmol), ethyl acetoacetate (0.56 g, 4.3 mmol) 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 (0.51 g) 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), 1498 cm^{-1} (C=C, aromatic). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 2.22 (s, 6H, CH_3 DHP), 1.51–1.40 (m, 2H, CH_2), 1.14 (t, 6H, $J=7.1$ Hz, OCH_2CH_3), 0.84 ppm (t, 3H, $J=7.3$ Hz, CH_3). *Anal.* calcd. for $\text{C}_{33}\text{H}_{37}\text{N}_7\text{O}_4$: 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 mmol), methyl acetoacetate (0.37 g, 2.9 mmol) 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). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 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 $\text{C}_{32}\text{H}_{35}\text{N}_7\text{O}_4$: 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 mmol), methyl acetoacetate (0.41 g, 3.6 mmol) 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). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 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 $\text{C}_{31}\text{H}_{33}\text{N}_7\text{O}_4$: 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 mmol), ethyl acetoacetate (0.47 g, 3.6 mmol) 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), 1496 cm^{-1} (C=C, aromatic). ^1H 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, $\text{CH}_3\text{CH}_2\text{CH}_2$), 2.13 (s, 6H, CH_3 DHP), 1.49–1.29 (m, 2H, CH_2), 1.08 (t, 6H, $J=7$ Hz, OCH_2CH_3), 0.79 ppm (t, 3H, $J=7.4$ Hz, CH_3). *Anal.* calcd. for $\text{C}_{33}\text{H}_{37}\text{N}_7\text{O}_4$: 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)-carboxaldehyde derivatives with 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 ^1H NMR. ^1H NMR spectra of regioisomer **3** showed the benzylic hydrogens ($\text{N}-\text{CH}_2\text{Ph}$) were more deshielded (5.51 ppm) than benzylic hydrogens 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 ^1H NMR, infrared, mass spectroscopy and elemental analysis. Based on ^1H NMR of compounds **5** and **7** and depending on the type of regioisomers, protons of H-N, H-C₄, OCH_2CH_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 ^1H NMR spectra 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 diastereotopic hydrogens of the methylene group. Similar splitting pattern for diethyl 4-(nitroaryl)-1,4-dihydropyridine-3,5-dicarboxylate derivatives has been reported previously.^{13,18}

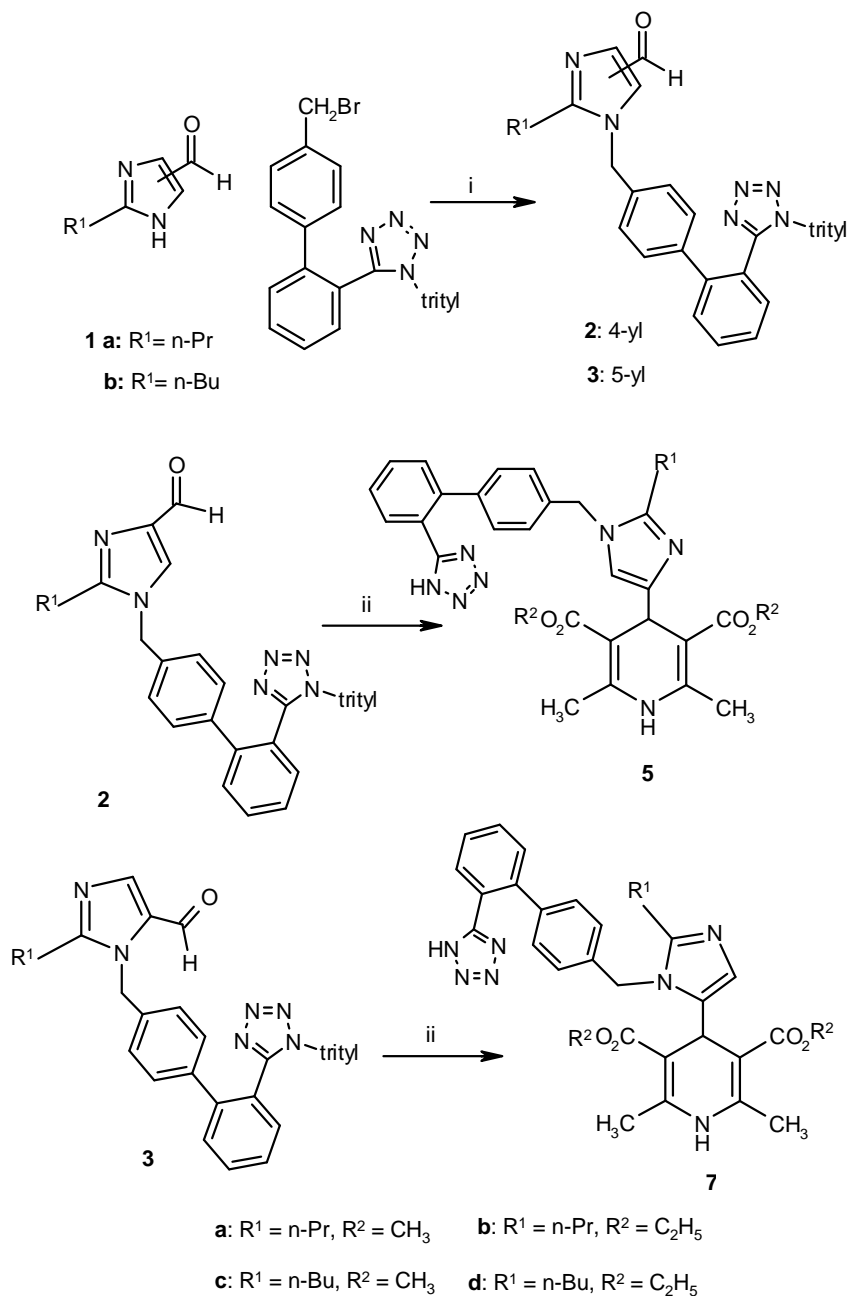
In addition, mass spectroscopy analysis of **5** and **7** showed expectable fragmentation and hence established the structure of dihydropyridine derivatives. The Mass spectrum fragmentation pattern of compound **5a** is shown in Figure 2 and is in agreement with the suggested structure. Comparable fragmentations were

previously reported for some dihydropyridine derivatives.^{13,19-21}

In the second method, trityl protected regioisomer **2** or **3** were subjected to classic Hantzsch reaction to afford the final analogs in moderate yields. ¹H 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) K₂CO₃, DMF, room temperature and then isomer resolution; ii) **first method:** 1) HCl 10% to afford deprotected compound **4** and **6**; 2) CH₃COCO₂R², NH₃ 25%, reflux; **second method:** CH₃COCO₂R², NH₃ 25%, reflux (deprotection and ring closure in one pot)

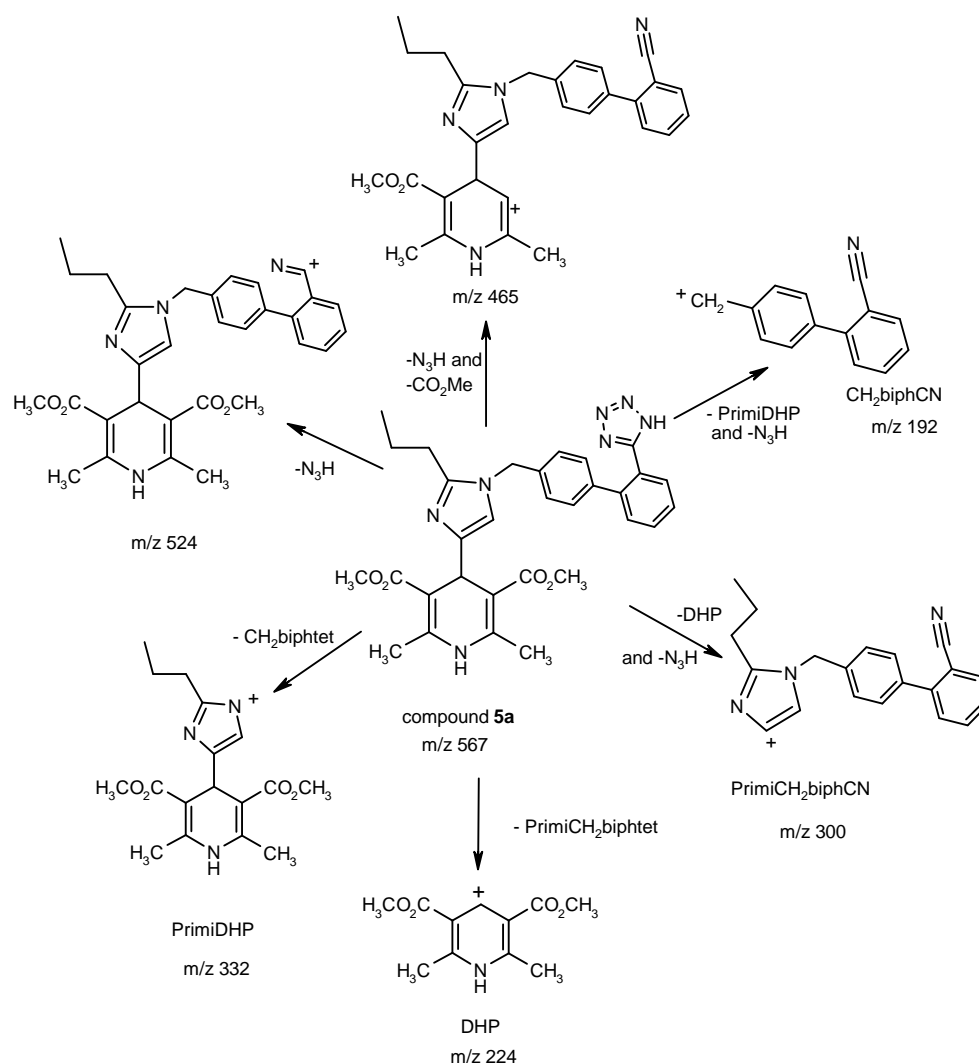


Figure 2. Proposed fragmentation pathways of compound 5a in mass spectroscopy

Conclusion

Eight novel dihydropyridines analogs were synthesized using classic Hantzsch condensation reaction. The key structural elements present in an AT₁ 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 ¹H NMR and mass spectroscopy analysis. The dihydropyridines analogs were obtained by two methods. The second method was more efficient than the first 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.

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