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Synthesis and Characterization of 2-Alkyl-1-[4-(5-carboxy-1,2,3-thiadiazole-4-yl)benzyl]-4-chloro-1H-imidazole-5-carboxaldehydes

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Starting from ethyl 4-(4-methylphenyl)-1,2,3-thiadiazole-5-carboxylate (**8**), 2-alkyl-1-[4-(5-carboxy-1,2,3-thidiazole-4-yl)benzyl]-4-chloro-1H-imidazole-5-carboxaldeydes (**4a,4b**) were prepared.

Key Words: Synthesis, Imidazole, 1,2,3-Thidiazole, Angiotensin antagonists.

INTRODUCTION

The circulating Renin-Angiotensin System (RAS) plays an important role in cardiovascular homeostasis. Angiotensin II (Ang II), which is potentially cleaved from Ang I by the angiotensin converting enzyme (ACE) and chymase, plays a central role in the pathophysiology of hypertension, cardiac hypertrophy, congestive heart failure and coronary heart disease[1]. Research efforts have focused in the treatment of disease by blocking its release and more recently by competing its action on Ang II subtype 1 (AT 1) receptor[2]. This approach generated in the pharmaceutical market, losartan (**1**)[3], the first long-acting and orally-active non-peptide Ang II receptor antangonist. The discovery of losartan, and subsequently other nonpetidic Ang II antagonists [*e.g.*, eprosartan (**2**)][4], has generated considerable interest in the search for new analogues of **1**. Recently, the synthesis of compound **3**, having 2-butyl-4-chloro-5-formylimidazole moiety which showed potent Ang II antagonist activity (IC_{50} = 0.94 μM) has been reported[5]. In continuation of our research for developing new Ang II antagonists[6], we focused our studies on the replacement of the terminal phenyl ring of compound **3** with its non-classical bioisoester 1,2,3-thiadiazole ring to give compounds **4a** and **4b**.

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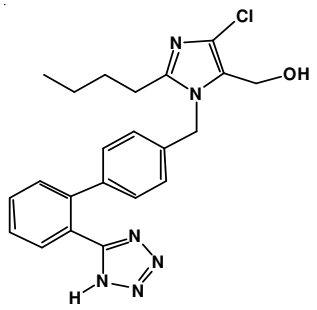

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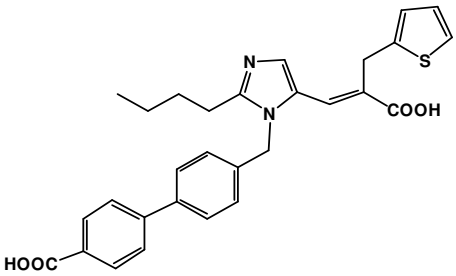

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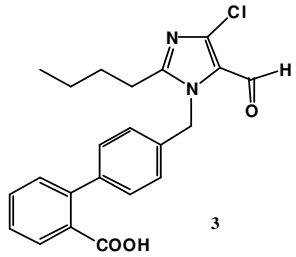

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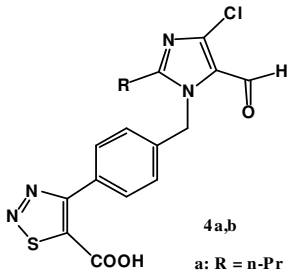


4a,b

a: R = n-Pr
b: R = n-Bu

EXPERIMENTAL

All the chemicals and solvents were purchased from Merck AG and Aldrich Chemical Company. Melting points were determined on a Kofler hot stage apparatus and uncorrected. ^{1}H NMR spectra were run on a Bruker FT-80 spectrometer. TMS was used as internal standard. The FT-IR spectra were recorded on a Nicollet 550 spectrophotometer. Elemental analyses were carried out on a CHN-O rapid elemental analyzer (GmbH-Germany) for C, H and N. Merck silica gel 60 F_{254} plates were used for analytical TLC; column chromatography was performed on Merck silica gel (70-230 mesh). Yields are of purified product and were not optimized.

Ethyl 3-(4-methylphenyl)-3-oxopropanoate semicarbazone (7): A solution of semicarbazide hydrochloride (**6**) (5.56 g, 50 mmol) and sodium acetate (4.10 g, 50 mmol) in 20 mL water was slowly added to a stirring solution of compound (**5**)[7] (10 g, 48 mmol) in 40 mL ethanol at 0°C. The mixture was stirred at 0°C for 5 h then kept at -10°C for 36 h. The white crystals was filtered and washed with 50 mL water to give 5.96 g (46 %) of **7**, m.p. 209-221°C. ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, *J* = 7.2 Hz, 3H). 2.37 (s, 3H), 3.75 (s, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 5.74 (brs, 2H, NH_2), 7.21 (d, *J* = 8.3 Hz, 2H), 7.62 (d, *J* = 8.3 Hz, 2H), 8.93 ppm (brs, 1H, NH).

Ethyl 4-(4-methylphenyl)-1,2,3-thidiazole-5-carboxylate (8): To compound **7** (3.5 g, 13 mmol), $SOCl_2$ (4 mL) was added drop wise and the mixture was stirred at room temperature for 4 h. To the reaction mixture

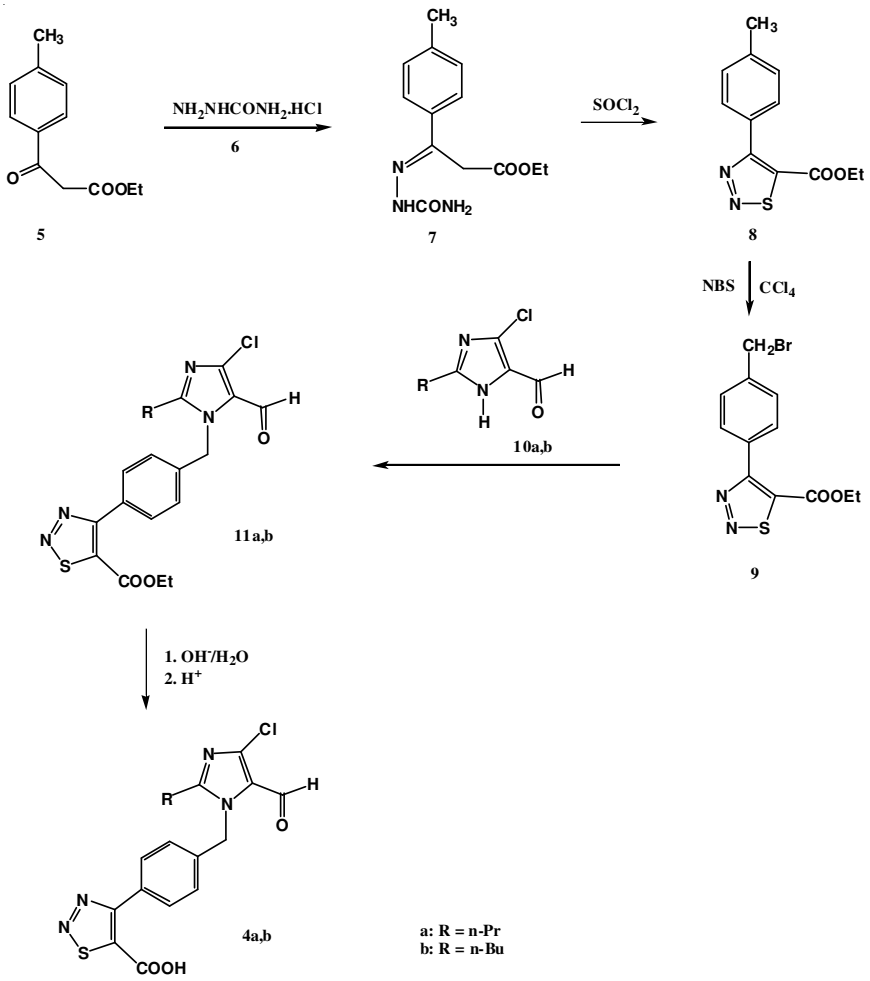
CH_2Cl_2 (100 mL) was added and slowly mixed with 100 mL of saturated sodium bicarbonate solution and filtered. Organic phase was separated, dried (sodium sulfate) and filtered. Dichloromethane was removed and the residue was purified by silica gel column chromatography (CH_2Cl_2). The crystallization was performed by $CHCl_3$: hexane (1:1) to give 1.75 g (53 %) of compound **8**. m.p. 60-63°C; IR (KBr, cm^{-1}): 1720 ν(C=O); ^1H NMR ($CDCl_3$) δ: 1.34 (t, *J* = 7.1 Hz, 3H). 2.43 (s, 3H), 4.38 (q, *J* = 7.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.81 ppm (d, *J* = 8.1 Hz, 2H). Anal. Calcd. for $C_{12}H_{12}O_2S$: C, 58.06; H, 4.84; N, 11.29. Found: C, 58.30; H. 4.62; N, 11.45.

Ethyl 4-(4-bromomethylphenyl)-1,2,3-thiadiazole-5-carboxylate (9): To a solution of compound **8** (2 g, 8 mmol) in CCl_4 (50 mL) N-bromo succinimide (1.5 g, 8.5 mmol) and benzoyl peroxide (100 mg) was added. The solution was refluxed for 8 h. After cooling the solution was filtered and the solvent was evaporated under reduced pressure. The residue was used for next step without further purification; IR (KBr, cm^{-1}): 1720 ν(C=O); ^1H NMR ($CDCl_3$) δ: 1.43 (t, *J* = 7.2 Hz, 3H). 4.38 (q, *J* = 7.1 Hz, 2H), 4.58 (s, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.83 ppm (d, *J* = 8.0 Hz, 2H).

4-Chloro-[4-(5-ethoxycarbonyl-1,2,3-thiadiazole-4-yl)benzyl]-2-propyl-1H- imidazole-5-carbaldehyde (11a): A solution of compound **9** (1.8 g, 5.8 mmol), of **10a**[8] (1 g, 5.8 mmol) and sodium carbonate (300 mg) in 50 mL dry DMF was stirred at 40°C for 36 h. Water (100 mL) was added and extraction was performed with diethyl ether (3 × 60 mL). The ether was removed and the residue was purified by silica gel column chromatography (ether:hexane, 1:1) to give 680 mg (28 %) of **11a** as a colourless oil; IR (KBr, cm^{-1}) 1720, 1660 ν(C=O). ^1H NMR ($CDCl_3$) δ: 0.91 (t, *J* = 7 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.72 (m, 2H), 2.61 (m, 2H), 4.33 (q, *J* = 7.2 Hz), 5.6 (s, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 2H), 9.73 ppm (s, 1H, CHO). Anal. Calcd. for $C_{19}H_{19}ClN_4O_3S$: C, 54.48; H, 4.57; N, 13.37. Found: C, 54.36; H, 4.54; N, 13.28.

2-Butyl-4-chloro-1-[4-(5-ethoxycaronyl-1,2,3-thiadiazole-4-yl)benzyl]-1H-imidazole-5-carbaldehyde (11b): This compound was synthesized from **9** and **10b**[8] as described for **11a** in 42 % yield. IR (KBr, cm^{-1}) 1721, 1658 ν(C=O). ^1H NMR ($CDCl_3$) δ: 0.91 (t, *J* = 7 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.72 (m, 2H), 2.5 (m, 2H), 2.92 (t, *J* = 7 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 5.6 (s, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8 Hz, 2H), 9.72 ppm (s, 1H, CHO). Anal. Calcd. for $C_{20}H_{21}ClN_4O_3S$: C, 55.49; H, 4.86; N, 12.95. Found: C, 55.70; H, 5.12; N, 12.79.

1-[4-(5-Carboxy-1,2,3-thiadiazole-4-yl)benzyl]-4-chloro-2-propyl-1H-imidazol-5-carbaldehyde (4a): To a solution of compound **6a** (800 mg, 1.91 mmol) in ethanol (15 mL), a 10 % NaOH solution (7 mL) was added and stirred for 12 h at room temperature. The solvent was removed



Scheme-I

under reduced pressure and the residue was dissolved in 5 mL of water and pH adjusted to 3.5 with 10 % HCl. The precipitate was washed with water and recrystallized from methanol to give 520 mg (70 %) of **4a** m.p. 135-138°C; IR (KBr, cm^{-1}) 1705, 1662 ν(C=O). ^1H NMR ($CDCl_3$) δ: 0.95 (t, *J* = 6.8 Hz, 3H), 1.75 (m, 2H), 2.5 (t, *J* = 7.3 Hz, 2H), 5.64 (s, 2H), 7.17 (d, *J* = 7.7, 2H), 7.95 (d, *J* = 7.7, 2H), 9.76 (s, 1H), 12.70 ppm (bs,1H). Anal. Calcd. for $C_{17}H_{15}ClN_4O_3S$: C, 52.24; H, 3.84; N, 14.34. Found: C, 52.37; H, 3.82; N, 14.4.

2-Butyl-1-[4-(5-carboxy-1,2,3-thiadiazole-4-yl)benzyl]-4-chloro-1H-imidazole-5-carboxaldehyde (4b): This compound was prepared from **11b** as described for the **4a** in 70 % yield. m.p. 142-145°C; IR (KBr, cm^{-1}) 1709, 1660 ν(C=O). ^1H NMR ($CDCl_3$) δ: 0.97 (t, *J* = 6.8 Hz, 3H), 1.74 (m, 2H), 2.1 (m, 2H), 2.95 (t, *J* = 7 Hz, 2H), 5.64 (s, 2H), 7.17 (d, *J* = 7.7 Hz,

2H,), 7.95 (d, J = 7.7 Hz, 2H), 9.76 (s, 1H), 12.57 ppm (bs, 1H). Anal. Calcd. for $C_{18}H_{17}N_4O_3SCl$: C, 53.40, H, 4.20; N, 13.87. Found: C, 53.46; H, 4.09; N, 13.69.

RESULTS AND DISCUSSION

A facile route for the synthesis of 2-alkyl-1-[4-(5-carboxy-1,2,3-thiadiazole-4-yl)benzyl]-4-chloro-1H-imidazole-5-carbaldehydes (**4a-b**) has been presented in this paper. For preparation of compound **4**, 2-alkyl-4(5)-chloro-1H-imidazole-5(4)-carbaldehyde (**10**)[8] was condensed with compound **9** to provide regioselective isomer 1-arylmethyl-4-chloro-5-formyl-1H-imidazole **11**. Hydrolysis of **11** to the target compound **4** was carried out with ethanolic sodium hydroxide at room temperature followed by acidification (**Scheme-I**).

For the synthesis of 4-arylbenzyl bromide (**9**), the ethyl 3-(4-methylphenyl)-3-oxopropanoate (**5**)[7] was reacted with semicarbazide hydrochloride (**6**) to give **7**. Reaction of **7** with thionyl chloride according to the method of Lalezari *et al.*[9] gave compound **8**. Compound **8** was brominated with N-bromosuccinimide in the presence of benzoyl peroxide to give the corresponding bromomethyl analogue **9** (**Scheme-I**).

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