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Synthesis of Four New 3-Imidazolyl-2-Azidoacrylate Derivatives Bearing Biphenyl Tetrazole Moiety as Potential Angiotensin II Receptor Antagonist

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ABSTRACT

Background: The renin angiotensin system which is stimulated by angiotensin II, leads to increase in blood pressure. An angiotensin II receptor antagonist can control effectively hypertension. Synthesis of new compounds that have the key structural elements present in angiotensin receptor antagonists is of interest. Herein, we report the synthesis of novel Alkyl 2-azido-3-[1-[[2'-(tetrazol-5-yl) biphenyl-4-yl]methyl]-2-alkylimidazolyl]acrylate (4 and 6). ***Methods:*** 2-Alkyl-4(5)-hydroxymethylimidazoles were synthesized via Weidenhagen reaction using copper salt, an aldehyde, dihydroxyacetone and concentrated ammonium hydroxide. 2-Alkyl-4(5)-hydroxymethylimidazoles were oxidized by heating with MnO_2 in CH_2Cl_2:dioxane to its carboxaldehyde derivatives. The carboxaldehyde derivatives were reacted with tritylated [4´-(bromomethyl) biphenyl-2-yl]tetrazole in presence of potassium carbonate to give two regioisomers 1 & 2 that separated by column chromatography. The regioisomers 1 & 2 were employed in the synthesis of 2-azidoacrylate derivatives 3 & 5 using sodium alkoxide and alkyl α-azidoacetate. Consequently, the protecting group of tetrazole was removed by stirring the compound **3** and **5** in 10% hydrochloric acid solution at room temperature. ***Results:*** The regioisomers 1 & 2 were separated chromatographically in 1:3 proportions using 70: 30 toluene: ethyl acetate as eluent, respectively. The alkyl 3-substituted imidazol-2-azido acrylate derivatives were synthetized as oily form in 19-25% yield. The deprotection of tetrazole was afforded light yellow oily final compounds in 60-65% yield. ***Conclusion:*** Four new alkyl α-azidoacrylate derivatives bearing biphenyl tetrazole moiety were synthetized via Knoevenagel condensation. The protecting group was removed in acidic media to afford final compounds 4 and 6. The chemical structures of synthesized compounds were characterized by FT-IR and ^{1}HNMR spectroscopies.

Introduction

Hypertension is one of the most common cardiovascular diseases. The renin angiotensin system which is stimulated by angiotensin II, leads to increase in blood pressure. An angiotensin II receptor antagonist can control effectively hypertension.[1] Synthesis of new compounds that have the key structural elements present in angiotensin receptor antagonists is of interest. This new compounds lead to investigate structure activity relationships and pharmacological tools for more study.

Herein, we report the synthesis of novel Alkyl 2-azido-3-[1-[[2'-(tetrazol-5-yl) biphenyl-4-yl]methyl]-2-alkylimidazolyl]acrylate (**4** and **6**) (scheme 1). These analogs have similarity to Losartan and Eprosartan. They have 2-alky-1-[[2'-(tetrazol-5-yl) biphenyl-4-yl]methyl]- imidazole and also 3-[2-alkyl-N-(substituted)imidazolyl]-acrylate moiety that are seen in Losartan and Eprosartan series, respectively (Figure 1). The pharmacological activity should be evaluated with comparing these new molecules with standard Losartan on angiotensin II receptor in future studies.

Materials and Methods

N-(triphenylmethyl-5-[4´-(bromomethyl) biphenyl-2-yl] tetrazole was purchased from Sinosource Pharma Ltd. (Hengsha Guangzhou, China). Methyl (or Ethyl) 2-azidoacetate was prepared according to the literature.[2] 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.

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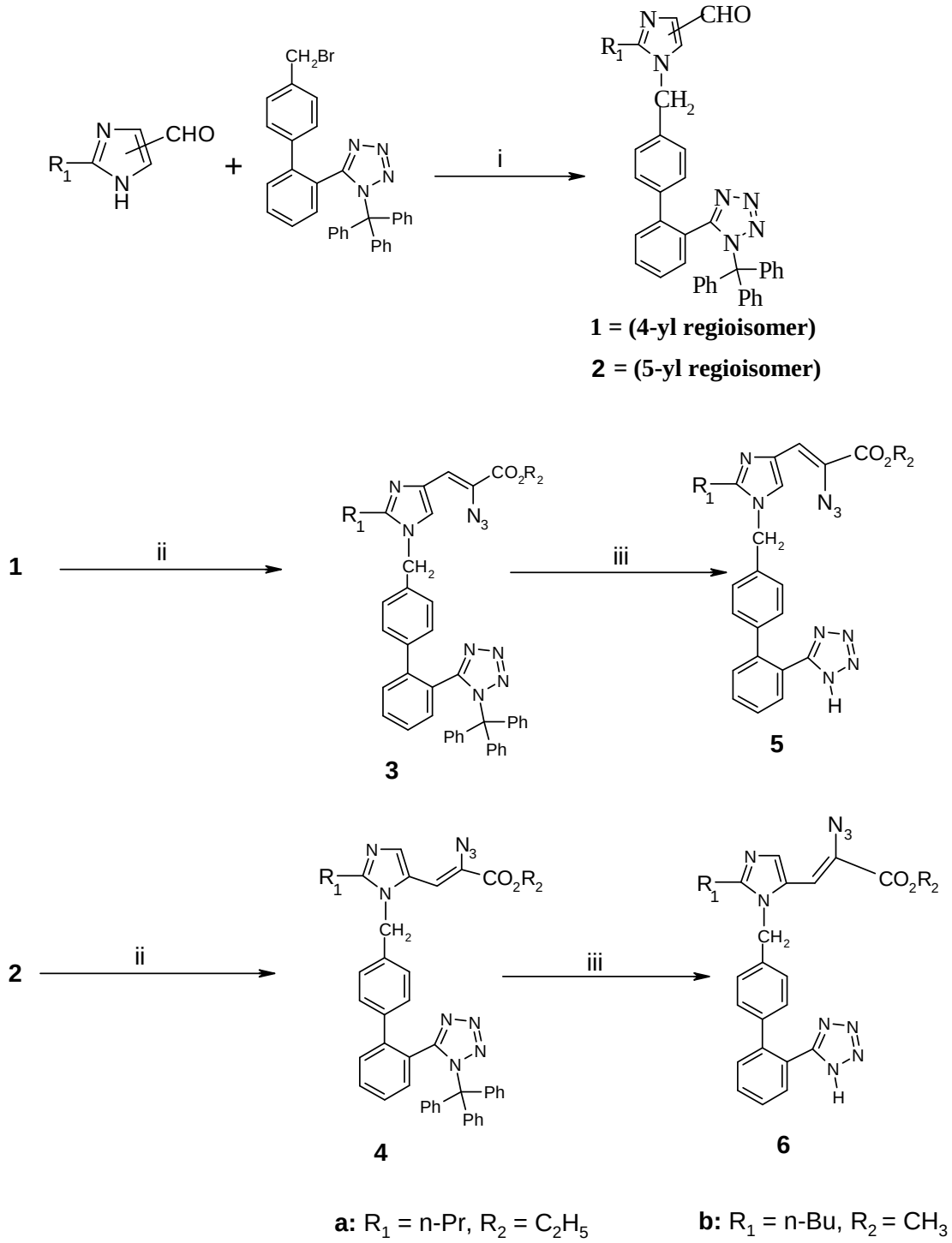
Mass spectra were obtained using a Finnigan Mat TSQ-70 spectrometer at 70 eV (Finnigan Mat, Bremen, Germany). The FT-IR spectrum was recorded on a Shimadzu FTIR 4300 spectrometer (Potassium bromide disks) (Shimadzu, Kyoto, Japan). The purity of compounds was confirmed by TLC using different mobile phases.

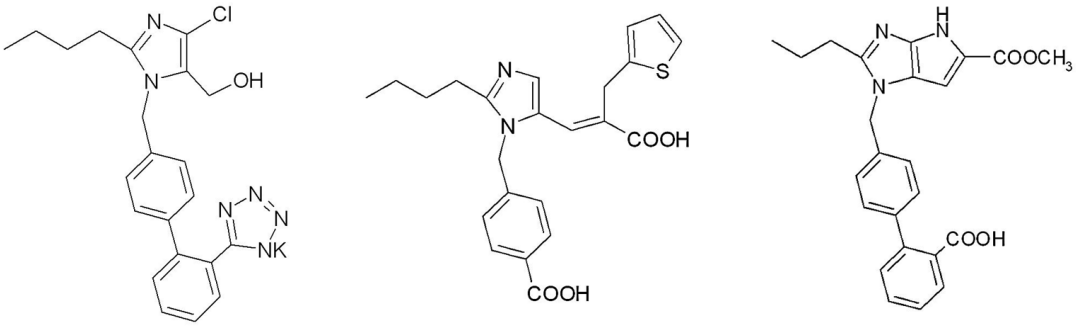


Scheme 1. Condition of synthesis: i) K_2CO_3, DMF; ii) sodium alkoxide, $N_3CH_2CO_2CH_3$ or C_2H_5; iii) HCl 10%, THF.

2-n-propyl-4(5)-hydroxymethyl-1H-imidazole

Butyraldehyde (45 mL, 500 mmol) was added to a solution of copper acetate monohydrate (88 g, 440 mmol) in 665 mL concentrated ammonium hydroxide (NH_4OH) and then a solution of dihydroxyacetone dimmer (20 g, 200 mmol) in 20 mL water was added dropwise over 40 min. and the stirring mixture was heated in a water bath for 5 hrs. The reaction mixture

was cooled in an ice-bath and the imidazole-copper complex was filtered and washed with water (3 × 200 mL). The obtained cake was then boiled in 250 mL of acetone, suction filtered, and dried in an oven to constant weight at 40 °C to afford green color complex (40 g). Hydrogen sulfide (H_2S) gas was passed through the suspension of the complex in water (1 L) for over one hour at 80 °C. The black precipitate of Cu_2S was filtered, while still hot and washed with water (2×100 mL). The filtrate was concentrated under reduced pressure to afford the title compound, in a yield of 53%. mp. 95-98 °C, ^{1}HNMR (DMSO-d_6): δ 6.70 (s, 1H, H-imidazol), 4.33 (s, 2H, CH2O), 2.53(t, 2H, J= 7.4 Hz, $CH_3CH_2\underline{CH_2}$), 1.80 -1.41 (m, 2H, $CH_3\underline{CH_2}CH_2$), 0.87 ppm (t, 3H, J= 7.4 Hz, CH_3).



Losartan Eprosartan pyrollo[2,3-d]imidazole derivatives

Figure 1. Chemical structure of Losartan, Eprosartan and active pyrolloimidazole derivative.

2-n-Butyl-4(5)-hydroxymethyl-1H-imidazole

This compound was prepared by the method described for the synthesis of 2-n-propyl-4(5)-hydroxymethyl-1H-imidazole, in a yield of 54%. mp. 77-79 °C, ^{1}HNMR (DMSO-d_6): δ 6.67(s, 1H, H-imidazol), 4.30(s, 2H, CH_2O), 2.49(t, 2H, J=7.4 Hz, $CH_3CH_2CH_2\underline{CH_2}$), 1.74-1.14(m, 4H, $CH_3\underline{CH_2}\underline{CH_2}CH_2$), 0.94 ppm (t, 3H, J=7.2 Hz, CH_3).

2-n-Propyl-imidazole-4(5)-carboxaldehyde

A mixture of 2-n-propyl-4(5)-hydroxymethyl-1H-imidazole (14 g, 100 mmol), activated manganese dioxide (26.25 g, 300 mmol) and 180 mL of dichloromethane and dioxane (1:1) was refluxed for 12 hr. The mixture was filtered through Celite, while still hot and the precipitate was washed with warm mixture of dichloromethane and dioxane (3 × 30 mL). The combined filtrates were concentrated under reduced pressure to give the crude residue. The crude residue was then crystallized from ethyl acetate and n-hexane to afford 2-n-propyl-imidazole-4(5)-carboxaldehyde (10.2 g, 92% yield) as off-white crystals. mp 98-100 °C. R_f= 0.5 (90% chloroform, 10% methanol; FT-IR (KBr) 3126(N-H), 1689 cm^{-1}(C=O). ^{1}HNMR ($CDCl_3$): δ 9.69 (s, 1H, CHO), 7.79 (s, 1H, H-imidazol), 2.83(t, 2H, J= 7.8 Hz, $CH_3CH_2\underline{CH_2}$), 1.91 -1.71 (m, 2H, $CH_3\underline{CH_2}CH_2$), 1.04 ppm (t, 3H, J= 8 Hz, CH_3).

2-n-Butyl-imidazole-4(5)-carboxaldehyde

This compound was prepared by the method described for the synthesis of 2-n-propyl-imidazole-4(5)-carboxaldehyde, in a yield of 90%. mp. 110-112 °C, R_f= 0.45 (90% chloroform, 10% methanol); FT-IR (KBr) 3150(N-H), 1675 cm^{-1}(C=O). ^{1}HNMR ($CDCl_3$): δ 9.68(s, 1H, CHO), 7.75(s, 1H, H-imidazol), 2.84(t, 2H, J=7.8 Hz, $CH_3CH_2CH_2\underline{CH_2}$), 1.80-1.73(m, 2H, $CH_3CH_2\underline{CH_2}CH_2$), 1.52-1.33(m, 2H, $CH_3\underline{CH_2}CH_2CH_2$), 0.97 ppm (t, 3H, J=7.3 Hz, CH_3).

2-Propyl-1-[[2´-[(triphenylmethyl) tetrazole-5-yl] biphenyl -4-yl] methyl] imidazole-4(5)-carboxaldehyde synthesis (1a and 2a)

To a solution of 2-propyl-imidazole-4(5)-carboxaldehyde (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 30 mL of water 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 (**2a**) (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 (**1a**) (regioisomer of higher R*f* value).

1a: mp. 128 – 130 °C, FT-IR (KBr) 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 ortho trityl), 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).

2a: mp. 144 – 146 °C, FT-IR (KBr) ν 3050 (C-H, aromatic), 2964 (C-H, aliphatic), 1666 cm^{-1} (C=O). ^1H 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 ortho trityl), 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-Butyl-1-[[2´-[(triphenylmethyl) tetrazole-5-yl] biphenyl -4-yl] methyl] imidazole-4(5)-carboxaldehyde synthesis (1b and 2b)

These compounds were prepared by the method described for (**1a, 2a**).

1b: mp. 134-136 °C, FT-IR (KBr) ν 3050 (C-H, aromatic), 2958 (C-H, aliphatic), 1605 cm^{-1} (C=O). ^1H 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 ortho trityl), 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).

2b: mp. 148-150 °C, FT-IR (KBr) ν 3050 (C-H, aromatic), 2950 (C-H, aliphatic), 1672 cm^{-1} (C=O). ^1H 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 ortho trityl), 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).

General method for Alkyl 2-azido-3-substituted-acrylate synthesis

The metallic sodium (0.74 g, 32 mmol, 4 equiv.) was dissolved in alcohol (5 mL) and cooled to reach -15 °C. Methyl (or Ethyl) 2-azidoacetate (3.7g, 32 mmol, 4 equiv.) was added dropwise to the cooled solution and stirred for 30 min. at that temperature. The alkyl 2-azido-3-substituted- acrylate (8 mmol, 1 equiv.) was dissolved in 10 mL tetrahydrofuran and added dropwise to sodium alkoxide solution during 1 hr. After three hours stirring at -15 °C, the reaction mixture was added to a saturated solution of ammonium chloride (80 ml) and extracted with diethyl ether (3 × 40 mL). The organic layer was washed once with water and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 75:25 as eluent) to afford the title compound.

Ethyl 2-azido-3-[1-[[2'-[N-(triphenylmethyl) tetrazol-5-yl] biphenyl-4-yl]methyl]-2-propylimidazol-4-yl] acrylate (3a)

Oily compound in a yield of 25%, R_f = 0.5 (50% light petroleum ether, 50% ethyl acetate);
FT-IR (KBr): ν 2113(N_3), 1704(C=O,ester), 1625 cm^{-1}(C=C). ^1HNMR ($CDCl_3$) δ 7.99 (dd, 1H, $J_{3',4'}$=4, $J_{3',5'}$ =2 Hz H-3´ phenyl), 7.61(s, 1H, H imidazol), 7.55-7.25 (m, 12H, H aromathic trityl and biphenyl), 7.15(dd , 2H, J=8 Hz, H-$_{2\ ,\ 6}$ phenyl), 7.12(s, 1H, H-vinyl), 6.95(dd, 6H, $J_{2'',3''}$ =1.4, $J_{2'',4''}$ =1 Hz, ortho trityl), 6.82 (d, 2H, J=7.9 Hz, H-3,5 phenyl), 5.00(s, 2H, NCH_2), 4.34(q, 2H, J= 10.6 Hz, $O\underline{CH_2}CH_3$), 2.57(t, 2H, J= 8Hz, $CH_3CH_2\underline{CH_2}$), 1.86-1.65 (m, 2H, $CH_3\underline{CH_2}CH_2$), 1.36-1.29(m, 3H, $OCH_2\underline{CH_3}$), 0.96 ppm (t, 3H, J= 8Hz, CH_3).

Ethyl 2-azido-3-[1-[[2'-[N-(triphenylmethyl) tetrazol-5-yl] biphenyl-4-yl]methyl]-2-propylimidazol-5-yl] acrylate (4a)

Oily compound in a yield of 19%, R_f = 0.65 (50% light petroleum ether, 50% ethyl acetate);
FT-IR (KBr): ν 2117(N_3), 1708(C=O, ester), 1616 cm^{-1}(C=C). ^1HNMR ($CDCl_3$): δ 7.93(dd, 1H, , $J_{3',4'}$ =4, $J_{3',5'}$ =2 Hz H-3´ phenyl), 7.82 (s, 1H, H imidazol), 7.56-7.24 (m, 12H, H aromathic trityl and biphenyl), 7.12(d, 2H, J=12Hz, H-2,6 phenyl), 6.96 (dd, 6H, $J_{2'',3''}$ =1.6, $J_{2'',4''}$ =1.2 Hz, ortho trityl), 6.80 (d, 2H, J= 8.0 Hz, H-3,5 phenyl), 6.7 0(s, 1H, H-vinyl), 5.51(s, 2H, NCH_2), 4.25(q, 2H, J= 10.6 Hz, $O\underline{CH_2}CH_3$), 2.53(t, 2H, J= 8 Hz, $CH_3CH_2\underline{CH_2}$), 1.87 -1.64 (m, 2H, $CH_3\underline{CH_2}CH_2$), 0.91 ppm (t, 3H, J= 6 Hz, CH_3).

Methyl 2-azido-3-[1-[[2'-[N-(triphenylmethyl) tetrazol-5-yl] biphenyl-4-yl]methyl]-2-butylimidazol-4-yl] acrylate (3b)

Oily compound in a yield of 25%, R_f = 0.6 (75% light petroleum ether, 25% ethyl acetate); FT-IR (KBr): ν 2119(N_3), 1708(C=O, ester), 1625 cm^{-1}(C=C). ^1HNMR ($CDCl_3$) δ 7.97(dd, 1H, H-3´ phenyl), 7.61(s, 1H, H imidazol), 7.57-7.25(m, 12H, H aromathic trityl and biphenyl), 7.11(s, 1H, H-vinyl), 6.94(d, 6H, J=7.2 Hz, ortho trityl), 6.80(d, 2H, J=7.9 Hz, H-3,5 phenyl), 5.00(s, 2H, NCH_2), 3.89(s, 3H, OCH_3), 2.60(t, 2H, J=7.2 Hz, $CH_3CH_2CH_2\underline{CH_2}$), 1.73-1.61 (m, 2H, $CH_3CH_2\underline{CH_2}CH_2$), 1.45- 1.26 (m, 2H, $CH_3\underline{CH_2}CH_2CH_2$), 0.91 ppm (t, 3H, J=7.2 Hz, CH_3).

Methyl 2-azido-3-[1-[[2'-[N-(triphenylmethyl) tetrazol-5-yl] biphenyl-4-yl]methyl]-2-butylimidazol-5-yl] acrylate (4b)

Oily compound in a yield of 15%, R_f = 0.7 (50% light petroleum ether, 50% ethyl acetate);
FT-IR (KBr): ν 2125(N_3), 1712(C=O, ester), 1616 cm^{-1}(C=C). ^1HNMR ($CDCl_3$): δ 7.91 (dd, 1H, H-3´ phenyl), 7.67(s, 1H, H imidazol), 7.62-7.16 (m, 12H, H aromathic trityl and biphenyl), 6.99(d, 6H, J=7.1 Hz, ortho trityl), 6.72(d, 2H, J=8.0 Hz, H-3,5 phenyl), 6.60(s, 1H, H-vinyl), 5.05(s, 2H, NCH_2), 3.71(s, 3H,

OCH_3), 2.58(t, 2H, J=7.5 Hz, $CH_3CH_2CH_2CH_2$), 1.70-1.29 (m, 4H, $CH_3CH_2CH_2CH_2$), 0.89 ppm (t, 3H, J=7.2 Hz, CH_3).

General method for removal of protective trityl group

A solution of tritylated Alkyl 2-azido-3-substituted-acrylate (3.8 mmoles) in a mixture of tetrahydrofuran (55 mL) and 10% HCl (27.5 mL) was stirred at 25°C for 4 hours. The reaction mixture was basified with addition of 30 mL of 10% sodium hydroxide. The mixture was concentrated under vacuum to remove tetrahydrofuran and then water (30 mL) was added to the residue and filtered to remove the triphenylmethanol. Finally pH of the filtrate was adjusted to 3-4 using 10% HCl and filtered again to separate Alkyl 2-azido-3-substituted- acrylate.

Ethyl 2-azido-3-[1-[[2'-(tetrazol-5-yl) biphenyl-4-yl]methyl]-2-propylimidazol-4-yl] acrylate (5a)

Oily liquid, R_f = 0.65(95% chloroform, 5% methanol); FT-IR (KBr): ν 2120(N_3), 1700(C=O,ester), 1635 cm^{-1}(C=C). ^{1}H NMR (DMSO-d_6) δ 7.72 (s, 1H, H imidazole),7.62–7.39 (m, 4H, H aromatic), 7.09 (d, 2H, J=8.2 Hz, H-2,6 phenyl), 7.05(s, 1H, H-vinyl), 7.01 (d, 2H, J=8.4 Hz, H-3,5 phenyl), 5.15 (s, 2H, NCH_2), 4.11–3.93 (m, 2H, OCH_2), 2.64 (t, 2H, J=7.4 Hz, $CH_3CH_2\underline{CH_2}$), 1.51–1.40 (m, 2H, CH_2), 1.36 -1.29 (m, 3H, $OCH_2\underline{CH_3}$), 0.84 ppm (t, 3H, J=7.3 Hz, CH_3).

Ethyl 2-azido-3-[1-[[2'-(tetrazol-5-yl) biphenyl-4-yl]methyl]-2-propylimidazol-5-yl] acrylate (6a)

Oily liquid, R_f = 0.6 (95% chloroform, 5% methanol); FT-IR (KBr): ν 2123(N_3), 1716(C=O, ester), 1622 cm^{-1}(C=C).^{1}H NMR (DMSO-d_6) δ 7.82 (s, 1H, H imidazol), 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), 6.7 0(s, 1H, H-vinyl), 5.26 (s, 2H, NCH_2), 3.98–3.75 (m, 2H, OCH_2), 2.32 (t, 2H, J=7.4 Hz, $CH_3CH_2\underline{CH_2}$), 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).

Methyl 2-azido-3-[1-[[2'-(tetrazol-5-yl) biphenyl-4-yl]methyl]-2-butylimidazol-4-yl] acrylate (5b)

Oily liquid, R_f = 0.55 (95% chloroform, 5% methanol); FT-IR (KBr): ν 2123(N_3), 1703(C=O, ester), 1623 cm^{-1}(C=C). ^{1}H NMR (DMSO-d_6) δ 7.65(s, 1H, H imidazol),7.63 –7.47 (m, 4H, H aromatic), 7.15(s, 1H, H-vinyl), 7.10 (d, 2H, J=8.3 Hz, H-2,6 phenyl), 6.99 (d, 2H, J=8.3 Hz, H-3,5 phenyl), 5.11 (s, 2H, NCH_2), 3.56 (s, 3H, OCH_3), 2.61 (t, 2H, J=8 Hz, $CH_3CH_2CH_2\underline{CH_2}$), 1.46–1.14 (m, 4H, CH_2), 0.83 ppm (t, 3H, J=7.3 Hz, CH_3).

Methyl 2-azido-3-[1-[[2'-(tetrazol-5-yl) biphenyl-4-yl]methyl]-2-butylimidazol-5-yl] acrylate (6b)

Oily liquid, R_f = 0.6 (95% chloroform, 5% methanol); FT-IR (KBr): ν 2118(N_3), 1707(C=O, ester), 1628 cm^{-1}(C=C). ^{1}H NMR (DMSO-d_6) δ 7.86(s, 1H, H imidazol), 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), 6.77(s, 1H, H-vinyl),5.32 (s, 2H, NCH_2), 3.38 (s, 3H, OCH_3), 2.38 (t, 2H, J=7.2 Hz, $CH_3CH_2CH_2\underline{CH_2}$), 1.44–1.11 (m, 4H, CH_2), 0.77 ppm (t, 3H, J=7.2 Hz, CH_3).

Results and Discussion

Angiotensin receptor blockers (ARBs) such as Losartan and Eprosartan (Figure 1) were developed from 1-benzylimidazol-5-acetic acid derivatives, which antagonize angiotensin II (Ang II) by preventing angiotensin II from binding to angiotensin II receptor (AT_1) on vascular smooth muscle. As a result, blood vessels dilate and blood pressure is reduced.[1,3] On the base of structure activity relationships studied, the angiotensin II receptor antagonists are structurally divided into two series. One series is related to Losartan that have 2-alky-1-[[2'-(tetrazol-5-yl) biphenyl-4-yl]methyl]-imidazole moiety. The importance of biphenyl tetrazole moiety has been proven in the structure activity relationship studies. The other series is Eprosartan and the only Eprosartan had been entered to market. Eprosartan series have 3-[2-alkyl-N-(substituted)imidazolyl]-acrylate moiety.[1]

On the other hand, previously Akhavan et al. was reported that methyl 2-n-propyl-1-[(2´-carboxybiphenyl-4-yl)methyl]pyrrolo[2,3-d]imidazole-5-carboxylate (Figure 1) could antagonize the induced-angiotensin II contraction in guinea pig ileum and its pA_2 was 8.5 (Losartan, pA_2 = 9.9).[4] Therefore, we suggest that analogs have the key structural elements present in an angiotensin receptor antagonists such as 2-alky-1-[[2'-(tetrazol-5-yl) biphenyl-4-yl]methyl]-imidazole and 3-imidazolyl-acrylate moieties could be pharmacologically active.

Scheme 1 shows synthesis of novel compounds **4a-d** and **6a-d**. 2-alkyl-4(5)-hydroxymethyl-1H-imidazole was synthesized via Weidenhagen reaction using copper salt, an aldehyde, dihydroxyacetone and concentrated ammonium hydroxid.[5-8] 2-Alkyl-imidazole-4(5)-carboxaldehyde was prepared from oxidation its alcoholic derivative using activated magnesium dioxide.[9,10] 2-Alkyl-imidazole-4(5)-carboxaldehyde was reacted with *N*-(triphenylmethyl-5-[4´-(bromomethyl) biphenyl-2-yl] tetrazole in the presence of anhydrous K_2CO_3 to give two regioisomers **1** and **2**. The two regioisomers were separated by column chromatography.[10-12] Each of regioisomer was separately reacted with alkyl 2-azidoacetate in the presence of alkoxide salt to afford the tritylated alkyl 3-substituted-2-azido-acrylate derivatives.[11,13] Deprotection of the tetrazole group was achieved in acidic solution using 10% HCl to prepare alkyl 3-substituted-2-azido-acrylate derivatives as final products **4** and **6**.[9]

The synthesis of the (hydroxymethyl)imidazole intermediates can achieve directly from following three method. First, the methyl alkylimidate hydrochloride

was reacted with 1,3-dihydroxyacetone dimer in the presence of high-pressure liquid ammonia.[14] Although the yields of (hydroxymethyl)imidazoles were generally good (70-75%), the reaction performance and purification step is often difficult. The second method is hydroxymethylation of 2-substitutedimidazole in formalin. The reaction initially proceeded to give hydroxymethylation in the 5-position and or in the 4-position, giving a mixture of mono- and bis(hydroxymethylation) products.[15] Third, Weidenhagen synthesis is used simply for (hydroxymethyl)imidazole synthesis.[5-8] An aldehyde react with 1,3-dihydroxyacetone dimmer and copper acetate in concentrated ammonium hydroxide solution at 80-100 °C. The purification of imidazole analogs was achieved by boiling copper-imidazole complex in acetone. The cleavage of complex with H_2S gas offered pure imidazole analog in a good yield (50-60%).

Although the imidazole-4(5)-carboxaldehyde analogs were synthesized directly from reaction of an amidine and 2-bromo-3-ethoxy-2-propenal,[16] the imidazole-4(5)-carboxaldehyde analogs can be prepared by oxidation of (hydroxymethyl)imidazoles in the presence of activated manganese dioxide[9,10] or ceric ammonium nitrate/H_2O.[9] The 2-n-propyl-1H-imidazol-4(5)-carboxaldehyde and 2-n-butyl-1H-imidazol-4(5)-carboxaldehyde were prepared by oxidation through activated MnO_2 in excellent yield (90-93%). The adsorption of imidazolecarboxaldehydes to MnO_2 is occurred in the oxidation process and decrease the yield of reaction. So, the problem can dissolve using hot solvent extraction.

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 **1** and **2** in 1:2 ratio respectively (Scheme 1). The regioisomers were then separated using column chromatography.[10] The structures of regioisomers were confirmed by ^{1}H NMR. ^{1}H NMR spectra of regioisomer **3** showed the benzylic hydrogens (*N*-CH_2Ph) were more deshielded (5.51 ppm) than benzylic hydrogens of regioisomer 1 (5.00 ppm).

Knoevenagel condensation was achieved via reaction of methyl or ethyl azidoacetate and 4 or 5-imidazolecarboxaldehydes bearing biphenyl tritylated tetrazole moiety (compound **1** and **2**). The reaction proceeded in the presence of sodium alkoxide solution at -15 °C to afford 3-substituted imidazolyl-2-azidoacrylates (compounds **3** and **5**). Compound **1** and **2** has very low solubility in methanol or ethanol. Therefore, the reaction did not progress after stirring for 3 hr. This problem was dissolved using tetrahydrofuran as cosolvent. In the first step, compound **1** and **2** were dissolved in THF and then it was added dropwise to the cooled reaction mixture. The progress of reaction was monitored by TLC. The synthesis of compound **3** and **5** was characterized by FT-IR and ^{1}HNMR. The peak in 2125 cm^{-1} is related to the presence of N_3 group at FT-IR spectra. The ^{1}HNMR spectrum showed vinylic proton in the chemical shift of 7.1 ppm.

The protecting group of tetrazole was removed by stirring the compound **3** and **5** in 10% hydrochloric acid solution about 4 hr. at room temperature. After adjusting pH to 8-9, the trityl group was precipitated as triphenylmethanol. The filtrate was acidified to pH 3-4 to form compound **4** and **6** as light yellow oil in a good yield (60-65%).

Meanwhile, we tried to do thermolysis of azidoacrylates (compounds **3** and **5**) for synthesis pyrroloimidazole heterocycles. This reaction which is called Hemetsberger-Knittel reaction was achieved by heating compound **3** and **5** in xylene at 140 °C.[17] The reaction mixture was done under nitrogen gas for 30 minutes. After evaporation of xylene in vacuum, the residue was purified by column chromatography. Two compounds were isolated from chromatography. The chemical structure of isolated compounds did not confirmed by NMR spectroscopy. The nitrene which is produced from thermolysis of azide group is probably caused to react with the tetrazole or trityl group.

Conclusion

The two regioisomers of substituted imidazol-4 or 5-carboxaldehydes bearing tritylated biphenyl tetrazole moiety were synthesized and isolated by column chromatography in 1:3 proportions, respectively. Knoevenagel condensation was achieved via reaction of azidoacetate and substituted imidazol-4 or 5-carboxaldehydes using tetrahydrofuran as co-solvent. The protecting group was removed in acidic media to afford final compounds **4** and **6.** The chemical structures of synthesized compounds were characterized by FT-IR and ^{1}HNMR spectroscopies.

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Conflict of interests

The author claims that there is no conflict of interest.

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