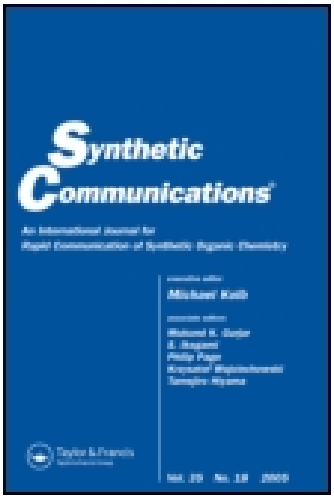

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New Synthesis of Analogues of the Antihypertensive Active Pharmaceutical Ingredient Irbesartan

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New Synthesis of Analogues of the Antihypertensive Active Pharmaceutical Ingredient Irbesartan

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Abstract: A simple and new synthetic approach to various analogues of Irbesartan is described.

Keywords: Active pharmaceutical ingredient, analogues, angiotensin, antihypertensive drug, Irbesartan

INTRODUCTION

Sartans such as Irbesartan,[1] Valsartan,[2], Candesartan,[3] Olmesartan,[4] Telmisartan,[5] and Losartan[6] belong to a class of antihypertensive active pharmaceutical ingredients. They function as specific and competitive angiotensin I receptor antagonists, thereby blocking the actions of endogenous ligand angiotensin II and in turn preventing the increase in blood pressure.

In continuation of our work on the synthesis of Irbesartan,[7] herein we report a new general approach to the synthesis of various analogues of Irbesartan.

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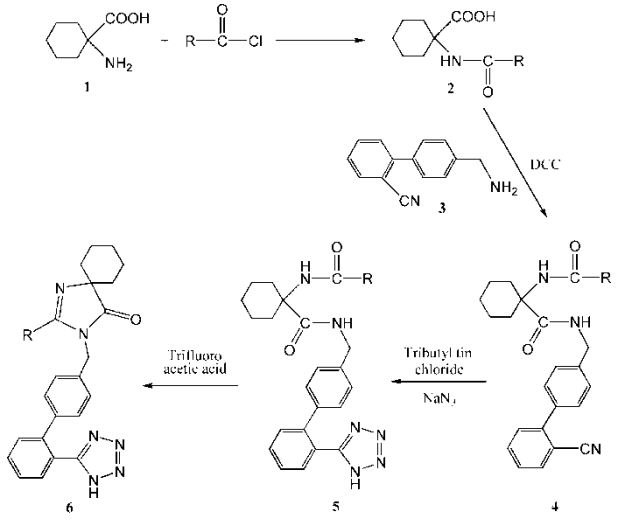
DISCUSSION

Acylation of 1-amino-cyclohexanecarboxylic acid **1**[8] with propionyl chloride in the presence of water and sodium hydroxide yielded 1-propionylamino-cyclohexane carboxylic acid **2a**. Its condensation with 4′-aminomethyl-biphenyl-2-carbonitrile **3**[9] in the presence of dicyclohexyl carbodiimide (DCC) and a catalytic amount of 1-hydroxybenzotriazole (HOBT) in methylene chloride gave 1-propionylamino-cyclohexanecarboxylic acid (2′-cyano-biphenyl-4-ylmethyl)-amide (**4a**). Reaction of **4a** with tributyltin chloride and sodium azide in xylene produced the tetrazole derivative **5a**. Trifluoro acetic acid–mediated dehydrative cyclization of **5a** in toluene yielded 2-alkyl-3-[2′-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro[4.5]dec-1-en-4-one **6a**.

To verify the generality of this synthetic sequence, it was extended to three other acid chlorides, and in all the cases corresponding tetrazolyl diaza-spiro compounds were obtained as the final products in good yields. All these compounds are fully characterized based on their IR, ^{1}H NMR, and mass spectral data and also by elemental analysis. IR spectra of compounds **4a–d** were characterized by the presence of CN and two carbonyl absorptions at $\sim$2225 cm^{-1}, 1720 and 1655 cm^{-1} respectively. Compounds **5a–d** showed NH absorptions at $\sim$3363, 3330, 3060 and carbonyl at $\sim$1730 cm^{-1}. The final compounds **6a–d** exhibited C=O and NH absorptions at $\sim$1730 cm^{-1} and $\sim$3420 cm^{-1} respectively. ^{1}H NMR spectra of **6a–d** are characterized by signals due to benzylic protons in the region 4.5–4.8 δ and aromatic protons at 7.0–8.0 δ.

In conclusion, we have disclosed a simple, general, and new synthetic route for the preparation of the new analogues of Irbesartan.



Compounds 2, 4, 5 & 6 R	a	b	c	d
	C_2H_5	C_3H_7	C_4H_9	C_5H_{11}

EXPERIMENTAL

^{1}H NMR spectra were measured on a Gemini 200-MHz FTNMR spectrometer, and the chemical shifts were reported as δ values in ppm relative to TMS as an internal standard. The IR spectra were recorded in the solid state as KBr dispersion using Perkin Elmer FT-IR spectrophotometer. Mass spectra were recorded on Shimadzu LCMS-QP 8000, LC-MS, and AB-4000 Q-trap LC-MS/MS.

General Procedure for the Preparation of 1-Acylamino-cyclohexanecarboxylic Acid (2a–d)

1-Amino-cyclohexanecarboxylic acid (**1**, 50.0 g, 0.349 mol) was added to a solution of sodium hydroxide (55.9 g, 1.398 mol) in water (200 mL) at 0–10°C and stirred for 10–15 min. The appropriate acyl chloride (0.699 mol) in toluene (100 mL) was added slowly over 90 min at 0–10°C. After completion of the reaction, water (250 mL) was added to the reaction mass and stirred for 15–30 min. The organic and aqueous layers were separated, and the aqueous layer was washed with toluene (50 mL). The aqueous layer pH was adjusted to 2.0–2.5 using HCl and stirred for 15–30 min. The solid was filtered and washed with water (50 mL). To the wet compound, cyclohexane (150 mL) was added and stirred for 45 min. The solid was filtered, washed with cyclohexane (50 mL), and dried to yield **2a–d**.

Data

1-Propionylamino-cyclohexanecarboxylic acid (2a)

Yield: 80%; IR (cm^{-1}): 3363.3 (N-H), 1735.7 (C═O), 1715.6 (C═O); ^{1}H NMR ($CDCl_3$): 1.1–1.3 (t, 3H, CH_3), 1.3–2.2 (m, 10H, CH_2), 2.2–2.4 (q, 2H, CH_2); mass: 200 (M^+); anal. calcd. for $C_{10}H_{17}NO_3$ (199.12): C, 60.28; H, 8.60; N, 7.03; found: C, 60.15; H, 8.64; N, 7.01.

1-Butyrylamino-cyclohexanecarboxylic acid (2b)

Yield: 76%; IR (cm^{-1}): 3338.7 (N-H), 1736.7 (C═O), 1709.6 (C═O); ^{1}H NMR ($CDCl_3$): 0.8–1.1 (t, 3H, CH_3), 1.3–2.0 (m, 12H, CH_2), 2.2–2.4 (t, 2H, CH_2); mass: 214 (M^+); anal. calcd. for $C_{11}H_{19}NO_3$ (213.14): C, 61.95; H, 8.98; N, 6.57; found: C, 61.99; H, 8.92; N, 6.49.

1-Pentanoylamino-cyclohexanecarboxylic acid (2c)

Yield: 74%; IR (cm^{-1}): 3365.7 (N-H), 1734.7 (C═O), 1714.2 (C═O); ^{1}H NMR ($CDCl_3$): 0.8–1.0 (t, 3H, CH_3), 1.2–1.5 (sext, 2H, CH_2), 1.5–2.2 (m, 12H, CH_2), 2.2–2.4 (t, 2H, CH_2); mass: 228 (M^+); anal. calcd. for $C_{12}H_{21}NO_3$ (227.15): C, 63.41; H, 9.31; N, 6.16; found: C, 63.37; H, 9.35; N, 6.21.

1-Hexanoylamino-cyclohexanecarboxylic acid (2d)

Yield: 78%; IR (cm^{-1}): 3340.5 (N-H), 1731.6 (C═O), 1708.9 (C═O); ^1H NMR ($CDCl_3$): 0.8–1.0 (t, 3H, CH_3), 1.2–2.2 (m, 16H, CH_2), 2.2–2.4 (t, 2H, CH_2); mass: 242 (M^+); anal. calcd. for $C_{13}H_{23}NO_3$ (241.17): C, 64.70; H, 9.61; N, 5.80; found: C, 64.65; H, 9.64; N, 5.89.

General Procedure for the Preparation of 1-Acylamino-cyclohexanecarboxylic Acid (2′-Cyano-biphenyl-4-ylmethyl)-amide (4a–d)

Compound **2** (0.312 mol) and HOBT (6.5 g, 0.048 mol) were added to a solution of **3** (0.240 mol) in methylene chloride (750 mL) and stirred at rt for 10–15 min. To this mixture, DCC (49.5 g, 0.240 mol) in methylene chloride (150 mL) was added slowly. After completion of the reaction, it was filtered and washed with methylene chloride (100 mL). The organic layer was washed with saturated sodium bicarbonate solution (250 mL) and water (150 mL) and concentrated. Cyclohexane (250 mL) was added to the residue and stirred for 45 minutes at rt. The isolated compound was filtered, washed with cyclohexane (125 mL), and dried to yield **4a–d**.

Data

1-Propionylamino-cyclohexanecarboxylic acid (2′-cyano-biphenyl-4-ylmethyl)-amide (4a)

Yield: 88%; IR (cm^{-1}): 3327.8 (N-H), 3308.3 (N-H), 2224.4 (CN), 1719.5 (C═O), 1652.4 (C═O); ^1H NMR ($CDCl_3$): 1.1–1.2 (t, 3H, CH_3), 1.3–1.5 (m, 6H, CH_2), 1.6–1.8 (m, 2H, CH_2), 1.8–2.0 (m, 2H, CH_2), 2.2–2.3 (t, 2H, CH_2), 4.4–4.6 (s, 2H, Ar-CH_2), 7.3–7.6 (m, 6H, Ar-H), 7.6–7.7 (m, 1H, Ar-H), 7.7–7.9 (d, 1H, Ar-H); mass: 390 (M^+); anal. calcd. for $C_{24}H_{27}N_3O_2$ (389.21): C, 74.01; H, 6.99; N, 10.79; found: C, 73.90; H, 6.85; N, 10.84.

1-Butyrylamino-cyclohexanecarboxylic acid (2′-cyano-biphenyl-4-ylmethyl)-amide (4b)

Yield: 82%; IR (cm^{-1}): 3332.2 (N-H), 3310.3 (N-H), 2223.7 (CN), 1720.4 (C═O), 1655.8 (C═O); ^1H NMR ($CDCl_3$): 0.8–1.0 (t, 3H, CH_3), 1.2–1.5 (m, 8H, CH_2), 1.6–1.8 (sext, 2H, CH_2), 1.8–2.0 (t, 2H, CH_2), 2.1–2.3 (t, 2H, CH_2), 4.5–4.7 (s, 2H, Ar-CH_2), 7.4–7.6 (m, 6H, Ar-H), 7.6–7.7 (t, 1H, Ar-H), 7.7–7.8 (d, 1H, Ar-H); mass: 404 (M^+); anal. calcd. for $C_{25}H_{29}N_3O_2$ (403.23): C, 74.41; H, 7.24; N, 10.41; found: C, 74.45; H, 7.20; N, 10.35.

1-Pentanoylamino-cyclohexanecarboxylic acid (2′-cyano-biphenyl-4-ylmethyl)-amide (4c)

Yield: 85%; IR (cm^{-1}): 3337.4 (N-H), 3306.5 (N-H), 2222.0 (CN), 1721.0 (C═O), 1650.2 (C═O); ^1H NMR ($CDCl_3$): 0.9–1.0 (t, 3H, CH_3), 1.2–1.5 (m, 6H, CH_2), 1.6–2.0 (m, 8H, CH_2), 2.1–2.3 (t, 2H, CH_2),

4.4–4.6 (s, 2H, Ar-CH_2), 7.3–7.5 (m, 6H, Ar-H), 7.6–7.7 (t, 1H, Ar-H), 7.7–7.9 (d, 1H, Ar-H); mass: 418 (M^+); anal. calcd. for $C_{26}H_{31}N_3O_2$ (417.24): C, 74.79; H, 7.48; N, 10.06; found: C, 74.72; H, 7.37; N, 9.56.

1-Hexanoylamino-cyclohexanecarboxylic acid (2′-cyano-biphenyl-4-yl methyl)-amide (4d)

Yield: 82%; IR (cm^{-1}): 3338.7 (N-H), 3302.6 (N-H), 2222.8 (CN), 1720.5 (C═O), 1655.8 (C═O); ^{1}H NMR ($CDCl_3$): 0.8–0.9 (t, 3H, CH_3), 1.1–1.3 (m, 2H, CH_2), 1.4–2.1 (m, 14H, CH_2), 2.1–2.3 (t, 2H, CH_2), 4.3–4.4 (s, 2H, Ar-CH_2), 7.3–7.7 (m, 5H, Ar-H), 7.7–7.8 (t, 1H, Ar-H), 7.9–8.1 (d, 1H, Ar-H), 8.0–8.1 (d, 1H, Ar-H); mass: 432 (M^+); anal. calcd. for $C_{27}H_{33}N_3O_2$ (431.26): C, 75.14; H, 7.71; N, 9.74; found: C, 75.18; H, 7.65; N, 9.67.

Preparation of 1-acylamino-cyclohexanecarboxylic acid [2′-(1*H*-tetrazol-5-yl)-biphenyl-4-yl methyl]-amide (5a–d)

A mixture of **4** (0.128 mol), o-xylene (50 mL), tributyltin chloride (124.9 g, 0.384 mol), and sodium azide (24.96 g, 0.384 mol) was refluxed until reaction completion. To the reaction mass at 25–35°C, acetone (400 mL) and water (500 mL) were added and stirred. The pH of the reaction mass was adjusted to 4.0–4.5 using acetic acid, and cyclohexane (500 mL) was added to this and stirred for solid isolation. The isolated solid was filtered, washed with cyclohexane (150 mL), and dried to a constant weight to yield **5a–d**.

1-Propionylamino-cyclohexanecarboxylic acid [2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amide (5a)

Yield: 84%; IR (cm^{-1}): 3363.6 (N-H), 3304.0 (N-H), 3059.9 (N-H), 1670.9 (C═O), 1630.4 (C═O); ^{1}H NMR ($CDCl_3$): 0.9–1.0 (t, 3H, CH_3), 1.3–1.8 (m, 10H, CH_2), 2.1–2.3 (q, 2H, CH_2), 4.2–4.3 (s, 2H, Ar- CH_2), 7.0–7.1 (d, 1H, Ar-H), 7.2–7.4 (d, 1H, Ar-H), 7.4–7.7 (m, 5H, Ar-H), 7.9–8.0 (t, 1H, Ar-H); mass: 433 (M^+); anal. calcd. for $C_{24}H_{28}N_6O_2$ (432.23): C, 66.65; H, 6.53; N, 19.43; found: C, 66.70; H, 6.51; N, 19.39.

1-Butyrylamino-cyclohexanecarboxylic acid [2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amide (5b)

Yield: 86%; IR (cm^{-1}): 3364.4 (N-H), 3302.3 (N-H), 3061.6 (N-H), 1672.0 (C═O), 1626.6 (C═O); ^{1}H NMR ($CDCl_3$): 0.9–1.0 (t, 3H, CH_3), 1.4–1.9 (m, 12H, CH_2), 2.2–2.3 (t, 2H, CH_2), 4.3–4.5 (s, 2H, Ar-CH_2), 7.0–7.3 (m, 6H, Ar-H), 7.5–7.6 (m, 1H, Ar-H), 7.6–7.7 (m, 1H, Ar-H); mass: 447 (M^+); anal. calcd. for $C_{25}H_{30}N_6O_2$ (446.24): C, 67.24; H, 6.77; N, 18.82; found: C, 67.20; H, 6.76; N, 18.79.

1-Pentanoylamino-cyclohexanecarboxylic acid [2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amide (5c)

Yield: 80%; IR (cm^{-1}): 3311.4 (N-H), 3337.6 (N-H), 3063.0 (N-H), 1677.5 (C═O), 1629.3 (C═O); ^{1}H NMR ($CDCl_3$): 0.8–0.9 (t, 3H, CH_3),

1.2–1.9 (m, 14H, CH_2), 2.1–2.3 (t, 2H, CH_2), 4.3–4.4 (s, 2H, Ar-CH_2), 7.0–7.1 (d, 1H, Ar-H), 7.1–7.2 (d, 1H, Ar-H), 7.4–7.6 (m, 5H, Ar-H), 7.7–7.8 (d, 1H, Ar-H); mass: 461 (M^+); anal. calcd. for $C_{26}H_{32}N_6O_2$ (460.26): C, 67.80; H, 7.00; N, 18.25; found: C, 67.75; H, 6.99; N, 18.30.

1-Hexanoylamino-cyclohexanecarboxylic acid [2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amide (5d)

Yield: 83%; IR (cm^{-1}): 3352.6 (N-H), 3305.4 (N-H), 3059.4 (N-H), 1673.5 (C═O), 1626.1 (C═O); ^{1}H NMR ($CDCl_3$): 0.8–1.0 (t, 3H, CH_3), 1.2–2.1 (m, 16H, CH_2), 2.2–2.3 (t, 2H, CH_2), 4.3–4.4 (s, 2H, Ar-CH_2), 7.0–7.1 (d, 1H, Ar-H), 7.2–7.3 (d, 1H, Ar-H), 7.5–7.8 (m, 6H, Ar-H); mass: 475 (M^+); anal. calcd. for $C_{27}H_{34}N_6O_2$ (474.27): C, 68.33; H, 7.22; N, 17.71; found: C, 68.28; H, 7.20; N, 17.77.

General Procedure for the Preparation of 2-Alkyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro[4.5]dec-1-en-4-one (6a–d)

A mixture of **5** (0.115 mol), toluene (500 mL) and trifluoroacetic acid (39.5 g, 0.347 mol) was refluxed azeotropically until reaction completion. The reaction mass was cooled to rt. The isolated solid was filtered and washed with toluene (50 mL). Water (250 mL) was added to the wet compound, and pH was adjusted to 4–5 using caustic lye. The isolated solid was filtered, washed with water (50 mL), and dried to a constant weight at 60–70°C. Recrystallization using isopropyl alcohol yielded **6a–d**.

Data

2-Ethyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro[4.5]dec-1-en-4-one (6a)

Yield: 74%; IR (cm^{-1}): 3419.4 (N-H), 1731.6 (C═O); ^{1}H NMR ($CDCl_3$): 1.0–1.2 (t, 3H, CH_3), 1.3–1.8 (m, 10H, CH_2), 2.3–2.4 (q, 2H, CH_2), 4.6–4.7 (s, 2H, Ar-CH_2), 7.0–7.2 (m, 4H, Ar-H), 7.4–7.5 (d, 1H, Ar-H), 7.5–7.7 (m, 2H, Ar-H), 7.9–8.0 (d, 1H, Ar-H); mass: 415 (M^+); ^{13}C NMR ($CDCl_3$): 186.44, 164.50, 156.00, 141.57, 139.36, 135.99, 131.51, 131.01, 130.86, 129.95, 128.27, 126.96, 123.49, 78.36, 77.71, 69.97, 48.57, 43.28, 33.42, 25.30, 24.99, 22.59, 21.40, 10.11; anal. calcd. for $C_{24}H_{26}N_6O$ (414.22): C, 69.54; H, 6.32; N, 20.27; found: C, 69.70; H, 6.34; N, 20.29.

2-Propyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro[4.5]dec-1-en-4-one (6b)

Yield: 72%; IR (cm^{-1}): 3424.1 (N-H), 1731.4 (C═O); ^{1}H NMR ($CDCl_3$): 0.9–1.0 (t, 3H, CH_3), 1.3–1.8 (m, 12H, CH_2), 2.2–2.3 (t, 2H, CH_2), 4.5–4.7 (s, 2H, Ar-CH_2), 7.0–7.1 (s, 1H, Ar-H), 7.1–7.2 (s, 1H, Ar-H), 7.4–7.6

(m, 5H, Ar-H), 7.8–7.9 (d, 1H, Ar-H); mass: 429 (M^+); ^{13}C NMR ($CDCl_3$): 186.07, 162.39, 155.58, 140.85, 138.85, 135.47, 130.91, 130.52, 130.47, 129.47, 127.80, 126.37, 123.18, 77.63, 76.36, 69.59, 48.46, 33.01, 30.44, 30.11, 26.67, 20.99, 19.16, 19.10, 13.22; anal. calcd. for $C_{25}H_{28}N_6O$ (428.23): C, 70.07; H, 6.59; N, 19.61; found: C, 70.15; H, 6.58; N, 19.64.

2-Butyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro[4.5]dec-1-en-4-one (6c)

Yield: 70%; IR (cm^{-1}): 3331.2 (N-H), 1727.9 (C═O); ^1H NMR ($CDCl_3$): 0.8–0.9 (t, 3H, CH_3), 1.2–1.8 (m, 14H, CH_2), 2.1–2.3 (t, 2H, CH_2), 4.6–4.7 (s, 2H, Ar-CH_2), 7.0–7.2 (m, 4H, Ar-H), 7.4–7.5 (d, 1H, Ar-H), 7.5–7.6 (t, 1H, Ar-H), 7.6–7.7 (t, 1H, Ar-H) 7.9–8.0 (d, 1H, Ar-H); mass: 443 (M^+); ^{13}C NMR ($CDCl_3$): 185.43, 163.34, 161.18, 156.47, 156.14, 140.88, 139.21, 135.47, 130.91, 130.72, 130.56, 129.61, 127.93, 126.39, 123.74, 109.31, 77.63, 69.59, 42.83, 32.98, 28.33, 28.02, 24.74, 22.09, 21.04, 13.48; anal. calcd. for $C_{26}H_{30}N_6O$ (442.25): C, 70.56; H, 6.83; N, 18.99; found: C, 70.58; H, 6.80; N, 19.05.

2-Pentyl-3-[2′-(1*H*-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,3-diaza-spiro[4.5]dec-1-en-4-one (6d)

Yield: 74%; IR (cm^{-1}): 3437.6 (N-H); 1732.7 (C═O); ^1H NMR ($CDCl_3$): 0.8–0.9 (t, 3H, CH_3), 1.2–1.8 (m, 16H, CH_2), 2.1–2.3 (t, 2H, CH_2), 4.6–4.7 (s, 2H, Ar-CH_2), 7.0–7.2 (m, 4H, Ar-H), 7.4–7.5 (d, 1H, Ar-H), 7.5–7.6 (t, 1H, Ar-H), 7.6–7.7 (t, 1H, Ar-H), 7.9–8.0 (d, 1H, Ar-H); mass: 457 (M^+); ^{13}C NMR ($CDCl_3$): 185.05, 163.57, 156.16, 140.82, 139.12, 135.25, 130.74, 130.56, 130.47, 129.47, 127.74, 126.29, 123.69, 77.63, 77.00, 79.36, 69.36, 42.73, 32.84, 30.94, 28.41, 25.58, 24.87, 24.62, 21.87, 20.91, 13.60; anal. calcd. for $C_{27}H_{32}N_6O$ (456.26): C, 71.03; H, 7.06; N, 18.41; found: C, 71.12; H, 7.01; N, 18.38.

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